Minocycline Hydrochloride Extended-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 Minocycline Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Tests 6* and *7* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 6* was validated using an ACE C18 brand of L1 column. The typical retention time for minocycline is about 7.2 min.

The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

The Minocycline Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

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

Minocycline Hydrochloride Extended-Release Tablets

DEFINITION

Minocycline Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of minocycline ($C_{23}H_{27}N_3O_7$).

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 absorption spectrum of the major peak of the *Sample solution* and that of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Protect solutions containing minocycline from light.

Buffer: 3.5 g/L of tetrabutylammonium hydrogen sulfate, 2 g/L of anhydrous citric acid, and 6.8 g/L of monobasic potassium phosphate. Adjust with 10 N sodium hydroxide to a pH of 7.0.

Mobile phase: Acetonitrile and *Buffer* (24:76)

Diluent: Acetonitrile and water (20:80)

Standard solution: 0.045 mg/mL of minocycline from USP Minocycline Hydrochloride RS in *Diluent*. Store at 4° and use within 24 h.

Sample stock solution: Nominally about 0.9 mg/mL of minocycline from Tablets prepared as follows. Transfer a suitable portion of finely powdered Tablets (NLT 10) to a suitable volumetric flask. Add acetonitrile, using 20% of the final volume, and mix vigorously for 15 min. Add water, using 65% of the final volume, and mix vigorously for 30 min. Dilute with water to volume and mix.

Sample solution: Nominally 0.045 mg/mL of minocycline from *Sample stock solution* in *Diluent*. Centrifuge and use the clear supernatant. Store at 4° and use within 24 h.

Chromatographic system

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

Mode: LC

Detector: UV 277 nm. When this procedure is used for *Identification* test *B*, use a diode array detector set at 200–400 nm.

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Column: 35°

Autosampler: 4°

Flow rate: 1.3 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of minocycline ($C_{23}H_{27}N_3O_7$) 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 Minocycline Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of minocycline in the *Sample solution* (mg/mL)
P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

Test 1

Protect solutions containing minocycline from light.

Medium: pH 6.8 phosphate buffer; 900 mL

Apparatus 2: 50 rpm

Times: 1, 2, and 5 h

Standard stock solution: 0.5 mg/mL of minocycline from USP Minocycline Hydrochloride RS in *Medium*

Standard solution: (*L*/900) mg/mL of minocycline from *Standard stock solution* in *Medium*, where *L* is the label claim of minocycline in mg/Tablet

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

Instrumental conditions

Mode: UV

Analytical wavelength: 348 nm

Cell: See *Table 1*.

Table 1

Tablet Strength (mg)	Cell Path Length (cm)
45	0.5
90	0.2
135	0.2

Blank: *Medium*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Autozero the instrument using the *Blank*.

Calculate the concentration (C_i) of minocycline ($C_{23}H_{27}N_3O_7$) in the sample withdrawn from the vessel at each time point (*i*):

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

A_U = absorbance of the *Sample solution* at time point *i*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount (Q_i) of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	20–45
2	2	40–70
3	5	NLT 85

The percentages of the labeled amounts of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Protect solutions containing minocycline from light.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Times: 1, 2, and 4 h
Standard solution: 0.0225 mg/mL of minocycline from USP Minocycline Hydrochloride RS in *Medium*
Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of *Medium*. Pass through a suitable filter. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Instrumental conditions
Mode: UV
Analytical wavelength: 348 nm
Cell: 1 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Autozero the instrument using the *Blank*.
Calculate the concentration (C_i) of minocycline ($C_{23}H_{27}N_3O_7$) in the sample withdrawn from the vessel at each time point (i):

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

A_U = absorbance of the *Sample solution* at time point i
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
D = dilution factor (mL/mL)
P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount (Q_i) of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)	
		45 mg/Tablet	90 mg/Tablet and 135 mg/Tablet
1	1	40–60	40–60
2	2	70–95	70–90
3	4	NLT 85	NLT 85

The percentages of the labeled amounts of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Protect solutions containing minocycline from light.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Times: 0.5, 1.5, and 4 h
Standard solution: 0.021 mg/mL of minocycline from USP Minocycline Hydrochloride RS in *Medium*
Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of *Medium*. Pass through a suitable filter. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Instrumental conditions
Mode: UV
Analytical wavelength: 265 nm
Cell: 1 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Autozero the instrument using the *Blank*.
Calculate the concentration (C_i) of minocycline ($C_{23}H_{27}N_3O_7$) in the sample withdrawn from the vessel at each time point (i):

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

A_U = absorbance of the *Sample solution* at time point i
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
D = dilution factor (mL/mL)
P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount (Q_i) of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)
V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	0.5	NMT 40
2	1.5	50–95
3	4	NLT 85

The percentages of the labeled amounts of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Protect solutions containing minocycline from light.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Times: 1, 2, and 4 h
Standard solution: (L/900) mg/mL of minocycline from USP Minocycline Hydrochloride RS in *Medium*, where L is the label claim of minocycline in mg/Tablet
Sample solution: At the times specified, withdraw 5 mL of the solution under test and replace with 5 mL of *Medium*. Pass through a suitable filter. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Instrumental conditions
Mode: UV
Analytical wavelength: 353 nm
Cell: 1 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Autozero the instrument using the *Blank*.
Calculate the concentration (C_i) of minocycline ($C_{23}H_{27}N_3O_7$) in the sample withdrawn from the vessel at each time point (i):

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

A_U = absorbance of the *Sample solution* at time point i
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
D = dilution factor (mL/mL)
P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount (Q_i) of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)
V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)	
		45/Tablet and 90 mg/Tablet	135 mg/Tablet
1	1	35–50	35–50
2	2	63–78	67–82
3	4	NLT 90	NLT 90

The percentages of the labeled amounts of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.
Protect solutions containing minocycline from light.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Times: 1, 2, and 4 h
Mobile phase: Dimethylformamide, tetrahydrofuran, 0.2 M ammonium oxalate solution, and 0.01 M edetate disodium solution (120:80:600:180). Adjust with ammonium hydroxide to a pH of 7.2.
Standard stock solution: 0.55 mg/mL of minocycline from USP Minocycline Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Minocycline Hydrochloride RS to a suitable volumetric flask, and dissolve with 70% of the flask volume of *Medium* and sonicate for 5 min. Dilute with *Medium* to volume.
Standard solution: (L/900) mg/mL of minocycline from *Standard stock solution* in *Medium*, where L is the label claim of minocycline in mg/Tablet
Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of *Medium*. Pass through a suitable filter and dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Column: 40°
Autosampler: 10°
Flow rate: 1.5 mL/min
Injection volume: 50 µL
Run time: NLT 1.5 times the retention time of minocycline
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of minocycline ($C_{23}H_{27}N_3O_7$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of minocycline from the *Sample solution* at time point *i*
r_S = peak response of minocycline from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount (Q_i) of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of minocycline in the portion of sample withdrawn at the specified time point (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (%)				
		45 mg/ Tablet	65, 90 and 115 mg/ Tablet	80 mg/ Tablet	105 mg/ Tablet	135 mg/ Tablet
1	1	40–60	40–60	40–60	40–60	30–50
2	2	75–95	70–95	75–95	70–85	60–80
3	4	NLT 80	NLT 85	NLT 85	NLT 85	NLT 80

The percentages of the labeled amount of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 7: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.
Protect solutions containing minocycline from light.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Times: 1, 2, and 4 h
Standard stock solution: 0.75 mg/mL of minocycline from USP Minocycline Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Minocycline Hydrochloride RS to a suitable volumetric flask, and dissolve with 50% of the flask volume of *Medium* and sonicate to dissolve. Dilute with *Medium* to volume.
Standard solution: 0.015 mg/mL of minocycline in *Medium* from the *Standard stock solution*
Sample solution: At the times specified, withdraw 15 mL of the solution under test and replace with 15 mL of *Medium*. Pass through a suitable filter. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Instrumental conditions and **Analysis:** Proceed as directed in *Test 2*.
Tolerances: See *Table 7*.

Table 7

Time Point (*i*)	Time (h)	Amount Dissolved (%)			
		45 mg/Tablet	80 mg/Tablet	105 mg/ Tablet	135 mg/ Tablet
1	1	30–55	25–50	30–65	50–80
2	2	55–75	60–90	NLT 85	NLT 85
3	4	NLT 85	NLT 85	NLT 85	NLT 85

The percentages of the labeled amounts of minocycline ($C_{23}H_{27}N_3O_7$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-Sep-2019)

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

IMPURITIES

Change to read:

• **Organic Impurities**
Protect solutions containing minocycline from light.
Buffer, Mobile phase, and **Diluent:** Prepare as directed in the *Assay*.
Standard stock solution: Use the *Standard solution* as directed in the *Assay*.
Standard solution: 0.009 mg/mL of minocycline from *Standard stock solution* in *Diluent*. Store at 4° and use within 24 h.
Sample solution: Use the *Sample stock solution* as directed in the *Assay*.
Sensitivity solution: 0.9 µg/mL of minocycline from *Standard solution* in *Diluent*. Store at 4° and use within 24 h.
System suitability solution: Heat a portion of the *Standard stock solution* at 60° for about 2 h and cool. This solution contains a mixture of 4-epiminocycline and minocycline. Store at 4° and use within 24 h.
Chromatographic system: Proceed as directed in the *Assay*, except use a flow rate of 1 mL/min.
System suitability
Samples: *Standard solution*, *Sensitivity solution*, and *System suitability solution*
Suitability requirements
Resolution: NLT 4.6 between minocycline and 4-epiminocycline, *System suitability solution*
Tailing factor: NMT 1.5, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity 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 minocycline from the *Standard solution*
C_S = concentration of USP Minocycline Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of minocycline in the *Sample solution* (mg/mL)

P = potency of minocycline in USP Minocycline Hydrochloride RS (µg/mg)
F = conversion factor, 0.001 mg/µg

Acceptance criteria: See *Table* ▲8.▲ (RB 1-Sep-2019)The reporting threshold is 0.1%.

Table ▲8▲ (RB 1-Sep-2019)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
4-Epiminocycline[a]	0.38	4.0
Desmethyl minocycline[b, c]	0.46	—
Sancycline[b, d]	0.68	—
5a,6-Anhydrominocycline[b, e]	0.81	—
Hydroxymethylminocycline[b, f]	0.92	—
Minocycline	1.0	—
Any individual unspecified degradation product	—	0.2
Total degradation products[g]	—	2.0

[a] (4*R*,4a*S*,5a*R*,12a*S*)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.
[b] Process impurities are controlled in the drug substance and are not to be reported here. They are not included in total degradation products.
[c] (4*S*,4a*S*,5a*R*,12aS)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-7-methylamino-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.
[d] 6-Demethyl-6-deoxytetracycline; (4*S*,4a*S*,5a*R*,12a*S*)-4-Dimethylamino-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.
[e] (4*S*,4a*S*,12a*S*)-4,7-Bis(dimethylamino)-3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydrotetracene-2-carboxamide.
[f] (4*S*,4a*S*,5a*R*,12a*S*)-4,7-Bis(dimethylamino)-3,10,12,12a-tetrahydroxy-*N*-(hydroxymethyl)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide.
[g] Total degradation products does not include 4-epiminocycline.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Store in tightly closed containers 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 Minocycline Hydrochloride RS