Doxycycline Hyclate Delayed-Release 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 Hyclate Delayed-Release Tablets monograph. The purpose of the revision is to add Dissolution Test 5 for a generic product approved by the FDA.

The Doxycycline Hyclate Delayed-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into the *First Supplement* to *USP 41—NF 36*.

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

Doxycycline Hyclate Delayed-Release Tablets

DEFINITION

Doxycycline Hyclate Delayed-Release Tablets contain an amount of Doxycycline Hyclate equivalent to 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*.

ASSAY

• **PROCEDURE**

Mobile phase: Transfer 0.77 g of ammonium acetate, 0.75 g of sodium hydroxide, 0.50 g of tetrabutylammonium hydrogen sulfate, and 0.40 g of edetate disodium to a 1000-mL volumetric flask. Add 850 mL of water, and dissolve. Add 70 g of tertiary butyl alcohol with the aid of water, dilute with water to volume, and adjust with acetic acid or ammonium hydroxide to a pH of 9.00 ± 0.05.

Standard solution: 1.16 mg/mL of doxycycline hyclate in methanol and water (1:9). Transfer USP Doxycycline Hyclate RS to a suitable volumetric flask, and add methanol to 10% of the final volume. Sonicate for 5 min or until dissolved. Dilute with water to volume. Protect the *Standard solution* from light. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.

Sample solution: Equivalent to 1 mg/mL of doxycycline in a mixture of methanol and water (1:9) from NLT 10 Tablets, crushed. Prepare the solution as follows. Weigh and crush NMT 2 Tablets at a time in a suitable mortar. Transfer a weighed portion of the powder to a suitable volumetric flask, add methanol to 10% of the final volume, and sonicate. Dilute with water to volume, sonicating as necessary. Pass through a suitable filter. Protect the *Sample solution* from light.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 25-cm; packing L21
Column temperature: 52 ± 2°
Flow rate: 1 mL/min
Injection volume: 15 µL
Run time: 1.7 times the retention time of the doxycycline peak

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0% from six replicate injections

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:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of doxycycline in the *Standard solution* (mg/mL)
C_U = nominal concentration of doxycycline in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Test 1: Proceed as directed for *Dissolution* ⟨711⟩, *Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*.

Acid stage
Medium: 0.06 N hydrochloric acid; 900 mL, degassed with helium
Apparatus 1: 50 rpm
Time: 20 min
Standard solution: 0.128 mg/mL of USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS. [NOTE—Sonicate if necessary to dissolve.]
Sample solution: Pass portions of the solution under test through a suitable PVDF filter of 0.45-µm pore size.
Detector: UV 346 nm
Cell: 0.1-cm quartz
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:

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

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
Level 1 (6 Tablets tested): No individual value is more than 30% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved in 20 min.
Level 2 (6 Tablets tested): NMT 2 individual values of the 12 tested are greater than 30% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) in 20 min.

Buffer stage
Conduct this stage of testing on separate Tablets, selecting those that were not previously subjected to the *Acid stage* testing.
Medium: pH 5.5 neutralized phthalate buffer (see *Reagents, Indicators, and Solutions—Buffers*); 900 mL, degassed
Apparatus 1: 50 rpm
Time: 30 min
Standard solution: 0.128 mg/mL of USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS. [NOTE—Sonicate if necessary to dissolve.]
Sample solution: Pass portions of the solution under test through a suitable PVDF filter of 0.45-µm pore size.
Analysis: Determine the percentage of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved by the procedure described for the *Acid stage*.

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 the product meets USP *Dissolution Test 2*. Proceed as directed for *Dissolution* ⟨711⟩*, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*.

Acid stage

Medium, Apparatus 1, Time, Blank, and **Analysis:** Proceed as directed for *Acid stage* in *Test 1*.

Standard solution: (*L*/900) mg/mL of USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS. Sonicate if necessary to dissolve.

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

Detector: UV 345 nm

Cell: See *Table 1*.

Table 1

Tablet Strength (mg/Tablet)	Cell Size (cm)
75	0.5
100	0.5
150	0.2

Tolerances

Level 1 (6 Tablets tested)**:** No individual value is more than 50% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved in 20 min.

Level 2 (6 Tablets tested)**:** NMT 2 individual values of the 12 tested are greater than 50% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) in 20 min.

Buffer stage

Conduct this stage of testing on separate Tablets, selecting those that were not previously subjected to the *Acid stage* testing.

Medium: pH 5.5 neutralized phthalate buffer (see *Reagents, Indicators, and Solutions—Buffers*); 1000 mL, degassed

Apparatus 1 and **Analysis:** Proceed as directed for *Buffer stage* in *Test 1*.

Time: 45 min

Standard solution: (*L*/1000) mg/mL of USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS. Sonicate if necessary to dissolve.

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

Detector and **Cell:** Proceed as directed for *Acid stage* in *Test 2*.

Tolerances: NLT 70% (*Q*) of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*. Proceed as directed for *Dissolution* ⟨711⟩*, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*.

Acid stage

Apparatus 1 and **Time:** Proceed as directed for *Acid stage* in *Test 1*.

Medium: 0.06 N hydrochloric acid; 900 mL

Standard solution: Prepare the solutions as directed in *Table 2* from USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.

Table 2

Tablet Strength (mg/Tablet)	Concentration of Doxycycline (mg/mL)
75	0.1
100	0.1
150	0.17

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

Detector: UV 345 nm

Cell: 0.2 cm

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:

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

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: See *Table 3*.

Table 3

Level	Number of Tablets Tested	Tolerances: Tablets Labeled to Contain 75 or 100 mg of Doxycycline	Tolerances: Tablets Labeled to Contain 150 mg of Doxycycline
A_1	6	No individual value exceeds 50% at 20 min.	No individual value exceeds 30% at 20 min.
A_2	6	Average of 12 units ($A_1 + A_2$) is NMT 50% at 20 min, and no individual unit is greater than 65% dissolved.	Average of 12 units ($A_1 + A_2$) is NMT 30% at 20 min, and no individual unit is greater than 45% dissolved.
A_3	12	Average of 24 units ($A_1 + A_2 + A_3$) is NMT 50% at 20 min, and no individual unit is greater than 65% dissolved.	Average of 24 units ($A_1 + A_2 + A_3$) is NMT 30% at 20 min, and no individual unit is greater than 45% dissolved.

Buffer stage

Conduct this stage of testing on separate Tablets, selecting those that were not previously subjected to the *Acid stage* testing.

Medium: pH 5.5 neutralized phthalate buffer (see *Reagents, Indicators, and Solutions—Buffers*); 1000 mL

Apparatus 1: 50 rpm

Time: 60 min

Standard solution: Prepare the solutions as directed in *Table 4* from USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of

doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.

Table 4

Tablet Strength (mg/Tablet)	Concentration of Doxycycline (mg/mL)
75	0.1
100	0.1
150	0.15

Sample solution: Pass portions of the solution under test through a suitable filter.
Detector: UV 345 nm
Cell: 0.2 cm
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:

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

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*, 1000 mL
Tolerances: See *Table 5*.

Table 5

Tablets Labeled to Contain 75 or 100 mg of Doxycycline	Tablets Labeled to Contain 150 mg of Doxycycline
NLT 80% (*Q*) of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) is dissolved.	NLT 70% (*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 the product meets USP *Dissolution Test 4*. Proceed as directed for *Dissolution* ⟨711⟩*, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*.
Acid stage
Medium: 0.06 N hydrochloric acid; 900 mL, degassed
Apparatus 1: 50 rpm
Time: 20 min
Standard solution: 0.1 mg/mL of doxycycline from USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.
Sample solution: Pass portions of the solution under test through a suitable filter.
Detector: UV 345 nm
Cell: 0.2-cm quartz
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:

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

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
Level 1 (6 Tablets tested): No individual value is more than 30% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) dissolved in 20 min.
Level 2 (6 Tablets tested): NMT 2 individual values of the 12 tested are greater than 30% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) in 20 min.
Buffer stage
Conduct this stage of testing on separate Tablets, selecting those that were not previously subjected to the *Acid stage* testing.
Medium: pH 5.5 neutralized phthalate buffer (see *Reagents, Indicators, and Solutions—Buffers*); 1000 mL, degassed
Apparatus 1: 50 rpm
Time: 30 min
Standard solution: 0.1 mg/mL of doxycycline from USP Doxycycline Hyclate RS in *Medium*
Sample solution: Pass portions of the solution under test through a suitable filter. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.
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:

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

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*, 1000 mL
Tolerances: NLT 75% (*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 the product meets USP *Dissolution Test 5*. Proceed as directed for *Dissolution* ⟨711⟩*, Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*.
Acid stage
Medium: 0.06 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Time: 20 min
Standard solution: 0.06 mg/mL of doxycycline from USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.
Sample solution: Pass portions of the solution under test through a suitable filter.
Detector: UV 345 nm
Cell: 1.0 cm
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:

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

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: See *Table 6*.

Table 6

Level	Number of Tablets Tested	Tolerances
A_1	6	No individual value exceeds 50% at 20 min.
A_2	6	Average of 12 units ($A_1 + A_2$) is NMT 50% at 20 min, and no individual unit is greater than 65% dissolved.
A_3	12	Average of 24 units ($A_1 + A_2 + A_3$) is NMT 50% at 20 min, and no individual unit is greater than 65% dissolved.

Buffer stage
Conduct this stage of testing on separate Tablets, selecting those that were not previously subjected to the *Acid stage* testing.
Medium: pH 5.5 neutralized phthalate buffer (see *Reagents, Indicators, and Solutions—Buffers*); 900 mL
Apparatus 1: 100 rpm
Time: 30 min
Standard solution: 0.06 mg/mL of doxycycline from USP Doxycycline Hyclate RS in *Medium*. Calculate the concentration, C_S, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.
Sample solution: Pass portions of the solution under test through a suitable filter.
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:

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

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 80% (Q) of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$) is dissolved. ● (RB 1-Aug-2017)

- **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

- **Organic Impurities**
Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard stock solution: 1.16 mg/mL of doxycycline hyclate in methanol and water (1:9). Transfer USP Doxycycline Hyclate RS to a suitable volumetric flask, and add methanol to 10% of the final volume. Sonicate for 5 min or until dissolved. Dilute with water to volume. Protect the solution from light. Calculate the concentration, in mg/mL of doxycycline, using the designated potency, in µg/mg of doxycycline in USP Doxycycline Hyclate RS.
Standard solution: 0.02 mg/mL of doxycycline from the *Standard stock solution*. Protect the solution from light.
Sensitivity solution: 1 µg/mL of doxycycline from the *Standard solution*. Protect the solution from light.
System suitability stock solution: 0.04 mg/mL each of USP Oxytetracycline Hydrochloride RS, USP Methacycline Hydrochloride RS, and USP Doxycycline Related Compound A RS. Protect the solution from light.
System suitability solution: Transfer 5 mL of the *Standard stock solution* into a 25-mL volumetric flask. Heat on a steam bath for 60 min, and gently evaporate to dryness on a hot plate (partial degradation of doxycycline to 4-epidoxycycline). Add 3 mL of the *System suitability stock solution* to the flask, and dilute with water to volume. Pass through a suitable filter. Protect the solution from light.
System suitability
Samples: *Standard solution*, *Sensitivity solution*, and *System suitability solution*
Suitability requirements
Signal-to-noise ratio: NLT 10 for doxycycline, *Sensitivity solution*
Resolution: NLT 1.5 between doxycycline and 6-epidoxycycline, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Sample solution* and *Standard solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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 doxycycline in the *Standard solution* (mg/mL)
C_U = nominal concentration of doxycycline in the *Sample solution* (mg/mL)
F = relative response factor (see *Table* ●*7*)● (RB 1-Aug-2017)
Acceptance criteria: See *Table* ●*7*.● (RB 1-Aug-2017)

Table ●**7**● (RB 1-Aug-2017)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxytetracycline	0.3	1.0	0.5
4-Epidoxycycline[a]	0.4	1.0	1.0
Methacycline	0.6	1.0	2.0
6-Epidoxycycline (doxycycline related compound A)[b]	0.7	0.86	2.0
Doxycycline	1.0	—	—

[a] (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 monohydrate.
[b] (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 monohydrate.

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 test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Doxycycline Hyclate RS
  USP Doxycycline Related Compound A RS
  6-Epidoxycycline, or (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.
  $C_{22}H_{24}N_2O_8$ 444.43
  USP Methacycline Hydrochloride RS
  USP Oxytetracycline Hydrochloride RS