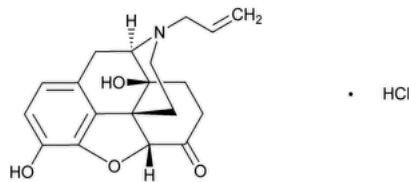


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Naloxone Hydrochloride

Change to read:



C₁₉H₂₁NO₄ · HCl 363.84
Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5α)-;
17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride CAS RN®: 357-08-4; UNII: F850569PQR.
Dihydrate
▲C₁₉H₂₁NO₄ · HCl · 2H₂O▲ (USP 1-Dec-2022) 399.87 CAS RN®: 51481-60-8; UNII: 5Q187997EE.

Change to read:

DEFINITION

Naloxone Hydrochloride is anhydrous or contains two molecules of water of hydration. It contains NLT 98.0% and NMT ▲102.0%▲ (USP 1-Dec-2022) of naloxone hydrochloride (C₁₉H₂₁NO₄ · HCl), calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A. SPECTROSCOPIC IDENTIFICATION TESTS (197), Infrared Spectroscopy:** 197K▲ or 197A▲ (USP 1-Dec-2022)

Sample: ▲Dissolve about 150 mg of Naloxone Hydrochloride in 25 mL of [water](#) in a small separator and add a few drops of 6 N [ammonium hydroxide](#) slowly until no more white precipitate is formed. Extract with three 5-mL portions of [chloroform](#) and pass the extracts through a dry filter, collecting the filtrate in a small flask. Evaporate the filtrate on a steam bath to dryness, and dry the residue at 105° for 1 h.▲ (USP 1-Dec-2022)

Acceptance criteria: Meets the requirements

Add the following:

- ▲ **B.** The retention time of the naloxone peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.▲ (USP 1-Dec-2022)

ASSAY

Change to read:

PROCEDURE

▲**Buffer:** 0.005 M [sodium 1-octanesulfonate](#) in [water](#). Adjust with 50% (v/v) [phosphoric acid](#) solution to a pH of 2.0.
Solution A: [Acetonitrile](#), [tetrahydrofuran](#), and *Buffer* (20:40:940)
Solution B: [Acetonitrile](#), [tetrahydrofuran](#), and *Buffer* (170:40:790)
Mobile phase: See [Table 1](#).

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
40	0	100
50	0	0

Time (min)	Solution A (%)	Solution B (%)
51	100	0
60	100	0

Standard solution: 0.225 mg/mL of [USP Naloxone RS](#) in 0.1 N [hydrochloric acid](#)

Sample solution: 0.25 mg/mL of Naloxone Hydrochloride in 0.1 N [hydrochloric acid](#)

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 230 nm

Column: 4.0-mm × 12.5-cm; 5-μm packing [L1](#)

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 20 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of naloxone hydrochloride ($C_{19}H_{21}NO_4 \cdot HCl$) in the portion of Naloxone Hydrochloride taken:

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

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

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

C_S = concentration of [USP Naloxone RS](#) in the *Standard solution* (mg/mL)

C_U = concentration of Naloxone Hydrochloride in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of naloxone hydrochloride, 363.84

M_{r2} = molecular weight of naloxone, 327.38

Acceptance criteria: 98.0%–102.0% on the dried basis ▲ (USP 1-Dec-2022)

OTHER COMPONENTS

• CONTENT OF CHLORIDE

Sample: About 300 mg

Analysis: Dissolve the *Sample* in 50 mL of [methanol](#) contained in a 125-mL conical flask, and add 5 mL of [glacial acetic acid](#) and 2 drops of [eosin Y TS](#). Titrate with [0.1 N silver nitrate VS](#) to a pink endpoint. Each milliliter of 0.1 N silver nitrate is equivalent to 3.545 mg of chloride.

Acceptance criteria: 9.54%–9.94% on the dried basis

IMPURITIES

Delete the following:

▲ **NOROXYMORPHONE HYDROCHLORIDE** [(–)-4,5α-EPOXY-3,14-DIHYDROXYMORPHINAN-6-ONE HYDROCHLORIDE] AND **OTHER IMPURITIES** ▲ (USP 1-Dec-2022)

Add the following:

▲ **LIMIT OF NALOXONE RELATED COMPOUND D**

Buffer: 1.58 g/L of [ammonium hydrogen carbonate](#) in [water](#) prepared as follows. Dissolve 1.58 g of ammonium hydrogen carbonate in 950 mL of [water](#), adjust with [ammonium hydroxide](#) to a pH of 9.0, and dilute with [water](#) to 1000 mL.

Solution A: [Acetonitrile](#) and *Buffer* (20:80)

Solution B: [Acetonitrile](#) and *Buffer* (40:60)

Mobile phase: See [Table 2](#).

Table 2