## Doxycycline Tablets

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| **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 Tablets monograph. The purpose of the revision is to add *Dissolution Test 2* for a generic product approved by the FDA. A *Labeling* section was also added.

The Doxycycline Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

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

# Doxycycline Tablets

## DEFINITION

Doxycycline Tablets contain 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.** The UV spectrum 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 from NLT 20 Tablets prepared as follows. Transfer a suitable portion of finely powdered Tablets to a suitable volumetric flask. Add 50% of the final volume of *Diluent*, dissolve, dilute with *Diluent* to volume, and mix well. Centrifuge a portion of the solution and use the supernatant. [NOTE—The use of a centrifuge speed at 3,000 rpm for 10 min may be suitable. ]

**Chromatographic system**
(See *Chromatography* ⟨621⟩*, System Suitability*.)
**Mode:** LC
**Detector:** UV 270 nm. For *Identification B*, 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 ($C_{22}H_{24}N_2O_8$) 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⟩

**▲Test 1▲** (RB 1-Apr-2018)
**Medium:** 0.01 N hydrochloric acid; 900 mL
**Apparatus 2:** 75 rpm
**Time:** 60 min
**Standard solution:** 0.01 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. Dilute a portion of the filtrate 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
**Cell:** 1 cm
**Blank:** *Medium*

**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Determine the percentage of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved:

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

$A_U$ = 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/Tablet)
$V$ = volume of *Medium*, 900 mL
$P$ = potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)

**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*.
Protect solutions containing doxycycline from light.
**Medium:** 0.01 N hydrochloric acid; 900 mL
**Apparatus 2:** 75 rpm
**Time:** 15 min
**Standard solution:** 0.01 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. Dilute a portion of the filtrate 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
**Cell:** 1 cm
**Blank:** *Medium*
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Determine the percentage of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved:

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

$A_U$ = 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/Tablet)
$D$ = dilution factor for the *Sample solution*, if applicable
$V$ = volume of *Medium*, 900 mL
$P$ = potency of doxycycline in USP Doxycycline Hyclate RS (µg/mg)
$F$ = conversion factor, 0.001 mg/µg

**Tolerances:** NLT 80% *(Q)* of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) is dissolved. ▲ (RB 1-Apr-2018)

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

## IMPURITIES

• **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:** 7.0 µg/mL of USP Doxycycline Hyclate RS in *Diluent*
**Sample solution:** Nominally 2.0 mg/mL of doxycycline from NLT 20 Tablets prepared as follows. Transfer a suitable portion of finely powdered Tablets to a suitable volumetric flask. Add 50% of the final volume of *Diluent*, dissolve, dilute with *Diluent* to volume, and mix well. Centrifuge a portion of the solution and use the supernatant. [NOTE—The use of a centrifuge speed at 3,000 rpm for 10 min may be suitable. ]
**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 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 peaks less than 0.1%.

**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)[b, d] | 0.88 | — |
| Doxycycline | 1.0 | — |
| Any individual unspecified impurity | — | 0.3 |
| Total impurities | — | 2.5 |

[a] (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.
[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*,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. Main degradation product.
[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.

***Add the following:***

▲• **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used. ▲ (RB 1-Apr-2018)

• **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