Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Jun-2022
Document Type: USP Monographs
DocId: GUID-D178E159-353B-441B-AD20-1502DFB672AA_5_en-US
DOI: https://doi.org/10.31003/USPNF_M6350_05_01
DOI Ref: if9p6

Atracurium Besylate

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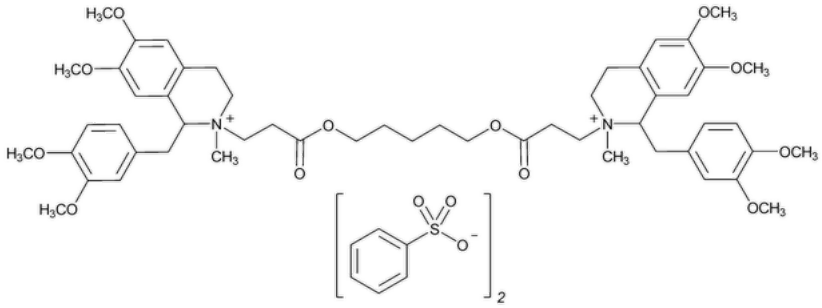

$C_{65}H_{82}N_2O_{18}S_2$ 1243.48

Isoquinolinium, 2,2'-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]]bis[1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-, dibenzenesulfonate;

▲2-(2-Carboxyethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium benzenesulfonate, pentamethylene ester▲ (ERR 1-Jun-2022) CAS RN®: 64228-81-5; UNII: 40AX66P76P.

DEFINITION

Atracurium Besylate contains NLT 96.0% and NMT 102.0% of $C_{65}H_{82}N_2O_{18}S_2$, calculated on the anhydrous basis. It contains NLT 5.0% and NMT 6.5% of the *trans-trans* isomer, NLT 34.5% and NMT 38.5% of the *cis-trans* isomer, and NLT 55.0% and NMT 60.0% of the *cis-cis* isomer.

IDENTIFICATION

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**

• **B.** The retention times of the three main isomeric peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: 10.2 g of monobasic potassium phosphate in a 1000-mL volumetric flask. Dissolve in 950 mL of water. While stirring, adjust with phosphoric acid to a pH of 3.1, and dilute with water to volume.

Solution A: Acetonitrile, methanol, and *Buffer* (20:5:75)

Solution B: Acetonitrile, methanol, and *Buffer* (20:30:50)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
5	80	20
15	40	60
25	40	60
30	0	100
45	0	100
50	80	20

Standard solution: 1 mg/mL of USP Atracurium Besylate RS in *Solution A*

Sample solution: 1 mg/mL of Atracurium Besylate in *Solution A*

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; 5-µm base-deactivated packing L1

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

[Note—Refer to *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between the atracurium *trans-trans* isomer and the *cis-trans* isomer peaks; NLT 1.5 between the atracurium *cis-trans* isomer and the *cis-cis* isomer peaks

Relative standard deviation: NMT 2.0%, for the *cis-cis* isomer peak

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = sum of the peak responses for the *trans-trans* isomer, the *trans-cis* isomer, and the *cis-cis* isomer from the *Sample solution*

r_S = sum of the peak responses for the *trans-trans* isomer, the *trans-cis* isomer, and the *cis-cis* isomer from the *Standard solution*

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

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

Acceptance criteria: 96.0%–102.0%, calculated on the anhydrous basis. It contains NLT 5.0% and NMT 6.5% of the *trans-trans* isomer, NLT 34.5% and NMT 38.5% of the *cis-trans* isomer, and NLT 55.0% and NMT 60.0% of the *cis-cis* isomer.

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.2%
- **Organic Impurities**

Buffer, Solution A, Solution B, Mobile phase, Chromatographic system, and **Sample solution:** Proceed as directed in the *Assay*.

Standard solution: 0.01 mg/mL of USP Atracurium Besylate RS in *Solution A*

System suitability solution: 1 mg/mL of USP Atracurium Besylate RS in *Solution A*

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between the atracurium *trans-trans* isomer and the *cis-trans* isomer peaks; NLT 1.5 between the atracurium *cis-trans* isomer and the *cis-cis* isomer peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms, and measure all of the peak responses, except the three main isomeric peaks.

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

$$\text{Result} = (r_U/r_T) \times (C_S/C_U) \times (1/F) \times 100$$

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

r_T = sum of peak responses due to the atracurium *cis-cis*, *trans-trans*, and *cis-trans* isomers from the *Standard solution*

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

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

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. [Note—Disregard any peak less than 0.05%.]

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Impurity E[a]	0.2	1.0	1.5
Impurity F[b]	0.25	1.0	1.0
Impurity G (laudanosine)[c]	0.3	2.0	1.0
Impurity D	0.45[d] and 0.5[e]	1.0	1.5[p]
Atracurium *trans-trans* isomer	0.8	—	—
Atracurium *cis-trans* isomer	0.9	—	—
Atracurium *cis-cis* isomer	1.0	—	—
Impurity A	1.04[f] and 1.08[i]	1.0	1.5[p]
Impurity I	1.07[g] and 1.12[k]	1.0	1.0[p]
Impurity H	1.07[h] and 1.12[l]	1.0	1.0[p]
Impurity K[j]	1.09 and 1.12	1.0	1.0[p]
Impurity B[m]	1.15	1.0	0.1
Impurity C	1.2[n] and 1.3[o]	1.0	1.0[p]
Any individual impurity	—	1.0	0.1
Total impurities	—	—	3.5

[a] 3-[1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinio]propanoate.

[b] 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium.

[c] 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.

[d] *trans* Isomer of 1-(3,4-dimethoxybenzyl)-2-[3-[(5-hydroxypentyl)oxy]-3-oxopropyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium.

[e] *cis* Isomer of 1-(3,4-dimethoxybenzyl)-2-[3-[(5-hydroxypentyl)oxy]-3-oxopropyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium.

[f] *cis-trans* Isomer of 1-(3,4-dimethoxybenzyl)-2-[13-[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]-3,11-dioxo-4,10-dioxatridecyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium.

[g] *cis-trans* Isomer of 2,2'-[(3-methylpentane-1,5)-diylbis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium].

[h] *cis-trans* Isomer of 2,2'-[hexane-1,6-diylbis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium].

[i] *cis-cis* Isomer of 1-(3,4-dimethoxybenzyl)-2-[13-[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]-3,11-dioxo-4,10-dioxatridecyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium.

[j] 2,2'-[(Hexane-1,5)-diylbis(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro isoquinolinium].

[k] *cis-cis* Isomer of 2,2'-[(3-methylpentane-1,5)-diylbis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium].

[l] *cis-cis* Isomer of 2,2'-[hexane-1,6-diylbis[oxy(3-oxopropane-1,3-diyl)]]bis[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro isoquinolinium].

[m] Pentane-1,5-diyl bis[3-[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)propanoate].

[n] *trans* Isomer of 1-(3,4-dimethoxybenzyl)-2-(3,11-dioxo-4,10-dioxatridec-12-enyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium benzenesulfonate.

[o] *cis* Isomer of 1-(3,4-dimethoxybenzyl)-2-(3,11-dioxo-4,10-dioxatridec-12-enyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium benzenesulfonate.

[p] Impurity consists of two isomers that are separated under these conditions; integrate both peaks for the impurity calculations.

• **Limit of Impurity J (Methyl Benzenesulfonate)**

Buffer, Solution A, and **Solution B:** Prepare as directed in the *Assay*.

Standard stock solution: 0.2 mg/mL of Impurity J (methyl benzenesulfonate) in acetonitrile

Standard solution: 1 µg/mL of Impurity J (methyl benzenesulfonate) in *Solution A* from *Standard stock solution*

Sample solution: 10 mg/mL of Atracurium Besylate in *Solution A*

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	80	20
5	80	20
15	75	25
25	75	25
30	55	45
38	0	100
45	0	100

Chromatographic system

Mode: LC

Detector: UV 217 nm

Column: 4.6-mm × 25-cm; 5-µm base-deactivated packing L1

Flow rate: 1 mL/min

Injection size: 100 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Measure the responses for the Impurity J (methyl benzenesulfonate) peaks.

Acceptance criteria: NMT 0.01%, the peak response of the *Sample solution* being NMT that of the *Standard solution*

SPECIFIC TESTS

• **Water Determination, *Method I*⟨921⟩:** NMT 5.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers, in a cold place. [Note—Atracurium Besylate is unstable at room temperature.]

• **USP Reference Standards ⟨11⟩**

USP Atracurium Besylate RS

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

Topic/Question	Contact	Expert Committee
ATRACURIUM BESYLATE	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 50(1)
Current DocID: GUID-D178E159-353B-441B-AD20-1502DFB672AA_5_en-US
DOI: https://doi.org/10.31003/USPNF_M6350_05_01
DOI ref: if9p6