EAG/Panel/Working Party	Antibiotics
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Notes: New Monograph	

Colistimethate Inhalation Powder, hard capsule

Colistimethate Preparations

Action and use
Antibacterial.

DEFINITION
Colistimethate Inhalation Powder, hard capsule consists of Colistimethate Sodium, in *microfine powder* or aerodynamically equivalent, either alone or combined with a suitable carrier. The capsule is loaded into a dry-powder inhaler to generate an aerosol.

The inhalation powder, hard capsule complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION
The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of Preparations for Inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

IDENTIFICATION
A. In the test for Composition, the retention times of the peaks due to the six colistimethate components in the chromatogram obtained with solution (1) are similar to those of the respective peaks in the chromatogram obtained with solution (2).

B. Yield reaction B characteristic of *sodium salts*, Appendix VI.

TESTS

Uniformity of delivered dose
Complies with the requirements stated under Inhalation Powders using the following method of analysis.

Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose, qualitatively weighing the collected dose. Repeat the procedure as described for pre-metered systems under Powders for Inhalation, Uniformity of Delivered Dose.

Free colistin
Dissolve a quantity of the capsule contents containing 1,000,000 IU in 3 mL of *water*, add 0.1 mL of a 10% w/v solution of *silicotungstic acid* and allow to stand for 10 to 20 seconds. The resulting solution is not more opalescent than *reference suspension II*, Appendix IV A.

Composition
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Store all solutions at 5°.

(1) Dissolve a quantity of the capsule contents in sufficient *water* to produce a solution containing 500,000 IU of colistimethate sodium per mL. Dilute 1 mL of the reconstituted solution to 20 mL with *methanol*.

(2) Dissolve 10 mg of *colistimethate sodium for peak identification EPCRS* in 0.25 mL of *water* and dilute to 5.0 mL with *methanol*.

(3) Dissolve 5 mg of *E1 colistimethate sodium for peak identification EPCRS* in 0.25 mL of *water* and dilute to 5.0 mL with *methanol*.

(4) Dissolve 1.5 mg of *E2 colistimethate sodium for peak identification EPCRS* in 0.25 mL of *water* and dilute to 5.0 mL with *methanol*.

(5) Dilute 1.5 mL of solution (2) to 25.0 mL with *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 2.1 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (1.7 µm) (Waters Acquity UPLC CSH C18 is suitable) and a (5 cm × 2.1 mm) guard column.

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

(c) Use a flow rate of 0.3 mL per minute.

(d) Use a column temperature of 30°.

(e) Use an autosampler temperature of 5°.

(f) Use a detection wavelength of 210 nm.

(g) Inject 2 µL of each solution.

MOBILE PHASE

Mobile phase A 1 volume of *acetonitrile* and 19 volumes of a 0.78 % w/v solution of *sodium dihydrogen phosphate dihydrate* previously adjusted to pH 6.5 with 1 M *sodium hydroxide.*

Mobile phase B 1 volume of *acetonitrile* and 1 volume of a 0.78 % w/v solution of *sodium dihydrogen phosphate dihydrate* previously adjusted to pH 6.5 with 1 M *sodium hydroxide.*

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Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 -10	80 → 68	20 → 32
10 - 35	68 → 53	32 → 47
35 - 36	53 → 80	47 → 20
36 - 44	80	20

Use the chromatogram supplied with *colistimethate sodium for identification EPCRS* and the chromatogram obtained with solution (2) to identify peaks due to CMS E1ASM6, CMS E2ASM8, CMS E1ASM8, CMS E2ASM6, CMS E2ASM4 and CMS E1ASM4..

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to CMS E1ASM6 (retention time about 13 minutes) are: CMS E2ASM8, about 0.2; CMS E1ASM8, about 0.4; CMS E2ASM6, about 0.7; CMS E2ASM4, about 1.8; CMS E1ASM4, about 2.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2):

the difference in retention times between 2 consecutive injections is less than 0.1 minutes and the drift in retention time of CMS E1ASM6 from start to end of sequence is less than 0.5 minutes;

the *peak-to-valley ratio* is at least 1.2, where *Hp* is the height above the baseline of the peak with a relative retention of 2.37 and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to CMS E1ASM4;

The test is not valid unless, in the chromatogram obtained with solution (5), the *signal-to-noise* ratio of the peak due to CMS E1ASM6 is at least 50.

LIMITS

Using the chromatogram obtained with solution (1), disregard any peak present at less than 0.05% and calculate the percentage content of colistimethate sodium components in the injection by *normalisation*. The proportions are within the following limits:

CMS E1ASM8, 5.0 to 9.5%;

CMS E1ASM6, 6.5 to 9.5%;

CMS E1ASM4, 2.0 to 5.0%;

CMS E2ASM8, 0.5 to 2.0%;

CMS E2ASM6, 0.5 to 2.5%;

CMS E2ASM4, maximum 1.5%;

the sum of peaks related to CMS E1 and CMS E2 is not less than 77.0%.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, as described in the test for Composition.

Use the chromatogram supplied with *E1 colistimethate sodium for peak identification EPCRS* and the chromatogram obtained with solution (3) to identify peaks due to components of CMS E1.

Use the chromatogram supplied with *E2 colistimethate sodium for peak identification EPCRS* and the chromatogram obtained with solution (4) to identify peaks due to components of CMS E2.

LIMITS

In the chromatogram obtained with solution (1):

the area of any unspecified impurity is not greater than 2.0% by *normalisation*;

the sum of all unspecified impurities is not greater than 7.0% by *normalisation.*

Disregard any peak related to CMS E1 or CMS E2 and any peak with an area less than 0.50% by *normalisation*.

ASSAY

Mix the contents of the 10 capsules 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. For a capsule of average content weight, the upper fiducial limit of error is not less than 95.0% and the lower fiducial limit of error is not more than 115.0% of the stated number of IU.

STORAGE

Colistimethate Inhalation Powder, hard capsules should be protected from light.

LABELLING

The label states (1) the total number of IU (units) and (2) the number of IU (Units) per mg in each capsule.