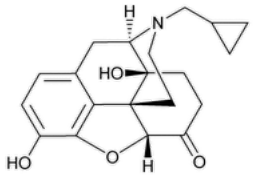
Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-FE8B56F2-FF0F-4373-B4A4-206C91E01C87_5_en-US
DOI: https://doi.org/10.31003/USPNF_M55530_05_01
DOI Ref: 80sod

Naltrexone Hydrochloride



• HCl

$C_{20}H_{23}NO_4 \cdot HCl$ 377.86

Morphinan-6-one, 17-(cyclopropylmethyl)-4,5-epoxy-3,14- dihydroxy-, hydrochloride, (5α)-;

17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy morphinan-6-one hydrochloride CAS RN®: 16676-29-2; UNII: Z6375YW9SF.

Free base

$C_{20}H_{23}NO_4$ 341.41 CAS RN®: 16590-41-3; UNII: 5S6W795CQM.

Dihydrate

$C_{20}H_{23}NO_4 \cdot HCl \cdot 2H_2O$ 413.89 CAS RN®: 850808-02-5; UNII: 5P80UKS30B.

DEFINITION

Naltrexone Hydrochloride contains NLT 98.0% and NMT 102.0% of naltrexone hydrochloride ($C_{20}H_{23}NO_4 \cdot HCl$), calculated on the anhydrous, solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K▲ (CN 1-May-2020)

Sample: Dissolve 150 mg of Naltrexone Hydrochloride in 25 mL of water in a small separator. 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.

Acceptance criteria: Meets the requirements

• **B.** The retention time of the naltrexone peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Solution A: Dissolve about 1.08 g of sodium 1-octanesulfonate and about 23.8 g of sodium acetate in 800 mL of water. Add 1.0 mL of triethylamine and 200 mL of methanol, and adjust with glacial acetic acid to a pH of 6.5 ± 0.1.

Solution B: Dissolve about 1.08 g of sodium 1-octanesulfonate and about 23.8 g of sodium acetate in 400 mL of water. Add 1.0 mL of triethylamine and 600 mL of methanol, and adjust with glacial acetic acid to a pH of 6.5 ± 0.1.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
35	0	100
36	100	0
53	100	0

Standard solution: 2.25 mg/mL of USP Naltrexone RS prepared as follows. Transfer an amount of USP Naltrexone RS to a suitable volumetric flask, add 15% of the final volume of methanol and 6% of the final volume of 0.1 N hydrochloric acid, and dissolve by swirling. Dilute with 0.1 M phosphoric acid to volume.

System suitability stock solution: 0.3 mg/mL of USP Naltrexone Related Compound A RS prepared as follows. Transfer a quantity of USP Naltrexone Related Compound A RS to a suitable volumetric flask, add 30% of the final volume of methanol, and dissolve by swirling. Dilute with 0.1 M phosphoric acid to volume.

System suitability solution: 1.125 mg/mL of USP Naltrexone RS and 0.015 mg/mL of USP Naltrexone Related Compound A RS prepared as follows. Transfer suitable volumes of *System suitability stock solution* and *Standard solution* to an adequate volumetric flask, and dilute with 0.1 M phosphoric acid to volume.

Sample solution: 2.5 mg/mL of Naltrexone Hydrochloride in 0.1 M phosphoric acid

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 15-cm; 4-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

[NOTE—The relative retention times for naltrexone and naltrexone related compound A are 1.0 and 1.26, respectively.]

Suitability requirements

Resolution: NLT 2.0 between naltrexone and naltrexone related compound A, *System suitability solution*

Tailing factor: NMT 1.4, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of naltrexone hydrochloride ($C_{20}H_{23}NO_4 \cdot HCl$) in the portion of Naltrexone 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 naltrexone from the *Sample solution*

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

C_S = concentration of USP Naltrexone RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of naltrexone hydrochloride, 377.86

M_{r2} = molecular weight of naltrexone, 341.41

Acceptance criteria: 98.0%–102.0% on the anhydrous, solvent-free basis

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

• **LIMIT OF TOTAL SOLVENTS:** The sum of water and total solvents (methanol and ethanol) is NMT 5.0% for the anhydrous form and NMT 11.0% for the dihydrate form.

• **ORGANIC IMPURITIES**

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

Sensitivity solution: 2.25 µg/mL of USP Naltrexone RS in 0.1 M phosphoric acid from *Standard solution*

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between naltrexone and naltrexone related compound A, *System suitability solution*

Tailing factor: NMT 1.4, *Standard 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 in the portion of Naltrexone Hydrochloride taken:

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

r_U = peak response of each impurity from the *Sample solution*

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

C_S = concentration of USP Naltrexone RS in the *Standard solution* (mg/mL)

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

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Noroxymorphone[a]	0.55	1.0	0.5
10-Hydroxynaltrexone[b]	0.70	1.0	0.5
Naltrexone	1.00	1.0	—
Naltrexone related compound A	1.26	1.0	0.5
2,2'-Bisnaltrexone[c]	1.80	2.3	0.5
10-Ketonaltrexone[d]	1.99	4.0	0.5
Any unspecified impurity	—	1.0	0.5
Total impurities	—	—	1.5

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

[b] 17-Cyclopropylmethyl-4,5α-epoxy-3,10,14-trihydroxymorphinan-6-one.

[c] 17,17'-Bis(cyclopropylmethyl)-4,5α:4',5'α-diepoxy-3,3',14,14'-tetrahydroxy-2,2'-bimorphinanyl-6,6'-dione.

[d] 17-Cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxymorphinan-6,10-dione.

SPECIFIC TESTS

- **Content of Chloride**

  Sample solution: Transfer about 300 mg of Naltrexone Hydrochloride to a 250-mL conical flask, add 50 mL of methanol, 50 mL of water, and 3 mL of nitric acid. Mix to dissolve.

  Analysis: Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Each milliliter of 0.1 N silver nitrate is equivalent to 3.545 mg of chloride.

  Acceptance criteria: 9.20%–9.58%, calculated on the anhydrous, solvent-free basis

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

  Sample solution: 25 mg/mL of Naltrexone Hydrochloride in water

  Acceptance criteria: −187° to −197°, calculated on the anhydrous, solvent-free basis

- **Water Determination** ⟨921⟩, *Method I*: Determine the water content as directed. [Note—The result of this test is used in the calculation in the test for *Limit of Total Solvents*.]

- **Clarity of Solution**

  Sample solution: Dissolve 1.0 g of Naltrexone Hydrochloride in 50 mL of water.

  Analysis: Determine the turbidity of the *Sample solution* (see *Nephelometry, Turbidimetry, and Visual Comparison* ⟨855⟩).

  Acceptance criteria: NMT 3 NTUs

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **USP Reference Standards** ⟨11⟩

  USP Naltrexone RS

  USP Naltrexone Related Compound A RS

  17-(But-3-en-1-yl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride.

  $C_{20}H_{23}NO_4 \cdot HCl$ 377.86

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

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

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(6)

Current DocID: GUID-FE8B56F2-FF0F-4373-B4A4-206C91E01C87_5_en-US

DOI: https://doi.org/10.31003/USPNF_M55530_05_01

DOI ref: 80sod