Fexofenadine Hydrochloride Tablets

Type of Posting	Revision Bulletin
Posting Date	26–Oct–2018
Official Date	01–Nov–2018
Expert Committee	Chemical Medicines Monographs 5
Reason for Revision	Compliance

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 ($C_{32}H_{39}NO_4 \cdot HCl$).

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 polytetrafluoroethlyene 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° oven for 1 h at 105°. Prepare a bromide dispersion from the residue.

Acceptance criteria: The IR absorption spectrum of the potassium bromide dispersion of the residue from the sample exhibits maxima only at the same wavelengths as that of a potassium bromide dispersion from the Standard.

• **B.** The retention time of the major peak in the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

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 stock 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 L11
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 $C_{32}H_{39}NO_4 \cdot HCl$ 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 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 $C_{32}H_{39}NO_4 \cdot HCl$ 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*

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:

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

r_U = peak area from the *Sample solution*
r_S = peak area from the *Standard solution*
C_S = concentration of USP Fexofenadine Hydrochloride RS in the *Standard solution* (mg/mL)
L = Tablet label claim (mg)
D = dilution factor of the *Sample solution*
V = volume of *Medium*, 900 mL

Tolerances: NLT 60% (*Q*) of the labeled amount of $C_{32}H_{39}NO_4 \cdot HCl$ is dissolved in 10 min; NLT 80% (*Q*) of the labeled amount of $C_{32}H_{39}NO_4 \cdot HCl$ is dissolved in 30 min.

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. Use paddles and shafts coated with Teflon.
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 259 nm
Column: 4.6-mm × 15-cm; packing L11
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:

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

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)
V = volume of *Medium*, 900 mL
L = Tablet label claim (mg)

Tolerances: NLT 75% (*Q*) of the labeled amount of $C_{32}H_{39}NO_4 \cdot HCl$ is dissolved.

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 for Tablets labeled to contain 30 mg or 60 mg, and 1800 mL for Tablets labeled to contain 180 mg
Apparatus 2: 50 rpm
Time: 45 min
Buffer solution: 6.64 g/L of monobasic sodium phosphate monohydrate and 0.84 g/L of sodium perchlorate monohydrate in water. Add 4 mL/L of triethylamine. Adjust with phosphoric acid to a pH of 2.3 ± 0.1.
Mobile phase: *Buffer solution* and acetonitrile (65:35)
Standard stock solution: 0.5 mg/mL of USP Fexofenadine Hydrochloride RS in *Mobile phase*. This solution is stable for 3.5 months under refrigeration or for 18 days at room temperature.
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of 0.07 mg/mL of USP Fexofenadine Hydrochloride RS. This solution is stable for 8 days under refrigeration or for 24 h at room temperature.
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 220 nm
Column: 4.6-mm × 10-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 2.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Column efficiency: NLT 1000 theoretical plates
Relative standard deviation: NMT 2.0%
Calculate the percentage of fexofenadine hydrochloride dissolved in the portion of Tablets taken:

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

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 2: 75 rpm
Time: 15 min

Buffer solution: 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 × 25-cm; 5-µm packing L11
Column temperature: 25°
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 hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) dissolved in the portion of Tablets taken:

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

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)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) is dissolved. ▲ (RB 1-Nov-2018)

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

IMPURITIES

Organic Impurities

• **Procedure**

Solution A, Solution B, Diluent, Mobile phase, Standard stock solution, Sample stock solution, and **Sample solution:** Prepare as directed in the *Assay*.
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 × 25-cm; 5-µm packing L11
Column temperature: 35°
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:

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

r_U = peak area of fexofenadine related compound A in the *Sample stock solution*
r_S = peak area of fexofenadine related compound A in the *Standard solution*
C_S = concentration of fexofenadine related compound A in the *Standard solution* (mg/mL)
C_U = concentration of fexofenadine hydrochloride in the *Sample stock solution*

Calculate the percentage of the decarboxylated degradant [(±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene] 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 area of the decarboxylated degradant in the *Sample stock solution*
r_S = peak area of fexofenadine in the *Standard solution*
C_S = concentration of USP Fexofenadine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of fexofenadine hydrochloride in the *Sample stock solution*
F = relative response factor (see *Impurity Table 1*)

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 = peak area for each individual unknown impurity in the *Sample stock solution*
F = difference in concentration between the *Sample stock solution* and the *Sample solution*, 66.7
r_S = peak area response for fexofenadine in the *Sample solution*
r_T = 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

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fexofenadine related compound A	1.6	—	0.4
Decarboxylated degradant	6.7	1.1	0.15
Fexofenadine	1.0	—	—
Any individual other impurity	—	1.0	0.2

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-piperidinyl]butyl]-α,α-dimethyl.
  $C_{32}H_{37}NO_4$ 499.65