Colistin Tablets

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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**: **Colistin Tablets**

Colistin Sulphate Tablets

Usual strength. 10,00,000 Units (equivalent to 80 mg).

Identification

Solution A. Disperse a quantity of the powdered tablets containing 2,00,000 IU of Colistin Sulphate in *water* with the aid of ultrasound for 10 minutes with intermittent shaking and dilute to 10.0 ml with *water*, filter

A. Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel*.

NOTE—Carry out the test protected from light.

Mobile phase. A mixture of 75 volumes of *phenol* and 25 volumes of *water.*

Test solution. To 0.5 ml of solution A in a sealed tube, add 0.5 ml of *hydrochloric acid*, heat at 135° for 5 hours, evaporate to dryness on a water-bath, continue to heat until any residual hydrogen chloride has been removed, dissolve the residue in 0.5 ml of *water* and centrifuge, if necessary.

Reference solution (a). A 0.25 per cent w/v solution of L-*leucine IPRS* in *water*.

Reference solution (b). A 0.25 per cent w/v solution of L-*threonine IPRS* in *water*.

Reference solution (c). A 0.25 per cent w/v solution of L- *phenylalanine IPRS* in *water*.

Reference solution (d). A 0.25 per cent w/v solution of L-*serine IPRS* in *water.*

Apply to the plate 5 µl of each solution, as 10-mm bands. Place the plate in the tank so that it is not in contact with the mobile phase and expose it to the vapour of the mobile phase. After exposure of the plate to the mobile phase vapour for at least 12 hours, develop to 12 cm. Remove the plate, heat it at 100° to 105°, spray with *ninhydrin solution* and heat at 110° for 5 minutes. The principal zone in the chromatogram obtained with the test solution corresponds to that in the chromatograms obtained with reference solution (a) and (b), but shows no zones corresponding to those in the chromatograms obtained with reference solution (c) and (d); the chromatogram obtained with the test solution also shows a zone with a very low R_f value of 2, 4-diaminobutyric acid.

B. Heat 0.5 ml of solution A with 0.5 ml of *chromotropic acid-sulphuric acid solution* at 100° for 30 minutes. No purple colour is produced (distinction from colistin sulphomethate).

C. Solution A gives reaction (A) of sulphates (2.3.1).

Tests

Composition. Determine by liquid chromatography (2.4.14).

Test solution. Shake a quantity of the powdered tablets containing 6,00,000 IU of Colistin Sulphate in 40 ml of *water* and dilute to 50.0 ml with *acetonitrile* and filter.

Reference solution (a). Dissolve 5 mg of *colistin for system suitability A IPRS* in 8 ml of *water* and dilute to 10.0 ml with *acetonitrile.*

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with a mixture of 20 volumes of *acetonitrile* and 80 volumes of *water*.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with end capped octadecylsilane bonded to porous silica (3.0 µm) (Such as YMC Pack-pro),
- column temperature: 50°,

– mobile phase: a mixture of 22 volumes of *acetonitrile* and 78 volumes of a solution prepared by dissolving 4.46 g of *anhydrous sodium sulphate* in 900 ml of *water*, adjusted to pH 2.4 with *dilute orthophosphoric acid* and dilute to 1000 ml with *water*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 215 nm,
– injection volume: 20 µl.

Name	Relative retention time	Correction factor
Polymyxin E4	0.3	---
Polymyxin E2-Val	0.3	---
Polymyxin E6	0.39	---
Polymyxin E2-I	0.42	---
Polymyxin E2	0.5	---
Polymyxin impurity A[1]	0.53	---
Polymyxin E3	0.56	---
Polymyxin E1-Nva	0.6	---
Polymyxin E1-I	0.8	---
Polymyxin 2,3-dehydro E1	0.9	0.3
Polymyxin E1(Retention time about 21 minutes)	1.0	---
Polymyxin E1-7MOA	1.1	---
Polymyxin impurity B[2]	1.3	---

[1]unknown structure,
[2][*N*^{4}-Dab^5]polymyxin E1.

Inject reference solution (a) to identify the peaks due to polymyxin E4, polymyxin E2-Val, polymyxin E6, polymyxin E2-I, polymyxin E2, polymyxin impurity A, polymyxin E3, polymyxin E1-Nva, polymyxin E1-I, polymyxin 2,3-dehydro E1, polymyxin E1, polymyxin E1-7MOA and polymyxin impurity B.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to polymyxin E6 and polymyxin E2-I is not less than 2.0 and polymyxin 2,3-dehydro E1 and polymyxin E1 is not less than 3.0, the peak-to-valley ratio (Hp/Hv) is not less than 1.1, where Hp is the height above the baseline of the peak due to polymyxin impurity A and Hv is the height above the baseline of the lowest point of the curve separating this peak due to polymyxin E2 in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio for the peak due to polymyxin E2 is not less than 10 in the chromatogram obtained with reference solution (b).

Inject the test solution. Run the chromatogram 1.5 times the retention time of polymyxin E1. The area of any peak corresponding to polymyxin E1-I is not more than 8.5 per cent, the area of any peak corresponding to polymyxin E3 is not more than 5.5 per cent, the area of any peak corresponding to polymyxin E1-7MOA is not more than 5.0 per cent, the area of any peak corresponding to polymyxin E6 and polymyxin E1-Nva, each of, is not more than 4.5 per cent, the sum of the areas of the peaks corresponding to polymyxin E4 and polymyxin E2-Val is not more than 3.0 per cent, the area of any peak corresponding to polymyxin E2-I is not more than 2.5 per cent, the area of any peak corresponding to polymyxin 2,3-dehydro E1 is not more than 1.5 per cent, and the sum of the areas of polymyxin E4, polymyxin E2-Val, polymyxin E6, polymyxin E2-I, polymyxin E2, polymyxin E3, polymyxin E1-Nva, polymyxin E1-I, polymyxin 2,3-dehydro E1and polymyxin E1 peaks is not less than 86.0 per cent, calculated by area normalisation.

Related substances. Determine by liquid chromatography (2.4.14). as described under Composition.

In the chromatogram obtained with the test solution, the area of any peak corresponding to polymyxin impurity B is not more than 4.0 per cent, the area of any secondary peak is not more than 2.5 per cent, the area of not more than 4 such secondary peaks exceed 1.0 per cent and the sum of the areas of all the secondary peaks is not more than 11.0 per cent, calculated by area normalisation. Ignore the peak due to polymyxin E4, polymyxin E2-Val, polymyxin E6, polymyxin E2-I, polymyxin E2, polymyxin E3, polymyxin E1-Nva, polymyxin E1-I, polymyxin 2,3-dehydro E1and polymyxin E1 peaks and any peak with an area less than 0.35 per cent.

Other tests. Comply with the tests stated under Tablets.

Assay. Weigh and powder 20 tablets. Dissolve a suitable quantity of the powder in *phosphate buffer pH 6.0*. Determine by the microbiological assay of antibiotics (2.2.10).

The precision of the assay is such that the fiducial limits of error are not less than 95 per cent and not more than 105 per cent of the estimated potency. The upper fiducial limit of error is not less than 97.0 per cent and the lower fiducial limit of error is not more than 110.0 per cent of the stated number of units.

Storage. Store protected from light and moisture.

Labelling. The label states the number of Units (IU) in each tablet.