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Aminophylline Injection

DEFINITION

Aminophylline Injection is a sterile solution of Aminophylline in Water for Injection, or is a sterile solution of Theophylline in Water for Injection prepared with the aid of Ethylenediamine. It contains, in each mL, an amount of aminophylline ($C_{16}H_{24}N_{10}O_4$) equivalent to NLT 93.0% and NMT 107.0% of the labeled amount of anhydrous theophylline ($C_7H_8N_4O_2$).

Aminophylline Injection may contain an excess of Ethylenediamine, but no other substance may be added for the purpose of pH adjustment. [Note—Do not use the Injection if crystals have separated.]

IDENTIFICATION

• **A.**

Analysis: Dilute a volume of Injection equivalent to 500 mg of aminophylline with water to 20 mL, and add, with constant stirring, 1 mL of 3 N hydrochloric acid or enough to completely precipitate the theophylline, and filter. To the filtrate 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 precipitate melts at 164°–171°.

Change to read:

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

Analysis: Wash the precipitated theophylline from *IdentificationA* 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.

• **C.** 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 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.

Sample solution: Nominally 0.17 mg/mL of anhydrous theophylline in water prepared as follows. Transfer 8.5 mg of anhydrous theophylline from a volume of Injection to a 50-mL 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 Injection 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: A volume of Injection 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 with *Titrant*. Each mL of 0.1 N hydrochloric acid is equivalent to 3.005 mg of ethylenediamine ($C_2H_8N_2$).

Acceptance criteria: 166–192 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 25 mg of anhydrous aminophylline from a volume of Injection to a 25-mL volumetric flask. Dissolve and dilute with water to volume.

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 theophylline related compound D in the portion of Injection 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 Injection 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 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.

SPECIFIC TESTS

- **pH** ⟨791⟩**:** 8.6–9.0
- **Particulate Matter in Injections** ⟨788⟩**:** Meets the requirements for small-volume injections
- **Other Requirements:** Meets the requirements in *Injections and Implanted Drug Products* ⟨1⟩
- **Bacterial Endotoxins Test** ⟨85⟩**:** It contains NMT 1.0 USP Endotoxin Unit/mg of aminophylline.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in single-dose containers from which carbon dioxide has been excluded, preferably of Type I glass, protected from light. Store at controlled room temperature.
- **Labeling:** Label the Injection 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 INJECTION	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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