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Ergotamine Tartrate and Caffeine Tablets

DEFINITION

Ergotamine Tartrate and Caffeine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of ergotamine tartrate [$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$] and of caffeine ($C_8H_{10}N_4O_2$).

[NOTE—Throughout the following procedures, protect samples, the Reference Standards, and solutions containing them by conducting the procedures without delay, under subdued light, or using low-actinic glassware.]

IDENTIFICATION

• **A.** The retention times of the ergotamine and caffeine peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**

Buffer: Triethylamine, sulfuric acid, and water (4:0.5:2000) adjusted with sulfuric acid or 1 N sodium hydroxide to a pH of 3.0

Solution A: Acetonitrile and *Buffer* (15:85)

Solution B: Acetonitrile and *Buffer* (42:58)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
12	0	100
17	0	100
17.5	100	0
25	100	0

Diluent: 10 g/L of tartaric acid in water. Use *d*- or *l*-tartaric acid. Do not use a racemic mixture. Use a freshly prepared solution.

Ergotamine tartrate stock solution: 0.2 mg/mL of USP Ergotamine Tartrate RS in *Diluent* prepared as follows. Transfer a suitable quantity of USP Ergotamine Tartrate RS to an appropriate volumetric flask, and add 66% of the flask volume of *Diluent*. Sonicate for 5 min, and allow the solution to equilibrate to room temperature. Dilute with *Diluent* to volume.

Standard stock solution: 0.01 mg/mL of USP Ergotamine Tartrate RS and 1 mg/mL of USP Caffeine RS in *Diluent* prepared as follows. Transfer a suitable quantity of USP Caffeine RS to an appropriate volumetric flask, and add 66% of the flask volume of *Diluent*. Sonicate for 5 min, and allow the solution to equilibrate to room temperature. Add a suitable volume of *Ergotamine tartrate stock solution*, and dilute with *Diluent* to volume.

Standard solution: 0.001 mg/mL of USP Ergotamine Tartrate RS and 0.1 mg/mL of USP Caffeine RS from *Standard stock solution* in *Diluent*

System suitability solution: 0.001 mg/mL of USP Ergotaminine RS in *Standard solution*

Sample stock solution: Transfer NLT 10 Tablets to a 1-L volumetric flask. Add *Diluent* to 66% of the flask volume. Shake mechanically for NLT 45 min to promote dissolution. It may be necessary to loosen and retighten the closure multiple times during the shaking to relieve pressure. Dilute with *Diluent* to volume. Use within 9 h.

Sample solution: Nominally 0.001 mg/mL of ergotamine tartrate and 0.1 mg/mL of caffeine from *Sample stock solution* in *Diluent*. Pass through a suitable filter, and use the filtrate within 9 h.

Chromatographic system

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

Mode: LC

Detectors: UV 254 nm (for caffeine), in series with a fluorometric detector (for ergotamine and ergotaminine), with excitation at 250 nm and detection at 435 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 60 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for caffeine, ergotamine, and ergotaminine are 1.0, 2.6, and 2.8, respectively.]

Suitability requirements

Resolution: NLT 1.5 for ergotamine and ergotaminine, *System suitability solution*

Tailing factor: NMT 2.0 for ergotamine, *Standard solution*

Relative standard deviation: NMT 2.0% each for caffeine and ergotamine, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of 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 of caffeine at 254 nm from the *Sample solution*

r_S = peak response of caffeine at 254 nm from the *Standard solution*

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

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

Calculate the percentage of the labeled amount of ergotamine tartrate [$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$] in the portion of Tablets taken:

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

r_U = peak response of ergotamine at 435 nm from the *Sample solution*

r_S = peak response of ergotamine at 435 nm from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0% each of the labeled amounts of caffeine and ergotamine tartrate

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩**

Medium: 10 g/L of tartaric acid in water. Use *d*- or *l*-tartaric acid. Do not use a racemic mixture. Use a freshly prepared solution; 900 mL.

Apparatus 2: 75 rpm

Time: 30 min

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

Sample solution: Pass a portion of the solution under test through a suitable filter, and discard the first portion of the filtrate.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of caffeine ($C_8H_{10}N_4O_2$) dissolved:

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

r_U = peak response of caffeine at 254 nm from the *Sample solution*

r_S = peak response of caffeine at 254 nm from the *Standard solution*

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

V = volume of *Medium,* 900 mL

L = label claim (mg/Tablet)

Calculate the percentage of the labeled amount of ergotamine tartrate $[(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6]$ dissolved:

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

r_U = peak response of ergotamine at 435 nm from the *Sample solution*

r_S = peak response of ergotamine at 435 nm from the *Standard solution*

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances

Caffeine: NLT 75% (*Q*) of the labeled amount of caffeine ($C_8H_{10}N_4O_2$) is dissolved.

Ergotamine tartrate: NLT 70% (*Q*) of the labeled amount of ergotamine tartrate $[(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6]$ is dissolved.

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

IMPURITIES

• **Limit of Ergotaminine and Other Ergotamine-Related Impurities**

Buffer: 0.93 g/L of ammonium carbonate in water passed through a suitable filter. Add 6.7 mL of diethylamine per L.

Mobile phase: Acetonitrile and *Buffer* (50:60)

Diluent: Acetonitrile and methanol (50:50)

Standard stock solution: 0.4 mg/mL of USP Ergotamine Tartrate RS prepared as follows. Transfer a suitable quantity of USP Ergotamine Tartrate RS to an appropriate volumetric flask, and add 10% of the flask volume of acetonitrile. Add *Diluent* to 66% of the final flask volume, and sonicate, if needed. Allow the solution to equilibrate to room temperature, and dilute with *Diluent* to volume. Store refrigerated, and use within 24 h.

Standard solution: 0.004 mg/mL of USP Ergotamine Tartrate RS from *Standard stock solution* in *Diluent*. Store refrigerated, and use within 24 h.

System suitability solution: 0.004 mg/mL of USP Ergotaminine RS in the *Standard solution*. Store refrigerated, and use within 24 h.

Sensitivity solution: 0.2 µg/mL of USP Ergotamine Tartrate RS from the *Standard solution* in *Diluent*. Store refrigerated, and use within 24 h.

Sample solution: Nominally 0.4 mg/mL of ergotamine tartrate from NLT 20 Tablets prepared as follows. Finely powder NLT 20 Tablets. Transfer a portion of the powder, equivalent to 10 mg of ergotamine tartrate, to an appropriate container. Add 25.0 mL of *Diluent* to the container, and sonicate, if needed. Allow the solution to equilibrate to room temperature. Centrifuge a portion, pass the supernatant through a suitable filter, and discard NLT the first 3 mL of the filtrate. Store refrigerated, and use within 1 h.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Autosampler temperature: 5°

Flow rate: 1.3 mL/min

Injection volume: 60 µL

Run time: NLT 3.9 times the retention time of ergotamine

System suitability

Samples: *Standard solution, System suitability solution,* and *Sensitivity solution*

[Note—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 for ergotamine and ergotaminine, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each degradation product in the portion of Tablets taken:

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

r_U = peak response of each degradation product from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ergotamine	1.0	—
Unidentified impurity 1	1.55	1.5
Ergotaminine	2.85	2.0
Any individual degradation product	—	0.5
Total degradation products	—	4.0

- **Limit of Theophylline and Other Caffeine-Related Impurities**

Buffer: 1.6 g/L of anhydrous sodium acetate in water adjusted with glacial acetic acid to a pH of 4.5

Mobile phase: Acetonitrile and *Buffer* (95:5)

Standard stock solution: 0.2 mg/mL of USP Caffeine RS in *Mobile phase* prepared as follows. Transfer a suitable quantity of USP Caffeine RS to an appropriate volumetric flask, and add 66% of the flask volume of *Mobile phase*. Sonicate for NLT 10 min, and allow the solution to equilibrate to room temperature. Dilute with *Mobile phase* to volume.

Standard solution: 0.002 mg/mL of USP Caffeine RS from *Standard stock solution* in *Mobile phase*

System suitability solution: 0.002 mg/mL of USP Theophylline RS in the *Standard solution*

Sensitivity solution: 0.1 µg/mL of USP Caffeine RS from the *Standard solution* in *Mobile phase*

Sample stock solution: Nominally 1 mg/mL of caffeine from NLT 10 Tablets prepared as follows. Finely powder NLT 10 Tablets. Transfer a portion of the powder, equivalent to 250 mg of caffeine, to a 250-mL volumetric flask, and add 66% of the flask volume of *Mobile phase*. Sonicate for NLT 45 min with occasional shaking, and allow the solution to equilibrate to room temperature. Dilute with *Mobile phase* to volume.

Sample solution: Nominally 0.2 mg/mL of caffeine from *Sample stock solution* prepared as follows. Transfer a suitable quantity of *Sample stock solution* to an appropriate volumetric flask, and dilute with *Mobile phase* to volume. Pass through a suitable filter, and discard the first portion of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 265 nm

Column: 4.6-mm × 25-cm; 5-µm packing L3

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: NLT 3 times the retention time of caffeine

System suitability

Samples: *Standard solution, System suitability solution,* and *Sensitivity solution*

[NOTE—See *Table 3* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between caffeine and theophylline, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each degradation product in the portion of Tablets taken:

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

r_U = peak response of each degradation product 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_U = nominal concentration of caffeine in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard peaks less than 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Caffeine	1.0	—	—
Theophylline	1.3	1.2	0.1
1,3,9-Trimethyl xanthine[a]	1.7	1.2	0.1
Formyl 1,3-dimethyl-5,6-diaminouracil[b]	2.4	1.9	0.1
Any individual degradation product	—	1.0	0.2
Total degradation products	—	—	0.4

[a] 1,3,9-Trimethyl-3,9-dihydro-1*H*-purine-2,6-dione.

[b] *N*-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Caffeine RS

USP Ergotamine Tartrate RS

USP Ergotaminine RS

USP Theophylline RS

Topic/Question	Contact	Expert Committee
ERGOTAMINE TARTRATE AND CAFFEINE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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