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Theophylline in Dextrose Injection

DEFINITION

Theophylline in Dextrose Injection is a sterile solution of Theophylline and Dextrose in Water for Injection. It contains NLT 93.0% and NMT 107.0% of the labeled amount of anhydrous theophylline ($C_7H_8N_4O_2$) and NLT 95.0% and NMT 105.0% of the labeled amount of dextrose ($C_6H_{12}O_6 \cdot H_2O$).

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*.
- **C.**

Sample solution: Theophylline in Dextrose Injection

Analysis: Add a few drops of the *Sample solution* to 5 mL of hot alkaline cupric tartrate TS.

Acceptance criteria: A red-to-orange precipitate of cuprous oxide is formed.

ASSAY

- **Theophylline**

Solution A: 10 mM ammonium acetate prepared as follows. Transfer 771 mg of ammonium acetate to a 1-L volumetric flask, and dissolve in 80% of the flask volume of water. Adjust with glacial acetic acid to a pH of 4.8 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: 0.1 mg/mL of USP Theophylline RS

Sample solution: Nominally 0.1 mg/mL of theophylline prepared as follows. Transfer 5 mg of 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. For *Identification 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°

Flow rate: 0.4 mL/min

Injection volume: 1 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

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 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%

- **Dextrose**

Sample solution: Nominally 2–5 g of dextrose per 100 mL, prepared as follows. Transfer a volume of Injection containing 2–5 g of dextrose to a 100-mL volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, and dilute with water to volume.

Analysis

Sample: *Sample solution*

Determine the angular rotation in a suitable polarimeter tube (see *Optical Rotation ⟨781⟩*).

Calculate the percentage of the labeled amount of dextrose ($C_6H_{12}O_6 \cdot H_2O$) in the portion of Injection taken:

$$\text{Result} = [(100 \times a)/(l \times \alpha)] \times (1/C_U) \times (M_{r1}/M_{r2}) \times 100$$

a = observed angular rotation of the *Sample solution* (°)

l = length of the polarimeter tube (dm)

α = midpoint of the specific rotation range for anhydrous dextrose, 52.9°

C_U = nominal concentration of dextrose in the *Sample solution* (g/100 mL)

M_{r1} = molecular weight of dextrose monohydrate, 198.17

M_{r2} = molecular weight of anhydrous dextrose, 180.16

Acceptance criteria: 95.0%–105.0%

IMPURITIES

- **Organic Impurities**

Solution A, Solution B, and **Mobile phase:** Prepare as directed in the *Assay*.

System suitability solution: 0.4 µg/mL each of USP Theophylline Related Compound D RS and 5-hydroxymethylfurfural

Standard solution: 0.4 µg/mL each of USP Theophylline RS and USP Theophylline Related Compound D RS

Sample solution: Nominally 400 µg/mL of theophylline in water prepared as follows. Transfer 4 mg of theophylline from a volume of Injection to a 10-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 L7

Column temperature: 40°

Flow rate: 0.4 mL/min

Injection volume: 2.5 µL

System suitability

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

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

Suitability requirements

Resolution: NLT 1.1 between theophylline related compound D and 5-hydroxymethylfurfural, *System suitability solution*

Relative standard deviation: NMT 5.0% for theophylline and theophylline related compound D, *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* (µg/mL)

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

C_U = nominal concentration of theophylline in the *Sample solution* (µg/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	0.44	0.2
5-HMF[a]	0.47	—
Theophylline	1.0	—
Any other individual unspecified degradation product	—	0.2
Total degradation products	—	0.5

[a] 5-Hydroxymethylfurfural; the content of this impurity is controlled in the *Limit of 5-Hydroxymethylfurfural and Related Substances* test.

• **LIMIT OF 5-HYDROXYMETHYLFURFURAL AND RELATED SUBSTANCES**

Cation-exchange column: Proceed as directed in *Chromatography ⟨621⟩* using a chromatographic tube capable of providing a 0.8- × 4-cm bed volume (or 2 mL) of 100- to 200-mesh, strongly acidic styrene-divinylbenzene cation-exchange resin. Condition the column by washing with 30 mL of water, discarding the eluate.

Sample solution: Pass a volume of Injection containing 100 mg of hydrous dextrose through the resin bed in the *Cation-exchange column*, allowing the sample to flow down the wall of the column so as not to disturb the resin bed, and collect the eluate in a 50-mL volumetric

flask. Wash the column with 25 mL of water, and collect the eluate in the same 50-mL volumetric flask. Dilute the eluate with water to volume.

Blank solution: Pass 27 mL of water through a freshly conditioned *Cation-exchange column*, collecting the eluate in a 50-mL volumetric flask. Fill with water to volume.

Instrumental conditions

Mode: UV

Analytical wavelength: 284 nm

Cell: 1 cm

Blank: *Blank solution*

Analysis

Samples: *Sample solution* and *Blank solution*

Determine the absorbance of the *Sample solution* and *Blank solution* with a suitable spectrophotometer.

Acceptance criteria: The absorbance is NMT 0.25.

SPECIFIC TESTS

- **Bacterial Endotoxins Test ⟨85⟩:** NMT 1.0 USP Endotoxin Unit/mg of anhydrous theophylline
- **pH ⟨791⟩**

Sample solution: NMT 5% of dextrose from a portion of Injection in water, diluted with water if necessary

Acceptance criteria: 3.5–6.5

- **Other Requirements:** It meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in single-dose containers, preferably of Type I or Type II glass, or of a suitable plastic material. Store at controlled room temperature.
- **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

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

Topic/Question	Contact	Expert Committee
THEOPHYLLINE IN DEXTROSE 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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