

Paroxetine Hydrochloride

$C_{19}H_{20}FNO_3 \cdot HCl$ 365.83
 Hemihydrate 374.83

Piperidine, 3-[(1,3-benzodioxol-5-yl)oxy)methyl]-4-(4-fluorophenyl)-, hydrochloride, (3*S*-*trans*)-;
 (-)-(3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-[[[3,4-methylenedioxy]phenoxy]methyl]piperidine hydrochloride [78246-49-8].

DEFINITION

Paroxetine Hydrochloride is anhydrous or contains one-half molecule of water of hydration. It contains NLT 98.5% and NMT 102.0% of $C_{19}H_{20}FNO_3 \cdot HCl$, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

A. INFRARED ABSORPTION <197M>

Standard solution: Dissolve USP Paroxetine Hydrochloride RS in a mixture of water and isopropyl alcohol (1 in 10). Heat to 70° to dissolve, recrystallize, and dry the residue under vacuum at 50° for 3 h.

Sample solution: Dissolve a suitable portion of Paroxetine Hydrochloride in a mixture of water and isopropyl alcohol (1 in 10). Heat to 70° to dissolve, recrystallize, and dry the residue under vacuum at 50° for 3 h.

B. IDENTIFICATION TESTS—GENERAL, Chloride <191>

Meets the requirements
Sample solution: 10 mg/mL of solution in a mixture of methanol and water (1:1)

ASSAY

PROCEDURE

Buffer: 0.05 M ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.5.

Mobile phase: Acetonitrile, triethylamine, and Buffer (30:1:70). [NOTE—The ratios from 25:1:75 to 40:1:70 are acceptable variations to meet system suitability requirements.] Adjust with glacial acetic acid to a pH of 5.5.

System suitability solution: 0.5 mg/mL of USP Paroxetine Hydrochloride RS and 0.5 mg/mL of USP Paroxetine Related Compound B RS

Standard solution: 0.5 mg/mL of USP Paroxetine Hydrochloride RS

Sample solution: 0.5 mg/mL of Paroxetine Hydrochloride

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 295 nm

Column: 4.6-mm × 25-cm; packing L13

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

Sample: System suitability solution

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

Suitability requirements

Resolution: NLT 2.0 between paroxetine related compound B and paroxetine

Tailing factor: NMT 2.0 for paroxetine

Relative standard deviation: NMT 2.0% for paroxetine

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of $C_{19}H_{20}FNO_3 \cdot HCl$ in the portion of Paroxetine Hydrochloride 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 the Standard solution (mg/mL)

C_U = concentration of the Sample solution (mg/mL)

Acceptance criteria: 98.5%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

Inorganic Impurities

• **RESIDUE ON IGNITION (281):** NMT 0.1%

• **HEAVY METALS, Method II (231):** NMT 20 ppm

Organic Impurities

[NOTE—Perform either Procedure 3 or Procedure 4, depending on the synthetic route. Procedure 4 is recommended if paroxetine related compound F or G are potential impurities.]

PROCEDURE 1: LIMIT OF RELATED COMPOUND C

Mobile phase: *n*-Hexane, absolute alcohol, trifluoroacetic acid, and water (900:100:2:2)

Diluent: *n*-Hexane and absolute alcohol (1:1)

Standard solution: 0.1 mg/mL of USP Paroxetine Related Compound C RS in Diluent

Sample solution: 5.0 mg/mL of Paroxetine Hydrochloride in Diluent

System suitability solution: Mix the Diluent, Standard solution, and Sample solution to obtain a solution containing 0.1 mg/mL of USP Paroxetine Related Compound C RS and 0.1 mg/mL of Paroxetine Hydrochloride.

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 295 nm

Column: 4.6-mm × 25-cm; packing L51

Column temperature: 30°

Flow rate: 1.0 mL/min

Injection size: 5 µL

System suitability

Sample: System suitability solution

[NOTE—The relative retention times for paroxetine related compound C and paroxetine are about 0.6 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between paroxetine and paroxetine related compound C

Tailing factor: NMT 2.5 for the paroxetine related compound C peak

Relative standard deviation: NMT 10.0% for paroxetine related compound C

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride 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 paroxetine related compound C in the Standard solution (mg/mL)

C_U = concentration of Paroxetine Hydrochloride in the Sample solution (mg/mL)

Acceptance criteria: NMT 0.1% of paroxetine related compound C

PROCEDURE 2: LIMIT OF 1-METHYL-4-(*p*-FLUOROPHENYL)-1,2,3,6-TETRAHYDROPYRIDINE

Solution A: Dissolve 30 g of sodium perchlorate in 900 mL of water. Add 3.5 mL of phosphoric acid and 2.4 mL of triethylamine. Dilute with water to 1000 mL. Adjust with phosphoric acid or triethylamine to a pH of 2.0. Make adjustments if necessary.

Solution B: Acetonitrile, filtered and degassed

Diluent: Acetonitrile and water (1:4)

Standard solution: 42 ng/mL of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine, obtained from USP Paroxetine Related Compound E Mixture RS, in Diluent

Sample solution: 42 mg/mL of Paroxetine Hydrochloride in *Diluent*. [NOTE—Sonicate as necessary.]

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	85	15
20	80	20
27	55	45
36	55	45
38	85	15
45	85	15

Chromatographic system

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

Mode: LC

Detector: UV 242 nm

Column: 4.0-mm × 25-cm; packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection size: 75 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine and paroxetine are about 0.6 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 15.0% for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine, determined from three replicate injections of the *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Paroxetine Related Compound E Mixture RS in the *Standard solution* (mg/mL)

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

I = fraction by weight of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in the USP Paroxetine Related Compound E Mixture RS

Acceptance criteria: NMT 1 ppm

PROCEDURE 3

Solution A: Tetrahydrofuran, trifluoroacetic acid, and water (20:1:180)

Solution B: Acetonitrile, tetrahydrofuran, and trifluoroacetic acid (180:20:1)

Diluent: Tetrahydrofuran and water (1:9)

Standard solution: 1 µg/mL of USP Paroxetine Hydrochloride RS in *Diluent*

Sample solution: 1 mg/mL of Paroxetine Hydrochloride in *Diluent*

System suitability solution: 1 mg/mL of USP Paroxetine System Suitability Mixture A RS in *Diluent*. [NOTE—Sonicate as necessary.]

Mobile phase: See the gradient table below.

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

Chromatographic system

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

Mode: LC

Detector: UV 285 nm

Column: 4.6-mm × 25-cm; packing L7

Column temperature: 40°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—Identify the peaks using the relative retention times given in *Impurity Table 1*.]

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Paroxetine related compound A ^a	0.66	—	0.1
Paroxetine related compound B ^b	0.73	—	0.3
Paroxetine	1.0	—	—
Any unspecified impurity	—	—	0.1
Total impurities	—	—	1.0

^a (3*S*,4*R*)-3-[(Benzodioxol-5-yl)oxy)methyl]-4-(4-methoxyphenyl)piperidine hydrochloride.

^b *trans*-4-Phenyl-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine hydrochloride.

Suitability requirements

Resolution: NLT 2.0 between paroxetine related compound A and paroxetine related compound B

Tailing factor: 0.8–2.0 for paroxetine related compound A

Relative standard deviation: NMT 2.0% for paroxetine related compound A

Analysis

Samples: *Diluent*, *Standard solution*, and *Sample solution*

Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken:

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

r_U = peak area of each impurity of the *Sample solution*, excluding peaks obtained from the chromatogram of the *Diluent*

r_S = peak area of paroxetine of the *Standard solution*

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

C_U = concentration of Paroxetine Hydrochloride, on the anhydrous basis, in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: NMT 0.3% of paroxetine related compound B; NMT 0.1% of any other individual impurity

Total impurities: NMT 1.0%

PROCEDURE 4

Buffer: Dissolve 3.4 g of monobasic potassium phosphate and 3.4 g of tetrabutylammonium hydrogen sulfate in 1.0 L of water.

Solution A: Acetonitrile and Buffer (2:98)

Solution B: Acetonitrile and Buffer (4:6)

Diluent: Acetonitrile and Buffer (1:9)

System suitability solution: Prepare a solution containing the following in *Diluent*: 2 mg/mL of USP Paroxetine Hydrochloride RS, 10 µg/mL of USP Paroxetine Related Compound B RS, 10 µg/mL of USP Paroxetine Related Compound F RS, and 4 µg/mL of USP Paroxetine Related Compound G RS.

Standard solution: Prepare a solution containing the following in *Diluent*: 4 mg/mL of USP Paroxetine Hydrochloride RS, 10 µg/mL of USP Paroxetine Related Compound B RS, 10 µg/mL of USP Paroxetine Related Compound F RS, and 4 µg/mL of USP Paroxetine Related Compound G RS.

Sample solution: 0.5 mg/mL of Paroxetine Hydrochloride in *Diluent*

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
70	40	60
90	0	100
95	0	100
95.1	100	0
110	100	0

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 15-cm; packing L1

Flow rate: 1.0 mL/min

Injection size: 25 µL

System suitability

Sample: *System suitability solution*

[NOTE—Identify the peaks using the relative retention times given in *Impurity Table 2*.]

Impurity Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Paroxetine related compound B ^a	0.91	—	0.5
Paroxetine related compound F ^b	0.96	—	0.2
Paroxetine	1.0	—	—
Paroxetine related compound G ^c	1.34	—	0.2

^a *trans*-4-Phenyl-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine hydrochloride.

^b *trans*-(-)-1-Methyl-3-[1,3-benzodioxol-5-yloxy)methyl]-4-(fluorophenyl)piperidine.

^c (+)-*trans*-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine.

Impurity Table 2 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any unspecified impurity	—	—	0.1
Total impurities	—	—	1.0

^a *trans*-4-Phenyl-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine hydrochloride.

^b *trans*-(-)-1-Methyl-3-[1,3-benzodioxol-5-yloxy)methyl]-4-(fluorophenyl)piperidine.

^c (+)-*trans*-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine.

Suitability requirements

Relative standard deviation: NMT 10.0% each of paroxetine related compound B, paroxetine related compound F, paroxetine hydrochloride, and paroxetine related compound G

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of paroxetine related compound B, paroxetine related compound F, and paroxetine related compound G in the portion of Paroxetine Hydrochloride 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 of the corresponding impurity peak from the *Standard solution*

C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (mg/mL)

C_U = concentration of Paroxetine Hydrochloride, on the anhydrous basis, in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: See *Impurity Table 2*.

Total impurities: NMT 1.0%

SPECIFIC TESTS

- WATER DETERMINATION, Method I (921):** NMT 1.5% for the anhydrous form; 2.2%–2.8% for the hemihydrate form

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve the anhydrous form in tight containers. Preserve the hemihydrate form in well-closed containers. Store at controlled room temperature.
- LABELING:** Label the article to indicate whether it is the anhydrous form or the hemihydrate form, and label it to indicate with which impurity tests the article complies.
- USP REFERENCE STANDARDS (11)**
 - USP Paroxetine Hydrochloride RS
 - USP Paroxetine Related Compound B RS
 - USP Paroxetine Related Compound C RS
 - USP Paroxetine Related Compound E Mixture RS
 - USP Paroxetine Related Compound F RS
 - USP Paroxetine Related Compound G RS
 - USP Paroxetine System Suitability Mixture A RS