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Acetaminophen and Codeine Phosphate Oral Suspension

DEFINITION

Acetaminophen and Codeine Phosphate Oral Suspension is a suspension of Acetaminophen and Codeine Phosphate in a suitable aqueous vehicle. It contains NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$) and codeine phosphate hemihydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$).

IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B. Thin-Layer Chromatography**

Standard solution: 12 mg/mL each of USP Acetaminophen RS and USP Codeine Phosphate RS in methanol

Sample solution: Transfer a volume of Oral Suspension, equivalent to 12 mg of codeine phosphate, to a separator. Add 1 mL of ammonium hydroxide and 5 mL of methylene chloride, shake for 1 min, and allow the layers to separate. Use the clear lower layer.

Chromatographic system

(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Developing solvent system: Methanol and ammonium hydroxide (49:1)

Application volume: 10 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Develop the chromatogram in the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Locate the spots on the plate by examination under short-wavelength UV light.

Acceptance criteria: The R_F values of the two principal spots of the *Sample solution* correspond to those of the *Standard solution*.

ASSAY

- **Procedure**

Diluent: Methanol and 0.01 N sodium hydroxide (30:70)

Mobile phase: Dissolve 4.9 g of monobasic potassium phosphate in 900 mL of water, adjust with phosphoric acid to a pH of 3.9, and add 216 mg of sodium 1-octanesulfonate. Add 100 mL of acetonitrile, and filter.

Codeine phosphate standard stock solution: 0.5 mg/mL of USP Codeine Phosphate RS in *Diluent*

Standard stock solution: Transfer a quantity of 5*J* mg of USP Acetaminophen RS (*J* being the ratio of the labeled amount, in mg, of acetaminophen to the labeled amount, in mg, of codeine phosphate hemihydrate) and 10.0 mL of *Codeine phosphate standard stock solution* to a 100-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume.

System suitability stock solution: 0.02 mg/mL of sodium benzoate and 0.03 mg/mL of methylparaben in *Diluent*

System suitability solution: Transfer 10.0 mL of the *System suitability stock solution* to a 50-mL volumetric flask, add 10.0 mL of *Standard stock solution*, and dilute with *Mobile phase* to volume.

Standard solution: 0.01 mg/mL of USP Codeine Phosphate RS and 0.01*J* mg/mL of USP Acetaminophen RS in *Mobile phase*. Prepare by diluting 10.0 mL of the *Standard stock solution* with *Mobile phase* to 50 mL in a volumetric flask.

Sample stock solution: Nominally 0.5 mg/mL of acetaminophen and 0.5 mg/mL of codeine phosphate hemihydrate in *Diluent* prepared as follows. Transfer a measured volume of well-mixed Oral Suspension, equivalent to 50 mg of acetaminophen, to a 100-mL volumetric flask. Add 50 mL of *Diluent*, and mix by mechanical means for 30 min. Dilute with *Diluent* to volume. Foaming may be minimized by adding a few drops of acetonitrile before diluting with *Diluent* to volume. Centrifuge a portion of this mixture.

Sample solution: Dilute 10.0 mL of the clear supernatant from the *Sample stock solution* with *Mobile phase* to 50 mL in a volumetric flask.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L11

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for acetaminophen, benzoate, codeine, and methylparaben are about 0.25, 0.5, 1.0, and 1.3, respectively.]

Suitability requirements

Resolution: NLT 2 between each pair of adjacent peaks, *System suitability solution*

Tailing factor: NMT 2 for each analyte peak, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) in the portion of Oral Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of acetaminophen from the *Sample solution*

r_S = peak response of acetaminophen from the *Standard solution*

C_S = concentration of USP Acetaminophen RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of acetaminophen in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

Calculate the percentage of the labeled amount of codeine phosphate hemihydrate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) in the portion of Oral Suspension taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of codeine from the *Sample solution*

r_S = peak response of codeine from the *Standard solution*

C_S = concentration of USP Codeine Phosphate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of codeine phosphate hemihydrate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of codeine phosphate hemihydrate, 406.37

M_{r2} = molecular weight of anhydrous codeine phosphate, 397.37

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Uniformity of Dosage Units** ⟨905⟩

For single-unit containers

Acceptance criteria: Meets the requirements

• **Deliverable Volume** ⟨698⟩

For multiple-unit containers

Acceptance criteria: Meets the requirements

IMPURITIES

• **4-Aminophenol in Acetaminophen-Containing Drug Products** ⟨227⟩**:** Meets the requirements

SPECIFIC TESTS

• **pH** ⟨791⟩**:** 4.0–6.1

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

• **USP Reference Standards** ⟨11⟩

USP Acetaminophen RS

USP Codeine Phosphate RS

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

Topic/Question	Contact	Expert Committee
ACETAMINOPHEN AND CODEINE PHOSPHATE ORAL SUSPENSION	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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