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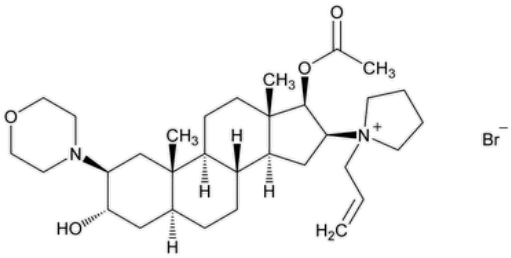
Rocuronium Bromide

Change to read:



$C_{32}H_{53}BrN_2O_4$ ▲609.69▲ (ERR 1-Dec-2022)

Pyrrolidinium, 1-[(2β,3α,5α,16β,17β)-17-(acetyloxy)-3- hydroxy-2-(4-morpholinyl)androstan-16-yl]-1- (2-propenyl)-, bromide;

1-Allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide, 17-acetate CAS RN®: 119302-91-9; UNII: I65MW4OFHZ.

DEFINITION

Rocuronium Bromide contains NLT 98.0% and NMT 102.0% of rocuronium bromide ($C_{32}H_{53}BrN_2O_4$), calculated on the anhydrous and 2-propanol-free or acetic acid-free basis.

IDENTIFICATION

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

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

• **C.** **Identification Tests—General ⟨191⟩, *Bromide***

Sample solution: 10 mg/mL

Acceptance criteria: Meets the requirements of test *B*

ASSAY

• **Procedure**

Diluent: Acetonitrile and water (90:10)

Buffer: 4.53 g/L of tetramethylammonium hydroxide pentahydrate. Adjust the solution with phosphoric acid to a pH of 7.4.

Mobile phase: Acetonitrile and *Buffer* (90:10)

Standard solution: 1 mg/mL of USP Rocuronium Bromide RS in *Diluent*

Sample solution: 1 mg/mL of Rocuronium Bromide in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L3

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 5 µL

System suitability

[Note—The system may need equilibration for 4 h.]

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of rocuronium bromide ($C_{32}H_{53}BrN_2O_4$) in the portion of the sample 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 Rocuronium Bromide RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the anhydrous and 2-propanol-free or acetic acid-free basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Change to read:

• **Organic Impurities**

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

Peak identification solution: 1 mg/mL of USP Rocuronium Peak Identification Mixture RS in *Diluent*

Standard solution: 0.01 mg/mL of USP Rocuronium Bromide RS in *Diluent*

Sample solution: 10 mg/mL of Rocuronium Bromide in *Diluent*

Run time: 2.5 times the retention time for rocuronium

System suitability

[Note—The system may need equilibration for 4 h.]

Sample: *Peak identification solution*

Suitability requirements

Peak-to-valley ratio: The ratio of the height of the rocuronium related compound H peak to the height of the valley between the rocuronium related compound H peak and the rocuronium peak is NLT 1.5.

Resolution: NLT 3.5 between rocuronium and rocuronium related compound C

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Rocuronium Bromide taken:

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

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

r_S = peak response of rocuronium bromide from the *Standard solution*

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

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

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

[Note—Disregard any peak eluting before rocuronium bromide related compound A, and any peak with an area less than 0.5 times that of the principal peak from the *Standard solution*.]

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Rocuronium related compound A[a]	0.20	2.1	0.2
Rocuronium related compound G[b]	0.44	2.3	0.1
Rocuronium related compound F[c]	0.75	0.79	0.1
Rocuronium related compound B[d]	0.80	1.0	0.3
Rocuronium related compound D[e]	0.90	1.0	0.1
Rocuronium related compound H[f]	0.95	2.9	0.1
Rocuronium bromide	1.0	—	—
Rocuronium related compound C[g]	1.20	1.0	0.3
Rocuronium related compound E[h]	1.53	1.0	0.1
Any individual unspecified impurity	—	—	0.10
Total impurities	—	—	1.5

[a] 3α-Hydroxy-2β-(morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstan-17β-yl acetate.

▲[b] 2β-(Morpholin-4-yl)-16β-(pyrrolidin-1-yl)-5α-androstane-3α,17β-diol.▲ (ERR 1-Dec-2022)

[c] 1-[3α,17β-Bis(acetyloxy)-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

[d] 1-[3α,17β-Bis(acetyloxy)-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

[e] 1-[3α-(Acetyloxy)-17β-hydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

[f] 1-[17β-(Acetyloxy)-2-(morpholin-4-yl)-3-oxo-5α-androst-1-en-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

[g] 1-[3α,17β-Dihydroxy-2β-(morpholin-4-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

[h] 1-[17β-(Acetyloxy)-3α-hydroxy-2β-(pyrrolidin-1-yl)-5α-androstan-16β-yl]-1-(prop-2-enyl)pyrrolidinium.

• **Limit of 2-Propanol**

[Note—Perform this test only if 2-propanol is a known organic manufacturing process impurity.]

Standard stock solution: Transfer 35.0 µL of ethyl ether, 32.0 µL of 2-propanol, and 19.0 µL of methylene chloride to a 100-mL volumetric flask containing 90 mL of dimethylformamide (DMF), and dilute with DMF to volume.

Standard solution: Transfer 2.5 mL of the *Standard stock solution* to a 25-mL volumetric flask containing 20 mL of DMF, and dilute with DMF to volume.

Dilute standard solution: Transfer 1.0 mL of the *Standard solution* and 4.0 mL of water to a 20-mL headspace vial. Immediately close the vial with a cap, and mix.

Sample solution: Transfer 50 mg of Rocuronium Bromide to a 20-mL headspace vial. Dissolve in 1.0 mL of DMF. Add 4 mL of water, immediately close the vial with a cap, and mix.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 60-m fused silica; coated with a 1.8-µm layer of liquid phase G43

Temperatures

Injector: 140°

Detector: 280°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	8
50	20	250	8

Carrier gas: Helium with a linear velocity of 55 cm/s or nitrogen with a linear velocity of 25 cm/s

Injection type: Split ratio, 1:6

Head space autosampler

Sample equilibration temperature: 90°

Sample equilibration time: 15 min

Transfer line temperature: 140°

System suitability

Sample: *Dilute standard solution*

[Note—The relative retention times for ethyl ether, 2-propanol, and methylene chloride are 0.87, 1.0, and 1.08, respectively.]

Suitability requirements

Resolution: NLT 1.0 between ethyl ether and 2-propanol; NLT 1.0 between 2-propanol and methylene chloride

Relative standard deviation: NMT 10.0% for the 2-propanol peak

Analysis

Samples: *Dilute standard solution* and *Sample solution*

Calculate the percentage of 2-propanol in the portion of Rocuronium Bromide taken:

$$\text{Result} = [(r_U/r_S) \times (V \times D/W) \times 100]/F$$

r_U = peak response of 2-propanol from the *Sample solution*

r_S = peak response of 2-propanol from the *Dilute standard solution*

V = volume of 2-propanol taken to prepare the *Standard stock solution* (µL)

D = relative density of 2-propanol, 0.786 mg/µL

W = weight of Rocuronium Bromide taken to prepare the *Sample solution* (mg)

F = dilution factor for the *Standard solution*, 1000

Acceptance criteria: NMT 1.0%

• **Limit of Acetic Acid**

[Note—Perform this test only if acetic acid is a known organic manufacturing process impurity.]

Mobile phase: 6.1 g of sodium perchlorate in 800 mL of water. Adjust with 1 N sulfuric acid to a pH of 2.0. Dilute to 1 L.

Standard solution: 0.2 mg/mL of glacial acetic acid in *Mobile phase*

Sample solution: 6.0 mg/mL of Rocuronium Bromide in *Mobile phase*. [Note—Sonication may be necessary to completely dissolve the rocuronium bromide.]

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 15-cm; packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[NOTE—The retention time of acetic acid is about 3.8 min.]

Suitability requirements

Column efficiency: NLT 5000 theoretical plates

Tailing factor: NMT 1.8

Relative standard deviation: NMT 5.0% for three injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of acetic acid in the portion of Rocuronium Bromide taken:

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

r_U = peak response for acetic acid from the *Sample solution*

r_S = peak response for acetic acid from the *Standard solution*

C_S = concentration of acetic acid in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 5.0%

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method Ic* ⟨921⟩**:** NMT 4.0%
- **pH** ⟨791⟩

Sample solution: 10 mg/mL

Acceptance criteria: 7.0–9.5

- **OPTICAL ROTATION,** *Specific Rotation* ⟨781S⟩

Sample solution: 10 mg/mL in 0.05 M hydrochloric acid

Acceptance criteria: 28.5°–32.0°, measured on the anhydrous and solvent-free basis at 20°

- **COLOR AND ACHROMICITY** ⟨631⟩

Reference solution: Mix 33 mL of *Matching Fluid G* and 67 mL of water.

Sample solution: 10 mg/mL of Rocuronium Bromide in water

Analysis: Proceed as directed for *Color and Achromicity* ⟨631⟩.

Acceptance criteria: The *Sample solution* is not more intensely colored than the *Reference solution*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light and moisture. Store in the freezer. If the article contains acetic acid, store it between 2° and 8°.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Rocuronium Bromide RS

USP Rocuronium Peak Identification Mixture RS

Mixture of approximately 0.2% to 0.4% each of rocuronium related compound A, rocuronium related compound B, rocuronium related compound C, rocuronium related compound D, rocuronium related compound E, rocuronium related compound F, rocuronium related compound G, and rocuronium related compound H in a matrix of rocuronium bromide.

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

Topic/Question	Contact	Expert Committee
ROCURONIUM BROMIDE	Documentary Standards Support	SM42020 Small Molecules 4

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

Chromatographic Database Information: Chromatographic Database

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