Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2014
Document Type: USP Monographs
DocId: GUID-08FC5286-8F86-4F14-9EED-EC76A77E5F60_1_en-US
DOI: https://doi.org/10.31003/USPNF_M4576_01_01
DOI Ref: 3ztz9



# Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

## DEFINITION

Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

## IDENTIFICATION

**A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

## ASSAY

• **Cetirizine Hydrochloride**

**Buffer:** 3.5 g/L of monobasic ammonium phosphate and 1.0 g/L of tetrabutylammonium bisulfate in water. Adjust with phosphoric acid to a pH of 2.5.

**Diluent:** Methanol and *Buffer* (2:3)

**Solution A:** Acetonitrile, methanol, and *Buffer* (9:2:29)

**Solution B:** Acetonitrile

**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 100 | 0 |
| 27.0 | 100 | 0 |
| 30.0 | 0 | 100 |
| 30.1 | 100 | 0 |
| 35.0 | 100 | 0 |

**Standard stock solution:** 0.5 mg/mL of USP Cetirizine Hydrochloride RS in *Diluent*. [Note—Sonicate to dissolve.]

**Standard solution:** 0.025 mg/mL of USP Cetirizine Hydrochloride RS in *Diluent* from the *Standard stock solution*

**Sample solution:** 0.025 mg/mL of cetirizine hydrochloride (from NMT 10 finely powdered Tablets) prepared as follows. Dissolve the Tablets first in methanol, using 22.5% of the final flask volume. Sonicate for NLT 20 min with vigorous swirling every 5 min. To the solution add a volume of *Buffer* equal to 26% of the final flask volume. Allow the solution to equilibrate to room temperature. Dilute with *Diluent* to volume. Pass a portion through a membrane filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4.6-mm × 15-cm; 3.5-µm packing L1

**Temperatures**

**Column:** 30°

**Autosampler:** 5°

**Flow rate:** 1 mL/min

**Injection volume:** 25 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Column efficiency:** NLT 3000 theoretical plates

**Tailing factor:** NMT 1.5

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) in the portion of Tablets taken:

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

$r_U$ = peak response of cetirizine from the *Sample solution*

$r_S$ = peak response of cetirizine from the *Standard solution*

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

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

**Acceptance criteria:** 90.0%–110.0%

- **Pseudoephedrine Hydrochloride**

**Buffer:** 0.8 g/L of ammonium acetate in water. To 1 L of the solution add 1.0 mL of triethylamine. Adjust with glacial acetic acid to a pH of 4.5.

**Mobile phase:** Acetonitrile and *Buffer* (3:7)

**Standard solution:** 0.5 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Mobile phase*. [Note—Sonicate to dissolve.]

**Sample stock solution:** 2.4 mg/mL of pseudoephedrine hydrochloride (from 5 finely powdered Tablets) prepared as follows. Dissolve the crushed Tablets first in acetonitrile, using 24% of the final flask volume. Sonicate for NLT 15 min. To the solution add a volume of *Buffer* equal to 56% of the final flask volume. Sonicate for NLT 15 min. Shake the flask for NLT 10 min. Allow the solution to equilibrate to room temperature. Dilute with *Mobile phase* to volume. Centrifuge a portion for 15 min to obtain a clear supernatant.

**Sample solution:** 0.5 mg/mL of pseudoephedrine hydrochloride in *Mobile phase* from the *Sample stock solution.* Pass the solution through a membrane 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; 5-µm packing L9

**Flow rate:** 1.5 mL/min

**Injection volume:** 25 µL

**Run time:** 2 times the retention time of pseudoephedrine

**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 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 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* (mg/mL)

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

**Acceptance criteria:** 90.0%–110.0%

## PERFORMANCE TESTS

- **Dissolution ⟨711⟩**

**Test 1**

**Medium:** 0.1 N hydrochloric acid; 500 mL, deaerated

**Apparatus 1:** 100 rpm

**Time:** 30 min for cetirizine hydrochloride and 30 min (used only for adjustments in the calculations); 1, 2, and 6 h for pseudoephedrine hydrochloride

**Buffer:** 0.77 g/L of ammonium acetate in water. To 1 L of the solution add 1.0 mL of triethylamine. Adjust with glacial acetic acid to a pH of 4.5 ± 0.05.

**Mobile phase:** Acetonitrile and *Buffer* (3:7)

**Standard stock solution:** 0.5 mg/mL of USP Cetirizine Hydrochloride RS in water

**Standard solution:** 0.24 mg/mL of USP Pseudoephedrine Hydrochloride RS and 0.01 mg/mL of USP Cetirizine Hydrochloride RS in *Medium* from the *Standard stock solution*

**Sample solution:** At the times specified, withdraw 5 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size, discarding the first few mL.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV, 230 nm for cetirizine hydrochloride, 254 nm for pseudoephedrine hydrochloride

**Column:** 4.6-mm × 15-cm; 5-µm packing L9

**Flow rate:** 1.5 mL/min

**Injection volume:** 25 µL

**Run time:** 2 times the retention time of pseudoephedrine

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0 for both cetirizine and pseudoephedrine

**Relative standard deviation:** NMT 2.0% for both cetirizine and pseudoephedrine

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of cetirizine hydrochloride dissolved:

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

$r_U$ = peak response of cetirizine from the *Sample solution*

$r_S$ = peak response of cetirizine from the *Standard solution*

$C_S$ = concentration of cetirizine hydrochloride in the *Standard solution* (mg/mL)

$L$ = label claim for cetirizine hydrochloride (mg/Tablet)

$V$ = volume of *Medium,* 500 mL

Calculate the percentage of pseudoephedrine hydrochloride dissolved at each time point:

$$Q_{30} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_1 = (Q_{30} \times 5/500) + [(r_U/r_S) \times (C_S/L) \times 495 \times 100]$$

$$Q_2 = (Q_{30} \times 5/500) + (Q_1 \times 5/495) + [(r_U/r_S) \times (C_S/L) \times 490 \times 100]$$

$$Q_6 = (Q_{30} \times 5/500) + (Q_1 \times 5/495) + (Q_2 \times 5/490) + [(r_U/r_S) \times (C_S/L) \times 485 \times 100]$$

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

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

$C_S$ = concentration of pseudoephedrine hydrochloride in the *Standard solution* (mg/mL)

$L$ = label claim for pseudoephedrine hydrochloride (mg/Tablet)

$V$ = initial volume of *Medium*, 500 mL

**Tolerances**

**Cetirizine hydrochloride:** NLT 80% ($Q$) of the labeled amount of cetirizine hydrochloride is dissolved in 30 min.

**Pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$):** See *Table 2*.

**Table 2**

| Time (h) | Amount Dissolved |
|---|---|
| 1 | 30%–50% |
| 2 | 50%–70% |
| 6 | NLT 80% |

The percentages of the labeled amount of pseudoephedrine hydrochloride 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:** 0.1 N HCl; 500 mL

**Apparatus 1:** 100 rpm

**Time:** 30 min for cetirizine hydrochloride and 30 min (used only for adjustments in the calculations); 1, 2, 4 and 8 h for pseudoephedrine hydrochloride

**Buffer:** 6.8 g/L of sodium acetate and 16.2 g/L of sodium 1-octanesulfonate

**Mobile phase:** Methanol and *Buffer* (50:50). Adjust with glacial acetic acid to a pH of 5.5.

**Standard solution:** 0.01 mg/mL of USP Cetirizine Hydrochloride RS and 0.24 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Medium*

**Sample solution:** Pass a 5-mL portion of the solution under test through a suitable filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 242 nm

**Column:** 4.6-mm × 10-cm; 5-µm packing L1

**Column temperature:** 35°

**Flow rate:** 2 mL/min

**Injection volume:** 100 µL

**System suitability**

[Note—The relative retention times for pseudoephedrine and cetirizine are 1.0 and 2.9, respectively.]

**Sample:** *Standard solution*

**Suitability requirements**

**Column efficiency:** NLT 2000 theoretical plates for both pseudoephedrine and cetirizine

**Tailing factor:** NMT 2.0 for both pseudoephedrine and cetirizine

**Relative standard deviation:** NMT 2.0% for both pseudoephedrine and cetirizine

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) dissolved:

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

$r_U$ = peak response of cetirizine from the *Sample solution*

$r_S$ = peak response of cetirizine from the *Standard solution*

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

$L$ = label claim (mg/Tablet)

$V$ = volume of *Medium*, 500 mL

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 ($i$) shown in *Table 3*:

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

$r_U$ = 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* (mg/mL)

Calculate the percentage of the labeled amounts ($Q_i$) of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at each time point ($i$) shown in *Table 3*:

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

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

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

$$\text{Result}_4 = \{[C_4 \times [V - (3 \times V_S)]] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_5 = \{[C_5 \times [V - (4 \times V_S)]] + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

$V$ = volume of the *Medium* (500 mL)

$V_S$ = volume of the *Sample solution* withdrawn from the *Medium* (mL)

$L$ = label claim for pseudoephedrine hydrochloride (mg/Tablet)

**Tolerances**

**Cetirizine hydrochloride:** NLT 75% (*Q*) of the labeled amount of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) is dissolved.

**Pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$):** See *Table 3*.

**Table 3**

| Time Point (*i*) | Time (h) | Amount Dissolved |
|---|---|---|
| 1 | 0.5 | — |
| 2 | 1 | 30%–50% |
| 3 | 2 | 50%–70% |
| 4 | 4 | 70%–90% |
| 5 | 8 | NLT 80% |

The percentages of the labeled amount of pseudoephedrine hydrochloride dissolved at the times specified conform to *Acceptance Table 2* in ⟨711⟩.

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

**IMPURITIES**

• **Cetirizine Hydrochloride Related Compounds**

**Buffer, Diluent, Solution A,** and **Solution B:** Proceed as directed in the *Assay* for *Cetirizine hydrochloride*.

**Mobile phase:** See *Table 4*.

**Table 4**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 100 | 0 |
| 27 | 100 | 0 |
| 45 | 60 | 40 |
| 65 | 60 | 40 |
| 65.1 | 100 | 0 |
| 75 | 100 | 0 |

**Standard stock solution:** 0.5 mg/mL of USP Cetirizine Hydrochloride RS in *Diluent*. [Note—Sonicate to dissolve.]

**Standard solution:** 1 µg/mL of USP Cetirizine Hydrochloride RS in *Diluent* from the *Standard stock solution*

**Sample stock solution:** 0.5 mg/mL of cetirizine hydrochloride (from NMT 10 finely powdered Tablets) prepared as follows. Dissolve the Tablets first in methanol, using 70% of the final flask volume. Sonicate for 15 min, and then shake for 15 min. Allow the solution to cool to

room temperature, and dilute with methanol to volume. Centrifuge a portion for 10 min.

**Sample solution:** 0.2 mg/mL of cetirizine hydrochloride in *Buffer* from the *Sample stock solution.* Pass a portion through a suitable membrane filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4.6-mm × 15-cm; 3.5-µm packing L1

**Temperatures**

**Column:** 30°

**Autosampler:** 5°

**Flow rate:** 1 mL/min

**Injection volume:** 25 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Column efficiency:** NLT 1300 theoretical plates

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 5.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

$r_U$ = peak response of the individual impurity from the *Sample solution*

$r_S$ = peak response of cetirizine from the *Standard solution*

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

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

$F$ = relative response factor (see *Table 5*)

**Acceptance criteria:** See *Table 5*.

[NOTE—Disregard any peak less than 0.05% of the main peak.]

**Table 5**

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Cetirizineethanol[a] | 0.54 | 1.4 | 0.3 |
| Chlorobenzhydryl piperazine (CBHP)[b] | 0.57 | 1.5 | 0.3 |
| Cetirizine | 1.0 | — | — |
| Cetirizine acetic acid[c] | 1.30 | 1.1 | 0.3 |
| Cetirizine *N*-oxide[d] | 1.47 | 1.2 | 0.3 |
| Any unspecified degradation product | — | 1.0 | 0.2 |
| Total impurities | — | — | 0.8 |

[a] 2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethanol.

[b] 1-[(4-Chlorophenyl)phenylmethyl]piperazine.

[c] 2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]acetic acid.

[d] 2-[4-[(4-Chlorophenyl)phenylmethyl]-1-oxide-1-piperazinyl]ethoxy]acetic acid.

- **Pseudoephedrine Hydrochloride Related Compounds**

**Buffer:** 11.2 g/L of sodium perchlorate monohydrate in water. Adjust with hydrochloric acid to a pH of 2.7.

**Solution A:** Methanol and *Buffer* (3:17)

**Solution B:** Methanol and *Buffer* (1:1)

**Diluent:** *Solution A*

**Mobile phase:** See *Table 6*.

**Table 6**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 100 | 0 |
| 10 | 100 | 0 |
| 35 | 28 | 72 |

**Standard stock solution:** 0.48 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Diluent*

**Standard solution:** 4.8 µg/mL of USP Pseudoephedrine Hydrochloride RS in *Diluent* from the *Standard stock solution*

**System suitability stock solution:** 49 µg/mL of ephedrine in *Diluent* from USP Ephedrine Sulfate RS

**System suitability solution:** 1.96 µg/mL of ephedrine and 0.46 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Standard stock solution* from the *System suitability stock solution* and the *Standard stock solution*, respectively

**Sample stock solution:** 2.4 mg/mL of pseudoephedrine hydrochloride (from NMT 25 finely powdered Tablets) prepared as follows. Dissolve the Tablets first in methanol, using 75% of the final flask volume. Sonicate for NLT 15 min, and then shake for 15 min. Allow the solution to cool to room temperature, and dilute with methanol to volume. Centrifuge a portion for 10 min.

**Sample solution:** 0.48 mg/mL of pseudoephedrine hydrochloride in *Diluent* from the *Sample stock solution.* Pass a portion through a suitable membrane filter of 0.45-µm pore size.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 212 nm

**Column:** 4.6-mm × 25-cm; 4-µm packing L11

**Column temperature:** 40°

**Flow rate:** 1 mL/min

**Injection volume:** 30 µL

**System suitability**

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

**Suitability requirements**

**Resolution:** NLT 1.3 between ephedrine and pseudoephedrine, *System suitability solution*

**Tailing factor:** NMT 1.5, *Standard solution*

**Relative standard deviation:** NMT 3.0%, *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

$r_U$ = peak response of the individual impurity 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* (mg/mL)

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

$F$ = relative response factor (see *Table 7*)

**Acceptance criteria:** See *Table 7*.

[Note—Disregard any peak less than 0.05% of the main peak.]

**Table 7**

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Ephedrine[a,b] | 0.95 | — | — |
| Pseudoephedrine | 1.0 | — | — |
| Methcathinone[c] | 1.1 | 1.1 | 0.2 |
| Any unspecified degradation product | — | 1.0 | 0.2 |
| Total pseudoephedrine related impurities | — | — | 0.5 |

[a] [*R*-(*R**,*S**)]-α-[1-(Methylamino)ethyl]-benzenemethanol.

[b] For system suitability and identification purposes only.

[c] 2-Methylamino-1-phenylpropan-1-one.

**Sum of cetirizine and pseudoephedrine related impurities:** NMT 1.0%

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.
- **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 Cetirizine Hydrochloride RS
USP Ephedrine Sulfate RS
USP Pseudoephedrine Hydrochloride RS

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| CETIRIZINE HYDROCHLORIDE AND PSEUDOEPHEDRINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS | Documentary Standards Support | SM52020 Small Molecules 5 |

**Chromatographic Database Information:** Chromatographic Database

**Most Recently Appeared In:**
Pharmacopeial Forum: Volume No. PF 36(1)

**Current DocID: GUID-08FC5286-8F86-4F14-9EED-EC76A77E5F60_1_en-US**
**DOI: https://doi.org/10.31003/USPNF_M4576_01_01**
**DOI ref: 3ztz9**