Doxycycline Capsules

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Expert Committee	Chemical Medicines Monographs 1

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 1 Expert Committee intends to revise the Doxycycline Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 3* to the monograph.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Praveen Pabba, Scientific Liaison to the Chemical Medicines Monographs 1 Expert Committee (301-816-8540 or pkp@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

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

- **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 ($C_{22}H_{24}N_2O_8$) 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

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

Test 1
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

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.

▲**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Acid stage medium: Dilute hydrochloric acid, pH 1.1 (prepare by transferring 8.5 mL of hydrochloric acid to 1 L of water. Mix well, and adjust with hydrochloric acid to a pH of 1.1 ± 0.05, if necessary); 750 mL

Buffer stage medium: pH 6.0 phosphate buffer (after 2 h, add 200 mL of 76 g/L of trisodium phosphate dodecahydrate previously heated to 37 ± 0.5° to the *Acid stage medium*. Adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.0 ± 0.05); 950 mL

Apparatus 2: 75 rpm with a suitable sinker

Times: 2 h in *Acid stage medium*; 4 h in *Buffer stage medium*. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.

Acid stage standard solution: 0.015 mg/mL of USP Doxycycline Hyclate RS in *Acid stage medium*

Buffer stage standard solution: 0.015 mg/mL of USP Doxycycline Hyclate RS in *Buffer stage medium*

Acid stage sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate. Replace the portion removed with the same volume of the appropriate *Acid stage medium*. Dilute with the *Acid stage medium*, if necessary.

Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate. Dilute with *Buffer stage medium*, if necessary.

Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelengths: 268 nm for *Acid stage*; 275 nm for *Buffer stage*

System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%, *Acid stage standard solution* and *Buffer stage standard solution*

Analysis
Samples: *Acid stage standard solution*, *Buffer stage standard solution*, *Acid stage sample solution*, and *Buffer stage sample solution*
Calculate the concentration (C_i) of doxycycline ($C_{22}H_{24}N_2O_8$) in the portion of sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = (A_i/A_S) \times C_S \times D \times P \times F$$

A_i = absorbance from the *Acid stage sample solution* or *Buffer stage sample solution* at time point i
A_S = absorbance from the *Acid stage standard solution* or *Buffer stage standard solution* at time point i
C_S = concentration of USP Doxycycline Hyclate RS in the *Acid stage standard solution* or *Buffer stage standard solution* (mg/mL)
D = dilution factor, if needed
P = potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved in the *Acid stage* (A) and *Buffer stage* (B):

$$\text{Result}_A = C_1 \times V_A \times (1/L) \times 100$$
$$\text{Result}_B = [(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100$$

C_i = concentration of doxycycline in the portion of the sample withdrawn at time point i (mg/mL)
V_A = volume of *Acid stage medium* (750 mL)
L = label claim (mg/Capsule)
V_B = volume of *Buffer stage medium* (950 mL)
V_S = volume of *Acid stage sample solution* withdrawn and replaced with *Acid stage medium* (mL)

Tolerances
Acid stage: NLT 80% (Q) of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) is dissolved.
Buffer stage: NLT 85% (Q) of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) is dissolved.▲ (TBD)

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

IMPURITIES

• **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	0.5
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.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **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