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Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets

DEFINITION

Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$), diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$), and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

IDENTIFICATION

• **A.** The retention time of the acetaminophen peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Acetaminophen*.

• **B.** The retention time of the diphenhydramine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Diphenhydramine Hydrochloride*.

• **C.** The retention time of the pseudoephedrine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay* for *Pseudoephedrine Hydrochloride*.

ASSAY

• **Acetaminophen**

Solution A: Transfer 6.8 g of monobasic potassium phosphate to a 1000-mL volumetric flask, and add water to dissolve. Add 2.0 mL of triethylamine, and dilute with water to volume. Adjust with phosphoric acid to a pH of 4.0.

Diluent: Acetonitrile and *Solution A* (11:89)

Mobile phase: Acetonitrile and *Solution A* (6:94)

Standard solution: 25 µg/mL of USP Acetaminophen RS, 12.5 µg/mL of USP Diphenhydramine Hydrochloride RS, and 30 µg/mL of USP Pseudoephedrine Hydrochloride RS in *Diluent*

Sample stock solution: Nominally 5 mg/mL of acetaminophen in *Diluent* prepared as follows. Transfer an amount nominally equivalent to 500 mg of acetaminophen from NLT 20 finely powdered Tablets to a 100-mL volumetric flask, add 75 mL of *Diluent*, shake, and sonicate for 15 min. Dilute with *Diluent* to volume.

Sample solution: Nominally 25 µg/mL of acetaminophen from the *Sample stock solution* in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; packing L10

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for the acetaminophen, diphenhydramine, and pseudoephedrine peaks

Relative standard deviation: NMT 2.0% determined from the acetaminophen, diphenhydramine hydrochloride, and pseudoephedrine hydrochloride responses for replicate injections

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* (µg/mL)

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

Acceptance criteria: 90.0%–110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$)

- **Diphenhydramine Hydrochloride**

Solution A, Diluent, Mobile phase, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay* for *Acetaminophen*.

Sample stock solution: Nominally 0.125 mg/mL of diphenhydramine hydrochloride in *Diluent* prepared as follows. Transfer an amount nominally equivalent to 12.5 mg of diphenhydramine hydrochloride from a portion of finely powdered Tablets (NLT 20) to a 100-mL volumetric flask, add 75 mL of *Diluent*, and sonicate for 15 min. Dilute with *Diluent* to volume.

Sample solution: Nominally 12.5 µg/mL of diphenhydramine hydrochloride from the *Sample stock solution* in *Diluent*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) in the portion of Tablets taken:

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

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

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

C_S = concentration of USP Diphenhydramine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of diphenhydramine hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$)

- **Pseudoephedrine Hydrochloride**

Solution A, Diluent, Mobile phase, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay* for *Acetaminophen*.

Sample stock solution: Nominally 0.3 mg/mL of pseudoephedrine hydrochloride in *Diluent* prepared as follows. Transfer an amount nominally equivalent to 30 mg of pseudoephedrine hydrochloride from a portion of finely powdered Tablets (NLT 20) to a 100-mL volumetric flask, add 75 mL of *Diluent*, and sonicate for 15 min. Dilute with *Diluent* to volume.

Sample solution: Nominally 30 µg/mL of pseudoephedrine hydrochloride from the *Sample stock solution* in *Diluent*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Tablets taken:

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

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

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

C_S = concentration of USP Pseudoephedrine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of pseudoephedrine hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$)

PERFORMANCE TESTS

- **Dissolution** ⟨711⟩, *Procedure, Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms, Procedure for a pooled sample for immediate-release dosage forms*

Medium: pH 5.8 phosphate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Solution A, Diluent, Mobile phase, Standard solution, and **Chromatographic system:** Proceed as directed in the *Assay* for *Acetaminophen*.

Sample solution A: Combine equal volumes of the filtered solutions, and use the pooled sample.

Sample solution B: Transfer 5.0 mL of *Sample solution A* to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume.

Analysis: Using *Sample solution A* and the *Standard solution*, and making any necessary volumetric adjustments, proceed as directed in the *Assay* for *Diphenhydramine Hydrochloride* and the *Assay* for *Pseudoephedrine Hydrochloride*, and determine the percentage of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved. Using *Sample solution B* and the *Standard solution*, and making any necessary volumetric adjustments, proceed as directed in the *Assay* for *Acetaminophen*, and determine the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved.

Tolerances: NLT 75% (*Q*) of the labeled amount of acetaminophen ($C_8H_9NO_2$), diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$), and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) is dissolved.

For Tablets labeled as chewable

Medium: pH 5.8 phosphate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 900 mL

Apparatus 2: 75 rpm

Time: 45 min

Tolerances: NLT 75% (*Q*) of the labeled amount of acetaminophen ($C_8H_9NO_2$), diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$), and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

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

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards ⟨11⟩**

USP Acetaminophen RS

USP Diphenhydramine Hydrochloride RS

USP Pseudoephedrine Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
ACETAMINOPHEN, DIPHENHYDRAMINE HYDROCHLORIDE, AND PSEUDOEPHEDRINE HYDROCHLORIDE 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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