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Ciprofloxacin Infusion

General Notices

Ciprofloxacin Intravenous Infusion

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

EAG ABS	Antibiotics
Contact Details	stephen.maddocks@mhra.gov.uk peter.crowley@mhra.gov.uk
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Notes:	**REVISED** Dissolution, Related Substances and Assay updated **NOTE: Related substances limits revised** If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Fluoroquinolone antibacterial.

DEFINITION

Ciprofloxacin Infusion is a sterile solution, in Glucose Infusion or in Sodium Chloride Infusion, of ciprofloxacin lactate prepared by the interaction of Ciprofloxacin and Lactic Acid. It is supplied as a ready-to-use solution.

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

Content of ciprofloxacin, $C_{17}H_{18}FN_3O_3$

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) Dilute a quantity of the infusion with sufficient *water* to produce a solution containing the equivalent of 0.05% w/v of ciprofloxacin.

(2) 0.058% w/v of *ciprofloxacin hydrochloride BPCRS* in *water*.

(3) Mix 1 volume of solution (1) and 1 volume of solution (2).

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} HPTLC plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 10 µL of each solution, as bands.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, allow it to dry in air for 15 minutes and examine under *ultraviolet light (254 nm* and *365 nm)*.

MOBILE PHASE

10 volumes of *acetonitrile*, 20 volumes of 13.5M *ammonia*, 40 volumes of *dichloromethane* and 40 volumes of *methanol*.

CONFIRMATION

The principal band in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2). The principal band in the chromatogram obtained with solution (3) appears as a single, compact band.

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

(1) Dilute a quantity of the infusion, if necessary, with *water* to produce a solution containing the equivalent of 0.2% w/v of Ciprofloxacin.

(2) 0.07% w/v of *lithium lactate BPCRS* in *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 7.8 mm) packed with a strong cation-exchange resin of sulfonated, cross-linked *styrene-divinylbenzene copolymer* in the hydrogen form (7 to 11 µm) (Aminex HPX-87 H is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.6 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 208 nm.

(f) Inject 20 µL of each solution.

MOBILE PHASE

15 volumes of *acetonitrile* and 85 volumes of 0.0025M *sulfuric acid*.

After each analysis the column should be rinsed with a mixture of 0.005M *sulfuric acid* and *acetonitrile* and then regenerated with 0.025 M *sulfuric acid*.

CONFIRMATION

The chromatogram obtained with solution (1) shows a peak due to lactate with the same retention time as the principal peak in the chromatogram obtained with solution (2).

C. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is the same as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Acidity

For infusions prepared in Glucose Infusion

pH, 3.5 to 4.6, Appendix V L.

For infusions prepared in Sodium Chloride Infusion

pH, 3.9 to 4.5, Appendix V L.

Colour of solution

The infusion is not more intensely coloured than *reference solution GY_6*, Appendix IV B, Method II.

5-Hydroxymethylfurfural

Infusions prepared in Glucose Infusion comply with the following test. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dilute 1 volume of the infusion to 4 volumes with the mobile phase (contains 1.25% w/v of glucose).
(2) 0.000625% w/v of *5-hydroxymethylfurfural* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Assay may be used.

LIMITS

In the chromatogram obtained with solution (1) the area of any peak corresponding to 5-hydroxymethylfurfural is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.05%, calculated with reference to the glucose content).

Related substances

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

(1) Dilute a quantity of the infusion with sufficient mobile phase to produce a solution containing the equivalent of 0.01% w/v of Ciprofloxacin.
(2) Dilute 1 volume of solution (1) to 20 volumes with the mobile phase and further dilute 1 volume to 10 volumes with the mobile phase.
(3) 0.01% w/v of *ciprofloxacin impurity standard BPCRS* in the mobile phase.
(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil BDS).
(b) Use isocratic 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 a detection wavelength of 278 nm.

(f) Inject 25 µL of each solution.

(g) For solution (1), allow the chromatography to proceed for twice the retention time of ciprofloxacin.

MOBILE PHASE

13 volumes of *acetonitrile* and 87 volumes of a 0.245% w/v solution of *orthophosphoric acid* the pH of which has been adjusted to 3.0 with *triethylamine*.

When the chromatograms are recorded under the prescribed conditions the retention time of ciprofloxacin is about 9 minutes. Retention times relative to ciprofloxacin are: impurity E, about 0.4; impurity F, about 0.5; impurity B, about 0.6; impurity C, about 0.7; impurity D, 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 ciprofloxacin impurity B and ciprofloxacin impurity C is at least 1.3.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to ciprofloxacin impurities B, C, D and E using solution (2) and multiply the area of these peaks by the following correction factors: 0.7, 0.6, 1.4 and 6.7 respectively.

In the chromatogram obtained with solution (1):

tthe area of any peak corresponding to impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity E is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 1.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.7%).

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

Bacterial endotoxins

The endotoxin limit concentration is 0.5 IU per mL, Appendix XIV C.

ASSAY

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

(1) Dilute a quantity of the infusion with sufficient of the mobile phase to produce a solution containing the equivalent of 0.001% w/v of Ciprofloxacin.

(2) 0.001% w/v of *ciprofloxacin hydrochloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions stated under related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{17}H_{18}FN_3O_3$ in the infusion using the declared content of $C_{17}H_{18}FN_3O_3$,HCl in *ciprofloxacin hydrochloride BPCRS*. Each mg of $C_{17}H_{18}FN_3O_3$,HCl is equivalent to 0.9010 mg of $C_{17}H_{18}FN_3O_3$.

STORAGE

Ciprofloxacin Infusion should be protected from light. It should not be refrigerated.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ciprofloxacin.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C, D, E and F listed under Ciprofloxacin.