

BRIEFING

Escitalopram Oxalate. This USP Pending Monograph was posted on the USP website as Draft 2 on November 30, 2009. The Monograph Development—Psychiatrics and Psychoactives Expert Committee has reviewed the following comment that was received, and has approved the monograph as an Authorized USP Pending Monograph, Version 2.

- Comment: The names of impurities in *Impurity Table 1* are inconsistent with the names provided in the *Escitalopram Tablets* monograph, Authorized v.1, posted May 29, 2009.
- Response: Comment incorporated. Impurities in *Impurity Table 1* are renamed to be consistent with the names provided in the *Escitalopram Tablets* monograph, Authorized v.1.

It is proposed to replace the *Loss on Drying* test with the KF based test for *Water Determination*. Different forms of Escitalopram Oxalate can be tested with this proposal. Consequently, the label claim is also changed from the dried to the anhydrous basis.

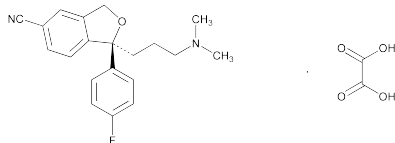
The proposed liquid chromatographic procedure in the test for *Organic Impurities* is based on analyses performed with the Inertsil brand of L7 column. The typical retention time is about 10.9 min for the escitalopram peak and about 9.9 min for the citalopram related compound D peak. The liquid chromatographic procedure in the test for *Limit of R-Citalopram* is based on analyses performed with the Chiral Pack AD-H brand of L51 column. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Inertsil brand of L7 column. The typical retention time for the escitalopram peak is about 9.8 min.

The monograph is rewritten to be consistent with the USP monograph redesign initiative.

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Escitalopram Oxalate

v. 2 Authorized May 1, 2010



$C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ 414.43
S-(+)-5-Isobenzofurancarboxonitrile, 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-, oxalate;
S-(+)-1-[3-(Dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalan-carboxonitrile oxalate [219861-08-2].

DEFINITION

Escitalopram Oxalate contains NLT 98.0% and NMT 102.0% of $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION (197K)**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the test for *Limit of R-Citalopram*.
- **C. IDENTIFICATION TESTS—GENERAL, Oxalate (191)**
Sample solution: 1 mg/mL in water
Analysis: Neutralize the *Sample solution* with 0.1 N sodium hydroxide.

ASSAY

- **PROCEDURE**
Buffer: 6.8 g of monobasic potassium phosphate in 995 mL of water. Add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 6.0 ± 0.1.

Mobile phase: Acetonitrile, methanol, and *Buffer* (4:5:11). To 1 L of the mixture, slowly add 0.94 g of sodium 1-hexane sulfonate, with constant stirring to dissolve.

Standard solution: 0.1 mg/mL of USP Escitalopram Oxalate RS in *Mobile phase*

Sample solution: 0.1 mg/mL of Escitalopram Oxalate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; packing L7

Flow rate: 1.5 mL/min

Injection size: 20 µL

Run time: 2.5 times the retention time of escitalopram oxalate

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 5000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ in the portion of Escitalopram Oxalate 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 Escitalopram Oxalate RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

Inorganic Impurities

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

• **HEAVY METALS, Method II (231):** NMT 10 ppm

Organic Impurities

• **PROCEDURE**

Buffer: 6.8 g of monobasic potassium phosphate in 995 mL of water. Add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 6.0 ± 0.1.

Solution A: Acetonitrile, methanol, and *Buffer* (4:5:11). To 1 L of the mixture, slowly add 0.94 g of sodium 1-hexane sulfonate, with constant stirring to dissolve.

Solution B: Acetonitrile and *Buffer* (7:3)

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15.0	100	0
37.0	65	35
37.1	100	0
45.0	100	0

System suitability solution: 1.0 µg of USP Escitalopram Oxalate RS and 1.5 µg of USP Citalopram Related Compound D RS in *Solution A*

Standard solution: 1 µg/mL of USP Escitalopram Oxalate RS in *Solution A*

Sample solution: 1 mg/mL of Escitalopram Oxalate in *Solution A*

Chromatographic system

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

2 / Escitalopram Oxalate

Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 25-cm; packing L7
Flow rate: 1.5 mL/min
Injection size: 20 µL

System suitability

Sample: System suitability solution

Suitability requirements

Resolution: NLT 1.7 between citalopram related compound D and escitalopram

Relative standard deviation: NMT 10.0% for the escitalopram peak

Analysis

[NOTE—Measure the responses for all the peaks except that due to oxalic acid.]

Samples: Standard solution and Sample solution

Calculate the percentage of each individual impurity in the portion of Escitalopram Oxalate taken:

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

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 (mg/mL)

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

F = relative response factor (see Impurity Table 1)

Acceptance criteria

Individual impurities: See Impurity Table 1. [NOTE—Values of the relative response factors, F, are based on the oxalate salt of each impurity.]

Total impurities: NMT 0.8%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxalic acid ^a	0.15	—	—
Escitalopram amide (also known as amide escitalopram) ^b	0.36	0.72	0.15
Escitalopram related compound A ^c	0.47	1.2	0.15
Escitalopram 3-oxo (also known as 3-Oxo escitalopram) ^d	0.83	0.54	0.15
Citalopram related compound D ^e	0.91	0.89	0.15
Escitalopram	1.0	—	—

^a For identification only.

^b (S)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carboxamide.

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

^d (S)-1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-oxo-1,3-dihydroisobenzofuran-5-carbonitrile.

^e 1-(4'-Fluorophenyl)-1-(3-methylamino)propyl)-1,3-dihydro isobenzofuran-5-carbonitrile.

^f (S)-[1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-yl]-(4-fluorophenyl)methanone.

Impurity Table 1 (continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Escitalopram fluorophenyl ketone ^f	2.77	0.40	0.10
Any unspecified individual impurity	—	1.0	0.10

^a For identification only.

^b (S)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carboxamide.

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

^d (S)-1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-oxo-1,3-dihydroisobenzofuran-5-carbonitrile.

^e 1-(4'-Fluorophenyl)-1-(3-methylamino)propyl)-1,3-dihydro isobenzofuran-5-carbonitrile.

^f (S)-[1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-yl]-(4-fluorophenyl)methanone.

SPECIFIC TESTS

• LIMIT OF R-CITALOPRAM

Mobile phase: n-Hexane, dehydrated alcohol, and diethylamine (975:25:1)

Standard stock solution: 0.03 mg/mL of USP R-Citalopram Oxalate RS prepared as follows: Dissolve USP R-Citalopram Oxalate RS in 5% of the flask volume of dehydrated alcohol, and dilute with Mobile phase to volume. [NOTE—Sonication may be used to aid dissolution.]

System suitability solution: 0.6 µg/mL of R-citalopram and 0.4 mg/mL of escitalopram prepared as follows: Dissolve USP Escitalopram Oxalate RS in 10% of the flask volume of dehydrated alcohol, and add a suitable volume of Standard stock solution. Dilute with Mobile phase to volume. [NOTE—Sonication may be used to aid dissolution.]

Sample solution: 0.4 mg/mL of Escitalopram Oxalate prepared as follows: Dissolve Escitalopram Oxalate in 10% of the flask volume of dehydrated alcohol, and dilute with Mobile phase to volume. [NOTE—Sonication may be used to aid dissolution.]

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 5-µm packing L51

Temperature: 40°

Flow rate: 1.5 mL/min

Injection size: 10 µL

Run time: 1.6 times the retention time of escitalopram oxalate

System suitability

Sample: System suitability solution

[NOTE—The relative retention times for R-citalopram and escitalopram are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between R-citalopram and escitalopram

Analysis

Sample: Sample solution

Calculate the percentage of R-citalopram in the portion of Escitalopram Oxalate taken:

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

r_U = peak response of R-citalopram from the Sample solution

r_S = sum of the peak responses of R-citalopram and escitalopram from the Sample solution

- Acceptance criteria: NMT 1.0%
- **PH (791):** 2.0 and 3.5
 - **Sample solution:** 10 mg/mL in water
 - **WATER DETERMINATION, Method I (921):** NMT 1.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at room temperature.
- **USP REFERENCE STANDARDS (11)**
USP Escitalopram Oxalate RS

USP Citalopram Related Compound D RS
[1-(4'-fluorophenyl)-1-(3-(methylamino)propyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrochloride]
(C₁₉H₁₉FN₂O · HCl 346.83)
USP R-Citalopram Oxalate RS
[[R-(-)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalanarbonitrile oxalate]]
(C₂₀H₂₁FN₂O · C₂H₂O₄ 414.44)