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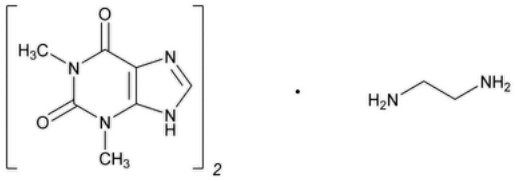
Aminophylline



$C_{16}H_{24}N_{10}O_4$ 420.43
$C_{16}H_{24}N_{10}O_4 \cdot 2H_2O$ 456.46

1*H*-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compd. with 1,2-ethanediamine (2:1);
Theophylline compound with ethylenediamine (2:1).

Anhydrous CAS RN®: 317-34-0; UNII: 27Y3KJK423.

Dihydrate CAS RN®: 5897-66-5; UNII: C229N9DX94.

DEFINITION

Aminophylline is anhydrous or contains NMT two molecules of water of hydration. It contains NLT 84.0% and NMT 87.4% of anhydrous theophylline ($C_7H_8N_4O_2$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

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

Sample: 500 mg of Aminophylline

Analysis: Dissolve the *Sample* in 20 mL of water, add, with constant stirring, 1 mL of 3 N hydrochloric acid, filter (retain the filtrate), wash the precipitate with small portions of cold water, and dry at 105° for 1 h.

Acceptance criteria: The IR spectrum of theophylline so obtained corresponds to that of USP Theophylline RS.

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

• **C.**

Sample: The filtrate obtained in *Identification A*.

Analysis: To the *Sample* add 0.5 mL of benzenesulfonyl chloride and 5 mL of 1 N sodium hydroxide to render alkaline. Shake by mechanical means for 10 min, add 5 mL of 3 N hydrochloric acid to acidify, chill, collect the precipitated disulfonamide of ethylenediamine, wash with water, recrystallize from water, and dry at 105° for 1 h.

Acceptance criteria: The dried precipitate melts at 164°–171°.

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 water to 80% of the flask volume. 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

Time (min)	Solution A (%)	Solution B (%)
8.3	10	90
8.31	98	2
12	98	2

Impurity stock solution: 25 µg/mL of USP Theophylline Related Compound F RS in water

System suitability solution: 0.8 mg/mL of USP Theophylline RS and 1 µg/mL of USP Theophylline Related Compound F RS in water prepared as follows. Transfer 21 mg of USP Theophylline RS to a 25-mL volumetric flask and add 15 mL of water. Sonicate to dissolve, add 1 mL of *Impurity stock solution*, and dilute with water to volume.

Standard solution: 0.17 mg/mL of USP Theophylline RS in water. Sonicate to dissolve as needed.

Sample solution: 0.2 mg/mL of Aminophylline 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*

Suitability requirements

Resolution: NLT 2.0 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 Aminophylline 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 Aminophylline in the *Sample solution* (mg/mL)

Acceptance criteria: 84.0%–87.4% of theophylline on the anhydrous basis

OTHER COMPONENTS

• **Content of Ethylenediamine**

Sample: 500 mg of Aminophylline

Diluent: Water

Titrimetric system

Mode: Direct titration

Titrant: 0.1 N hydrochloric acid VS

Endpoint detection: Visual

Analysis: Dissolve the *Sample* in 30 mL of *Diluent*, add methyl orange TS, and titrate. Each mL of 0.1 N hydrochloric acid is equivalent to 3.005 mg of ethylenediamine ($C_2H_8N_2$).

Acceptance criteria: 157–175 mg of ethylenediamine ($C_2H_8N_2$) per gram of theophylline ($C_7H_8N_4O_2$) found in the *Assay*

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.15%

• **Organic Impurities**

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

Standard stock solution: 25.0 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 in water

Standard solution: 1.0 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 in water, from *Standard stock solution*

Sample solution: 1.0 mg/mL of Aminophylline in water

System suitability

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

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

Suitability requirements

Resolution: NLT 2.0 between theophylline and theophylline related compound F, *System suitability solution*

Relative standard deviation: NMT 3.0% for each peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of caffeine, theophylline related compound B, theophylline related compound C, theophylline related compound D, and theophylline related compound F in the portion of Aminophylline 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, theophylline related compound D, or theophylline related compound F from the *Sample solution*

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

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

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

Calculate the percentage of dimethyl uric acid, theobromine, and any other individual unspecified impurity in the portion of Aminophylline taken:

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

r_U = peak response of dimethyl uric acid, theobromine, or 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 Aminophylline in the *Sample solution* (mg/mL)

F = relative response factor

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

Table 2

Name	Relative Retention Time	Relative Response Factor	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
Dimethyl uric acid[a]	0.76	0.55	0.10
Theobromine[b]	0.82	1.0	0.10
Theophylline	1.0	—	—
Theophylline related compound F	1.09	—	0.10

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Caffeine	1.20	—	0.10
Any other individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.3

[a] 1,3-Dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione.

[b] 3,7-Dihydro-3,7-dimethylpurine-2,6(1*H*)-dione.

SPECIFIC TESTS

• **Water Determination** ⟨921⟩, *Method I*

Sample: 1.5 g of Aminophylline

Solvent: 50 mL of chloroform and anhydrous methanol (50:50) in place of anhydrous methanol

Acceptance criteria

Anhydrous: NMT 0.75%

Hydrous: NMT 7.9%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

• **Labeling:** Label it to indicate whether it is anhydrous or hydrous, and also to state the content of anhydrous theophylline.

• **USP Reference Standards** ⟨11⟩

USP Caffeine RS

USP Theophylline RS

USP Theophylline Related Compound B RS

3-Methyl-1*H*-purine-2,6-dione;
Also known as 3-Methyl-3,7-dihydro-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

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
AMINOPHYLLINE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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