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Escitalopram Oral Solution

DEFINITION

Escitalopram Oral Solution contains an amount of escitalopram oxalate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of escitalopram ($C_{20}H_{21}FN_2O$).

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*.

Add the following:

▲• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

Buffer: 6.1 g/L of monobasic potassium phosphate. To each liter of this solution add 1.5 mL of triethylamine. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (32:68)

Diluent: Acetonitrile and *Buffer* (25:75)

Standard solution: ▲32 µg/mL of USP Escitalopram Oxalate RS (equivalent to 25 µg/mL of escitalopram)▲ (USP 1-May-2021) in *Diluent*

Sample solution: Nominally 25 µg/mL of escitalopram from a suitable volume of Oral Solution, prepared as follows. ▲Transfer a suitable portion of Oral Solution to an appropriate volumetric flask. Add 50% of the flask volume of▲ (USP 1-May-2021) *Diluent*, and sonicate for 10 min with intermittent shaking. Allow the solution to cool, and dilute with *Diluent* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm. ▲For *Identification B*, use a diode array detector in the range of 210–400 nm.▲ (USP 1-May-2021)

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

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: ▲NLT▲ (USP 1-May-2021) 2.1 times the retention time of escitalopram

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT ▲1.0%▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of escitalopram ($C_{20}H_{21}FN_2O$) 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 escitalopram from the *Sample solution*

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

C_S = concentration of USP Escitalopram Oxalate RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of escitalopram in the *Sample solution* (µg/mL)

M_{r1} = molecular weight of escitalopram, ▲▲ (USP 1-May-2021) 324.39

M_{r2} = molecular weight of escitalopram oxalate, 414.43

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Deliverable Volume ⟨698⟩:** Meets the requirements

IMPURITIES

Change to read:

• **Limit of Citalopram Related Compound B**

▲Dilute▲ (USP 1-May-2021) phosphoric acid: ▲Transfer 5 mL of phosphoric acid to a 50-mL volumetric flask containing about 25 mL of water. Cool and dilute with water to volume.▲ (USP 1-May-2021)

Solution A: 6.8 g/L of monobasic potassium phosphate. ▲Adjust▲ (USP 1-May-2021) with ▲*Dilute▲ (USP 1-May-2021)* *phosphoric acid* to a pH of 3.0.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
13	60	40
15	60	40
16	90	10
20	90	10

Diluent: Acetonitrile and *Solution A* (30:70)

Standard solution: 0.6 µg/mL of USP Escitalopram Oxalate RS▲(equivalent to 0.5 µg/mL of escitalopram)▲ (USP 1-May-2021) in *Diluent*

System suitability solution: 0.6 µg/mL of USP Citalopram Related Compound B RS in *Standard solution*

Sample solution: Nominally ▲250 µg/mL▲ (USP 1-May-2021) of escitalopram from a suitable volume of Oral Solution in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 237 nm

Column: 2.1-mm × 7.5-cm; 3-µm packing L1

Column temperature: 45°

Flow rate: 0.5 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for citalopram related compound B and escitalopram are about 0.81 and 1.0, respectively. Use the *System suitability solution* to identify ▲citalopram related compound B.▲ (USP 1-May-2021)]

Suitability requirements

Resolution: NLT 2.0 between citalopram related compound B and escitalopram, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of citalopram related compound B 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 related compound B from the *Sample solution*

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

C_S = concentration of USP Escitalopram Oxalate RS in the *Standard solution* ▲(µg/mL)▲ (USP 1-May-2021)

C_U = nominal concentration of escitalopram in the *Sample solution* ▲(µg/mL)▲ (USP 1-May-2021)

M_{r1} = molecular weight of escitalopram, ▲▲ (USP 1-May-2021) 324.39

M_{r2} = molecular weight of escitalopram oxalate, 414.43

Acceptance criteria: NMT 0.2%

Change to read:

• **Organic Impurities**

Solution A: 6.6 g/L of dibasic ammonium phosphate in water. To each liter of this solution add 2 mL of triethylamine. Adjust with phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile and methanol (60:40)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
10	70	30
20	60	40
35	60	40
36	80	20
45	80	20

Diluent: Acetonitrile and *Solution A* (30:70)

Standard stock solution: ▲320 µg/mL of USP Escitalopram Oxalate RS (equivalent to 250 µg/mL of escitalopram)▲ (USP 1-May-2021) in *Diluent*

System suitability solution: 1.0 µg/mL of USP Citalopram Related Compound C RS in *Standard stock solution*

Standard solution: ▲3.2 µg/mL of USP Escitalopram Oxalate RS (equivalent to 2.5 µg/mL of escitalopram)▲ (USP 1-May-2021) from *Standard stock solution* in *Diluent*

▲**Sensitivity solution:** 0.32 µg/mL of USP Escitalopram Oxalate RS (equivalent to 0.25 µg/mL of escitalopram) from *Standard solution* in *Diluent*▲ (USP 1-May-2021)

Sample solution: Nominally ▲250 µg/mL▲ (USP 1-May-2021) of escitalopram from a suitable volume of Oral Solution in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution*, *Standard solution*, ▲and *Sensitivity solution*▲ (USP 1-May-2021)

Suitability requirements

Resolution: NLT 2.0 between citalopram related compound C and escitalopram, *System suitability solution*

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

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

▲**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Oral Solution 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 individual impurity from the *Sample solution*

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

C_S = concentration of USP Escitalopram Oxalate RS in the *Standard solution* ▲(µg/mL)▲ (USP 1-May-2021)

C_U = nominal concentration of escitalopram in the *Sample solution* ▲(µg/mL)▲ (USP 1-May-2021)

M_{r1} = molecular weight of escitalopram, ▲▲ (USP 1-May-2021) 324.39

M_{r2} = molecular weight of escitalopram oxalate, 414.43

F = relative response factor for each individual impurity (see *Table 3*)

Acceptance criteria: See *Table 3*. ▲The reporting threshold is 0.10%.▲ (USP 1-May-2021)

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxalic acid[a]	0.06	—	—
5-Dimethylaminobutyryl citalopram[b,c]	0.42	—	—
Citalopram related compound A[d]	0.48	1.0	0.2
Citalopram related compound B[e]	0.75	—	—
Desfluorocitalopram[f,c]	0.90	—	—
Citalopram related compound C▲▲ (USP 1-May-2021)	0.92	2.56	0.3
Citalopram related compound D[g,c]	0.99	—	—
Escitalopram	1.0	—	—
Citalopram related compound E[h]	1.09	1.0	0.2
Citalopram chloromethyl ▲▲ (USP 1-May-2021) ammonium salt[i,c]	1.1	—	—
Citalopram alkene dimer[j,c]	1.6	—	—
Citalopram related compound H[k,c]	1.7	—	—
Any individual unspecified ▲impurity▲ (USP 1-May-2021)	—	1.0	0.2
Total impurities[l]	—	—	0.7

[a] Not included in total impurities. For identification purposes only.

[b] 1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-5-(4-dimethylaminobutyryl)-1,3-dihydroisobenzofuran.

[c] Process impurity listed for information only. Do not include in total impurities.

[d] ▲1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide.▲ (USP 1-May-2021)

[e] This impurity is monitored and controlled using the test for *Limit of Citalopram Related Compound B*. It is listed here for identification purposes only.

[f] 1-[3-(Dimethylamino)propyl]-1-phenyl-1,3-dihydroisobenzofuran-5-carbonitrile.

[g] ▲1-(4-Fluorophenyl)-1-(3-methylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile.▲ (USP 1-May-2021)

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

[i] *N*-Chloromethyl-3-[5-cyano-1-(4-flurorphenyl)-1,3-dihydroisobenzofuran-1-yl]-*N*,*N*-dimethylpropan-1-ammonium chloride.

[j] 3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-*N*-{5-cyano-2-[4-(dimethylamino)-1-(4-fluorophenyl)but-1-enyl]benzyl}-*N*,*N*-dimethylpropan-1-ammonium chloride.

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

[l] Sum of all impurities from the tests for *Organic Impurities* and *Limit of Citalopram Related Compound B*.

SPECIFIC TESTS

• **pH ⟨791⟩:** 4.0–5.0

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 10^2 cfu/mL. The total yeasts and molds count does not exceed 10^1 cfu/mL. It meets the requirement of the test for absence of *Escherichia coli*.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in light-resistant containers. Store at controlled room temperature.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Citalopram Related Compound B RS

1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile oxalate.

▲$C_{20}H_{21}FN_2O_2 \cdot C_2H_2O_4$ 430.43▲ (USP 1-May-2021)

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 1-May-2021)

USP Escitalopram Oxalate RS

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

Topic/Question	Contact	Expert Committee
ESCITALOPRAM ORAL SOLUTION	Documentary Standards Support	SM42020 Small Molecules 4

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