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Lopinavir and Ritonavir Oral Solution

DEFINITION

Lopinavir and Ritonavir Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amounts of lopinavir ($C_{37}H_{48}N_4O_5$) and ritonavir ($C_{37}H_{48}N_6O_5S_2$).

IDENTIFICATION

• **A.** The retention times of the lopinavir and ritonavir peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the Assay.

ASSAY

• LOPINAVIR AND RITONAVIR

Buffer: 4.1 g/L of monobasic potassium phosphate in water

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

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

Mobile phase: Acetonitrile, methanol, tetrahydrofuran, and *Buffer* (175:100:100:625). Separately filter the *Buffer* and the premixed solvents before combining them to make the *Mobile phase*.

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

Standard solution: 0.025 mg/mL each of [USP Lopinavir RS](#) and [USP Ritonavir RS](#) in *Solution B* from the *Standard stock solution*

Sample stock solution: Nominally 4 mg/mL of lopinavir and 1 mg/mL of ritonavir in *Solution A* prepared as follows. Transfer a volume of Oral Solution equivalent to 400 mg of lopinavir and 100 mg of ritonavir to a 100-mL volumetric flask with the aid of several small portions of *Solution A*, and then dilute with *Solution A* to volume.

Sample solution: Nominally 0.05 mg/mL of lopinavir and 0.0125 mg/mL of ritonavir in *Solution B* from the *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 215 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 for the ritonavir peak

Relative standard deviation: NMT 2.0% each for ritonavir and lopinavir

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentages of the labeled amounts of lopinavir ($C_{37}H_{48}N_4O_5$) and 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 of the corresponding analyte from the *Sample solution*

r_S = peak response of the corresponding analyte from the *Standard solution*

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



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

Acceptance criteria: 90.0%–110.0% of the labeled amounts of lopinavir ($C_{37}H_{48}N_4O_5$) and ritonavir ($C_{37}H_{48}N_6O_5S_2$)

PERFORMANCE TESTS

• [DELIVERABLE VOLUME \(698\)](#)

For multiple-unit containers

Acceptance criteria: Meets the requirements

IMPURITIES

• ORGANIC IMPURITIES

Buffer A: 4.1 g/L of monobasic potassium phosphate in water

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

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

Solution B: Acetonitrile, butyl alcohol, and *Buffer A* (15:5:80)

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

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

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

Standard solution: 0.01 mg/mL each of [USP Lopinavir RS](#) and [USP Ritonavir RS](#) from *Standard stock solution* in *Solution B*

Peak identification solution: Transfer a weighed portion of Oral Solution to a crimp-top container. Add an amount of citric acid equivalent to 1% by weight of the Oral Solution taken and mix until dissolved. Seal the container, and heat at 50° for approximately 4 days. Use this degradation solution and follow the procedure described below in the *Sample stock solution* and *Sample solution* sections to prepare the *Peak identification solution*.

Sample stock solution: Transfer 5 mL of Oral Solution with the aid of several small portions of *Solution C* to a 100-mL volumetric flask, and dilute with *Solution C* to volume.

Sample solution: Dilute 25.0 mL of *Sample stock solution* with *Solution B* to 50.0 mL. Transfer 15.0 mL of this solution to a 50-mL centrifuge tube that has been previously rinsed with methanol and dried. Add 20.0 mL of *n*-heptane, and shake vigorously until a uniform emulsion is formed. Vent the tube periodically while shaking. Centrifuge the emulsion for about 5 min. Carefully remove the top heptane layer by aspiration, leaving the clear *Sample solution* layer. The middle viscous, cloudy layer should be considered part of the heptane layer for removal by aspiration. Precondition a strong anion-exchange cartridge (quaternary ammonium functionality on a styrene/divinylbenzene base) with a sorbent mass of 600 mg by rinsing the cartridge with 3 mL of methanol, then 3 mL of *Solution C*, and repeating these rinse steps. Dry the cartridge for about 10 min with the aid of a low vacuum. Transfer 5.0 mL of the clear *Sample solution* to the preconditioned cartridge. With the aid of a vacuum, slowly pass the *Sample solution* completely through the cartridge, collect the extract in a 5-mL volumetric flask, and then dilute with *Solution C* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm and 240 nm

Column: 4.6-mm × 15-cm; 3-μm packing L26

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 50 μL

Run time: 2 times the retention time of lopinavir

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.5 between the ritonavir and lopinavir peaks at 215 nm

Tailing factor: 0.8–1.2 for the ritonavir peak at 240 nm

Relative standard deviation: NMT 3.0% for the lopinavir peak at 215 nm; NMT 3.0% for the ritonavir peak at 240 nm

Analysis

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

[NOTE—Determine the relative retention values (*r*) for the components listed in [Table 1](#) and [Table 2](#), using the time measured at the first baseline deflection of the *Standard solution* chromatogram as the void volume (t_M).]

To identify the ritonavir impurities, determine the relative retention value from the 240-nm chromatogram relative to ritonavir (see [Table 1](#)). The *Peak identification solution* may also be used to identify ritonavir degradants. Unspecified ritonavir impurities are assigned

according to the algorithm outlined in [Table 3](#).

Calculate the percentage of each ritonavir 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 individual 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)

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

F = relative response factor (see [Table 1](#))

Acceptance criteria: See [Table 1](#).

Table 1

Name	Relative Retention Value (r)	Relative Response Factor	Acceptance Criteria, NMT (%)
Ureidovaline ^a	0.03	—	— ^b
N-Deacylvaline ritonavir ^c	0.11	0.81	0.8
Glycerol carbamate analog ^d	0.14	0.62	0.2
Acetamidoalcohol ^e	0.15	—	— ^b
Hydroxypropyl carbamate analog ^f	0.24 ^g	0.59	0.5
2,5-Thiazolylmethylidicarbamate ^h	0.24 ⁱ	—	— ^b
Hydroxyritonavir ^j	0.36	0.86	0.3
Hydantoin aminoalcohol ^k	0.39	0.73	0.4
Ritonavir hydroperoxide ^l	0.44 ⁱ	0.88	0.2
Ethyl carbamate analog ^m	0.45 ⁱ	0.66	0.7
Hydantoin-oxazolidinone derivative ⁿ	0.50	—	— ^b
Ethyl analog ^o	0.64	—	— ^b
O-Acyl isomer ^p	0.74	1.1	0.2
BOC-aminoalcohol ^q	0.81	—	— ^b
Isobutoxycarbonyl aminoalcohol ^r	0.81	—	—