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Rifabutin Capsules

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-rifabutin-caps-20231229.

DEFINITION

Rifabutin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$).

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U

Standard solution: 20 µg/mL of USP Rifabutin RS in methanol, prepared with the aid of sonication. Pass through a filter of 0.5-µm or finer pore size.

Sample solution: Nominally 20 µg/mL of rifabutin prepared as follows. Suspend a quantity of Capsule contents, equivalent to 200 mg of rifabutin, in 20 mL of methanol. Sonicate for 5 min, and pass through a suitable filter of 0.5-µm or finer pore size. Dilute a portion of the filtrate with methanol to obtain a solution containing 20 µg/mL of rifabutin.

Acceptance criteria: Meet the requirements

• **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

Change to read:

• **Procedure**

Solution A: 13.6 g/L of monobasic potassium phosphate

Mobile phase: Acetonitrile and *Solution A* (50:50). Adjust with ▲2 N sodium hydroxide▲ (RB 1-Jan-2024) to a pH of 6.5 ± 0.1. Pass through a suitable filter of 0.5-µm or finer pore size.

System suitability solution: Dissolve 10 mg of Rifabutin in 2 mL of methanol, add 1 mL of ▲2 N sodium hydroxide▲ (RB 1-Jan-2024), and allow to stand for 4 min. Add 1 mL of ▲2 N hydrochloric acid▲ (RB 1-Jan-2024), and dilute with *Mobile phase* to 50 mL. [Note—Portions of this solution may be stored in the frozen state for future use.]

Standard solution: 0.5 mg/mL of USP Rifabutin RS prepared as follows. Transfer an amount of USP Rifabutin RS to a suitable volumetric flask. Add acetonitrile to fill 10% of the volume of the flask, and dilute with *Mobile phase* to volume.

Sample solution: Nominally 0.5 mg/mL of rifabutin prepared as follows. Remove the contents of NLT 20 Capsules, weigh, and determine the average weight of the Capsule contents. Transfer a portion of the powder, equivalent to 25 mg of rifabutin, to a 50-mL volumetric flask, add 5 mL of acetonitrile, and dilute with *Mobile phase* to volume. Pass through a suitable filter of 0.5-µm or finer pore size.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 12.5-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of the rifabutin peak

System suitability

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

[Note—The chromatogram of the *System suitability solution* exhibits a major peak for a degradant, two minor peaks for degradants, and a major peak for rifabutin at relative retention times of about 0.5, 0.6, 0.8, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.3 between the rifabutin peak and the degradant peak eluting at a relative retention time of about 0.8, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$) in the portion of Capsules taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution**

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Standard solution: A known concentration of USP Rifabutin RS in *Medium*

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium* to a concentration similar to that of the *Standard solution*, taking into account its designated potency.

Instrumental conditions

Mode: UV

Analytical wavelength: 280 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the percentage of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$) dissolved:

$$(A_U/A_S) \times C_S \times D \times (V/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

D = dilution factor of the *Sample solution*, if needed

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$) is dissolved.

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A: 13.6 g/L of monobasic potassium phosphate in water

Solution B: Acetonitrile and *Solution A* (40:60). Adjust with 2 N sodium hydroxide to a pH of 6.5.

Solution C: Acetonitrile and *Solution A* (70:30). Adjust with 2 N sodium hydroxide to a pH of 6.5.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	90	10
50	84	16
70	65	35
80	55	45
90	40	60
95	90	10
100	90	10

Diluent: Acetonitrile and *Solution A* (50:50). Adjust with 2 N sodium hydroxide to a pH of 6.5.

System suitability solution: Prepare as directed in the *Assay*.

Standard stock solution: 0.75 mg/mL of USP Rifabutin RS prepared as follows. Transfer an amount of USP Rifabutin RS to a suitable volumetric flask and dissolve it by adding acetonitrile to fill 20% of the final volume of the flask. Sonicate, if necessary. Dilute with *Diluent* to volume.

Standard solution: 0.0075 mg/mL of USP Rifabutin RS in *Diluent* from *Standard stock solution*

Sensitivity solution: 0.75 µg/mL of USP Rifabutin RS in *Diluent* from *Standard solution*

Sample solution: Nominally 0.75 mg/mL of rifabutin prepared as follows. Remove the contents of NLT 20 Capsules as completely as possible, weigh, and determine the average weight of the Capsule contents. Transfer a portion of the crushed powder, equivalent to 75 mg of rifabutin, to a 100-mL volumetric flask and add 20 mL of acetonitrile. Sonicate for 5 min. Add 50 mL of *Diluent* and sonicate for 5 more min. Dilute with *Diluent* to volume. [NOTE—The *Sample solution* is stable up to 25 h at 10°.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Temperatures

Autosampler: 10°

Column: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 4.0 between the rifabutin 21*R* epimer and rifabutin peaks, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (F_1/F_2) \times 100$$

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

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

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

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

P = potency of USP Rifabutin RS (µg/mg)

F_1 = conversion factor (0.001 mg/µg)

F_2 = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Rifabutin *N*-oxide[a]	0.3	0.72	0.70
16-Desacetylrifabutin[b]	0.40	0.92	1.0
Rifabutin 14*R* epimer[c]	0.63	0.89	1.0
3-Aminorifamycin S[d,e]	0.73	—	—
Rifabutin 21*R* epimer[f]	0.82	0.86	1.0
Rifabutin	1.0	1.0	—
Didehydrorifabutin[g]	1.60	1.0	0.50
Any unspecified impurity	—	1.0	▲0.5▲ (RB 1-Jan-2024)
Total impurities	—	—	4.5

[a] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-16-Acetyloxy-6,18,20-trihydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2',3':7,8]naphtho[1,2-*d*]imidazole-2,4'-piperidine]-5,10,26(3*H*,9*H*)-trione 1'-oxide.

[b] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-Tetrahydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2',3':7,8]naphtho[1,2-*d*]imidazole-2,4'-piperidine]-5,10,26(3*H*,9*H*)-trione.

[c] (9*S*,12*E*,14*R*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,18,20-Trihydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-5,10,26-trioxo-3,5,9,10-tetrahydrospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2',3':7,8]naphtho[1,2-*d*]imidazole-2,4'-piperidine]-16-yl acetate.

[d] (2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*,24*E*)-8-Amino-5,17,19-trihydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,6,9,11-tetraoxo-1,2,6,9-tetrahydro-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-21-yl acetate.

[e] This is a process impurity and is not included in total impurities.

[f] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*R*,22*E*,24*Z*)-6,18,20-Trihydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-5,10,26-trioxo-3,5,9,10-tetrahydrospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2',3':7,8]naphtho[1,2-*d*]imidazole-2,4'-piperidine]-16-yl acetate.

[g] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,18,20-Trihydroxy-1'-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl21-methylene-5,10,26-trioxo-3,5,9,10-tetrahydrospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2',3':7,8]naphtho[1,2-*d*]imidazole-2,4'-piperidine]-16-yl acetate.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, protected from light and from excessive heat. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Rifabutin RS

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

Topic/Question	Contact	Expert Committee
RIFABUTIN CAPSULES	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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