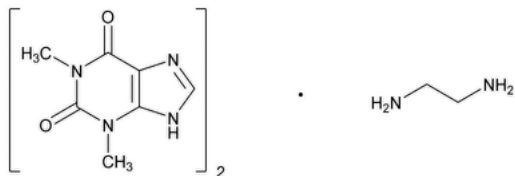


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Aminophylline



$C_{16}H_{24}N_4O_4$ 420.43

$C_{16}H_{24}N_4O_4 \cdot 2H_2O$ 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



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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 (C₇H₈N₄O₂) 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 (C₂H₈N₂).

Acceptance criteria: 157–175 mg of ethylenediamine (C₂H₈N₂) per gram of theophylline (C₇H₈N₄O₂) 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](#).