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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-µm packing L1

Column temperature: 50°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

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

• **Dissolution ⟨711⟩**

Test 1

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) × (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-µm packing L11

Column temperature: 60°

Flow rate: 2.0 mL/min

Injection volume: 50 µL

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

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

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 Dissolved (%)
1	1	20–40
2	2	35–55
3	8	NLT 80

The percentages of the labeled amount of oxymorphone hydrochloride ($C_{17}H_{19}NO_4 \cdot HCl$) 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 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 Dissolved (%)
1	1	30–50
2	4	65–85
3	10	NLT 85

The percentages of the labeled amount of oxymorphone hydrochloride ($C_{17}H_{19}NO_4 \cdot HCl$) 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 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-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 212 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

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):

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

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

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

C_i = concentration of 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_S = volume of the *Sample solution* withdrawn at each time point (i) (mL)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	15–40
2	4	45–70
3	14	NLT 80

The percentages of the labeled amount of oxymorphone hydrochloride ($C_{17}H_{19}NO_4 \cdot HCl$) 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 the product meets USP *Dissolution Test 4*.

Medium: 50 mM phosphate buffer, pH 6.8 (dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water, and add 77 mL of 0.2 N sodium hydroxide and 500 mL of water. Adjust with 0.2 N sodium hydroxide or 0.2 N hydrochloric acid to a pH of 6.8 and dilute with water to 1 L); 900 mL

Apparatus 2: 50 rpm

Times: 1, 4, and 10 h

Buffer: Triethylamine and water (2:1000). Adjust with phosphoric acid or 5 N sodium hydroxide to a pH of 6.8.

Mobile phase: Acetonitrile and *Buffer* (14:86)

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

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

Chromatographic system

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

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L11

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 10 µL for 10-, 15-, 20-, 30-, and 40-mg strengths; 20 µL for 5- and 7.5-mg strengths

Run time: NLT 1.5 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*):

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

$$Result_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$Result_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of 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_S = volume of the *Sample solution* withdrawn at each time point (*i*) (mL)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)		
		For 5-, 7.5-, 10-, 15-, and 20-mg Strengths	For 30-mg Strengths	For 40-mg Strengths
1	1	25–45	25–45	15–40
2	4	65–90	60–80	50–70
3	10	NLT 80	NLT 80	NLT 80

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

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

IMPURITIES

• **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:

$$Result = (r_U/r_T) \times (1/F) \times 100$$

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 6*)

Acceptance criteria: See *Table 6.* Disregard any peaks less than 0.05%.

Table 6

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

[a] 4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one *N*-oxide.

[b] 4,5α-Epoxy-3,10,14-trihydroxy-17-methylmorphinan-6-one.

[c] 4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6,10-dione.

[d] Process impurities, not included in the total degradation products.

[e] 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-7-ene-6-one.

[f] 1-Bromo-4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one.

[g] 2,2'-Bioxymorphone.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.
- **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 Oxymorphone RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
OXYMORPHONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

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