

Doxycycline Hyclate Tablets

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| Type of Posting | Notice of Intent to Revise |
| Posting Date | 26-Aug-22 |
| 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 Hyclate Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 5* to accommodate drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

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 Yanyin Yang, Senior Scientist III (301-692-3623 or yanyin.yang@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 Hyclate Tablets

DEFINITION

Doxycycline Hyclate Tablets contain the equivalent of NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$).

IDENTIFICATION

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

• **B. SPECTROSCOPIC IDENTIFICATION TESTS** (197), *Infrared Spectroscopy*: 197A

Standard solution: Transfer about 25 mg of [USP Doxycycline Hyclate RS](#) to a suitable flask. Add 25 mL of [acetonitrile](#) and mix for approximately 5 min with a magnetic stir bar. Pass the solution through a suitable filter, and remove the solvent by natural evaporation or by using a rotary evaporator under vacuum.

Sample solution: Transfer powdered Tablets (NLT 25), equivalent to 25 mg of doxycycline hyclate, to a suitable flask. Add 25 mL of [acetonitrile](#) and mix for approximately 5 min with a magnetic stir bar. Pass the solution through a suitable filter, and remove the solvent by natural evaporation or by using a rotary evaporator under vacuum.

Analysis: Examine the spectra of the *Standard solution* and the *Sample solution* in the range between 2000 and 650 cm^{-1} .

Acceptance criteria: The *Sample solution* exhibits bands at about 1663, 1611, 1576, 1453, 1213, 1037, 1002, 935, and 659 cm^{-1} , similar to the *Standard solution*.

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 ± 0.2 .

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 |

| Time (min) | Solution A (%) | Solution B (%) |
|------------|----------------|----------------|
| 6.0 | 90 | 10 |
| 9.0 | 90 | 10 |

Diluent: 0.01 N [hydrochloric acid](#)

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. When stored in a refrigerator, this solution may be used for 14 days.

Standard solution: 0.3 mg/mL of [USP Doxycycline Hyclate RS](#) in *Diluent*. Sonicate as needed to dissolve.

Sample solution: Nominally 0.25 mg/mL of doxycycline in *Diluent*, prepared as follows. Transfer a suitable portion of NLT 20 finely powdered Tablets to a suitable volumetric flask. Add 50% of the final volume of *Diluent*, sonicate for about 5 min, shake for about 15 min, and dilute with *Diluent* to volume. Pass a portion of this solution through a suitable filter of 0.2- μ m pore size.

Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

Mode: LC

Detector: UV 350 nm

Column: 2.1-mm \times 5-cm; 1.7- μ m packing [L7](#). [NOTE—A 1.7- μ m guard column with packing [L7](#) was used during method validation.]

Column temperature: 60°

Flow rate: 0.6 mL/min

Injection volume: 5 μ L

System suitability

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

[NOTE—See [Table 2](#) for relative retention times.]

Suitability requirements

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

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

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

F = conversion factor, 0.001 mg/ μg

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** <711>

Protect solutions containing doxycycline from light.

Test 1

Medium: [Water](#); 900 mL

Apparatus 2: 75 rpm, the distance between the blade and the inside bottom of the vessel being maintained at 4.5 ± 0.5 cm during the test

Time: 90 min

Standard solution: [USP Doxycycline Hyclate RS](#) in *Medium*

Sample solution: Dilute with *Medium*, if necessary, to a concentration that is similar to the *Standard solution*.

Instrumental conditions

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

Mode: UV-Vis

Analytical wavelength: 276 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:

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of doxycycline in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

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: [Water](#); 900 mL

Apparatus 2: 50 rpm, the distance between the blade and the inside bottom of the vessel being maintained at 4.5 ± 0.5 cm during the test

Time: 30 min

Standard solution: 22 µg/mL of doxycycline from [USP Doxycycline Hyclate RS](#), in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter.

Blank: *Medium*

Instrumental conditions

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

Mode: UV-Vis

Analytical wavelength: 276 nm

Cell: 0.5 cm

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of doxycycline in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

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

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

Protect solutions containing doxycycline from light.

Medium: [Water](#); 900 mL

Apparatus 2: 75 rpm

Time: 30 min

Standard solution: 0.016 mg/mL of doxycycline from [USP Doxycycline Hyclate RS](#), in *Medium*.

Sonicate, if necessary, in a cool water bath.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and dilute with *Medium*, to a concentration that is similar to the *Standard solution*.

Instrumental conditions

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

Mode: UV-Vis

Analytical wavelength: 276 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of doxycycline in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 900 mL

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

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Protect solutions containing doxycycline from light.

Medium: [Water](#); 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Standard solution: 0.020 mg/mL of doxycycline from [USP Doxycycline Hyclate RS](#), in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, to a concentration that is similar to the *Standard solution*.

Instrumental conditions

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

Mode: UV-Vis

Analytical wavelength: 276 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of doxycycline in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 900 mL

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

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

Protect all solutions containing doxycycline from light.

Medium: 0.1 N [hydrochloric acid](#); 500 mL, deaerated

Apparatus 1: 100 rpm

Time: 30 min

Standard solution: 0.016 mg/mL of doxycycline from [USP Doxycycline Hyclate RS](#) in *Medium*.

Sonicate to dissolve if needed.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size. Discard the first 2 mL of the filtrate. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Instrumental conditions

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

Mode: UV

Analytical wavelength: 268 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of doxycycline in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (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

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

Standard solution: 1.5 µg/mL of [USP Doxycycline Hyclate RS](#) in *Diluent*

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 1.5 between doxycycline related compound A and doxycycline, *System suitability solution*

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

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each impurity in the portion of Tablets 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 any impurity peaks less than 0.2%.

Table 2

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|------|-------------------------|------------------------------|
|------|-------------------------|------------------------------|

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|--|-------------------------|------------------------------|
| Methacycline ^{a,b} | 0.64 | — |
| 4-Epidoxycycline ^c | 0.79 | 1.5 |
| Doxycycline related compound A (6-epidoxycycline) ^{a,d} | 0.88 | — |
| Doxycycline | 1.0 | — |
| Any individual unspecified impurity | — | 0.5 |
| Total impurities | — | 2.0 |

^a Process impurities are controlled in the drug substance and are not to be reported here. They are not included in total impurities.

^b (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-naphthacenecarboxamide.

^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-naphthacenecarboxamide.

^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-naphthacenecarboxamide.

ADDITIONAL REQUIREMENTS

● **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

● **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

● **USP REFERENCE STANDARDS** (11)

[USP Doxycycline Hyclate RS](#)

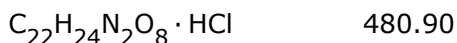
[USP Doxycycline Related Compound A RS](#)

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

(4*S*,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-naphthacenecarboxamide.



(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-naphthacenecarboxamide, hydrochloride.



[USP Methacycline Hydrochloride RS](#)

Page Information:

Not Applicable

Current DocID:

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