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Aminophylline Oral Solution

DEFINITION

Aminophylline Oral Solution is an aqueous solution of Aminophylline, prepared with the aid of Ethylenediamine. It contains an amount of aminophylline ($C_{16}H_{24}N_{10}O_4$) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of anhydrous theophylline ($C_7H_8N_4O_2$). Aminophylline Oral Solution may contain an excess of ethylenediamine, but no other substance may be added for the purpose of pH adjustment.

IDENTIFICATION

Change to read:

- A.** **SPECTROSCOPIC IDENTIFICATION TESTS** (197), **Infrared Spectroscopy: 197K** (CN 1-MAY-2020)
Analysis: Transfer a volume of Oral Solution equivalent to 500 mg of aminophylline to a suitable container and add, with constant stirring, 1 mL of 3 N hydrochloric acid or enough to completely precipitate the theophylline. Filter (retain the filtrate), wash the precipitate with small portions of cold water until free from chloride, and dry at 105° for 1 h.
Acceptance criteria: The IR spectrum of theophylline so obtained matches that of [USP Theophylline RS](#).
- B.**
Analysis: To the filtrate obtained in *Identification A* 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 an appropriate amount of ammonium acetate to a volumetric flask and dissolve in water (about 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
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 2 µg/mL of [USP Theophylline Related Compound F RS](#) in water prepared as follows. Transfer 1 mg of [USP Theophylline RS](#) to a 25-mL volumetric flask and add 15 mL of water. Sonicate to dissolve, add 2 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: Nominally 0.17 mg/mL of anhydrous theophylline in water prepared as follows. Transfer an appropriate amount of anhydrous theophylline from a volume of Oral Solution to a suitable volumetric flask. Dissolve and dilute with water to volume.

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 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) in the portion of Oral Solution taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

OTHER COMPONENTS

• CONTENT OF ETHYLENEDIAMINE

Sample: A volume of Oral Solution equivalent to 500 mg of aminophylline

Diluent: Water

Titrimetric system

Mode: Direct titration

Titrant: 0.1 N hydrochloric acid VS

Endpoint detection: Visual

Analysis: If necessary, dilute the *Sample* with *Diluent* to 30 mL, 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: 176–283 mg of ethylenediamine ($C_2H_8N_2$) per gram of theophylline ($C_7H_8N_4O_2$) found in the Assay

IMPURITIES

• ORGANIC IMPURITIES

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

Standard solution: 2.0 μg/mL each of [USP Theophylline RS](#) and [USP Theophylline Related Compound D RS](#) in water

Sample solution: Nominally 1.0 mg/mL of anhydrous aminophylline in water prepared as follows. Transfer an appropriate amount of anhydrous aminophylline from a volume of Oral Solution to a suitable volumetric flask. Dissolve and dilute with water to volume.

System suitability

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

[NOTE—See [Table 2](#) for 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 present in the *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of theophylline related compound D in the portion of Oral Solution taken:

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

r_U = peak response of theophylline related compound D from the *Sample solution*

r_S = peak response of theophylline related compound D from the *Standard solution*

C_S = concentration of [USP Theophylline Related Compound D RS](#) in the *Standard solution* (mg/mL)

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

Calculate the percentage of any other individual unspecified degradation product in the portion of Oral Solution taken:

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

r_U = peak response of any other individual unspecified degradation product 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 = nominal concentration of anhydrous theophylline in the *Sample solution* (mg/mL)

Acceptance criteria: See [Table 2](#). Disregard peaks less than 0.086%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Theophylline related compound C ^{a,b}	0.36	—
Theophylline related compound B ^{a,c}	0.63	—
Theophylline related compound D	0.69	0.2
Dimethyl uric acid ^{a,d}	0.76	—
Theobromine ^{a,e}	0.82	—
Theophylline	1.0	—
Theophylline related compound F ^a	1.09	—
Caffeine ^a	1.20	—
Any other individual unspecified degradation product	—	0.2
Total degradation products	—	0.5

^a Process impurity included for identification only and not to be included in the calculation of total degradation products.

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

^c 3-Methyl-1*H*-purine-2,6-dione.

^d 1,3-Dimethyl-7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione.

^e 3,7-Dihydro-3,7-dimethylpurine-2,6(1*H*)-dione.

SPECIFIC TESTS

- **pH (791):** 8.5–9.7

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** Label the Oral Solution to state the content of anhydrous theophylline.
- **USP REFERENCE STANDARDS (11).**

[USP Theophylline RS](#)

[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 ORAL SOLUTION	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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