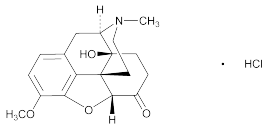
Oxycodone Hydrochloride



$C_{18}H_{21}NO_4 \cdot HCl$ 351.82

Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)-;
4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride [124-90-3].

DEFINITION

Oxycodone Hydrochloride contains NLT 97.0% and NMT 103.0% of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$), calculated on the anhydrous, solvent-free basis.

IDENTIFICATION

- **A. PROCEDURE**

  Sample solution: Dissolve 250 mg in 25 mL of water.

  Analysis: Render the 25 mL of *Sample solution* alkaline with 6 N ammonium hydroxide. Allow the mixture to stand until a precipitate is formed. Filter, wash the precipitate with 50 mL of cold water, and dry at 105° for 2 h.

  Acceptance criteria: The precipitate melts between 218° and 223°, but the range between the beginning and the end of melting does not exceed 2° (see *Melting Range or Temperature* ⟨741⟩).

- **B. INFRARED ABSORPTION ⟨197K⟩:** Use a portion of the dried precipitate obtained in *Identification* test *A*.

Add the following:

•**C.** The retention time of the oxycodone peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.• (IRA 1-Nov-2015)

ASSAY

Change to read:

- **PROCEDURE**

  Mobile phase: 0.005 M sodium 1-hexanesulfonate, methanol, triethylamine, and phosphoric acid (900:100:2:5). Adjust with 50% sodium hydroxide solution to a pH of 2.5 ± 0.1 and filter.

  System suitability solution: 13 µg/mL of codeine phosphate and 9 µg/mL of oxycodone in *Mobile phase*

  Standard solution: 0.9 mg/mL of USP Oxycodone RS in *Mobile phase*

  Sample solution: 1 mg/mL of Oxycodone Hydrochloride in *Mobile phase.* [NOTE—Pass a portion of this solution through a filter of 0.5-µm or finer pore size, and use the filtrate as the *Sample solution*.]

  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 206 nm
  Column: 3.9-mm × 15-cm; 4-µm packing L7
  Column temperature: 50°
  Flow rate: 1.5 mL/min
  Injection volume: 10 µL
  •**Run time:** NLT 2 times the retention time of oxycodone• (IRA 1-Nov-2015)

  System suitability
  Samples: *System suitability solution* and *Standard solution*
  [NOTE—The relative retention times for codeine and oxycodone are about 0.8 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 3.0 between codeine and oxycodone, *System suitability solution*
  Tailing factor: 0.75–1.25, *Standard solution*
  Relative standard deviation: NMT 2.0% from replicate injections, *Standard solution*

  Analysis
  Samples: *Standard solution* and *Sample solution*
  • (IRA 1-Nov-2015)
  Calculate the percentage of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) in the portion of Oxycodone Hydrochloride taken:

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

  r_U = peak response from the *Sample solution*
  r_S = peak response from the *Standard solution*
  C_S = concentration of USP Oxycodone RS in the *Standard solution* (mg/mL)
  C_U = 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

  Acceptance criteria: 97.0%–103.0% on the anhydrous, solvent-free basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.05%. [NOTE—Use of sulfuric acid is omitted.]

Add the following:

•• **LIMIT OF ALCOHOL**

Internal standard stock solution: Transfer 6.0 mL of isopropyl alcohol to a 500-mL volumetric flask, and dilute with water to volume. [NOTE—The isopropyl alcohol must be free of alcohol impurities.]

Internal standard solution: Transfer 5.0 mL of the *Internal standard stock solution* to a 100-mL volumetric flask, and dilute with water to volume.

Standard stock solution: 16 mg/mL of alcohol (C_2H_5OH) in water

Standard solution: Pipet 3.0 mL of the *Standard stock solution* and 5.0 mL of the *Internal standard stock solution* into a 100-mL volumetric flask, and dilute with water to volume.

Sample solution: Transfer about 240 mg of Oxycodone Hydrochloride to a 15-mL centrifuge tube, add 5.0 mL of the *Internal standard solution*, and mix to dissolve.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: GC
Detector: Flame ionization
Column: 4-mm × 1.8-m glass; packed with 80- to 100-mesh support S3
Carrier gas: Helium
Temperatures
Injection port: 170°
Column: 150°. [NOTE—Condition the column overnight at 235° with a slow flow of carrier gas.]

Detector: 170°
Injection volume: 5 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2 between isopropyl alcohol and alcohol
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of alcohol (C_2H_5OH) in the portion of Oxycodone Hydrochloride taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of the alcohol peak to the isopropyl alcohol from the *Sample solution*
R_S = peak response ratio of the alcohol peak to the isopropyl alcohol from the *Standard solution*
C_S = concentration of alcohol in the *Standard solution* (mg/mL)
C_U = concentration of Oxycodone Hydrochloride in the *Sample solution* (mg/mL)
Acceptance criteria: NMT 1.0%● (IRA 1-Nov-2015)

Change to read:

- **ORGANIC IMPURITIES**

●[NOTE—On the basis of the synthetic route, perform either (a) *Procedure 1* and *Procedure 2* or (b) *Procedure 3*. *Procedure 1* and *Procedure 2* are recommended if 8β-hydroxyoxycodone (7,8-dihydro-8β-14-dihydroxycodeinone) is a potential impurity.]● (IRA 1-Nov-2015)

Procedure ●1● (IRA 1-Nov-2015)
Analysis: Use the chromatogram of the *Sample solution* from the *Assay* to calculate the percentage of each impurity in the portion of Oxycodone Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response for each impurity
r_T = sum of the responses of all the peaks
Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Oxymorphone	0.31	0.15
●Noroxymorphone[a]● (IRA 1-Nov-2015)	0.33	0.15
●10-Hydroxyoxycodone[b]● (IRA 1-Nov-2015)	0.53	0.15
●6-α Oxycodol[c]● (IRA 1-Nov-2015)	0.67	0.25
●8β-Hydroxyoxycodone (7,8-dihydro-8β-14-dihydroxycodeinone)[d]● (IRA 1-Nov-2015)	0.71	0.15
Hydrocodone	1.19	0.15
Individual unspecified impurity	—	0.10
Total impurities	—	2.0

●[a] 4,5α-Epoxy-3,14-dihydroxymorphinan-6-one.
[b] 4,5α-Epoxy-10α,14-dihydroxy-3-methoxy-17-methylmorphinan-6-one.
[c] 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6α,14-diol.
[d] 4,5α-Epoxy-8β,14-dihydroxy-3-methoxy-17-methylmorphinan-6-one.
● (IRA 1-Nov-2015)

Procedure ●2:● (IRA 1-Nov-2015) Limit of Oxycodone Related Compound A (14-Hydroxycodeinone) and Oxycodone Related Compound C (Codeinone)
Solution A: Dissolve 3.45 g of monobasic sodium phosphate in 1000 mL of water. Add 5.41 g of sodium dodecyl sulfate and mix. Filter and adjust with 50% (w/v) sodium hydroxide solution to a pH of 7.50 ± 0.05.
Solution B: Water and phosphoric acid (9:1)
Mobile phase: Prepare a mixture of acetonitrile, methanol, and *Solution A* (15.8: 12.0: 72.2), and adjust with *Solution B* to a pH of 7.80 ± 0.01.
Diluent: Prepare a mixture of water and *Solution B* (9:1).
Unspiked oxycodone hydrochloride solution: 50 mg/mL of USP Oxycodone Hydrochloride RS in *Diluent*
System suitability solution: 100 µg/mL of USP Oxycodone Hydrochloride RS and 5 µg/mL each of USP Oxycodone Related Compound A RS and USP Oxycodone Related Compound C RS in *Diluent*
Standard solution: 50 mg/mL of USP Oxycodone Hydrochloride RS and 0.5 µg/mL each of USP Oxycodone Related Compound A RS and USP Oxycodone Related Compound C RS in *Diluent*
Sample solution: 50 mg/mL of Oxycodone Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 3.0-mm × 15-cm; 3.5-µm packing L1
Column temperature: 40°
Flow rate: 0.7 mL/min
Injection volume: 5 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for oxycodone related compound C, oxycodone related compound A, and oxycodone are about 0.44, about 0.85, and 1.0, respectively.]
Suitability requirements
Resolution: NLT 4 between oxycodone related compound A and oxycodone related compound C, *System suitability solution*
Tailing factor: NMT 2.0, *System suitability solution*
Relative standard deviation: NMT 20% for oxycodone related compound A and oxycodone related compound C, *Standard solution*
Analysis
Samples: *Diluent*, *Unspiked oxycodone hydrochloride solution*, *Standard solution*, and *Sample solution*
Calculate the percentage of oxycodone related compound A and oxycodone related compound C in the portion of Oxycodone Hydrochloride taken:

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

r_U = peak response of oxycodone related compound A or oxycodone related compound C from the *Sample solution*
r_S = peak response of oxycodone related compound A or oxycodone related compound C minus the response of the *Unspiked oxycodone hydrochloride solution* from the *Standard solution*
C_S = concentration of USP Oxycodone Related Compound A RS or USP Oxycodone Related Compound C RS in the *Standard solution* (mg/mL)
C_U = concentration of Oxycodone Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Oxycodone related compound C[a]	0.44	0.001
Oxycodone related compound A[b]	0.85	0.001
Oxycodone	1.0	—

[a] Codeinone ($C_{18}H_{19}NO_3$).
[b] 14-Hydroxycodeinone ($C_{18}H_{21}NO_4$).

(Procedure •2• (IRA 1-Nov-2015) postponed indefinitely)

•Procedure 3

Buffer: Mix 4.0 mL of heptafluorobutyric acid with 2000 mL of water and adjust with ammonium hydroxide to a pH of 2.3 ± 0.1.
Solution A: Methanol and *Buffer* (23:77)
Solution B: Methanol, tetrahydrofuran, and *Buffer* (20:3:77)
Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	100	0
2	100	0
30	0	100
55	0	100
55.1	100	0
65	100	0

Diluent: Mix 3.0 mL of trifluoroacetic acid with 1000 mL of water.
System suitability solution: 0.0067 mg/mL each of USP Hydrocodone RS and USP Oxycodone Related Compound A RS, and 3.0 mg/mL of USP Oxycodone Hydrochloride RS in *Diluent*
Standard solution: 0.0067 mg/mL of USP Hydrocodone RS in *Diluent*
Sample solution: 3.0 mg/mL of Oxycodone Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 25-cm; 3-µm packing L1
Column temperature: 38°
Flow rate: 0.8 mL/min
Injection volume: 50 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between oxycodone and hydrocodone; NLT 1.0 between hydrocodone and oxycodone related compound A, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Oxycodone Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of hydrocodone from the *Standard solution*
C_S = concentration of USP Hydrocodone RS in the *Standard solution* (mg/mL)
C_U = concentration of Oxycodone Hydrochloride in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of hydrocodone hydrochloride, 335.83
M_{r2} = molecular weight of hydrocodone, 299.36
F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*. Disregard any peaks below 0.03%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxymorphone hydrochloride	0.54	0.93	0.15
1-Hydroxyoxycodone hydrochloride[a]	0.69	1.00	0.15
6-Oxycodol hydrochloride[b]	0.79	1.16	0.25
Oxycodone hydrochloride	1.00	—	—
Hydrocodone hydrochloride	1.14	1.00	0.50
14-Hydroxycodeinone hydrochloride (oxycodone related compound A hydrochloride)[c]	1.18	0.99	0.25
Noroxycodone hydrochloride[d]	1.26	0.94	0.50

[a] 4,5α-Epoxy-1,14-dihydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.
[b] 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6,14-diol hydrochloride.
[c] 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-7-ene-6-one (oxycodone related compound A hydrochloride salt).
[d] 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Table 4 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Individual unspecified impurity	—	—	0.10
Total impurities	—	—	1.5

[a] 4,5α-Epoxy-1,14-dihydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.
[b] 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6,14-diol hydrochloride.
[c] 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-7-ene-6-one (oxycodone related compound A hydrochloride salt).
[d] 4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

● (IRA 1-Nov-2015)

SPECIFIC TESTS

- **CONTENT OF CHLORIDE**
  Sample solution: 6 mg/mL in methanol
  Analysis: To 50 mL of the *Sample solution*, add 5 mL of glacial acetic acid and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of chloride.
  Acceptance criteria: 9.8%–10.4% on the anhydrous, solvent-free basis
- **OPTICAL ROTATION ⟨781S⟩,** *Specific Rotation*
  Sample solution: 25 mg/mL of Oxycodone Hydrochloride in water on the anhydrous, solvent-free basis
  Acceptance criteria: –137° to –149°
- **WATER DETERMINATION ⟨921⟩,** *Method I*: NMT 7.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

Add the following:

●• **LABELING:** The label states with which *Organic Impurities* procedure the article complies if *Organic Impurities, Procedure 1* is not used.● (IRA 1-Nov-2015)

Change to read:

- **USP REFERENCE STANDARDS ⟨11⟩**
  •USP Hydrocodone RS
  ● (IRA 1-Nov-2015)
  USP Oxycodone RS
  USP Oxycodone Hydrochloride RS
  USP Oxycodone Related Compound A RS
  •Also known as 14-Hydroxycodeinone; 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-7-ene-6-one.
  $C_{18}H_{19}NO_4$ 313.35● (IRA 1-Nov-2015)
  USP Oxycodone Related Compound C RS
  •Also known as Codeinone; 4,5α-Epoxy-3-methoxy-17-methylmorphinan-7-ene-6-one.
  $C_{18}H_{19}NO_3$ 297.35● (IRA 1-Nov-2015)