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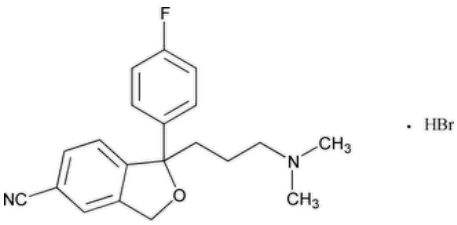
Citalopram Hydrobromide



$C_{20}H_{21}FN_2O \cdot HBr$ 405.30

5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, monohydrobromide;

1-[3-(Dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile monohydrobromide CAS RN®: 59729-32-7; UNII: I1E9D14F36.

DEFINITION

Citalopram Hydrobromide contains NLT 98.0% and NMT 102.0% of citalopram hydrobromide ($C_{20}H_{21}FN_2O \cdot HBr$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

- **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C.** Identification Tests—General **191**, *Bromide*

Sample solution: 10 mg/mL of Citalopram Hydrobromide in water

Acceptance criteria: Meets the requirements of test *B*

ASSAY

- **Procedure**

Buffer: Dissolve 1 g of sodium acetate in 800 mL of water, and add 6 mL of triethylamine. Adjust with acetic acid to a pH of 4.6, and dilute with water to 1 L.

Mobile phase: Acetonitrile and *Buffer* (20:80). The apparent pH is 5.0 ± 0.1. Make adjustments, if necessary.

Diluent: Methanol and water (50:50)

System suitability solution: 1 µg/mL each of USP Citalopram Hydrobromide RS and USP Citalopram Related Compound D RS in *Diluent*

Standard solution: 0.625 mg/mL of USP Citalopram Hydrobromide RS in *Diluent*

Sample solution: 0.625 mg/mL of Citalopram Hydrobromide in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 239 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 1.3 times the retention time of citalopram

System suitability

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

Suitability requirements

Resolution: NLT 1.8 between citalopram related compound D and citalopram, *System suitability solution*

Column efficiency: NLT 3000 theoretical plates, *Standard solution*

Tailing factor: NMT 3.0, *Standard solution*

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

Analysis

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

Verify that there are no interfering peaks, using the *Diluent*.

Calculate the percentage of citalopram hydrobromide ($C_{20}H_{21}FN_2O \cdot HBr$) in the portion of Citalopram Hydrobromide 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 USP Citalopram Hydrobromide RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

• **Residue on Ignition** ⟨281⟩

Analysis: Moisten the sample with 2 mL of nitric acid and 5 drops of sulfuric acid.

Acceptance criteria: NMT 0.1%

• **Organic Impurities, Procedure 1**

[Note—On the basis of the synthetic route used, perform either *Procedure 1* or *Procedure 2*. However, if the chloro and bromo analogs are potential related compounds in the synthetic route used, *Procedure 2* is recommended.]

Buffer, Mobile phase, Diluent, System suitability solution, and **Sample solution:** Proceed as directed in the *Assay*.

Standard solution: 0.625 µg/mL of USP Citalopram Hydrobromide RS in *Diluent*

Sensitivity solution: 0.0625 µg/mL of USP Citalopram Hydrobromide RS in *Diluent*

Chromatographic system: Proceed as directed in the *Assay*, except use a *Run time* of 1.7 times the retention time of citalopram.

System suitability

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

[Note—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.8 between citalopram related compound D and citalopram, *System suitability solution*

Tailing factor: 0.8–1.5 for citalopram, *System suitability solution*

Relative standard deviation: NMT 5% for citalopram, *System suitability solution*

Signal-to-noise ratio: NLT 3, *Sensitivity solution*

Analysis

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

Verify that there are no interfering peaks, using the *Diluent*.

Calculate the percentage of each impurity in the portion of Citalopram Hydrobromide taken:

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

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

r_S = peak response of citalopram from the *Standard solution*

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

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

M_{r1} = molecular weight of citalopram, 324.39

M_{r2} = molecular weight of citalopram hydrobromide, 405.30

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor[a]	Acceptance Criteria, NMT (%)
Citalopram ketone[b]	0.13	0.34	0.1
Citalopram related compound A	0.18	0.77	0.1
Citalopram open ring[c]	0.26	0.99	0.1
Citalopram related compound B[d]	0.40	0.98	0.1
Citalopram related compound C	0.67	0.69	0.1
Citalopram related compound D	0.90	1.04	0.1
Citalopram	1.0	—	—
Citalopram related compound E[e]	1.29	0.91	0.1
Individual unknown impurity	—	1.0	0.1
Total impurities	—	—	0.5

[a] The relative response factors provided are for each impurity relative to citalopram (free base).

[b] 4-(Dimethylamino)-1-{1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-yl}butan-1-one.

[c] 4-[4-(Dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile.

[d] 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile.

[e] 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile-*N*-oxide.

- **Organic Impurities, Procedure 2**

Buffer: To each L of 2.7 g/L of monobasic potassium phosphate in water prepared, add 1 mL of *N,N*-dimethyloctylamine, and adjust with phosphoric acid to a pH of 3.0.

Solution A: Methanol, tetrahydrofuran, and *Buffer* (24:6:70)

Solution B: Acetonitrile and *Buffer* (80:20)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
18	100	0
40	10	90

Time (min)	Solution A (%)	Solution B (%)
45	10	90
46	100	0
55	100	0

Diluent: Acetonitrile and *Buffer* (30:70)

System suitability solution: 1.5 µg/mL each of USP Citalopram Hydrobromide RS, USP Citalopram Related Compound A RS, USP Citalopram Related Compound C RS, USP Citalopram Related Compound D RS, USP Citalopram Related Compound G RS, and USP Citalopram Related Compound H RS in *Diluent*

Standard solution: 1.5 µg/mL of USP Citalopram Hydrobromide RS in *Diluent*

Sample solution: 1.5 mg/mL of Citalopram Hydrobromide in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 224 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 0.8 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between citalopram and citalopram related compound D; NLT 4.0 between citalopram related compound G and citalopram related compound H

Tailing factor: NMT 1.5 for citalopram

Relative standard deviation: NMT 2.0% for citalopram

Analysis

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

Chromatograph the *System suitability solution*, and identify the components on the basis of their relative retention times, as shown in *Table 3*.

Calculate the percentage of each impurity in the portion of Citalopram Hydrobromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak area of each impurity from the *Sample solution*

r_S = peak area of citalopram from the *Standard solution*

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

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

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor[a]	Acceptance Criteria, NMT (%)
Bromide[b]	0.24	—	—

Name	Relative Retention Time	Relative Response Factor[a]	Acceptance Criteria, NMT (%)
Citalopram related compound A	0.40	0.73	0.15
Citalopram related compound C	0.88	1.7	0.15
Citalopram	1.0	—	—
Citalopram related compound D	1.09	0.93	0.15
Citalopram related compound G	2.20	1.2	0.15
Citalopram related compound H	2.30	1.1	0.15
Individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.75

[a] The relative response factors provided are for each impurity relative to citalopram hydrobromide.

[b] This peak is due to the counterion. It is not an impurity and should not be included in the *Total impurities*.

SPECIFIC TESTS

• **Optical Rotation,** *Specific Rotation* ⟨781S⟩

Sample solution: 25 mg/mL of Citalopram Hydrobromide in methanol

Acceptance criteria: −0.2° to +0.2° at 20°

• **pH** ⟨791⟩

Sample solution: 5 mg/mL of Citalopram Hydrobromide in water

Acceptance criteria: 5.5–6.5

• **Water Determination,** *Method I* ⟨921⟩

Sample: 250 mg of Citalopram Hydrobromide

Acceptance criteria: NMT 0.5%

• **Completeness of Solution**

Blank: 96% alcohol

Sample solution: 25 mg/mL of Citalopram Hydrobromide in 96% alcohol

Analytical wavelength: 410 nm

Acceptance criteria: Absorbance is NMT 0.040 in a 1-cm quartz cell

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature.

• **Labeling:** If a procedure for *Organic Impurities* other than *Procedure 1* is used, then the labeling states with which *Organic Impurities* procedure the article complies.

• **USP Reference Standards** ⟨11⟩

USP Citalopram Hydrobromide RS

USP Citalopram Related Compound A RS

1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide.

$C_{20}H_{23}FN_2O_2$ 342.41

USP Citalopram Related Compound C RS

3-(3-Dimethylaminopropyl)-3-(4-fluorophenyl)-6-cyano-1(3*H*)-isobenzofuranone oxalate.

$C_{20}H_{19}FN_2O_2 \cdot C_2H_2O_4$ 428.42

USP Citalopram Related Compound D RS

[Note—May be available as a hydrochloride or a hydrobromide salt.]

1-(4-Fluorophenyl)-1-(3-methylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrochloride.

$C_{19}H_{19}FN_2O \cdot HCl$ 346.83

1-(4-Fluorophenyl)-1-(3-methylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide. $C_{19}H_{19}FN_2O \cdot HBr$ 391.28

USP Citalopram Related Compound G RS

3-[5-Chloro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-*N*,*N*-dimethylpropan-1-amine hydrobromide.

$C_{19}H_{21}ClFNO \cdot HBr$ 414.74

USP Citalopram Related Compound H RS

3-[5-Bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-*N*,*N*-dimethylpropan-1-amine hydrobromide.

$C_{19}H_{21}BrFNO \cdot HBr$ 459.19

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

Topic/Question	Contact	Expert Committee
CITALOPRAM HYDROBROMIDE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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