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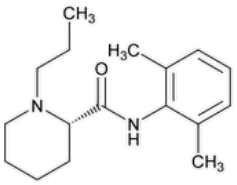
Ropivacaine Hydrochloride

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb/ropivacaine-hcl-20210223.

Change to read:



• HCl • H_2O

$C_{17}H_{26}N_2O \cdot HCl \cdot H_2O$ 328.88

(*S*)-(−)-1-Propylpiperidine-2-carboxylic acid (2,6-dimethylphenyl)amide hydrochloride monohydrate;

(*S*)-(−)-1-Propyl-2',6'-pipecoloxylidine hydrochloride monohydrate CAS RN®: 132112-35-7.

UNII: V910P86109.

▲$C_{17}H_{26}N_2O \cdot HCl$ 310.86

(*S*)-*N*-(2,6-Dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride CAS RN®: 98717-15-8.

UNII: 35504LBE2T.▲ (RB 24-Feb-2021)

DEFINITION

Ropivacaine Hydrochloride contains NLT 98.5% and NMT 101.0% of $C_{17}H_{26}N_2O \cdot HCl$, calculated on the anhydrous basis.

IDENTIFICATION

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

• **B.** **Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

Sample solution: 10 mg/mL

ASSAY

• **Procedure**

Sample solution: Dissolve 1000 mg of Ropivacaine Hydrochloride in 10 mL of water and 40 mL of alcohol. Add 1.0 mL of 1 N hydrochloric acid.

Analysis: Titrate with 1 N sodium hydroxide VS. Two equivalence points are obtained; the difference in titrant volume corresponds to the amount of ropivacaine hydrochloride (see *Titrimetry ⟨541⟩*). Each mL of 1 N sodium hydroxide is equivalent to 310.9 mg of anhydrous ropivacaine hydrochloride ($C_{17}H_{26}N_2O \cdot HCl$).

Acceptance criteria: 98.5%–101.0% on the anhydrous basis

IMPURITIES

Organic Impurities

• **Procedure 1**

Buffer solution: Combine 1.3 mL of monobasic sodium phosphate solution (138 g/L) and 32.5 mL of disodium hydrogen phosphate dihydrate solution (89 g/L), and dilute with water to 1 L. The pH of this solution is 8.0. Make adjustments if necessary.

Mobile phase: Acetonitrile and *Buffer solution* (1:1)

System suitability solution: 10 µg/mL of each of USP Ropivacaine Hydrochloride RS and USP Bupivacaine Hydrochloride RS in *Mobile phase*

Sample solution 1: 2.75 mg/mL of Ropivacaine Hydrochloride in *Mobile phase*

Sample solution 2: 2.75 µg/mL of Ropivacaine Hydrochloride from *Sample solution 1* diluted with *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

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

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

[NOTE—Check the stability of the baseline by injecting *Mobile phase*. Run the chromatogram for at least 15 min.]

Samples: *System suitability solution* and *Sample solution 2*

[NOTE—The relative retention times for ropivacaine and bupivacaine are about 1.0 and 1.6, respectively.]

Suitability requirements

Resolution: NLT 6 between ropivacaine and bupivacaine, *System suitability solution*

Signal-to-noise ratio: NLT 10 for ropivacaine, *Sample solution 2*

Analysis

Samples: *System suitability solution* and *Sample solution 1*

Calculate the percentage of each impurity in the portion of Ropivacaine Hydrochloride taken:

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

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria

Bupivacaine: NMT 0.2%

Any other individual impurity: Less than 0.1%

Total impurities: NMT 0.5%

- **PROCEDURE 2: LIMIT OF ROPIVACAINE RELATED COMPOUND A**

Buffer solution, Mobile phase, and **Chromatographic system:** Prepare as directed in *Procedure 1*.

Standard solution: 0.13 µg/mL of USP Ropivacaine Related Compound A RS in *Mobile phase*

Sample solution: 10 mg/mL of Ropivacaine Hydrochloride in *Mobile phase*

System suitability

Sample: *Standard solution*

Suitability requirements

Signal-to-noise ratio: NLT 10 for ropivacaine related compound A

Analysis

Samples: *Standard solution* and *Sample solution*

Acceptance criteria: The response for any peak corresponding to ropivacaine related compound A (2,6-dimethylaniline) in the *Sample solution* is not greater than the response of the major peak in the *Standard solution* (NMT 10 ppm).

- **PROCEDURE 3: ENANTIOMERIC PURITY**

Background electrolyte solution: 9.31–10.29 mg/mL of phosphoric acid in water. The pH is between 2.9 and 3.1. If necessary, adjust the pH with triethanolamine to 2.9–3.1.

Run buffer: 13.3 mg/mL of heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin in *Background electrolyte solution*. [NOTE—This solution is freshly prepared and passed through a 0.45-µm filter.]

System suitability solution: 15 µg/mL of each USP Ropivacaine Hydrochloride RS and USP Ropivacaine Related Compound B RS in water

Sample solution 1: 2 mg/mL of Ropivacaine Hydrochloride in water

Sample solution 2: 0.01 mg/mL of ropivacaine hydrochloride from *Sample solution 1* diluted with water

Capillary rinsing procedure: Use separate *Run buffer* vials for capillary rinse and sample analysis. Rinse the capillary with water for 1 min, with 0.1 N sodium hydroxide for 10 min, and with water for 3 min. If a new or dry capillary is being used, increase the sodium hydroxide rinse time to 30 min. Rinse the capillary between injections as follows: water for 1 min, 0.1 N sodium hydroxide for 4 min, and water for 1 min, then *Run buffer* for 4 min. Rinse times are based on a rinse pressure of 1 bar.

Capillary electrophoresis system

Detector: UV 206 nm

Column: 50-µm × 72-cm fused silica

Column temperature: 30°

Applied voltage: 375 V/cm

Initial ramping: 500 V/s, positive polarity, and a resulting current of 40–45 µA

Injection volume: Equal volumes

System suitability

Samples: *System suitability solution* and *Sample solution 2*

[NOTE—The relative migration times for ropivacaine related compound B (R enantiomer) and ropivacaine (S enantiomer) are about 0.96 and 1.0, respectively.]

Suitability requirements

Signal-to-noise ratio: NLT 10, *Sample solution 2*

Resolution: NLT 3.7 between ropivacaine related compound B and ropivacaine, *System suitability solution*

[NOTE—The analysis run time is about 30 min. If needed, increase the resolution by increasing the concentration of heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin or by lowering the system temperature.]

Analysis

Samples: *Run buffer*, water, and *Sample solution 1*

Inject *Run buffer* and water to ensure there are no interfering peaks (50 mbar for 5.0 s followed by injection of *Run buffer* at 50 mbar for 1.0 s). Inject *Sample solution 1* into the electrophoresis system, record the electropherograms, and measure the peak responses for ropivacaine and ropivacaine related compound B.

Calculate the percentage of ropivacaine related compound B in the portion of Ropivacaine Hydrochloride taken:

$$\text{Result} = (r_R/M_R)/(r_S/M_S) \times 100$$

r_R = peak response of ropivacaine related compound B from *Sample solution 1*

M_R = migration time of ropivacaine related compound B (min)

r_S = peak response of ropivacaine from *Sample solution 1*

M_S = migration time of ropivacaine (min)

[NOTE—After the analysis, rinse the capillary for 10 min with 0.1 N sodium hydroxide, then for 10 min with water. Dry the capillary before storage.]

Acceptance criteria: NMT 0.5% of ropivacaine related compound B

SPECIFIC TESTS

• **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** The level of bacterial endotoxins is such that the requirements under the relevant dosage form monograph(s) in which Ropivacaine Hydrochloride is used can be met. Where the label states that Ropivacaine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirements under the relevant dosage form monograph(s) in which Ropivacaine Hydrochloride is used can be met.

• **COLOR**

Sample solution: Transfer an aliquot of Ropivacaine Hydrochloride, 480–500 mg, into a 25-mL volumetric flask, and dissolve in and dilute with water to volume. Pass the solution through a 5-µm polyvinylidene filter (PVDF).

Spectrometric conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV-Vis

Analytical wavelengths: 405 and 436 nm

Cell: 5 cm

Analysis

Sample: *Sample solution*

Immediately measure the absorbance of the *Sample solution*, using water as the reference.

Acceptance criteria: NMT 0.030 at 405 nm, and NMT 0.025 at 436 nm

• **CLARITY**

Hydrazine sulfate solution: 10 mg/mL of hydrazine sulfate in water. Allow to stand 4–6 h.

Hexamethylenetetramine solution: Transfer 2.5 g of hexamethylenetetramine to a 100-mL glass-stoppered flask, and dissolve in 25 mL of water.

Opalescence standard stock suspension: To the flask containing the *Hexamethylenetetramine solution*, add 25.0 mL of *Hydrazine sulfate solution*, mix, and allow to stand for 24 h. This suspension is stable for up to 2 months when stored in a glass container free from surface defects. The suspension must not adhere to the flask and must be well mixed before use.

Opalescence standard suspension: Dilute 15.0 mL of the *Opalescence standard stock suspension* with water to 1000 mL. This suspension should be freshly prepared and may be stored for NMT 24 h.

Standard suspension 1: *Opalescence standard suspension* and water (5:95). Shake before use.

Standard suspension 2: *Opalescence standard suspension* and water (10:90). Shake before use.

Sample solution: 480–500 mg of Ropivacaine Hydrochloride in a 25-mL volumetric flask. Dilute with water to volume.

Analysis:

Samples: *Standard suspension 1*, *Standard suspension 2*, and *Sample solution*

Use identical tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm. The depth of the layer is 40 mm. Compare the solutions in diffused daylight 5 min after the preparation of *Standard suspension 1* and *Standard suspension 2*, viewing vertically against a black background. The diffusion of light must be such that *Standard suspension 1* can readily be distinguished from water, and *Standard suspension 2* can readily be distinguished from *Standard suspension 1*.

Acceptance criteria: The *Sample solution* is considered clear if its clarity is the same as that of water or if its opalescence is not more pronounced than that of *Standard suspension 1*.

• **pH** ⟨791⟩**:** 4.5–6.0, in a solution (10 mg/mL)

Change to read:

• **Water Determination** ⟨921⟩, *Method I, Method Ia*: ▲For monohydrate form,▲ (RB 24-Feb-2021) 5.0%–6.0%. Perform the determination on 0.0900–0.1100 g of sample.

▲For anhydrous form, NMT 1.0%.▲ (RB 24-Feb-2021)

• **Sterility Tests** ⟨71⟩**:** Where the label states that Ropivacaine Hydrochloride is sterile, it meets the requirements.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at room temperature.

Change to read:

• **Labeling:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. ▲If it is an anhydrous form, it is so labeled.▲ (RB 24-Feb-2021)

• **USP Reference Standards** ⟨11⟩

USP Bupivacaine Hydrochloride RS

USP Ropivacaine Hydrochloride RS

USP Ropivacaine Related Compound A RS

2,6-Dimethylaniline hydrochloride.

$C_8H_{11}N \cdot HCl$ 157.64

USP Ropivacaine Related Compound B RS

(*R*)-Ropivacaine hydrochloride monohydrate; (*R*)-(+)-1-propylpiperidine-2-carboxylic acid (2,6-dimethylphenyl)-amide hydrochloride monohydrate; (*R*)-*N*-(2,6-Dimethylphenyl)-1-propylpiperidine-2-carboxamide hydrochloride monohydrate.

$C_{17}H_{26}N_2O \cdot HCl \cdot H_2O$ 328.88

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

Topic/Question	Contact	Expert Committee
ROPIVACAINE HYDROCHLORIDE	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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