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 (C18H21NO3 · HCl) and pseudoephedrine hydrochloride (C10H15NO · 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 Rf values for fexofenadine and pseudoephedrine are 0.17 and 0.39, respectively.

  **Acceptance criteria:** The Rf value of fexofenadine hydrochloride in the Sample solution is comparable to that of fexofenadine hydrochloride in Standard solution A. The Rf 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 ephedrine.
  
  **Related compounds stock solution:** Dissolve quantities of USP Fexofenadine Related Compound A RS and decarboxylated degradant1 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
  
  **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, centrifugate the Sample 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 x 5-cm; 5-µm packing L6 connected in series to a 4.6-mm x 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, and decarboxylated degradant are 1.0, 1.2, and 3.1, respectively (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

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

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2 Fexofenadine

Analysis

Samples: Standard solution and Sample solution
Calculate separately the percentage of the labeled amount of fexofenadine hydrochloride (C\textsubscript{32}H\textsubscript{39}NO\textsubscript{4} · HCl) and pseudoephedrine hydrochloride (C\textsubscript{10}H\textsubscript{15}NO · HCl) in the Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

- \(r_U\) = 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\textsubscript{32}H\textsubscript{39}NO\textsubscript{4} · HCl and C\textsubscript{10}H\textsubscript{15}NO · HCl dissolved.

Tolerances
Fexofenadine hydrochloride (C\textsubscript{32}H\textsubscript{39}NO\textsubscript{4} · 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\textsubscript{10}H\textsubscript{15}NO · HCl): See Table 1.

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 min</td>
<td>NMT 36%</td>
</tr>
<tr>
<td>3 h</td>
<td>45%–69%</td>
</tr>
<tr>
<td>5 h</td>
<td>61%–80%</td>
</tr>
<tr>
<td>12 h</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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\textsubscript{32}H\textsubscript{39}NO\textsubscript{4} · HCl and C\textsubscript{10}H\textsubscript{15}NO · HCl dissolved.
Tolerances
Fexofenadine hydrochloride (C₁₂H₁₉NO₄·HCl): NLT 80% (Q) of the labeled amount is dissolved in 45 min.
Pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl): See Table 2.

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>NMT 35%</td>
</tr>
<tr>
<td>2 h</td>
<td>38%–58%</td>
</tr>
<tr>
<td>4 h</td>
<td>56%–76%</td>
</tr>
<tr>
<td>12 h</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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. Media: 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 (C₁₂H₁₉NO₄·HCl): NLT 80% (Q) of the labeled amount is dissolved in 30 min.
Pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl): See Table 3.

Table 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>NMT 35%</td>
</tr>
<tr>
<td>2 h</td>
<td>38%–58%</td>
</tr>
<tr>
<td>4 h</td>
<td>56%–76%</td>
</tr>
<tr>
<td>12 h</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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 (C₁₂H₁₉NO₄·HCl): NLT 80% (Q) of the labeled amount is dissolved in 30 min.
Pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl): See Table 4.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>10%–30%</td>
</tr>
<tr>
<td>7</td>
<td>35%–65%</td>
</tr>
<tr>
<td>23</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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

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 ephedrine 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 ephedrine, 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:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_u} \right) \times 100
\]

\( r_u \) = 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 from the Standard solution
\( C_u \) = nominal concentration of fexofenadine hydrochloride in the Sample solution (mg/mL)

Calculate the percentage of ephedrine in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_u} \right) \times \left( \frac{1}{F} \right) \times 100
\]

\( r_u \) = peak height response for ephedrine 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 ephedrine, 0.394

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

\[
\text{Result} = r_u \times r_3 + r_4 \times 100
\]

\( r_u \) = 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
\( r_3 \) = peak area response for fexofenadine hydrochloride from the Reference solution
\( r_4 \) = 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Fexofenadine related compound A</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Decarboxylated degradant</td>
<td>3.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Tertiary dehydrated impurity</td>
<td>1.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Relative to pseudoephedrine.
* Relative to fexofenadine.
* (−)-4-(1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl)-isopropylbenzene.
* 4-[4-(Diphenylmethylenyl)-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 stock 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 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:** 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:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_u} \right) \times \left( \frac{1}{F} \right) \times 100
\]

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ORGANIC IMPURITIES, PROCEDURE 3

Fexofenadine

Official October 1, 2010

Revision Bulletin

Fexofenadine

Official October 1, 2010

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:

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

- \( r_U \) = 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 Sample 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Meta fexofenadine</td>
<td>1.14</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Fexofenadine related compound A</td>
<td>1.38</td>
<td>0.83</td>
<td>0.4</td>
</tr>
<tr>
<td>Tertiary dehydrated impurity*</td>
<td>2.25</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Individual unspecified impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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

- **ORGANIC IMPURITIES, PROCEDURE 4**

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

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**Mode:** LC  
**Detector:** UV 215 nm  
**Column:** 4.6-mm × 25-cm; 5-µm packing L1  
**Flow rate:** 1 mL/minute  
**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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \( r_U \) = 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**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor*</th>
<th>Acceptance Criteria, NMT(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>0.43</td>
<td>0.40</td>
<td>0.1</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>0.55</td>
<td>1.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Response factors relative to benzoic acid.  
* Ephedrine is not quantitated in this method. A separate method is used for the quantitation of this impurity.  
* 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.  
  - C₂₂H₃₇NO₄ 499.65  
  - USP Pseudoephedrine Hydrochloride RS

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