# Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

» Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

**Packaging and storage—**Preserve in well-closed containers, and store at controlled room temperature.

***Add the following:***

•**Labeling—**When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.•3

**USP Reference standards** ⟨11⟩**—***USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A RS. USP Pseudoephedrine Hydrochloride RS.*

***Change to read:***

**Identification—**

**A:**■1S *(USP32)* The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

**B:**■1S *(USP32)* *Thin-Layer Chromatographic Identification Test* ⟨201⟩—•4

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

*Test solution*—Weigh and finely powder not fewer than 4 Tablets. Transfer powdered Tablets, equivalent to 30 mg of fexofenadine hydrochloride and 60 mg of pseudoephedrine hydrochloride, into a suitable vessel, and add 5 mL of methanol. Cap the vessel, and shake vigorously for about 2 minutes. Pass the resulting suspension through a suitable 0.45-µm filter. Use the filtrate.

*Fexofenadine hydrochloride standard solution*—Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride RS in methanol to obtain a solution having a known concentration of about 6 mg per mL.

*Pseudoephedrine hydrochloride standard solution*—Dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in methanol to obtain a solution having a known concentration of about 12 mg per mL.

*Application volume:* 10 µL.

*Developing solvent solution:* a mixture of toluene, dehydrated alcohol, and ammonium hydroxide (50 : 45 : 5).

*Procedure*—Proceed as directed in the chapter, 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 (approximately 5 minutes). Allow the plate to cool, and examine under UV light at 254 nm. The $R_F$ values are about 0.17 for fexofenadine and 0.39 for pseudoephedrine. The $R_F$ value of fexofenadine hydrochloride in the test sample is comparable to that of fexofenadine hydrochloride in the Standard solution. The $R_F$ value of pseudoephedrine hydrochloride in the test sample is comparable to that of pseudoephedrine hydrochloride in the Standard solution.

***Change to read:***

**Dissolution** ⟨711⟩**—**

•TEST 1—•3

*Medium:* 0.001 N hydrochloric acid; 900 mL.

*Apparatus 2:* 50 rpm.

*Times:* fexofenadine hydrochloride: 15 and 45 minutes; pseudoephedrine hydrochloride: 45 minutes; 3, 5, and 12 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by using the following method.

*Buffer solution*—Dissolve 14.0 g of monobasic sodium phosphate monohydrate in 2 L of water. Adjust with 85% phosphoric acid to a pH of 2.00 ± 0.05.

*Mobile phase*—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

*Standard solution*—[NOTE—A small amount of methanol, not to exceed 0.5% of the total volume, can be used to dissolve the fexofenadine hydrochloride.] Dissolve accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, to obtain a solution containing known concentrations similar to those expected in the solution under test.

*Test solution*—Use portions of the solution under test passed through a 0.45-µm nylon filter.

*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column containing packing L6. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fexofenadine and pseudoephedrine is not less than 3.0; the tailing factor is not more than 1.5 for fexofenadine and for pseudoephedrine; and the relative standard deviation for replicate injections is not more than 2.0%.

*Procedure*—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the peak responses for fexofenadine and pseudoephedrine. Calculate the amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved.

*Tolerances*—For fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$), not less than 65% (*Q*) of the labeled amount is dissolved in 15 minutes and not less than 80% (*Q*) of the labeled amount is dissolved in 45 minutes; the percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* under *Dissolution* ⟨711⟩.

| Time | Amount dissolved (average) |
|---|---|
| 45 minutes | not more than 36% |
| 3 hours | between 45% and 69% |
| 5 hours | between 61% and 80% |
| 12 hours | not less than 80% |

•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 minutes; pseudoephedrine hydrochloride: 30 minutes; 2, 4, and 12 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and of pseudoephedrine

hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by using the following method.

*Buffer solution*—Dissolve about 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*—Prepare a filtered and degassed mixture of *Buffer solution,* methanol, and acetonitrile (4 : 3 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

*Fexofenadine standard stock solution*—Transfer about 66 mg, accurately weighed, of USP Fexofenadine Hydrochloride RS to a 100-mL volumetric flask. Add 10 mL of methanol, and swirl until dissolved. Add about 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 about 66 mg, accurately weighed, of USP Pseudoephedrine Hydrochloride RS to a 100-mL volumetric flask. Add 10 mL of methanol, and swirl until dissolved. Add about 50 mL of *Medium,* and mix. Allow the solution to equilibrate to room temperature, and dilute with *Medium* to volume.

*Working standard solution*—Transfer 10.0 mL of *Fexofenadine standard stock solution* and 20.0 mL of *Pseudoephedrine standard stock solution* to a 100-mL volumetric flask, dilute with *Medium* to volume, and mix.

*Test solution*—Pass a portion of the solution under test through a suitable filter having a porosity of 0.45 µm.

*Chromatographic system*—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column containing 5-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fexofenadine and pseudoephedrine is not less than 2.0; the tailing factor for the fexofenadine peak is not more than 2.0, and for the pseudoephedrine peak, not more than 2.5; and the relative standard deviation for replicate injections for both peaks is not more than 2.0%.

*Procedure*—Separately inject equal volumes (about 10 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, and record the peak responses for fexofenadine and pseudoephedrine. Calculate the amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved.

*Tolerances*—For fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$), not less than 80% (*Q*) of the labeled amount is dissolved in 45 minutes; and the percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* under *Dissolution* ⟨711⟩.

| Time | Amount dissolved (average) |
|---|---|
| 30 minutes | not more than 35% |
| 2 hours | between 38% and 58% |
| 4 hours | between 56% and 76% |
| 12 hours | not less than 80% |

•[3]•

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 minutes; pseudoephedrine hydrochloride: 1, 3, 5, and 12 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by using the following procedure.

*Buffer solution*—Dissolve 6.64 g of monobasic sodium phosphate in 1000 mL of water, adjust to a pH of 2.50 ± 0.05 with phosphoric acid.

*Mobile phase*—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (3 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩)

*Standard solution*—[NOTE—A small amount of methanol, not exceeding 0.5% of the final total volume, can be used to dissolve fexofenadine hydrochloride.] Dissolve accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in *Medium*, and dilute quantitatively, and stepwise if necessary, to obtain a solution containing known concentrations similar to those expected in the solution under test.

*Test solution*—Pass a portion of the solution under test through a PVDF or nylon 0.45-µm filter.

*Chromatographic system*—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column containing packing L1. The flow rate is about 2.5 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the tailing factor is not more than 2.0 for fexofenadine and peseudoephedrine; and the relative standard deviation for replicate injections is not more than 2.0%.

*Procedure*—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the peak responses for fexofenadine and pseudoephedrine. Calculate the amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved.• (RB 2-Nov-2009)

*Tolerances*—For fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$), not less than 80% (*Q*) of the labeled amount is dissolved in 30 minutes; the percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* under *Dissolution* ⟨711⟩.•

| Time (hours) | Amount dissolved |
|---|---|
| 1 | between 10% and 35% |
| 3 | between 25% and 55% |
| 5 | between 40% and 65% |
| 12 | not less than 65% |

• (RB 2-Nov-2009)

TEST 4—For products labeled with a dosing interval of 24 hours. 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 minutes; pseudoephedrine hydrochloride: 3, 7, and 23 hours.

Determine the percentages of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by using the chromatographic procedure described in *Test 1.*

*Tolerances*—For fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$), not less than 80% (*Q*) of the labeled amount is dissolved in 30 minutes; the percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Acceptance Table 2* under *Dissolution* ⟨711⟩.

| Time (hours) | Amount dissolved (average) |
|---|---|
| 3 | between 10% and 30% |
| 7 | between 35% and 65% |
| 23 | not less than 80% |

• (RB 1-Mar-2009)

**Uniformity of dosage units** ⟨905⟩**:** meet the requirements.

***Change to read:***

**Related compounds—**

*Buffer solution, Mobile phase, System suitability preparation,* and *Chromatographic system*—Proceed as directed in the *Assay*.

*Standard solution*—Use the *Standard preparation,* prepared as directed in the *Assay*.

*Reference solution*—Use the *Assay preparation.*

*Test solution*—Use the *Assay stock preparation,* prepared as directed in the *Assay*.

*Chromatographic system* (see *Chromatography* ⟨621⟩)—Chromatograph the *System suitability preparation* as directed for *Procedure:* the relative retention times are about 1.2 for ephedrone and 1.0 for pseudoephedrine; the resolution, *R*, between pseudoephedrine and ephedrone is not less than 1.7; and the relative standard deviation for replicate injections is not more than 1.0% based on the pseudoephedrine peak. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.2 for fexofenadine related compound A, 3.1 for decarboxylated degradant, and 1.0 for fexofenadine; the resolution, *R,* between fexofenadine and fexofenadine related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 1.0% based on the fexofenadine peak and not more than 3.0% based on the individual peaks for fexofenadine related compound A and decarboxylated degradant.

*Procedure*—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Reference solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of fexofenadine related compound A and decarboxylated degradant in the portion of Tablets taken by the formula:

$$100(C_S / C_T)(r_i / r_S)$$

in which $C_S$ is the concentration, in mg per mL, of either USP Fexofenadine Related Compound A RS or decarboxylated degradant in the *Standard solution;* $C_T$ is the nominal concentration, in mg per mL, of fexofenadine •hydrochloride•$_{.4}$ in the *Test solution;* $r_i$ is the individual peak area of either fexofenadine related compound A or decarboxylated degradant obtained from the *Test solution;* and $r_S$ is the peak area of fexofenadine related compound A obtained from the *Standard solution*. Calculate the percentage of ephedrone in the portion of Tablets taken by the formula:

$$(100/F)(C_S / C_T)(r_i / r_S)$$

in which $F$ is the relative response factor for ephedrone ($F$ is 0.394); $C_S$ is the concentration, in mg per mL, of USP Pseudoephedrine Hydrochloride RS in the *Standard solution;* $C_T$ is the nominal concentration, in mg per mL, of pseudoephedrine •hydrochloride•$_{.4}$ in the *Test solution;* $r_i$ is the peak height for ephedrone obtained from the *Test solution;* and $r_S$ is the peak height for pseudoephedrine obtained from the *Standard solution*. Calculate the percentage of any other impurities in the portion of Tablets taken by the formula:

$$100r_i / (25r_S + r_T)$$

in which $r_i$ is the individual peak area response for an individual unknown impurity in the *Test solution;* 25 is the difference in concentration between the *Test solution* and the *Reference solution;* $r_S$ is the peak area response for fexofenadine •hydrochloride•$_{.4}$ obtained from the *Reference solution;* and $r_T$ is the sum of the peak area responses of all unknown impurities in the *Test solution*. Disregard any peak below 0.05%.

| Compound | Relative Retention Time | Acceptance Criteria |
|---|---|---|
| Pseudoephedrine | 1.0 | — |
| Ephedrone | 1.2[a] | not more than 0.2% |
| Fexofenadine | 1.0 | — |
| Fexofenadine related compound A | 1.2[b] | not more than 0.4% |
| Decarboxylated degradant[1] | 3.1[b] | not more than 0.2% |
| •Tertiary dehydrated impurity[2]•$_{.4}$ | 1.8 | not more than 0.2% |
| Any other individual impurity | — | •not more than 0.2%•$_{.4}$ |
| Total impurities | — | not more than 0.8% |

[a] Relative to pseudoephedrine.
[b] Relative to fexofenadine.
[1] (±)-4-(1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene.
•[2] 4-[4{4-(Diphenylmethylene)-1-piperidinyl}-1-hydroxybutyl]-2,2-dimethyl phenyl acetic acid.•$_{.4}$

***Change to read:***

**Assay—**

*Buffer solution*—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*—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

*System suitability preparation*—Transfer an accurately weighed quantity, about 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 about 90° for 60 minutes. 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, and mix. The degradation of pseudoephedrine hydrochloride by this process produces the related compound ephedrone.

*Related compounds preparation*—Dissolve accurately weighed quantities of USP Fexofenadine Related Compound A RS and decarboxylated degradant•*•$_{.4}$ in a volume of methanol, and dilute quantitatively, and stepwise if necessary, with *Buffer solution* to maintain a ratio of methanol and *Buffer solution* (60 : 40). Dilute quantitatively, and stepwise if necessary, with methanol and *Buffer solution* (60 : 40) to obtain a solution having known concentrations of 0.2 mg per mL for each component. Dilute 10.0 mL of this solution with *Mobile phase* to 100 mL to obtain a final solution having known concentrations of 0.02 mg per mL for each component.

*Standard stock preparation*—Dissolve accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 0.4 mg per mL and 0.8 mg per mL of fexofenadine •hydrochloride•$_{.4}$ and pseudoephedrine •hydrochloride,•$_{.4}$ respectively.

*Available from USP as USP Fexofenadine Related Compound C AS, Cat# 1270446.•$_{.4}$

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

*Assay stock preparation*—Transfer not fewer than 10 whole Tablets to a 500-mL volumetric flask. Add 300 mL of methanol, and shake by mechanical means at high speed for 60 minutes. Sonicate the flask for 60 minutes at 40°. Add 150 mL of *Buffer solution,* and sonicate for 60 minutes at 40°. Vent the flask, and vigorously shake the flask by hand at 15-minute intervals during the mechanical shaking and sonication steps. Cool to room temperature, and dilute with *Buffer solution* to volume to obtain a solution containing approximately 1.2 mg of fexofenadine •hydrochloride•4 per mL and 2.4 mg of pseudoephedrine •hydrochloride•4 per mL. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

*Assay preparation*—Dilute 4.0 mL of the *Assay stock preparation* filtrate with *Mobile phase* to 100 mL. The final concentrations of fexofenadine •hydrochloride•4 and pseudoephedrine •hydrochloride•4 are 0.048 mg per mL and 0.096 mg per mL, respectively.

*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 5-cm column that contains 5-µm packing L6 connected in series to a 4.6-mm × 25-cm column that contains 5-µm packing L11. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. Chromatograph the *System suitability preparation* as directed for *Procedure:* the relative retention times are about 1.2 for ephedrone and 1.0 for pseudoephedrine; the resolution, *R*, between pseudoephedrine and ephedrone is not less than 1.7; and the relative standard deviation for replicate injections is not more than 1.0% based on the pseudoephedrine peak. Chromatograph the *Standard preparation,*•4 and record the peak responses as directed for *Procedure:* the relative retention times are about 1.2 for fexofenadine related compound A, 3.1 for decarboxylated degradant, and 1.0 for fexofenadine; the resolution, *R,* between fexofenadine and fexofenadine related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 1.0% based on the fexofenadine peak.

*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the fexofenadine and pseudoephedrine peaks. Calculate the percentage of the label claim of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Tablets taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which $C_S$ is the concentration, in mg per mL, of either USP Fexofenadine Hydrochloride RS or USP Pseudoephedrine Hydrochloride RS in the *Standard preparation;* $C_T$ is the nominal concentration, in mg per mL, of either fexofenadine •hydrochloride•4 or pseudoephedrine •hydrochloride•4 in the *Assay preparation;* and $r_U$ and $r_S$ are the peak responses obtained for either fexofenadine or pseudoephedrine from the *Assay preparation* and the *Standard preparation,* respectively.