Status: Currently Official on 16-Feb-2025
Official Date: Official Prior to 2013
Document Type: USP Monographs
DocId: GUID-79E8E419-A69C-48A9-9569-2E152FD4F9DF_1_en-US
DOI: https://doi.org/10.31003/USPNF_M2754_01_01
DOI Ref: 76am0

Ribavirin Tablets

DEFINITION
Ribavirin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$).

IDENTIFICATION
• **A.** The retention time of the ribavirin peak from the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
• **Procedure**

Buffer: 4.0 g/L of sodium dihydrogen phosphate dihydrate in water. Adjust with 5% sodium hydroxide solution to a pH of 5.0 ± 0.05. Pass the solution through a suitable filter of 0.45-µm pore size.

Mobile phase: Acetonitrile and *Buffer* (1:49)

Diluent: Acetonitrile and water (3:7)

Standard stock solution: 0.6 mg/mL of USP Ribavirin RS in *Diluent*

Standard solution: 0.03 mg/mL of USP Ribavirin RS in *Mobile phase* from the *Standard stock solution*

Sample stock solution: Transfer a portion of ribavirin, equivalent to 1000 mg of ribavirin from finely powdered Tablets (NLT 10), to a 1000-mL volumetric flask. Add about 750 mL of *Diluent*, and sonicate with occasional shaking for 30 min. Cool to room temperature, dilute with *Diluent* to volume, and mix. Centrifuge, and decant the supernatant.

Sample solution: 0.03 mg/mL of ribavirin in *Mobile phase* from the *Sample stock solution*. Pass the solution through a suitable filter of 0.45-µm pore size.

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

Mode: LC

Detector: UV 207 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 20 µL

Run time: 10 min

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ribavirin ($C_8H_{12}N_4O_5$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer and **Mobile phase:** Proceed as directed in the *Assay*.

Standard solution: 0.22 mg/mL of USP Ribavirin RS in *Medium*

Sample solution: Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Calculate the percentage of ribavirin ($C_8H_{12}N_4O_5$) dissolved:

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

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

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

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) is dissolved.

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

IMPURITIES

• **Organic Impurities: Procedure 1**

If uracil and/or uridine are known impurities, *Procedure 2* is recommended.

Solution A: 3.4 g/L of potassium dihydrogen phosphate in water. Adjust with 5% potassium hydroxide solution to a pH of 5.00 ± 0.05. Pass the solution through a suitable filter of 0.45-µm pore size.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
30	90	10
40	75	25

Time (min)	Solution A (%)	Solution B (%)
50	50	50
55	50	50
56	100	0
70	100	0

Standard stock solution: 0.4 mg/mL of USP Ribavirin RS in *Solution A*

Standard solution: 1 µg/mL of USP Ribavirin RS in *Solution A* from the *Standard stock solution*

Sample solution: Transfer a portion of ribavirin, equivalent to 100 mg of ribavirin from finely powdered Tablets (NLT 20), to a 200-mL volumetric flask. Add about 150 mL of *Solution A*, and sonicate with occasional shaking for 15 min. Cool to room temperature, dilute with *Solution A* to volume, and mix. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 20 µL

Run time: 70 min. [NOTE—Data collection is only for the first 55 min. The remaining gradient steps re-equilibrate the column.]

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—Impurities are listed in *Table 2*.]

Calculate the percentage of any unknown impurity in the portion of Tablets taken:

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

r_U = peak response of any unknown impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 2*. Disregard any peak area less than 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Triazole acid[a,b]	0.35	—
Ribavirin acid[a,c]	0.40	—
Triazole amide[a,d]	0.64	—
Ribavirin	1.0	—

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ribavirin 5-isomer[a,e]	1.37	—
Ribavirin methyl ester[a,f]	2.09	—
Ribavirin 5'-acetyl[a,g]	2.43	—
Ribavirin 5'-benzoyl[a,h]	4.83	—
Individual unknown impurity	—	0.10
Total impurities	—	0.30

[a] These are process impurities listed for information only.

[b] 1*H*-1,2,4-Triazole-3-carboxylic acid.

[c] 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylic acid.

[d] 1*H*-1,2,4-Triazole-3-carboxamide.

[e] 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-5-carboxamide.

[f] Methyl 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylate.

[g] 1-(5-*O*-Acetyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide.

[h] 1-(5-*O*-Benzoyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide.

- **Organic Impurities: Procedure 2**

Buffer: 3.0 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 6.0 ± 0.1. Pass the solution through a suitable filter of 0.45-µm pore size.

Mobile phase: Methanol and *Buffer* (1:39)

Standard stock solution: 1 mg/mL each of USP Ribavirin RS, USP Ribavirin Related Compound A RS, USP Ribavirin Related Compound D RS, USP Uracil RS, and USP Uridine RS in water. Sonicate with occasional shaking to dissolve the solids.

Standard solution: 0.01 mg/mL each of USP Ribavirin RS, USP Ribavirin Related Compound A RS, USP Ribavirin Related Compound D RS, USP Uracil RS, and USP Uridine RS in water from the *Standard stock solution*

Sensitivity solution: 0.5 µg/mL of USP Ribavirin RS from the *Standard solution* in water

Sample solution: 1.0 mg/mL. Transfer a portion of ribavirin, equivalent to 1000 mg of ribavirin from finely powdered Tablets (NLT 20), to a 1000-mL volumetric flask. Add about 500 mL of water, and sonicate with occasional shaking for 15 min. Shake the solution for 15 min, and cool to room temperature. Dilute with water to volume, and centrifuge the solution for 10 min.

Chromatographic system

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

Mode: LC

Detector: UV 207 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection size: 10 µL

Run time: NLT 4.3 times the retention time of the ribavirin peak

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

[Note—Impurities are listed in *Table 3*.]

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

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

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

r_S = peak response of corresponding reference standard from the *Standard solution* (use ribavirin for any other individual impurity)

C_S = concentration of corresponding reference standard in the *Standard solution* (mg/mL)

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

Acceptance criteria: See *Table 3*. Disregard any peak area less than 0.05%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ribavirin related compound A[a]	0.55	0.25
Ribavirin related compound D[b]	0.73	0.25
Uracil[c]	0.89	0.25
Ribavirin	1.00	—
Uridine[d]	1.71	0.25
Any other individual impurity	—	0.17
Total impurities	—	1.0

[a] 1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylic acid.

[b] 1*H*-1,2,4-Triazole-3-carboxamide.

[c] Pyrimidine-2,4(1*H*,3*H*)-dione.

[d] 1-β-D-Ribofuranosylpyrimidine-2,4(1*H*,3*H*)-dione.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store between 15°–30°.

• **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states with which *Organic Impurities* test the article complies.

• **USP Reference Standards** ⟨11⟩

USP Ribavirin RS

USP Ribavirin Related Compound A RS

1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylic acid.

$C_8H_{11}N_3O_6$ 245.19

USP Ribavirin Related Compound D RS

1*H*-1,2,4-Triazole-3-carboxamide.

$C_3H_4N_4O$ 112.09

USP Uracil RS

Pyrimidine-2,4(1*H*,3*H*)-dione.

$C_4H_4N_2O_2$ 112.09

USP Uridine RS

1-β-D-Ribofuranosylpyrimidine-2,4(1*H*,3*H*)-dione.

$C_9H_{12}N_2O_6$ 244.20

Topic/Question	Contact	Expert Committee
RIBAVIRIN TABLETS	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

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 37(5)

Current DocID: GUID-79E8E419-A69C-48A9-9569-2E152FD4F9DF_1_en-US
DOI: https://doi.org/10.31003/USPNF_M2754_01_01
DOI ref: 76am0