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Acetaminophen Extended-Release Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-acetamiophen-ert-20231117.

DEFINITION
Acetaminophen Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$).

IDENTIFICATION
• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K
Sample: A portion of powdered Tablets
Acceptance criteria: Meet the requirements
• **B.** The retention time of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
• **Procedure**
Solution A: Phosphoric acid and water (1:9)
Mobile phase: Methanol, *Solution A*, and water (300:1:700)
Standard solution: 0.65 mg/mL of USP Acetaminophen RS in *Mobile phase*. Prepare by first dissolving in methanol, and then diluting with *Mobile phase* to volume.
Sample stock solution: Transfer 10 Tablets to a 250-mL volumetric flask containing 50 mL of water and a magnetic stir bar. Stir for at least 30 min or until the coating has dissolved. Add 150 mL of methanol, and stir for 45 min. Tablet cores should be disintegrated at least 15 min before ending the stirring. Remove the magnetic stir bar, and rinse into the flask with methanol. Dilute with methanol to volume, and centrifuge. Use the clear supernatant.
Sample solution: Dilute 5 mL of the *Sample stock solution* with *Mobile phase* to 200 mL.
Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 295 nm
Column: 3.9-mm × 15-cm; packing L1
Flow rate: 2.0 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 3.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Acetaminophen RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of acetaminophen in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
Change to read:

- **Dissolution** ⟨711⟩

Test 1

Medium: Simulated gastric fluid TS (without enzyme); 900 mL

Apparatus 2: 50 rpm

Times: 15 min, 1 h, and 3 h

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

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium* to obtain a concentration similar to that of the *Standard solution*

Instrumental conditions

Mode: UV

Analytical wavelength: 280 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved.

Tolerances: See *Table 1*.

Table 1

Time	Amount Dissolved
15 min	45%–65%
1 h	60%–85%
3 h	NLT 85%

The percentages of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in ⟨711⟩.

For gelatin-coated Tablets

Medium, Apparatus, Standard solution, Sample solution, Instrumental conditions, and **Analysis:** Proceed as directed in *Test 1*.

Times: 30 min, 90 min, and 4 h

Tolerances: See *Table 2*.

Table 2

Time	Amount Dissolved
30 min	40%–60%
90 min	55%–85%
4 h	NLT 80%

The percentages of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in ⟨711⟩.

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

Medium, Apparatus, Standard solution, Sample solution, Instrumental conditions, and **Analysis:** Proceed as directed in *Test 1*.

Times: 15 min, 1 h, and 3 h

Tolerances: See *Table 3*.

Table 3

Time	Amount Dissolved
15 min	40%–60%
1 h	55%–75%
3 h	NLT 80%

The percentages of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in ⟨711⟩.

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

Medium: Simulated gastric fluid TS (without enzyme); 900 mL

Apparatus 2: 50 rpm

Times: 30, 90, and 240 min

Standard stock solution: 1.44 mg/mL of USP Acetaminophen RS in methanol. Sonicate to dissolve, if necessary.

Standard solution: (*L*/9000) mg/mL of USP Acetaminophen RS from *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of *Medium*. Pass the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: 280 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of acetaminophen ($C_8H_9NO_2$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result}_i = (A_U/A_S) \times C_S \times D$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Acetaminophen RS in the *Standard solution* (mg/mL)

D = dilution factor for the *Sample solution*

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of acetaminophen in the portion of sample withdrawn at time point *i* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (min)	Amount Dissolved (%)
1	30	45–65
2	90	65–85
3	240	NLT 85

The percentages of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved at the times specified conform 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*.

Medium: Gastric fluid, simulated,TS (without enzyme); deaerated, 900 mL

Apparatus 2: 50 rpm

Times: 15, 60, and 180 min

Mobile phase: Methanol, glacial acetic acid, and water (20:1:79)

Standard solution: 0.72 mg/mL of USP Acetaminophen RS prepared as follows. Transfer an appropriate quantity of USP Acetaminophen RS to a suitable volumetric flask, add 2% of the flask volume of methanol, and if necessary, sonicate to dissolve. Dilute with *Medium* to volume.

Sample solution: At the times specified, pass a portion of the solution under test through a suitable filter, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 5 µL

Run time: NLT 1.7 times of the retention time of acetaminophen

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of acetaminophen ($C_8H_9NO_2$) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}_i = (r_U/r_S) \times C_S$$

r_U = peak response of acetaminophen from the *Sample solution*

r_S = peak response of acetaminophen from the *Standard solution*

C_S = concentration of USP Acetaminophen RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of acetaminophen in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point from the *Medium* (mL)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (min)	Amount Dissolved (%)
1	15	45–65
2	60	60–80
3	180	NLT 80

The percentages of the labeled amount of acetaminophen ($C_8H_9NO_2$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.▲ (RB 1-Dec-2023)

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **4-Aminophenol in Acetaminophen-Containing Drug Products ⟨227⟩:** Meet the requirements

ADDITIONAL REQUIREMENTS

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

• **Labeling:** Where the Tablets are gelatin-coated, the label so states. When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

• **USP Reference Standards** ⟨11⟩
USP Acetaminophen RS

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

Topic/Question	Contact	Expert Committee
ACETAMINOPHEN EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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