In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Fexofenadine Hydrochloride Tablets monograph. The purpose for the revision is to add *Dissolution Test 4* to accommodate an FDA-approved drug product with different dissolution conditions and tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using a Zorbax SB-Phenyl brand of L11 column. The typical retention time for fexofenadine is about 2.9 min.

The Fexofenadine Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Gerald Hsu, Ph.D., Senior Scientific Liaison (240-221-2097 or gdh@usp.org).
Fexofenadine Hydrochloride Tablets

DEFINITION
Fexofenadine Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of fexofenadine hydrochloride (C22H19NO4·HCl).

IDENTIFICATION
• A. INFRARED ABSORPTION (197K)
  Standard solution: Transfer 60 mg of USP Fexofenadine Hydrochloride RS to a suitable capped tube and add 10 mL of a mixture of acetonitrile and methanol (10:1).
  Sample solution: Transfer an equivalent to 60 mg of fexofenadine hydrochloride, from a sufficient number of weighed and finely powdered Tablets, to a suitable capped tube, and add 10 mL of a mixture of acetonitrile and methanol (10:1).

Analysis: Shake or mix the Standard solution and Sample solution on a vortex mixer for 1–2 min to disperse the sample. Allow the solution to stand for 10 min, or centrifuge for 2–3 min. Pass the liquid into a 50-mL beaker using a 0.45-µm polytetrafluoroethylene syringe filter. Evaporate the solvent until about 0.5 mL remains, using a stream of nitrogen with gentle heating (do not exceed 75°). Add 5 mL of water and 5 drops of dilute hydrochloric acid, and stir to induce precipitation. Chill in an ice bath for 30 min. Filter the solution through a 10- to 15-µm sintered-glass crucible. Dry the precipitate in an air oven for 1 h at 105° then dry on a vortex mixer for 1–2 min to disperse the solution and shake by mechanical means at a high speed for 30 min or until the Tablets are fully disintegrated and finely dispersed. Add acetonitrile (sufficient to fill the flask to 80% of its volume), and shake by mechanical means for 60 min. Dilute with Diluent to volume. Pass a portion of this solution through a polytetrafluoroethylene filter having a 0.45-µm or finer pore size, and use the filtrate. Dilute, if necessary, with Diluent to obtain a solution containing an equivalent to 1.2 mg/mL of fexofenadine hydrochloride.

Sample solution: 0.018 mg/mL from the Sample solution in Mobile phase

ASSAY
• PROCEDURE
  Solution A: Glacial acetic acid and water (17:983). Dilute 100 mL of this solution with water to 1 L.
  Solution B: Dilute 15 mL of a solution containing acetonitrile and triethylamine (1:1) with Solution A to 1 L. Adjust with phosphoric acid to a pH of 5.25.
  Diluent: Acetonitrile and Solution A (3:1)
  Mobile phase: Acetonitrile and Solution B (9:16)
  Standard stock solution: 0.25 mg/mL of USP Fexofenadine Hydrochloride RS in Diluent
  Standard solution: 0.015 mg/mL from the Standard stock solution in Mobile phase

Sample stock solution: Transfer a sufficient number of whole Tablets (NLT 10) to a suitable volumetric flask, add Solution A (equivalent to 20% of the total flask volume), and shake by mechanical means at a high speed for 30 min or until the Tablets are fully disintegrated and finely dispersed. Add acetonitrile (sufficient to fill the flask to 80% of its volume), and shake by mechanical means for 60 min. Dilute with Diluent to volume. Pass a portion of this solution through a polytetrafluoroethylene filter having a 0.45-µm or finer pore size, and use the filtrate. Dilute, if necessary, with Diluent to obtain a solution containing an equivalent to 1.2 mg/mL of fexofenadine hydrochloride.

Sample solution: 0.018 mg/mL from the Sample solution in Mobile phase

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection size: 20 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 C22H19NO4·HCl in the portion of Tablets taken:

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

\( r_U \) = peak response from the Sample solution
\( r_S \) = peak response 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)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)

Test 1
Medium: 0.001 N hydrochloric acid; 900 mL, deaerated
Apparatus 2: 50 rpm
Time: 10 and 30 min
Determine the percentages of the labeled amount of C22H19NO4·HCl dissolved by using the following method.

Solution A: 1.0 g of monobasic sodium phosphate, 0.5 g of sodium perchlorate, and 0.3 mL of concentrated phosphoric acid in 300 mL of water
Mobile phase: Acetonitrile and Solution A (7:3)

Standard solution: USP Fexofenadine Hydrochloride RS in Medium to obtain a solution having a known concentration similar to that expected for the solution under test. [Note—A small amount of methanol, not exceeding 0.5% of the total volume, can be used to dissolve fexofenadine hydrochloride.]

System suitability solution: 0.44 mg/mL of USP Fexofenadine Related Compound A RS in water. Transfer 1.0 mL of this solution into a vial, and add 40 mL of the Standard solution. [Note—A small amount of glacial acetic acid, not exceeding 5% of the total volume, can be used to dissolve fexofenadine related compound A.]

Sample solution: Pass portions of the solution under test through a glass fiber filter having a 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 10-cm; packing L1
Flow rate: 1 mL/min
Injection size: 2–3 µg column load of fexofenadine hydrochloride

System suitability
Samples: Standard solution and System suitability solution

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Suitability requirements

Resolution: NLT 2.0 between fexofenadine and fexofenadine related compound A, System suitability solution

Relative standard deviation: NMT 2.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of \( C_{32}H_{39}NO_{4} \cdot HCl \) dissolved in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_s}{r_U} \right) \times \left( \frac{C_s}{L} \right) \times D \times V \times 100
\]

- \( r_U \) = peak area from the Sample solution
- \( r_s \) = peak area from the Standard solution
- \( C_s \) = concentration of the appropriate Standard solution (mg/mL)
- \( L \) = Tablet label claim (mg)
- \( D \) = dilution factor of the Sample solution
- \( V \) = volume of Medium, 900 mL

Tolerances: NLT 75% (Q) of the labeled amount of \( C_{32}H_{39}NO_{4} \cdot HCl \) is dissolved.

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: 50 rpm

Time: 30 min

Determine the percentages of the labeled amount of \( C_{32}H_{39}NO_{4} \cdot HCl \) dissolved by using the following method.

Solution A: 7 mg/mL of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.0 ± 0.05.

Mobile phase: Acetonitrile and Solution A (2:3)

Standard solution 1: Transfer 20 mg of USP Fexofenadine Hydrochloride RS to a 100-mL volumetric flask. Add 3.0 mL of methanol, and mix. Dilute with Medium to volume.

Standard solution 2: Transfer 15.0 mL of Standard solution 1 to a 50-mL volumetric flask. Dilute with Medium to volume.

Standard solution 3: Transfer 7.5 mL of Standard solution 1 to a 50-mL volumetric flask. Dilute with Medium to volume.

Sample solution: Pass portions 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 220 nm

Column: 4.6-mm x 15-cm; packing L1

Flow rate: 1.5 mL/min

Injection size: 10 µL for Standard solution 1 and 30 µL for Standard solutions 2 and 3

System suitability

Sample: Any of the Standard solutions

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solutions 1, 2, and 3 and the Sample solution

Calculate the percentage of \( C_{32}H_{39}NO_{4} \cdot HCl \) dissolved in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_s}{r_U} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100
\]

- \( r_U \) = peak response from the Sample solution
- \( r_s \) = peak response from the Standard solution
- \( C_s \) = concentration of the Standard solution (mg/mL)
- \( L \) = Tablet label claim (mg)
- \( V \) = volume of Medium, 900 or 1800 mL

Tolerances: NLT 75% (Q) of the labeled amount of fexofenadine hydrochloride is dissolved.

Test 4: 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, degassed

Apparatus: 75 rpm

Time: 15 min

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Buffer phase: 6.64 g/L of monobasic sodium phosphate monohydrate and 0.84 g/L of sodium perchlorate in water. Adjust with phosphoric acid to a pH of 2.0.

Mobile phase: Acetonitrile, Buffer solution, and triethylamine (50: 50: 0.3)

Standard stock solution: 0.55 mg/mL of USP Fexofenadine Hydrochloride RS in 0.01 N hydrochloric acid

Standard solution: Dilute the Standard stock solution with Medium to obtain a final concentration of 0.22 mg/mL of USP Fexofenadine Hydrochloride RS. Pass a portion of the solution through a suitable filter of 0.45-μm pore size.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm x 25-cm; 5-μm packing L11

Column temperature: 35°C

Flow rate: 1.5 mL/min

Injection volume: 20 μL

Run time: NLT 2.7 times the retention time of fexofenadine

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: Standard solution and Sample solution

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

\[
\text{Result} = \left(\frac{r_I}{r_S}\right) \times \left(\frac{C_I}{C_S}\right) \times (1/L) \times 100
\]

\[r_I = \text{peak area from the Sample solution}\]
\[r_S = \text{peak area from the Standard solution}\]
\[C_I = \text{concentration of the Sample solution (mg/mL)}\]
\[C_S = \text{concentration of the Standard solution (mg/mL)}\]
\[V = \text{volume of Medium, 900 mL}\]
\[L = \text{label claim (mg/Tablet)}\]

Tolerances: NLT 80% (Q) of the labeled amount of fexofenadine hydrochloride (C\(_{12}\)H\(_{21}\)NO\(_4\)· HCl) is dissolved.

*Uniformity of Dosage Units (905):* Meet the requirements

**IMPURITIES**

**Organic Impurities**

- Procedure


Standard solution: 0.015 mg/mL of fexofenadine hydrochloride and 0.0045 mg/mL of fexofenadine related compound A from Quantitative limit solution and the Standard stock solution in Mobile phase

System suitability stock solution: Dilute 4.0 mL of the Standard stock solution with Mobile phase to 100 mL.

System suitability solution: Dilute 6.0 mL of the System suitability stock solution with Mobile phase to 100 mL.

Quantitative limit solution: 0.05 mg/mL of USP Fexofenadine Related Compound A RS in Diluent

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm x 25-cm; 5-μm packing L11

Column temperature: 35°C

Flow rate: 1.5 mL/min

Injection size: 20 μL

System suitability

Samples: Standard solution and System suitability solution

[Note—For the relative retention times, see Impurity Table 1.]

Suitability requirements

Resolution: NLT 7 between fexofenadine and fexofenadine related compound A, Standard solution

Tailing factor: NMT 2.0, Standard solution

Relative standard deviation: NMT 6%, System suitability solution; NMT 2.0% and NMT 3.0% for fexofenadine and fexofenadine related compound A, Standard solution

Analysis

Samples: Standard solution, Sample stock solution, and Sample solution

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

\[
\text{Result} = \left(\frac{r_I}{r_S}\right) \times \left(\frac{C_I}{C_S}\right) \times (1/F) \times 100
\]

\[r_I = \text{peak area of the decarboxylated degradant in the Sample solution stock}\]
\[r_S = \text{peak area of the decarboxylated degradant in the Sample solution}\]
\[C_I = \text{concentration of USP Fexofenadine Hydrochloride RS in the Standard solution (mg/mL)}\]
\[C_S = \text{concentration of fexofenadine hydrochloride in the Sample stock solution}\]
\[F = \text{relative response factor (see Impurity Table 1)}\]

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

\[
\text{Result} = \frac{r_I}{(F \times r_S + r_I)} \times 100
\]

\[r_I = \text{peak area for each individual unknown impurity in the Sample stock solution}\]
\[F = \text{difference in concentration between the Sample stock solution and the Sample solution, 66.7}\]
\[r_S = \text{peak area response for fexofenadine in the Sample solution}\]
\[r_I = \text{sum of the peak areas of all unknown impurities in the Sample stock solution}\]

[Note—Disregard any peak below 0.05%.]
Acceptance criteria

Individual impurities: See Impurity Table 1.
Total impurities: NMT 0.5%

### Impurity Table 1

<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 related compound A</td>
<td>1.6</td>
<td>—</td>
<td>0.4</td>
</tr>
<tr>
<td>Decarboxylated degradant</td>
<td>6.7</td>
<td>1.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any individual other impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### 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.
- **USP Reference Standards (11)**
  - USP Fexofenadine Hydrochloride RS
  - USP Fexofenadine Related Compound A RS
  - Benzeneacetic acid, 4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidiny]butyl]-α,α-dimethyl. $C_{14}H_{23}NO_4$ 499.65