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Bupivacaine Hydrochloride and Epinephrine Injection

DEFINITION

Bupivacaine Hydrochloride and Epinephrine Injection is a sterile solution of Bupivacaine Hydrochloride and Epinephrine or Epinephrine Bitartrate in Water for Injection. It contains NLT 93.0% and NMT 107.0% of the labeled amount of bupivacaine hydrochloride ($C_{18}H_{28}N_2O \cdot HCl$). The content of epinephrine ($C_9H_{13}NO_3$) does not exceed 0.001% (1 in 100,000). It contains the equivalent of NLT 90.0% and NMT 115.0% of the labeled amount of epinephrine ($C_9H_{13}NO_3$).

IDENTIFICATION

• **A.**

Procedure 1

Sample solution: Nominally 2 mg/mL of bupivacaine hydrochloride in 0.01 N hydrochloric acid from Injection

Analysis: Proceed as directed in *Identification—Organic Nitrogenous Bases* ⟨181⟩, beginning with "Transfer the liquid to a separator".

Acceptance criteria: Meets the requirements

Procedure 2

Sample solution: Use the *Sample solution* from *Procedure 1: Bupivacaine Hydrochloride* in the *Assay*.

Acceptance criteria: The retention time of the bupivacaine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in *Procedure 1: Bupivacaine Hydrochloride* in the *Assay*.

• **B.**

Sample: Nominally equivalent to 50 µg of epinephrine from Injection

Analysis: Pipet the *Sample* into a suitable container, add 0.1 mL of *Ferro-citrate solution* and 2.0 mL of *Buffer solution* (prepared as directed in *Epinephrine Assay* ⟨391⟩), mix, and allow the solution to stand for 10 min. Filter the solution.

Acceptance criteria: The filtrate is violet in color and may turn brownish.

ASSAY

• **Procedure 1: Bupivacaine Hydrochloride**

Buffer: 1.94 g/L of monobasic potassium phosphate and 2.48 g/L of dibasic potassium phosphate in water. Adjust, if necessary, with 1 N potassium hydroxide or 1 M phosphoric acid to a pH of 6.8.

Mobile phase: Acetonitrile and *Buffer* (65:35). Adjust, if necessary, with 1 M phosphoric acid to a pH of 7.7 ± 0.2. Pass the solution through a membrane filter of 1-µm or finer pore size, and degas.

Internal standard solution: 1.3 mg/mL of dibutyl phthalate in methanol

Standard solution: 0.5 mg/mL of USP Bupivacaine Hydrochloride RS, prepared as follows. In a 100-mL volumetric flask, dissolve 50 mg of USP Bupivacaine Hydrochloride RS in 10.0 mL of water, using sonication if necessary. Add 10 mL of *Internal standard solution*, and dilute with methanol to volume.

Sample solution: Nominally 0.5 mg/mL of bupivacaine hydrochloride, prepared as follows. In a 100-mL volumetric flask, transfer an amount of Injection equivalent to 50 mg of bupivacaine hydrochloride, add 10.0 mL of *Internal standard solution*, and dilute with methanol to volume.

Chromatographic system

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

Mode: LC

Detector: UV 263 nm

Column: 4-mm × 30-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for bupivacaine and dibutyl phthalate are about 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 2.0 between bupivacaine and dibutyl phthalate

Relative standard deviation: NMT 1.0% for the ratio of bupivacaine to the internal standard from three replicate Injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of bupivacaine hydrochloride ($C_{18}H_{28}N_2O \cdot HCl$) in the portion of Injection taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of bupivacaine to the internal standard from the *Sample solution*

R_S = peak response ratio of bupivacaine to the internal standard from the *Standard solution*

C_S = concentration of USP Bupivacaine Hydrochloride RS, calculated on the anhydrous basis, in the *Standard solution* (mg/mL)

C_U = nominal concentration of bupivacaine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 93.0%–107.0%

- **Procedure 2: Epinephrine**

Mobile phase: Prepare a mixture of water, methanol, and 2 M monobasic sodium phosphate (900:50:50), containing 40 mg/L of edetate disodium, 0.4 mL/L of phosphoric acid, and 0.4 g/L of sodium 1-octanesulfonate. Make adjustments, if necessary, to obtain a retention time of NLT 11 min for the epinephrine peak.

System suitability solution: 2 µg/mL each of epinephrine bitartrate and dopamine hydrochloride in *Mobile phase*

Standard solution: 2 µg/mL of USP Epinephrine Bitartrate RS in *Mobile phase*

Sample solution: Nominally 1 µg/mL of epinephrine, prepared as follows. In a 25-mL volumetric flask, transfer an amount of Injection equivalent to 25 µg of epinephrine, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: Electrochemical held at a potential of +0.75 V

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for epinephrine and dopamine are about 1.0 and 2, respectively.]

Suitability requirements

Resolution: NLT 6.0 between the epinephrine and dopamine peaks, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of epinephrine ($C_9H_{13}NO_3$) in the portion of Injection taken:

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

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

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

C_S = concentration of USP Epinephrine Bitartrate RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of epinephrine in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of epinephrine, 183.21

M_{r2} = molecular weight of epinephrine bitartrate, 333.30

Acceptance criteria: 90.0%–115.0%

SPECIFIC TESTS

- **Color and Clarity**

Standard solution: Transfer 2.0 mL of 0.100 N iodine VS to a 500-mL volumetric flask and dilute with water to volume.

Sample solution: Injection

Analysis 1: Visually examine a portion of the *Sample solution* in a suitable clear glass test tube against a white background.

Acceptance criteria 1: The *Sample solution* is not pinkish, and it contains no precipitate.

Analysis 2: Perform *Analysis 2* if any yellow color is observed in the *Sample solution*. Concomitantly determine the absorbances of the *Sample solution* and the *Standard solution* in 1-cm cells with a suitable spectrophotometer set at 460 nm.

Acceptance criteria 2: The absorbance of the *Sample solution* does not exceed that of the *Standard solution.*

- **Bacterial Endotoxins Test ⟨85⟩:** NMT 1.6 USP Endotoxin Units/mg of bupivacaine hydrochloride
- **pH ⟨791⟩:** 3.3–5.5

• **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light. Injection labeled to contain 0.5% or less of bupivacaine hydrochloride may be packaged in 50-mL multiple-dose containers.

• **Labeling:** The label indicates that Injection is not to be used if its color is pinkish or darker than slightly yellow, or if it contains a precipitate.

• **USP Reference Standards ⟨11⟩**

USP Bupivacaine Hydrochloride RS

USP Epinephrine Bitartrate RS

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

Topic/Question	Contact	Expert Committee
BUPIVACAINE HYDROCHLORIDE AND EPINEPHRINE INJECTION	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. Information currently unavailable

Current DocID: GUID-74F51D4A-3EAA-403D-908D-50D246506D9C_3_en-US
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