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Diphenhydramine and Pseudoephedrine Capsules

» Diphenhydramine and Pseudoephedrine Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

Packaging and storage—Preserve in tight containers.

Labeling—Label Capsules to state both the contents of the active moieties and the contents of the salts used in formulating the article.

USP Reference standards ⟨11⟩—
USP Diphenhydramine Hydrochloride RS
USP Pseudoephedrine Hydrochloride RS

Identification—

A: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

B: *Developing solvent*—Prepare a mixture of acetonitrile, methylene chloride, and *n*-propylamine (56:40:4).

Standard solution—Dissolve about 12.5 mg of USP Diphenhydramine Hydrochloride RS and 30 mg of USP Pseudoephedrine Hydrochloride RS in 5.0 mL of water in a 50-mL centrifuge tube.

Test solution—Transfer an amount of Capsule contents, equivalent to about 12.5 mg of diphenhydramine hydrochloride and about 30.0 mg of pseudoephedrine hydrochloride, to a 50-mL centrifuge tube. Add 5.0 mL of water, and shake.

Procedure—To each centrifuge tube add 5.0 mL of a saturated solution of sodium carbonate and 10 mL of methylene chloride. Insert the stoppers into the tubes and shake for about 1 minute. Centrifuge at about 2000 rpm for about 10 minutes until the layers are well separated. Draw off and discard the top layer. Add 5 g of anhydrous sodium sulfate to the remaining solution, insert the stopper tightly, and shake. Separately apply 30 µL (3 × 10 µL) each of the *Test solution* and the *Standard solution* to a suitable unactivated thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel mixture (see *Chromatography* ⟨621⟩) and allow the spots to dry. Develop the chromatograms in a paper lined chromatographic chamber equilibrated with the *Developing solvent* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate, air-dry, place the plate in an iodine chamber, and allow to develop over several hours: the R_F values of the principal spots obtained from the *Test solution* correspond to those obtained from the *Standard solution*.

Dissolution, *Procedure for a Pooled Sample* ⟨711⟩—
Medium: water, 900 mL.
Apparatus 1: 100 rpm.
Time: 30 minutes.
Procedure—Inject a measured volume (about 50 µL) of a filtered portion of the solution under test into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Determine the quantities of $C_{17}H_{21}NO \cdot HCl$ and of $C_{10}H_{15}NO \cdot HCl$ dissolved by employing the procedures set forth in the *Assay*, making any necessary modifications.
Tolerances—Not less than 75% *(Q)* of the labeled amounts of $C_{17}H_{21}NO \cdot HCl$ and of $C_{10}H_{15}NO \cdot HCl$ are dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Related compounds—
Mobile phase—Prepare as directed in the *Assay*.
Diluting solution—Prepare a mixture of water, acetonitrile and methanol (64:26:10).
Standard solution—Transfer accurately weighed quantities of about 5 mg each of benzhydrol and benzophenone to a 500-mL volumetric flask, dissolve in *Diluting solution*, using heat and sonication if necessary, dilute with *Diluting solution* to volume, and mix. Dilute 5.0 mL of this solution quantitatively with *Diluting solution* to 25.0 mL, mix, and filter.
Test solution—Transfer 10 Capsules to a 500-mL volumetric flask, add about 350 mL of *Diluting solution*, sonicate in warm water at about 40° to effect dissolution, and cool. Dilute with *Diluting solution* to volume, and mix. Dilute 5.0 mL of this solution with *Diluting solution* to 25.0 mL, mix, and filter.
Resolution solution—Prepare a solution in *Diluting solution* containing about 2 µg each of benzhydrol and benzophenone, and 100 µg of USP Diphenhydramine Hydrochloride RS, per mL.

Chromatographic system—Proceed as directed for *Chromatographic system* under *Assay*. Chromatograph 50 µL of the *Resolution solution:* the resolution, *R,* between benz hydrol and diphenhydramine is not less than 1.3 and the resolution, *R,* between diphenhydramine and benzophenone is not less than 2.0.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution,* and record the areas of the benzhydrol and benzophenone peaks. Calculate the amounts of benzhydrol and benzophenone in the Capsules taken by the formula:

$$C(r_U/r_S)$$

in which C is the concentration of either benzhydrol or benzophenone, in µg per mL, in the *Standard solution,* and r_U and r_S are the areas of the corresponding analyte peaks obtained from the *Test solution* and the *Standard solution,* respectively: the sum of the amounts of benzhydrol and benzophenone does not exceed 2% (w/w) of the diphenhydramine hydrochloride.

Assay—

Aqueous solution—Dissolve 1.7 g of sodium 1-heptanesulfonate and 0.8 mL of triethylamine in about 800 mL of water, adjust with glacial acetic acid to a pH of 3.3 ± 0.05, dilute with water to 1 L, mix, and filter.

Mobile phase—Prepare a filtered and degassed mixture of *Aqueous solution*, acetonitrile, and methanol (64:26:10). Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Standard preparation—Transfer about 25 mg of USP Diphenhydramine Hydrochloride RS, accurately weighed, to a 100-mL volumetric flask. Add 25*J* mg of USP Pseudoephedrine Hydrochloride RS, accurately weighed, *J* being the ratio of the labeled amount, in mg, of pseudoephedrine hydrochloride to the labeled amount, in mg, of diphenhydramine hydrochloride per capsule, dissolve in 0.5% glacial acetic acid, dilute with 0.5% glacial acetic acid to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with 0.5% glacial acetic acid to volume, and mix.

Assay preparation—Remove as completely as possible, the contents of not less than 10 Capsules, and weigh accurately. Mix the combined contents, and transfer an accurately weighed portion of the powder, equivalent to about 25 mg of diphenhydramine hydrochloride, to a 100-mL volumetric flask. Dissolve in 0.5% glacial acetic acid, dilute with 0.5% glacial acetic acid to volume, mix, and filter. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with 0.5% glacial acetic acid to volume, and mix.

Chromatographic system—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the resolution, *R,* between the pseudoephedrine and diphenhydramine peaks is not less than 3.0. For each analyte peak, the tailing factor is not greater than 2.0, and the relative standard deviation for replicate injections is not greater than 2.0%.

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 peak areas for the two analytes. The relative retention times are about 1.0 for pseudoephedrine and 3.0 for diphenhydramine. Calculate the quantity, in mg, of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) in the portion of Capsules taken by formula:

$$C(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Diphenhydramine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the quantity, in mg, of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Capsules taken by the same formula changing the terms to refer to pseudoephedrine hydrochloride.

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

Topic/Question	Contact	Expert Committee
DIPHENHYDRAMINE AND PSEUDOEPHEDRINE CAPSULES	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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