

Status: Currently Official on 16-Feb-2025
 Official Date: Official as of 01-Dec-2015
 Document Type: USP Monographs
 DocId: GUID-2646004B-8D87-40BF-8AFE-69A2F89381B1_1_en-US
 DOI: https://doi.org/10.31003/USPNF_M73768_01_01
 DOI Ref: ge307

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Ritonavir Oral Solution

DEFINITION

Ritonavir Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of ritonavir ($C_{37}H_{48}N_6O_5S_2$).

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

Buffer: 4.1 g/L of monobasic potassium phosphate

Mobile phase: Acetonitrile, methanol, tetrahydrofuran (stabilizer-free), and *Buffer* (17.5:10:10:62.5). Filter the required solutions individually prior to use.

Diluent: Acetonitrile and *Buffer* (50:50)

Standard solution: 25 µg/mL of [USP Ritonavir RS](#) in *Diluent*

Sample solution: Nominally 25 µg/mL of ritonavir in *Diluent* from a measured volume of Oral Solution

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–1.2

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ritonavir ($C_{37}H_{48}N_6O_5S_2$) in the portion of Oral Solution 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 Ritonavir RS](#) in the *Standard solution* (µg/mL)

C_U = nominal concentration of ritonavir in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• DELIVERABLE VOLUME (698)

For multiple-unit containers

Acceptance criteria: Meets the requirements

IMPURITIES**• ORGANIC IMPURITIES**

[NOTE—Ritonavir is alkali sensitive. All glassware should be prerinsed with distilled water before use to remove residual detergent contamination.]

Buffer A: 4.1 g/L of monobasic potassium phosphate

Buffer B: 3.8 g/L of monobasic potassium phosphate and 0.25 g/L of dibasic potassium phosphate

Solution A: Acetonitrile and *Buffer A* (50:50)

Solution B: Acetonitrile and *Buffer A* (65:35)

Solution C: Butyl alcohol and *Buffer A* (8:92)

Mobile phase: Acetonitrile, butyl alcohol, tetrahydrofuran (stabilizer-free), and *Buffer B* (18:5:8:69). Adjust with 1 M phosphoric acid or 1 M potassium hydroxide to a pH of 6.3 ± 0.1 , if necessary.

Cleaning solution: Acetonitrile, butyl alcohol, tetrahydrofuran (stabilizer-free), and *Buffer A* (30:8:13:49)

Peak identification solution: Transfer 5–10 g of Oral Solution to a suitable sealed container. Add an amount of citric acid equivalent to 1% by weight of Oral Solution taken, and mix until dissolved. Seal the container, and heat at 70° for 24 h. Transfer 5.0 mL of the thermally degraded sample to a 200-mL volumetric flask. Dissolve and dilute with *Solution B* to volume.

Standard stock solution: 0.1 mg/mL of [USP Ritonavir RS](#) in *Solution A*

Standard solution: 10 µg/mL of [USP Ritonavir RS](#) in *Solution C* from the *Standard stock solution*

Sample stock solution: Nominally 2 mg/mL of ritonavir in *Solution B* prepared as follows. Transfer a measured volume of Oral Solution equivalent to 400 mg of ritonavir to a 200-mL volumetric flask, and dilute with *Solution B* to volume.

Sample solution: Nominally 1 mg/mL of ritonavir prepared as follows. Transfer 25.0 mL of the *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Solution C* to volume. Transfer 15.0 mL of the solution to a 50-mL centrifuge tube that has been previously rinsed with methanol and dried. Add 20.0 mL of heptane, then stopper the tube. Shake the tube vigorously until a uniform emulsion is obtained, making sure to vent periodically. Centrifuge the resulting emulsion for about 5 min. Carefully aspirate off the top layer (heptane), leaving the clear bottom layer (*Sample solution*) in the tube. The centrifuged emulsion will have three distinct layers. The top layer (clear heptane) and the bottom layer (*Sample solution*) are separated by a viscous white cloudy layer. The middle layer should be considered part of the top layer for removal by aspiration. Repeat the extraction steps, and analyze the *Sample solution*.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm; 3-µm packing L26. Wash the column with the *Cleaning solution* after each injection of the *Peak identification solution* and each injection of the *Sample solution* for about 26 min, and equilibrate with *Mobile phase* for about 30 min. Store in the *Cleaning solution* after the analysis is completed.

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: 1.8 times the retention time of ritonavir

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.8–1.2

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Peak identification solution*, *Standard solution*, and *Sample solution*

[NOTE—Determine the relative retention value (*r*) for the components listed in [Table 1](#) as directed in [Chromatography \(621\)](#), using the time measured at the baseline deflection of the *Standard solution* chromatogram as the void volume (t_M).]

Calculate the percentage of each impurity in the portion of Oral Solution taken:

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

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

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

C_S = concentration of [USP Ritonavir RS](#) in the *Standard solution* (mg/mL)