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Theophylline Extended-Release Capsules

DEFINITION

Theophylline Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of anhydrous 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 0.77 g 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 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

Diluent: Dilute 138 mL of ammonium hydroxide solution with water to 1 L.

Standard solution: 0.2 mg/mL of USP Theophylline RS

Sample stock solution: Nominally 4 mg/mL of theophylline prepared as follows. Transfer the contents of a suitable number of Capsules to a 500-mL volumetric flask. Add 150 mL of *Diluent* and heat on a hot plate to just boiling with occasional stirring. Remove from the hot plate and sonicate for 5 min while still hot. Cool to ambient temperature and dilute with water to volume.

Sample solution: Nominally 0.2 mg/mL of theophylline from *Sample stock solution*. Centrifuge and use the supernatant.

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 ± 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 Capsules 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: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

[Note—The following tests, which were assigned numbers chronologically, are placed in groups corresponding to product dosing intervals. Thus, individual tests do not necessarily appear in numerical order.]

For products labeled for dosing every 12 h

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*. Proceed as directed for *Dissolution ⟨711⟩, Procedure, Apparatus 1 and 2, Delayed-Release Dosage Forms, Method B Procedure* except to use *Acceptance Table 2*.

Medium: pH 1.2 simulated gastric fluid (without pepsin) for the first hour; pH 6.0 phosphate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 900 mL

Apparatus 2: 50 rpm

Times: 1, 2, 4, 6, and 8 h

Standard solution: A known concentration of USP Theophylline RS in *Medium*

Sample solution: Filtered portions of the solution under test. Dilute with *Medium*, if necessary, to a concentration that is similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: Maximum absorbance at about 271 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at each time point using the UV absorption.

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved (%)
1	3–15
2	20–40
4	50–75
6	65–100
8	NLT 80

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Solution A: 6.8 g/L of monobasic potassium phosphate. Adjust with either 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 4.5 ± 0.05.

Medium: *Solution A*; 900 mL

Apparatus 2: 75 rpm

Times: 1, 2, 4, and 8 h

Analysis: Proceed as directed in *Test 1*.

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved (%)
1	10–30
2	30–55
4	55–80
8	NLT 80

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*. Proceed as directed for *Dissolution ⟨711⟩, Procedure, Apparatus 1 and 2, Delayed-Release Dosage Forms, Method B Procedure* except to use *Acceptance Table 2*.

Medium: pH 1.2 simulated gastric fluid (without pepsin) for 1 h; pH 7.5 simulated intestinal fluid (without enzyme); 900 mL

Apparatus 2: 50 rpm

Times: 1, 2, 3, 4, and 7 h

Analysis: Proceed as directed in *Test 1*.

Tolerances: See *Table 4*.

Table 4

Time (h)	Amount Dissolved (%)
1	1–17
2	30–60
3	50–90
4	NLT 65
7	NLT 85

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*. Proceed as directed for *Dissolution ⟨711⟩, Procedure, Apparatus 1 and 2, Delayed-Release Dosage Forms, Method A Procedure* except to use *Acceptance Table 2*.

Medium: pH 3.0 phosphate buffer prepared by adjusting 0.05 M potassium phosphate buffer with phosphoric acid to a pH of 3.0 ± 0.05, for the first 3.5 h, followed by the addition of 5.3 M sodium hydroxide to adjust to a pH of 7.4 ± 0.05; 900 mL

Apparatus 2: 50 rpm

Times: 1, 2, 3.5, and 5 h

Analysis: Proceed as directed in *Test 1*.

Tolerances: See *Table 5*.

Table 5

Time (h)	Amount Dissolved (%)
1	13–38
2	25–50
3.5	37–65
5	85–115

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium, Apparatus 2, and **Analysis:** Proceed as directed in *Test 4*.

Times: 1, 3.5, 5, 7, and 10 h

Tolerances: See *Table 6*.

Table 6

Time (h)	Amount Dissolved (%)
1	10–30
3.5	30–60
5	50–80
7	NLT 65
10	NLT 80

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 7: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

Solution A: Dissolve 40.8 g of monobasic potassium phosphate in 6 L of water, add 667 mg of octoxynol 9, and adjust with dilute hydrochloric acid or sodium hydroxide to a pH of 4.5.

Medium: *Solution A*; 900 mL

Apparatus 2: 50 rpm

Times: 1, 2, 4, and 8 h

Analysis: Proceed as directed in *Test 1*.

Tolerances: See *Table 7*.

Table 7

Time (h)	Amount Dissolved (%)
1	10–40
2	35–70
4	60–90

Time (h)	Amount Dissolved (%)
8	NLT 85

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 8: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

Medium: pH 7.5 simulated intestinal fluid (without enzyme); 900 mL

Apparatus 1: 100 rpm

Times: 1, 2, 4, 6, and 8 h

Analysis: Proceed as directed in *Test 1*.

Tolerances: See *Table 8*.

Table 8

Time (h)	Amount Dissolved (%)
1	3–30
2	15–50
4	45–80
6	NLT 70
8	NLT 85

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 9: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 9*.

Medium 1: 0.1 N hydrochloric acid; 900 mL

Medium 2: Simulated intestinal fluid (without enzyme); 900 mL

Apparatus 1: 50 rpm

Times: 1, 2, 3, 4, and 6 h

Determine the percentage of the labeled amount of theophylline dissolved at the times specified, using *Medium 1* for the first h and *Medium 2* for the next 5 h.

Analysis: Proceed as directed in *Test 1*.

Tolerances: See *Table 9*.

Table 9

Time (h)	Amount Dissolved (%)
1	5–15
2	25–45
3	50–65
4	NLT 70
6	NLT 85

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 10: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 10*. Proceed as directed for *Test 3*.

Times: 1, 2, 4, and 8 h

Tolerances: See *Table 10*.

Table 10

Time (h)	Amount Dissolved (%)
1	6–27
2	25–50
4	65–85
8	NLT 80

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

For products labeled for dosing every 24 h

Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: 0.05 M pH 6.6 phosphate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 1000 mL

Apparatus 1: 100 rpm

Times: 1, 2, 4, 5, and 8 h

Analysis: Proceed as directed in *Test 1*.

Tolerances: See *Table 11*.

Table 11

Time (h)	Amount Dissolved (%)
1	5–15
2	12–30
4	25–50
5	30–60
8	55–75

The percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) dissolved at the times given conforms to *Dissolution ⟨711⟩, Acceptance Table 2*.

Change to read:

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

Procedure for content uniformity

Standard solution: 12 µg/mL of USP Theophylline RS

Sample solution: Nominally 12 µg/mL of theophylline, prepared as follows. Using a mortar and pestle, triturate the contents of 1 Capsule with 20 mL of water. With the aid of water, transfer the mixture to a 100-mL volumetric flask. Add 25 mL of 6 N ammonium hydroxide, shake or sonicate for 45 min, and cool to room temperature. Dilute with water to volume. Filter a portion of the mixture, discarding the first 20 mL of the filtrate. Dilute a portion of the filtrate with water to obtain the solution.

Instrumental conditions

Mode: UV

Analytical wavelength: Maximum absorbance at about 270 nm

Cell: 1 cm

Blank: Water

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Concomitantly determine the absorbance of the *Sample solution* and *Standard solution*.

Calculate the percentage of the labeled amount of theophylline ($C_7H_8N_4O_2$) in each Capsule 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, Sample stock solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

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

System suitability solution: 1 µg/mL each of USP Theophylline RS and USP Theophylline Related Compound D RS from the *Standard stock solution*

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

Sample solution: Nominally 1.0 mg/mL of theophylline from the *Sample stock solution*. Centrifuge and use the supernatant.

System suitability

Sample: *System suitability solution*

[Note—See *Table 12* for relative retention times.]

Suitability requirements

Relative standard deviation: NMT 5.0% for the theophylline and theophylline related compound D RS peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of theophylline related compound D in the portion of Capsules 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 Capsules 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 12*. Disregard peaks less than 0.1%.

Table 12

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Theophylline related compound D	0.45	0.2
Theophylline	1.0	—
Any other individual unspecified degradation product	—	0.2
Total degradation products	—	0.5

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.

• **Labeling:** The labeling indicates whether the product is intended for dosing every 12 or 24 h, and states with which in vitro *Dissolution Test* the product complies.

• **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 EXTENDED-RELEASE CAPSULES	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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