Doxycycline for Injection

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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. 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 arnd-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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Doxycycline for Injection

Doxycycline for Injection is a sterile material consisting of Doxycycline Hyclate with or without buffering agents and other excipients. It is filled in a sealed container.

The injection is constituted by dissolving the contents of the sealed container in the requisite amount of sterile Water for Injections or with suitable diluents immediately before use.

The constituted solution complies with the requirements for Clarity of solution and Particulate matter stated under Parenteral Preparations (Injections).

Doxycycline for Injection contains doxycycline hyclate equivalent to not less than 90.0 per cent and not more than 120.0 per cent of the stated amount of doxycycline, $C_{22}H_{24}N_2O_8$.

Usual strengths. 100 mg per vial.

The contents of the sealed container comply with the requirements stated under Parental Preparations (Powder for Injections) and with the following requirements.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

pH (2.4.24). 1.8 to 3.3, determined in the constituted solution as directed in the labelling.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE— Protect the solutions from light.

Test solution. Dissolve the contents of a container in *0.01 M hydrochloric acid* (20 per cent of the final volume) in a suitable volumetric flask and dilute to volume with *0.01 M hydrochloric acid* to obtain a solution containing 0.2 per cent w/v of Doxycycline.

Reference solution (a). A solution of *doxycycline hyclate IPRS* containing 0.1 per cent w/v of doxycycline in *0.01 M hydrochloric acid.*

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 100.0 ml with the *0.01 M hydrochloric acid*. Dilute 1.0 ml of the solution to 10.0 ml with *0.01 M hydrochloric acid.*

Reference solution (c). A solution containing of 0.1 per cent w/v, each of, *doxycycline related compound A IPRS* and *methacycline hydrochloride IPRS* in *0.01 M hydrochloric acid*.

Reference solution (d). Transfer 5 ml of reference solution (a) to a 25-ml volumetric flask, heat on a steam bath for 60 minutes, and evaporate to dryness on a hot plate, taking care not to char the residue. Dissolve the residue in *0.01 M hydrochloric acid*, add 0.5 ml of reference solution (c), and dilute to volume with *0.01 M hydrochloric acid*, filter. (This solution contains a mixture of 4-epidoxycycline, doxycycline related compound A, methacycline, and doxycycline).

Chromatographic system
- a stainless steel column 5 cm x 2.1 mm, packed with octylsilane bonded to porous silica (1.7 µm) (such as ACQUITY UPLC BEH C8),
- guard column a stainless steel column 5 cm x 2.1 mm, packed with octylsilane bonded to porous silica (1.7 µm) (such as Van Guard UPLC BEH C8),
- column temperature: 60°,

– mobile phase: A. a buffer solution prepared by dissolving 3.1 g of *potassium dihydrogen orthophosphate*, 0.5 g of *sodium edetate* and 0.5 ml of *triethylamine* in 850 ml water and mix, dilute to 1000 ml with *water*, adjusted to pH 8.5 with *1 M sodium hydroxide,*

B. *methanol,*

– a gradient programme using the conditions given below,
– flow rate: 0.6 ml per minute,
– spectrophotometer set at 270 nm,
– injection volume: 5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
2	90	10
4	60	40
6	90	10
9	90	10

Name	Relative retention time
Methacycline [1]*	0.64
4-epidoxycycline [2]	0.79
Doxycycline related compound A (6-epidoxycycline)[3]*	0.88
Doxycycline	1.0

* Process impurity, included for identification only, not calculated and included in total degradation products.
[1](4S,4aR,5S,5aR,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methylene-1,11-dioxo-2-naphthacenecarboxamide.
[2](4R,4aR,5S,5aR,6R,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.
[3](4S,4aR,5S,5aR,6S,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.

Inject reference solution (b) and (d). The test is not valid unless the resolution between the peaks due to methacycline and 4-epidoxycycline is not less than 1.5, between the peaks due to 4-epidoxycycline and doxycycline related compound A is not less than 1.5 and between the peaks due to doxycycline related compound A and doxycycline is not less than 2.0 in the chromatogram obtained with reference solution (d) and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to 4-epidoxycycline is not more than 22 times the area of the principal peak in the chromatogram obtained with reference solution (b) (2.2 per cent), the area of any other secondary peak is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than 55 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5.5 per cent). Ignore any peak with an area is not less than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Bacterial Endotoxins (2.2.3). Not more than 1.14 Endotoxin Unit per mg of doxycycline.

Sterility (2.2.11). Complies with the test for sterility.

Loss on drying (2.4.19). Not more than 2.0 per cent for the article containing added substances; Not more than 4.0 per cent for the article containing no added substances determined, on 0.1 g by drying in a capillary-stoppered bottle under vacuum at 60° at a pressure not exceeding 5 mm for 3 hours.

Assay. Determine by liquid chromatography (2.4.14).

NOTE— Protect the solutions from light.

Test solution. Dissolve the contents of a container in of *0.01 M hydrochloric acid* (1 per cent of the final volume) in a suitable volumetric flack and dilute to volume with *0.01 M hydrochloric acid* to obtain a solution containing 0.01 per cent w/v of Doxycycline.

Reference solution. A solution of *doxycycline hyclate IPRS* containing 0.01 per cent w/v of doxycycline in *0.01 M hydrochloric acid.*

Use the chromatographic system as described under Related substances.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{22}H_{24}N_2O_8$ in the injection.

1 mg of doxycycline hyclate is equivalent to 0.8664 mg of doxycycline.

Storage. Store protected from light.