Limit of transplatin—

Mobile phase, Stock standard solution, Working standard solution, Standard preparation, Resolution solution, and *Chromatographic system*—Proceed as directed in the test for *Limit of transplatin* under *Cisplatin*.

Test solution—Quantitatively dissolve the contents of 1 container with water to yield a 0.5 mg per mL solution of Cisplatin.

Test preparation—Prepare as directed for *Test preparation* in the test for *Transplatin* under *Cisplatin*.

Procedure—Proceed as directed for *Procedure* in the test for *Limit of transplatin* under *Cisplatin*. Calculate the percentage of transplatin taken by the formula:

$$0.1(CV/W)(r_U / r_S)$$

in which C is the concentration, in µg per mL, of the *Standard preparation*; V is the volume, in mL, of the constituted container contents; W is the labeled amount, in mg, of Cisplatin per container; and r_U and r_S are the peak areas obtained from the *Test preparation* and the *Standard preparation*, respectively. Not more than 2.0% is found.

Other requirements—It meets the requirements for *Labeling* under *Injections* ⟨1⟩.

Assay—

Mobile phase, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Cisplatin*.

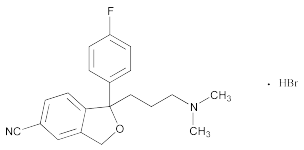
Assay preparation—Quantitatively dissolve the Cisplatin in 1 container by sonicating for 5 minutes with dimethylformamide to yield a Cisplatin concentration of about 1.0 mg per mL. Filter 5 mL through a suitable membrane filter, and collect the filtrate after discarding the first mL passing through the filter.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Cisplatin*. Calculate the quantity, in mg, of $Cl_2H_6N_2Pt$ in the container taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Cisplatin RS in the *Standard preparation*; V is the volume, in mL, of the constituted container contents; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

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 [59729-32-7].

» Citalopram Hydrobromide contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{21}FN_2O \cdot HBr$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Labeling—If a test for *Related compounds* other than *Test 1* is used, then the labeling states with which *Related compounds* test 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.
$C_{20}H_{23}FN_2O_2$ 342.22

USP Citalopram Related Compound C RS
3-(3-*N,N*-Dimethylamino)-1-(4-fluorophenyl)-6-cyano-1(3*H*)-isobenzofuranone.
$C_{20}H_{19}FN_2O_2$ 338.22

USP Citalopram Related Compound D RS
1-(4-Fluorophenyl)-1-(3-(methylamino)propyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrochloride.
$C_{19}H_{19}FN_2O \cdot HCl$ 346.83

USP Citalopram Related Compound G RS
1-(4′-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane hydrobromide.
$C_{19}H_{21}FNOCl \cdot HBr$ 414.74

USP Citalopram Related Compound H RS
1-(4′-Fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane hydrobromide.
$C_{19}H_{21}FNOBr \cdot HBr$ 459.1

Completeness of solution—The absorbance at 410 nm of a 2.5% w/v solution, in 96% alcohol, against a sample solvent in a 1-cm quartz cell is not more than 0.040.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

C: A solution of 10 mg per mL meets the requirement of the silver nitrate precipitate test for *Bromide* ⟨191⟩.

Specific rotation ⟨781S⟩**:** between –0.2° and +0.2° at 20°.

Test solution: 25 mg per mL, in methanol.

pH ⟨791⟩**:** between 5.5 and 6.5, in a solution (0.5 in 100).

Water, *Method I* ⟨921⟩**:** not more than 0.5%, using about 250 mg of sample.

Residue on ignition ⟨281⟩**:** not more than 0.1%. The sample is moistened with 2 mL of nitric acid and 5 drops of sulfuric acid.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

NOTE—On the basis of the synthetic route used, per form either *Test 1* or *Test 2*. However, if the chloro and bromo analogs are potential related compounds in the synthetic route used, *Test 2* is recommended.

TEST 1—

Buffer, Mobile phase, Diluent, and *Chromatographic system*—Proceed as directed in the *Assay*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay*.

Working standard solution—Dilute the *Standard solution* with *Diluent,* quantitatively and stepwise if necessary, to obtain a solution having a concentration of 0.625 µg per mL of citalopram hydrobromide.

System suitability solution—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS and USP Citalopram Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.001 mg per mL.

Sensitivity solution—Dilute 5.0 mL of the *Working standard solution* with *Diluent* to 50 mL to obtain a solution having 0.0625 µg of citalopram hydrobromide per mL.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Inject the *Diluent* as directed for *Procedure* to verify that there are no interfering peaks. Chromatograph the *Sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is at least 3. Chromatograph the *System suitability*

solution, and record the peak responses as directed for *Procedure:* the resolution, *R,* between citalopram related compound D and citalopram is not less than 1.8; the tailing factor for the citalopram hydrobromide peak is not less than 0.8 and not more than 1.5; and the relative standard deviation for replicate injections, based on the citalopram peak, is not more than 5%.

NOTE—For the purpose of identification, the approximate relative retention times are 0.90 for citalopram related compound D and 1.0 for citalopram hydrobromide.

Table 1

Related Compound	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
1-(3-Dimethylaminopropyl)-1-(4′-fluorophenyl)-5-(4-dimethylaminobutyryl)-1,3-dihydrobenzofuran	0.13	0.34	NMT* 0.1
Citalopram related compound A	0.18	0.77	NMT 0.1
4-[4-Dimethylamino-1-(4′-fluorophenyl)-1-hydroxy-1-butyl]-3-hydroxymethyl benzonitrile	0.26	0.99	NMT 0.1
Citalopram related compound B	0.40	0.98	NMT 0.1
Citalopram related compound C	0.67	0.69	NMT 0.1
Citalopram related compound D	0.90	1.04	NMT 0.1
Citalopram hydrobromide	1.0	1.0	—
Citalopram related compound E	1.29	0.91	NMT 0.1
Individual unknown impurity	—	1.0	NMT 0.1 each
Total impurities	—	—	NMT 0.5

*NMT = not more than.

Procedure—Separately inject equal volumes (about 20 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms for about 40 minutes, and measure the responses for the major peaks. Calculate the percentage of related compounds in the portion of Citalopram Hydrobromide taken by the formula:

$$100(C_S / C_T)(r_i / r_S)(324.39/405.30)(1/F)$$

in which C_S and C_T are the concentrations, in mg per mL, of Citalopram Hydrobromide in the *Working standard solution* and the *Test solution,* respectively; r_i is the peak response for each impurity obtained from the *Test solution;* r_S is the peak response for the citalopram peak, obtained from the *Working standard solution;* 324.39 and 405.30 are the molecular weights for citalopram and citalopram hydrobromide, respectively; and *F* is the relative response factor for each impurity relative to citalopram (free base), as presented in *Table 1.*

TEST 2—

Buffer—Dissolve about 2.7 g of monobasic potassium phosphate in 1000 mL of water, add 1 mL of *N,N*-dimethyloctylamine, stir, and adjust with phosphoric acid to a pH of 3.0.

Diluent—Prepare a mixture of *Buffer* and acetonitrile (70:30).

Solution A—Prepare a mixture of *Buffer,* methanol, and tetrahydrofuran (70:24:6).

Solution B—Prepare a mixture of acetonitrile and *Buffer* (80:20).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed in *Table 2* for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities 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* to obtain a final solution having a concentration of 1.5 µg per mL of each compound.

Test solution—Dissolve an accurately weighed quantity of Citalopram Hydrobromide in a suitable volume of *Diluent* to obtain a solution having a final concentration of 1.5 mg per mL of citalopram hydrobromide.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 224-nm detector and a 4.6-mm × 25-cm column that contains 5- µm packing L1. The flow rate is about 0.8 mL per minute. The column temperature is maintained at 40 °. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–18	100	0	isocratic
18–40	100→10	0→90	linear gradient
40–45	10	90	isocratic
45–46	10→100	90→0	linear gradient
46–55	100	0	re-equilibration

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between citalopram and citalopram related compound D is not less than 2.0, and that between citalopram related compound G and citalopram related compound H is not less than 4.0; and the relative standard deviation for the citalopram peak in replicate injections is not more than 2.0%.

NOTE—For the purpose of identification, the approximate relative retention times of citalopram related compounds are provided in *Table 2*.

Table 2

Related Compound	Relative Retention Time	Limit (%)
Citalopram related compound A	0.40	NMT* 0.15
Citalopram related compound C	0.88	NMT 0.15
Citalopram	1.0	—
Citalopram related compound D	1.09	NMT 0.15
Citalopram related compound G	2.20	NMT 0.15
Citalopram related compound H	2.30	NMT 0.15
Individual unspecified impurity	—	NMT 0.1
Total specified and unspecified impurities	—	NMT 0.75

*NMT = not more than.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each citalopram related compound

in the portion of Citalopram Hydrobromide taken by the formula:

$$100(C_S / C_T)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of each citalopram related compound in the *Standard solution;* C_T is the concentration of citalopram hydrobromide in the *Test solution;* r_i is the peak area of each impurity obtained from the *Test solution;* and r_S is the peak area of each corresponding impurity obtained from the *Standard solution.* Calculate the percentage of each unspecified impurity using the same formula above, but using the concentration, in mg per mL, of citalopram free base in the *Standard solution* for C_S and the response for the citalopram peak obtained from the *Standard solution* for r_S. [NOTE—Disregard the peak due to bromide which may appear at a relative retention time of about 0.24.]

Assay—

Buffer—In a 1-L volumetric flask, dissolve about 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 volume.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (80:20). The apparent pH is 5.0 ± 0.1. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of methanol and water (1:1).

Standard preparation—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.625 mg per mL.

Assay preparation—Transfer about 62.5 mg of Citalopram Hydrobromide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix to obtain a solution containing 0.625 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 150-mm × 4.6-mm column that contains 5- µm packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 50 °. Inject the *Diluent* to verify that there are no interfering peaks. Inject the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3000 theoretical plates; the tailing factor is not more than 3.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms for about 30 minutes, and measure the responses for the major peaks. Calculate the quantity, in percentage of $C_{20}H_{21}FN_2O \cdot HBr$, in the portion of Citalopram Hydrobromide taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Citalopram Oral Solution

DEFINITION

Citalopram Oral Solution contains an amount of citalopram hydrobromide equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of citalopram free base ($C_{20}H_{21}FN_2O$). It may contain a suitable preservative.

IDENTIFICATION

- **PROCEDURE:** The retention time of the citalopram peak of the *Sample solution* corresponds to that of the *Standard solution,* as obtained in the *Assay.*

ASSAY

- **PROCEDURE**

Solution A: Methanol and acetonitrile (1:9)

Buffer: 6.1 g/L of monobasic potassium phosphate in water. Add 1.5 mL of triethylamine per L of the solution. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: *Solution A* and *Buffer* (7:18)

Diluent: Acetonitrile and *Buffer* (1:3)

Standard solution: 0.25 mg/mL of USP Citalopram Hydrobromide RS

Sample solution: Transfer a suitable volume of Oral Solution to a suitable volumetric flask to obtain 0.2 mg/mL final concentration of citalopram free base. Add 50% of the flask volume of *Diluent,* and sonicate at room temperature for 3 min with intermittent shaking. Allow the solution to cool, and dilute with *Diluent* to volume. [NOTE—The *Sample solution* may be filtered through either a PVDF or nylon membrane filter of suitable pore size.]

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

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

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection size: 10 µL

Run time: 2 times the retention time of citalopram

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{20}H_{21}FN_2O$ in the portion of Oral Solution taken:

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

r_U = peak response of citalopram 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 = nominal concentration of citalopram in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of citalopram free base, 324.39

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

Acceptance criteria: 90.0%–110.0% of citalopram free base ($C_{20}H_{21}FN_2O$)

IMPURITIES

Organic Impurities

- **PROCEDURE**

Solution A: Acetonitrile, methanol, and tetrahydrofuran (17:1:2)

Buffer: Dissolve 3.0 g of 1-octane sulphonic acid sodium salt in 1 L of water. Add 2 mL of triethylamine and 5 mL of tetra-*n*-butyl ammonium hydroxide, 40 per cent in water. Mix and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: *Solution A* and *Buffer* (1:3)

Diluent: Acetonitrile and water (1:3)

System suitability solution: 6 µg/mL of USP Citalopram Related Compound D RS and 1.3 mg/mL of USP Citalopram Hydrobromide RS in *Diluent*

Standard solution: 6.3 µg/mL of USP Citalopram Hydrobromide RS in *Diluent*