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Fluconazole for Oral Suspension

DEFINITION

Fluconazole for Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$). It may contain a suitable preservative.

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*.

ASSAY

• **Procedure**

Diluted phosphoric acid: Phosphoric acid (1 in 10)

Buffer: 2.72 g/L of monobasic potassium phosphate, adjusted with *Diluted phosphoric acid* to a pH of 2.5

Mobile phase: Acetonitrile and *Buffer* (20:80)

Diluent: Methanol and water (50:50)

System suitability solution: 0.1 mg/mL of USP Fluconazole RS and 0.024 mg/mL of USP Sodium Benzoate RS in *Diluent*

Standard solution: 0.1 mg/mL of USP Fluconazole RS in *Diluent*

Sample solution: Reconstitute the sample as directed on the label. Transfer an accurately weighed quantity of the suspension to a suitable volumetric flask to obtain a nominal concentration of 0.1 mg/mL of fluconazole. Sonicate in 70% of the flask volume of *Diluent* for 20 min with intermittent shaking. Dilute with *Diluent* to final volume, mix, centrifuge, and pass through a suitable membrane filter.

Chromatographic system

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

Mode: LC

Detector: 260 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 5.0 between the fluconazole and benzoate peaks

Tailing factor: NMT 2.0 for the fluconazole peak

Relative standard deviation: NMT 2.0% for the fluconazole peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) in the portion of Fluconazole for Oral Suspension 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 the *Standard solution*

C_U = nominal concentration of the *Sample solution*

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Medium: Water; 900 mL for 200 mg/5 mL suspension; 500 mL for 50 mg/5 mL suspension

Apparatus 2: 50 rpm

Time: 30 min

Standard stock solution: 1.1 mg/mL of USP Fluconazole RS in methanol

Standard solution

200 mg/5 mL suspension: 0.22 mg/mL of USP Fluconazole RS in *Medium* from the *Standard stock solution*

50 mg/5 mL suspension: 0.11 mg/mL of USP Fluconazole RS in *Medium* from the *Standard stock solution*

Sample solution: Reconstitute the suspension according to the label instructions. Weigh, and transfer an amount of the reconstituted suspension equivalent to 1 dose to the vessel. At the time specified withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size.

Mobile phase: Acetonitrile and water (20:80)

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

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

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) dissolved (Q):

$$\text{Result} = (r_U/r_S) \times C_S \times (V_1/V_2) \times (1/L) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

V_1 = volume of *Medium* (900 mL or 500 mL)

V_2 = volume of the reconstituted suspension in the *Sample solution* (mL). [Note—This is equivalent to the weight (g) of the reconstituted suspension in the *Sample solution* divided by the density of the reconstituted solution (g/mL).]

L = label claim (mg/mL)

Tolerances: NLT 85% (Q) of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Water; 900 mL for 200 mg/5 mL suspension; 500 mL for 50 mg/5 mL suspension

Apparatus 2: 75 rpm

Time: 30 min

Mobile phase: Methanol and water (40:60). Adjust with glacial acetic acid to a pH of 3.4.

Standard solution: 0.055 mg/mL of USP Fluconazole RS and 0.025 mg/mL of USP Sodium Benzoate RS in *Medium*

Sample solution: Reconstitute the suspension according to the label instructions. Weigh, and transfer an amount of the reconstituted suspension equivalent to one dose to the vessel. At the time specified withdraw an aliquot of the solution under test (5.0 mL for 50 mg/5 mL; 2.5 mL for 200 mg/5 mL), transfer to a 10-mL volumetric flask, and dilute with *Medium* to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 261 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 40 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between fluconazole and sodium benzoate

Tailing factor: NMT 2.0 for the fluconazole peak

Relative standard deviation: NMT 2.0% for the fluconazole peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) dissolved (Q):

$$\text{Result} = (r_U/r_S) \times C_S \times (V_1/V_2) \times (1/L) \times 100$$

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

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

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

V_1 = volume of *Medium* (900 mL or 500 mL)

V_2 = volume of the reconstituted suspension in the *Sample solution* (mL). [NOTE—This is equivalent to the weight (g) of the reconstituted suspension in the *Sample solution* divided by the density of the reconstituted solution (g/mL).]

L = label claim (mg/mL)

Tolerances: NLT 85% (Q) of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) is dissolved.

• **DELIVERABLE VOLUME ⟨698⟩:** Meets the requirements for oral suspension packaged in multiple-unit containers

IMPURITIES

• **PROCEDURE**

Solution A: 0.63 g/L of ammonium formate in water

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	87	13
20	87	13
35	60	40
50	60	40
52	87	13
60	87	13

Diluent: Acetonitrile and *Solution A* (13:87)

System suitability solution: 0.3 mg/mL of USP Fluconazole RS, 3 µg/mL of USP Fluconazole Related Compound B RS, and 3 µg/mL of USP Fluconazole Related Compound C RS in *Diluent*. [NOTE—The use of sonication and stepwise dilutions may be appropriate.]

Standard solution: 6 µg/mL of USP Fluconazole RS in *Diluent*. [NOTE—The use of sonication and stepwise dilutions may be appropriate.]

Sample solution: Reconstitute the sample as directed on the label. Transfer an accurately weighed quantity of the suspension to a suitable volumetric flask to obtain a nominal concentration of 3 mg/mL of fluconazole. Sonicate in 40% of the flask volume of *Diluent* for 20 min with intermittent shaking. Dilute with *Diluent* to final volume, mix, centrifuge, and pass through a suitable membrane filter.

Chromatographic system

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

Mode: LC

Detector: 260 nm

Column: 4.6-mm × 12.5-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between the fluconazole related compound B and fluconazole related compound C peaks and NLT 4.0 between the fluconazole related compound C and fluconazole peaks, *System suitability solution*

Tailing factor: NMT 2.0 for the fluconazole peak, *System suitability solution*

Relative standard deviation: NMT 5.0% for the fluconazole peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Fluconazole for Oral Suspension taken:

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

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

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

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Fluconazole related compound A[a]	0.45	—[b]
Fluconazole isomer[c]	0.51	—[b]
Fluconazole related compound B	0.71	—[b]
Fluconazole related compound C	0.78	—[b]
Fluconazole	1.0	—
Any other individual, unspecified impurity	—	0.25

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Total impurities	—	0.4

[a] 2-[2-Fluoro-4-(1*H*-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1*H*-1,2,4-triazol-1-yl)-propan-2-ol.

[b] These are process impurities which are included in the table for identification only. These impurities are controlled in the drug substance. They are not to be reported for the drug product and should not be included in the total impurities.

[c] 2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)propan-2-ol.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 10^2 cfu/g, and the total combined molds and yeasts count does not exceed 5×10^1 cfu/g. It meets the requirements of the test for absence of *Escherichia coli*.

• **pH ⟨791⟩:** 3.0–5.0, in a suspension reconstituted as directed by the labeling

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Store dry powder below 30°. Store reconstituted suspension at 5°–30°, and protect from freezing.

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

• **USP Reference Standards ⟨11⟩**

USP Fluconazole RS

USP Fluconazole Related Compound B RS

2-(4-Fluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

$C_{13}H_{13}FN_6O$ 288.28

USP Fluconazole Related Compound C RS

1,1'-(1,3-Phenylene)di(1*H*-1,2,4-triazole).

$C_{10}H_8N_6$ 212.21

USP Sodium Benzoate RS

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

Topic/Question	Contact	Expert Committee
FLUCONAZOLE FOR ORAL SUSPENSION	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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