Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

DEFINITION

Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets contain NLT 95.0% and NMT 105.0% of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) 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*.
- **B. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST ⟨201⟩**

Standard solution A: 6 mg/mL of USP Fexofenadine Hydrochloride RS in methanol

Standard solution B: 12 mg/mL of USP Pseudoephedrine Hydrochloride RS in methanol

Sample solution: Transfer the equivalent of 30 mg of fexofenadine hydrochloride and 60 mg of pseudoephedrine hydrochloride from finely powdered Tablets (NLT 4) into a suitable vessel, and add 5 mL of methanol. Cap the vessel, and shake vigorously for 2 min. Pass the resulting suspension through a suitable filter of 0.45-µm pore size. Use the filtrate.

Adsorbent: 0.2-mm layer of high-performance thin-layer chromatographic silica gel mixture. Dry the plate at 105° for 1 h before use.

Application volume: 10 µL

Developing solvent system: Toluene, dehydrated alcohol, and ammonium hydroxide (50:45:5)

Analysis: Proceed as directed, using the *Developing solvent system*. After removal of the plate, mark the solvent front, and allow the plate to air-dry. Heat the plate at 105° until the odor of ammonia disappears (about 5 min). Allow the plate to cool, and examine under UV light at 254 nm. [NOTE—The R_F values for fexofenadine and pseudoephedrine are 0.17 and 0.39, respectively.]

Acceptance criteria: The R_F value of fexofenadine hydrochloride in the *Sample solution* is comparable to that of fexofenadine hydrochloride in *Standard solution A*. The R_F value of pseudoephedrine hydrochloride in the *Sample solution* is comparable to that of pseudoephedrine hydrochloride in *Standard solution B.*

ASSAY

- **PROCEDURE**

Solution A: Dissolve 6.8 g of sodium acetate and 16.22 g of sodium 1-octanesulfonate in water and dilute with water to 1 L. Adjust with glacial acetic acid to a pH of 4.6.

Mobile phase: Methanol and *Solution A* (13:7)

Diluent: Methanol and *Solution A* (3:2)

System suitability solution: Transfer 40 mg of USP Pseudoephedrine Hydrochloride RS to a 50-mL volumetric flask. Add 5 mL of *tert*-butylhydroperoxide solution, and sonicate. Cover the flask opening with aluminum foil, and place the flask in an oven at 90° for 60 min. Remove from the oven, and allow to cool. Add 35 mL of *Mobile phase*, and cool to room temperature. Dilute with *Mobile phase* to volume. The degradation of pseudoephedrine hydrochloride by this process produces the related compound ephedrone.

Related compounds stock solution: Dissolve quantities of USP Fexofenadine Related Compound A RS and decarboxylated degradant[1] in a volume of methanol, and dilute with *Solution A* to obtain a ratio of methanol to *Solution A* of 3:2. Dilute with *Diluent* to obtain a solution having concentrations of 0.2 mg/mL for each component.

Related compounds solution: 0.02 mg/mL each of USP Fexofenadine Related Compound A RS and decarboxylated degradant from *Related compounds stock solution* diluted with *Mobile phase*

Standard stock solution: 0.4 mg/mL of fexofenadine hydrochloride and 0.8 mg/mL of pseudoephedrine hydrochloride from USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS, respectively, in *Mobile phase*

Standard solution: Dilute 6.0 mL of the *Standard stock solution* and 15.0 mL of the *Related compounds solution* with *Mobile phase* to 50 mL to obtain a solution having known concentrations of 0.096 mg/mL of pseudoephedrine hydrochloride, 0.048 mg/mL of fexofenadine hydrochloride, 0.006 mg/mL of fexofenadine related compound A, and 0.006 mg /mL of decarboxylated degradant.

Sample stock solution: Nominally equivalent to 1.2 mg/mL of fexofenadine hydrochloride and 2.4 mg/mL of pseudoephedrine hydrochloride. To prepare, transfer NLT 10 whole Tablets to a 500-mL volumetric flask. Add 300 mL of methanol, and shake by mechanical means at high speed for 60 min. Sonicate the flask for 60 min at 40°. Add 150 mL of *Solution A*, and sonicate for 60 min at 40°. Vent the flask, and vigorously shake the flask by hand at 15-min intervals during the mechanical shaking and sonication steps. Cool to room temperature, and dilute with *Solution A* to volume to obtain a final concentration. Pass a portion of this solution through a filter of 0.45-µm or finer pore size, and use the filtrate.

Sample solution: 0.048 mg/mL and 0.096 mg/mL of fexofenadine hydrochloride and pseudoephedrine hydrochloride, respectively, from the *Sample stock solution* diluted with *Mobile phase*

[NOTE—Alternatively, centrifuge the *Sample stock solution* and use the supernatant to prepare the *Sample solution*. Filter the *Sample solution* before analysis.]

Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 5-cm; 5-µm packing L6 connected in series to a 4.6-mm × 25-cm; 5-µm packing L11
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection size: 20 µL

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

[NOTE—The relative retention times for pseudoephedrine and ephedrone are 1.0 and 1.2, respectively (*System suitability solution*); and for fexofenadine, fexofenadine related compound A, and decarboxylated degradant are 1.0, 1.2, and 3.1, respectively (*Standard solution*).]

Suitability requirements
Resolution: NLT 1.5 between pseudoephedrine and ephedrone, *System suitability solution*; NLT 2.0 between fexofenadine and fexofenadine related compound A, *Standard solution*
Relative standard deviation: NMT 1.0% for replicate injections based on the pseudoephedrine peak, *System suitability solution*; NMT 1.0% for replicate injections based on the fexofenadine peak, *Standard solution*

[1] Available from USP as USP Fexofenadine Related Compound C AS, Cat# 1270446.

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate separately the percentage of the labeled amount of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the Tablets taken:

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

r_U = peak response of either fexofenadine or pseudoephedrine from the *Sample solution*
r_S = peak response of either fexofenadine or pseudoephedrine from the *Standard solution*
C_S = concentration of either USP Fexofenadine Hydrochloride RS or USP Pseudoephedrine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of either fexofenadine hydrochloride or pseudoephedrine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩

Test 1
Medium: 0.001 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Times
Fexofenadine hydrochloride: 15 and 45 min
Pseudoephedrine hydrochloride: 45 min; 3, 5, and 12 h
Solution A: 7.0 mg/mL of monobasic sodium phosphate monohydrate in water. Adjust with 85% phosphoric acid to a pH of 2.00 ± 0.05.
Mobile phase: Acetonitrile and *Solution A* (9:11)
Standard solution: Dissolve quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in *Medium*, and dilute to obtain a solution containing known concentrations similar to those expected in the *Sample solution*. [NOTE—A small amount of methanol, NMT 0.5% of the total volume, can be used to dissolve the fexofenadine hydrochloride.]
Sample solution: Pass a portion of the solution under test through a suitable nylon filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 25-cm; packing L6
Flow rate: 1 mL/min
Injection size: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between fexofenadine and pseudoephedrine
Tailing factor: NMT 1.5 for fexofenadine and pseudoephedrine
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentages of $C_{32}H_{39}NO_4 \cdot HCl$ and $C_{10}H_{15}NO \cdot HCl$ dissolved.
Tolerances
Fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$): NLT 65% (*Q*) of the labeled amount is dissolved in 15 min and NLT 80% (*Q*) of the labeled amount is dissolved in 45 min.
Pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$): See *Table 1*.

Table 1

Time	Amount Dissolved
45 min	NMT 36%
3 h	45%–69%
5 h	61%–80%
12 h	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 the product meets USP *Dissolution Test 2*.
Medium: 0.001 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Times
Fexofenadine hydrochloride: 45 min
Pseudoephedrine hydrochloride: 30 min; 2, 4, and 12 h
Solution A: 2.7 mg/mL of monobasic potassium phosphate and 2.2 mg/mL of sodium 1-octanesulfonate in water. Adjust with phosphoric acid to a pH of 2.50 ± 0.05.
Mobile phase: Methanol, acetonitrile, and *Solution A* (3:3:4)
Fexofenadine standard stock solution: Transfer 66 mg of USP Fexofenadine Hydrochloride RS to a 100-mL volumetric flask. Add 10 mL of methanol, and swirl until dissolved. Add 50 mL of *Medium*, and mix. Allow the solution to equilibrate to room temperature, and dilute with *Medium* to volume.
Pseudoephedrine standard stock solution: Transfer 66 mg of USP Pseudoephedrine Hydrochloride RS to a 100-mL volumetric flask. Add 10 mL of methanol, and swirl until dissolved. Add 50 mL of *Medium*, and mix. Allow the solution to equilibrate to room temperature, and dilute with *Medium* to volume.
Standard solution: 66 µg/mL of USP Fexofenadine Hydrochloride RS and 132 µg/mL of USP Pseudoephedrine Hydrochloride RS from a mixture of *Fexofenadine standard stock solution* and *Pseudoephedrine standard stock solution* diluted with *Medium*
Sample solution: Pass a 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 215 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Flow rate: 1.5 mL/min
Injection size: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between fexofenadine and pseudoephedrine
Tailing factor: NMT 2.0 for fexofenadine and NMT 2.5 for pseudoephedrine
Relative standard deviation: NMT 2.0% for both peaks
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentages of $C_{32}H_{39}NO_4 \cdot HCl$ and $C_{10}H_{15}NO \cdot HCl$ dissolved.

Tolerances

Fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$): NLT 80% (*Q*) of the labeled amount is dissolved in 45 min.

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

Table 2

Time	Amount Dissolved
30 min	NMT 35%
2 h	38%–58%
4 h	56%–76%
12 h	NLT 80%

The percentages of the labeled amount of pseudoephedrine hydrochloride 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 the product meets USP *Dissolution Test 3*.

Medium: 0.001 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Times

Fexofenadine hydrochloride: 30 min

Pseudoephedrine hydrochloride: •0.5, 2, 4,• (RB 1-Oct-2010) and 12 h

•**Buffer solution:** 6.64 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 2.50 ± 0.05.

Mobile phase: *Buffer solution* and acetonitrile (3:2)

Standard solution: [NOTE—A small amount of methanol, not exceeding 0.5% of the final total volume, can be used to dissolve fexofenadine hydrochloride.] Prepare a solution in *Medium* containing known concentrations of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS similar to those expected in the solution under test.

Sample solution: Pass a portion of the solution under test through a suitable PVDF or nylon filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 2.5 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for fexofenadine and pseudoephedrine

Relative standard deviation: NMT 2.0% for both peaks

Calculate the percentages of fexofenadine hydrochloride and pseudoephedrine hydrochloride dissolved.•(RB 2-Nov-2009)

Tolerances

Fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$): NLT 80% (*Q*) of the labeled amount is dissolved in 30 min.

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

•**Table 3**

Time (h)	Amount Dissolved
0.5	13%–33%
2	35%–55%
4	50%–70%
12	NLT 80%

• (RB 1-Oct-2010)

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

Test 4: For products labeled with a dosing interval of 24 h. If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 4*.

Medium: 0.001 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Times

Fexofenadine hydrochloride: 30 min

Pseudoephedrine hydrochloride: 3, 7, and 23 h

Determine the percentages of the labeled amounts of fexofenadine hydrochloride and of pseudoephedrine hydrochloride dissolved by using the chromatographic procedure described in *Test 1*.

Tolerances

Fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$): NLT 80% (*Q*) of the labeled amount is dissolved in 30 min.

Pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$): See *Table 4*.

Table 4

Time (h)	Amount Dissolved
3	10%–30%
7	35%–65%
23	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

[NOTE—On the basis of knowledge of the product, perform either: (a) *Organic Impurities, Procedure 1* or (b) *Organic Impurities, Procedure 2*, *Organic Impurities, Procedure 3*, and *Organic Impurities, Procedure 4*.]

• **ORGANIC IMPURITIES, PROCEDURE 1**

Solution A, Mobile phase, System suitability solution, Diluent, Related compounds stock solution, Related compounds solution, Standard stock solution, and **Standard solution:** Proceed as directed in the *Assay*.

Sample solution: Use the *Sample stock solution*, prepared as directed in the *Assay*.

Reference solution: Use the *Sample solution*, prepared as directed in the *Assay*.

Chromatographic system

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

Mode, Detector, Column, Column temperature, Flow rate, and **Injection size:** Proceed as directed in the *Assay*.

System suitability

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

[NOTE—The relative retention times for pseudoephedrine and ephedrone are 1.0 and 1.2, respectively (*System suitability solution*); and for fexofenadine, fexofenadine related compound A, and decarboxylated degradant are 1.0, 1.2, and 3.1, respectively (*Standard solution*).]

Suitability requirements

Resolution: NLT 1.7 between pseudoephedrine and ephedrone, *System suitability solution*; NLT 2.0 between fexofenadine and fexofenadine related compound A, *Standard solution*

Relative standard deviation: NMT 1.0% for replicate injections based on the pseudoephedrine peak, *System suitability solution*; NMT 1.0% for replicate injections based on the fexofenadine peak and NMT 3.0% based on the individual peaks for fexofenadine related compound A and decarboxylated degradant, *Standard solution*

Analysis

Samples: *Sample solution* and *Reference solution*

Calculate the percentage of fexofenadine related compound A and decarboxylated degradant in the portion of Tablets taken:

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

r_U = individual peak area response of either fexofenadine related compound A or decarboxylated degradant from the *Sample solution*

r_S = peak area response of fexofenadine related compound A or decarboxylated degradant from the *Standard solution*

C_S = concentration of either USP Fexofenadine Related Compound A RS or decarboxylated degradant in the *Standard solution* (mg/mL)

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

Calculate the percentage of ephedrone 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 height response for ephedrone from the *Sample solution*

r_S = peak height response for 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 for ephedrone, 0.394

Calculate the percentage of any other impurities in the portion of Tablets taken:

$$\text{Result} = r_U/(F \times r_S + r_T) \times 100$$

r_U = individual peak area response for an individual unknown impurity from the *Sample solution*

F = difference in concentration between the *Sample solution* and the *Reference solution*, 25

r_S = peak area response for fexofenadine hydrochloride from the *Reference solution*

r_T = sum of the peak area responses of all unknown impurities from the *Sample solution*

[NOTE—Disregard any peak below 0.05%.]

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Pseudoephedrine	1.0	—
Ephedrone	1.2[a]	0.2
Fexofenadine	1.0	—
Fexofenadine related compound A	1.2[b]	0.4
Decarboxylated degradant[c]	3.1[b]	0.2
Tertiary dehydrated impurity[d]	1.8	0.2
Any other individual impurity	—	0.2
Total impurities	—	0.8

[a] Relative to pseudoephedrine.

[b] Relative to fexofenadine.

[c] (±)-4-(1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene.

[d] 4-[4{4-(Diphenylmethylene)-1-piperidinyl}-1-hydroxybutyl]-2,2-dimethyl phenyl acetic acid.

• **ORGANIC IMPURITIES, PROCEDURE 2**

Solution A: Dissolve 2.7 g of monobasic potassium phosphate and 2.2 g of sodium 1-octanesulfonate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.50 ± 0.05.

Mobile phase: Methanol and *Solution A* (3:2)

Standard stock solution: 0.18 mg/mL USP Fexofenadine Hydrochloride RS in *Mobile phase*

Standard solution: 0.0108 mg/mL of USP Fexofenadine Hydrochloride RS in *Mobile phase*, prepared from the *Standard stock solution*

Sensitivity solution: 0.54 µg/mL of USP Fexofenadine Hydrochloride RS in *Mobile phase*, prepared from the *Standard solution*

Sample solution: Weigh and finely powder 9 Tablets, and quantitatively transfer the ground powder to a 500-mL volumetric flask, with the aid of 200 mL of *Mobile phase*. Sonicate for 10 min, and add an additional 100 mL of *Mobile phase*. Shake by mechanical means for 30 min, and dilute with *Mobile phase* to volume. Pass a portion of the solution through a polyproplyene or polysulfone membrane filter of 0.45-µm pore size, and discard at least the first 10 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 20 µL

[NOTE—The run time is six times the retention time of fexofenadine.]

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Signal-to-noise: NLT 10, *Sensitivity solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the amount of each impurity as a percentage of the label claim of fexofenadine hydrochloride 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 for individual impurities from the *Sample solution*
r_S = peak response for fexofenadine from the *Standard solution*
C_S = concentration of USP Fexofenadine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of fexofenadine hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor for each impurity (see *Table 6*)

Acceptance criteria: See *Table 6*.

Table 6

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fexofenadine	1.0	1.0	—
Meta fexofenadine	1.14	1.0	0.2
Fexofenadine related compound A	1.38	0.83	0.4
Tertiary dehydrated impurity[a]	2.25	1.3	0.2
Individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	0.5

[a] 4-[4{4-(Diphenylmethylene)-1-piperidinyl}-1-hydroxybutyl]-2,2-dimethyl phenyl acetic acid.

- **ORGANIC IMPURITIES, PROCEDURE 3**

Solution A: 4 mg/mL of ammonium acetate
Mobile phase: Methanol and *Solution A* (19:1)
Diluent: Methanol and water (1:1)
Standard stock solution: 0.18 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Diluent*
Standard solution: 0.0216 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Diluent*, prepared from the *Standard stock solution*
Sensitivity solution: 1.08 µg/mL of USP Pseudoephedrine Hydrochloride RS in *Diluent*, prepared from the *Standard solution*
Sample solution: Weigh and finely powder 9 Tablets, and quantitatively transfer the ground powder to a 500-mL volumetric flask, with the aid of 200 mL of *Diluent*. Sonicate for 10 min, and add an additional 100 mL of *Diluent*. Shake by mechanical means for 30 min, dilute with *Diluent* to volume, and mix. Pass a portion of the solution through a polypropylene or polysulfone membrane filter of 0.45-µm pore size, and discard at least the first 10 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 25-cm; 5-µm packing L3
Flow rate: 1 mL/min
Injection size: 20 µL
System suitability
Samples: *Standard solution* and *Sensitivity solution*
Suitability requirements
Signal-to-noise: NLT 10, *Sensitivity solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the amount of each impurity as a percentage of the label claim of pseudoephedrine hydrochloride 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 for individual impurities from the *Sample solution*
r_S = peak response for 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, equal to 0.52 for ephedrone (RRT, 0.85 relative to the pseudoephedrine peak) and 1 for all other impurities

Acceptance criteria
Individual impurities: NMT 0.2% of ephedrone; NMT 0.1% for any individual unspecified impurity

- **ORGANIC IMPURITIES, PROCEDURE 4**

Solution A: Dissolve 2.7 g of monobasic potassium phosphate and 2.2 g of sodium 1-octanesulfonate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.50 ± 0.05.
Solution B: Methanol and *Solution A* (2:3)
Solution C: Methanol and *Solution A* (7:3)
Diluent: Methanol and water (1:1)
Mobile Phase: See *Table 7*.

Table 7

Time (min)	Solution B (%)	Solution C (%)
0	100	0
40	100	0
41	0	100
65	0	100
66	100	0
90	100	0

Standard stock solution: 0.18 mg/mL of USP Benzoic Acid RS in *Diluent*
Standard solution: 0.0216 mg/mL of USP Benzoic Acid RS in *Diluent*, prepared from the *Standard stock solution*
Sensitivity solution: 1.08 µg/mL of USP Benzoic Acid RS in *Diluent*, prepared from the *Standard solution*
Sample solution: Weigh and finely powder 9 Tablets, and quantitatively transfer the ground powder to a 500-mL volumetric flask, with the aid of 200 mL of *Diluent*. Sonicate for 10 min, and add an additional 100 mL of *Diluent*. Shake by mechanical means for 30 min, dilute with *Diluent* to volume, and mix. Pass a portion of the solution through a polypropylene or polysulfone membrane filter of 0.45-µm pore size, and discard at least the first 10 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection size: 10 µL

System suitability
Samples: *Standard solution* and *Sensitivity solution*
Suitability requirements
Signal-to-noise: NLT 10, *Sensitivity solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the amount of each impurity as a percentage of the label claim of pseudoephedrine hydrochloride 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 for individual impurities from the *Sample solution*
r_S = peak response for benzoic acid from the *Standard solution*
C_S = concentration of USP Benzoic Acid RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of pseudoephedrine hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor for each impurity (see *Table 8*)

Acceptance criteria
Individual impurities: See *Table 8*.
Total impurities: The combined total impurities from *Procedure 3* and *Procedure 4* is NMT 0.3%.

Table 8

Name	Relative Retention Time	Relative Response Factor[a]	Acceptance Criteria, NMT(%)
Benzaldehyde	0.43	0.40	0.1
Benzoic acid	0.55	1.0	0.1
Ephedrone[b]	0.97	—	—
Pseudoephedrine	1.0	0.52	—
Individual unspecified impurity	—	0.52[c]	0.1

[a] Response factors relative to benzoic acid.
[b] Ephedrone is not quantitated in this method. A separate method is used for the quantitation of this impurity.
[c] The response factor of pseudoephedrine relative to that of benzoic acid is used in the calculation of individual unspecified impurities.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **LABELING:** When more than one *Dissolution Test* is given, the labeling states the test used only if *Test 1* is not used. If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states with which *Procedures* the article complies.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Benzoic Acid RS
  USP Fexofenadine Hydrochloride RS
  USP Fexofenadine Related Compound A RS
  Benzeneacetic acid, 4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl.
  $C_{32}H_{37}NO_4$ 499.65
  USP Pseudoephedrine Hydrochloride RS