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Fluconazole in Dextrose Injection

DEFINITION

Fluconazole in Dextrose Injection is a sterile solution containing Fluconazole and Dextrose. It contains NLT 90.0% and NMT 110.0% of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$).

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*.
- **B. Test for Dextrose**

Analysis: Add a few drops of the Injection (1 in 20) to 5 mL of hot alkaline cupric tartrate TS.

Acceptance criteria: A red to orange precipitate of cuprous oxide is formed.

ASSAY

- **Procedure**

Buffer: 0.82 g/L of anhydrous sodium acetate in water. Adjust with 1 N acetic acid solution to a pH of 5.0.

Diluent: Methanol and *Buffer* (20:80)

Solution A: Methanol and *Buffer* (5:95)

Solution B: Acetonitrile and methanol (60:40)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
9	80	20
15	15	85
18	80	20
25	80	20

System suitability solution: 0.04 mg/mL each of benzyl alcohol and USP Fluconazole RS in *Diluent*

Standard solution: 0.2 mg/mL of USP Fluconazole RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of fluconazole from Injection in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 261 nm

Column: 4.0-mm × 10-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

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

[Note—The relative retention times for benzyl alcohol and fluconazole are about 0.8 and 1.0, respectively, from the *System suitability solution*.]

Suitability requirements

Resolution: NLT 1.8 between benzyl alcohol and fluconazole, *System suitability solution*

Tailing factor: NMT 1.5 for the fluconazole peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

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 Injection taken:

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

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)

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **Organic Impurities Procedure 1: For Nonpolar Impurities**

Buffer, Diluent, Solution A, and **Solution B:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	77	23
5	77	23
30	40	60
43	77	23
50	77	23

System suitability solution: 2.4 µg/mL of 1,4-benzoquinone and 20 µg/mL of USP Fluconazole RS in *Diluent*

Standard solution: 2 µg/mL of USP Fluconazole RS in *Diluent*

Sample solution: Nominally 1.0 mg/mL of fluconazole from Injection in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 261 nm

Column: 4.0-mm × 10-cm; 3-µm packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

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

[Note—The relative retention times for 1,4-benzoquinone and fluconazole are about 0.5 and 1.0, respectively, *System suitability solution*.]

Suitability requirements

Resolution: NLT 5.0 between 1,4-benzoquinone and fluconazole, *System suitability solution*

Tailing factor: NMT 1.5 for the fluconazole peak, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

[Note—For the following calculations, do not include peaks eluting before fluconazole and do not include impurities at relative retention times of 2.00–2.12 and 3.14–3.26. The disregarded impurities at the specified relative retention times are process impurities monitored in the drug substance. Furthermore, disregard any peak due to an excipient or any peak less than 0.02%. This test is for determination of the late-eluting peaks, and hence the early-eluting peaks are not quantitated using this procedure.]

Calculate the percentage of the largest unknown nonpolar impurity in the portion of Injection taken:

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

r_U = peak response of the largest unknown nonpolar 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)

Calculate the percentage of total unknown nonpolar impurities in the portion of Injection taken:

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

r_T = sum of the peak responses of all the unknown impurities 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

Largest unknown nonpolar impurity: NMT 0.1%

Total unknown nonpolar impurities: NMT 0.5%

- **Organic Impurities Procedure 2: For Polar Impurities**

Buffer, Diluent, Solution A, Solution B, Mobile phase, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 2 µg/mL of USP Fluconazole RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of fluconazole from Injection in *Diluent*

System suitability

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

[Note—The relative retention times for benzyl alcohol and fluconazole are about 0.8 and 1.0, respectively, *System suitability solution*.]

Suitability requirements

Resolution: NLT 1.8 between benzyl alcohol and fluconazole, *System suitability solution*

Tailing factor: NMT 1.5 for the fluconazole peak, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

[Note—The relative retention times are listed in *Table 3*.]

Calculate the percentage of the single largest unknown polar impurity in the portion of Injection taken:

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

r_U = peak response of the largest unknown polar 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)

Calculate the percentage of total unknown polar impurities in the portion of Injection taken:

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

r_T = sum of the peak responses of all the unknown polar impurities 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 3*. Disregard any peak due to an excipient or any peak less than 0.03%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Hydroxymethylfurfural[a]	0.22–0.28	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Aminofluconazole quaternary salt[c]	0.30–0.36	—[b]
Unidentified dextrose-related impurity	0.37–0.43	—
Fluconazole isomer[d]	0.47–0.59	—[b]
Fluconazole diol[e]	0.68–0.74	—[b]
Cyclohexanone[f]	0.77–0.83	—
Fluconazole	1.0	—
Largest unknown polar impurity	—	0.1
Total unknown polar impurities	—	0.5
Total unknown polar and nonpolar impurities (sum of results from *Procedure 1* and *Procedure 2*)	—	1.0

[a] 5-Hydroxymethylfurfural.

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

[c] 4-Amino-1-(2-(2,4-difluorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propyl)-4*H*-1,2,4-triazolium bromide.

[d] 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.

[e] 2-(2,4-Difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propane-1,2-diol.

[f] Potential impurity associated with drug product packaged in bags.

SPECIFIC TESTS

- **Sterility Tests ⟨71⟩:** Meets the requirements
- **Bacterial Endotoxins Test ⟨85⟩:** NMT 0.416 USP Endotoxin Units/mg of fluconazole
- **Other Requirements:** Meets the requirements in *Injections and Implanted Drug Products ⟨1⟩*

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Store at controlled room temperature.
- **USP Reference Standards ⟨11⟩**
  USP Fluconazole RS

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

Topic/Question	Contact	Expert Committee
FLUCONAZOLE IN DEXTROSE INJECTION	Documentary Standards Support	SM12020 Small Molecules 1

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