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Acetaminophen, Aspirin, and Caffeine Tablets

DEFINITION

Acetaminophen, Aspirin, and Caffeine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$), aspirin ($C_9H_8O_4$), and caffeine ($C_8H_{10}N_4O_2$).

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*.

ASSAY

• **Procedure**

Inject the *Standard solution* and the *Sample solution* within 8 h of preparation.

Mobile phase: Methanol, glacial acetic acid, and water (28:3:69)

Diluent: Methanol and glacial acetic acid (95:5)

Internal standard solution: 6 mg/mL of benzoic acid in methanol

Standard stock solution: 0.25 mg/mL of USP Acetaminophen RS, 0.25*J* mg/mL of USP Aspirin RS, and 0.25*J'* mg/mL of USP Caffeine RS in *Diluent* (*J* being the ratio of the labeled amount, in milligrams, of aspirin to the labeled amount, in milligrams, of acetaminophen per Tablet; and *J'* being the ratio of the labeled amount, in milligrams, of caffeine to the labeled amount, in milligrams, of acetaminophen per Tablet)

Standard solution: 0.1 mg/mL of USP Acetaminophen RS, 0.1*J* mg/mL of USP Aspirin RS, and 0.1*J'* mg/mL of USP Caffeine RS in *Diluent*, prepared as follows. Transfer 20.0 mL of the *Standard stock solution* and 3.0 mL of *Internal standard solution* to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Sample stock solution: Nominally 2.5 mg/mL of acetaminophen in *Diluent* prepared as follows. Transfer an equivalent of 250 mg of acetaminophen, from NLT 20 finely powdered Tablets, to a 100-mL volumetric flask. Add 75 mL of *Diluent*, and shake by mechanical means for 30 min. Dilute with *Diluent* to volume.

Sample solution: Nominally 0.1 mg/mL of acetaminophen in *Diluent* prepared as follows. Transfer 2.0 mL of the *Sample stock solution* and 3.0 mL of *Internal standard solution* to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

Column: 4.6-mm × 10-cm; 5-µm packing L1

Column temperature: 45 ± 1°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for acetaminophen, caffeine, aspirin, benzoic acid, and salicylic acid are about 0.3, 0.5, 0.8, 1.0, and 1.2, respectively.]

Suitability requirements

Resolution: NLT 1.4 between any of the analyte and internal standard peaks

Tailing factor: NMT 1.2 for each analyte peak

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate individually the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$), aspirin ($C_9H_8O_4$), and caffeine ($C_8H_{10}N_4O_2$) 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, aspirin, or caffeine to the internal standard from the *Sample solution*

R_S = peak response ratio of acetaminophen, aspirin, or caffeine to the internal standard from the *Standard solution*

C_S = concentration of the corresponding USP Reference Standard in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0% of the labeled amount of acetaminophen, aspirin, and caffeine

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Medium: Water; 900 mL

Apparatus 2: 100 rpm

Time: 60 min

Mobile phase, Diluent, Internal standard solution, Standard stock solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: Transfer 20.0 mL of *Standard stock solution*, 3.0 mL of *Internal standard solution*, and 20 mL of water to a 50-mL volumetric flask, and allow to stand for 30 s. Dilute with *Diluent* to volume. Use within 8 h.

Sample solution: Transfer 20.0 mL of a filtered portion of the solution under test to a 50-mL volumetric flask. Add 3.0 mL of *Internal standard solution* and 20 mL of *Diluent*, mix, and allow to stand for 30 s. Dilute with *Diluent* to volume.

Analysis: Proceed as directed for *Analysis* in the *Assay*.

Calculate individually the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$), aspirin ($C_9H_8O_4$), and caffeine ($C_8H_{10}N_4O_2$) dissolved:

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

R_U = peak response ratio of acetaminophen, aspirin, or caffeine to the internal standard from the *Sample solution*

R_S = peak response ratio of acetaminophen, aspirin, or caffeine to the internal standard from the *Standard solution*

C_S = concentration of the corresponding USP Reference Standard in the *Standard solution* (mg/mL)

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

Tolerances: NLT 75% (*Q*) of the labeled amount of acetaminophen ($C_8H_9NO_2$), aspirin ($C_9H_8O_4$), and caffeine ($C_8H_{10}N_4O_2$) is dissolved.

• **Uniformity of Dosage Units** ⟨905⟩, *Content Uniformity*: Meet the requirements with respect to acetaminophen, aspirin, and caffeine

IMPURITIES

• **Limit of Salicylic Acid**

Mobile phase and **Diluent:** Prepare as directed in the *Assay*.

Standard solution: 0.02 mg/mL of USP Salicylic Acid RS in *Diluent*

Sample solution: Nominally 2.5 mg/mL of aspirin in *Diluent*, prepared as follows. Transfer an equivalent of 250 mg of aspirin, from NLT 20 finely powdered Tablets, to a 100-mL volumetric flask. Add 75 mL of *Diluent*, and shake by mechanical means for 30 min. Dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 302 nm

Column: 4.6-mm × 10-cm; 5-µm packing L1

Column temperature: 45 ± 1°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.6

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of salicylic acid ($C_7H_6O_3$) relative to the labeled amount of aspirin in the portion of Tablets taken:

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

r_U = peak response of salicylic acid from the *Sample solution*

r_S = peak response of salicylic acid from the *Standard solution*

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

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

Acceptance criteria: NMT 3.0%

- **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 Aspirin RS
USP Caffeine RS
USP Salicylic Acid RS

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

Topic/Question	Contact	Expert Committee
ACETAMINOPHEN, ASPIRIN, AND CAFFEINE 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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