Oxycodone Hydrochloride Extended-Release Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	25-Apr-2025
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Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 2 Expert Committee intends to revise the Oxycodone Hydrochloride Extended-Release Tablets monograph. Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Oxycodone Hydrochloride Extended-Release Tablets monograph to add *Dissolution Test 2*.

The molecular weight for oxycodone free base in the *Assay* and *Dissolution* test was updated to match the RSCEP and chemical information for free base. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*. Existing references to reagents have been updated for consistency with the reagent entry. The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

Dissolution Test 2 was validated using the Kinetex C18 brand of column with L1 packing. The typical retention time for oxycodone hydrochloride is about 1.2 min.

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 Jasmine Lawrence, Scientist III (301-230-6363 or jasmine.lawrence@usp.org).

[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*.

Notice of Intent to Revise
Official: To Be Determined

Oxycodone Hydrochloride Extended-Release Tablets

DEFINITION

Oxycodone Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$).

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

Change to read:

● **Procedure**

Buffer solution: 7.8 g/L of potassium phosphate, monobasic in water, adjusted with phosphoric acid to a pH of 3.0

Mobile phase: Acetonitrile and *Buffer solution* (10:90)

Diluent: Acetonitrile and simulated gastric fluid TS without enzyme (10:20)

0.85% phosphoric acid: 10 mL/L of phosphoric acid in water

Standard stock solution: 0.9 mg/mL of USP Oxycodone RS in *0.85% phosphoric acid*

Standard solution: 0.09 mg/mL of USP Oxycodone RS in *Diluent* from the *Standard stock solution*

Sample stock solution: Nominally (*L*/100) mg/mL of oxycodone hydrochloride where *L* is the label claim in mg/Tablets. Transfer 10 Tablets into a 1000-mL volumetric flask, and add 900 mL of *Diluent*. Stir until the Tablets are completely dispersed. Dilute with *Diluent* to volume. Physically manipulate the Tablets as necessary to ensure complete dispersion within 24 h with stirring in *Diluent*. Protect this solution from light.

Sample solution: Nominally about 0.1 mg/mL of oxycodone hydrochloride in *Diluent* from the *Sample stock solution*. Pass through a suitable filter of 0.45-µm pore size. For Tablets labeled to contain 10 mg, use the *Sample stock solution* directly.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm. For *Identification B*, use a diode array detector in the range of 200–350 nm.

Column: 3.0-mm × 25-cm; 5-µm packing L1

Column temperature: 60°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

Run time: NLT 1.4 times the retention time of oxycodone

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.7–1.2

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of oxycodone from the *Sample solution*

r_S = peak response of oxycodone from the *Standard solution*

C_S = concentration of USP Oxycodone RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of oxycodone hydrochloride in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of oxycodone hydrochloride, 351.82

M_{r2} = molecular weight of oxycodone base, ▲315.37▲ (TBD)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲**Test 1**▲ (TBD)

Medium: Simulated gastric fluid TS without enzymes; 900 mL

Apparatus 1: 100 rpm. Include a stainless-steel spring across the underside of the top of each of the baskets to prevent Tablet adhesion to the underside of the top of the baskets during the test.

Times: 1, 4, and 12 h

0.85% phosphoric acid: 10 mL/L of phosphoric acid in water

Mobile phase: Transfer 28.0 g of potassium phosphate, monobasic into a 4-L flask, and dissolve with 3600 mL of water. Adjust with phosphoric acid to a pH of 3.0. Add 400 mL of acetonitrile, and mix.

Standard stock solution: 0.9 mg/mL of USP Oxycodone RS in *0.85% phosphoric acid*

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a solution having a concentration of 0.009 mg/mL of USP Oxycodone RS for Tablets labeled to contain 10, 15, 20, 30, and 40 mg, and 0.063 mg/mL of USP Oxycodone RS for Tablets labeled to contain 60 and 80 mg.

Sample solution: Pass the solution under test through a suitable filter of 1.0- or 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 3.0-mm × 25-cm; 5-µm packing L1

Column temperature: 60°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

Run time: NLT 3.7 times the retention time of oxycodone

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.7–1.2

Relative standard deviation: NMT 2%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response of oxycodone from the *Sample solution*

r_S = peak response of oxycodone from the *Standard solution*

C_S = concentration of USP Oxycodone RS in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of oxycodone hydrochloride, 351.82

M_{r2} = molecular weight of oxycodone base, ▲315.37▲ (TBD)

Calculate the percentage of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) released 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 oxycodone hydrochloride in the portion of the sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 1* for Tablets labeled to contain 10, 15, 20, and 60 mg; see *Table 2* for Tablets labeled to contain 30 and 40 mg; see *Table 3* for Tablets labeled to contain 80 mg.

Table 1

Time Point (*i*)	Time (h)	Amount Released (%)
1	1	15–35
2	4	55–75
3	12	NLT 85

Table 2

Time Point (*i*)	Time (h)	Amount Released (%)
1	1	15–35
2	4	60–80
3	12	NLT 85

Table 3

Time Point (*i*)	Time (h)	Amount Released (%)
1	1	15–35
2	4	52–72
3	12	NLT 85

The percentages of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) 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*.

Medium: Simulated gastric fluid TS without enzymes; 900 mL

Apparatus 1: 100 rpm

Times: 1, 4, and 10 h

Solution A: Dissolve 0.5 g of sodium 1-heptanesulfonate monohydrate in 500 mL of water and add 2.5 mL of glacial acetic acid. Adjust with 1 N sodium hydroxide to a pH of 3.5.

Solution B: Acetonitrile

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	80	20
0.5	70	30
1	80	20
2	80	20

Standard stock solution: 0.45 mg/mL of USP Oxycodone Hydrochloride RS in *Medium*

Standard solution: (*L*/900) mg/mL of USP Oxycodone Hydrochloride RS prepared from the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: At the times specified, withdraw about 10 mL of the solution under test and pass through a suitable filter of 0.2-µm pore size. Discard an appropriate volume of filtrate so that a consistent result can be obtained. Replace the volume withdrawn with an equal volume of fresh *Medium*.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 2.1-mm × 50-cm; 2.6-µm packing L1

Column temperature: 30°

Flow rate: 0.25 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of oxycodone hydrochloride from the *Sample solution*

r_S = peak response of oxycodone hydrochloride from the *Standard solution*

C_S = concentration of USP Oxycodone Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) released 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 oxycodone hydrochloride in the portion of sample withdrawn at time point i (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 Released (%)
1	1	15–35
2	4	53–78
3	10	NLT 80

The percentages of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) 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**

Buffer solution, Mobile phase, Diluent, 0.85% phosphoric acid, Standard stock solution, Sample stock solution, and **Sample solution:** Prepare as directed in the *Assay*.

Standard solution: 0.9 µg/mL of USP Oxycodone RS in *Diluent* from the *Standard stock solution*

Sensitivity solution: 0.0001 mg/mL of USP Oxycodone RS in *Diluent* from the *Standard solution*

System suitability stock solution: 0.1 mg/mL of USP Oxycodone Related Compound B RS in *0.85% Phosphoric acid*

System suitability solution: 0.9 µg/mL of USP Oxycodone RS and 0.001 mg/mL of USP Oxycodone Related Compound B RS prepared by diluting the *System suitability stock solution* with the *Standard solution*

Chromatographic system

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

Mode: LC

Detector: UV 206 nm

Column: 4.6-mm × 25-cm; 3-µm packing L1

Column temperature: 60°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

Run time: NLT 4.5 times the retention time of oxycodone

System suitability

Samples: *Standard solution*, *Sensitivity solution*, and *System suitability solution*

Suitability requirements

Relative standard deviation: NMT 5.0%, *Standard solution*

Resolution: NLT 8.0 between oxycodone and oxycodone related compound B, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each degradation product 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 degradation product from the *Sample solution*

r_S = peak response of oxycodone from the *Standard solution*

C_S = concentration of USP Oxycodone RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of oxycodone hydrochloride in the *Sample solution* (mg/mL)

F = relative response factor of each degradation product (see ▲*Table 6*▲ (TBD))

Acceptance criteria: See ▲*Table 6*.▲ (TBD) The reporting threshold is 0.1%.

▲Table 6▲ (TBD)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxycodone	1.0	1.00	—
Oxycodone related compound B	1.6	0.94	0.5
Any unspecified degradation product	—	1.00	0.2
Total degradation products	—	—	1.0

ADDITIONAL REQUIREMENTS

● **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

Add the following:

▲● **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (TBD)

Change to read:

● **USP Reference Standards** ⟨11⟩

USP Oxycodone RS

▲ USP Oxycodone Hydrochloride RS▲ (TBD)

USP Oxycodone Related Compound B RS

4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one *N*-oxide.

$C_{18}H_{21}NO_5$ 331.36

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