Doxycycline

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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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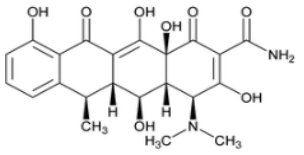
Doxycycline



$C_{22}H_{24}N_2O_8$. H_2O Mol. Wt. 462.5
$C_{22}H_{24}N_2O_8$ Mol. Wt. 444.4

Doxycycline is 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, [4*S*-(4α,4aα,5α,5aα,6α,12aα)]-, monohydrate.

Doxycycline contains not less than 880 µg per mg and not more than 980 µg per mg of $C_{22}H_{24}N_2O_8$.

Category. Antibacterial.

Description. A yellow, crystalline powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *doxycycline monohydrate IPRS* or with the reference spectrum of doxycycline.

B. 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). 5.0 to 6.5, determined in a 1.0 per cent w/v solution.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Protect the solutions from light.

Test solution. Dissolve 50 mg of the substance under examination in *0.01M hydrochloric acid* with the aid of ultrasound and dilute to 25.0 ml with *0.01 M hydrochloric acid.*

Reference solution (a). A solution containing 0.0002 per cent w/v, each of, *doxycycline monohydrate IPRS* and *methacycline hydrochloride IPRS* in *0.01 M hydrochloric acid.*

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

Reference solution (c). A 0.12 per cent w/v solution of *doxycycline hyclate IPRS* in *0.01 M hydrochloric acid.*

Reference solution (d). Transfer 5.0 ml of reference solution (c) 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 (b), and dilute to volume with *0.01 M hydrochloric acid,* filter. This solution contains a mixture of 4-epidoxycycline, methacycline, doxycycline related compound A, and doxycycline.

Reference solution (e). A 0.0001 per cent w/v solution of *doxycycline monohydrate IPRS* in *0.01 M hydrochloric acid.*

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),
– column temperature. 60°,
– mobile phase: A. a buffer solution prepared by dissolving 3.1 g of *monobasic potassium orthophosphate* and 0.5 g of *disodium edetate* in 850 ml of *water*, add 0.5 ml of *triethylamine*, and 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
6	85	15
8	60	40
8.1	90	10
10.0	90	10

Name	Relative retention time	Correction factor
Methacycline[1]	0.51	---
4-epidoxycycline[2]	0.60	---
Doxycycline related compound A (6-epidoxycycline)[3]	0.72	1.49
Doxycycline	1.0	---
Doxycycline related compound F[4]	1.2	1.52

[1](4*S*,4a*R*,5*S*,5a*R*,12a*S*)-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](4*R*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-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](4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide, monohydrochloride,
[4](4*S*,4a*R*,5*S*,5a*R*,6*R*,12a*S*)-2-acetyl-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-4a,5a,6,12a-tetrahydrotetracene-1,11(4*H*,5*H*)-dione.

Inject reference solution (a) (d) and (e). 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), the relative standard deviation for replicate injections is not more than 5.0 per cent for each peaks in the chromatogram obtained with reference solution (a) and the signal to noise ratio is not less than 10 in the chromatogram obtained with reference solution (e).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peaks corresponding to methacycline is not more than 20 times the area of the corresponding peak in the chromatogram obtained with reference solution (a) (2.0 per cent), the area of any peaks corresponding to doxycycline related compound A is not more than 20 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent), the area of any peak corresponding to 4-epidoxycycline is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any peak corresponding to doxycycline related compound F is not more than 10 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent). Ignore any peak with an area is less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Crystallinity (2.4.37). Complies with the test for crystallinity.

Water (2.3.43). 3.6 per cent to 4.6 per cent, determined on 1.0 g.

Assay. Determine by liquid chromatography (2.4.14).

NOTE-Protect the solution from light.

Test solution. Dissolve 50 mg of the substance under examination in *0.01 M hydrochloric acid* with the aid of ultrasound and dilute to 50.0 ml with *0.01 M hydrochloric acid.* Dilute 1.0 ml of the solution to 10.0 ml with *0.01 M hydrochloric acid*.

Reference solution. A 0.01 per cent w/v solution of *doxycycline monohydrate IPRS* 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 1.0 per cent.

Inject the reference solution and the test solution.

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

Storage. Store protected from light and moisture.

Solubility. Freely soluble in dilute acid and in alkali hydroxide solution, very slightly soluble in *ethanol* and in *water*, practically insoluble in *chloroform* and in *ether*.