

Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Apr-2023
Document Type: USP Monographs
DocId: GUID-E33ED93E-019C-4361-9C79-102A3BBB41B6_4_en-US
DOI: https://doi.org/10.31003/USPNF_M11175_04_01
DOI Ref: 01p7z

Caffeine Citrate Injection

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-caffeine-citrate-inj-20230331.

DEFINITION

Caffeine Citrate Injection is a sterile solution containing Caffeine and citric acid in Water for Injection. 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 ⟨191⟩, *Citrate*:** 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 Injection

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 Injection in water prepared as follows. Transfer a volume of Injection, 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 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 Injection 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 Injection 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

• **Color and Clarity**

Analysis: Transfer a suitable portion of the Injection to a clear glass test tube, and visually examine the solution in a well-lighted area.

Acceptance criteria: The solution is colorless and free of haze, obvious turbidity, and precipitate.

• **Bacterial Endotoxins Test ⟨85⟩:** NMT 0.25 USP Endotoxin Units/mg of caffeine

• **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

• **Particulate Matter in Injections ⟨788⟩:** NMT 150 particles are equal to or greater than 10 µm, and NMT 25 particles are equal to or greater than 25 µm.

• **Other Requirements:** It meets the requirements under *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in single-dose, tight containers ▲preferably▲ (RB 1-Apr-2023) of Type I glass, and store 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 INJECTION	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 43(6)

Current DocID: GUID-E33ED93E-019C-4361-9C79-102A3BBB41B6_4_en-US

DOI: https://doi.org/10.31003/USPNF_M11175_04_01

DOI ref: 01p7z