Pseudoephedrine Hydrochloride Extended-Release Tablets

Type of Posting	Revision Bulletin
Posting Date	22–Feb–2019
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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 Pseudoephedrine Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 4* to accommodate FDA-approved drug products with different conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using the Inertsil ODS-3V brand of column with L1 packing. The typical retention time for pseudoephedrine is about 5.5 min.

The revision also necessitates a change in the table numbering in *Dissolution Test 2.*

The Pseudoephedrine Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Yanyin Yang, Associate Scientific Liaison (301-692-3623 or yanyin.yang@usp.org).

Pseudoephedrine Hydrochloride Extended-Release Tablets

DEFINITION

Pseudoephedrine Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

IDENTIFICATION

• **A. Infrared Absorption** ⟨197K⟩

Sample: Triturate a number of Tablets, nominally equivalent to 180 mg of pseudoephedrine hydrochloride. Filter with about 10 mL of chloroform collected using vacuum filtration. Maintain the vacuum until no further filtrate can be collected, and evaporate the chloroform on a steam bath, taking care to avoid overheating. Recrystallize the residue from a small amount of dehydrated alcohol.

Acceptance criteria: Meet the requirements

• **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**

Mobile phase: Alcohol and ammonium acetate solution (1 in 250) (850:150). Filter, and degas

Standard solution: 1.2 mg/mL of USP Pseudoephedrine Hydrochloride RS in alcohol

Sample stock solution: Transfer NLT 20 Tablets to a suitable container, add 500 mL of alcohol, and homogenize until the Tablets are dispersed. Quantitatively transfer the contents of the container to a 1000-mL volumetric flask, dilute with alcohol to volume, mix, and allow to stand for the solids to settle.

Sample solution: Transfer 25.0 mL of the supernatant from the *Sample stock solution* into a 50-mL volumetric flask, dilute with alcohol to volume, and mix. Pass a portion of this solution through a filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; packing L3

Flow rate: 0.7 mL/min

Injection volume: 10 µL

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 percentage of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) 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 Pseudoephedrine Hydrochloride RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

For Tablets labeled for dosing every 12 h

Test 1

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Times: 1, 3, and 6 h

Mobile phase and **System suitability:** Proceed as directed in the *Assay*.

Standard solution: 0.13 mg/mL of USP Pseudoephedrine Hydrochloride RS in water

Sample solution: Filter a portion of the solution under test.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; packing *L3*

Flow rate: 0.7 mL/min

Injection volume: 50 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved.

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved (%)
1	25–45
3	50–75
6	NLT 75

The percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform 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*.

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Times: 1, 3, and 6 h

Standard solution: A known concentration of USP Pseudoephedrine Hydrochloride RS in *Medium*.

Sample solution: Pass portions of the solution under test through a filter of 0.45-µm pore size, and suitably dilute with *Medium*.

Analysis: Calculate the percentage of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by comparing the maximum absorbance of *Sample solution* with that of *Standard solution* at about 214 nm.

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved (%)
1	25–45
3	60–80

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Table 2 *(continued)*

Time (h)	Amount Dissolved (%)
6	NLT 80

The percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) 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, Apparatus,and **Times:** Proceed as directed in *Test 1*.

Solution A: Acetonitrile and water (45:55)

Mobile phase: 2.5 g/L of docusate sodium in *Solution A*. Add 1.0 mL of phosphoric acid. Adjust with ammonia water, 25% to a pH of 3.2.

Standard solution: (*L*/900) mg/mL of USP Pseudoephedrine Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet.

Sample solution: Withdraw a portion of the solution under test from each vessel at the specified time point and pass through a suitable filter of 0.45-µm pore size. Replace the portion of solution withdrawn with an equal volume of *Medium* previously equilibrated to 37.0° ± 0.5°.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of pseudoephedrine

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 concentration (C_i) of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the sample withdrawn from the vessel at each time point *i*:

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

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

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

C_S = concentration of USP Pseudoephedrine Hydrochloride RS in the *Standard solution*

Calculate the percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) 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 pseudoephedrine hydrochloride in the portion of sample withdrawn at time point *i* (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Tablet)

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

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	27–47
2	3	53–73
3	6	NLT 80

The percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-Mar-2019)

For Tablets labeled for dosing every 24 h

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

Medium: 0.9% sodium chloride in water; 50 mL

Apparatus 7 (see **Drug Release** ⟨724⟩**):** 30 cycles/min; 2–3 cm amplitude. To prepare the sample, see *Figure 1*.

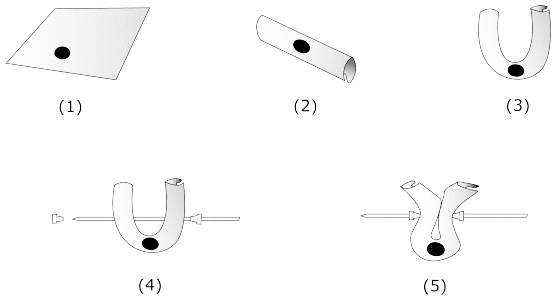

Figure 1. Steps to prepare the sample. (1) Place 1 Tablet on a 5-cm × 5-cm nylon netting. (2) Fold the netting over the Tablet. Continue folding until the Tablet is enclosed in the netting. (3) Fold the netting so that the two open ends meet. The Tablet should be enveloped in the center of the netting. (4) Insert a rod (see Drug Release ⟨724⟩, Figure 4c) through the netting to secure the Tablet. (5) Secure the netting with HPLC plastic ferrules or other appropriate device. Trim the excess netting. Attach each sample holder to the vertically reciprocating sample holder.

Times: 2, 8, 14, and 24 h

Solution A: Transfer 200 mL of water to a 1000-mL volumetric flask. Add 3.4 mL of phosphoric acid and 5 mL of triethylamine. Add water to almost 900 mL. Adjust with 1 N sodium hydroxide to a pH of about 6.8, dilute with water to volume, and mix.

Mobile phase: Methanol and *Solution A* (100:900)

System suitability solution: 0.4 mg/mL of USP Pseudoephedrine Hydrochloride RS in water

Sample solution: Solution under test

Standard solution: Known concentrations of USP Pseudoephedrine Hydrochloride RS in water, in a range

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around the expected concentration of the *Sample solution* at each time interval.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 5-cm; packing L1
Flow rate: 1.5 mL/min
Injection volume: 10 µL

System suitability
Sample: *System suitability solution*
Suitability requirements
Tailing factor: NMT 2
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Sample solution* and *Standard solution*
Measure the major peak responses of the *Standard solution* and *Sample solution*. Construct a calibration curve by plotting the peak response versus concentrations of the *Standard solution*. Determine the amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at each time interval from a linear regression analysis of the calibration curve.

Tolerances: See *Table* ▲*4*▲ (RB 1-Mar-2019).

Table ▲**4**▲ (RB 1-Mar-2019)

Time (h)	Amount Dissolved (%)
2	20–35
8	40–65
14	60–90
24	NLT 85

The percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** 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 Pseudoephedrine Hydrochloride RS

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