Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Jul-2020
Document Type: USP Monographs
DocId: GUID-C41867A6-F713-4D3E-A9E2-C771BFBE56D3_2_en-US
DOI: https://doi.org/10.31003/USPNF_M27320_02_01
DOI Ref: 5im02

Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution

» Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$), and not less than 80.0 percent and not more than 120.0 percent of the labeled amount of atropine sulfate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$].

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩—
USP Atropine Sulfate RS
USP Diphenoxylate Hydrochloride RS

Identification—The retention times of two major peaks in the chromatogram of the *Assay preparation* correspond to the atropine and diphenoxylate peaks in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Uniformity of dosage units ⟨905⟩—
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements with respect to diphenoxylate hydrochloride.

Deliverable volume ⟨698⟩—
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.

pH ⟨791⟩**:** between 3.0 and 4.3, determined in a dilution of the Oral Solution with an equal volume of water.

Alcohol Determination ⟨611⟩ **:** between 13.5% and 16.5% of C_2H_5OH.

Change to read:

Assay—

Solution A—Transfer 192 mg of sodium 1-pentanesulfonate monohydrate to a suitable container, add 200 mL of water, and sonicate to dissolve. Add 800 mL of water and 1.0 mL of phosphoric acid, and mix.

Solution B—Transfer 192 mg of sodium 1-pentane sulfonate monohydrate to a suitable container, add 200 mL of water, and sonicate to dissolve. Add 800 mL of acetonitrile, 1.0 mL of phosphoric acid, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Solution B* and *Solution A* (66:34). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Atropine stock preparation—Dissolve an accurately weighed quantity of USP Atropine Sulfate RS in dehydrated alcohol, and dilute quantitatively, and stepwise if necessary, with dehydrated alcohol to obtain a solution having a known concentration of about 0.04 mg per mL.

Standard preparation—Transfer about 20 mg of USP Diphenoxylate Hydrochloride RS to a 200-mL volumetric flask, add about 100 mL of dehydrated alcohol, and sonicate to dissolve. Accurately add 5.0 mL of *Atropine stock preparation* and 34 mL of water, and mix. Allow the solution to reach room temperature, and then dilute with dehydrated alcohol to volume. This solution contains about 0.1 mg of diphenoxylate hydrochloride and about 0.001 mg of atropine sulfate per mL.

Assay preparation—Transfer an accurately measured volume of the Oral Solution, equivalent to about 2.5 mg of diphenoxylate hydrochloride, based on the label claim, to a 25-mL volumetric flask, wash inside of the pipet with small portions of dehydrated alcohol, add the washings to the flask, dilute with dehydrated alcohol to volume, and mix. Pass a portion of the solution obtained through a 0.45-µm PTFE filter, discarding the first few mL, and use the clear filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L10. The flow rate is about 1.7 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.35 for atropine and 1.0 for diphenoxylate; the resolution, *R,* between atropine and diphenoxylate is not less than 5.0; the tailing factor is not more than 1.5 for atropine; and the relative standard deviation for replicate injections is not more than 2.0% for diphenoxylate and not more than 5.0% for atropine. [Note—If a significant tailing of the diphenoxylate peak is observed (greater than 2.5), it is recommended to maintain the column temperature at 25°, to stabilize the system.]

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$) in the portion of Oral Solution taken by the formula:

$$25C_D(r_U/r_S)$$

in which 25 is the volume, in mL, of the *Assay preparation;* C_D is the concentration, in mg per mL, of USP Diphenoxylate Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the diphenoxylate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Calculate the quantity, in mg, of atropine sulfate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$] in the portion of Oral Solution taken by the formula:

$$(▲694.84/676.82▲_{(ERR\ 1\text{-}Jul\text{-}2020)})(25)C_A(r_U/r_S)$$

in which ▲694.84▲ (ERR 1-Jul-2020) and ▲676.82▲ (ERR 1-Jul-2020) are the molecular weights of atropine sulfate monohydrate and anhydrous atropine sulfate, respectively; 25 is the volume, in mL, of the *Assay preparation;* C_A is the concentration, in mg per mL, of USP Atropine Sulfate RS in the *Standard preparation;* and r_U and r_S are the atropine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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

Topic/Question	Contact	Expert Committee
DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE ORAL SOLUTION	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 31(6)

Current DocID: GUID-C41867A6-F713-4D3E-A9E2-C771BFBE56D3_2_en-US
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