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Acetaminophen and Diphenhydramine Citrate Tablets

DEFINITION

Acetaminophen and Diphenhydramine Citrate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$) and diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$).

IDENTIFICATION

• **A.** The retention times of the major peaks of the *Sample solution*, obtained in *Procedure 1: Acetaminophen* and for *Procedure 2: Diphenhydramine Citrate* for the *Assay*, relative to the retention times of the respective internal standards, correspond to those of the respective *Standard solution*.

ASSAY

Change to read:

• **Procedure 1: Acetaminophen**

Mobile phase: Methanol and water (40:60)

Diluent: Methanol and water▲(20:80)▲ (USP 1-Dec-2020)

Internal standard solution: 8.0 mg/mL of ▲USP Guaifenesin RS▲ (USP 1-Dec-2020) in *Diluent*

Standard stock solution: 0.5 mg/mL of USP Acetaminophen RS, prepared as follows. Transfer 50 mg of USP Acetaminophen RS to a 100-mL volumetric flask. Dissolve in 2.5 mL of methanol, and dilute with water to volume.

Standard solution: 0.02 mg/mL of acetaminophen from *Standard stock solution* and 0.8 mg/mL of guaifenesin from *Internal standard solution*, in *Mobile phase*

Sample stock solution: Nominally 0.5 mg/mL of acetaminophen prepared as follows. Transfer a portion of the powder from NLT 20 finely powdered Tablets,▲▲ (USP 1-Dec-2020) equivalent to an appropriate amount of acetaminophen, to a suitable volumetric flask. Add 25% of the total volume of methanol, and shake by mechanical means for 10 min. Dilute with water to volume.

Sample solution: Nominally 0.02 mg/mL of acetaminophen prepared as follows. Transfer 2.0 mL of *Sample stock solution* to a 50-mL volumetric flask, add 5.0 mL of *Internal standard solution*, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 35°▲▲ (USP 1-Dec-2020)

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for acetaminophen and guaifenesin are 0.5 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 6.0 between▲acetaminophen and guaifenesin▲ (USP 1-Dec-2020)

Tailing factor: NMT 2 for the▲acetaminophen peak▲ (USP 1-Dec-2020)

Relative standard deviation: NMT ▲2.0%▲ (USP 1-Dec-2020) for the peak response ratios

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 ratio of acetaminophen to the internal standard from the *Sample solution*

R_S = peak response ratio of acetaminophen to the internal standard 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%

Change to read:

• **Procedure 2: Diphenhydramine Citrate**

Diluent: Methanol and water▲(50:50)▲ (USP 1-Dec-2020)

Mobile phase: Methanol, water, and glacial acetic acid (61:38:1) containing 1.0813 g of sodium 1-octanesulfonate in each 1000 mL of solution

Internal standard solution: 8 mg/mL of ▲USP Xylometazoline Hydrochloride RS▲ (USP 1-Dec-2020) in water

Standard solution: 0.38 mg/mL of USP Diphenhydramine Citrate RS and 0.8 mg/mL of ▲USP Xylometazoline Hydrochloride RS▲ (USP 1-Dec-2020) from *Internal standard solution* in *Diluent*

Sample solution: Nominally 0.38 mg/mL of diphenhydramine citrate prepared as follows. Transfer a portion of the powder from NLT 20 finely powdered Tablets,▲▲ (USP 1-Dec-2020) equivalent to 38 mg of diphenhydramine citrate, to a 100-mL volumetric flask. Add 65 mL of *Diluent*, and shake by mechanical means for 15 min. Add 5.0 mL of *Internal standard solution*, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 265 nm

Column: 3.9-mm × 30-cm; packing L1

Column temperature: 35°▲▲ (USP 1-Dec-2020)

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for diphenhydramine▲▲ (USP 1-Dec-2020) and xylometazoline are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.5 between ▲diphenhydramine and xylometazoline▲ (USP 1-Dec-2020)

Tailing factor: NMT 1.7 for the ▲diphenhydramine▲ (USP 1-Dec-2020) peak

Relative standard deviation: NMT 2.0% for the peak response ratios

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of diphenhydramine citrate to the internal standard from the *Sample solution*

R_S = peak response ratio of diphenhydramine citrate to the internal standard from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

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

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Analysis: Calculate the percentages of the labeled amount of acetaminophen ($C_8H_9NO_2$) and diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) dissolved. ▲[Note—Proceed using *Procedure 1: Acetaminophen* and *Procedure 2: Diphenhydramine Citrate* in the *Assay*. Volumetric adjustment may be needed.]

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 900 mL

L = label claim of acetaminophen or diphenhydramine citrate (mg/Tablet)

▲ (USP 1-Dec-2020)

Tolerances: NLT 75% (*Q*) of the labeled amount of acetaminophen ($C_8H_9NO_2$) and diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) is dissolved.

Change to read:

• **Uniformity of Dosage Units** ⟨905⟩, *Content Uniformity*: Meet the requirements▲▲ (USP 1-Dec-2020)

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.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Acetaminophen RS

USP Diphenhydramine Citrate RS

▲USP Guaifenesin RS

USP Xylometazoline Hydrochloride RS▲ (USP 1-Dec-2020)

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

Topic/Question	Contact	Expert Committee
ACETAMINOPHEN AND DIPHENHYDRAMINE CITRATE 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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