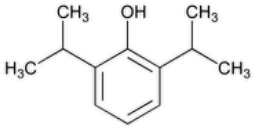
Status: Currently Official on 16-Feb-2025
Official Date: Official as of 01-Mar-2024
Document Type: USP Monographs
DocId: GUID-BDF82E0F-DFA0-4D9F-B253-2D53F75D0300_5_en-US
DOI: https://doi.org/10.31003/USPNF_M70460_05_01
DOI Ref: 4fvpq

Propofol



$C_{12}H_{18}O$ 178.28
Phenol, 2,6-bis(1-methylethyl);
2,6-Diisopropylphenol CAS RN®: 2078-54-8; UNII: YI7VU623SF.

DEFINITION
Propofol contains NLT 98.0% and NMT 102.0% of propofol ($C_{12}H_{18}O$).

IDENTIFICATION
• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197F
• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay, Procedure 1* or *Procedure 2*.

ASSAY
• **Procedure 1**
[Note—This is to be performed in conjunction with *Organic Impurities, Procedure 1*.]

Internal standard solution: 10 mg/mL of USP 2,4,6-Tritertbutylphenol RS in methanol

Standard solution: 10 mg/mL of USP Propofol RS in *Internal standard solution*

Sample solution: 10 mg/mL of Propofol in *Internal standard solution*

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m; coated with a 1.2-µm phase G16

Temperatures

Detector: 300°

Injection port: 250°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
145	—	145	20
145	5	200	5

Carrier gas: Helium

Flow rate: 8 mL/min

Injection volume: 1.0 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 1.5% for the peak response ratio of propofol to the internal standard for five replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of propofol ($C_{12}H_{18}O$) in the portion of Propofol taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0%

Change to read:

• **Procedure 2**

[Note—This is to be performed in conjunction with *Organic Impurities, Procedure 2*.]

Mobile phase: Hexane, acetonitrile, and ▲alcohol, absolute▲ (ERR 1-Mar-2024) (990: 7.5: 1)

Standard solution: 2.4 mg/mL of USP Propofol RS in hexane

Sample solution: 2.4 mg/mL of Propofol in *hexane*

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

Column: 4.6-mm × 20-cm; 5-µm packing L3

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of propofol ($C_{12}H_{18}O$) in the portion of Propofol taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0%

IMPURITIES

• **Organic Impurities, Procedure 1**

[Note—On the basis of knowledge of the manufacturing process, either (1) *Organic Impurities, Procedure 1* is performed in conjunction with *Limit of Propofol Related Compound A*, *Limit of Propofol Related Compound B, Procedure 1*, and *Assay, Procedure 1*; or (2) *Organic Impurities, Procedure 2* is performed in conjunction with *Limit of Propofol Related Compound B, Procedure 2* and the *Assay, Procedure 2*.]

System suitability solution: 100 mg/mL of USP Propofol Resolution Mixture RS in methanol

Standard solution: 0.1 mg/mL of USP Propofol RS in methanol

Sample solution: 100 mg/mL of Propofol in methanol

Chromatographic system: Proceed as directed in the *Assay, Procedure 1*.

System suitability

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

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 2 between propofol and 2-isopropyl-6-*n*-propylphenol, *System suitability solution*

Relative standard deviation: NMT 3.5% for six replicate injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Propofol taken:

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

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

r_S = peak response for propofol from the *Standard solution*

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Propofol related compound C	0.18	0.1
Propofol	1.0	—
2-Isopropyl-6-*n*-propylphenol	1.1	0.1
Any unspecified impurity	—	0.1
Total impurities	—	0.3

- **ORGANIC IMPURITIES, PROCEDURE 2**

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay, Procedure 2*.

System suitability solution: 0.1 µL/mL of USP Propofol RS and 0.3 µL/mL of USP Propofol Related Compound B RS in hexane

Peak identification solution: 0.25 mg/mL of USP Propofol Related Compound A RS, 100 µL/mL of the Propofol that is under test, and 5 µL/mL of USP Propofol Related Compound C RS in hexane

Sample solution: 100 mg/mL of Propofol in hexane

Reference solution: 0.1 mg/mL of Propofol in hexane from the *Sample solution*

System suitability

Samples: *System suitability solution* and *Peak identification solution*

[NOTE—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 4.0 between propofol related compound B and propofol, *System suitability solution*

Analysis

Samples: *Sample solution* and *Reference solution*

Calculate the percentage of each impurity in the portion of Propofol taken:

$$\text{Result} = (r_U/r_S) \times (1/F) \times D \times 100$$

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

r_S = peak response of propofol from the *Reference solution*

F = relative response factor (see *Table 3*)

D = dilution factor used to prepare the *Reference solution*, 0.001

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Propofol related compound C	0.5	0.2	0.2
Propofol	1.0	—	—
Propofol related compound A	5.0	4.0	0.01
Any unspecified impurity	—	1.0	0.05
Total impurities	—	—	0.3

• **Limit of Propofol Related Compound A**

[Note—This test is to be performed in conjunction with *Organic Impurities, Procedure 1*.]

Mobile phase: Acetonitrile, methanol, and water (50:10:40)

Standard solution: 20 µg/mL of USP Propofol Related Compound A RS in methanol

Sample solution: 20 mg/mL of Propofol in methanol

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 15-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 6000 theoretical plates

Relative standard deviation: NMT 15% for six replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of propofol related compound A in the portion of Propofol taken:

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

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

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

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

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

Acceptance criteria: NMT 0.1% of propofol related compound A

• **Limit of Propofol Related Compound B, Procedure 1**

[Note—This is to be performed in conjunction with *Organic Impurities, Procedure 1*.]

Sample: Propofol

Instrumental conditions

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

Mode: UV

Analytical wavelength: 330 nm

Blank: Air

Analysis: Measure the absorbance of the *Sample* using air as the blank.

Acceptance criteria: NMT 0.1%; the absorbance of the *Sample* is NMT 0.4 absorbance units.

• **Limit of Propofol Related Compound B, Procedure 2**

[Note—This is to be performed in conjunction with *Organic Impurities, Procedure 2*.]

Mobile phase: Prepare as directed in the *Assay, Procedure 2*.

Standard solution: 5 µg/mL of USP Propofol Related Compound B RS in hexane

Sample solution: 50 mg/mL of Propofol in hexane

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 20-cm; 5-µm packing L3

Flow rate: 2 mL/min

Injection volume: 20 µL

Analysis

Samples: *Standard solution* and *Sample solution*

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

Calculate the percentage of propofol related compound B in the portion of Propofol taken:

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

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

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

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

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

Acceptance criteria: NMT 0.05% of propofol related compound B

SPECIFIC TESTS

• **Refractive Index** ⟨831⟩**:** 1.5125–1.5145 at 20°

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers under an atmosphere of inert gas, and protect from light. Store at controlled room temperature.

• **Labeling:** The labeling indicates the *Organic Impurities* procedure with which the article complies if a procedure other than *Organic Impurities, Procedure 1* is used.

• **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 Propofol Related Compound B RS

2,6-Diisopropyl-1,4-benzoquinone;
Also known as 2,6-Diisopropylcyclohexa-2,5-diene-1,4-dione.
$C_{12}H_{16}O_2$ 192.26

USP Propofol Related Compound C RS

2,6-Diisopropylphenyl isopropyl ether;
Also known as 2-Isopropoxy-1,3-diisopropylbenzene.
$C_{15}H_{24}O$ 220.36

USP Propofol Resolution Mixture RS

Contains a mixture of the following two compounds:

Propofol.

2-Isopropyl-6-*n*-propylphenol.

USP 2,4,6-Tritertbutylphenol RS

2,4,6-Tri-*tert*-butylphenol.

$C_{18}H_{30}O$ 262.44

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

Topic/Question	Contact	Expert Committee
PROPOFOL	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

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(6)

Current DocID: GUID-BDF82E0F-DFA0-4D9F-B253-2D53F75D0300_5_en-US

DOI: https://doi.org/10.31003/USPNF_M70460_05_01

DOI ref: 4fvpq