Betamethasone and Neomycin Nasal Drops

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Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	**Medicinal Chemicals 3**
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Action and use

Glucocorticoid + Aminoglycoside antibacterial

DEFINITION

Betamethasone and Neomycin Nasal Drops contain Betamethasone Sodium Phosphate and Neomycin Sulfate in a suitable vehicle.

The nasal drops comply with the requirements stated under Nasal Preparations and with the following requirements.

Content of betamethasone sodium phosphate, $C_{22}H_{28}FNa_2O_8P$

95.0 to 110.0% of the stated amount of betamethasone sodium phosphate.

IDENTIFICATION

For betamethasone sodium phosphate

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions in water.
(1) Use the nasal drops, diluted if necessary with water, to contain 0.1% w/v of Betamethasone Sodium Phosphate.
(2) 0.1% w/v of betamethasone sodium phosphate BPCRS.
(3) A mixture of equal volumes of solutions (1) and (2).
(4) A mixture of equal volumes of solution (2) and a 0.1% w/v solution of prednisolone sodium phosphate BPCRS.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F_{254}.

(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, heat at 110° for 10 minutes and examine under ultraviolet light (254 nm).

MOBILE PHASE

prepared the mobile phase immediately before use. 20 volumes of acetic anhydride, 20 volumes of water and 60 volumes of butan-1-ol.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (4) shows two principal spots with almost identical Rf values.

CONFIRMATION

The chromatograms obtained with solutions (1), (2) and (3) show single principal spots with similar Rf values.

B. In the Assay for betamethasone, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

For neomycin sulfate

C. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.
(1) Dilute a quantity of the nasal drops with water, if necessary, to produce a solution containing 0.5% w/v of Neomycin Sulfate.
(2) 0.5% w/v of neomycin sulfate EPCRS in water.
(3) Equal volumes of solutions (1) and (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel (Merck silica gel 60 plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 1 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air, spray with 1% w/v solution of ninhydrin in butan-1-ol and heat at 105° for 2 minutes.

MOBILE PHASE

20 volumes of chloroform, 40 volumes of 13.5M ammonia and 60 volumes of methanol.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows a single red spot.

CONFIRMATION

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

(D) To a quantity of the nasal drops containing 10 mg of Neomycin Sulfate add 1 mL of a 0.2% w/v solution of ninhydrin in water. Heat on a water bath for 5 minutes. A purple colour develops.

TESTS

ACIDITY OR ALKALINITY

The pH of the nasal drops is 7.1 to 7.5, Appendix V L.

Related substances

For neomycin sulfate

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

(1) Dilute a quantity of the nasal drops with the mobile phase to produce a solution containing 0.05% w/v of Neomycin Sulfate.
(2) 0.0025% w/v of framycetin sulfate EPCRS in the mobile phase.
(3) 0.01% w/v of neomycin sulfate CRS and 0.005% w/v of neamine EPCRS (neamycin impurity A) in the mobile phase.
(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Column: 25 cm × 4.6 mm packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS C18 is suitable).
(b) Column temperature: 25°.
(c) Mobile phase: To 6.0 volumes of carbonate-free sodium hydroxide solution and 20 volumes of trifluoroacetic acid, add sufficient water to produce 1000 volumes.
(d) Use a flow rate of 0.7 mL per minute.
(e) Post column solution: dilute 1 volume of carbonate-free sodium hydroxide solution to 25 volumes with carbon dioxide-free water, which is added pulse-less to the column effluent using a 375 µL polymeric mixing coil.
(f) Post column addition flow rate: 0.5 mL per minute.
(g) Pulsed amperometric detector with a gold indicator electrode, a silver-silver chloride reference electrode and a stainless steel auxiliary electrode which is the cell body, held at respectively 0.00 V detection, + 0.80 V oxidation and -0.60 V reduction potentials, with pulse durations according to the instrument used.
(h) Inject 10µL of each solution.
(i) Allow the chromatography to proceed for 1.5 times the retention time of the peak due to neomycin B.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to neomycin B (retention time about 10 minutes) are: impurity A, about 0.65; impurity C, about 0.9; impurity G, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between impurity C and nemycin B is at least 2.0. If necessary, adjust the volume of the carbonate-free sodium hydroxide solution in the mobile phase.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (2%);

the area of any peak corresponding to impurity C is not less than three times the area of the principal peak in the chromatogram obtained with solution (4) (3%) and is not greater than three times the area of the principal peak in the the chromatogram obtained with solution (2) (15%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (5%);

the sum of the areas of *secondary peaks*, excluding impurities A and C, is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (15%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (1%).

Related substances

For betamethasone sodium phosphate

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

(1) Dilute the nasal drops, if necessary, to give a solution containing 0.10% w/v of Betamethasone Sodium Phosphate in the mobile phase.
(2) Dilute 1 volume of solution (1) to 50 volumes in the mobile phase.
(3) 0.0060% w/v each of betamethasone sodium phosphate BPCRS and betamethasone with the mobile phase.
(4) Dilute 1 volume of solution (2) to 20 volumes with 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) (Spherisorb ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 241 nm.
(f) Inject 20 µL of each solution.
(g) For solutions (1) and (2) record the chromatogram for three times the retention time of the principal peak.

MOBILE PHASE

40 volumes of methanol and 60 volumes of citro-phosphate buffer pH 5.0.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to [API] (retention time about [T] minutes) [is/ are]: impurity [U], about [V]; impurity [W], about [X] and impurity [Y], about [Z].

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to betamethasone sodium phosphate and betamethasone is at least 3.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to betamethasone is not greater than 1.3 times the area of the principal peak in the chromatogram obtained with solution (2) (2.6%);

the area of any other secondary peak is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (3%);

the sum of the areas of all secondary peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%).

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

ASSAY

For neomycin sulfate

Dilute a quantity of the nasal drops containing 3500 IU to 50 mL with sterile phosphate buffer pH 8.0; dilute 10 mL of the resulting solution to 100 mL with the same solvent and carry out the microbiological assay of antibiotics, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. The upper fiducial limit of error is not less than 90.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU per mL.

For betamethasone sodium phosphate

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

(1) Mix a quantity of the nasal drops containing 5 mg of Betamethasone Sodium Phosphate with 10 mL of methanol and dilute to 25 mL with water.
(2) 0.02% w/v solution of betamethasone sodium phosphate BPCRS in water.
(3) 0.0060% w/v each of betamethasone sodium phosphate BPCRS and betamethasone with the mobile phase.

SYSTEM SUITABILITY

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peaks due to betamethasone sodium phosphate and betamethasone is at least 3.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}FNa_2O_8P$ in solution (2) by measuring the absorbance, Appendix II B, of an aliquot diluted with water to contain 0.002% w/v of Betamethasone Sodium Phosphate at the maximum at 241 nm and taking 297 as the value of A(1%, 1 cm) at the maximum at 241 nm. Calculate the content of betamethasone sodium phosphate, $C_{22}H_{28}FNa_2O_8P$, in the nasal drops from the chromatograms obtained and using the calculated content of $C_{22}H_{28}FNa_2O_8P$, in betamethasone sodium phosphate BPCRS.

STORAGE

Betamethasone and Neomycin Nasal Drops should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of neomycin sulfate and betamethasone sodium phosphate.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Neomycin Sulfate and Betamethasone Sodium Phosphate.