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Propofol Injectable Emulsion

DEFINITION

Propofol Injectable Emulsion contains Propofol in a 10% (w/v) oil-in-water sterile emulsion. The aqueous component contains glycerol, a suitable antimicrobial agent, and Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of propofol ($C_{12}H_{18}O$). It contains a suitable emulsifying agent.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U. ▲[Note—Alternatively, the UV spectra of the major peak of the *Sample solution* and the *Standard solution* as obtained in the *Assay* may be used to meet the *Acceptance criteria*.]▲ (USP 1-Dec-2021)

Medium: Isopropyl alcohol

Standard solution: 100 µg/mL ▲of USP Propofol RS in *Medium*▲ (USP 1-Dec-2021)

Sample solution: ▲Nominally 100 µg/mL of propofol from Injectable Emulsion prepared as follows.▲ (USP 1-Dec-2021) Dilute a volume of Injectable Emulsion, equivalent to 10 mg of propofol, with ▲*Medium*▲ (USP 1-Dec-2021) to 100 mL.

Wavelength range: 200–450 nm

▲**Acceptance criteria:** Meets the requirements▲ (USP 1-Dec-2021)

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

ASSAY

Change to read:

• **Procedure**

Diluent: Dilute 68 mL of water with isopropyl alcohol to 1 L.

Mobile phase: Tetrahydrofuran and water (40:60)

Standard solution: 0.8 mg/mL of USP Propofol RS in *Diluent*

Sample solution: ▲Nominally 0.8 mg/mL of propofol prepared as follows.▲ (USP 1-Dec-2021) Transfer a volume of well-shaken Injectable Emulsion, equivalent to about 40 mg of propofol, to a 50-mL volumetric flask. Dissolve in and dilute with isopropyl alcohol to volume, and mix. ▲▲ (USP 1-Dec-2021)

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

▲[Note—For the alternative procedure in *Identification A*, use a diode array detector in the range of 200–400 nm.]▲ (USP 1-Dec-2021)

Column: 5-mm × 10-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

▲▲ (USP 1-Dec-2021)

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of propofol ($C_{12}H_{18}O$) in the portion of Injectable Emulsion taken:

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

r_U = peak response ▲of propofol▲ (USP 1-Dec-2021) from the *Sample solution*

r_S = peak response ▲of propofol▲ (USP 1-Dec-2021) from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Change to read:

• **Limit of Free Fatty Acids**

[Note—To obtain a titer of sufficient sensitivity for the blank reagent, it is necessary to add stearic acid at a concentration of approximately 1.0 mmol/L. ▲For formulations containing known components that interfere with the quantitation of free fatty acids, the quantities of these components should be determined and subtracted from the final result.]

Titrimetric system

(See *Titrimetry* ⟨541⟩.)

Mode: Direct titration

Titrant: 0.05 M sodium hydroxide VS

Endpoint detection: Potentiometric▲ (USP 1-Dec-2021)

Blank titration: Weigh about 142.3 mg of stearic acid into a 500-mL volumetric flask. Dissolve in and dilute with dehydrated alcohol to volume to obtain the blank solution. Pipet 10 mL of the blank solution into a 100-mL beaker, and proceed as directed in the *Analysis*, beginning with "Add 0.5 mL of 0.05 N hydrochloric acid".

Calculate the blank correction, *B*, in mmol/L:

$$\text{Result} = (N \times V_{TB}/V_B) - N_{SA}$$

N = concentration of the *Titrant* (mmol/L)

V_{TB} = volume of the *Titrant* added between the first and second inflection points for the *Blank titration* (mL)

V_B = volume of the blank solution used for the analysis (mL)

N_{SA} = concentration of stearic acid (mmol/L)

Analysis

Sample: A volume of Injectable Emulsion, nominally equivalent to 100 mg of propofol

Transfer the *Sample* to a 100-mL beaker. Add 0.5 mL of 0.05 N hydrochloric acid, then dilute with a solution of alcohol and water (45:20) to 60 mL. Titrate with ▲*Titrant*▲ (USP 1-Dec-2021) to a potentiometric endpoint using a suitable electrode.

Calculate the free fatty acid content, in mmol/L:

$$\text{Result} = (N \times V_T/V_S) - B$$

N = concentration of the *Titrant* (mmol/L)

V_T = volume of the *Titrant* added between the first and second inflection points (mL)

V_S = volume of Injectable Emulsion used for the analysis (mL)

B = blank correction factor (mmol/L), calculated as shown above

Acceptance criteria: NMT 7 mmol/L

Change to read:

• **Organic Impurities**

Diluent, Mobile phase, and **Sample solution:** Proceed as directed in the *Assay*.

System suitability solution: ▲0.8 mg/mL of USP Propofol RS, 0.002 mg/mL of USP Propofol Related Compound A RS, and 0.0008 mg/mL of USP Propofol Related Compound B RS in *Diluent*▲ (USP 1-Dec-2021)

Standard solution: 0.002 mg/mL of USP Propofol Related Compound A RS and 0.0008 mg/mL of USP Propofol Related Compound B RS in *Diluent*

Chromatographic system: Proceed as directed in the *Assay*, except for the *Detector*.

Detector: 254 nm

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for propofol related compound B, propofol, and propofol related compound A are about 0.8, 1.0, and 2.5, respectively.]

Suitability requirements

Resolution: NLT 2.5 between propofol and propofol related compound B

▲▲ (USP 1-Dec-2021)

Tailing factor: NMT 1.5 for the propofol peak

Relative standard deviation: NMT 2% for the propofol peak

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of propofol related compound A and propofol related compound B in the portion of Injectable Emulsion taken:

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

r_U = peak response of propofol related compound A or propofol related compound B from the *Sample solution*

r_S = peak response of propofol related compound A or propofol related compound B from the *Standard solution*

C_S = concentration of USP Propofol Related Compound A RS or USP Propofol Related Compound B RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 0.5% of propofol related compound A; NMT 0.5% of propofol related compound B

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST ⟨85⟩:** It contains NMT 0.33 USP Endotoxin Units/mg of propofol.
- **STERILITY TESTS ⟨71⟩:** Meets the requirements
- **pH ⟨791⟩:** 4.5–8.5
- **GLOBULE SIZE DISTRIBUTION IN LIPID INJECTABLE EMULSIONS ⟨729⟩:** Meets the requirements
- **OTHER REQUIREMENTS:** It meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve under an inert atmosphere of nitrogen. Store at controlled room temperature. Do not freeze.
- **LABELING:** Label it to include the following: Shake well before use. Do not use if there is evidence of excessive creaming or aggregation, if large droplets are visible, or if there are other forms of phase separation indicating that the stability of the product has been compromised. Slight creaming, which should disappear after shaking, may be visible upon prolonged standing.

Change to read:

- **USP REFERENCE STANDARDS ⟨11⟩**

USP Propofol RS

USP Propofol Related Compound A RS

3,3'-5,5'-Tetraisopropyldiphenol;

▲Also known as 3,3',5,5'-Tetraisopropylbiphenyl-4,4'-diol.

$C_{24}H_{34}O_2$ 354.53▲ (USP 1-Dec-2021)

USP Propofol Related Compound B RS

2,6-Diisopropyl-1,4-benzoquinone.

▲$C_{12}H_{16}O_2$ 192.26▲ (USP 1-Dec-2021)

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

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