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Olanzapine and Fluoxetine Capsules

DEFINITION

Olanzapine and Fluoxetine Capsules contain an amount of Olanzapine and Fluoxetine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% each of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) and fluoxetine ($C_{17}H_{18}F_3NO$).

IDENTIFICATION

• **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

Add the following:

▲• **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Aug-2019)

ASSAY

Change to read:

• **Procedure**

Buffer: 37 mg/L of disodium ethylenediaminetetraacetate in water. Add 3.3 mL of phosphoric acid, and adjust with 50% sodium hydroxide to a pH of 2.5. Dissolve 8.7 g of sodium dodecyl sulfate in the resulting solution.

Mobile phase: Acetonitrile and *Buffer* (1:1)

Standard solution: 0.12 mg/mL of USP Olanzapine RS and 0.45 mg/mL of USP Fluoxetine Hydrochloride RS in *Mobile phase*

Sample solution: Nominally 0.06–0.18 mg/mL of olanzapine and 0.25–0.5 mg/mL of fluoxetine in *Mobile phase* from a counted number of Capsules prepared as follows. Place the Capsules (including shells) into a suitable volumetric flask and fill to about half volume with *Mobile phase*. Mix for NLT 30 min. If disintegration is incomplete, sonicate for NMT 5 min. Dilute with *Mobile phase* to volume, mix, and filter or centrifuge.

Chromatographic system

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

Mode: LC

Detector: UV 227 nm. ▲For *Identification B*, use a diode array detector in the range of 210–400 nm.▲ (USP 1-Aug-2019)

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L7

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 10 µL

Run time: 2.5 times the retention time of olanzapine

System suitability

Sample: *Standard solution*

[Note—The relative retention times for olanzapine and fluoxetine are 1.0 and 1.5, respectively.]

Suitability requirements

Resolution: NLT 2.0 between olanzapine and fluoxetine

Relative standard deviation: NMT 2.0% for the olanzapine and fluoxetine peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) in the portion of Capsules taken:

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

r_U = peak response of olanzapine from the *Sample solution*

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

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

C_U = nominal concentration of olanzapine in the *Sample solution* (mg/mL)

Calculate the percentage of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$) in the portion of Capsules taken:

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

r_U = peak response of fluoxetine from the *Sample solution*

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

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

C_U = nominal concentration of fluoxetine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of fluoxetine, 309.33

M_{r2} = molecular weight of fluoxetine hydrochloride, 345.79

Acceptance criteria: 90.0%–110.0% ▲each of olanzapine and fluoxetine▲ (USP 1-Aug-2019)

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated. [Note—Helium sparging recommended.]

Apparatus 2: 50 rpm, with 3-prong sinkers

Time: 30 min for both olanzapine and fluoxetine

Standard solution: USP Olanzapine RS and USP Fluoxetine Hydrochloride RS in *Medium* to obtain a final concentration of (*L*/1000) mg/mL each, where *L* is label claim, in mg/Capsule.

Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Buffer, Mobile phase, Chromatographic system, System suitability, and **Analysis:** Proceed as directed in the *Assay*.

Calculate the percentage of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) dissolved:

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

r_U = peak response of olanzapine from the *Sample solution*

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

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

L = label claim for olanzapine (mg/Capsule)

V = volume of *Medium*, 900 mL

Calculate the percentage of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$) dissolved:

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

r_U = peak response of fluoxetine from the *Sample solution*

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

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

L = label claim for fluoxetine (mg/Capsule)

M_{r1} = molecular weight of fluoxetine, 309.33

M_{r2} = molecular weight of fluoxetine hydrochloride, 345.79

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amounts of olanzapine ($C_{17}H_{20}N_4S$) and fluoxetine ($C_{17}H_{18}F_3NO$) are dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

Buffer and **Mobile phase:** Prepare as directed in the *Assay*.

System suitability solution: 0.1 mg/mL of USP Olanzapine RS, 0.11 mg/mL of USP Fluoxetine Hydrochloride RS, and 0.002 mg/mL each of α[(2-methylamino)ethyl] benzyl alcohol, trifluoro-*p*-cresol, USP Fluoxetine Related Compound B RS, and USP Olanzapine Related Compound B RS in *Mobile phase*

▲Sensitivity solution: 3 µg/mL of USP Olanzapine RS, 3 µg/mL of USP Fluoxetine Hydrochloride RS, and 0.06 µg/mL each of α[(2-methylamino)ethyl] benzyl alcohol, trifluoro-*p*-cresol, USP Fluoxetine Related Compound B RS, and USP Olanzapine Related Compound B RS in *Mobile phase*▲ (USP 1-Aug-2019)

Standard solution: 2 µg/mL of USP Olanzapine RS and 8 µg/mL of USP Fluoxetine Hydrochloride RS in *Mobile phase*

Sample solution: Empty the Capsules, and combine the contents in a suitable container. The contents of the Capsules may be powdered in a mortar, if necessary. Transfer an amount of the sample to a suitable volumetric flask to obtain nominally 0.2 mg/mL of olanzapine and 0.27–1.7 mg/mL of fluoxetine, and fill to about 70% volume with *Mobile phase*. Mix for about 5 min. Dilute with *Mobile phase* to volume, mix, and filter or centrifuge.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Temperatures

Autosampler: 5°

Column: 35°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: 1.5 times the retention time of fluoxetine

System suitability

Samples: *System suitability solution*, *▲Sensitivity solution,*▲ (USP 1-Aug-2019) and *Standard solution*

Suitability requirements

[Note—Identify the peaks using *Table 1*.]

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
α[(2-Methylamino)ethyl] benzyl alcohol[a]	0.22	—	0.25
Olanzapine related compound B[b]	0.24	1.73	0.20
Trifluoro-*p*-cresol[a]	0.30	—	0.25
Fluoxetine related compound B[a]	0.31	—	0.25
Olanzapine	0.63	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fluoxetine	1.0	—	—
Any individual fluoxetine related degradation product	—	—	0.25
Any individual olanzapine related degradation product[c]	—	1.0	0.20
Total impurities (fluoxetine related)[d]	—	—	0.40
Total impurities (olanzapine related)[e]	—	—	1.5

[a] Fluoxetine related degradation product.

[b] Olanzapine related degradation product.

[c] Any other degradation product with a relative retention time <0.63 except fluoxetine related degradation products, and any degradation product with a relative retention time >1.0.

[d] Sum of all specified fluoxetine related degradation products and any other fluoxetine related degradation product with relative retention times ▲between▲ (USP 1-Aug-2019) 0.63 and 1.0.

[e] Sum of all specified olanzapine degradation products, any other degradation product with a relative retention time <0.63 except fluoxetine related degradation products, and any degradation product with relative retention time >1.0.

Resolution: NLT 1.9 between α[(2-methylamino)ethyl] benzyl alcohol and olanzapine related compound B, *System suitability solution*

Tailing factor: NMT 1.8 for olanzapine and fluoxetine, *System suitability solution* and *Standard solution*

▲**Relative standard deviation:** NMT 2.0% for the olanzapine and fluoxetine peaks, *Standard solution*

Signal-to-noise ratio: NLT 3 for the α[(2-methylamino)ethyl] benzyl alcohol peak, *Sensitivity solution*▲ (USP 1-Aug-2019)

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—Peaks eluting before a relative retention time of 0.63 and after a relative retention time of 1.0, excluding any peak with relative retention times of 0.22, 0.30, and 0.31, are olanzapine related degradation products.]

Calculate the percentage of each olanzapine related degradation product in the portion of Capsules 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 olanzapine from the *Standard solution*

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

C_U = nominal concentration of olanzapine in the *Sample solution* (mg/mL)

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

[NOTE—Peaks eluting at relative retention times of 0.22, 0.30, and 0.31, and any peaks between a relative retention time of 0.63 and 1.0, are fluoxetine related degradation products.]

Calculate the percentage of each fluoxetine related degradation product in the portion of Capsules taken:

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

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

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

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

C_U = nominal concentration of fluoxetine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of fluoxetine, 309.33

M_{r2} = molecular weight of fluoxetine hydrochloride, 345.79

Acceptance criteria: See *Table 1*.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Fluoxetine Hydrochloride RS▲▲ (USP 1-Aug-2019)

USP Fluoxetine Related Compound B RS

N-Methyl-3-phenylpropylamine.

$C_{10}H_{15}N$ ▲149.24▲ (USP 1-Aug-2019)

USP Olanzapine RS▲▲ (USP 1-Aug-2019)

USP Olanzapine Related Compound B RS

2-Methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepin-4[5*H*]-one.

$C_{12}H_{10}N_2OS$ 230.29

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

Topic/Question	Contact	Expert Committee
OLANZAPINE AND FLUOXETINE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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