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Acetaminophen and Codeine Phosphate Oral Solution

DEFINITION

Acetaminophen and Codeine Phosphate Oral Solution 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 solutions* correspond to those of the *Standard solutions*, as obtained in the *Assays* for *Acetaminophen* and *Codeine Phosphate*.

• **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 Solution, 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.

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

Chromatographic system

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

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

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

• **Acetaminophen**

Mobile phase: Methanol and water (3:7)

Standard solution: 0.48 mg/mL of USP Acetaminophen RS in *Mobile phase*

Sample solution: Nominally 0.48 mg/mL of acetaminophen in *Mobile phase*, prepared by adding a volume of Oral Solution, equivalent to 120 mg of acetaminophen, to a 250-mL volumetric flask. Dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

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 Solution 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*

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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%

• **Codeine Phosphate**

Mobile phase: Dissolve 4.44 g of docusate sodium in 1000 mL of a mixture of methanol, tetrahydrofuran, phosphoric acid, and water (600:40:1:360) with stirring, and pass through a membrane filter of 0.45-µm or finer pore size.

Diluent: Methanol and water (3:7)

Standard solution: 0.12 mg/mL of USP Codeine Phosphate RS in *Diluent*

Sample solution: Nominally 0.12 mg/mL of codeine phosphate hemihydrate in *Diluent*, prepared by adding a volume of Oral Solution, equivalent to 12 mg of codeine phosphate hemihydrate, to a 100-mL volumetric flask. Dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

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 Solution 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 phosphate from the *Sample solution*

r_S = peak response of codeine phosphate 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 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

• **Alcohol Determination ⟨611⟩, *Method II*** (if present)**:** 90.0%–120.0% of the labeled quantity of alcohol (C_2H_5OH), acetone being used as the internal standard

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

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