Fexofenadine Hydrochloride Tablets

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 5 Expert Committee has revised the Fexofenadine Hydrochloride Tablets monograph. The purpose for the revision is to revise the *Acceptance criteria* in the *Assay* from “NLT 95.0% and NMT 105.0%” to “NLT 93.0% and NMT 107.0%,” based on a manufacturer’s approved specifications. The *Definition* is also revised accordingly.

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

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

Revision Bulletin
Official: January 1, 2021

Fexofenadine Hydrochloride Tablets

DEFINITION

Change to read:

Fexofenadine Hydrochloride Tablets contain NLT ▲93.0%▲ (RB 1-Jan-2021) and NMT ▲107.0%▲ (RB 1-Jan-2021) of the labeled amount of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$).

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 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

Change to read:

- **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 volume: 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: ▲93.0%–107.0%▲ (RB 1-Jan-2021)

PERFORMANCE TESTS

- **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 volume: 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 volume: 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 volume: 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.

- **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 volume: 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

2-(4-{4-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]butanoyl}phenyl)-2-methylpropanoic acid;
Also known as Benzeneacetic acid, 4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl.

$C_{32}H_{37}NO_4$ 499.65

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