

BRIEFING

Escitalopram Oxalate. This monograph was posted on the USP Web site as a draft Pending Standard for public comment. The MD-PP Expert Committee has reviewed all comments received, and has approved the monograph as an Authorized USP Pending Standard. The following is a summary of the comments received and the Expert Committee's responses:

Comment 1: Commenter requested that the limit proposed in the test for *Limit of R-citalopram* (0.15%) be increased to NMT 1.0%, based on the tentatively approved product.

Response 1: Comment incorporated.

Comment 2: The tests and the specification in the proposal do not reflect the currently approved product.

Response 2: Comment not incorporated, because the proposal is based on a tentatively approved submission.

Comment 3: The name for escitalopram related compound A should be changed to citalopram related compound D, because the chemical structures are identical. Citalopram related compound D is already in the USP Reference Standards catalog.

Response 3: Comment incorporated.

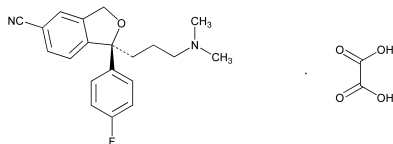
The proposed liquid chromatographic procedure in the test for *Related compounds* is based on analyses performed with the Inertsil brand of L7 column. The typical retention time is about 10.9 minutes for the escitalopram peak and about 9.9 minutes for the citalopram related compound D peak. The liquid 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 minutes. Interested parties are invited to submit their comments.

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Add the following:

Escitalopram Oxalate

v.1 Authorized May 23, 2008



$C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ 414.43

S-(+)-5-Isobenzofurancarboxylic acid, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, oxalate.

S-(+)-1-[3-(Dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate. [219861-08-2].

» Escitalopram Oxalate contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$, calculated on the dried basis.

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*. *USP R-citalopram Oxalate RS*.

Identification—

A: *Infrared Absorption* (197K).

B: The retention time of the major peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *System suitability solution*, as obtained in the test for *Limit of R-citalopram*.

C: Dissolve about 10 mg of Escitalopram Oxalate in 10 mL of water, and neutralize the solution with 0.1 N sodium hydroxide solution. The solution meets the requirements of the test for *Oxalate* (191).

pH (791): between 2.0 and 3.5.

Test solution: 10 mg per mL, in water.

Loss on drying (731)—Dry it at 105° for 3 hours: it loses not more than 1.0% of its weight.

Residue on ignition (281): not more than 0.1%.

Heavy metals, Method II (231): not more than 0.001%.

Limit of R-citalopram—

Mobile phase—Prepare a mixture of *n*-hexane, dehydrated alcohol, and diethylamine (975 : 25 : 1).

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R-Citalopram stock solution—Transfer about 3 mg of USP *R-Citalopram Oxalate RS*, accurately weighed, to a 100-mL volumetric flask. Add 5 mL of dehydrated alcohol, sonicate for 2 minutes, and dilute with *Mobile phase* to volume to obtain a solution having a known concentration of 0.03 mg per mL of *R-citalopram oxalate*.

System suitability solution—Transfer about 20 mg of USP Escitalopram Oxalate RS, accurately weighed, to a 50-mL volumetric flask. Add 5 mL of dehydrated alcohol, sonicate for 2 minutes, add 1 mL of *R-Citalopram stock solution*, and dilute with *Mobile phase* to volume to obtain a solution having a known concentration of 0.6 µg of *R-citalopram* per mL and 0.4 mg of escitalopram per mL.

Test solution—Transfer about 20 mg of Escitalopram Oxalate, accurately weighed, to a 50-mL volumetric flask. Add 5 mL of dehydrated alcohol, sonicate for 2 minutes, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L51. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the relative retention times are 0.9 for *R-citalopram* and 1.0 for escitalopram; and the resolution, *R*, between *R-citalopram* and escitalopram is not less than 1.5.

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, record the chromatogram for about 1.6 times the retention time of escitalopram oxalate, and measure the responses for the major peaks. Calculate the percentage of *R-citalopram* in the portion of Escitalopram Oxalate taken by the formula:

$$100(r_U / r_S)$$

in which r_U is the individual peak response of *R-citalopram*; and r_S is the sum of the peak responses of *R-citalopram* and escitalopram obtained from the *Test solution*: not more than 1.0% of *R-citalopram* is found.

Related compounds—

Buffer solution—Prepare as directed in the *Assay*.

Solution A—Prepare as directed for *Mobile phase* in the *Assay*.

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (7:3).

Diluent—Use *Solution A*.

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

System suitability solution—Dissolve USP Escitalopram Oxalate RS and USP Citalopram Related Compound D RS in *Diluent* to obtain a solution having a known concentration of about 1.0 µg of escitalopram oxalate per mL and about 1.5 µg of citalopram related compound D per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Escitalopram Oxalate RS in *Diluent* to obtain a solution having a known concentration of about 0.001 mg of escitalopram oxalate per mL.

Test solution—Dissolve an accurately weighed quantity of Escitalopram Oxalate in *Diluent* to obtain a solution having a concentration of about 1.0 mg per mL.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	Solution A %	Solution B %	Elution
0–15	100	0	isocratic
15–37	100→65	0→35	linear gradient
37–37.1	65→100	35→0	linear gradient
37.1–45	100	0	re-equilibration

Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the resolution, *R*, between citalopram related compound D and escitalopram is not less than 1.7. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections of escitalopram is not more than 10.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for about 4 times the retention time of escitalopram oxalate, and measure the responses for all the peaks except that due to oxalic acid. Identify the components using *Table 1*. Calculate the percentage of each of the related compounds in the portion of Escitalopram Oxalate taken by the formula:

$$100(C_s / C_T)(1 / F)(r_i / r_s)$$

in which *C_s* is the concentration, in mg per mL, of USP Escitalopram Oxalate RS in the *Standard solution*; *C_T* is the concentration of escitalopram oxalate, in mg per mL, in the *Test solution*; *F* is the relative response factor (see *Table 1* for values); *r_i* is the peak response for each impurity obtained from the *Test solution*; and *r_s* is the peak response of escitalopram obtained from the *Standard solution*: the limits are specified in *Table 1*. [NOTE—Values of the relative response factors, *F*, are based on the oxalate salt of each impurity.]

Table 1

Compound	Relative Retention Time	Relative Response Factor, <i>F</i>	Limit (%)
Oxalic acid*	0.15	—	—
Escitalopram related compound D ¹	0.36	0.72	NMT 0.15
Escitalopram related compound B ²	0.47	1.2	NMT 0.15
Escitalopram related compound C ³	0.83	0.54	NMT 0.15
Citalopram related compound D ⁴	0.91	0.89	NMT 0.15
Escitalopram	1.0	—	—
Escitalopram related compound E ⁵	2.77	0.40	NMT 0.10
Any other unspecified impurity	—	1.0	NMT 0.10
Total impurities	—	—	NMT 0.8

* For identification only.

¹ 1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarboxylic acid amide.

² (–) 4-[(4-Dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)]-3-(hydroxymethyl)benzoxazole hemi(+)-di-*p*-toluoyltartrate.

³ 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-oxo-5-cyanophthalan oxalate.

⁴ 1-(4'-Fluorophenyl)-1-(3-methylamino)propyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrochloride.

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

Assay—

Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 995 mL of water, and add 5 mL of triethylamine. Adjust with phosphoric acid to a pH of 6.0 ± 0.1.

Mobile phase—Prepare a mixture of *Buffer solution*, methanol, and acetonitrile (11 : 5 : 4). To the mixture, slowly add 0.94 g of sodium 1-hexane sulfonate, with constant stirring, to dissolve. Filter and degas before use.

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Standard preparation—Dissolve an accurately weighed quantity of USP Escitalopram Oxalate RS in *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Escitalopram Oxalate in *Mobile phase* to obtain a solution having a concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for the escitalopram peak.

Procedure—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms for about 2.5 times the retention time of escitalopram oxalate, and measure the responses for the major peak. Calculate the percentage of $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ in the portion of Escitalopram Oxalate 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. ■