Theophylline Oral Solution

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 5
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Theophylline Oral Solution monograph. The purpose for the revision is to widen the limit for Total impurities based on FDA approval.

Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Theophylline Oral Solution Revision Bulletin supersedes the currently official Theophylline Oral Solution monograph. The Revision Bulletin will be incorporated into the *Second Supplement* of *USP 40–NF 35*.

Should you have any questions, please contact Ren-Hwa Yeh, Ph.D., Senior Scientific Liaison, (301–998–6818 or rhy@usp.org).

Theophylline Oral Solution

DEFINITION

Theophylline Oral Solution contains NLT 95.0% and NMT 105.0% of the labeled amount of theophylline ($C_7H_8N_4O_2$).

IDENTIFICATION

- **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** 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 771 mg/L of ammonium acetate to a suitable flask, and dissolve in water. Adjust with glacial acetic acid to a pH of 5.4 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	93.5	6.5
2.5	93.5	6.5
5.0	10	90
5.1	93.5	6.5
7.0	93.5	6.5

Standard solution: 0.2 mg/mL of USP Theophylline RS in water

Sample solution: Nominally 0.2 mg/mL of theophylline from Oral Solution in water. Centrifuge and use the supernatant.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 270 nm. For *Identification* test *A*, use a photodiode array detector in the range of 210–400 nm.

Column: 2.1-mm × 10-cm; 1.7-µm packing L7

Column temperature: 40 ± 2°

Flow rate: 0.4 mL/min

Injection volume: 1 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2

Relative standard deviation: NMT 1.0%

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 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: 95.0%–105.0%

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Solution A, Solution B, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*.

Impurity stock solution: 0.1 mg/mL each of USP Theophylline RS and USP Theophylline Related Compound D RS in water

System suitability solution: 10 µg/mL each of USP Theophylline RS and USP Theophylline Related Compound D RS from *Impurity stock solution*, and 10 µg/mL of USP Saccharin Sodium RS in water

Standard solution: 2.0 µg/mL each of USP Theophylline RS and USP Theophylline Related Compound D RS from *Impurity stock solution* in water

Sample solution: Nominally 1.0 mg/mL of theophylline from a portion of Oral Solution in water. Centrifuge and use the supernatant.

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between theophyllidine and saccharin, *System suitability solution*

Relative standard deviation: NMT 3.0% for theophylline and theophylline related compound D peaks, *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 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 theophylline in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*. Disregard peaks less than 0.1%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Theophylline related compound D	0.45	0.2
Saccharin[a]	0.50	—
Theophylline	1.0	—
Any other individual unspecified degradation product	—	0.2
Total impurities	—	●1.0● (RB 1-Feb-2017)

[a] Included as a potential excipient. Do not include in the calculation of total impurities.

SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** ⟨**61**⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨**62**⟩**:** Meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*. The total aerobic microbial count does not exceed 1×10^2 cfu/mL, and the total combined molds and yeasts count does not exceed 5×10^1 cfu/mL.
- **pH** ⟨**791**⟩**:** 3.0–4.7
- **ALCOHOL DETERMINATION** ⟨**611**⟩**,** *Method II* (if present)
  Analysis: Use acetone as the internal standard.
  Acceptance criteria: 90.0%–115.0% of the labeled amount of alcohol (C_2H_5OH)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **LABELING:** Label it to indicate the alcohol content (if present).

Change to read:

- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Alcohol Determination—Acetonitrile RS
  USP Alcohol Determination—Alcohol RS
  USP Saccharin Sodium RS
  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● (ERR 1-Feb-2017)