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Caffeine Citrate Oral Solution

DEFINITION

Caffeine Citrate Oral Solution is a sterile aqueous solution containing Caffeine and citric acid. It contains NLT 90.0% and NMT 110.0% of the labeled amount of caffeine citrate ($C_{14}H_{18}N_4O_9$). It contains no bacteriostat or other preservative.

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** **Identification Tests—General, *Citrate*⟨191⟩:** Meets the requirements
- **C.**

Solution A: Transfer 4 g of potassium iodide to a 100-mL volumetric flask, and add 10 mL of water. Shake until the potassium iodide is dissolved. Add 2 g of iodine to the volumetric flask, and shake until dissolved. Dilute with water to volume.

Sample solution: 5.0 mL of Oral Solution

Analysis: Transfer the *Sample solution* to a 25-mL centrifuge tube, and add 5 drops of *Solution A*. Add 0.5 mL of 2.0 M hydrochloric acid.

Acceptance criteria: A brown precipitate that dissolves on neutralization with 0.5 mL of sodium hydroxide TS is produced.

ASSAY

- **Procedure**

Mobile phase: Acetonitrile, tetrahydrofuran, and 0.01 M sodium acetate (5:4:191) adjusted with glacial acetic acid to a pH of 4.5

Theophylline stock solution: 0.02 mg/mL of theophylline in water

Standard solution: 0.2 mg/mL of USP Caffeine RS and 0.004 mg/mL of theophylline from *Theophylline stock solution* in water

Sample solution: Nominally 0.4 mg/mL of caffeine citrate (equivalent to 0.2 mg/mL of caffeine) from Oral Solution in water prepared as follows. Transfer a volume of Oral Solution, equivalent to 50 mg of caffeine, to a 250-mL volumetric flask. Dilute with water to volume, pass through a polyvinylidene difluoride or equivalent membrane of 0.45-µm pore size, and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 6.0 between theophylline and caffeine

Tailing factor: NMT 2.0 each for the theophylline and caffeine

Relative standard deviation: NMT 2.0% for caffeine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_A), in mg/mL, of caffeine citrate in the *Sample solution*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

M_{r1} = molecular weight of caffeine citrate, 386.31

M_{r2} = molecular weight of caffeine, 194.19

Calculate the percentage of the labeled amount of caffeine citrate ($C_{14}H_{18}N_4O_9$) in the portion of Oral Solution taken:

$$\text{Result} = (C_A/C_U) \times 100$$

C_A = concentration of caffeine citrate in the *Sample solution*

C_U = nominal concentration of caffeine citrate in the *Sample solution*

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **Organic Impurities**

Mobile phase, Theophylline stock solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 5 µg/mL of caffeine and 0.1 µg/mL of theophylline from the *Standard solution* in water

System suitability

Sample: *Sensitivity solution*

Suitability requirements

Sensitivity: The theophylline peak is discernible.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Oral Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_A) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

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

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

C_A = concentration of caffeine citrate in the *Sample solution* as determined in the *Assay*

M_{r1} = molecular weight of caffeine citrate, 386.31

M_{r2} = molecular weight of caffeine, 194.19

F = relative response factor, (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Theobromine	0.4	1.13	0.10
Paraxanthine	0.6	0.909	0.10
Theophylline	0.7	1.10	0.10
Caffeine	1.0	—	—
Any individual impurity	—	1.0	0.10
Total impurities	—	—	0.1

SPECIFIC TESTS

• **Sterility Tests ⟨71⟩:** It meets the requirements of the *Test for Sterility of the Product to Be Examined, Membrane Filtration*.

• **pH ⟨791⟩:** 4.2–5.2

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in single-dose, tight containers, and store at a temperature between 15°–30°.

• **USP Reference Standards ⟨11⟩**

USP Caffeine RS

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

Topic/Question	Contact	Expert Committee
CAFFEINE CITRATE ORAL SOLUTION	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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