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Doxycycline Hyclate Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-doxycycline-hyclate-tabs-20221118.

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
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-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 350 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

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 (µg/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-µm 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.▲ (RB 9-Nov-2022)

- **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 (%)
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*,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.

[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. 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*,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.

$C_{22}H_{24}N_2O_8$ 444.44

(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 hydrochloride.

$C_{22}H_{24}N_2O_8 \cdot HCl$ 480.90

USP Methacycline Hydrochloride RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
DOXYCYCLINE HYCLATE TABLETS	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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