



## Fluoxetine Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	27-Oct-2023
<b>Targeted Official Date</b>	To Be Determined, Revision Bulletin
<b>Expert Committee</b>	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Fluoxetine Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Fluoxetine Tablets monograph to add *Dissolution Test 2. Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*. Existing references to reagents have been updated for consistency with the reagent entry.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.<sup>1</sup>

Should you have any questions, please contact Jasmine McFarland, Scientist III (301-230-6363 or [jasmine.mcfarland@usp.org](mailto:jasmine.mcfarland@usp.org)).

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<sup>1</sup> This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the [USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF](#).

## Fluoxetine Tablets

### DEFINITION

Fluoxetine Tablets 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

• **A. SPECTROSCOPIC IDENTIFICATION TESTS (197), *Infrared Spectroscopy*: 197K**

**Sample:** Transfer 1 Tablet to a suitable container, dissolve in 10 mL of [chloroform](#), and pass through a suitable filter. Rinse the container with 5 mL of [chloroform](#), and pass the rinsings through a suitable filter. Evaporate the combined filtrate in a hood with the aid of a current of air and mild heat to dryness.

**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

**Change to read:**

• **PROCEDURE**

**Solution A:** 7.1 g/L of [sodium 1-pentane-sulfonate](#) in [water](#). To each L add 2.9 mL of [glacial acetic acid](#), and adjust with 5 N [sodium hydroxide](#) solution to a pH of 5.0.

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

**System suitability stock solution:** 0.2 mg/mL of [▲ \$\alpha,\alpha,\alpha\$ -trifluoro-\*p\*-cresol▲](#) (TBD) in *Mobile phase*

**System suitability solution:** 0.02 mg/mL of [▲ \$\alpha,\alpha,\alpha\$ -trifluoro-\*p\*-cresol▲](#) (TBD) from *System suitability stock solution* and 0.11 mg/mL of [USP Fluoxetine Hydrochloride RS](#) in *Mobile phase*

**Standard solution:** 0.1 mg/mL of [USP Fluoxetine Hydrochloride RS](#) in *Mobile phase*

**Sample stock solution:** Transfer 10 Tablets to a 1000-mL volumetric flask. Add 500 mL of *Mobile phase*, and shake to disintegrate the Tablets. Dilute with *Mobile phase* to volume, and sonicate for 10 min.

**Sample solution:** Nominally 0.1 mg/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- $\mu$ m packing [L7](#)

**Column temperature:** 38°

**Flow rate:** 1 mL/min

**Injection volume:** 10  $\mu$ L

### System suitability

**Sample:** *System suitability solution*

## Suitability requirements

**Resolution:** NLT 4.0 between fluoxetine and 4-trifluoromethylphenol

**Tailing factor:** NMT 1.7 for fluoxetine

**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 Tablets 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* (mg/mL)

$C_U$  = nominal concentration of fluoxetine in the *Sample solution* (mg/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

### Change to read:

- [DISSOLUTION](#) <711>

#### ▲Test 1▲ (TBD)

**Medium:** 0.1 N [hydrochloric acid](#); 1000 mL

**Apparatus 1:** 100 rpm

**Time:** 15 min

**Solution A, Mobile phase, and System suitability solution:** Prepare as directed in the Assay.

**Sample solution:** Pass 20 mL of the solution under test through a suitable filter.

**Standard solution:** [USP Fluoxetine Hydrochloride RS](#) in *Medium* having a known concentration similar to that of the *Sample solution*

### 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:** 20 μL

### System suitability

**Sample:** *System suitability solution*

### Suitability requirements

**Resolution:** NLT 2.0 between fluoxetine and 4-trifluoromethylphenol

**Tailing factor:** NMT 1.7 for fluoxetine

**Relative standard deviation:** NMT 2.0%

## Analysis

**Samples:** *Sample solution* and *Standard solution*

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

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

$r_U$  = 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* (mg/mL)

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

$M_{r1}$  = molecular weight of fluoxetine, 309.33

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

**Tolerances:** NLT 80% (Q) of the labeled amount of fluoxetine ( $C_{17}H_{18}F_3NO$ ) is dissolved.

▲ **Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

**Medium:** 0.1 N [hydrochloric acid](#); 500 mL

**Apparatus 1:** 100 rpm

**Time:** 15 min

**Solution A:** Dissolve 7.1 g of [sodium 1-pentane-sulfonate](#) in 1000 mL of [water](#), and add 2.9 mL of [glacial acetic acid](#). Adjust with 5 N [sodium hydroxide solution](#) to a pH of 5.0.

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

**System suitability stock solution:** 0.2 mg/mL of  [\$\alpha,\alpha,\alpha\$ -trifluoro-\*p\*-cresol](#) in *Mobile phase*

**System suitability solution:** 0.02 mg/mL of  [\$\alpha,\alpha,\alpha\$ -trifluoro-\*p\*-cresol](#) from the *System suitability stock solution* and 0.11 mg/mL of [USP Fluoxetine Hydrochloride RS](#) in *Mobile phase*

**Standard solution:** 0.1 mg/mL of [USP Fluoxetine Hydrochloride RS](#) in *Medium*

**Sample solution:** Pass a portion of solution through a suitable filter of 0.45- $\mu$ m pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

### Chromatographic system

(See [Chromatography <621>](#), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 227 nm

**Column:** 4.6-mm  $\times$  7.5-cm; 3.5- $\mu$ m packing [L7](#)

**Column temperature:** 38°

**Flow rate:** 1 mL/min

**Injection volume:** 20  $\mu$ L

### System suitability

**Sample:** *System suitability solution*

#### Suitability requirements

**Resolution:** NLT 2.0 between fluoxetine and 4-trifluoromethylphenol

**Tailing factor:** NMT 1.7 for fluoxetine

**Relative standard deviation:** NMT 2.0%

## Analysis

**Samples:** *Standard solution* and *Sample solution*

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

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

$r_U$  = peak response of fluoxetine from the *Sample solution*

$r_S$  = peak response of fluoxetine from the *Standard solution*

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

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

$M_{r1}$  = molecular weight of fluoxetine, 309.33

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

**Tolerances:** NLT 80% (Q) of the labeled amount of fluoxetine ( $C_{17}H_{18}F_3NO$ ) is dissolved. ▲ (TBD)

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

## IMPURITIES

### • ORGANIC IMPURITIES

**Solution A:** 6.5 g/L of sodium 1-octanesulfonate in water. To each L add 2.9 mL of phosphoric acid, and adjust with 5 N sodium hydroxide solution to a pH of 3.0.

**Mobile phase:** Acetonitrile and *Solution A* (43:57)

**Impurity identification solution:** Nominally 2.2 mg/mL of fluoxetine hydrochloride from USP Fluoxetine Hydrochloride RS prepared as follows. Transfer 22 mg of USP Fluoxetine Hydrochloride RS to a 10-mL 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 or  $\alpha$ -[2-(methylamino)ethyl]benzenemethanol.]

**System suitability solution:** 0.001 mg/mL of USP Fluoxetine Related Compound B RS and 0.015 mg/mL of USP Fluoxetine Hydrochloride RS prepared as follows. Transfer suitable quantities of USP Fluoxetine Related Compound B RS and USP Fluoxetine Hydrochloride RS to a 10-mL volumetric flask. Add 0.2 mL of *Impurity identification solution* and dilute with *Mobile phase* to volume.

**Standard solution:** 0.015 mg/mL of USP Fluoxetine Hydrochloride RS in *Mobile phase*

**Sensitivity solution:** 0.2  $\mu$ g/mL of USP Fluoxetine Hydrochloride RS from *Standard solution* in *Mobile phase*

**Sample solution:** 2 mg/mL of fluoxetine from Tablets prepared as follows. Transfer 10 Tablets to a suitable volumetric flask and add 50% of the final flask volume of *Mobile phase*. Shake to disintegrate and dilute with *Mobile phase* to volume. Sonicate the resulting solution for 10 min, pass a portion 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  $\times$  15-cm; 3.5- $\mu$ m packing L7

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 20  $\mu$ L

**Run time:** NLT 3 times the retention time of fluoxetine

## System suitability

**Samples:** Mobile phase, System suitability solution, Standard solution, and Sensitivity solution

**Injection order:** Mobile phase, Sensitivity solution, System suitability solution, and Standard solution

[NOTE—See [Table 1](#) for the relative retention times.]

## Suitability requirements

**Resolution:** NLT 4.5 between aminomethyl-1-phenylpropanol and fluoxetine related compound B, System suitability solution

**Relative standard deviation:** NMT 5.0%, Standard solution

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

## Analysis

**Samples:** Standard solution and Sample solution

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

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

$r_U$  = peak response of each impurity from the Sample solution

$r_S$  = peak response of fluoxetine from the Standard solution

$C_S$  = concentration of [USP Fluoxetine Hydrochloride RS](#) in the Standard solution (mg/mL)

$C_U$  = nominal concentration of fluoxetine in the Sample solution (mg/mL)

$M_{r1}$  = molecular weight of fluoxetine, 309.33

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

**Acceptance criteria:** See [Table 1](#).

**Table 1**

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Aminomethyl-1-phenylpropanol <sup>a</sup>	0.19	0.25
Fluoxetine related compound B	0.26	0.25
Fluoxetine	1.0	—
Any individual unspecified impurity	—	0.25
Total impurities	—	0.80

<sup>a</sup> 3-Methylamino-1-phenylpropan-1-ol; also known as  $\alpha$ -[2-(Methylamino)ethyl]benzenemethanol.

## ADDITIONAL REQUIREMENTS

● **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

### Add the following:

▲ **LABELING:** The labeling states the *Dissolution* test used only if *Test 1* is not used. ▲ (TBD)

● **USP REFERENCE STANDARDS** (11)

[USP Fluoxetine Hydrochloride RS](#)

[USP Fluoxetine Related Compound B RS](#)

*N*-Methyl-3-phenylpropan-1-amine;

also known as *N*-Methyl-3-phenylpropylamine.

$C_{10}H_{15}N$

149.24

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**Page Information:**

Not Applicable

**Current DocID:**

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