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Fentanyl Citrate and Ropivacaine Hydrochloride Compounded Injection

DEFINITION

Fentanyl Citrate and Ropivacaine Hydrochloride Compounded Injection contains NLT 90.0% and NMT 110.0% of the labeled amount of fentanyl ($C_{22}H_{28}N_2O$) and ropivacaine hydrochloride ($C_{17}H_{26}N_2O \cdot HCl$).

Prepare Fentanyl Citrate and Ropivacaine Hydrochloride Compounded Injection containing 2 µg/mL of fentanyl and 1 mg/mL of ropivacaine hydrochloride as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Fentanyl (as fentanyl citrate injection[a]), equivalent to	200 µg of fentanyl
Ropivacaine Hydrochloride (as ropivacaine hydrochloride injection[b]), equivalent to	100 mg of ropivacaine hydrochloride
Sodium Chloride for Injection (0.9%), a sufficient quantity to make	100 mL

[a] Fentanyl Citrate 50-µg/mL injection, Hospira, Lake Forest, IL.

[b] Ropivacaine Hydrochloride 0.5% (5 mg/mL) injection, Fresenius Kabi, Lake Zurich, IL.

Aseptically withdraw and combine 4 mL of the *Fentanyl Citrate injection* (50 µg/mL) (equivalent to 200 µg of fentanyl) and 20 mL of *Ropivacaine Hydrochloride injection* (5 mg/mL) (equivalent to 100 mg of ropivacaine hydrochloride) into an appropriate sterile container. Bring the preparation to a final volume of 100 mL with *Sodium Chloride for Injection (0.9%)*. Pass through a sterile filter of 0.22-µm pore size.
[NOTE—Do not use a cellulose ester filter membrane for sterilization due to potential for adsorption.]

ASSAY

• **PROCEDURE**

Solution A: Add 2.72 g of dibasic potassium phosphate to 800 mL of water. Adjust with phosphoric acid to a pH of 5.8. Add 200 mL of methanol and mix well.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Methanol (%)	Solution A (%)
0.0	20	80
3.0	20	80
28.0	50	50
28.5	55	45
34.0	55	45
34.5	20	80
40	20	80

Standard solution: 2 µg/mL of fentanyl and 0.075 mg/mL of ropivacaine hydrochloride prepared from USP Fentanyl Citrate RS and USP Ropivacaine Hydrochloride RS in water

Ropivacaine hydrochloride sample solution: Transfer 0.75 mL of Injection into a 10-mL volumetric flask, and dilute with water to volume.

Fentanyl sample solution: 2 µg/mL of fentanyl from Injection

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 10-cm; 2.6-µm packing L1

Column temperature: 40°

Flow rate: 0.8 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[NOTE—The retention times for ropivacaine hydrochloride and fentanyl are about 14.4 and 24.6 min, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for both fentanyl and ropivacaine hydrochloride

Relative standard deviation: NMT 2.0% for both fentanyl and ropivacaine hydrochloride from replicate injections

Analysis

Samples: *Standard solution*, *Ropivacaine hydrochloride sample solution*, and *Fentanyl sample solution*

Calculate the percentage of the labeled amount of fentanyl ($C_{22}H_{28}N_2O$) and ropivacaine hydrochloride ($C_{17}H_{26}N_2O \cdot HCl$) in the portion of Injection taken:

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

r_U = peak response of fentanyl or ropivacaine hydrochloride from the relevant *Sample solution*

r_S = peak response of fentanyl or ropivacaine hydrochloride from the *Standard solution*

C_S = concentration of fentanyl or ropivacaine hydrochloride in the *Standard solution* (µg/mL or mg/mL, respectively)

C_U = nominal concentration of fentanyl or ropivacaine hydrochloride in the relevant *Sample solution* (µg/mL or mg/mL, respectively)

Acceptance criteria: 90.0%–110.0%

• **ENANTIOMERIC PURITY**

Mobile phase: Add 0.418 g of monobasic sodium phosphate and 0.941 g of dibasic sodium phosphate to 465 mL of water. Adjust with sodium hydroxide to a pH of 7.2 and add 35 mL of isopropanol. Mix well.

System suitability solution: Dissolve suitable quantities of USP Ropivacaine Hydrochloride RS and USP Ropivacaine Related Compound B RS in water. Dilute quantitatively, and stepwise, with water to obtain a solution containing about 75 µg/mL and 0.75 µg/mL, respectively.

Sample solution: Transfer 0.75 mL of Injection into a 10-mL volumetric flask, and dilute with water to volume.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4-mm × 10-cm; packing L41

Column temperature: 25°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for ropivacaine related compound B and ropivacaine hydrochloride are about 0.75 and 1.0, respectively.]

Suitability requirement

Resolution: NLT 1.5 between ropivacaine related compound B (*R*-enantiomer) and ropivacaine (*S*-enantiomer)

Analysis

Sample: *Sample solution*

Calculate the percentage of ropivacaine related compound B (*R*-enantiomer) in the portion of Injection taken:

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

r_U = peak response of ropivacaine related compound B (*R*-enantiomer)

r_T = sum of the peak responses of ropivacaine (*S*-enantiomer) and ropivacaine related compound B (*R*-enantiomer)

Acceptance criteria: NMT 2.0%

SPECIFIC TESTS

Change to read:

• **pH** ⟨791⟩**:** ▲4.0–6.0▲ (USP 1-May-2024)

• **Sterility Tests** ⟨71⟩, *Test for Sterility of the Product to Be Examined, Membrane Filtration*: Meets the requirements

• **Bacterial Endotoxins Test** ⟨85⟩: NMT 50.0 USP Endotoxin Units/mg of fentanyl and NMT 2.5 USP Endotoxin Units/mg of ropivacaine hydrochloride

• **Particulate Matter in Injections** ⟨788⟩: Meets the requirements

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Package in a light-resistant, single-dose container. Store at controlled room temperature or in a refrigerator.

• **Beyond-Use Date:** In the absence of passing a sterility and endotoxin test, the beyond-use dates in *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩ apply. After successful completion of sterility and endotoxin testing, NMT 90 days after the date on which it was compounded when stored at controlled room temperature or in a refrigerator.

• **Labeling:** Label it to indicate that it is for use in a single patient only, and to state the *Beyond-Use Date*.

• **USP Reference Standards** ⟨11⟩

USP Fentanyl Citrate RS
USP Ropivacaine Hydrochloride RS
USP Ropivacaine Related Compound B RS

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

Topic/Question	Contact	Expert Committee
FENTANYL CITRATE AND ROPIVACAINE HYDROCHLORIDE COMPOUNDED INJECTION	Brian Serumaga Science Program Manager	CMP2020 Compounding 2020

Chromatographic Database Information: Chromatographic Database

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