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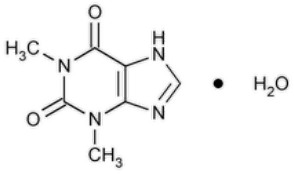
Theophylline



$C_7H_8N_4O_2 \cdot H_2O$ 198.18
$C_7H_8N_4O_2$ 180.17
1*H*-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, monohydrate;
Theophylline monohydrate CAS RN®: 5967-84-0; UNII: C137DTR5RG.
Anhydrous CAS RN®: 58-55-9; UNII: 0I55128JYK.

DEFINITION

Theophylline contains one molecule of water of hydration or is anhydrous. It contains NLT 97.0% and NMT 102.0% of theophylline ($C_7H_8N_4O_2$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Solution A: 10 mM ammonium acetate prepared as follows. Transfer 770.8 mg of ammonium acetate to a 1-L volumetric flask, and dissolve in 80% flask volume of water. Adjust with glacial acetic acid to a pH of 5.5 and dilute with water to volume. Pass through a suitable filter of 0.2-µm pore size.

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	98	2
7	50	50
7.3	10	90
8.3	10	90
8.31	98	2
12	98	2

Impurity stock solution: 0.2 mg/mL of USP Theophylline Related Compound F RS in water

System suitability solution: 1 mg/mL of USP Theophylline RS and 1 µg/mL of USP Theophylline Related Compound F RS, from *Impurity stock solution*, in water. Sonicate as needed to aid in the dissolution.

Standard solution: 0.2 mg/mL of USP Theophylline RS in water

Sample solution: 0.2 mg/mL of Theophylline in water

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Column temperature: 40°

Flow rate: 0.4 mL/min

Injection volume: 1 µL

System suitability

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

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

Suitability requirements

Resolution: NLT 1.5 between theophylline and theophylline related compound F, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of theophylline ($C_7H_8N_4O_2$) in the portion of Theophylline taken:

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

r_U = peak response of theophylline from the *Sample solution*

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

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

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

Acceptance criteria: 97.0%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.15%
- **Organic Impurities**

Solution A, Solution B, Mobile phase, Impurity stock solution, and **System suitability solution:** Proceed as directed in the *Assay*.

Standard stock solution: 50 µg/mL each of USP Caffeine RS, USP Theophylline RS, USP Theophylline Related Compound B RS, USP Theophylline Related Compound C RS, USP Theophylline Related Compound D RS, and USP Theophylline Related Compound F RS

Standard solution: 1 µg/mL each of USP Caffeine RS, USP Theophylline RS, USP Theophylline Related Compound B RS, USP Theophylline Related Compound C RS, USP Theophylline Related Compound D RS, and USP Theophylline Related Compound F RS, from *Standard stock solution*, in water

Sample solution: 1.0 mg/mL of Theophylline in water

Chromatographic system

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

Mode: LC

Detector

For unspecified impurities with absorption maxima near 220 nm: UV 220 nm

For specified impurities and unspecified impurities with absorption maxima near 270 nm: UV 270 nm

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Column temperature: 40°

Flow rate: 0.4 mL/min

Injection volume: 1 µL

System suitability

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

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

Suitability requirements

Resolution: NLT 1.5 between theophylline and theophylline related compound F, *System suitability solution*

Relative standard deviation: NMT 3.0% for each peak present in the *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

For impurities detected at 270 nm

Calculate the percentage of caffeine, theophylline related compound B, theophylline related compound C, and theophylline related compound D in the portion of Theophylline taken:

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

r_U = peak response of caffeine, theophylline related compound B, theophylline related compound C, or theophylline related compound D from the *Sample solution*

r_S = peak response of the corresponding Reference Standard from the *Standard solution*

C_S = concentration of USP Caffeine RS, USP Theophylline Related Compound B RS, USP Theophylline Related Compound C RS, or USP Theophylline Related Compound D RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of any other individual unspecified impurity with absorption maxima near 270 in the portion of Theophylline taken:

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

r_U = peak response of any other individual unspecified impurity from the *Sample solution*

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

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

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

For impurities detected at 220 nm

Calculate the percentage of any other individual unspecified impurity with absorption maxima near 220 in the portion of Theophylline taken:

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

r_U = peak response of any other individual unspecified impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 2*. Disregard peaks less than 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Theophylline related compound C	0.36	0.10
Theophylline related compound B	0.63	0.10
Theophylline related compound D	0.69	0.10

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Theophylline	1.0	—
Theophylline related compound F[a]	1.09	—
Caffeine	1.20	0.10
Any other individual unspecified impurity	—	0.10
Total impurities	—	0.5

[a] Included for establishing system suitability only.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° for 4 h.

Acceptance criteria: The hydrous form loses 7.5%–9.5% of its weight, and the anhydrous form loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

• **Labeling:** Label it to indicate whether it is hydrous or anhydrous.

• **USP Reference Standards ⟨11⟩**

USP Caffeine RS

USP Theophylline RS

USP Theophylline Related Compound B RS
3-Methyl-1*H*-purine-2,6-dione.
$C_6H_6N_4O_2$ 166.14

USP Theophylline Related Compound C RS
N-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)formamide.
$C_7H_{10}N_4O_3$ 198.18

USP Theophylline Related Compound D RS
Theophyllidine;
N-Methyl-5-(methylamino)-1*H*-imidazole-4-carboxamide hydrochloride monohydrate.
$C_6H_{10}N_4O \cdot HCl \cdot H_2O$ 208.65

USP Theophylline Related Compound F RS
Etophylline;
7-(2-Hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione.
$C_9H_{12}N_4O_3$ 224.22

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

Topic/Question	Contact	Expert Committee
THEOPHYLLINE	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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