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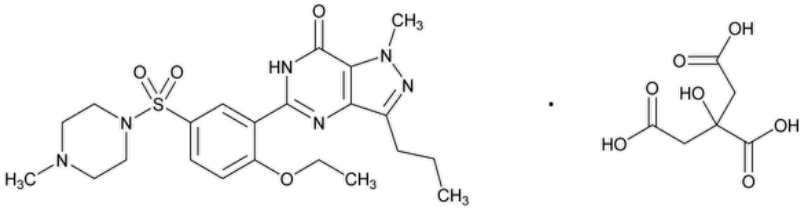
Sildenafil Citrate



$C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ 666.70

Piperazine, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1);
1-[[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate (1:1) CAS RN®: 171599-83-0; UNII: BW9B0ZE037.

Sildenafil

$C_{22}H_{30}N_6O_4S$ 474.58 CAS RN®: 139755-83-2; UNII: 3M7OB98Y7H.

DEFINITION

Sildenafil Citrate contains NLT 98.0% and NMT 102.0% of sildenafil citrate ($C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

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

ASSAY

• **Procedure**

Buffer: Dilute 7 mL of triethylamine with water to 1 L. Stir, and adjust with phosphoric acid to a pH of 3.0 ± 0.1.

Mobile phase: *Buffer*, methanol, and acetonitrile (58:25:17)

Standard solution: 0.028 mg/mL of USP Sildenafil Citrate RS in *Mobile phase*

Sample solution: 0.028 mg/mL of Sildenafil Citrate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 290 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.85% for six replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of sildenafil citrate ($C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$) in the portion of the sample taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **Residue on Ignition ⟨281⟩**

Sample: NLT 0.5 g

Acceptance criteria: NMT 0.1%

- **Limit of Imidazole**

Diluent: Methanol, water, and ammonium hydroxide (15:5:1)

Standard solution 1: 0.035 mg/mL of USP Imidazole RS in *Diluent*

Standard solution 2: 0.0175 mg/mL of USP Imidazole RS in *Diluent* from *Standard solution 1*

Sample solution: 17.5 mg/mL of Sildenafil Citrate in *Diluent*

System suitability solution: Mix equal volumes of *Sample solution* and *Standard solution 1*.

Chromatographic system

(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.2-mm layer of chromatographic silica gel mixture with a particle size of 2–10 µm (HPTLC plates)

Application volume: 10 µL. [Note—Apply as 6-mm bands.]

Developing solvent system: Methylene chloride, ethyl acetate, alcohol, and ammonium hydroxide (50:30:20:1)

System suitability

Sample: *System suitability solution*

Suitability requirements: The chromatogram shows two clearly separated zones.

Analysis:

Samples: *Standard solution 2* and *Sample solution*

Develop the plate over a distance of about two-thirds of the length of the plate. Dry at 100° for about 15 min, and cool. Expose the plate to iodine vapor until the plate is light brown, and examine the plate under UV light at 254 nm. [Note—The retardation factors for citrate, imidazole, and sildenafil are about 0, 0.25, and 0.4, respectively.]

Acceptance criteria: Any spot corresponding to imidazole in the *Sample solution* is not more intense than the principal spot from *Standard solution 2* (0.1%).

- **Organic Impurities**

Buffer, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*, except to run the chromatograph for 3 times the retention time of sildenafil.

Identification solution: 7.5 µg/mL of USP Sildenafil Related Compound A RS in *Mobile phase*

System suitability solution: Dissolve 70 mg of Sildenafil Citrate in 1 mL of a solution of hydrogen peroxide and anhydrous formic acid (2:1). Allow to stand for at least 10 min to generate sildenafil *N*-oxide, and then dilute with *Mobile phase* to 250 mL.

Sample solution: 0.7 mg/mL of Sildenafil Citrate in *Mobile phase*

Diluted sample solution: 1.4 µg/mL of sildenafil citrate in *Mobile phase* from the *Sample solution*

Sensitivity solution: 0.35 µg/mL of sildenafil citrate in *Mobile phase* from the *Diluted sample solution*

System suitability

Samples: *Diluted sample solution*, *Sensitivity solution*, and *System suitability solution*

[Note—The relative retention times for sildenafil, sildenafil *N*-oxide, and sildenafil related compound A are about 1.0, 1.2, and 1.7, respectively.]

Suitability requirements

Resolution: NLT 2.5 between sildenafil *N*-oxide and sildenafil, *System suitability solution*

Tailing factor: NMT 1.5 for the sildenafil peak, *Diluted sample solution*

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

Analysis

Samples: *Identification solution*, *Diluted sample solution*, and *Sample solution*

[Note—Identify sildenafil related compound A from the *Identification solution*.]

Calculate the percentage of sildenafil related compound A and any other unspecified individual impurity in the portion of Sildenafil Citrate taken:

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

r_U = peak response of sildenafil related compound A or any other unspecifed impurity from the *Sample solution*

r_S = peak response of sildenafil from the *Diluted sample solution*

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

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

Acceptance criteria

Sildenafil related compound A: NMT 0.3%

Any other unspecified individual impurity: NMT 0.10%

Total unspecified impurities: NMT 0.3%

Total impurities: NMT 0.5%. Disregard any peak less than 0.05%.

SPECIFIC TESTS

• **Water Determination, *Method I*⟨921⟩:** NMT 2.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in air-tight containers, and store at room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Imidazole RS $C_3H_4N_2$ 68.08

USP Sildenafil Citrate RS

USP Sildenafil Related Compound A RS

5-[2-Ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-(2-methylpropyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;
Also known as 1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-isobutyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazine.
$C_{23}H_{32}N_6O_4S$ 488.61

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

Topic/Question	Contact	Expert Committee
SILDENAFIL CITRATE	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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