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Rufinamide Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-rufinamide-tabs-20220930.

DEFINITION

Rufinamide Tablets contain an amount of Rufinamide equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$).

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**

Buffer: 2.7 g/L of potassium dihydrogen phosphate in water

Diluent: Acetonitrile, methanol, and water (40:50:10)

Mobile phase: Methanol, tetrahydrofuran, and *Buffer* (15:5:80)

System suitability stock solution: 0.8 mg/mL of USP Rufinamide RS, and 0.02 mg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS in *Diluent*. [Note—USP Rufinamide Related Compound B RS is used for identification purposes only.]

System suitability solution: 0.08 mg/mL of USP Rufinamide RS, and 2 µg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS, in *Buffer* from the *System suitability stock solution*

Standard stock solution: 0.8 mg/mL of USP Rufinamide RS in *Diluent*

Standard solution: 0.08 mg/mL of USP Rufinamide RS in *Buffer* from the *Standard stock solution*

Sample stock solution: Nominally 0.8 mg/mL of rufinamide in *Diluent* from a portion of NLT 20 finely powdered Tablets. Sonicate for 10 min, and shake for 15 min. Centrifuge a portion of the suspension.

Sample solution: Nominally 0.08 mg/mL of rufinamide in *Buffer*, from a portion of suspension obtained from the *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm. For *Identification B*, use a diode array detector in the range of 190–400 nm.

Column: 4.6-mm × 12.5-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: NLT 2.3 times the retention time of rufinamide

System suitability

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

[Note—See *Table 9* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between rufinamide and rufinamide related compound A, *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 rufinamide ($C_{10}H_8F_2N_4O$) 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 Rufinamide RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Medium 1: 0.1 N hydrochloric acid

Medium 2: pH 6.8 phosphate buffer

Apparatus 4: With 22.6-mm cell, glass beads in the cone, with Tablet laying on the beads. Insert 320–350 mg of glass wool in the filter insert and then a glass microfiber filter of 2.7-µm pore size and a glass microfiber filter of 0.7-µm pore size.

Times: 5 and 12 h for the 200-mg Tablets; 6 and 16 h for the 400-mg Tablets

Flow rate: 16 mL/min, pulsating

Test intervals, media, and sample solutions for the 200-mg Tablets: See *Table 1*.

Table 1

Samples	Interval (min)	Volume (mL)	Medium
1	60	50	1
2	120	50	2
1	60	50	2
3	120	50	2

Test intervals (I_i): See *Table 2*.

Table 2

Interval	Time (min)
I_1	0–60
I_2	60–180
I_3	180–300
I_4	300–360
I_5	360–480
I_6	480–600
I_7	600–720

Sample solutions (V_i): See *Table 3*.

Table 3

V_1	eluate of test interval I_1; volume = 960 mL
V_2 to V_3	eluate of test interval I_2 to I_3; volume = 1920 mL, each
V_4	eluate of test interval I_4; volume 960 mL
V_5 to V_7	eluate of test interval I_5 to I_7; volume = 1920 mL, each

Test intervals, media, and sample solutions for the 400-mg Tablets: See *Table 4*.

Table 4

Samples	Interval (min)	Volume (mL)	Medium
1	60	50	1
1	60	50	2
3	120	50	2
1	120	50	2
2	180	50	2

Test intervals (I_i): See *Table 5*.

Table 5

Interval	Time (min)
I_1	0–60
I_2	60–120
I_3	120–240
I_4	240–360
I_5	360–480
I_6	480–600
I_7	600–780
I_8	780–960

Sample solutions (V_i): See *Table 6*.

Table 6

V_1	eluate of test interval I_1; volume = 960 mL
V_2	eluate of test interval I_2; volume = 960 mL
V_3 to V_6	eluate of test interval I_3 to I_6; volume = 1920 mL, each
V_7 to V_8	eluate of test interval I_7 to I_8; volume = 2880 mL, each

Mobile phase: Water, methanol, tetrahydrofuran, and acetic acid (100:50:13:0.12), with the addition of 206 mg of sodium pentanesulfonate, monohydrate

Standard stock solution: 600 µg/mL of USP Rufinamide RS in methanol

Standard solution 1: 60 µg/mL of rufinamide in *Medium 1* from the *Standard stock solution*

Standard solution 2: 60 µg/mL of rufinamide in *Medium 2* from the *Standard stock solution*

Standard solution 3: 12 µg/mL of rufinamide prepared as follows. Transfer 10 mL of the *Standard stock solution* to a 500-mL volumetric flask, add 40 mL of methanol, and dilute with *Medium 2* to volume.

Standard solution 4: 6 µg/mL of rufinamide in *Medium 2* from *Standard solution 3*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 10-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 20 µL

Run time: NLT 1.4 times the retention time of rufinamide

System suitability

Sample: *Standard solution 1*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Sample solutions* and *Standard solutions*

Calculate the percentage of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$) [$f(S_i)$] dissolved in the *Sample solution* (S_i) by the following steps:

Calculate the regression line for the *Standard solutions*:

$$y = ax + b$$

y = peak area of rufinamide from the *Standard solution*

a = slope

x = concentration of rufinamide in the *Standard solution* (µg/mL)

b = y-intercept

$$f(S_i) = [(y - b)/a] \times [(V_i)/(1000 \times L)] \times 100$$

y = peak area of rufinamide from the *Sample solution*

b = y-intercept

a = slope

V_i = volume of *Sample solution* (mL)

L = label claim (mg/Tablet)

Cumulative percentage of the Tablet label claim dissolved:

$$F\left(I_j\right) = \sum_{i=1}^{i} f\left(S_i\right)$$

i,j = indices of test interval

Tolerances

For Tablets labeled to contain 200 mg: See *Table 7*.

Table 7

Time (h)	Amount Released
5	NLT 60%
12	NLT 80%

For Tablets labeled to contain 400 mg: See *Table 8*.

Table 8

Time (h)	Amount Released
6	NLT 60%
16	NLT 80%

The percentages of the labeled amount of rufinamide dissolved in the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: pH 6.8 sodium phosphate buffer containing 2% sodium dodecyl sulfate (7.8 g/L of monobasic sodium phosphate dihydrate and 0.89 g/L of sodium hydroxide in water, adjusted with phosphoric acid or 1 N sodium hydroxide VS to a pH of 6.8; to each liter of this solution add 20.0 g of sodium dodecyl sulfate and sonicate to dissolve); 2000 mL

Apparatus 2: 50 rpm

Time: 1 h for 100-mg and 200-mg Tablets; 4 h for 400-mg Tablets

Buffer: 6.8 g/L of monobasic potassium phosphate in water

Mobile phase: Acetonitrile and *Buffer* (30:70)

Standard stock solution: 1 mg/mL of USP Rufinamide RS in methanol

Standard solution: 0.05 mg/mL of USP Rufinamide RS from the *Standard stock solution* diluted with *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and dilute with *Medium* if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 5 µL

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

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 rufinamide ($C_{10}H_8F_2N_4O$) dissolved:

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

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

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

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

V = volume of *Medium*, 2000 mL

D = dilution factor of the *Standard solution*

L = label claim of rufinamide (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$) is dissolved.▲ (RB 16-Sep-2022)

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

Medium: pH 6.8 phosphate buffer containing 2.5% of sodium lauryl sulfate (Dissolve 6.9 g of sodium phosphate monobasic, 0.95 g of sodium hydroxide, and 25 g of sodium lauryl sulfate in 1 L of water. Adjust with phosphoric acid or 5 N sodium hydroxide to a pH of 6.8.); 2000 mL

Apparatus 2: 75 rpm

Time: 30 min

Buffer: 1.74 g/L of potassium phosphate dibasic in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Diluent: Acetonitrile and methanol (50:50)

Standard solution: (L/2000) mg/mL of USP Rufinamide RS, where L is the label claim in mg/Tablet, prepared as follows. Transfer a suitable amount of USP Rufinamide RS to an appropriate volumetric flask. Dissolve in NMT 25% of the flask volume of *Diluent* using sonication. Dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

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

Temperature: 35°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: NLT 2.0 times the retention time of rufinamide

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 rufinamide ($C_{10}H_8F_2N_4O$) dissolved:

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

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

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

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

V = volume of *Medium*, 2000 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

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

System suitability stock solution: 0.8 mg/mL of USP Rufinamide RS, and 0.02 mg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS in *Diluent*. [Note—USP Rufinamide Related Compound B RS is used for identification purposes.]

System suitability solution: 0.08 mg/mL of USP Rufinamide RS, and 2 µg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS, in *Buffer* from the *System suitability stock solution*

Standard stock solution: 0.8 mg/mL of USP Rufinamide RS in *Diluent*

Standard solution: 0.4 µg/mL of USP Rufinamide RS from the *Standard stock solution* prepared as follows. Transfer a suitable volume of *Standard stock solution* to an appropriate volumetric flask. Add 10% of the flask volume of *Diluent*, and dilute with *Buffer* to volume.

Sensitivity solution: 0.04 µg/mL of USP Rufinamide RS from the *Standard solution* prepared as follows. Transfer a suitable volume of *Standard solution* to an appropriate volumetric flask. Add 10% of the flask volume of *Diluent*, and dilute with *Buffer* to volume.

System suitability

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

[Note—See *Table 9* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between rufinamide and rufinamide related compound A, *System suitability solution*

Tailing factor: NMT 1.5 for rufinamide, *System suitability solution*

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

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

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of any individual unspecified degradation product in the portion of Tablets taken:

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

r_U = peak response of each individual unspecified degradation product from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 9*. The reporting threshold is 0.05%.

Table 9

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Rufinamide	1.0	—
Rufinamide related compound A	1.2	—
Rufinamide related compound B	1.8	—
Any individual unspecified degradation product	—	0.1
Total degradation products	—	0.5

ADDITIONAL REQUIREMENTS

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

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

• **USP Reference Standards ⟨11⟩**

USP Rufinamide RS

USP Rufinamide Related Compound A RS

1-(2-Fluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide.

$C_{10}H_9FN_4O$ 220.20

USP Rufinamide Related Compound B RS

Methyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate.

$C_{11}H_9F_2N_3O_2$ 253.20

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

Topic/Question	Contact	Expert Committee
RUFINAMIDE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

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