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Doxycycline for Oral Suspension

DEFINITION

Doxycycline for Oral Suspension contains the equivalent of NLT 90.0% and NMT 125.0% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) when constituted as directed. It contains one or more suitable buffers, colors, diluents, flavors, and preservatives.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A

Standard: Transfer about 25 mg of USP Doxycycline Monohydrate RS to a suitable flask. Add 25 mL of acetonitrile and mix for approximately 10 min with a magnetic stir bar. Pass through suitable filter paper (Whatman #40 or equivalent), and remove the solvent by natural evaporation.

Sample: Place an amount of Doxycycline for Oral Suspension, nominally equivalent to about 25 mg of doxycycline, in a suitable flask. Add 25 mL of acetonitrile and mix for approximately 10 min with a magnetic stir bar. Pass through suitable filter paper (Whatman #40 or equivalent), and remove the solvent by natural evaporation.

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

Acceptance criteria: The *Sample* exhibits bands at about 1644, 1577, 1518, 1452, 1396, 1167, 995, and 952 cm^{-1}, similar to the *Standard*. ▲[Note—Peak positions may vary slightly (within ±10 cm^{-1}). Other peaks may be present in the spectra that do not appear in this list.]▲ (USP 1-Aug-2023)

• **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 ± 0.2.

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

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. Constitute Doxycycline for Oral Suspension as directed in the labeling. Transfer an accurately measured portion of the constituted suspension, freshly mixed and free from air bubbles, equivalent to about 25 mg of doxycycline, to a suitable volumetric flask. Add 50% of the final volume of *Diluent*, shake by mechanical means 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

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT ▲1.0%▲ (USP 1-Aug-2023)

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 Doxycycline for Oral Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response of doxycycline 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: 90.0%–125.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION ⟨711⟩**

Protect solutions containing doxycycline from light.

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 2: 25 rpm

Time: 10 min

Solution A: Transfer 1.36 g of monobasic potassium phosphate, 0.37 g of sodium hydroxide, 0.25 g of tetrabutylammonium hydrogen sulfate, and 0.2 g of edetate disodium to a 1000-mL volumetric flask. Add about 850 mL of water and mix. Add 75 g of tert-butyl alcohol and dilute with water to volume. Adjust with 1 N sodium hydroxide or 5 N hydrochloric acid to a pH of 8.0 ± 0.05.

Solution B: Acetonitrile and water (80:20)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0.0	100	0
13.0	100	0
15.0	20	80
21.0	20	80
▲23.0	100	0
30.0	100	0▲ (USP 1-Aug-2023)

▲▲ (USP 1-Aug-2023)

Standard solution: 32 µg/mL of USP Doxycycline Hyclate RS in *Medium*

Sample solution: Reconstitute the suspension according to the label instructions for three separate containers. Transfer and combine the contents of the three containers into a separate suitable flask. Determine the density of the suspension. Using suitable syringes, measure portions of the reconstituted suspension containing nominally 25 mg of doxycycline. With the paddles lowered, gently empty the contents of each syringe into each vessel containing *Medium*. Start the paddle rotation. At the specified time, ▲withdraw the solution under test▲ (USP 1-Aug-2023) and pass a portion through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 355 nm

Column: 4.6-mm × 25-cm; 5-µm packing L21

Temperatures

Autosampler: 10°

Column: 60°

Flow rate: 1.5 mL/min

Injection volume: 100 µL

▲▲ (USP 1-Aug-2023)

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\blacktriangle \text{Result} = (r_U/r_S) \times C_S \times (1/L) \times (d/W) \times V \times P \times F \times 100 \blacktriangle \text{ (USP 1-Aug-2023)}$$

r_U = peak response of doxycycline from the *Sample solution*

r_S = peak response of doxycycline from the *Standard solution*

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

L = label claim of Doxycycline for Oral Suspension (mg/5 mL)

▲ ▲ (USP 1-Aug-2023)

d = density of the *Sample solution* (g/mL)

W = weight of Doxycycline for Oral Suspension taken (g)

V = volume of *Medium*, 900 mL

▲P = potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)

F = conversion factor, 0.001 mg/µg▲ (USP 1-Aug-2023)

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

- **Deliverable Volume ⟨698⟩:** Meets the requirements
- **Uniformity of Dosage Units ⟨905⟩**

For single-unit containers

Acceptance criteria: Meets the requirements

IMPURITIES

Change to read:

- **Organic Impurities**

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

Standard solution: 1.5 µg/mL of USP Doxycycline Hyclate RS in *Diluent*

Sample solution: Nominally, a 0.25-mg/mL solution of doxycycline in *Diluent* is prepared as follows. Constitute Doxycycline for Oral Suspension as directed in the labeling. Transfer an accurately measured portion, freshly mixed and free from air bubbles, equivalent to about 25 mg of doxycycline, to a 100-mL volumetric flask. Add 50 mL of *Diluent* and shake by mechanical means for about 15 min. Dilute with *Diluent* to volume. Pass a portion of this solution through a suitable filter of 0.2-µm pore size.

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; and 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 Doxycycline for Oral Suspension 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*. ▲The reporting threshold is▲ (USP 1-Aug-2023) 0.1%.

Table 3

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]▲▲ (USP 1-Aug-2023)	0.88	—
Doxycycline	1.0	—
Any individual unspecified impurity	—	0.20
Total impurities	—	2.5

[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.

SPECIFIC TESTS

- **pH** ⟨791⟩

Sample solution: Constitute as directed in the labeling.

Acceptance criteria: 5.0–6.5

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store dry powder at controlled room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Doxycycline Hyclate RS

USP Doxycycline Monohydrate 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▲ (USP 1-Aug-2023)

(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.▲ (USP 1-Aug-2023)

$C_{22}H_{24}N_2O_8 \cdot HCl$ ▲480.90▲ (USP 1-Aug-2023)

USP Methacycline Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
DOXYCYCLINE FOR ORAL SUSPENSION	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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