



## Paroxetine Extended-Release Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	31-May-2024
<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 Paroxetine Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Paroxetine Extended-Release Tablets monograph to add *Dissolution Test 5*.

- *Dissolution Test 5* was validated using the Sunfire C18 brand of column with L1 packing. The typical retention time for paroxetine is about 6.5 min. This revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

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 Yanyin Yang, Senior Scientist II (301-692-3623 or [yanyin.yang@usp.org](mailto:yanyin.yang@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](#).

## Paroxetine Extended-Release Tablets

### DEFINITION

Paroxetine Extended-Release Tablets contain paroxetine hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ).

### IDENTIFICATION

- **A.** 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

**Buffer:** 3.9 g/L of [ammonium acetate](#) in [water](#). Adjust with [glacial acetic acid](#) to a pH of 4.5.

**Mobile phase:** [Acetonitrile](#), *Buffer*, and [triethylamine](#) (40:60:1). Adjust with [glacial acetic acid](#) to a pH of 5.5.

**Standard solution:** 0.5 mg/mL of [USP Paroxetine Hydrochloride RS](#) in [methanol](#)

**System suitability solution:** 0.5 mg/mL of [USP Paroxetine Related Compound B RS](#) in *Standard solution*

**Sample solution:** Nominally 0.5 mg/mL of paroxetine from NLT 10 Tablets prepared as follows. Transfer the required number of Tablets to a suitable volumetric flask. Add 80% of the flask volume of [methanol](#). Sonicate for 30 min followed by stirring for 30 min. Dilute with [methanol](#) to volume.

#### Chromatographic system

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

**Mode:** LC

**Detector:** UV 295 nm

**Column:** 4.6-mm × 25-cm; 5- $\mu$ m packing [L13](#)

**Flow rate:** 1 mL/min

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

#### System suitability

**Samples:** *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for paroxetine related compound B and paroxetine are 0.9 and 1.0, respectively.]

#### Suitability requirements

**Resolution:** NLT 1.5 between paroxetine related compound B and paroxetine, *System suitability solution*

**Tailing factor:** NMT 2.0 for paroxetine, *System suitability solution*

**Relative standard deviation:** NMT 2.0% for paroxetine, *Standard solution*

#### Analysis

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

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) 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 Paroxetine Hydrochloride RS](#) in the *Standard solution* (mg/mL)

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

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

**Acceptance criteria:** 90.0%–110.0%

## PERFORMANCE TESTS

### Change to read:

- **DISSOLUTION** (711).

#### Test 1

**Acid stage medium:** 0.1 N [hydrochloric acid](#); 750 mL

**Buffer stage medium:** 0.05 M tris buffer prepared as follows. Dissolve 6.06 g of [tris\(hydroxymethyl\)aminomethane](#) in 1 L of [water](#). Add 1.8 mL of [hydrochloric acid](#) to the resulting solution. Adjust with [hydrochloric acid](#) to a pH of 7.5; 1000 mL deaerated.

**Apparatus 1:** 100 rpm

**Times:** 2 h in *Acid stage*; 2, 4, and 12 h in *Buffer stage*

**Buffer and Mobile phase:** Proceed as directed in the *Assay*.

**Acid stage standard stock solution:** 0.33 mg/mL of paroxetine prepared as follows. Transfer a suitable amount of [USP Paroxetine Hydrochloride RS](#) to a suitable volumetric flask. Dissolve in 5% of the flask volume of [methanol](#). Dilute with *Acid stage medium* to volume.

**Acid stage standard solution:** Dilute the *Acid stage standard stock solution* with *Acid stage medium* to obtain a final concentration of  $(L/7500)$  mg/mL, where  $L$  is the label claim in mg.

**Buffer stage standard stock solution:** 0.25 mg/mL of paroxetine prepared as follows. Transfer a suitable amount of [USP Paroxetine Hydrochloride RS](#) to a suitable volumetric flask. Dissolve in 5% of the flask volume of [methanol](#). Dilute with *Buffer stage medium* to volume.

**Buffer stage standard solution:** Dilute the *Buffer stage standard stock solution* with *Buffer stage medium* to obtain a final concentration of  $(L/1000)$  mg/mL, where  $L$  is the label claim in mg.

**Acid stage sample solution:** Run the *Acid stage* for 2 h. Withdraw 10 mL of the solution under test and centrifuge. Use the centrifugate for analysis.

**Buffer stage sample solution:** Remove the *Acid stage medium* from the vessel and replace it with the *Buffer stage medium*. At the times specified, remove 10 mL of the solution under test and centrifuge. Use the centrifugate for analysis.

**Chromatographic system:** Proceed as directed in the *Assay*. For *Injection volume*, use 100  $\mu$ L for the *Acid stage* analysis and 10  $\mu$ L for the *Buffer stage* analysis.

#### System suitability

**Samples:** *Acid stage standard solution* and *Buffer stage standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2.0, *Acid stage standard solution* and *Buffer stage standard solution*

**Relative standard deviation:** NMT 3.0%, *Acid stage standard solution* and *Buffer stage standard solution*

## Analysis

**Samples:** *Acid stage standard solution, Buffer stage standard solution, Acid stage sample solution, and Buffer stage sample solution*

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved in the *Acid stage*:

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

$r_U$  = peak response from the *Acid stage sample solution*

$r_S$  = peak response from the *Acid stage standard solution*

$C_S$  = concentration of [USP Paroxetine Hydrochloride RS](#) in the *Acid stage standard solution* (mg/mL)

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

$V$  = volume of the *Acid stage medium*, 750 mL

$L$  = label claim (mg/Tablet)

Calculate the concentration ( $C_i$ ) of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point in the *Buffer stage*:

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

$r_i$  = peak response from the *Buffer stage sample solution* at each time point  $i$

$r_S$  = peak response from the *Buffer stage standard solution*

$C_S$  = concentration of [USP Paroxetine Hydrochloride RS](#) in the *Buffer stage standard solution* (mg/mL)

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

Calculate the percentage of the labeled amount ( $Q_i$ ) of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point ( $i$ ) in the *Buffer stage medium*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$  = concentration of paroxetine in the *Buffer stage medium* in the portion of sample withdrawn at time point  $i$  (mg/mL)

$V$  = volume of the *Buffer stage medium*, 1000 mL

$L$  = label claim (mg/Tablet)

$V_S$  = volume of the *Sample solution* withdrawn from the *Buffer stage medium* (mL)

## Tolerances

**Acid stage:** NMT 10% of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) is dissolved in 2 h.

**Buffer stage:** See [Table 1](#).

**Table 1**

Time Point (i)	Time (h)	Amount Dissolved (Tablets labeled to contain 12.5 mg of paroxetine)	Amount Dissolved (Tablets labeled to contain 25 mg of paroxetine)	Amount Dissolved (Tablets labeled to contain 37.5 mg of paroxetine)
1	2	15%–35%	10%–30%	20%–45%
2	4	40%–70%	40%–70%	60%–85%
3	12	NLT 80%	NLT 80%	NLT 80%

The percentages of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at the times specified conform to [Dissolution <711>](#), [Acceptance Table 2](#).

## Test 2

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

**Acid stage medium:** 0.1 N [hydrochloric acid](#); 750 mL

**Buffer stage medium:** 0.05 M tris buffer prepared as follows. Dissolve 6.06 g of

[tris\(hydroxymethyl\)aminomethane](#) in 900 mL of [water](#). Add 40 mL of 1.0 M [hydrochloric acid](#) to the resulting solution. Adjust with either 1.0 M [hydrochloric acid](#) or 1.0 M [sodium hydroxide](#) to a pH of 7.5. Dilute with [water](#) to 1 L; 1000 mL deaerated.

**Apparatus 2:** 150 rpm with suitable sinkers

**Times:** 2 h in *Acid stage*; 1, 2, 4, and 6 h in *Buffer stage*

**Acid stage standard stock solution:** 0.04 mg/mL of [USP Paroxetine Hydrochloride RS](#) prepared as follows. Transfer a suitable amount of [USP Paroxetine Hydrochloride RS](#) to a suitable volumetric flask. Dissolve in 2 mL of [methanol](#). Dilute with *Acid stage medium* to volume.

**Acid stage standard solution:** Dilute the *Acid stage standard stock solution* with *Acid stage medium* to obtain a final concentration of  $(L/7500)$  mg/mL of paroxetine, where  $L$  is the label claim in mg.

**Buffer stage standard solution:**  $(L/1000)$  mg/mL of paroxetine, where  $L$  is the label claim in mg prepared as follows. Transfer a suitable amount of [USP Paroxetine Hydrochloride RS](#) to a suitable volumetric flask. Dissolve in 2 mL of [methanol](#). Dilute with *Buffer stage medium* to volume.

**Acid stage sample solution:** Run the *Acid stage* for 2 h. Withdraw 10 mL of the solution under test, and filter. Use the filtrate for analysis.

**Buffer stage sample solution:** Remove the Tablet and sinker from the acid stage vessel and pat them dry. Introduce the Tablet and sinker into the dissolution vessel with 1000 mL of the *Buffer stage medium*. At the times specified, remove 10 mL of the solution under test and filter. Use the filtrate for analysis.

## Acid stage analysis

**Buffer:** Add 2.9 mL of [phosphoric acid](#) to 800 mL of [water](#). Adjust with 1 M [sodium hydroxide](#) to a pH of 6.0. Dilute with [water](#) to 1000 mL.

**Mobile phase:** [Acetonitrile](#) and *Buffer* (40:60)

## Chromatographic system

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

**Mode:** LC

**Detector:** UV 205 nm

**Column:** 4.6-mm × 25-cm; 5-μm packing [L1](#)

**Flow rate:** 2 mL/min

**Injection volume:** 50 μL for 12.5-mg Tablet; 20 μL for 25- and 37.5-mg Tablets

**Run time:** 2 times the retention time of paroxetine

### System suitability

**Sample:** *Acid stage standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

### Analysis

**Samples:** *Acid stage standard solution* and *Acid stage sample solution*

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved in the *Acid stage*:

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

$r_U$  = peak response from the *Acid stage sample solution*

$r_S$  = peak response from the *Acid stage standard solution*

$C_S$  = concentration of [USP Paroxetine Hydrochloride RS](#) in the *Acid stage standard solution* (mg/mL)

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

$V$  = volume of the *Acid stage medium*, 750 mL

$L$  = label claim (mg/Tablet)

### Buffer stage analysis

#### Instrumental conditions

**Mode:** UV

**Analytical wavelength:** 294 nm with 340 nm for background correction

**Blank:** *Buffer stage medium*

#### Analysis

**Samples:** *Buffer stage standard solution* and *Buffer stage sample solution*

Calculate the concentration ( $C_i$ ) of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point (i) in the *Buffer stage*:

$$\text{Result} = (A_i/A_S) \times C_S \times (M_{r1}/M_{r2})$$

$A_i$  = absorbance of the *Buffer stage sample solution* at time point  $i$

$A_S$  = absorbance of the *Buffer stage standard solution*

$C_S$  = concentration of [USP Paroxetine Hydrochloride RS](#) in the *Buffer stage standard solution* (mg/mL)

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point ( $i$ ) in the *Buffer stage medium*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$  = concentration of paroxetine in the *Buffer stage medium* in the portion of sample withdrawn at time point  $i$  (mg/mL)

$V$  = volume of the *Buffer stage medium*, 1000 mL

$L$  = label claim (mg/Tablet)

$V_S$  = volume of the *Sample solution* withdrawn from the *Buffer stage medium* (mL)

### Tolerances

**Acid stage:** NMT 10% of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) is dissolved in 2 h.

**Buffer stage:** See [Table 2](#).

**Table 2**

Time Point ( $i$ )	Time (h)	Amount Dissolved
1	1	NMT 20%
2	2	20%–45%
3	4	60%–90%
4	6	NLT 85%

The percentages of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at the times specified conform to [Dissolution <711>](#), [Acceptance Table 2](#).

### Test 3

If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 3*.

**Acid stage medium:** 0.1 N [hydrochloric acid](#); 750 mL

**Buffer stage medium:** 0.05 M tris buffer prepared as follows. Dissolve 42 g of [tris\(hydroxymethyl\)aminomethane](#) in 2000 mL of [water](#). Pass through a suitable filter of 0.45- $\mu$ m pore size. Add 5000 mL of [water](#) and adjust with [hydrochloric acid](#) to a pH of 7.5; 1000 mL deaerated.

**Apparatus 2:** 150 rpm with suitable sinkers

**Times:** 2 h in *Acid stage*; 2, 4, and 6 h in *Buffer stage*

**Solution A:** 1.36 g/L of [potassium phosphate monobasic](#) and 2.44 g/L of [sodium 1-decanesulfonate](#) in [water](#). Adjust with 0.5% [phosphoric acid](#) to a pH of 3.0.

**Mobile phase:** [Acetonitrile](#) and *Solution A* (45:55)

**Standard stock solution:** 0.042 mg/mL of [USP Paroxetine Hydrochloride RS](#) prepared as follows.

Transfer a suitable amount of [USP Paroxetine Hydrochloride RS](#) to a suitable volumetric flask. Add about 50% of the final flask volume of *Buffer stage medium* and sonicate for about 15 min to dissolve. Dilute with *Buffer stage medium* to volume.

**Standard solution:** 0.021 mg/mL of [USP Paroxetine Hydrochloride RS](#) prepared as follows. Mix equal portions of *Standard stock solution* and *Acid stage medium* in a suitable glass container.

**Acid stage sample solution:** Run the *Acid stage* for 2 h. Withdraw 10 mL of the solution under test. Centrifuge to obtain a clear supernatant. Mix equal portions of the supernatant and *Acid stage medium* in a suitable glass container. Use the resulting solution for analysis.

**Buffer stage sample solution:** Remove the Tablet in the sinker from the acid stage vessel. Add the Tablet in the sinker to the vessel with 1000 mL of *Buffer stage medium* and run the *Buffer stage*. At the times specified, remove 10 mL of the solution under test. Centrifuge to obtain a clear supernatant. Mix equal portions of the supernatant and *Acid stage medium* in a suitable glass container. Use the resulting solution for analysis.

### Chromatographic system

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

**Mode:** LC

**Detector:** UV 235 nm

**Column:** 4.6-mm × 15-cm; 5-μm packing [L1](#)

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 50 μL

**Run time:** About 1.5 times the retention time of paroxetine

### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2

**Relative standard deviation:** NMT 2.0%

### Analysis

**Samples:** *Standard solution*, *Acid stage sample solution*, and *Buffer stage sample solution*

Calculate the percentage of the labeled amount of paroxetine (C<sub>19</sub>H<sub>20</sub>FNO<sub>3</sub>) dissolved in the *Acid stage*:

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2}) \times D \times V \times (1/L) \times 100$$

$r_U$  = peak response from the *Acid stage sample solution*

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

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

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

$D$  = dilution factor

$V$  = volume of the *Acid stage medium*, 750 mL

$L$  = label claim (mg/Tablet)



Calculate the concentration ( $C_i$ ) of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point ( $i$ ) in the *Buffer stage*:

$$\text{Result}_i = (r_i/r_S) \times C_S \times (M_{r1}/M_{r2}) \times D$$

$r_i$  = peak response from the *Buffer stage sample solution* at time point  $i$

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

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

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

$D$  = dilution factor

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point ( $i$ ) in the *Buffer stage medium*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$  = concentration of paroxetine in the *Buffer stage medium* in the portion of sample withdrawn at time point  $i$  (mg/mL)

$V$  = volume of the *Buffer stage medium*, 1000 mL

$L$  = label claim (mg/Tablet)

$V_S$  = volume of the sample solution withdrawn from the *Buffer stage medium* (mL)

#### Tolerances

**Acid stage:** NMT 10% of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) is dissolved.

**Buffer stage:** See [Table 3](#).

**Table 3**

Time Point ( $i$ )	Time (h)	Amount Dissolved (%)
1	2	20–50
2	4	55–85
3	6	NLT 80

The percentages of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at the times specified conform to [Dissolution <711>](#), [Acceptance Table 2](#).

#### Test 4

If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 4*.

**Acid stage medium:** 0.1 N [hydrochloric acid](#); 750 mL

**Buffer stage medium:** 6.05 g/L of [tris\(hydroxymethyl\)aminomethane](#) in [water](#). Adjust with [hydrochloric acid](#) to a pH of 7.5; 1000 mL.

**Apparatus 2:** 150 rpm

**Times:** 2 h in *Acid stage*; 2, 4, and 8 h in *Buffer stage*

**Solution A:** 3.85 g/L of [ammonium acetate](#) in [water](#). Adjust with [glacial acetic acid](#) to a pH of 4.5.

**Mobile phase:** [Acetonitrile](#), *Solution A*, and [triethylamine](#) (35:65:1). Adjust with [glacial acetic acid](#) to a pH of 5.5.

**Acid stage standard stock solution:** 0.190 mg/mL of [USP Paroxetine Hydrochloride RS](#) prepared as follows. Transfer a suitable amount of [USP Paroxetine Hydrochloride RS](#) to a suitable volumetric flask. Add 4% of the flask volume of [methanol](#) and sonicate to dissolve. Dilute with *Acid stage medium* to volume.

**Acid stage standard solution:** 0.019 mg/mL of [USP Paroxetine Hydrochloride RS](#) from *Acid stage standard stock solution* in *Acid stage medium*

**Buffer stage standard stock solution:** 0.142 mg/mL of [USP Paroxetine Hydrochloride RS](#) prepared as follows. Transfer a suitable amount of [USP Paroxetine Hydrochloride RS](#) to a suitable volumetric flask. Add 4% of the flask volume of [methanol](#) and sonicate to dissolve. Dilute with *Buffer stage medium* to volume.

**Buffer stage standard solution:** 0.0142 mg/mL of [USP Paroxetine Hydrochloride RS](#) from *Buffer stage standard stock solution* in *Buffer stage medium*

**Acid stage sample solution:** At the time specified, withdraw 10 mL of the solution under test and pass through a suitable filter of 0.45- $\mu$ m pore size, discarding the first 2–3 mL of filtrate. Dilute, if needed, with *Acid stage medium* to a concentration that is similar to that of the *Acid stage standard solution*.

**Buffer stage sample solution:** Remove the *Acid stage medium* from the vessel and replace it with the *Buffer stage medium*. At the times specified, withdraw 10 mL of the solution under test and replace with 10 mL of *Buffer stage medium*. Pass the solution under test through a suitable filter of 0.45- $\mu$ m pore size, discarding the first 2–3 mL of filtrate. Dilute, if needed, with *Buffer stage medium* to a concentration that is similar to that of the *Buffer stage standard solution*.

### Chromatographic system

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

**Mode:** LC

**Detector:** UV 295 nm

**Column:** 4.6-mm  $\times$  15-cm; 3- $\mu$ m packing [L1](#)

#### Temperatures

**Autosampler:** 10°

**Column:** 35°

**Flow rate:** 1.2 mL/min

**Injection volume:** 100  $\mu$ L

**Run time:** NLT 2 times the retention time of paroxetine

### System suitability

**Samples:** *Acid stage standard solution* and *Buffer stage standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2, *Acid stage standard solution* and *Buffer stage standard solution*

**Relative standard deviation:** NMT 2.0%, *Acid stage standard solution* and *Buffer stage standard solution*

### Analysis

**Samples:** *Acid stage standard solution, Buffer stage standard solution, Acid stage sample solution, and Buffer stage sample solution*

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved in the *Acid stage* ( $Q_A$ ):

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

$r_U$  = peak response of paroxetine from the *Acid stage sample solution*

$r_S$  = peak response of paroxetine from the *Acid stage standard solution*

$C_S$  = concentration of [USP Paroxetine Hydrochloride RS](#) in the *Acid stage standard solution* (mg/mL)

$V$  = volume of the *Acid stage medium*, 750 mL

$D$  = dilution factor for the *Acid stage sample solution*

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

$L$  = label claim (mg/Tablet)

Calculate the concentration ( $C_i$ ) of paroxetine ( $C_{19}H_{20}FNO_3$ ) in the sample withdrawn from the vessel at each time point ( $i$ ) in the *Buffer stage*:

$$\text{Result}_i = (r_i/r_S) \times C_S \times D \times (M_{r1}/M_{r2})$$

$r_i$  = peak response of paroxetine from the *Buffer stage sample solution*

$r_S$  = peak response of paroxetine from the *Buffer stage standard solution*

$C_S$  = concentration of [USP Paroxetine Hydrochloride RS](#) in the *Buffer stage standard solution* (mg/mL)

$D$  = dilution factor for the *Buffer stage sample solution*

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point ( $i$ ) in the *Buffer stage*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100 + Q_A$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100 + Q_A$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100 + Q_A$$

$C_i$  = concentration of paroxetine in the portion of sample withdrawn at time point  $i$  (mg/mL)

$V$  = volume of the *Buffer stage medium*, 1000 mL

$L$  = label claim (mg/Tablet)

$Q_A$  = percentage of the labeled amount of paroxetine dissolved in the *Acid stage*

$V_S$  = volume of the sample solution withdrawn at each time point and replaced with *Buffer stage medium* (mL)

## Tolerances

**Acid stage:** NMT 25% of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) is dissolved.

**Buffer stage:** See [Table 4](#).

**Table 4**

<b>Time Point (i)</b>	<b>Time (h)</b>	<b>Amount Dissolved (%)</b>
1	2	23–43
2	4	50–70
3	8	NLT 80

The percentages of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at the times specified conform to [Dissolution](#) (711), [Acceptance Table 2](#).

**▲Test 5:** If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 5*.

**Acid stage medium:** 0.1 N [hydrochloric acid](#); 750 mL

**Buffer stage medium:** Dissolve 6 g of [tris\(hydroxymethyl\)aminomethane](#) in 1000 mL of [water](#). Adjust with [hydrochloric acid](#) to a pH of 7.5; 1000 mL, deaerated, if necessary.

**Apparatus 2:** 150 rpm with sinkers<sup>1</sup>

#### Times

**Acid stage:** 2 h

**Buffer stage:** 2, 4, and 8 h. The times in the *Buffer stage medium* do not include the time in the *Acid stage medium*.

**Solution A:** Dissolve 1.36 g of [potassium phosphate, monobasic](#) and 2.44 g of sodium 1-decanesulfonate monohydrate in 1000 mL of [water](#). Adjust with 5 mL/L of [phosphoric acid in water](#) to a pH of 3.0.

**Mobile phase:** [Acetonitrile](#) and *Solution A* (45:55)

**Standard stock solution:** 0.168 mg/mL of [USP Paroxetine Hydrochloride RS](#) in *Buffer stage medium*. Sonicate to dissolve, if necessary.

#### Standard solution

**For Tablets labeled to contain 25 mg:** 0.013 mg/mL of [USP Paroxetine Hydrochloride RS](#) prepared as follows. Dilute 8.0 mL of the *Standard stock solution* with *Buffer stage medium* to 50.0 mL. Further dilute 5.0 mL of the resulting solution with *Acid stage medium* to 10.0 mL.

**For Tablets labeled to contain 37.5 mg:** 0.021 mg/mL of [USP Paroxetine Hydrochloride RS](#) prepared as follows. Dilute 5.0 mL of the *Standard stock solution* with *Buffer stage medium* to 20.0 mL. Further dilute 5.0 mL of the resulting solution with *Acid stage medium* to 10.0 mL.

**Acid stage sample solution:** At the time specified, withdraw 10 mL of the solution under test and replace with 10 mL of pre-warmed *Acid stage medium*. Centrifuge the withdrawn portion and dilute 5.0 mL of the supernatant with *Acid stage medium* to 10.0 mL. [NOTE—A centrifuge speed of 6000 rpm for 10 min may be suitable.]

**Buffer stage sample solution:** After completion of the *Acid stage*, drain the *Acid stage medium* from the vessel. Transfer the tablet along with the sinker to a different vessel filled with the *Buffer stage medium* and start the *Buffer stage*. At the times specified, withdraw 10 mL of the solution under test

and replace with 10 mL of pre-warmed *Buffer stage medium*. Centrifuge the withdrawn portion and dilute 5.0 mL of the supernatant with *Acid stage medium* to 10.0 mL. [NOTE—A centrifuge speed of 6000 rpm for 10 min may be suitable.]

### Chromatographic system

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

**Mode:** LC

**Detector:** UV 235 nm

**Column:** 4.6-mm × 15-cm; 5-μm packing L1

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 50 μL

**Run time:** NLT 2.6 times the retention time of paroxetine

### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

### Analysis

**Samples:** *Standard solution*, *Acid stage sample solution*, and *Buffer stage sample solution*

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved in the *Acid stage* ( $Q_A$ ):

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

$r_U$  = peak response of paroxetine from the *Acid stage sample solution*

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

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

$V$  = volume of the *Acid stage medium*, 750 mL

$D$  = dilution factor for the *Acid stage sample solution*

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

$L$  = label claim (mg/Tablet)

Calculate the concentration ( $C_i$ ) of paroxetine ( $C_{19}H_{20}FNO_3$ ) in the sample withdrawn from the vessel at each time point ( $i$ ) in the *Buffer stage*:

$$\text{Result}_i = (r_i/r_S) \times C_S \times D \times (M_{r1}/M_{r2})$$

$r_i$  = peak response of paroxetine from the *Buffer stage sample solution*

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

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

$D$  = dilution factor for the *Buffer stage sample solution*

$M_{r1}$  = molecular weight of paroxetine, 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

Calculate the percentage of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at each time point ( $i$ ) in the *Buffer stage*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100 + Q_A$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100 + Q_A$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100 + Q_A$$

$C_i$  = concentration of paroxetine in the portion of sample withdrawn at time point  $i$  (mg/mL)

$V$  = volume of the Buffer stage medium, 1000 mL

$L$  = label claim (mg/Tablet)

$Q_A$  = percentage of the labeled amount of paroxetine dissolved in the Acid stage

$V_S$  = volume of the sample solution withdrawn at each time point and replaced with Buffer stage medium (mL)

### Tolerances

**Acid stage:** NMT 10% of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) is dissolved.

**Buffer stage:** See [Table 5](#).

Time Point ( $i$ )	Time (h)	Amount Dissolved (%)
1	2	14–34
2	4	49–69
3	8	NLT 80

The percentages of the labeled amount of paroxetine ( $C_{19}H_{20}FNO_3$ ) dissolved at the times specified conform to [Dissolution \(711\)](#), [Acceptance Table 2](#). ▲ (TBD)

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

### IMPURITIES

#### Change to read:

- **ORGANIC IMPURITIES**

**Solution A:** [Tetrahydrofuran](#), [water](#), and [trifluoroacetic acid](#) (20:180:1)

**Solution B:** [Acetonitrile](#), [tetrahydrofuran](#), and [trifluoroacetic acid](#) (180:20:1)

**Mobile phase:** See ▲ [Table 6](#).

Table 6 ▲ (TBD)

Time (min)	Solution A (%)	Solution B (%)
0	80	20
30	80	20

Time (min)	Solution A (%)	Solution B (%)
50	20	80
60	20	80
70	80	20
80	80	20

**System suitability solution:** 1 mg/mL of [USP Paroxetine Hydrochloride RS](#), 0.1 mg/mL of [USP Paroxetine System Suitability Mixture A RS](#), and 1 mg/mL of [USP Paroxetine Related Compound F RS](#) in [methanol](#). [NOTE—Sonication may be used to aid dissolution of the individual components.]

**Standard solution:** 0.01 mg/mL of [USP Paroxetine Hydrochloride RS](#) in [methanol](#)

**Sample solution:** Nominally 1 mg/mL of paroxetine from NLT 10 Tablets prepared as follows. Transfer a suitable number of Tablets to a suitable volumetric flask. Add 50% of the flask volume of [methanol](#). Sonicate for 30 min followed by stirring for 30 min. Dilute with methanol to volume. Mix and centrifuge. Use the clear centrifugate.

#### Chromatographic system

(See [Chromatography \(621\)](#), *System Suitability*.)

**Mode:** LC

**Detector:** UV 285 nm

**Column:** 4.6-mm × 25-cm; 5-μm packing [L7](#)

**Column temperature:** 40°

**Flow rate:** 1 mL/min

**Injection volume:** 20 μL

#### System suitability

**Samples:** *System suitability solution* and *Standard solution*

[NOTE—See [Table 7](#) (TBD) for the relative retention times.]

#### Suitability requirements

**Resolution:** NLT 1.5 between paroxetine related compound A and paroxetine related compound B;  
NLT 1.5 between paroxetine related compound F and paroxetine, *System suitability solution*

**Tailing factor:** NMT 2.0 for paroxetine, *Standard solution*

**Relative standard deviation:** NMT 5.0% for paroxetine, *Standard 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 from the *Sample solution*

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

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

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

$M_{r1}$  = molecular weight of paroxetine 329.37

$M_{r2}$  = molecular weight of paroxetine hydrochloride, 365.83

Acceptance criteria: See [Table 7](#).

**Table 7** (TBD)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Paroxetine related compound A <sup>a</sup>	0.67	—
Paroxetine related compound B <sup>a</sup>	0.75	—
Paroxetine related compound F <sup>a</sup>	0.90	—
Paroxetine	1.0	—
Ethoxyparoxetine <sup>b</sup>	1.2	0.2
Any unspecified degradation product	—	0.2
Total impurities	—	1.0

<sup>a</sup> Process impurities, included for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities of the drug product.

<sup>b</sup> (3*SR,4RS*)-3-(1,3-Benzodioxol-5-yloxy)methyl)-4-(4-ethoxyphenyl)piperidine.

## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** (11).

[USP Paroxetine Hydrochloride RS](#)

[USP Paroxetine Related Compound B RS](#)

*trans*-4-Phenyl-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine hydrochloride;

Also known as Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenyl-, hydrochloride (3*S-trans*).



[USP Paroxetine Related Compound F RS](#)

(3*S,4R*)-3-[(Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-1-methylpiperidine.



[USP Paroxetine System Suitability Mixture A RS](#)

Mixture of approximately 1% paroxetine related compound A [piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)-, hydrochloride (3*S-trans*)], and 1% paroxetine related compound B



[piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenyl-, hydrochloride (3*S-trans*)] in a matrix of paroxetine hydrochloride.

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<sup>1</sup> A suitable sinker is available as catalog No. PSCAPWST-18 (OEM reference 0104A00095) from <https://www.dissolutionaccessories.com>.

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**Page Information:**

Not Applicable

**Current DocID:**

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