

## Oxymorphone Hydrochloride Extended-Release Tablets

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<b>Expert Committee</b>	Chemical Medicines Monographs 2
<b>Reason for Revision</b>	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Oxymorphone Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* and *Dissolution Test 3* for generic products approved by the FDA.

- *Dissolution Test 2* was validated using the same chromatographic system as described in *Dissolution Test 1*.
- *Dissolution Test 3* was validated using a Luna C8 brand of L7 column. The typical retention time for oxymorphone is about 4.5 min.

The Oxymorphone Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *Second Supplement to USP 40–NF 35*.

Should you have any questions, please contact Hillary Cai, Ph.D., Scientific Liaison (301-230-3379 or [hzc@usp.org](mailto:hzc@usp.org)).

## Oxymorphone Hydrochloride Extended-Release Tablets

### DEFINITION

Oxymorphone Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of oxymorphone hydrochloride ( $C_{17}H_{19}NO_4 \cdot HCl$ ).

### 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 absorption spectra 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

**Solution A:** Dissolve 2.34 g of sodium 1-octanesulfonate monohydrate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.80.

**Solution B:** Acetonitrile and methanol (50:50)

**Mobile phase:** See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.00	77.0	23.0
2.50	77.0	23.0
17.50	54.0	46.0
25.00	31.0	69.0
25.05	1.5	98.5
32.50	1.5	98.5
32.55	77.0	23.0
38.00	77.0	23.0

**Diluent:** Methanol and phosphoric acid (1000:1)

**Standard stock solution:** 1.78 mg/mL of USP Oxymorphone RS in *Diluent*

**Standard solution:** 0.357 mg/mL of USP Oxymorphone RS in *Solution A* from the *Standard stock solution*

**Sample stock solution:** Nominally 2 mg/mL of oxymorphone hydrochloride in *Diluent* prepared as follows. Take NLT 8 Tablets, cut each into small pieces, and transfer to a suitable flask. Add a suitable volume of *Diluent* and shake for at least 16 h. Centrifuge at 3500 rpm for 5 min or until a clear supernatant is obtained.

**Sample solution:** Nominally 0.4 mg/mL of oxymorphone hydrochloride in *Solution A* from the *Sample stock solution*

#### Chromatographic system

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

Mode: LC

Detectors

Assay: UV 230 nm

Identification test B: Diode array UV 200–360 nm

Column: 4.6-mm × 7.5-cm; 3.5- $\mu$ m packing L1

Column temperature: 50°

Flow rate: 1.0 mL/min

Injection volume: 20  $\mu$ L

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of oxymorphone hydrochloride ( $C_{17}H_{19}NO_4 \cdot HCl$ ) 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 oxymorphone from the *Sample solution*

$r_S$  = peak response of oxymorphone from the *Standard solution*

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

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

$M_{r1}$  = molecular weight of oxymorphone hydrochloride, 337.80

$M_{r2}$  = molecular weight of oxymorphone, 301.34

Acceptance criteria: 90.0%–110.0%

### PERFORMANCE TESTS

#### Change to read:

#### DISSOLUTION (711)

##### Test 1 (RB 1-Dec-2016)

**Medium:** 45 mM phosphate buffer, pH 4.50 (dissolve 6.16 g of monobasic potassium phosphate in 1 L of water. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 4.50); 900 mL

**Apparatus 2:** 50 rpm, with sinker. [NOTE—The Sotax Helix sinker can be used.]

**Times:** 1, 2, and 8 h

**Mobile phase:** Dissolve 1.54 g of ammonium acetate in 925 mL of water and mix well. Add 75 mL of acetonitrile and adjust with trifluoroacetic acid to a pH of 4.50.

**Standard stock solution:** 0.2 mg/mL of USP Oxymorphone RS in *Medium*

**Standard solution:**  $[(L/900) \times (301.34/337.80)]$  mg/mL of USP Oxymorphone RS in *Medium* from the *Standard stock solution*, where *L* is the label claim in mg/Tablet

**Sample solution:** Withdraw 1.5 mL of the solution under test

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 7.5-cm; 4- $\mu$ m packing L11

Column temperature: 60°

Flow rate: 2.0 mL/min

Injection volume: 50  $\mu$ L

Run time: NLT 2 times the retention time of oxymorphone

## 2 Oxymorphone

### System suitability

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** 0.8–1.5

**Relative standard deviation:** NMT 2.0%

### Analysis

**Samples:** *Standard solution* and *Sample solution*  
 Calculate the percentage of the labeled amount of oxymorphone hydrochloride ( $C_{17}H_{19}NO_4 \cdot HCl$ ) dissolved at each time point ( $i$ ):

$$\text{Result}_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times V \times (1/L) \times 100$$

$r_U$  = peak response of oxymorphone from the *Sample solution*

$r_S$  = peak response of oxymorphone from the *Standard solution*

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

$M_{r1}$  = molecular weight of oxymorphone hydrochloride, 337.80

$M_{r2}$  = molecular weight of oxymorphone, 301.34

$V$  = volume of *Medium*, 900 mL

$L$  = label claim (mg/Tablet)

**Tolerances:** See *Table 2*.

**Table 2**

Time Point ( $i$ )	Time (h)	Amount Released (%)
1	1	20–40
2	2	35–55
3	8	NLT 80

• **Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

**Apparatus 2, Mobile phase, Standard stock solution, Standard solution, Sample solution, Chromatographic system, System suitability, and Analysis:** Proceed as directed in *Test 1*.

**Medium:** 50 mM phosphate buffer, pH 4.50 (dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 4.50); 900 mL

**Times:** 1, 4, and 10 h

**Tolerances:** See *Table 3*.

**Table 3**

Time point ( $i$ )	Time (h)	Amount Released (%)
1	1	30–50
2	4	65–85
3	10	NLT 85

The percentages of the labeled amount of oxymorphone hydrochloride ( $C_{17}H_{19}NO_4 \cdot HCl$ ) released at the times specified conform to *Dissolution* (711), *Acceptance Table 2*.

**Test 3:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

**Medium:** 50 mM phosphate buffer, pH 4.50 (dissolve 40.8 g of monobasic potassium phosphate in 6 L of

water. Adjust with 1 N potassium hydroxide or phosphoric acid to a pH of 4.50); 900 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 4, and 14 h

**Buffer:** 0.1 M ammonium phosphate prepared as follows. Dissolve 13.2 g of dibasic ammonium phosphate in 1 L of water, and mix well.

**Mobile phase:** Acetonitrile, methanol, and *Buffer* (5:25:70)

**Standard solution:** 0.0112 mg/mL of USP Oxymorphone RS in *Medium*

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45- $\mu$ m pore size.

### Chromatographic system

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

**Mode:** LC

**Detector:** UV 212 nm

**Column:** 4.6-mm  $\times$  15.0-cm; 5- $\mu$ m packing L7

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 50  $\mu$ L

**Run time:** NLT 2 times the retention time of oxymorphone

### 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 oxymorphone hydrochloride ( $C_{17}H_{19}NO_4 \cdot HCl$ ) 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 oxymorphone from the *Sample solution*

$r_S$  = peak response of oxymorphone from the *Standard solution*

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

$M_{r1}$  = molecular weight of oxymorphone hydrochloride, 337.80

$M_{r2}$  = molecular weight of oxymorphone, 301.34

Calculate the percentage of the labeled amount of oxymorphone hydrochloride ( $C_{17}H_{19}NO_4 \cdot HCl$ ) dissolved at each time point ( $i$ ):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_3)] + (C_1 \times V_3)\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times [V - (2 \times V_3)]) + [(C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

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

$V$  = volume of medium, 900 mL

$L$  = label claim (mg/Tablet)

$V_3$  = volume of the *Sample solution* withdrawn at each time point ( $i$ ) (mL)

**Tolerances:** See *Table 4*.

**Table 4**

Time Point (j)	Time (h)	Amount Released (%)
1	1	15–40
2	4	45–70
3	14	NLT 80

The percentages of the labeled amount of oxymorphone hydrochloride ( $C_{17}H_{19}NO_4 \cdot HCl$ ) released at the times specified conform to *Dissolution* (711), *Acceptance Table 2*.<sup>•</sup> (RB 1-Dec-2016)

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

**IMPURITIES**

**Change to read:**

• **ORGANIC IMPURITIES**

**Solution A, Solution B, Mobile phase, Diluent, Standard solution, Sample solution, and Chromatographic system:** Proceed as directed in the *Assay*.

**Sensitivity solution:** 0.357 µg/mL of USP Oxymorphone RS from the *Standard solution* prepared as follows. Add 20% of the total volume of *Diluent* and dilute with *Solution A* to volume.

**System suitability**

**Samples:** *Standard solution* and *Sensitivity solution*  
**Suitability requirements**

**Tailing factor:** 0.8–1.5, *Standard solution*

**Relative standard deviation:** NMT 2.0%, *Standard solution*

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

**Analysis**

**Sample:** *Sample solution*

Calculate the percentage of each individual degradation product in the portion of Tablets taken:

$$\text{Result} = (r_u/r_T) \times (1/F) \times 100$$

$r_u$  = peak response of each individual degradation product from the *Sample solution*

$r_T$  = sum of peak responses from the *Sample solution*

$F$  = relative response factor of each individual degradation product (see *Table 5*).<sup>•</sup> (RB 1-Dec-2016)

**Acceptance criteria:** See *Table 5*.<sup>•</sup> (RB 1-Dec-2016). Disregard any peaks less than 0.05%.

**Table 5** (RB 1-Dec-2016)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxymorphone related compound A <sup>a</sup> (oxymorphone <i>N</i> -oxide)	0.57	1.11	0.2
10-Hydroxyoxymorphone <sup>b</sup>	0.70	1.14	0.2
Oxymorphone	1.00	—	—
10-Ketooxymorphone <sup>c</sup>	1.33	0.97	0.2
Oxycodone <sup>d</sup>	1.82	—	—
14-Hydroxycodeinone <sup>d,e</sup>	1.89	—	—
1-Bromo oxymorphone <sup>d,f</sup>	1.89	—	—
2,2'-Bisoxymorphone <sup>g</sup>	2.28	2.36	0.2
Any individual unspecified degradation product	—	1.00	0.2
Total degradation products	—	—	1.0

<sup>a</sup> 4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one *N*-oxide.

<sup>b</sup> 4,5α-Epoxy-3,10,14-trihydroxy-17-methylmorphinan-6-one.

<sup>c</sup> 4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6,10-dione.

<sup>d</sup> Process impurities, not included in the total degradation products.

<sup>e</sup> 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-7-ene-6-one.

<sup>f</sup> 1-Bromo-4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one.

<sup>g</sup> 2,2'-Bisoxymorphone.

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

**Add the following:**

- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.<sup>•</sup> (RB 1-Dec-2016)
- **USP REFERENCE STANDARDS (11)**  
 USP Oxymorphone RS