Acetaminophen Oral Suspension

Type of Posting	Revision Bulletin, Postponement
Posting Date	27–Jul–2018
Official Date	01–Aug–2018
Expert Committee	Chemical Medicines Monographs 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Acetaminophen Oral Suspension monograph. The purpose for the revision is to postpone the implementation of the *Assay* and the test for *Organic Impurities* and the omission of the test for *4-Aminophenol in Acetaminophen-Containing Drug Products*.

The Acetaminophen Oral Suspension Revision Bulletin supersedes the revision of the Acetaminophen Oral Suspension monograph, which was published in the *First Supplement to USP 41–NF 36* and is scheduled to become official on 1–Aug–2018.

Should you have any questions, please contact Clydewyn M. Anthony, Ph.D., Senior Scientific Liaison (301-816-8139 or cma@usp.org).

Acetaminophen Oral Suspension

DEFINITION

Acetaminophen Oral Suspension is a suspension of Acetaminophen in a suitable aqueous vehicle. It contains NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen ($C_8H_9NO_2$).

IDENTIFICATION

• **A. Infrared Absorption ⟨197K⟩**

Sample: Transfer a volume of Oral Suspension, equivalent to 240 mg of acetaminophen, to a separator. Add 50 mL of ethyl acetate, and shake. Filter the ethyl acetate extract through a funnel containing glass wool and 10 g of anhydrous sodium sulfate. Collect the filtrate in a beaker, and evaporate on a steam bath to dryness. Dry the residue under vacuum over silica gel.

Acceptance criteria: The crystals so obtained meet the requirements.

Add the following:

▲• **B.** The retention time of the acetaminophen peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ 1S (USP41)

ASSAY

Add the following:

▲• **Procedure**

Mobile phase: Methanol and water (1:3)

Standard solution: 0.01 mg/mL of USP Acetaminophen RS in *Mobile phase*

Sample stock solution: Nominally 0.5 mg/mL of acetaminophen prepared as follows. Transfer 100 mg of acetaminophen from a volume of Oral Suspension, previously well shaken, to a 200-mL volumetric flask. Add 100 mL of *Mobile phase*, and shake by mechanical means for 10 min. Dilute with *Mobile phase* to volume.

Sample solution: Nominally 0.01 mg/mL of acetaminophen from the *Sample stock solution* in *Mobile phase*. Pass a portion of this solution through a filter of 0.5-µm pore size or finer, discarding the first 10 mL of the filtrate. Use the clear filtrate.

Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 243 nm
Column: 3.9-mm × 30-cm; packing L1
Flow rate: 1.5 mL/min
Injection volume: 10 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 1000 theoretical plates
Tailing factor: NMT 2.0
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 Oral Suspension 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%▲ (RB 1-Aug-2018)

Change to read:

• **Procedure**

▲**Solution A:** Acetonitrile, trifluoroacetic acid, and water (14: 0.1: 86)

Solution B: Acetonitrile, trifluoroacetic acid, and water (90: 0.1: 10)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.0	100	0
4.0	100	0
5.0	0	100
6.0	100	0
10.0	100	0

Diluent: Methanol, phosphoric acid, and water (50: 0.1: 50)

Standard stock solution: 1.6 mg/mL of USP Acetaminophen RS in *Diluent*

Standard solution: 0.064 mg/mL of USP Acetaminophen RS in *Solution A*, from *Standard stock solution*

Sample stock solution: Nominally 1.6 mg/mL of acetaminophen prepared as follows. Transfer a quantity equivalent to about 160 mg of acetaminophen from a volume of Oral Suspension, previously well shaken, to a 100-mL volumetric flask. Add 60 mL of *Diluent*, and shake by mechanical means for 30 min. Dilute with *Diluent* to volume. Mix well. Allow the sample to settle, or centrifuge.

Sample solution: Nominally 0.064 mg/mL of acetaminophen in *Solution A*, from *Sample stock solution*

Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 214 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L11
Flow rate: 1 mL/min
Injection volume: 30 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
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 Oral Suspension taken:

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

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)
C_U = nominal concentration of acetaminophen in the *Sample solution* (mg/mL)▲ (Postponed on 1-Aug-2018)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Uniformity of Dosage Units ⟨905⟩**
For single-unit containers: Meets the requirements
• **Deliverable Volume ⟨698⟩**
For multiple-unit containers: Meets the requirements

IMPURITIES

Delete the following:

▲• **4-Aminophenol in Acetaminophen-Containing Drug Products ⟨227⟩:** Meets the requirements▲ (Postponed on 1-Aug-2018)

Add the following:

▲• **Organic Impurities**
Solution A: 0.2% trifluoroacetic acid in water
Solution B: 0.2% trifluoroacetic acid in water
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0.0	98	2
1.0	98	2
8.0	80	20
9.0	5	95
10.0	5	95
10.5	98	2
13.0	98	2

Buffer: 10 mM sodium citrate dihydrate, with a pH of 4.0, prepared by adding 1.1 g of sodium citrate dihydrate and 1.3 g of citric acid monohydrate to a 1-L volumetric flask, dissolving, and diluting with water to volume. Adjust with sodium citrate dihydrate to increase the pH or with citric acid monohydrate to decrease the pH, if necessary, to achieve a pH of 4.0.
Diluent: Acetonitrile and *Buffer* (10:90)
Sensitivity solution: 0.16 µg/mL of USP Acetaminophen RS and 0.08 µg/mL of USP 4-Aminophenol RS in *Diluent*
Standard solution: 1.6 µg/mL each of USP Acetaminophen RS and USP 4-Aminophenol RS in *Diluent*
Sample solution: Nominally 1.6 mg/mL of acetaminophen in *Diluent* prepared as follows. Transfer a quantity equivalent to about 160 mg of acetaminophen from a volume of Oral Suspension, previously well shaken, to a 100-mL volumetric flask. Add 60 mL of *Diluent*, and shake by mechanical means for 1 h. Dilute with *Diluent* to volume. Mix well. Pass a portion of this solution through a suitable filter.
Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 272 nm
Column: 2.1-mm × 15-cm; 1.8-µm packing L1
Column temperature: 40°
Flow rate: 0.5 mL/min
Injection volume: 2.5 µL
System suitability
Samples: *Sensitivity solution* and *Standard solution*
[Note—See *Table 3* for relative retention times.]
Suitability requirements
Tailing factor: NMT 2.0 for acetaminophen and 4-aminophenol, *Standard solution*
Relative standard deviation: NMT 5.0% for acetaminophen and 4-aminophenol, *Standard solution*
Signal-to-noise ratio: NLT 10 for acetaminophen and 4-aminophenol, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of 4-aminophenol in the portion of Oral Suspension taken:

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

r_U = peak response of 4-aminophenol from the *Sample solution*
r_S = peak response of 4-aminophenol from the *Standard solution*
C_S = concentration of USP 4-Aminophenol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of acetaminophen in the *Sample solution* (mg/mL)

Calculate the percentage of acetaminophen dimer or any unspecified impurity in the portion of Oral Suspension taken:

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

r_U = peak response of acetaminophen dimer or any unspecified impurity 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)
C_U = nominal concentration of acetaminophen in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05% for any impurities.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
4-Aminophenol	0.28	0.15
Acetaminophen	1.0	—
Acetaminophen dimer[a]	1.57	0.15
Any unspecified impurity	—	0.15
Total impurities	—	2.0

[a] *N,N′*-(6,6′-Dihydroxy-[1,1′-biphenyl]-3,3′-diyl) diacetamide.▲ (Postponed on 1-Aug-2018)

SPECIFIC TESTS

• **pH ⟨791⟩:** 4.0–6.9

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Acetaminophen RS
  USP 4-Aminophenol RS