Minocycline Hydrochloride Extended-Release Tablets

Type of Posting	Notice of Intent to Revise
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Expert Committee	Chemical Medicines Monographs 1

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 1 Expert Committee intends to revise the Minocycline Hydrochloride Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 5* to the monograph.

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

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Praveen Pabba, Scientific Liaison to the Chemical Medicines Monographs 1 Expert Committee (301-816-8540 or pkp@usp.org).

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[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

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 5:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.
Protect solutions containing minocycline from light.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 40 mesh, 100 rpm
Times: 0.5, 1.5, and 4 h
Standard stock solution: 0.22 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 10% of the flask volume of *Medium*. Dilute with water to volume.
Standard solution: 0.022 mg/mL of minocycline in *Medium* from the *Standard stock solution*
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 discard the first 5 mL. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.
Instrumental conditions and **Analysis:** Proceed as directed in *Test 4*.
Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (%)			
		45, 55, 115, and 135 mg/Tablet	65 and 80 mg/Tablet	90 mg/Tablet	105 mg/Tablet
1	0.5	15–40	15–40	15–40	15–40
2	1.5	50–75	55–75	50–70	60–80
3	4	NLT 85	NLT 85	NLT 85	NLT 85

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*.▲ (TBD)

• **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* ▲*7*.▲ (TBD) The reporting threshold is 0.1%.

Table ▲**7**▲ (TBD)

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*,12a*S*)-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