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Sorafenib Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-sorafenib-tabs-20230526.

DEFINITION

Sorafenib Tablets contain an amount of Sorafenib Tosylate equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$).

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: 1 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.4.

Solution B: Alcohol, absolute, acetonitrile, and *Solution A* (16:24:60)

Solution C: Alcohol, absolute and acetonitrile (40:60)

Solution D: Water. Adjust with phosphoric acid to a pH of 2.4.

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

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	100	0
2	100	0
14	33	67

Diluent: *Solution C* and *Solution D* (75:25)

Standard solution: 0.22 mg/mL of USP Sorafenib Tosylate RS in *Diluent*. Sonicate to aid the dissolution. [Note—It is equivalent to 0.16 mg/mL of sorafenib in *Diluent*.]

Sample stock solution: Nominally equivalent to 4 mg/mL of sorafenib in *Diluent*, prepared as follows. Cut 5 Tablets into small pieces and transfer into a 250-mL volumetric flask. Add 150 mL of *Diluent*, shake for NLT 5 h until completely disintegrated and dispersed, and dilute with *Diluent* to volume. Sonicate for 30 min, and centrifuge a portion of this solution for 5 min or pass a portion of this solution through a polytetrafluoroethylene (PTFE) [or equivalent] filter of 0.45-µm pore size. Use the clear supernatant for the *Sample solution* preparation.

Sample solution: Nominally equivalent to 0.16 mg/mL of sorafenib in *Diluent*, from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 235 nm. For *Identification B*, use a diode array detector in the range of 190–400 nm.

Column: 4.6-mm × 10-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of sorafenib, 464.83

M_{r2} = molecular weight of sorafenib tosylate, 637.03

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

▲**Test 1**▲ (RB 1-Jun-2023)

Medium: 0.1 N hydrochloric acid containing 1% sodium lauryl sulfate; 900 mL

Apparatus 2: 100 rpm

Time: 15 min

Determine the percentage of the labeled amount of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) dissolved by using one of the following procedures.

Chromatographic procedure

Buffer: 1.0 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (45:55) for *Column A*, or acetonitrile and *Buffer* (50:50) for *Column B*

Standard stock solution: 1.54 mg/mL of USP Sorafenib Tosylate RS in methanol

Standard solution: 0.3 mg/mL of USP Sorafenib Tosylate RS, prepared as follows. Transfer 20 mL of *Standard stock solution* into a 100-mL volumetric flask and dilute with *Medium* to volume. [Note—It is equivalent to 0.22 mg/mL of sorafenib.]

Sample solution: Pass a portion of the solution under test through a filter of 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 266 nm

Columns

Column A: 2-mm × 5-cm; 5-µm packing L1

Column B: 3-mm × 5-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 2.5 mL/min for *Column A* or 3.0 mL/min for *Column B*

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of sorafenib, 464.83

M_{r2} = molecular weight of sorafenib tosylate, 637.03

Spectrophotometric procedure

Standard solution: 0.3 mg/mL of USP Sorafenib Tosylate RS, prepared as follows. Transfer an amount of USP Sorafenib Tosylate RS into a suitable volumetric flask, add methanol equivalent to 2.5% of the final volume, and dilute with *Medium* to volume. [NOTE—It is equivalent to 0.22 mg/mL of sorafenib.]

Sample solution: Centrifuge portions of the solution under test or pass through a suitable glass fiber filter of 1-µm pore size.

Instrumental conditions

Mode: UV

Analytical wavelength: 280 nm

Cell path length: 1 mm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of sorafenib, 464.83

M_{r2} = molecular weight of sorafenib tosylate, 637.03

Tolerances: NLT 75% (Q) of the labeled amount of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) is dissolved.

▲**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.1 N hydrochloric acid in water containing 1% sodium dodecyl sulfate; 900 mL

Apparatus 2: 100 rpm, with stationary basket (see ⟨711⟩, *Figures 2b* and *2c*)

Time: 15 min

Buffer: Dissolve 0.77 g of ammonium acetate in 1 L of water. Adjust with 2% (v/v) glacial acetic acid in water to a pH of 6.2.

Solution A: Acetonitrile and water (90:10)

Mobile phase: *Solution A* and *Buffer* (65:35)

Standard stock solution: 0.76 mg/mL of USP Sorafenib Tosylate RS in *Solution A*. Sonicate to dissolve.

Standard solution: 0.3 mg/mL of USP Sorafenib Tosylate RS from *Standard stock solution* in *Medium*

Sample solution: Pass a portion of the solution under test through suitable filter of 0.45-µm pore size, discarding the first 4 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 285 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of sorafenib

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 sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of sorafenib, 464.83

M_{r2} = molecular weight of sorafenib tosylate, 637.03

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) is dissolved.▲ (RB 1-Jun-2023)

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

IMPURITIES

• **Organic Impurities**

Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard stock solution: Use the *Standard solution* from the *Assay*.

Standard solution: 0.44 µg/mL of USP Sorafenib Tosylate RS in *Diluent*, from the *Standard stock solution*

System suitability solution: 0.44 µg/mL of USP Sorafenib Related Compound H RS in *Standard stock solution*

Sensitivity solution: 0.22 µg/mL of USP Sorafenib Tosylate RS in *Diluent*, from the *Standard solution*

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between the sorafenib related compound H and sorafenib peaks, *System suitability solution*

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

Analysis

Samples: *Sample solution* and *Standard solution*

Disregard the process impurity peaks listed in *Table 2*.

Table 2

Name	Relative Retention Time
Sorafenib impurity A[a]	0.12

Name	Relative Retention Time
Toluenesulphonic acid[b]	0.15
PAPE-ethyl carbamate[c]	0.34
Sorafenib impurity E[d]	0.46
Sorafenib impurity D[e]	0.47
Sorafenib impurity C[f]	0.58
Sorafenib impurity F[g]	0.82
Sorafenib impurity G[h]	0.93
Sorafenib related compound H	0.97
Sorafenib	1.00
Di(chlorotrifluoromethyl)phenylurea[i]	1.48

[a] 4-(4-Aminophenoxy)-*N*-methylpicolinamide.

[b] It is the counter ion of sorafenib and is present in the chromatogram of the *Sample solution*.

[c] Ethyl (4-((2-(methylcarbamoyl)pyridin-4-yl)oxy)phenyl)carbamate.

[d] *N*,*N*′-Bis{4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]phenyl}urea.

[e] Isopropyl {4-[2-(methylcarbamoyl)pyridin-4-yl]oxyphenyl}carbamate.

[f] 4-Chloro-3-(trifluoromethyl)aniline.

[g] *N*-Methyl-4-{4-[3-(3-trifluoromethylphenyl)ureido]phenoxy}picolinamide.

[h] Ethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate.

[i] 1,3-Bis[4-chloro-3-(trifluoromethyl)phenyl]urea.

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of sorafenib, 464.83

M_{r2} = molecular weight of sorafenib tosylate, 637.03

Acceptance criteria: See *Table 3*. The reporting threshold is 0.1%.

Table 3

Name	Acceptance Criteria, NMT (%)
Any individual unspecified impurity	0.2
Total impurities	0.5

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count is NMT 10^3 cfu/g, and the total combined molds and yeasts count is NMT 10^2 cfu/g. It meets the requirements of the tests for the absence of *Escherichia coli*.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at a temperature between 15° and 30° in a dry place.

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-Jun-2023)

• **USP Reference Standards ⟨11⟩**

USP Sorafenib Tosylate RS

USP Sorafenib Related Compound H RS

4-(4-{3-[2-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*-methylpicolinamide.

$C_{21}H_{16}ClF_3N_4O_3$ 464.83

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

Topic/Question	Contact	Expert Committee
SORAFENIB TABLETS	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

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