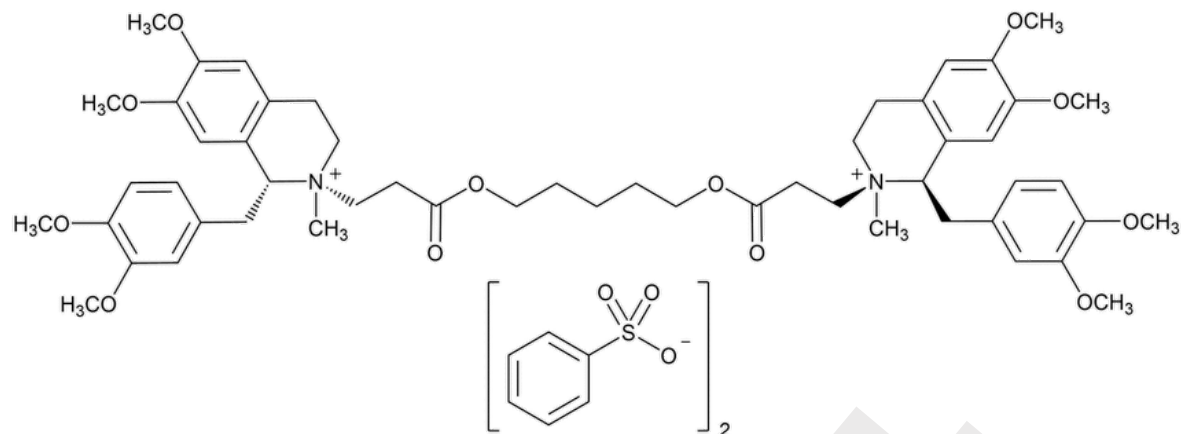


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Cisatracurium Besylate



$C_{65}H_{82}N_2O_{18}S_2$ 1243.48

Isoquinolinium, 2,2'-[1,5-pentanediy]bis[oxy(3-oxo-3,1-propanediy)]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-, dibenzenesulfonate, [1R-[1 α ,2 α (1'R*,2'R*)]]-;

(1R,2R)-2-(2-Carboxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium benzenesulfonate, pentamethylene ester CAS RN®: 96946-42-8; UNII: 80YS801MBS.

DEFINITION

Cisatracurium Besylate contains NLT 97.0% and NMT 102.0% of cisatracurium besylate ($C_{65}H_{82}N_2O_{18}S_2$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

- **A.** ▲ **SPECTROSCOPIC IDENTIFICATION TESTS (197), Infrared Spectroscopy: 197K** ▲ (CN 1-MAY-2020)
- **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

PROCEDURE

Buffer: 33.3 g/L of [ammonium formate](#) prepared as follows. Dissolve 32.8 g of [ammonium formate](#) in 984 mL of [water](#), and add 16 mL of [anhydrous formic acid](#).

Mobile phase: Acetonitrile, methanol, and *Buffer* (20:20:60)

Diluent: Acetonitrile, methanol, and water (20:20:60). Add 0.4 mL of anhydrous formic acid per 1 L.

System suitability solution: 0.7 mg/mL of [USP Cisatracurium Besylate System Suitability Mixture RS](#) in *Diluent*

Standard solution: 0.7 mg/mL of [USP Cisatracurium Besylate RS](#) in *Diluent*

Sample solution: 0.7 mg/mL of Cisatracurium Besylate in *Diluent*

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25.0-cm; 5- μ m packing [L1](#)

Flow rate: 1.5 mL/min

Injection volume: 20 μ L

Run time: NLT 2.5 times the retention time of cisatracurium

System suitability

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

[NOTE—See [Table 1](#) for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between the peaks for *R-cis-R'-trans*-atracurium and cisatracurium, *System suitability solution*

Tailing factor: NMT 1.7 for cisatracurium, *System suitability solution*

Relative standard deviation: NMT 1.5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of cisatracurium besylate ($C_{65}H_{82}N_2O_{18}S_2$) in the portion of Cisatracurium Besylate taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of [USP Cisatracurium Besylate RS](#) in the *Standard solution* (mg/mL)

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

Acceptance criteria: 97.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• [RESIDUE ON IGNITION \(281\)](#): NMT 0.1%

• **ORGANIC IMPURITIES**

Mobile phase, Diluent, System suitability solution, Standard solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Cisatracurium Besylate taken:

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

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

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See [Table 1](#). Disregard any peak representing less than 0.09% of the area of the major peak.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benzenesulfonic acid ^a	0.10	—
<i>cis</i> -Quaternary acid ^b	0.14	0.2
(<i>R</i>)- <i>N</i> -Methylaudanosine ^c	0.16	0.2
(<i>R</i>)-Laudanosine ^d	0.20	0.6
<i>cis</i> -Quaternary methyl ester ^e	0.23	0.4
<i>cis</i> -Quaternary alcohol ^f	0.29	0.5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
<i>R-trans-R'-trans</i> -Atracurium ^a	0.74	0.2
<i>R-cis-R'-trans</i> -Atracurium ^b	0.87	0.8
Cisatracurium	1.0	—
<i>trans</i> -Monoquatarnary compound ⁱ	1.17	0.5
<i>trans</i> -Monoacrylate ^j	1.28	0.5
<i>cis</i> -Monoquatarnary compound ^k	1.39	0.7
<i>cis-cis</i> -Triester analog ^l	1.46	0.4
<i>cis</i> -Monoacrylate ^m	1.56	1.0
Any individual unspecified impurity	—	0.1
Total impurities	—	3.0

^a This peak is due to the counterion and is not to be reported or included in total impurities.

^b (1*R*,2*R*)-2-(2-Carboxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium.

^c (*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2,2-dimethyl-1-veratrylisoquinolinium.

^d (*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinoline.

^e (1*R*,2*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[2-(methoxycarbonyl)ethyl]-2-methyl-1-veratrylisoquinolinium.

^f (1*R*,2*R*)-1,2,3,4-Tetrahydro-2-(9-hydroxy-3-oxo-4-oxanonyl)-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium.

^g (1*R*,1'*R*,2*S*,2'*S*)-2,2'-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium).

^h (1*R*,1'*R*,2*R*,2'*S*)-2,2'-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium).

ⁱ (1*R*,1'*R*,2*S*)-2-Methyl-2,2'-(3,11-dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-1-veratrylisoquinolinium).

^j (1*R*,2*S*)-2-(3,11-Dioxo-4,10-dioxo-12-tridecenyl)-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium).

^k (1*R*,1'*R*,2*R*)-2-Methyl-2,2'-(3,11-dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-1-veratrylisoquinolinium).

^l (1*R*,1'*R*,2*R*,2'*R*)-2,2'-(3,7,15-Trioxo-4,8,14-trioxa-heptadecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium).

^m (1*R*,2*R*)-2-(3,11-Dioxo-4,10-dioxo-12-tridecenyl)-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium).

• **LIMIT OF METHYL BENZENESULFONATE**

[NOTE—Prepare the solutions immediately before use. Methyl benzenesulfonate is slowly hydrolyzed in aqueous solutions.]

Mobile phase: Acetonitrile and [water](#) (45:55)

Internal standard solution: 1.2 mg/mL of methyl *p*-toluenesulfonate in acetonitrile

Standard stock solution A: 1.2 mg/mL of methyl benzenesulfonate in acetonitrile

Standard stock solution B: 48 µg/mL of methyl benzenesulfonate from *Standard stock solution A* in *Mobile phase* prepared as follows.

Transfer 2.0 mL of *Standard stock solution A* and 5.0 mL of *Internal standard solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Standard solution: 2.4 µg/mL of methyl benzenesulfonate from *Standard stock solution B* in *Mobile phase*

Sample solution: Nominally 0.2 g/mL of Cisatracurium Besylate in *Mobile phase* prepared as follows. Transfer 1.0 g of Cisatracurium Besylate into a suitable separator. Immediately add 25 µL of *Internal standard solution*, and dissolve the contents in 25 mL of [water](#) using vigorous shaking. Add 25 mL of ethyl acetate, and shake vigorously for 2 min. Allow the phases to separate until the aqueous layer is clear and for

NMT 2 h. Evaporate the organic layer to dryness in a current of air. Dissolve the residue in 5.0 mL of *Mobile phase* by sonication and gentle swirling.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 25.0-cm; 5-μm packing L1

Flow rate: 1 mL/min

Injection volume: 20 μL

Run time: 5 times the retention time of methyl benzenesulfonate

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 3.0 between methyl benzenesulfonate and methyl *p*-toluenesulfonate

Relative standard deviation: NMT 2.0% for methyl benzenesulfonate and methyl *p*-toluenesulfonate

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration of methyl benzenesulfonate in the portion of Cisatracurium Besylate taken:

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

R_U = peak height ratio of methyl benzenesulfonate to the internal standard from the *Sample solution*

R_S = peak height ratio of methyl benzenesulfonate to the internal standard from the *Standard solution*

C_S = concentration of methyl benzenesulfonate in the *Standard solution* (μg/mL)

C_U = nominal concentration of Cisatracurium Besylate in the *Sample solution* (g/mL)

Acceptance criteria: NMT 10 ppm

SPECIFIC TESTS

- **OPTICAL ROTATION (781S), [Procedures, Specific Rotation](#)**

Sample solution: 10.0 mg/mL in [acetonitrile](#)

Acceptance criteria: −60.0° to −54.0° at 20°, calculated on the anhydrous and solvent-free basis

- **WATER DETERMINATION (921):** NMT 5.0%.

[NOTE—*Method Ia* or *Method Ic* may be used.]

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store cold, desiccated.

- **USP REFERENCE STANDARDS (11).**

USP Cisatracurium Besylate RS

USP Cisatracurium Besylate System Suitability Mixture RS

Cisatracurium besylate.

R-trans-R'-trans-Atracurium besylate:

(1*R*,1'*R*,2*S*,2'*S*)-2,2'-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.



R-cis-R'-trans-Atracurium besylate:

(1*R*,1'*R*,2*R*,2'*S*)-2,2'-(3,11-Dioxo-4,10-dioxatridecamethylene)bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate.



Other related compounds.

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
CISATRACURIUM BESYLATE	Documentary Standards Support	SM42020 Small Molecules 4

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