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Ritonavir Capsules

DEFINITION

Ritonavir Capsules contain 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](#)

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

Mobile phase: Acetonitrile, methanol, [tetrahydrofuran \(stabilizer-free\)](#), and *Buffer* (7:4:4:25). Separately filter the *Buffer* and the pre-mixed solvents before combining to make the *Mobile phase*.

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

Sample stock solution: Nominally 1 mg/mL of ritonavir prepared as follows. Transfer Capsules (NLT 5) equivalent to 500 mg of ritonavir into a 500-mL volumetric flask, add about 250 mL of *Diluent*, and shake for at least 30 min or until the Capsules have visually disintegrated. Add 150 mL of acetonitrile, allow to cool to room temperature, and dilute to volume with *Diluent*.

Sample solution: Nominally 25 µg/mL of ritonavir in *Diluent* from the *Sample stock 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

Capacity factor: NLT 15

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 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 Ritonavir RS](#) in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS**Change to read:**

- [DISSOLUTION \(711\)](#).

▲Test 1▲ (RB 1-Apr-2018)

Medium: 0.1 N [hydrochloric acid](#) with 25 mM [polyoxyethylene 10 lauryl ether](#), 900 mL

Apparatus 2: 50 rpm, with sinkers

Time: 30 min

Buffer: 4.1 g/L of [monobasic potassium phosphate](#)

Mobile phase: Acetonitrile and *Buffer* (55:45). Adjust with [phosphoric acid](#) to a pH of 4.0 ± 0.1 .

Standard stock solution: 5.2 mg/mL of [USP Ritonavir RS](#) in methanol

Standard working solution: 104 µg/mL of [USP Ritonavir RS](#) in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 15-cm; 5-µm packing [L1](#)

Flow rate: 1.5 mL/min

Injection volume: 25 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 ritonavir ($C_{37}H_{48}N_6O_5S_2$) 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 Ritonavir RS](#) in the *Standard solution* (mg/mL)

L = ritonavir label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of ritonavir ($C_{37}H_{48}N_6O_5S_2$) is dissolved.

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

Medium: 0.1 N [hydrochloric acid](#) with 25 mM [polyoxyethylene 10 lauryl ether](#), 900 mL, degassed

Apparatus 2: 50 rpm, with sinker

Time: 20 and 120 min

Solution A: [Water](#) and [phosphoric acid](#) (98:2)

Buffer: [Water](#) adjusted with *Solution A* to a pH of 3.5

Mobile phase: Acetonitrile, methanol, and *Buffer* (500:100:400).

Standard stock solution: 0.56 mg/mL of [USP Ritonavir RS](#) in methanol

Standard solution: 0.11 mg/mL of [USP Ritonavir RS](#) in *Medium* from *Standard stock solution*

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 240 nm

Column: 4.6-mm × 15-cm; 5-µm packing [L7](#)

Column temperature: 30°

Flow rate: 1.8 mL/min**Injection volume:** 20 µL**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 concentration (C_i) of ritonavir ($C_{37}H_{48}N_6O_5S_2$) in the sample withdrawn from the vessel at each time point (i):

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

 r_U = peak response of ritonavir 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)Calculate the percentage of the labeled amount of ritonavir ($C_{37}H_{48}N_6O_5S_2$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

 C_i = concentration of ritonavir in the portion of sample withdrawn at the specified time point i (mg/mL) V = volume of *Medium*, 900 mL L = label claim of ritonavir (mg/Capsule) V_S = volume of the *Sample solution* withdrawn at each time point i (mL)**Tolerances:** See [Table 1](#).**Table 1**

Time Point (i)	Time (min)	Tolerances [▲] ▲ (ERR 1-Nov-2018)
1	20	20%–40%
2	120	NLT 80% [▲] (Q)▲ (ERR 1-Nov-2018)

▲ (RB 1-Apr-2018)

- [UNIFORMITY OF DOSAGE UNITS \(905\)](#): Meet the requirements

IMPURITIES**Change to read:**• **ORGANIC IMPURITIES**

[NOTE—Ritonavir is alkali sensitive. All glassware should be pre-rinsed 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 apparent pH to 6.3 ± 0.1 with [1 M phosphoric acid](#) or [1 M potassium hydroxide](#) if necessary.**Cleaning solution:** Acetonitrile, [butyl alcohol](#), [tetrahydrofuran \(stabilizer-free\)](#), and *Buffer A* (30:8:13:49)**Documents**

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