Colistimethate Sodium

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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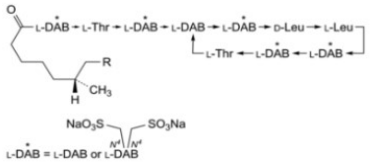
Change **to:** **Colistimethate Sodium**



DAB = 2,4-diaminobutanoic acid

Polymyxin E1 derivative: R=CH_3

Polymyxin E2 derivative: R= H

Between 2 and 5 of the L- DȦB residues are disubstituted at N^4

CMS E1ASM8: principal polymyxin E1 with 4 disubstituted residues.

CMS E1ASM6: principal polymyxin E1 with 3disubstituted residues.

CMS E1ASM4: principal polymyxin E1 with 2 disubstituted residues.

CMS E2ASM8: principal polymyxin E2 with 4 disubstituted residues.

CMS E2ASM6: principal polymyxin E2 with 3disubstituted residues.

CMS E2ASM4: principal polymyxin E2 with 2 disubstituted residues.

Colistimethate Sodium is prepared from colistin by the action of formaldehyde and sodium hydrogen sulphite to form a mixture of di to penta bis-sulphomethylated primary amine derivatives, mainly polymyxins E1 and E2.

Semi-synthetic product derived from a fermentation product.

Colistimethate Sodium contains not less than 11500 Units per mg, calculated on the dried basis.

Category. Antibacterial.

Description. A white or almost white, hygroscopic powder.

Identification

A. In the Composition, the peaks due to CMS E1ASM8, CMS E1ASM6, CMS E1ASM4, CMS E2ASM8, CMS E2ASM6 and CMS E2ASM4 in the chromatogram obtained with the test solution corresponds to the peaks in the chromatogram obtained with reference solution (a).

B. It gives reaction (b) of sodium salts (2.3.1).

Tests

Appearance of solution. A 1.6 per cent w/v solution in *water* is clear (2.4.1)

pH (2.4.24). 6.5 to 8.5, determined in a 1.0 per cent w/v solution in *carbon dioxide-free water*, measure after 30 minutes.

Free colistin. Dissolve 80 mg in 3 ml of *water*, add 0.1 ml of a 10.0 per cent w/v solution of *silicotungstic acid*; after 10 to 20 seconds, the solution is not more opalescent than opalescence standard OS2 (2.4.1).

Composition. Determine by liquid chromatography (2.4.14).

Buffer solution. A 0.78 per cent w/v solution of *sodium dihydrogen phosphate,* adjusted to pH 6.5 with *1M sodium hydroxide.*

Test solution. Dissolve 20 mg of the substance under examination in 0.5 ml of *water* and dilute to 10.0 ml with *methanol.*

Reference solution (a). Dissolve 10 mg of *colistimethate sodium for peak identification IPRS* in 0.25 ml of *water* and dilute to 5.0 ml with *methanol.*

Reference solution (b). Dissolve 2 mg of *E1 colistimethate sodium for peak identification IPRS* in 0.25 ml of *water* and dilute to 2.0 ml with *methanol.*

Reference solution (c). Dissolve 1.5 mg of *E2 colistimethate sodium for peak identification IPRS* in 0.25 ml of *water* and dilute to 5.0 ml with *methanol.*

Reference solution (d). Dilute 1.5 ml of the test solution to 25.0 ml with *methanol.*

Chromatographic system
– a stainless steel column 15 cm × 2.1 mm, packed with end-capped, charged surface, ethylene-bridged octadecylsilane bonded to porous silica (hybrid material) (1.7 µm),
–column temperature: 30°,
–sample temperature: 5°,
–mobile phase: A. a mixture of 5 volumes of *acetonitrile* and 95 volumes of buffer solution,
B. a mixture of 50 volumes of *acetonitrile* and 50 volumes of buffer solution,
– a gradient programme using the conditions given below,
– flow rate: 0.3 ml per minute,
– spectrophotometer set at 210 nm,
– injection volume: 2 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	80	20
10	68	32
35	53	47
40	80	20
45	80	20

Name	Relative retention time
CMS E2ASM8	0.22
CMS E1ASM8	0.39
CMS E2ASM6	0.71
CMS E1ASM6 (Retention time: about 13 minutes)	1.0
CMS E2ASM4	1.77
CMS E1ASM4	2.35

Inject reference solution (a) to identify the peaks due to CMS E1ASM8, CMS E1ASM6, CMS E1ASM4, CMS E2ASM8, CMS E2ASM6 and CMS E2ASM4.

The peak corresponding to the most abundant compound in the range of 11.0 to 14.5 minutes (CMS E1ASM6) in the chromatogram obtained with reference solution (a) is set as the identification reference peak (relative retention 1.00).

Inject reference solution (b) and (c) to identify all the peaks related to CMS E1 and CMS E2.

Inject reference solution (a). The difference in the retention times of CMS E1ASM6 in 2 consecutive injections of reference solution (a) is less than 0.1 minutes; the drift in the retention time of CMS E1ASM6 from the beginning to the end of the sequence is less than 0.5 minutes.

Inject reference solution (a) and (d). The test is not valid unless the column efficiency is not less than 50000 theoretical plates calculated for the peak due to CMS E1ASM6, the peak-to-valley ratio is not less than 1.2, where *Hp* = height above the baseline of the peak with a relative retention of about 2.37 and *Hv* = height above the baseline of the lowest point of the curve separating this peak from the peak due to CMS E1ASM4 in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 50 for the peak due to CMS E1ASM6 in the chromatogram obtained with reference solution (d).

Inject the test solution. The area of any peak corresponding to CMS E1ASM8 is not less than 5.0 per cent and not more than 9.5 per cent, the area of any peak corresponding to CMS E1ASM6 is not less than 6.5 per cent and not more than 9.5 per cent, the area of any peak corresponding to CMS E1ASM4 is not less than 2.0 per cent and not more than 5.0 per cent, the area of any peak corresponding to CMS E2ASM8 is not less than 0.5 per cent and not more than 2.0 per cent, the area of any peak corresponding to CMS E2ASM6 is not less than 0.5 per cent and not more than 2.5 per cent, the area of any peak corresponding to CMS E2ASM4 is not more than 1.5 per cent and the sum of the peaks related to CMS E1 and CMS E2 with an area more than 0.50 per cent is minimum 77.0 per cent. Ignore any peak with an area less the 0.05 per cent, calculated by area normalization method.

Related substances. Determine by liquid chromatography (2.4.14), as described under Composition with the following modifications.

Inject the test solution. The area of any other secondary peak (any peak with an area more than 0.50 per cent not related to CMS E1 or CMS E2) for each of, is not more than 1.5 per cent and the sum of the areas of all the secondary peaks (sum of all the peaks with an area more than 0.50 per cent not related to CMS E1 or CMS E2) is not more than 5.5 per cent. Ignore any peak with an area less than 0.05 per cent, calculated by area normalization method.

Sulphated ash (2.3.18). Between 16 per cent to 21 per cent, determined on 0.5 g.

Loss on drying (2.4.19). Not more than 5.0 per cent, determined on 1 g by drying under vacuum at 60° at a pressure not exceeding 0.7 kPa for 3 hours.

Pyrogens (2.2.8). If intended for use in the manufacture of parenteral preparation without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 1 ml of water for injections containing 2.5 mg of the substance under examination per milliliter.

Assay. Determine by the microbiological assay of antibiotics (2.2.10).

Storage. Store protected from light and moisture. If the substance is sterile the container is also sterile and tamper-evident.