Doxycycline Hyclate Tablets

Type of Posting	Revision Bulletin
Posting Date	26–Oct–2018
Official Date	01–Nov–2018
Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Doxycycline Hyclate Tablets monograph. The purpose for the revision is to add *Dissolution Test 3* to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

The Doxycycline Hyclate Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Praveen Pabba, Scientific Liaison (301-816-8540 or pkp@usp.org).

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. INFRARED ABSORPTION** ⟨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 RSand 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.▲ (RB 1-Nov-2018)

• **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	—

Table 2 *(continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
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.
  $C_{22}H_{24}N_2O_8$ 444.43
  (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