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Aminophylline Delayed-Release Tablets

DEFINITION

Aminophylline Delayed-Release 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 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.**

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. Wash the theophylline crystals so obtained with small quantities of ice-cold water, and dry at 105° for 1 h. Transfer 10 mg of the dried theophylline crystals to a porcelain dish, add 1 mL of hydrochloric acid and 100 mg of potassium chlorate, evaporate on a steam bath to dryness, and invert the dish over a vessel containing a few drops of 6 N ammonium hydroxide.

Acceptance criteria: The residue acquires a purple color, which is destroyed by solutions of fixed alkalies.

• **B.**

Analysis: Recrystallize the dried theophylline crystals from *Identification* test *A* from water, and dry at 105° for 1 h.

Acceptance criteria: The recrystallized theophylline melts at 270°–274°.

• **C.**

Analysis: To the filtrate obtained in *Identification* test *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, 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**

Sample solution: Transfer an equivalent to 2 g of aminophylline, from powdered Tablets (NLT 20), to a 200-mL volumetric flask with the aid of a mixture of 50 mL of water and 15 mL of 6 N ammonium hydroxide, and allow to stand for 30 min with frequent shaking, warming to 50° if necessary to dissolve the aminophylline. Cool the mixture to room temperature if it has been warmed, and add water to volume. Centrifuge 50 mL of the mixture; pipet a portion of the clear supernatant, equivalent to 250 mg of aminophylline, into a 250-mL conical flask; and dilute with water if necessary to make 40 mL. Add 8 mL of 6 N ammonium hydroxide and 20.0 mL of 0.1 N silver nitrate VS, mix, heat to boiling, and continue boiling for 15 min. Cool to between 5° and 10° for 20 min, then filter, preferably through a filtering crucible under reduced pressure, and wash the precipitate with three 10-mL portions of water. Acidify the combined filtrate and washings with nitric acid, and add an additional 3 mL of the acid. Cool, and add 2 mL of ferric ammonium sulfate TS.

Titrimetric system

Mode: Residual titration

Titrant: 0.1 N ammonium thiocyanate VS

Endpoint detection: Visual

Analysis: Titrate the excess silver nitrate with *Titrant*. Each mL of 0.1 N silver nitrate is equivalent to 18.02 mg of theophylline ($C_7H_8N_4O_2$).

Acceptance criteria: 93.0%–107.0%

OTHER COMPONENTS

• **CONTENT OF ETHYLENEDIAMINE**

Sample solution: Transfer a portion, equivalent to 350 mg of aminophylline, of the powdered Tablets 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 g of theophylline ($C_7H_8N_4O_2$) found in the *Assay*

PERFORMANCE TESTS

• **Disintegration ⟨701⟩:** 30 min, determined as directed in *Delayed-Release (Enteric-Coated) Tablets*

Change to read:

• **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 theophylline ($C_7H_8N_4O_2$) in each Tablet:

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

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)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **Labeling:** Label the Tablets to state the content of anhydrous theophylline.

• **USP Reference Standards ⟨11⟩**

USP Theophylline RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
AMINOPHYLLINE DELAYED-RELEASE TABLETS	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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