

Doxycycline Capsules

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Doxycycline Capsules monograph. The purpose of the revision is to widen the limit for 4-epidoxycycline from NMT 0.35% to NMT 0.5% in the test for *Organic Impurities* to accommodate the sponsor's FDA-approved specification.

The Doxycycline Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Praveen Pabba, Scientific Liaison (301-816-8540 or pkp@usp.org).

Doxycycline Capsules

DEFINITION

Doxycycline Capsules contain NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline (C₂₂H₂₄N₂O₈).

IDENTIFICATION

- **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• PROCEDURE

Protect solutions containing doxycycline from light.

Solution A: Transfer 3.1 g of monobasic potassium phosphate, 0.5 g of edetate disodium, and 0.5 mL of triethylamine to a 1000-mL volumetric flask. Add about 850 mL of water and mix. Dilute with water to volume and adjust with 1 N sodium hydroxide to a pH of 8.5 ± 0.1.

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.0	90	10
2.0	90	10
4.0	60	40
6.0	90	10
9.0	90	10

Diluent: 0.01 N hydrochloric acid

Standard solution: 0.12 mg/mL of USP Doxycycline Hyclate RS in *Diluent*. Sonicate as needed to dissolve.

Sample solution: Nominally 0.1 mg/mL of doxycycline in *Diluent*, prepared as follows. Transfer an adequate amount of doxycycline from the contents of NLT 20 Capsules to a suitable volumetric flask. Add 80% of the final volume of *Diluent*, sonicate for about 5 min, shake for about 15 min, and dilute with *Diluent* to volume. Centrifuge a portion of the solution for 10 min at 3000 rpm and use the supernatant for analysis.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 270 nm. For *Identification A*, a diode array detector may be used in the wavelength range of 200–400 nm.

Column: 2.1-mm × 5-cm; 1.7-μm packing L7.

[NOTE—A 1.7-μm guard column with packing L7 was used during method validation.]

Column temperature: 60°

Flow rate: 0.6 mL/min

Injection volume: 5 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of doxycycline (C₂₂H₂₄N₂O₈) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

- r_U = peak response from the *Sample solution*
- r_S = peak response from the *Standard solution*
- C_S = concentration of USP Doxycycline Hyclate RS in the *Standard solution* (mg/mL)
- C_U = nominal concentration of doxycycline in the *Sample solution* (mg/mL)
- P = potency of doxycycline in USP Doxycycline Hyclate RS (μg/mg)
- F = conversion factor, 0.001 mg/μg

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)

▲ Test 1▲ (RB 1-Jun-2017)

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 2: 75 rpm

Time: 60 min

Standard solution: A known concentration of USP Doxycycline Hyclate RS in *Medium*

Sample solution: Filter a portion of the solution under test and dilute with *Medium*, if necessary.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* (857).)

Mode: UV

Analytical wavelength: Maximum absorbance at about 268 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of doxycycline (C₂₂H₂₄N₂O₈) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times P \times F \times 100$$

- A_U = absorbance of the *Sample solution*
- A_S = absorbance of the *Standard solution*
- C_S = concentration of USP Doxycycline Hyclate RS in the *Standard solution* (mg/mL)
- L = label claim (mg/Capsule)
- V = volume of *Medium*, 900 mL
- P = potency of doxycycline in USP Doxycycline Hyclate RS (μg/mg)
- F = conversion factor, 0.001 mg/μg

Tolerances: NLT 85% (Q) of the labeled amount of doxycycline (C₂₂H₂₄N₂O₈) is dissolved.

▲ Test 2

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm, with sinkers

Time: 30 min

Standard solution: A known concentration of USP Doxycycline Hyclate RS in *Medium*

Sample solution: Filter a portion of the solution under test and dilute with *Medium*, if necessary.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* (857).)

Mode: UV

Analytical wavelength: 268 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times P \times F \times 100$$

- A_U = absorbance of the *Sample solution*
 A_S = absorbance of the *Standard solution*
 C_S = concentration of USP Doxycycline Hyclate RS in the *Standard solution* (mg/mL)
 L = label claim (mg/Capsule)
 V = volume of *Medium*, 900 mL
 P = potency of doxycycline in USP Doxycycline Hyclate RS ($\mu\text{g}/\text{mg}$)
 F = conversion factor, 0.001 mg/ μg

Tolerances: NLT 85% (Q) of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) is dissolved. \blacktriangle (RB 1-Jun-2017)

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Protect solutions containing doxycycline from light.

Mobile phase, Diluent, and Chromatographic system: Proceed as directed in the *Assay*.

System suitability stock solution 1: 1 mg/mL each of USP Doxycycline Related Compound A RS and USP Methacycline Hydrochloride RS in *Diluent*

System suitability stock solution 2: 1.2 mg/mL of USP Doxycycline Hyclate RS in *Diluent*

System suitability solution: Transfer 5 mL of *System suitability stock solution 2* to a 25-mL volumetric flask, heat on a steam bath for 60 min, and evaporate to dryness on a hot plate, taking care not to char the residue. Dissolve the residue in *Diluent*, add 0.5 mL of *System suitability stock solution 1*, and dilute with *Diluent* to volume. Pass the solution through a suitable filter and use the filtrate. This solution contains a mixture of 4-epidoxycycline, doxycycline related compound A, methacycline, and doxycycline.

[NOTE—The solution is stable up to 14 days when stored in a refrigerator at 2°–8°.]

Standard solution: 4.6 $\mu\text{g}/\text{mL}$ of USP Doxycycline Hyclate RS in *Diluent*

Sample solution: Nominally 2.0 mg/mL of doxycycline in *Diluent*, prepared as follows. Accurately weigh and transfer a portion of the composite equivalent to 100.0 mg of doxycycline to a 50-mL volumetric flask. Add 80% of the final volume of *Diluent*, sonicate for about 5 min, shake for about 15 min, and dilute with *Diluent* to volume. Centrifuge a portion of the solution for 10 min at 3000 rpm and use the supernatant for analysis.

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between methacycline and 4-epidoxycycline; NLT 1.5 between 4-epidoxycycline and doxycycline related compound A; NLT 2.0 between doxycycline related compound A and doxycycline, *System suitability solution*

Relative standard deviation: NMT 5.0% for the doxycycline peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
 Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

- r_U = peak response of each impurity from the *Sample solution*
 r_S = peak response of doxycycline from the *Standard solution*
 C_S = concentration of USP Doxycycline Hyclate RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of doxycycline in the *Sample solution* (mg/mL)
 P = potency of doxycycline in USP Doxycycline Hyclate RS ($\mu\text{g}/\text{mg}$)
 F = conversion factor, 0.001 mg/ μg

Acceptance criteria: See Table 2. Disregard peaks less than 0.1%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Methacycline ^{a, b}	0.64	—
4-Epidoxycycline ^c	0.79	\blacktriangle 0.5 \blacktriangle (RB 1-May-2018)
Doxycycline related compound A (6-epidoxycycline) ^{b, d}	0.88	—
Doxycycline	1.0	—
Any individual unspecified impurity	—	0.2
Total impurities	—	1.0

^a (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-naphthacene-carboxamide.

^b Process impurities that are controlled in the drug substance are not to be reported. They are not to be included in total impurities. They are listed here for information only.

^c (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-naphthacene-carboxamide.

^d (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-naphthacene-carboxamide.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Add the following:

- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used. \blacktriangle (RB 1-Jun-2017)

- **USP REFERENCE STANDARDS (11)**

USP Doxycycline Hyclate RS

USP Doxycycline Related Compound A RS

[NOTE—May be available as a free base or a hydrochloride salt.]

(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-naphthacene-carboxamide.

$C_{22}H_{24}N_2O_8$ 444.43

(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-naphthacene-carboxamide monohydrochloride.

$C_{22}H_{24}N_2O_8 \cdot \text{HCl}$ 480.13

USP Methacycline Hydrochloride RS