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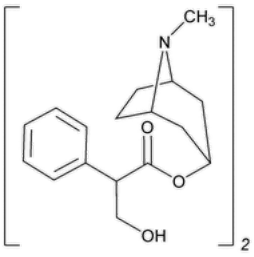
Atropine Sulfate

Change to read:



$\cdot H_2SO_4 \cdot H_2O$

$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$ ▲694.84▲ (ERR 1-Jul-2020)

Anhydrous 676.82

Benzeneacetic acid, α-(hydroxymethyl)-, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, *endo*-(±)-, sulfate (2:1) (salt), monohydrate; 1α*H*,5α*H*-Tropan-3-α-ol (±)-tropate (ester), sulfate (2:1) (salt) monohydrate CAS RN®: 5908-99-6; UNII: 03J5ZE7KA5.

Anhydrous CAS RN®: 55-48-1; UNII: KAE4PSB0Z3.

DEFINITION

Atropine Sulfate contains NLT 98.0% and NMT 102.0% of atropine sulfate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4$], calculated on the anhydrous basis.

[**Caution—**Handle atropine sulfate with exceptional care, because it is highly potent.]

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K or 197A
- **B. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Sulfate***

  Sample solution: 50 mg/mL

  Acceptance criteria: Meets the requirements
- **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

  Buffer: 1.8 g/L of monobasic potassium phosphate and 2.5 g/L of sodium 1-pentanesulfonate, adjusted with phosphoric acid to a pH of 2.5

  Diluent: Acetonitrile and *Buffer* (20:80)

  Solution A: Acetonitrile and *Buffer* (5:95)

  Solution B: Acetonitrile and *Buffer* (80:20)

  Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	92	8
11	79	21
15	46	54
15.1	92	8
20	92	8

[Note—The gradient was established on an HPLC system with a dwell volume of approximately 0.8 mL.]

System suitability solution: 1 µg/mL of USP Hyoscyamine Related Compound A RS and 0.5 mg/mL of USP Atropine Sulfate RS in *Diluent*

Sensitivity solution: 0.25 µg/mL of USP Atropine Sulfate RS in *Diluent*

Standard solution: 0.5 mg/mL of USP Atropine Sulfate RS in *Diluent*

Sample solution: 0.5 mg/mL of Atropine Sulfate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 5 µL

System suitability

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

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

Suitability requirements

Resolution: NLT 1.4 between hyoscyamine related compound A and atropine, *System suitability solution*

Tailing factor: 0.8–1.8 for atropine, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Signal-to-noise ratio: NLT 10 for atropine, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of atropine sulfate $[(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4]$ in the portion of Atropine Sulfate taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.2%
- **ORGANIC IMPURITIES**

Buffer, Diluent, Solution A, Solution B, Mobile phase, System suitability solution, Sensitivity 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 Atropine Sulfate taken:

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

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

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

F = relative response factor for each impurity (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tropic acid[a]	0.56	2.1	0.2
7-Hydroxyhyoscyamine[b]	0.66	1.0	0.2
Scopolamine[c]	0.72	1.0	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
6-Hydroxyhyoscyamine[d]	0.75	1.0	0.2
Hyoscyamine related compound A	0.97	1.2	0.3
Atropine	1.0	1.0	—
Littorine[e]	1.13	1.2	0.2
Apoatropine[f]	1.60	2.0	0.2
Any individual, unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.5

[a] 3-Hydroxy-2-phenylpropanoic acid; also known as (2*RS*)-3-Hydroxy-2-phenylpropanoic acid.

[b] (1*S*,3*R*,5*S*)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (*S*)-3-hydroxy-2-phenylpropanoate; also known as (1*S*,3*R*,5*S*,6*RS*)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate.

[c] (*S*)-(1*R*,2*R*,4*S*,5*S*,7*s*)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]nonan-7-yl 3-hydroxy-2-phenylpropanoate; also known as (*S*)-(1*R*,2*R*,4*S*,5*S*,7*s*)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate.

[d] (1*R*,3*S*,5*R*)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl (*S*)-3-hydroxy-2-phenylpropanoate; also known as (1*R*,3*S*,5*R*,6*RS*)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate.

[e] (1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-hydroxy-3-phenylpropanoate; also known as (1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-2-hydroxy-3-phenylpropanoate.

[f] (1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-phenylacrylate; also known as (1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 2-phenylpropenoate.

SPECIFIC TESTS

- **Optical Rotation ⟨781S⟩, *Procedures, Specific Rotation***
  Sample solution: 0.1 g/mL of Atropine Sulfate in water
  Temperature: 20°
  Path length: 1.0 or 2.0 dm
  Acceptance criteria: Between −0.50° and +0.05°
- **Water Determination ⟨921⟩, *Method I*:** NMT 4.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers.
- **USP Reference Standards ⟨11⟩**
  USP Atropine Sulfate RS
  USP Hyoscyamine Related Compound A RS

Norhyoscyamine sulfate; (1*R*,3*r*,5*S*)-8-Azabicyclo[3.2.1]octan-3-yl (*S*)-3-hydroxy-2-phenylpropanoate sulfate (2:1).
$(C_{16}H_{21}NO_3)_2 \cdot H_2SO_4$ 648.77

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

Topic/Question	Contact	Expert Committee
ATROPINE SULFATE	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

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