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Acetaminophen and Codeine Phosphate Tablets

DEFINITION

Acetaminophen and Codeine Phosphate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$) and codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$).

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 quantity of finely powdered Tablets, equivalent to 12 mg of codeine phosphate, to a separator. Add 5 mL of water, 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⟩, General Procedures, Thin-Layer Chromatography*.)

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 10 µL

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

Analysis

Samples: *Standard solution* and *Sample solution*

Allow the spots to dry after applying each sample to the adsorbent. Develop the chromatogram in the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. 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**

Solution A: Dissolve 2.04 g of monobasic potassium phosphate in about 950 mL of water. Add 2 mL of triethylamine, adjust with phosphoric acid to a pH of 2.35, and dilute with water to 1000 mL.

Mobile phase: Methanol and *Solution A* (8:92)

Codeine phosphate standard stock solution: 0.3 mg/mL of USP Codeine Phosphate RS in *Mobile phase*

Standard solution: 0.3 mg/mL of USP Acetaminophen RS and 0.3*J* mg/mL of codeine phosphate in *Mobile phase*, prepared as follows. Transfer an appropriate amount of USP Acetaminophen RS and a suitable volume (multiplied by *J*) of *Codeine phosphate standard stock solution* (*J* being the ratio of the labeled amount, in mg, of codeine phosphate to that of acetaminophen) to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume.

Sample stock solution: Nominally 3.0 mg/mL of acetaminophen and 3.0*J* mg/mL of codeine phosphate (equivalent to 2.93*J* mg/mL of anhydrous codeine phosphate) in *Mobile phase*, prepared as follows. Transfer a portion of the powder (equivalent to 300 mg of acetaminophen, from NLT 20 finely powdered Tablets) to a 100-mL volumetric flask. Add 75 mL of *Mobile phase*, and sonicate for 10 min. Dilute with *Mobile phase* to volume.

Sample solution: Dilute 5.0 mL of the *Sample stock solution* with *Mobile phase* to 50 mL, and pass a portion of the solution through a suitable filter of 1-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 30 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between acetaminophen and codeine

Relative standard deviation: NMT 2.0% for acetaminophen; NMT 3.0% for codeine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets 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)

Calculate the percentage of the labeled amount of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) in the portion of Tablets 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 in the *Sample solution* (mg/mL)

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

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

Acceptance criteria

Acetaminophen: 90.0%–110.0%

Codeine phosphate: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Analysis: Determine the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) and codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) dissolved by using the method set forth in the *Assay*, except use 0.01 N hydrochloric acid to prepare the *Codeine phosphate standard stock solution* and to make any other necessary volumetric adjustments.

Tolerances: NLT 75% (*Q*) of the labeled amount of acetaminophen ($C_8H_9NO_2$) and codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) is dissolved.

Change to read:

• **Uniformity of Dosage Units** ⟨905⟩: ▲Meet the requirements▲ (CN 1-Aug-2023)

Procedure for content uniformity

Solution A, Mobile phase, Codeine phosphate standard stock solution, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Sample stock solution: Transfer 1 Tablet to a 100-mL volumetric flask. Add 75 mL of *Mobile phase*, and sonicate for 10 min. Dilute with *Mobile phase* to volume.

Sample solution: Dilute 5.0 mL of the *Sample stock solution* with *Mobile phase* to 50 mL, and pass a portion through a suitable filter of 1-µm pore size.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in mg, of acetaminophen ($C_8H_9NO_2$) in the Tablet taken:

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

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)

F = dilution volume, 1000 mL

Calculate the quantity, in mg, of codeine phosphate ($C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot ½H_2O$) in the Tablet taken:

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

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)

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

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

F = dilution volume, 1000 mL

▲▲ (CN 1-Aug-2023)

IMPURITIES

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

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 TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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