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Echothiophate Iodide for Ophthalmic Solution

DEFINITION

Echothiophate Iodide for Ophthalmic Solution is sterile Echothiophate Iodide. It may contain Mannitol or other suitable diluent. It contains NLT 95.0% and NMT 115.0% of the labeled amount of echothiophate iodide ($C_9H_{23}INO_3PS$).

IDENTIFICATION

• **A.**

Sample solution: Nominally equivalent to 1.2 mg/mL of echothiophate iodide in water from Echothiophate Iodide for Ophthalmic Solution

Analysis: To 1 mL of the *Sample solution* add 0.2 mL of 2 N hydrochloric acid and 0.2 mL of 30% hydrogen peroxide. Add a few drops of solvent hexane, and shake.

Acceptance criteria: (1) The color turns brown after the addition of 30% hydrogen peroxide. (2) The solvent hexane acquires a pink color.

• **B.**

Analysis: To 5 mL of the *Sample solution* from *Identification* test *A* add 0.5 mL of sodium hydroxide solution (1 in 2), heat at 50° for 2 min, cool to room temperature, and add 1 mL of sodium nitroferricyanide TS.

Acceptance criteria: A deep-red color is produced.

ASSAY

• **Procedure**

In the preparation of all reagents, and throughout this procedure, wherever water is specified, use only water that has been distilled, boiled for 10 min, and cooled while protected from the atmosphere.

Solution A: Transfer 5.44 g of anhydrous dibasic sodium phosphate to a 100-mL volumetric flask, and add a volume of 1 N sodium hydroxide VS that contains 36.5 mEq of sodium hydroxide. Add 40 mL of water, shake to dissolve the sodium phosphate, and dilute with water to volume.

Solution B: Dilute 0.1 N iodine with water to 0.004 N, and standardize the solution on the day of use as follows. Weigh 150 mg of arsenic trioxide, and dissolve in 20 mL of 1 N sodium hydroxide, by warming if necessary, in a 500-mL volumetric flask. Dilute with 40 mL of water, add 2 drops of methyl orange TS, then add 3 N hydrochloric acid until the yellow color is changed to pink. Add 2 g of sodium bicarbonate, then add water to volume. Transfer 5.0 mL of this solution to a titration vessel, and add 50 mL of *Solution A* (see *Reagents, Indicators, and Solutions—Solutions*). Titrate with 0.004 N iodine, determining the endpoint potentiometrically, using platinum and silver–silver chloride electrodes. Calculate the normality. Each 197.8 µg of arsenic trioxide is equivalent to 1 mL of 0.004 N iodine.

Sample solution: Dissolve the contents of a counted number of vials of Echothiophate Iodide for Ophthalmic Solution, equivalent to 30 mg of echothiophate iodide, by adding 5 mL of water to each vial. Combine the solutions, and mix. Dilute a portion of the mixture, equivalent to 12 mg of echothiophate iodide, with water to 40 mL.

Analysis: To the *Sample solution* add 10.0 mL of *Solution A*, cover, and allow to stand for 20 min at 25 ± 3°. Add 2 mL of glacial acetic acid rapidly and with mixing. Titrate with *Solution B*, determining the endpoint potentiometrically, using platinum and silver–silver chloride electrodes. Correct for the amount of free thiol sulfur by repeating the procedure but adding the glacial acetic acid first, then *Solution A*, and titrating immediately. Subtract the volume of *Solution B* used in the second titration from that used in the first. Each mL of 0.004 N iodine is equivalent to 1.533 mg of echothiophate iodide ($C_9H_{23}INO_3PS$).

Acceptance criteria: 95.0%–115.0%

SPECIFIC TESTS

• **Completeness of Solution ⟨641⟩:** The contents of one container dissolve in 10 mL of carbon dioxide-free water to yield a clear solution.

• **Sterility Tests ⟨71⟩:** Meets the requirements

Change to read:

• **Water**

Dry all glassware used in the following procedure at 105° for 4 h, and store in a desiccator or dry box. Perform as many operations as possible in a dry box.

Solution A: Wash 150 g of 8- to 12-mesh type 3A molecular sieve with several portions of dehydrated alcohol to remove the fine particles. Place the washed molecular sieve in a shallow borosilicate glass tray, heat in an oven at 350° for 2 h, and cool in a dry box. Transfer the dry molecular sieve to a 1-L conical flask, add 700 mL of dehydrated alcohol, insert the stopper, and allow to stand for NLT 48 h before using.

Internal standard solution: Place 0.17 mL of methanol in a 100-mL volumetric flask, and add *Solution A* to volume. Prepare this solution fresh daily.

Standard solutions: Into three 25-mL volumetric flasks, each containing 15 mL of *Internal standard solution*, transfer 5, 40, and 75 µL of water, respectively. Dilute with *Internal standard solution* to volume. Prepare these solutions fresh daily.

Sample solution: Carefully remove the protective retainer and cap from five vials of Echothiophate Iodide for Ophthalmic Solution without removing the elastomeric septum closure. Discard the separated parts, and weigh each closed vial and contents. Inject through the septum of each vial 400 µL of *Internal standard solution*, using a suitable gas-tight syringe, and allow to stand for 1 h, swirling occasionally to dissolve the residue. After 1 h, remove 300 µL of solution from each vial by using a gas-tight syringe; transfer to a dry small-volume, sample-collecting vial equipped with a sampling valve system;[1] and mix the combined solutions.

Chromatographic system

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

Mode: GC

Detector: Thermal conductivity

Column: 2-mm × 1.8-m silylated glass; packed with 80- to 100-mesh surface-silanized packing S3

Temperatures

Column: 115°

Injection port: 200°

Detector: 225°

Carrier gas: Dry helium

Flow rate: 45 mL/min

Injection volume: 3–4 µL

System suitability

Samples: *Standard solutions*, chromatograph a sufficient number of injections

Suitability requirements

Resolution: NLT 2.0 between the water and methanol peaks

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solutions* and *Sample solution*

Measure the responses for the first (water) and second (methanol) major peaks obtained for each. Plot the ratios of the peak responses of water to methanol versus the concentration, in mg/mL, of water in each *Standard solution*. If the plot is not linear, discard it, and repeat the chromatography on additional portions of the *Standard solutions*. Similarly, inject a portion of the *Sample solution*, record the chromatogram, and measure the responses for the two major peaks. By comparison with the linear standard plot, determine the concentration, in mg/mL, of water in the *Sample solution* as that corresponding to the ratio of the peak responses of water to methanol from the *Sample solution*. Remove the elastomeric septum closure from each test vial, discard the contents, and rinse each vial and closure with several portions of methanol. Dry the vials and the closures in a stream of dry nitrogen, and subtract this weight from that of the closed vials and contents obtained as directed in the *Sample solution*.

Calculate the percentage of water content in the portion of Echothiophate Iodide for Ophthalmic Solution taken:

$$\text{Result} = [(C \blacktriangle\times \blacktriangle_{\text{(ERR 1-Nov-2021)}} V)/W] \times 100$$

C = concentration of water in the *Sample solution* (mg/mL)

V = volume of *Internal standard solution*, 0.4 mL

W = average weight of Echothiophate Iodide for Ophthalmic Solution in the vials (mg)

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, preferably of Type I glass, at controlled room temperature.

[1] Suitable sample-collecting vials and sampling valve systems are available as Catalog Nos. 13098 and 13099 3-mL and 5-mL vials and Catalog No. 10135 valve from Pierce Chemical Co., P.O. Box 117, Rockford, IL 61105.

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

Topic/Question	Contact	Expert Committee
ECHOTHIOPHATE IODIDE FOR OPHTHALMIC SOLUTION	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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