## Ribavirin Capsules

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In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Ribavirin Capsules monograph. The purpose for the revision is to add *Dissolution Test* 3 to accommodate the FDA approved specifications for the sponsor product.

The Ribavirin Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated into *USP 40–NF 35*.

Should you have any questions, please contact Shankari Shivaprasad, Ph.D., Scientific Liaison (301-230–7426 or sns@usp.org).

# Ribavirin Capsules

## DEFINITION

Ribavirin Capsules 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 major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

## ASSAY

• **PROCEDURE**

**Mobile phase:** Water. Adjust with sulfuric acid to a pH of 2.5.

**Standard solution:** 0.025 mg/mL of USP Ribavirin RS in *Mobile phase*

**Sample stock solution:** Transfer an equivalent to 50 mg of ribavirin, from contents of Capsules (NLT 20), to a 100-mL volumetric flask. Add about 50 mL of *Mobile phase*, and sonicate with occasional shaking for about 20 min. Cool to room temperature, and dilute with *Mobile phase* to volume.

**Sample solution:** Nominally 0.025 mg/mL of ribavirin in *Mobile phase* from *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:** 7.8-mm × 15-cm; 7-µm packing L17
**Column temperature:** 65°
**Flow rate:** 1 mL/min
**Injection volume:** 10 µL

**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Tailing factor:** 0.7–1.5
**Relative standard deviation:** NMT 2.0%

**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) in the portion of Capsules 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 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

***Change to read:***

• **DISSOLUTION** ⟨**711**⟩

●**Test 1**● (RB 1-Dec-2015)
**Medium:** Water; 900 mL
**Apparatus 1:** 100 rpm
**Time:** 30 min

Determine the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) dissolved by using one of the following procedures.

**Procedure 1**
**Mobile phase:** Proceed as directed in the *Assay*.
**Standard solution:** 22.5 µg/mL of USP Ribavirin RS in *Medium*
**Sample solution:** Pass the solution through a suitable filter of 0.45-µm pore size. Transfer 5.0 mL of the filtrate to a 50.0-mL volumetric flask, and dilute with *Medium* to volume.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 207 nm
**Column:** 7.8-mm × 30-cm; 9-µm packing L17
**Column temperature:** 65°
**Flow rate:** 1.5 mL/min
**Injection volume:** 20 µL
**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Relative standard deviation:** NMT 2.0%
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) dissolved:

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

$r_U$ = peak area from the *Sample solution*
$r_S$ = peak area from the *Standard solution*
$C_S$ = concentration of the *Standard solution* (mg/mL)
$L$ = label claim (mg/Capsule)
$V$ = volume of *Medium*, 900 mL
$D$ = dilution factor of the solution under test

**Procedure 2**
**Sulfuric acid solution:** 3% sulfuric acid
**Mobile phase:** Water. Adjust with *Sulfuric acid solution* to a pH of 2.5.
**Standard solution:** 0.02 mg/mL of USP Ribavirin RS in *Medium*
**Sample solution:** Pass the solution through a suitable filter of 0.8-µm pore size. Transfer 5.0 mL of the filtrate to a 50.0-mL volumetric flask, and dilute with water to volume.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 207 nm
**Column:** 7.8-mm × 10-cm; 9-µm packing L17
**Column temperature:** 40 ± 2°
**Flow rate:** 1 mL/min
**Injection volume:** 20 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 ribavirin ($C_8H_{12}N_4O_5$) dissolved:

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

$r_U$ = peak area from the *Sample solution*
$r_S$ = peak area from the *Standard solution*
$C_S$ = concentration of the *Standard solution* (mg/mL)
$L$ = label claim (mg/Capsule)
$V$ = volume of *Medium*, 900 mL
$D$ = dilution factor of the solution under test

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

•**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.
**Medium:** Water; 900 mL, deaerated
**Apparatus 1:** 100 rpm
**Time:** 15 min
**Buffer:** 4 g/L of sodium dihydrogen orthophosphate dihydrate in water. Adjust with 5% (v/v) sodium hydroxide solution to a pH of 5.0. Pass through a suitable filter of 0.45-µm or finer pore size.
**Mobile phase:** Acetonitrile and *Buffer* (2:98)
**Standard solution:** 0.22 mg/mL of USP Ribavirin RS in *Medium*. Sonicate, if necessary, to dissolve.
**Sample solution:** Pass a portion of the solution under test 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 volume:** 10 µL
**Run time:** NLT 1.9 times the retention time of ribavirin
**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 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 from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of USP Ribavirin RS in the *Standard solution* (mg/mL)
$L$ = label claim (mg/Capsule)
$V$ = volume of *Medium*, 900 mL
**Tolerances:** NLT 80% (*Q*) of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) is dissolved.
• (RB 1-Dec-2015)

•**Test 3:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.
**Medium:** 0.1 N hydrochloric acid; 900 mL
**Apparatus 1:** 100 rpm
**Time:** 30 min
**Standard solution:** 0.22 mg/mL of USP Ribavirin RS in *Medium*. Sonicate, if necessary, to dissolve.
**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm or finer pore size.
**Capsule blank solution:** Dissolve 6 empty Capsule shells in 900 mL of *Medium*. Pass through a suitable filter of 0.45-µm or finer pore size.
**Instrumental conditions**
**Mode:** UV
**Analytical wavelength:** UV 225 nm
**Cell:** 0.1 cm
**Blank:** *Medium*
**Analysis**
**Samples:** *Standard solution*, *Sample solution*, and *Capsule blank solution*
Calculate the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) dissolved:

$$\text{Result} = \{[A_U - (A_B/6)]/A_S\} \times C_S \times (1/L) \times V \times 100$$

$A_U$ = absorbance of the *Sample solution*
$A_B$ = absorbance of the *Capsule blank solution*
$A_S$ = absorbance of the *Standard solution*
$C_S$ = concentration of USP Ribavirin RS in the *Standard solution* (mg/mL)
$L$ = label claim (mg/Capsule)
$V$ = volume of *Medium*, 900 mL
**Tolerances:** NLT 80% (*Q*) of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) is dissolved.• (RB 1-Jun-2016)

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

## IMPURITIES

• **Organic Impurities**
**Mobile phase, Standard solution,** and **Chromatographic system:** Proceed as directed in the *Assay*.
**Sample solution:** Nominally 0.5 mg/mL of ribavirin in *Mobile phase* prepared as follows. Transfer an amount equivalent to 50 mg of ribavirin, from contents of Capsules (NLT 20), to a 100-mL volumetric flask. Add about 50 mL of *Mobile phase*, and sonicate with occasional shaking for about 20 min. Cool to room temperature, dilute with *Mobile phase* to volume, and mix. Pass the solution through a suitable filter of 0.45-µm pore size.
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of ribose triazolole carboxylic acid and any other unknown impurity in the portion of Capsules taken:

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

$r_U$ = peak response of ribose triazolole carboxylic acid or any other 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)
$F$ = relative response factor (see *Table 1*)
**Acceptance criteria:** See *Table 1*.

**Table 1**

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|---|---|---|---|
| Ribose triazolole carboxylic acid[a] | 0.7 | 0.7 | 0.25 |
| Ribavirin | 1.0 | — | — |
| Any individual unknown impurity | — | 1.0 | 0.10 |
| Total impurities | — | — | 1.0 |

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

## ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and store between 15° and 30°.

***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-Dec-2015)

- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Ribavirin RS