Atropine Sulfate Ophthalmic Solution

DEFINITION

Atropine Sulfate Ophthalmic Solution is a sterile, aqueous solution of Atropine Sulfate. It contains NLT 93.0% and NMT 107.0% of the labeled amount of atropine sulfate monohydrate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$]. It may contain suitable stabilizers and antimicrobial agents.

IDENTIFICATION

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

Delete the following:

▲• **B. IDENTIFICATION TESTS—GENERAL** ⟨191⟩**,** *Chemical Identification Tests, Sulfate*

Sample solution: Evaporate to dryness a quantity of Ophthalmic Solution. Prepare a solution from the residue that contains the equivalent of 50 mg of atropine sulfate/mL.

Acceptance criteria: Meets the requirements▲ (IRA 1-Nov-2019)

Add the following:

▲• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (IRA 1-Nov-2019)

ASSAY

Change to read:

• **PROCEDURE**

▲**Buffer A:** 6.8 g/L of sodium acetate in water. To each liter add 3.5 mL of triethylamine and 6.6 mL of glacial acetic acid. Adjust with glacial acetic acid, if needed, to a pH of 4.5.

Buffer B: 6.8 g/L of sodium acetate in water. To each liter add 4 mL of glacial acetic acid. Adjust with glacial acetic acid, if needed, to a pH of 4.5.

Mobile phase: Methanol and *Buffer A* (15:85)

Diluent: Methanol and *Buffer B* (15:85)

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

Sample solution: Nominally 0.5 mg/mL of atropine sulfate monohydrate from a volume of Ophthalmic Solution prepared as follows. Rinse a 100-mL volumetric flask with *Diluent*. Transfer about 33 mL of *Diluent* to the flask and then add a 5.0-mL aliquot of Ophthalmic Solution using a "to contain" pipet (see *Volumetric Apparatus* ⟨31⟩) to the flask. Shake vigorously. Dilute with *Diluent* to volume. Additional shaking may be needed to obtain a uniform solution.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm. For *Identification B*, use a diode array detector in the range of 190–400 nm.

Column: 4.6-mm × 15-cm; 5-µm packing L10

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of atropine

System suitability

Sample: *Standard solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atropine sulfate monohydrate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$] in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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 = nominal concentration of atropine sulfate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of atropine sulfate monohydrate, 694.84

M_{r2} = molecular weight of anhydrous atropine sulfate, 676.82▲ (IRA 1-Nov-2019)

Acceptance criteria: 93.0%–107.0%

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

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

System suitability solution: 0.005 mg/mL of atropic acid and 0.5 mg/mL of USP Atropine Sulfate RS in *Diluent*

System suitability

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

[NOTE—See *Table 1* for the relative response factors.]

Suitability requirements

Resolution: NLT 1.5 between atropic acid and atropine, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each specified and any unspecified degradation product in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each specified and any unspecified degradation product 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 = nominal concentration of atropine sulfate in the *Sample solution* (mg/mL)

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

M_{r1} = molecular weight of atropine sulfate monohydrate, 694.84

M_{r2} = molecular weight of anhydrous atropine sulfate, 676.82

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tropic acid[a]	0.69	2.0	7.0
Atropic acid[b]	0.87	12.2	1.0
Atropine	1.0	—	—
Apoatropine[c]	2.1	4.3	1.0
Any individual unspecified degradation product	—	1.0	1.0
Total impurities	—	—	7.0

[a] 3-Hydroxy-2-phenylpropanoic acid.
[b] 2-Phenylacrylic acid.
[c] (1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-phenylacrylate.▲ (IRA 1-Nov-2019)

SPECIFIC TESTS

- **pH** ⟨791⟩**:** 3.5–6.0
- **Sterility Tests** ⟨71⟩**:** Meets the requirements

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩
  USP Atropine Sulfate RS