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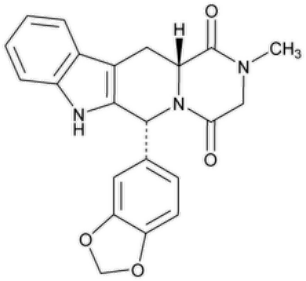
Tadalafil



$C_{22}H_{19}N_3O_4$ 389.40

Pyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6*R*-12a*R*)-; (6*R*,12a*R*)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl] pyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione CAS RN®: 171596-29-5; UNII: 742SXX0ICT.

DEFINITION

Tadalafil contains NLT 97.5% and NMT 102.5% of tadalafil ($C_{22}H_{19}N_3O_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Identification solution*, as obtained in the test for *Enantiomeric and Diastereomeric Purity*.

ASSAY

• **Procedure**

Solution A: Add 1.0 mL of trifluoroacetic acid to 1 L of water.

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

Standard solution: 0.1 mg/mL of USP Tadalafil RS in acetonitrile and *Solution A* (1:1); prepare by first dissolving the standard in acetonitrile, and then diluting with *Solution A* to final volume.

Sample solution: 0.1 mg/mL of Tadalafil in acetonitrile and *Solution A* (1:1); prepare by first dissolving the sample in acetonitrile, and then diluting with *Solution A* to final volume.

Chromatographic system

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

Mode: LC

Detector: 285 nm

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

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tadalafil ($C_{22}H_{19}N_3O_4$) in the portion of Tadalafil 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 USP Tadalafil RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 97.5%–102.5% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.10%, using a 1-g sample

• **Organic Impurities**

[Note—Do not use sonication during the preparation of analyte solutions.]

Solution A: Add 1.0 mL of trifluoroacetic acid to 1 L of water.

Solution B: Acetonitrile

Mobile phase: See *Table 1*. Return to original conditions and re-equilibrate the column.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
3	85	15
30	5	95
33	5	95

Standard solution: 0.4 µg/mL of USP Tadalafil RS in acetonitrile and *Solution A* (1:1); prepare by first dissolving the standard in acetonitrile, and then diluting with *Solution A* to final volume.

Sensitivity solution: 0.2 µg/mL of USP Tadalafil RS in acetonitrile and *Solution A* (1:1) from the *Standard solution*

System suitability stock solution: To generate the 6*R*,12a*S* diastereomer of tadalafil, dissolve 4.0 mg of Tadalafil in 50 mL of a mixture of isopropyl alcohol and acetonitrile (1:1). Add 1.0 mL of 1.0 M tetrabutylammonium hydroxide in methanol, and allow to stand at room temperature for 40 min. Add 1.0 mL of trifluoroacetic acid, and dilute with a mixture of isopropyl alcohol and acetonitrile (1:1) to 100 mL.

System suitability solution: Dissolve 40 mg of Tadalafil in 50 mL of acetonitrile. Add 2.0 mL of the *System suitability stock solution*, and dilute with *Solution A* to 100 mL.

Sample solution: 0.4 mg/mL of Tadalafil in acetonitrile and *Solution A* (1:1); prepare by first dissolving the sample in acetonitrile, and then diluting with *Solution A* to final volume.

Chromatographic system

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

Mode: LC

Detector: UV 285 nm

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

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for tadalafil and the 6*R*,12a*S* diastereomer of tadalafil are about 1.0 and 1.03, respectively.]

Suitability requirements

Tailing factor: NMT 1.5, *Standard solution*

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

Peak-to-valley ratio: The ratio of the height of the 6*R*,12a*S* diastereomer peak to the height of the valley between the 6*R*,12a*S* diastereomer peak and tadalafil is NLT 3.3, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tadalafil 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 tadalafil from the *Standard solution*

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

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

Acceptance criteria

[Note—Disregard peaks due to the 6*R*,12a*S* and 6*S*,12a*R* diastereomers of tadalafil, which co-elute at a retention time of about 1.03 relative to tadalafil. The diastereomers are controlled in the test for *Enantiomeric and Diastereomeric Purity*.]

Individual impurities: NMT 0.1%

Total impurities: NMT 0.3%

Reporting level for impurities: 0.05%

- **Enantiomeric and Diastereomeric Purity**

Mobile phase: Hexanes and isopropyl alcohol (50:50)

Diluent: Hexanes, isopropyl alcohol, and acetonitrile (40:40:20)

Identification solution: 0.5 mg/mL of USP Tadalafil RS in *Diluent*. [Note—This solution is used for *Identification* test *B*.]

Standard stock solution: 50 µg/mL of USP Tadalafil RS in *Diluent*

Standard solution: 0.5 µg/mL of USP Tadalafil RS in *Diluent* from the *Standard stock solution*

System suitability stock solution: To generate the 6*R*,12a*S* diastereomer of tadalafil, dissolve 25 mg of Tadalafil in 40 mL of *Diluent*. Add 1.0 mL of 1.0 M tetrabutylammonium hydroxide in methanol, and allow to stand at room temperature for 20 min. Add 1.0 mL of trifluoroacetic acid, and dilute with *Diluent* to 50 mL.

System suitability solution: Transfer 1.0 mL of the *System suitability stock solution* and 10 mL of the *Standard stock solution* to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Sensitivity solution: 0.25 µg/mL of USP Tadalafil RS in *Diluent* from *Standard solution*

Sample solution: 0.5 mg/mL of Tadalafil in *Diluent*

Chromatographic system

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

Mode: LC

Detector: 222 nm

Column: 4.6-mm × 25-cm; 10-µm packing L51

Column temperature: 30°

Flow rate: 0.75 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0, between the 6*R*,12a*S* diastereomer and tadalafil, *System suitability solution*

Tailing factor: NLT 0.8 and NMT 1.5, *Standard solution*

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

Signal-to-noise ratio: NLT 20, *Sensitivity solution*

Analysis

Samples: *Identification solution, Standard solution*, and *Sample solution*

Calculate the percentage of each stereoisomer impurity in the portion of Tadalafil taken:

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

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

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

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
6*R*,12a*S* diastereomer[a]	0.79	0.1
Tadalafil	1.0	—
6*S*,12a*S* enantiomer[b]	1.4	0.1
6*S*,12a*R* diastereomer[c]	1.7	0.1

[a] (6*R*,12a*S*)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione.

[b] (6*S*,12a*S*)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione.

[c] (6*S*,12a*R*)-6-(1,3-Benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry a sample under vacuum at 105° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Store at room temperature.

• **USP Reference Standards ⟨11⟩**

USP Tadalafil RS

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

Topic/Question	Contact	Expert Committee
TADALAFIL	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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