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Itraconazole Capsules

DEFINITION
Itraconazole Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$).

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.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **Procedure**

Solution A: 5.8 g/L of monobasic ammonium phosphate in water. Adjust with phosphoric acid to a pH of 2.0. Pass through a suitable filter of 0.45-µm pore size.

Solution B: Acetonitrile and tetrahydrofuran (90:10)

Mobile phase: *Solution A* and *Solution B* (45:55)

Diluent: Methanol and tetrahydrofuran (50:50)

Standard solution: 0.1 mg/mL of USP Itraconazole RS in *Diluent*. Sonicate, if necessary, to dissolve.

Sample stock solution: Nominally 1 mg/mL of itraconazole in *Diluent* prepared as follows. Transfer an amount nominally equivalent to 100 mg of itraconazole, from the contents of NLT 20 Capsules, to a 100-mL volumetric flask. Add 70 mL of *Diluent*, and sonicate for about 30 min. Dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally 0.1 mg/mL of itraconazole in *Diluent* from the *Sample stock solution*

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

Mode: LC

Detector: UV 225 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of itraconazole

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) in the portion of Capsules taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution ⟨711⟩**

Test 1

Medium: 0.25% (w/v) sodium lauryl sulfate in 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 75 rpm; with a three-prong sinker

Time: 45 min

Standard stock solution: 0.55 mg/mL of USP Itraconazole RS in 40% glacial acetic acid. Sonicate, if necessary, to dissolve.

Standard solution: 0.02 mg/mL of USP Itraconazole RS in *Medium* from the *Standard stock solution*

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*, to obtain a concentration similar to that of the *Standard solution*.

Blank: *Medium*

Instrumental conditions

Mode: UV

Analytical wavelength: 260 nm

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0% for 5 replicates

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) released:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, if applicable

Tolerances: NLT 80% (Q) of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. All solutions containing itraconazole should be stored in low-actinic or amber glassware and protected from light.

Medium: Simulated gastric fluid without enzymes, deaerated; 900 mL

Apparatus 2: 100 rpm; with a sinker, ▲if necessary▲ (USP 1-Aug-2021)

Time: 60 min

▲Quantify the amount of itraconazole dissolved by one of the following procedures.

Spectrophotometric procedure▲ (USP 1-Aug-2021)

Standard stock solution: 0.55 mg/mL of USP Itraconazole RS in methanol prepared as follows. Transfer a suitable amount of USP Itraconazole RS to a suitable volumetric flask and add about 80% of the flask volume of methanol. Heat the solution to 65° in a water bath, with intermittent stirring, until dissolved. Dilute with methanol to final volume.

Standard solution: 0.022 mg/mL of USP Itraconazole RS in *Medium* from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter and dilute with *Medium*, if necessary.

Blank: *Medium*

Instrumental conditions

Mode: UV

Analytical wavelength: 255 nm

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, if applicable

▲**Chromatographic procedure**

Buffer: 1 mL/L of triethylamine in water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (60:40)

Standard stock solution: 0.55 mg/mL of USP Itraconazole RS in acetonitrile. Sonicate, if necessary, to dissolve prior to final dilution.

Standard solution: 0.11 mg/mL of USP Itraconazole RS in *Medium* prepared from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter and dilute with *Medium*, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm x 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: NLT 1.5 times the retention time of itraconazole

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) dissolved:

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

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

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

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, if applicable▲ (USP 1-Aug-2021)

Tolerances: NLT 80% (Q) of the labeled amount of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

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

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
25	45	55
40	45	55
42	60	40

Time (min)	Solution A (%)	Solution B (%)
50	60	40

System suitability solution: 5 mg/mL of USP Itraconazole System Suitability Mixture RS in *Diluent*. Sonicate, if necessary, to dissolve.

Standard solution: 0.025 mg/mL of USP Itraconazole RS in *Diluent*. Sonicate, if necessary, to dissolve.

Sample solution: Nominally 5 mg/mL of itraconazole in *Diluent* prepared as follows. Combine the contents of NLT 20 Capsules and transfer a portion nominally equivalent to 500 mg of itraconazole to a 100-mL flask. Add about 70 mL of *Diluent* and sonicate for 30 min with intermittent shaking. Dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between itraconazole and *n*-butyl isomer, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Capsules taken:

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

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

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

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
4-Methoxy derivative[a,b]	0.28	—
4-Triazolyl isomer[b,c]	0.64	—
Propyl and isopropyl analog[b,d,e]	0.77	—
Epimer[b,f]	0.84	—
Itraconazole	1.0	—
n-Butyl isomer[b,g]	1.1	—
Didioxolanyl analog[b,h]	1.4	—
Any individual unspecified impurity	—	0.2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Total impurities	—	1.50

[a] 2-*sec*-Butyl-4-{4-[4-(4-methoxyphenyl)piperazin-1-yl]phenyl}-2*H*-1,2,4-triazol-3(4*H*)-one.

[b] Process-related impurity included in the table for identification only. Process-related impurities are controlled in the drug substance and are not to be reported or included in the total impurities of the drug product.

[c] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(4*H*-1,2,4-Triazol-4-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-*sec*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[d] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-propyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[e] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-isopropyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[f] 4-(4-{4-[4-({(2*RS*,4*RS*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-*sec*-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[g] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-butyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

[h] Mixture of 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one and 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-({(2*SR*,4*RS*)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **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 Itraconazole RS

USP Itraconazole System Suitability Mixture RS

This is a mixture of itraconazole, 4-triazolyl isomer, propyl analog, epimer, *n*-butyl isomer, and didioxolanyl analog (other impurities may also be present).

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

Topic/Question	Contact	Expert Committee
ITRACONAZOLE CAPSULES	Documentary Standards Support	SM12020 Small Molecules 1

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