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Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine

» Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of acetaminophen ($C_8H_9NO_2$), chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$), and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) or pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$].

[Note—The heading of this monograph does not constitute the official title. It is not intended that the name described herein be recognized as the official title or the common or usual name. The name for each article encompassed by this monograph shall be composed of the names of the active ingredients contained therein, as well as the quantitative amount of each active ingredient, and a statement of the function (or purpose) of the ingredient in the article.]

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—

USP Acetaminophen RS
USP Chlorpheniramine Maleate RS
USP Dextromethorphan Hydrobromide RS
USP Pseudoephedrine Hydrochloride RS
USP Pseudoephedrine Sulfate RS

Labeling—The label for each article encompassed by this monograph bears a name composed of the active ingredients. The label states the name and quantity of each active ingredient and indicates its function (or purpose) in the article. When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Identification—

A: If pseudoephedrine hydrochloride or pseudoephedrine sulfate is claimed in the labeling to be present, the chromatogram of the *Assay preparation*, obtained as directed in the *Assay for pseudoephedrine hydrochloride* or the *Assay for pseudoephedrine sulfate*, exhibits a major peak for pseudoephedrine, the retention time of which corresponds to that exhibited by the *Standard preparation*.

B: If acetaminophen is claimed in the labeling to be present, the chromatogram of the *Assay preparation*, obtained as directed in the *Assay for acetaminophen*, exhibits a major peak for acetaminophen, the retention time of which corresponds to that exhibited by the *Standard preparation*.

C: If chlorpheniramine maleate is claimed in the labeling to be present, the chromatogram of the *Assay preparation*, obtained as directed in the *Assay for chlorpheniramine maleate*, exhibits a major peak for chlorpheniramine, the retention time of which corresponds to that exhibited by the *Standard preparation*.

D: If dextromethorphan hydrobromide is claimed in the labeling to be present, the chromatogram of the *Assay preparation*, obtained as directed in the *Assay for dextromethorphan hydrobromide*, exhibits a major peak for dextromethorphan, the retention time of which corresponds to that exhibited by the *Standard preparation*.

Dissolution, *Procedure for a Pooled Sample* ⟨711⟩—

Test 1—

Medium: pH 5.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Test preparation—Mix 9.0 mL of a filtered portion of the solution under test with 1.0 mL of 1% phosphoric acid solution.

Procedure—Determine the amounts of pseudoephedrine hydrochloride or pseudoephedrine sulfate (as appropriate), acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide dissolved, employing the procedures set forth in the *Assay for pseudoephedrine hydrochloride* or *Assay for pseudoephedrine sulfate*, *Assay for acetaminophen*, *Assay for chlorpheniramine maleate*, and *Assay for dextromethorphan hydrobromide*, respectively, making any necessary volumetric adjustments.

Tolerances—Not less than 75% *(Q)* of the labeled amounts of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) or pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$], acetaminophen ($C_8H_9NO_2$), chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), and dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$) are dissolved in 45 minutes.

Test 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: water; 900 mL.

Apparatus, Time, Test preparation, Procedure, and *Tolerances*— Proceed as directed for *Test 1*.

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

Assay for pseudoephedrine hydrochloride (where pseudoephedrine hydrochloride is the salt form used, if present in the formulation)—

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (60:40) containing 0.34 g of monobasic potassium phosphate, 0.3 g of triethylamine hydrochloride, 0.15 g of sodium lauryl sulfate, and 0.1 mL of phosphoric acid in each 100 mL of solution. Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Standard preparation—Dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in water to obtain a solution having a known concentration of about 3.0 mg per mL. Transfer 1.0 mL of this solution to a 25-mL volumetric flask, add 2.5 mL of methanol, dilute with 0.1% phosphoric acid to volume, and mix.

Chlorpheniramine standard preparation—Prepare as directed for the *Standard preparation* in the *Assay for chlorpheniramine maleate*.

Dextromethorphan standard preparation—Prepare as directed for the *Standard preparation* in the *Assay for dextromethorphan hydrobromide*.

System suitability solution 1 (for Tablets that contain either all the four ingredients or a combination of three containing chlorpheniramine salt)—Mix equal volumes of the *Standard preparation* and the *Chlorpheniramine standard preparation*.

System suitability solution 2 (for Tablets that contain no chlorpheniramine salt)—Mix equal volumes of the *Standard preparation* and the *Dextromethorphan standard preparation*.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 6 mg of pseudoephedrine hydrochloride, to a 50-mL volumetric flask. Add 5 mL of methanol, and sonicate to disperse the powder. Dilute with 0.1% phosphoric acid to volume, mix, and filter.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 15-cm column that contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the pseudoephedrine peak is not greater than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%. Separately inject about 10 µL of *System suitability solution 1* or *System suitability solution 2*, as appropriate. The resolution, *R,* between pseudoephedrine and chlorpheniramine or between pseudoephedrine and dextromethorphan is not less than 2.0.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the pseudoephedrine peaks. Calculate the quantity, in mg, of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Tablets taken by the formula:

$$50C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Pseudoephedrine Hydrochloride RS in the *Standard preparation,* and r_U and r_S are the pseudoephedrine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for pseudoephedrine sulfate (where pseudoephedrine sulfate is the salt form used, if present in the formulation)—

Mobile phase, *Chlorpheniramine standard preparation*, *Dextromethorphan standard preparation*, *System suitability solutions*, and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride*.

Standard preparation—Dissolve an accurately weighed quantity of USP Pseudoephedrine Sulfate RS in water to obtain a solution having a known concentration of about 3.0 mg per mL. Transfer 2.0 mL of this solution to a 25-mL volumetric flask, add 2.5 mL of methanol, dilute with 0.1% phosphoric acid to volume, and mix.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 12 mg of pseudoephedrine sulfate, to a 50-mL volumetric flask. Add 5 mL of methanol, and sonicate to disperse the powder. Dilute with 0.1% phosphoric acid to volume, mix, and filter.

Procedure—Proceed as directed for *Procedure* in the *Assay for pseudoephedrine hydrochloride*. Calculate the quantity, in mg, of pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$] in the portion of Tablets taken by the formula:

$$50C(r_U/r_S)$$

in which the terms are as defined therein, pseudoephedrine sulfate being substituted for pseudoephedrine hydrochloride.

Assay for acetaminophen *(if present)*—

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and glacial acetic acid (79:20:1). Make adjustments, if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Standard preparation—Transfer about 50 mg of USP Acetaminophen RS, accurately weighed, to a 100-mL volumetric flask. Add 4 mL of methanol, and mix until solution is complete. Dilute with 0.1% phosphoric acid to volume, and mix.

Assay preparation—Weigh and powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of acetaminophen, to a 50-mL volumetric flask. Add about 7.5 mL of methanol, and sonicate to disperse the powder. Add 0.5 mL of phosphoric acid, dilute with water to volume, mix, and filter. Transfer 25.0 mL of the filtered solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak

responses as directed for *Procedure:* the tailing factor for the acetaminophen peak is not greater than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the acetaminophen peaks. Calculate the quantity, in mg, of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets taken by the formula:

$$200C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Acetaminophen RS in the *Standard preparation;* and r_U and r_S are the acetaminophen peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for chlorpheniramine maleate *(if present)*—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride*.

Standard preparation—Dissolve an accurately weighed quantity of USP Chlorpheniramine Maleate RS in water to obtain a solution having a known concentration of about 0.8 mg per mL. Quantitatively dilute a portion of this solution with 0.1% phosphoric acid to obtain a solution having a known concentration of about 8 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2 mg of chlorpheniramine maleate, to a 250-mL volumetric flask. Add 25 mL of methanol, and sonicate to disperse the powder. Add 1 mL of phosphoric acid, dilute with water to volume, mix, and filter.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the chlorpheniramine peaks. Calculate the quantity, in mg, of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) in the portion of Tablets taken by the formula:

$$250C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Chlorpheniramine Maleate RS in the *Standard preparation;* and r_U and r_S are the peak responses for chlorpheniramine obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for dextromethorphan hydrobromide *(if present)*—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride*.

Standard preparation—Dissolve an accurately weighed quantity of USP Dextromethorphan Hydrobromide RS in water to obtain a solution having a known concentration of about 0.6 mg per mL. Quantitatively dilute a portion of this solution with 0.1% phosphoric acid to obtain a solution having a known concentration of about 0.06 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6 mg of dextromethorphan hydrobromide, to a 100-mL volumetric flask. Add 10 mL of methanol, and sonicate to disperse the powder. Add 0.4 mL of phosphoric acid, dilute with water to volume, mix, and filter.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the dextromethorphan peaks. Calculate the quantity, in mg, of dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$) in the portion of Tablets taken by the formula:

$$(370.33/352.32)(100C)(r_U/r_S)$$

in which 370.33 and 352.32 are the molecular weights of dextromethorphan hydrobromide monohydrate and anhydrous dextromethorphan hydrobromide, respectively; C is the concentration, in mg per mL, of USP Dextromethorphan Hydrobromide RS in the *Standard preparation;* and r_U and r_S are the dextromethorphan 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
TABLETS CONTAINING AT LEAST THREE OF THE FOLLOWING--ACETAMINOPHEN AND SALTS OF CHLORPHENIRAMINE, DEXTROMETHORPHAN, AND PSEUDOEPHEDRINE	Documentary Standards Support	SM22020 Small Molecules 2

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