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Diphenoxylate Hydrochloride and Atropine Sulfate Tablets

» Diphenoxylate Hydrochloride and Atropine Sulfate Tablets contain not less than 90.0 percent and not more than 110.0 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 well-closed, 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*.

Dissolution ⟨711⟩—
Medium: 0.2 M acetic acid; 500 mL.
Apparatus 1: 150 rpm.
Time: 45 minutes.
Determine the amount of $C_{30}H_{32}N_2O_2 \cdot HCl$ dissolved by employing the following method.
Mobile phase—Prepare a suitable degassed mixture of acetonitrile and 0.05 M monobasic potassium phosphate (65:35).
Standard solution—Dissolve an accurately weighed quantity of USP Diphenoxylate Hydrochloride RS in methanol to obtain a solution having a known concentration of about 250 µg per mL. Pipet 10 mL of this solution into a 500-mL volumetric flask, dilute with *Dissolution Medium* to volume, mix, and filter.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 3.9-mm × 30-cm column that contains packing L11. The flow rate is about 1.0 mL per minute. Chromatograph replicate injections of the *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation is not more than 2.0%.
Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and of filtered portions of the solution under test into the chromatograph, record the chromatograms, measure the response for the major peak, and determine the amount of $C_{30}H_{32}N_2O_2 \cdot HCl$ dissolved.
Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{30}H_{32}N_2O_2 \cdot HCl$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements for *Content uniformity* with respect to diphenoxylate hydrochloride.

Change to read:

Assay—
Diluent—Use a mixture of acetonitrile and water (1:1).
Solution A—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 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 and 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 *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* 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 *Diluent,* and sonicate to dissolve. Accurately add 5.0 mL of *Atropine stock preparation,* and mix. Allow the solution to reach room temperature, and then dilute with *Diluent* 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 counted number of Tablets, equivalent to about 25 mg of diphenoxylate hydrochloride, based on the label claim, to a 250-mL volumetric flask, add approximately 100 mL of *Diluent,* and shake by mechanical means for at least 15 minutes or until the Tablets are completely disintegrated. Sonicate for an additional 15 minutes, allow the solution to reach room temperature, dilute with *Diluent* 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 Tablets taken by the formula:

$$250C_D(r_U/r_S)$$

in which 250 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 the Tablets taken by the formula:

$$(▲694.84/676.82▲_{(ERR\ 1\text{-}Jul\text{-}2020)})(250)C_A(r_U/r_S)$$

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; 250 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 TABLETS	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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