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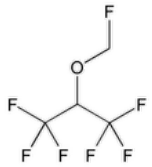
Sevoflurane



$C_4H_3F_7O$ 200.05

Propane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-;

Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether CAS RN®: 28523-86-6; UNII: 38LVP0K73A.

DEFINITION

Sevoflurane contains NLT 99.97% and NMT 100.00% of sevoflurane ($C_4H_3F_7O$).

IDENTIFICATION

• **A. Infrared Absorption**

Acceptance criteria: The IR absorption spectrum of Sevoflurane, obtained using a gas cell, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Sevoflurane RS.

ASSAY

• **Procedure**

Analysis: Using the results from the test for *Organic Impurities*, calculate the percentage of sevoflurane ($C_4H_3F_7O$) in the volume of Sevoflurane taken by subtracting the sum of percentages for all impurities found from 100.00%.

Acceptance criteria: 99.97%–100.00%

IMPURITIES

• **Limit of Fluoride**

[Note—Use plastic utensils throughout this test.]

Buffer solution: Transfer 110 g of sodium chloride and 1 g of sodium citrate to a 2000-mL volumetric flask. Dissolve in 700 mL of water. Carefully add 150 g of sodium hydroxide, and shake to dissolve. Cool to room temperature, and carefully add 450 mL of glacial acetic acid while stirring. Cool, add 600 mL of isopropyl alcohol, and dilute with water to volume. [Note—The pH of this solution is 5.0–5.5. This solution may be used for 6 weeks when stored at room temperature.]

Solution A: Transfer 221 mg of sodium fluoride, previously dried at 150° for 4 h, to a 100-mL volumetric flask. Add about 20 mL of water, and mix to dissolve. Add 1.0 mL of 0.01 N sodium hydroxide, and dilute with water to volume. Each mL of this solution contains 1 mg of fluoride. Store in a tightly closed, plastic container. [Note—This solution may be used for 2 weeks when stored in a refrigerator.]

Standard stock solution 1: 0.2 µg/mL of fluoride from *Solution A* in water

Standard stock solution 2: 0.5 µg/mL of fluoride from *Solution A* in water

Standard stock solution 3: 2 µg/mL of fluoride from *Solution A* in water

Standard stock solution 4: 5 µg/mL of fluoride from *Solution A* in water

Standard solution 1: 0.10 µg/mL of fluoride from *Standard stock solution 1* in *Buffer solution*

Standard solution 2: 0.25 µg/mL of fluoride from *Standard stocksolution 2* in *Buffer solution*

Standard solution 3: 1.0 µg/mL of fluoride from *Standard stocksolution 3* in *Buffer solution*

Standard solution 4: 2.5 µg/mL of fluoride from *Standard stocksolution 4* in *Buffer solution*

Sample solution: Pipet 50.0 mL of Sevoflurane and 50.0 mL of water into a separatory funnel, shake vigorously for 3 min, and allow the liquids to separate completely. Transfer 25.0 mL of the aqueous top layer to a 50-mL volumetric flask, and dilute with *Buffer solution* to volume.

Analysis

Samples: *Standard solutions 1–4* and *Sample solution*

Concomitantly measure the potentials, in mV, of *Standard solutions 1–4* and the *Sample solution* with a pH meter (see *pH* ⟨791⟩) capable of a minimum reproducibility of ±0.2 mV, and equipped with a fluoride-specific ion-indicating electrode and a glass-sleeved calomel reference electrode. When taking measurements, transfer the solution under test to a 100-mL beaker containing a polytef-coated stirring bar, and immerse the electrodes. Allow to stir on a magnetic stirrer having an insulated top until equilibrium is attained in about 2–3 min, and record the potential. Rinse the electrodes with the *Buffer solution*, and dry, taking care to avoid damaging the crystal of the specific-ion electrode. A satisfactory response is achieved if the difference between the potentials obtained with *Standard solution 4* and *Standard solution 2* is in the range between 50 and 60 mV. Plot the logarithms of the fluoride concentrations, in µg/mL, of *Standard solutions 1–4* versus potentials, in mV. From the graph and the measured potential of the *Sample solution,* determine the concentration, *C* (µg/mL) of fluoride in the *Sample solution*. Multiply *C* by 2 to obtain the concentration (µg/mL) of fluoride in the portion of Sevoflurane taken.

Acceptance criteria: NMT 2 µg/mL is found.

- **Limit of Nonvolatile Residue**

Analysis: Transfer 10.0 mL of Sevoflurane to an evaporating dish, evaporate to dryness on a steam bath, and dry the residue at 105° for 2 h.

Acceptance criteria: The weight of the residue does not exceed 1.0 mg.

- **Organic Impurities**

Internal standard solution: Use dimethoxymethane.

Ethylene dichloride identification solution: Transfer 2.0 mL of Sevoflurane to a vial, and seal with a cap and septum. Using a microsyringe, add 20 µL of ethylene dichloride through the septum of the vial, and mix thoroughly.

Sevoflurane related compounds stock solution: Transfer 20 mL of Sevoflurane to a 40-mL vial with a septum lid. Add 20 µL each of USP Sevoflurane Related Compound A RS, USP Sevoflurane Related Compound B RS, and USP Sevoflurane Related Compound C RS to the vial, and mix thoroughly.

Related compounds identification solution: Transfer 1.0 mL of *Ethylene dichloride identification solution* to a 10-mL volumetric flask, and dilute with Sevoflurane to volume. Transfer 2 mL of this solution and 5 mL of *Sevoflurane related compounds stock solution* to a 50-mL volumetric flask, dilute with Sevoflurane to volume, and mix thoroughly.

Standard solutions: Prepare in duplicate, proceeding for each as follows. Transfer 2.0 mL of ethylene dichloride to a screw-capped vial, immediately seal with a cap and septum, and place on a balance. Using a microsyringe, transfer about 20 µL of USP Sevoflurane RS to the vial by inserting the syringe needle through the septum. Record the quantity, in mg, of USP Sevoflurane RS added. Using the same method, transfer about 20 µL of the *Internal standard solution* to the vial, and record the quantity, in mg, of the solution added.

Control standard solution: Place a 40-mL vial with a septum lid on an analytical balance, and tare out the weight. Add 30 mL of ethylene dichloride to the vial, and seal tightly. Record the weight of the ethylene dichloride, and tare. Using a microsyringe, add 20 µL of the USP Sevoflurane RS through the septum of the vial, record the weight, and mix thoroughly. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, and dilute with ethylene dichloride to volume.

Sample solution: Transfer 20.0 mL of Sevoflurane to a vial, and insert the stopper. Using a microsyringe, add 5 µL of the *Internal standard solution* to the vial.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m fused-silica capillary column coated with a 3.0-µm film of liquid phase G43

Temperatures

Injection port: 200°

Detector: 225°

Column: See *Table 1*. Before use, condition the column overnight at a temperature of 250°.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	0	40	10
40	10	200	14

Carrier gas: Helium

Flow rate: 1 mL/min. [NOTE—The make-up gas flow rate is 20 mL/min.]

Injection volume: 2 µL

Injection type: Split ratio 1:20

System suitability

Samples: *Related compounds identification solution* and one of the *Standard solutions*

Suitability requirements

[NOTE—Identify the peaks using the relative retention times given in *Table 2*.]

Resolution: NLT 2.0 between sevoflurane related compound C and ethylene dichloride, *Related compounds identification solution*

Column efficiency: NLT 6000 theoretical plates for the sevoflurane peak, *Standard solution*

Relative standard deviation: NMT 3.0% from the peak area ratio of sevoflurane to the internal standard, *Standard solution*

Analysis

Samples: *Ethylene dichloride identification solution*, *Standard solutions*, *Control standard solution*, and *Sample solution*

Calculate the response factor for each of the *Standard solutions*:

$$\text{Result} = (W_I/W_S) \times R_S$$

W_I = weight of the internal standard in the *Standard solutions* (mg)

W_S = weight of USP Sevoflurane RS in the *Standard solutions* (mg)

R_S = peak area response ratio of sevoflurane to that of the internal standard from the *Standard solutions*

The response factors for the duplicate *Standard solutions* do not differ by more than 3.0% from their average.

Calculate the quantity, in µg/g, of each impurity in the portion of Sevoflurane ($C_4H_3F_7O$) taken:

$$\text{Result} = (S_1/S_2) \times (R_I/F_R) \times (1/F) \times 250$$

S_1 = specific gravity of the internal standard, 0.859

S_2 = specific gravity of sevoflurane, 1.525

R_I = peak area response ratio of the impurity to that of the internal standard from the *Sample solution*

F_R = average response factor obtained as directed above

F = respective relative response factor for the impurities (see *Table 2*)

Acceptance criteria

[NOTE—Do not include sevoflurane, the internal standard, or any peak identified as solvent carryover (ethylene dichloride). Also, disregard any peak with an area less than 30% of the average area of the principal peak from the *Control standard solution*.]

Individual impurities: NMT 25 µg/g of sevoflurane related compound A and NMT 100 µg/g of any other single impurity

Total impurities: NMT 300 µg/g

Table 2

Name	Relative Retention Time	Relative Response Factor
Sevoflurane related compound A	0.78	1.0
Sevoflurane related compound B	0.83	1.0
Sevoflurane	1.0	—
Internal standard (dimethoxymethane)	1.35	—

Name	Relative Retention Time	Relative Response Factor
Ethylene dichloride	2.28	—
Sevoflurane related compound C	2.31	0.46
Unknown impurities	—	1

SPECIFIC TESTS

• **Refractive Index** ⟨831⟩**:** 1.2745–1.2760 at 20°

• **Acidity or Alkalinity:** Transfer 20.0 mL of Sevoflurane and 20.0 mL of carbon dioxide-free water to a separatory funnel, shake for 3 min, and allow the layers to separate.

Acceptance criteria: The aqueous layer requires NMT 0.10 mL of 0.010 N sodium hydroxide or NMT 0.60 mL of 0.010 N hydrochloric acid for neutralization, bromocresol purple TS being used as the indicator.

• **Water Determination,** *Method I* ⟨921⟩**:** NMT 0.1%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature. Replace the cap securely after each use.

• **USP Reference Standards** ⟨11⟩

USP Sevoflurane RS

USP Sevoflurane Related Compound A RS

1,1,1,3,3-Pentafluoroisopropenyl fluoromethyl ether.

$C_4H_2F_6O$ 180.05

USP Sevoflurane Related Compound B RS

1,1,1,3,3,3-Hexafluoro-2-methoxy-propane.

$C_4H_4F_6O$ 182.06

USP Sevoflurane Related Compound C RS

1,1,1,3,3,3-Hexafluoro-2-propanol.

$C_3H_2F_6O$ 168.04

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

Topic/Question	Contact	Expert Committee
SEVOFLURANE	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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