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Fluoxetine Delayed-Release Capsules

DEFINITION

Fluoxetine Delayed-Release Capsules contain an amount of Fluoxetine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$).

IDENTIFICATION

Change to read:

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: **197F**▲ (CN 1-May-2020)

Sample: Transfer the contents of 3 Capsules to a suitable container and grind to a fine powder. Transfer a portion of the powder, equivalent to 40 mg of fluoxetine, to another suitable container, and dissolve in 25 mL of 0.1 N hydrochloric acid. Pass the resulting solution through a suitable filter. Transfer 10 mL of the filtrate to a separatory funnel, add 20 mL of methylene chloride, and mix. Allow the phases to separate, and transfer the organic layer to a small glass container. Evaporate to dryness with the aid of a current of air and mild heat. Redissolve the residue with a few drops of methylene chloride, and transfer to a potassium bromide plate. Dry or evaporate to a thin film with the aid of a stream of nitrogen.

Acceptance criteria: Meet the requirements

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

ASSAY

• **Procedure**

Solution A: Dissolve about 2.9 mL of glacial acetic acid and about 7.1 g of sodium 1-pentanesulfonate in 1 L of water. Adjust with 5 N sodium hydroxide to a pH of 5.0.

Mobile phase: Methanol and *Solution A* (67:33)

System suitability solution: 110 µg/mL of USP Fluoxetine Hydrochloride RS and 20 µg/mL of 4-trifluoromethylphenol in *Mobile phase*

Standard solution: 110 µg/mL of USP Fluoxetine Hydrochloride RS in *Mobile phase*

Sample stock solution: Nominally 0.2 mg/mL of fluoxetine from Capsules prepared as follows. Remove, as completely as possible, the contents of NLT 20 Capsules. Transfer a suitable portion of the contents to an appropriate volumetric flask and dissolve in 50% of the final flask volume of *Mobile phase*. Shake by mechanical means for 10 min and then sonicate for 5 min. Allow the solution to cool to room temperature and dilute with *Mobile phase* to volume.

Sample solution: Nominally 100 µg/mL of fluoxetine from *Sample stock solution* in *Mobile phase*. Pass through a suitable filter. Use the filtrate.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 227 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7

Column temperature: 38°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for 4-trifluoromethylphenol and fluoxetine are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4.0 between 4-trifluoromethylphenol and fluoxetine

Tailing factor: NMT 1.7 for the fluoxetine peak

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Fluoxetine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of fluoxetine in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of fluoxetine, 309.33

M_{r2} = molecular weight of fluoxetine hydrochloride, 345.79

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Acid stage

Acid stage medium: 0.1 N hydrochloric acid; 250 mL, deaerated

Apparatus 3: 12 dips/min (dpm), using a polypropylene 40-mesh screen on the top and bottom of the reciprocating cylinder

Time: 2 h; Operate the apparatus for 2 h at 12 dpm, withdraw an aliquot of the *Acid stage medium*, and allow the apparatus to proceed to the *Buffer stage*.

Standard solution: 0.036 mg/mL of USP Fluoxetine Hydrochloride RS in *Acid stage medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Use the filtrate.

Instrumental conditions

Mode: UV

Analytical wavelength: About 278 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times (M_{r1}/M_{r2}) \times V \times (1/L) \times 100$$

A_U = minimum of the first derivative of the absorbance of the *Sample solution*

A_S = minimum of the first derivative of the absorbance of the *Standard solution*

C_S = concentration of USP Fluoxetine Hydrochloride RS in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of fluoxetine, 309.33

M_{r2} = molecular weight of fluoxetine hydrochloride, 345.79

V = volume of *Acid stage medium*, 250 mL

L = label claim (mg/Capsule)

Tolerances: NMT 10% of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$) is dissolved.

Buffer stage

Buffer stage medium: pH 6.8 phosphate buffer (prepared by mixing 3 L of 0.1 N hydrochloric acid and 1 L of 0.2 M tribasic sodium phosphate, and adjusting, if necessary, with 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 6.8 ± 0.05); 250 mL, deaerated

Apparatus 3: 12 dips/min (dpm), using a polypropylene 40-mesh screen on the top and bottom of the reciprocating cylinder

Time: 45 min; Operate the apparatus for 45 min at 12 dpm, and withdraw an aliquot of the *Buffer stage medium*.

Standard solution: 0.36 mg/mL of USP Fluoxetine Hydrochloride RS in *Buffer stage medium*

Sample solution: Pass a portion of the solution under test through a filter of 0.45-µm pore size. Use the filtrate.

Instrumental conditions

Mode: UV

Analytical wavelengths: Maximum absorbance at about 264 and 290 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times (M_{r1}/M_{r2}) \times V \times (1/L) \times 100$$

A_U = absorbance at 264 nm − absorbance at 290 nm for the *Sample solution*

A_S = absorbance at 264 nm − absorbance at 290 nm for the *Standard solution*

C_S = concentration of USP Fluoxetine Hydrochloride RS in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of fluoxetine, 309.33

M_{r2} = molecular weight of fluoxetine hydrochloride, 345.79

V = volume of *Buffer stage medium*, 250 mL

L = label claim (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

Solution A: 6.5 g/L of sodium 1-octanesulfonate and 2.9 g/L of anhydrous sodium acetate in water adjusted with glacial acetic acid to a pH of 5.0

Mobile phase: Acetonitrile and *Solution A* (42:58)

Impurity identification solution A: 0.5 mg/mL of USP Fluoxetine Related Compound C RS in *Mobile phase*. [Note—The resulting solution contains 4-trifluoromethylphenol.]

Impurity identification solution B: Nominally 2.2 mg/mL of fluoxetine hydrochloride from USP Fluoxetine Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Fluoxetine Hydrochloride RS to an appropriate volumetric flask and dilute with 1 N sulfuric acid to volume. Heat the flask to 85° for 3 h, and allow to cool to room temperature. [Note—The resulting solution contains aminomethyl-1-phenylpropanol, which is also known as 3-methylamino-1-phenylpropan-1-ol and α-[2-(methylamino)ethyl]benzenemethanol.]

System suitability stock solution: 0.135 mg/mL of USP Fluoxetine Hydrochloride RS, 0.01 mg/mL of USP Fluoxetine Related Compound C RS from *Impurity identification solution A*, and nominally 0.044 mg/mL of fluoxetine from *Impurity identification solution B* prepared as follows. Transfer 13.5 mg of USP Fluoxetine Hydrochloride RS to a 100-mL volumetric flask and add 2 mL of *Impurity identification solution A* and 2 mL of *Impurity identification solution B*. Dilute with *Mobile phase* to volume.

System suitability solution: 5.4 µg/mL of USP Fluoxetine Hydrochloride RS and 0.4 µg/mL of USP Fluoxetine Related Compound C RS from *System suitability stock solution* in *Mobile phase*

Sensitivity solution: 0.43 µg/mL of USP Fluoxetine Hydrochloride RS from *System suitability solution* in *Mobile phase*

Sample solution: Nominally 0.4 mg/mL of fluoxetine from Capsules prepared as follows. Finely powder NLT 20 Capsules and transfer a suitable portion of the powder to an appropriate volumetric flask. Dissolve in and dilute with *Mobile phase* to volume. Pass the resulting solution through a suitable filter and use the filtrate.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: NLT 3 times the retention time of fluoxetine

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[Note—The relative retention times for 4-trifluoromethylphenol, fluoxetine related compound C, and fluoxetine are 0.49, 0.70, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between 4-trifluoromethylphenol and fluoxetine related compound C; NLT 6.0 between fluoxetine related compound C and fluoxetine, *System suitability solution*

Signal-to-noise ratio: NLT 10 for fluoxetine, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_i/r_T) \times 100$$

r_i = peak response of each impurity from the *Sample solution*

r_T = sum of all of the peak responses from the *Sample solution*

Acceptance criteria

Any individual impurity: NMT 0.2%

Total impurities: NMT 0.7%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Fluoxetine Hydrochloride RS

USP Fluoxetine Related Compound C RS

4-(Methyl{3-phenyl-3-[4-(trifluoromethyl)phenoxy]propyl}amino)-4-oxobutanoic acid;
also known as *N*-Methyl-*N*-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid.

$C_{21}H_{22}F_3NO_4$ 409.40

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
FLUOXETINE DELAYED-RELEASE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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