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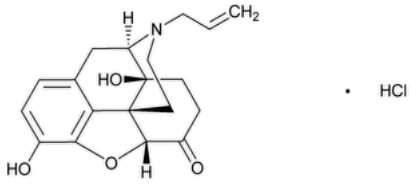
Naloxone Hydrochloride

Change to read:



• HCl

$C_{19}H_{21}NO_4 \cdot HCl$ 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

▲$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$▲ (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 ($C_{19}H_{21}NO_4 \cdot HCl$), 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	100

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

Time (min)	Solution A (%)	Solution B (%)
0	100	0
50	100	0
51	0	100
60	0	100

▲▲ (ERR 1-Dec-2022)

System suitability solution: 5 mg/mL of USP Naloxone RS and 0.0025 mg/mL of USP Naloxone Related Compound D RS in 0.1 N hydrochloric acid

Standard solution: 0.00125 mg/mL of USP Naloxone Related Compound D RS in 0.1 N hydrochloric acid

Sample solution: 25 mg/mL of Naloxone Hydrochloride in 0.1 N hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 2.0 mL/min

Injection volume: 10 µL

System suitability

Samples: ▲▲ (ERR 1-Dec-2022) *System suitability solution* and *Standard solution*

Suitability requirements

Tailing factor: NMT 1.8 for naloxone related compound D, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

▲▲ (ERR 1-Dec-2022)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of naloxone related compound D in the portion of Naloxone Hydrochloride taken:

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

r_U = peak response of naloxone related compound D from the *Sample solution*

r_S = peak response of naloxone related compound D from the *Standard solution*

C_S = concentration of USP Naloxone Related Compound D RS in the *Standard solution* (mg/mL)

C_U = concentration of Naloxone Hydrochloride in the *Sample solution* (mg/mL), calculated on the dried basis

Acceptance criteria: NMT 0.010%▲ (USP 1-Dec-2022)

Add the following:

▲• **Organic Impurities**

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

Sensitivity solution: 2.25 µg/mL of USP Naloxone RS in 0.1 N hydrochloric acid

System suitability solution: 4.5 mg/mL of USP Naloxone RS and 0.0245 mg/mL of USP Naloxone Related Compound D RS in 0.1 N hydrochloric acid

Sample solution: 5 mg/mL of Naloxone Hydrochloride in 0.1 N hydrochloric acid

System suitability

Samples: *Standard solution*, *Sensitivity solution*, and *System suitability solution*

Suitability requirements

Peak-to-valley ratio: NLT 2.0, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity other than naloxone related compound D in the portion of Naloxone 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 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), calculated on the dried basis

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

M_{r2} = molecular weight of naloxone, 327.38

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
10α-Hydroxynaloxone[a]	0.66	1.0	0.15
Noroxymorphone[b]	0.85	1.0	0.15
10β-Hydroxynaloxone[c]	0.95	1.0	0.15
Naloxone hydrochloride	1.00	—	—
Naloxone related compound D[d]	1.15	—	—
2,2'-Bisnaloxone[e]	3.22	2.0	0.15
3-*O*-Allylnaloxone[f]	3.46	1.0	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.8▲ (USP 1-Dec-2022)

[a] 4,5α-Epoxy-3,10α,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one.

[b] 4,5α-Epoxy-3,14-dihydroxymorphinan-6-one.

[c] 4,5α-Epoxy-3,10β,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one.

[d] For peak identification only. Naloxone related compound D is quantified in the *Limit of Naloxone Related Compound D* test.

[e] 4,5α:4',5'α-Diepoxy-3,3',14,14'-tetrahydroxy-17,17'-bis(prop-2-enyl)-2,2'-bimorphinanyl-6,6'-dione.

[f] 4,5α-Epoxy-14-hydroxy-17-(prop-2-enyl)-3-(prop-2-enyloxy)morphinan-6-one.

SPECIFIC TESTS

• **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

Sample solution: 25 mg/mL in water

Acceptance criteria: −170° to −181°

• **Loss on Drying** ⟨731⟩

Analysis: Dry at 105° to constant weight.

Acceptance criteria: NMT 0.5% for the anhydrous form and NMT 11.0% for the hydrous form

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at 25°, with excursions permitted between 15° and 30°.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Naloxone RS

▲Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, (5α).

$C_{19}H_{21}NO_4$ 327.38

USP Naloxone Related Compound D RS

4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-7-ene-6-one.

$C_{19}H_{19}NO_4$ 325.36▲ (USP 1-Dec-2022)

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

Topic/Question	Contact	Expert Committee
NALOXONE HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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