Tadalafil Tablets

Type of Posting	Revision Bulletin
Posting Date	25–Oct–2019
Official Date	01–Nov–2019
Expert Committee	Chemical Medicines Monographs 5
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Tadalafil Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test. In addition, Apparatus 2 in *Dissolution Test 1* is revised to indicate that suitable sinkers may be used if necessary. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using a Zorbax SB brand of L7 column. The typical retention time for tadalafil is about 2.0 min.

The Tadalafil Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison (301-998-6818 or rhy@usp.org).

Tadalafil Tablets

DEFINITION

Tadalafil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of tadalafil ($C_{22}H_{19}N_3O_4$).

IDENTIFICATION

• **A. Infrared Absorption** ⟨197⟩
[Note—Methods described in *Infrared Absorption* ⟨197K⟩, or ⟨197D⟩ may be used.]
Standard: Add 10 mg of USP Tadalafil RS to 15 mL of water. Shake for 20 min, centrifuge for 10 min, and discard the supernatant. Suspend the precipitate in 8 mL of ethyl acetate, and shake for 5 min. Centrifuge for 10 min, and collect the supernatant. Dry the supernatant under a stream of nitrogen. The supernatant may be heated up to 70° to aid evaporation of the ethyl acetate. [Note—Ethyl acetate must be completely removed to prevent interference in the spectrum.]
Sample: Transfer a quantity of Tablets, equivalent to 10–20 mg of tadalafil, into a suitable container. Add 15 mL of water, and shake for 10 min, or until the Tablets are completely dispersed. Centrifuge for 10 min, and discard the supernatant. Suspend the precipitate in 8 mL of ethyl acetate, and shake for 5 min. Centrifuge for 10 min, and collect the supernatant. Dry the supernatant under a stream of nitrogen. The supernatant may be heated up to 70° to aid evaporation of the ethyl acetate. [Note—Ethyl acetate must be completely removed to prevent interference in the spectrum.]
Acceptance criteria: Meet the requirements over the range from 1700–400 cm^{-1}

• **B.** 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**
Mobile phase: Acetonitrile, water, and trifluoroacetic acid (35:65: 0.1)
Diluent: Acetonitrile and water (1:1)
Standard solution: 0.25 mg/mL of USP Tadalafil RS in *Diluent*
System suitability solution: To partially convert tadalafil to the 6*R*,12a*S* diastereomer, transfer 25 mL of the *Standard solution* into a suitable container. Add 0.25 mL of 5 N sodium hydroxide, mix well, and let stand for 30 min. Neutralize the solution to pH 7 by drop-wise addition of trifluoroacetic acid. [Note—This solution is stable for 1 month when stored in a refrigerator.]
Sample solution: Place NLT 20 Tablets into an appropriate size volumetric flask. Fill the flask about halfway with *Diluent*, and shake the mixture for about 15 min to disintegrate the Tablets. If any large fragments remain, sonicate the solution for 2 min or until fragments are dispersed. Dilute with *Diluent* to volume, and mix. Allow the solution to stand for at least 1 h to further aid Tablet dissolution. If necessary, shake the solution and perform a secondary dilution to obtain a final nominal concentration of 0.25 mg/mL. Centrifuge or filter the solution. [Note—The initial concentration before a secondary dilution step should not exceed 6 mg/mL.]
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 285 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L7
Column temperature: 35°
Flow rate: 1.0 mL/min
Injection volume: 10 µL
System suitability
Samples: *Standard 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 1.2, respectively.]
Suitability requirements
Resolution: NLT 3 between tadalafil and the 6*R*,12a*S* diastereomer peak, *System suitability solution*
Tailing factor: NMT 1.5, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tadalafil ($C_{22}H_{19}N_3O_4$) in the portion of Tablets 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 = nominal concentration of tadalafil in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

Change to read:

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩
▲**Test 1**▲ (RB 1-Nov-2019)
Medium: 0.5% sodium dodecyl sulfate; 1000 mL
Apparatus 2: 50 rpm, ▲use suitable sinkers if necessary▲ (RB 1-Nov-2019)
Times: 10 and 30 min
Mobile phase: Methanol and water (50:50)
Standard stock solution: 0.25 mg/mL of USP Tadalafil RS in acetonitrile and water (1:1)
Standard solution: 0.0075 mg/mL of USP Tadalafil RS in *Medium* from the *Standard stock solution*
Sample solution: Pass a portion of the solution under test through a suitable filter.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 5.0-cm; 3.5-µm packing L7
Column temperature: 40°
Flow rate: 2.0 mL/min
Injection volume: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tadalafil ($C_{22}H_{19}N_3O_4$) dissolved at each time point (Q_i):

$$Q_{10} = (r_U/r_S) \times (C_S/L) \times V \times 100$$
$$Q_{30} = (Q_{10} \times v/V) + [(r_U/r_S) \times (C_S/L) \times (V - v) \times 100]$$

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)
L = label claim (mg/Tablet)

V = volume of *Medium*, 1000 mL
v = volume of the sample withdrawn at initial time point (mL)

Tolerances: NLT 40% (*Q*) of the labeled amount of tadalafil is dissolved in 10 min and NLT 80% (*Q*) of the labeled amount of tadalafil is dissolved in 30 min.

▲**Test 2:** If the product complies with this procedure, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium, Mobile phase, Standard stock solution, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in *Test 1*.
Apparatus 2: 50 rpm, use suitable sinkers if necessary
Time: 15 min
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tadalafil ($C_{22}H_{19}N_3O_4$) dissolved:

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

r_U = peak response of tadalafil 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)
V = volume of *Medium*, 1000 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of tadalafil ($C_{22}H_{19}N_3O_4$) is dissolved.▲ (RB 1-Nov-2019)

• **Uniformity of Dosage Units** ⟨905⟩
Procedure for content uniformity
Diluent: Acetonitrile and water (1:1)
Standard solution: 0.1–0.2 mg/mL of USP Tadalafil RS in *Diluent*
Sample solution: Add 1 Tablet to a suitable volumetric flask to prepare a solution having a nominal concentration of 0.1–0.2 mg/mL of tadalafil. Add a volume of *Diluent* equivalent to 50% of the volume of the flask, and mechanically shake for 15 min. Dilute with *Diluent* to volume, and pass a portion of the solution through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Cell: 0.1 cm
Analytical wavelength: Absorption maximum at about 285 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tadalafil ($C_{22}H_{19}N_3O_4$) in the Tablet taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Tadalafil RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of tadalafil in the *Sample solution* (mg/mL)

Acceptance criteria: Meet the requirements for coated Tablets

IMPURITIES

• **Organic Impurities**
Mobile phase, Diluent, Standard solution, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Sensitivity solution: 0.25 µg/mL of USP Tadalafil RS in *Diluent* from the *Standard solution*
System suitability
Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*
[Note—The relative retention times for tadalafil and the 6*R*,12a*S* diastereomer of tadalafil are about 1.0 and 1.2, respectively.]
Suitability requirements
Tailing factor: NMT 1.5, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Resolution: NLT 3 between tadalafil and the 6*R*,12a*S* diastereomer peak, *System suitability solution*
Signal-to-noise ratio: NLT 20, *Sensitivity solution*
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

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

Acceptance criteria
Individual impurities: NMT 0.2%
Total impurities: NMT 0.3%
Reporting level for impurities: 0.05%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

Add the following:

▲• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-Nov-2019)
• **USP Reference Standards** ⟨11⟩
USP Tadalafil RS