Oxycodone Hydrochloride

C_{18}H_{21}NO_{4} • HCl 351.82
Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methylhydrastine, 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} • 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 (197 K): 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. [Please refer to the previous version for the specific details.]

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

Oxycodone

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
Calculate the percentage of oxycodone hydrochloride (C_{18}H_{21}NO_{4} • HCl) in the portion of Oxycodone Hydrochloride taken: 
Result = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{C_0} \right) \times \left( \frac{M_2}{M_1} \right) \times 100
r_0 = 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_0 = concentration of Oxycodone Hydrochloride in the Sample solution (mg/mL)
M_1 = molecular weight of oxycodone base, 315.37
M_2 = molecular weight of oxycodone hydrochloride, 351.82
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_{3}H_{7}OH) in water

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.]
Unspiked oxycodone hydrochloride solution:

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times 100 \]

\( r_u \) = peak response for each impurity
\( r_s \) = sum of the responses of all the peaks

Acceptance criteria: See Table 1.

Table 1 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxymorphone</td>
<td>0.31</td>
<td>0.15</td>
</tr>
<tr>
<td>Noroxymorphone</td>
<td>0.33</td>
<td>0.15</td>
</tr>
<tr>
<td>10-Hydroxyoxycodone</td>
<td>0.53</td>
<td>0.15</td>
</tr>
<tr>
<td>6α-Oxycodone (ia)</td>
<td>0.67</td>
<td>0.25</td>
</tr>
<tr>
<td>8β,14-Dihydroxyoxycodone (7,8β-hydroxyoxycodone) (ia)</td>
<td>0.71</td>
<td>0.15</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1.19</td>
<td>0.15</td>
</tr>
</tbody>
</table>

**Procedure 2: (IRA 1-Nov-2015)**

Limit of Oxycodone Related Compounds A (14-Hydroxycodineone) 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°C

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:

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times 100 \]
Interim Revision Announcement
Official November 1, 2015

Oxycodone

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.

Acceptance criteria: See Table 2.

<table>
<thead>
<tr>
<th>Name</th>
<th>Retention Time</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone related compound C</td>
<td>0.44</td>
<td>0.001</td>
</tr>
<tr>
<td>Oxycodone related compound A*</td>
<td>0.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

* Codeine (C21H21NO4).
* 14-Hydroxycodeinone (C21H21NO4).

(Procedure 2 postponed indefinitely)

Procedure 3
Buffer: Mix 4.0 mL of heptfluorobutyric 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>
<thead>
<tr>
<th>Name</th>
<th>Retention Time</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxymorphine hydrochloride</td>
<td>0.54</td>
<td>0.93</td>
</tr>
<tr>
<td>3-Hydroxyoxycodone hydrochloride*</td>
<td>0.69</td>
<td>1.00</td>
</tr>
<tr>
<td>6-Oxycodol hydrochloride*</td>
<td>0.79</td>
<td>1.16</td>
</tr>
<tr>
<td>Oxycodone hydrochloride</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone hydrochloride</td>
<td>1.14</td>
<td>1.00</td>
</tr>
<tr>
<td>14-Hydroxycodeinone hydrochloride*</td>
<td>1.18</td>
<td>0.99</td>
</tr>
<tr>
<td>Noroxycodone hydrochloride*</td>
<td>1.26</td>
<td>0.94</td>
</tr>
</tbody>
</table>

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 Hydrochloride in Diluent
Sample solution: 3.0 mg/mL of Oxycodone Hydrochloride in Diluent
Chromatographic system
(See Chromatography (621), System Suitability.)

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### SPECIFIC TESTS

**Content of Chloride**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual unspecified impurity</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
</tbody>
</table>

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
  - USP Oxycodone RS
  - USP Oxycodone Hydrochloride RS
  - USP Oxycodone Related Compound A RS
  - Also known as 14-Hydroxycodeine;
  - 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-7-ene-6-one;
  - C_{18}H_{19}NO_{4} 313.35
  - USP Oxycodone Related Compound C RS
  - Also known as Codeinone;
  - 4,5α-Epoxy-3-methoxy-17-methylmorphinan-3-ene-6-one.
  - C_{18}H_{19}NO_{3} 297.35

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