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Aminophylline Tablets

DEFINITION

Aminophylline Tablets contain an amount of aminophylline equivalent to NLT 93.0% and NMT 107.0% of the labeled amount of anhydrous theophylline ($C_7H_8N_4O_2$).

[NOTE—The ammoniacal odor present in the vapor space above the Tablets is often quite strong, especially when bottles having suitably tight closures are newly opened. This is due to ethylenediamine vapor pressure build-up, a natural condition in the case of aminophylline.]

IDENTIFICATION

• **A. SPECTROSCOPIC IDENTIFICATION TESTS ⟨197⟩, *Infrared Spectroscopy*: 197K**

Analysis: Macerate a quantity of Tablets, equivalent to 500 mg of aminophylline, with 25 mL of water, and filter. The filtrate is alkaline to litmus. To the filtrate add 1 mL of 3 N hydrochloric acid, stir, and if necessary, chill to precipitate the theophylline. Filter, and retain the filtrate, free from washings. Use the filtrate in *Identification C*. Wash the theophylline crystals so obtained with small quantities of ice-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, and add 5 mL of 3 N hydrochloric acid to acidify. Chill, collect the precipitated disulfonamide of ethylenediamine, and wash with water. Recrystallize the washed precipitate 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
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.

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Sample solution: Nominally 0.17 mg/mL of anhydrous theophylline from NLT 20 finely powdered Tablets in water prepared as follows. Transfer 34 mg of anhydrous theophylline from a portion of the powder to a 200-mL volumetric flask. Add 20 mL of water and mix for 1 min. Add an additional 140 mL of water and sonicate for 30 min. Dilute with water to volume. Pass through a suitable filter of 0.22-µm pore size, discarding the first 2–3 mL.

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

Acceptance criteria: 93.0%–107.0%

OTHER COMPONENTS

• **Content of Ethylenediamine**

Sample solution: Transfer a portion of the powdered Tablets, equivalent to 350 mg of aminophylline, prepared in the *Assay*, into a 100-mL conical flask. Add 20 mL of water, and digest at 50°, with frequent shaking, for 30 min. Cool, filter into a 250-mL conical flask, and wash with water until the last washing is neutral to litmus. Use the combined filtrate and washings.

Titrimetric system

Mode: Direct titration

Titrant: 0.1 N hydrochloric acid VS

Endpoint detection: Visual

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

Acceptance criteria: 140–190 mg of ethylenediamine ($C_2H_8N_2$) per gram of theophylline ($C_7H_8N_4O_2$) found in the *Assay*

Change to read:

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

For uncoated or plain coated tablets

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Standard solution: USP Theophylline RS in *Medium*

Sample solution: Proceed as directed in the chapter for sample. Dilute with water to a concentration that is similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV-Vis

Analytical wavelength: UV about 269 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved.

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Tolerances: NLT 75% (*Q*) of the labeled amount of theophylline ($C_7H_8N_4O_2$) is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** ▲Meet the requirements▲ (CN 1-Aug-2023)

Procedure for content uniformity

Standard solution: 10 µg/mL of USP Theophylline RS

Sample solution: Place 1 Tablet in a 250-mL volumetric flask, add 200 mL of water, and shake by mechanical means until disintegration is complete. Add water to volume. Filter a portion of the mixture, discarding the first 20 mL of the filtrate.

Instrumental conditions

Mode: UV

Analytical wavelength: About 269 nm

Cell: 1 cm

Blank: Water

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of anhydrous theophylline ($C_7H_8N_4O_2$) in the Tablet taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

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

▲▲ (CN 1-Aug-2023)

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 from NLT 20 finely powdered Tablets in water prepared as follows. Transfer 10 mg of anhydrous aminophylline from a portion of the powder to a 10-mL volumetric flask. Add 5 mL of water and sonicate for 30 min. Dilute with water to volume. Pass through a suitable filter of 0.22-µm pore size, discarding the first 2–3 mL.

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, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of theophylline related compound D in the portion of Tablets 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 aminophylline in the *Sample solution* (mg/mL)

Calculate the percentage of any other individual unspecified 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 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)

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C_U = nominal concentration of aminophylline 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[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.

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ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **Labeling:** Label the Tablets 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 TABLETS	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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