



Doxycycline Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	26-Apr-2024
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 1

In accordance with the Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Small Molecules 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 revise the Doxycycline Capsules monograph to add *Dissolution Test 5*. The revision also necessitates a change in the table numbering in the test for *Organic Impurities*. Additionally, the *USP Reference Standards* section has been updated to add USP Doxycycline Monohydrate RS to support the *Dissolution Test 5*.

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 V. Durga Prasad, Senior Scientist II (91-40-4448-8723 or durgaprasad.v@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 (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

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](#) ($\mu\text{g}/\text{mg}$)

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.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution 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.

▲ For Capsules labeled to contain 40 mg of doxycycline

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Acid stage medium: Dilute hydrochloric acid, pH 1.1 (Prepare by transferring 8 mL of [hydrochloric acid](#) to 1 L of [water](#). Mix well, and adjust with [hydrochloric acid](#) to a pH of 1.1, if necessary.); 750 mL

Buffer stage medium: pH 6.0 phosphate buffer (Add 200 mL of pre-warmed solution containing 28.4 g of [sodium phosphate, dibasic, anhydrous](#) and 4 g of [sodium hydroxide](#) in 1 L of [water](#) to

Acid stage medium. Adjust with 2 N [sodium hydroxide](#) or 2 N [hydrochloric acid](#) to a pH of 6.0.);
950 mL

Apparatus 2: 75 rpm

Times: 30 and 120 min in *Acid stage medium*; 150 min in *Buffer stage medium*. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.

Solution A: Dissolve 28.4 g of [sodium phosphate, dibasic, anhydrous](#) and 4 g of [sodium hydroxide](#) in 1 L of [water](#).

Acid stage standard solution: 0.0137 mg/mL of [USP Doxycycline Monohydrate RS](#) in *Acid stage medium*. Sonicate to dissolve, if necessary.

Buffer stage standard stock solution: 0.104 mg/mL of [USP Doxycycline Monohydrate RS](#) prepared as follows. Transfer a quantity of [USP Doxycycline Monohydrate RS](#) to an appropriate volumetric flask and dissolve in 2% of the flask volume of [methanol](#). Sonicate to dissolve, if necessary. Dilute with *Buffer stage medium* to volume.

Buffer stage standard solution: 0.0208 mg/mL of [USP Doxycycline Monohydrate RS](#) from *Buffer stage standard stock solution* in *Buffer stage medium*

Acid stage sample solution: At the time specified, withdraw a portion of the solution under test, pass through a suitable filter of 10- μm pore size and replace with same volume of the *Acid stage medium* maintained at 37°. Pass through a suitable filter of 0.45- μm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. Dilute with *Acid stage medium* to a concentration similar to that of the *Acid stage standard solution*.

Acid stage excipients stock solution: Transfer placebo mixture equivalent to the weight of the excipients in one dosage unit and one empty Capsule shell in 100 mL of *Acid stage medium*. Heat at 37° for 60 min. Sonicate to dissolve, if necessary. To 10 mL of this solution, add 65 mL of *Acid stage medium* and mix. Pass through a suitable filter of 0.45- μm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Acid stage excipients solution: Transfer 5 mL of *Acid stage excipients stock solution* to a 20-mL volumetric flask. Dilute with *Acid stage medium* to volume.

Buffer stage sample solution: At the time specified, withdraw a portion of the solution under test, pass through a suitable filter of 10- μm pore size. Pass through a suitable filter of 0.45- μm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. Dilute with *Buffer stage medium* to a concentration similar to that of the *Buffer stage standard solution*.

Buffer stage excipients stock solution: To 75 mL of *Acid stage excipients stock solution*, add 20 mL of *Solution A*. Adjust with 2 N [sodium hydroxide](#) or 2 N [hydrochloric acid](#) to a pH of 6.0. Pass through a suitable filter of 0.45- μm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Buffer stage excipients solution: Transfer 5 mL of *Buffer stage excipients stock solution* to a 10-mL volumetric flask. Dilute with *Buffer stage medium* to volume.

Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy \(857\)](#).)

Mode: UV

Analytical wavelength: 345 nm

Blank: *Acid stage medium* or *Buffer stage medium*

Analysis

Samples: Acid stage standard solution, Buffer stage standard solution, Acid stage sample solution, Acid stage excipients solution, Buffer stage sample solution, and Buffer stage excipients solution

Calculate the concentration (C_i) of doxycycline ($C_{22}H_{24}N_2O_8$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = [(A_U - A_E)/A_S] \times C_S \times D \times P \times F$$

A_U = absorbance of the Acid stage sample solution or Buffer stage sample solution

A_E = absorbance of the Acid stage excipients solution or Buffer stage excipients solution

A_S = absorbance of the Acid stage standard solution or Buffer stage standard solution

C_S = concentration of USP Doxycycline Monohydrate RS in the Standard solution (mg/mL)

D = dilution factor for Acid stage sample solution or Buffer stage sample solution

P = potency of doxycycline in USP Doxycycline Monohydrate RS ($\mu\text{g}/\text{mg}$)

F = conversion factor, 0.001 mg/ μg

Calculate the percentage of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V_A \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V_A) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V_B) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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_S = volume of Acid stage sample solution withdrawn and replaced with Acid stage medium (mL)

V_B = volume of Buffer stage medium (950 mL)

Tolerances: See [Table 2](#).

Table 2		
Time Point (i)	Time (min)	Amount Dissolved (%)
1	30	45–65
2	120	50–70
3	150	NLT 80 (Q)

The percentages of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved at time points 1

and 2 conform to [Dissolution <711>](#), [Acceptance Table 2](#), and the percentages of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved at time point 3 conform to [Dissolution <711>](#), [Acceptance Table 4](#). ▲ (TBD)

- [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 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 3](#). ▲ (TBD) Disregard peaks less than 0.1%.

▲ **Table 3** ▲ (TBD)

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*,4*aR*,5*S*,5*aR*,12*aS*)-4-(Dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,10,12,12*a*-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 (4*R*,4*aR*,5*S*,5*aR*,6*R*,12*aS*)-4-(Dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide.

^d (4*S*,4*aR*,5*S*,5*aR*,6*S*,12*aS*)-4-(Dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide.

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.

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*,4*aR*,5*S*,5*aR*,6*S*,12*aS*)-4-(Dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide.



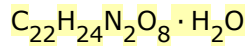
(4*S*,4*aR*,5*S*,5*aR*,6*S*,12*aS*)-4-(Dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide hydrochloride. $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_8 \cdot$

HCl 480.90

[USP Methacycline Hydrochloride RS](#)

▲ USP Doxycycline Monohydrate RS

(4S,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 monohydrate.



462.45 ▲ (TBD)

Page Information:

Not Applicable

Current DocID:

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