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Guaifenesin and Codeine Phosphate Oral Solution

» Guaifenesin and Codeine Phosphate Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of guaifenesin ($C_{10}H_{14}O_4$) and codeine phosphate ($C_{18}H_{21}NO_4 \cdot H_3PO_4 \cdot ½H_2O$).

Packaging and storage—Preserve in tight, light-resistant containers, at controlled room temperature.

USP Reference standards ⟨11⟩—

USP Codeine Phosphate RS
USP Guaifenesin RS

Identification—

A: The retention time of the codeine peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for codeine phosphate.*

B: The retention time of the guaifenesin peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for guaifenesin.*

Uniformity of dosage units ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.

Deliverable volume ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.

pH ⟨791⟩**:** between 2.3 and 3.0 if it contains alcohol, 5.0 to 5.5 if it does not contain alcohol.

Alcohol Determination ⟨611⟩ *(if present)*—

Standard stock solution—Dilute 10.0 mL of dehydrated alcohol with water to 100.0 mL.

Internal standard solution—Dilute 10 mL of acetone with water to 100 mL.

Standard preparation—Transfer 10.0 mL of *Standard stock solution* and 8.0 mL of *Internal standard solution* to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 250-mL volumetric flask, dilute with water to volume, and mix. This solution contains 0.02% (v/v) of alcohol.

Test preparation—Transfer 25/*k* mL of Oral Solution (*k* being the labeled percentage [v/v] of C_2H_5OH in the Oral Solution), accurately measured, to a 25-mL volumetric flask, add 2.0 mL of *Internal standard solution,* dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 250-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 1.8-m column that contains 5% liquid phase G16 on 100- to 120-mesh support S1A, and is programmed to maintain the column temperature at 50° for 5 minutes after injection, to increase to 100° at the rate of 20° per minute, to maintain the temperature at 100° for 2 minutes, and then to return to 50° before the next injection. The injection port is maintained at about 200°, and the detector block is maintained at about 250°. The carrier gas is dry helium flowing at a rate of about 30 mL per minute. Chromatograph the *Standard preparation,* and record the chromatogram as directed for *Procedure:* the relative retention times are about 0.3 for acetone and 1.0 for alcohol (C_2H_5OH); the resolution, *R,* between the acetone and alcohol peaks is not less than 2; the tailing factors for the acetone and alcohol peaks are not more than 1.5; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 2 µL) of the *Test preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage (v/v) of alcohol (C_2H_5OH) in the portion of Oral Solution taken by the formula:

$$(1250P/V)(R_U/R_S)$$

in which P is the percentage (v/v) of alcohol (C_2H_5OH) in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken to prepare the *Test preparation;* and R_U and R_S are the peak response ratios of alcohol to that of acetone obtained from the *Test preparation* and the *Standard preparation,* respectively: between 90.0% and 115.0% of the labeled amount of alcohol (C_2H_5OH) is found.

Assay for codeine phosphate—

Internal standard solution—Place about 45 mg of hydrocodone bitartrate in a flask containing about 5 mL of water, add 1 mL of 0.5 N sodium hydroxide and 50 mL of chloroform, insert the stopper into the flask, and shake by mechanical means for about 20 minutes. Allow the layers to separate, and filter the chloroform layer.

Standard preparation—Prepare a Standard stock solution of USP Codeine Phosphate RS in 0.1 N hydrochloric acid having a known concentration of about 2 mg per mL. Transfer 5.0 mL of this Standard stock solution to a suitable flask. Add 2 mL of 2.5 N sodium hydroxide, 8.0 mL of *Internal standard solution,* and 40 mL of chloroform, insert the stopper, and shake by mechanical means for 1 hour. Allow the layers to separate, and collect the chloroform layer.

Assay preparation—Transfer an accurately measured volume of Oral Solution, equivalent to about 10 mg of codeine phosphate, to a 200-mL flask containing about 5 mL of water, and swirl. Add 2 mL of 2.5 N sodium hydroxide, 8.0 mL of *Internal standard solution,* and 40 mL of chloroform, insert the stopper, and shake by mechanical means for 1 hour. Allow the layers to separate, and collect the chloroform layer.

Chromatographic system (see *Chromatography ⟨621⟩*)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 0.6-m column that contains 3% liquid phase G3 on 100- to 120-mesh support S1A, and is stabilized for isothermal operation. The column temperature is maintained at about 210°, the injection port temperature at about 250°, and the detector block temperature at about 300°. The carrier gas is dry helium flowing at a rate of about 25 mL per minute. Chromatograph the *Standard preparation,* and record the chromatogram as directed for *Procedure:* the relative retention times are about 0.75 for codeine and 1.0 for hydrocodone; the resolution, *R,* between the codeine and hydrocodone peaks is not less than 1; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 2 µL) of the *Assay preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of codeine phosphate hemihydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) in each mL of the Oral Solution taken by the formula:

$$(406.37/397.37)(5C/V)(R_U/R_S)$$

in which 406.37 and 397.37 are the molecular weights of codeine phosphate hemihydrate and anhydrous codeine phosphate, respectively; *C* is the concentration, in mg per mL, of USP Codeine Phosphate RS in the Standard stock solution used to prepare the *Standard preparation; V* is the volume, in mL, of Oral Solution taken to prepare the *Assay preparation;* and R_U and R_S are the peak response ratios of the codeine peak to the hydrocodone peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for guaifenesin—

Internal standard solution—Prepare a solution of dipropyl phthalate in chloroform containing about 12.5 mg per mL.

Standard preparation—Prepare a Standard stock solution of USP Guaifenesin RS in 0.1 N hydrochloric acid having a known concentration of about 4 mg per mL. Transfer 5.0 mL of this Standard stock solution to a suitable glass-stoppered flask, add 2 mL of 2.5 N sodium hydroxide, 8.0 mL of *Internal standard solution,* and 40 mL of chloroform, insert the stopper, and shake by mechanical means for 1 hour. Allow the layers to separate, and collect the chloroform layer. Extract the aqueous layer with two 20-mL portions of chloroform, and combine the three chloroform extracts. Transfer 5.0 mL of the combined chloroform extracts to a suitable glass-stoppered flask, add 1 mL of trifluoroacetic anhydride, and allow to stand for not less than 1 hour.

Assay preparation—Transfer an accurately measured volume of Oral Solution, equivalent to about 20 mg of guaifenesin, to a 200-mL flask containing about 5 mL of water, and swirl. Add 2 mL of 2.5 N sodium hydroxide, 8.0 mL of *Internal standard solution,* and 40 mL of chloroform, insert the stopper, and shake by mechanical means for 1 hour. Allow the layers to separate, and collect the chloroform layer. Extract the aqueous layer with two 20-mL portions of chloroform, and combine the three chloroform extracts. Transfer 5.0 mL of the combined chloroform extracts to a suitable glass-stoppered flask, add 1 mL of trifluoroacetic anhydride, and allow to stand for not less than 1 hour.

Chromatographic system (see *Chromatography ⟨621⟩*)—The gas chromatograph is equipped with a flame-ionization detector and a 4-mm × 1.2-m column that contains 3% liquid phase G6 on 100- to 120-mesh support S1A. The column temperature is maintained at about 170°, the injection port temperature is maintained at about 250°, and the detector block temperature is maintained at about 300°. The carrier gas is dry helium flowing at a rate of about 45 mL per minute. Chromatograph the *Standard preparation,* and record the chromatogram as directed for *Procedure:* the relative retention times are about 0.6 for the trifluoroacetyl derivative of guaifenesin and 1.0 for the trifluoroacetyl derivative of dipropyl phthalate; the resolution, *R,* between the guaifenesin and dipropyl phthalate peaks is not less than 1; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Assay preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of guaifenesin ($C_{10}H_{14}O_4$) in the portion of Oral Solution taken by the formula:

$$(W/V)(R_U/R_S)$$

in which *W* is the quantity, in mg, of USP Guaifenesin RS taken to prepare the *Standard preparation; V* is the volume, in mL, of Oral Solution taken to prepare the *Assay preparation;* and R_U and R_S are the peak response ratios of the guaifenesin peak to the dipropyl phthalate peak 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
GUAIFENESIN AND CODEINE PHOSPHATE ORAL SOLUTION	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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