Doxycycline Capsules

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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 add *Dissolution Test* 2 for a generic product approved by the FDA.

The Doxycycline Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 41–NF 36*.

Should you have any questions, please contact Praveen Pabba, Ph.D. 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 ($C_{22}H_{24}N_2O_8$).

IDENTIFICATION

Change to read:

• **A.** ■The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.■2S *(USP40)*

• **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

Change to read:

• **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 ($C_{22}H_{24}N_2O_8$) 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

■2S *(USP40)*

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 ($C_{22}H_{24}N_2O_8$) 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 (µg/mg)
F = conversion factor, 0.001 mg/µg■2S *(USP40)*

Tolerances: NLT 85% (Q) of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) 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 (µg/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. ● (RB 1-Jun-2017)

• **Uniformity of Dosage Units** ⟨**905**⟩**:** Meet the requirements

IMPURITIES

Add the following:

■● **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 µg/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 (µg/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	0.35
Doxycycline related compound A (6-epidoxycycline)[b,d]	0.88	—
Doxycycline	1.0	—
Any individual unspecified impurity	—	0.2
Total impurities	—	1.0

[a] (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.
[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] (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.
[d] (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.

■2S (*USP40*)

SPECIFIC TESTS

Delete the following:

■● **Water Determination** ⟨**921**⟩**,** *Method I***:** NMT 5.5%
■2S (*USP40*)

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. ● (RB 1-Jun-2017)

Change to read:

- **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.]
  (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.
  $C_{22}H_{24}N_2O_8$ 444.43
  (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.
  $C_{22}H_{24}N_2O_8 \cdot HCl$ 480.13
  USP Methacycline Hydrochloride RS■2S *(USP40)*