Edition: BP 2025 (Ph. Eur. 11.6 update)

Ritonavir Tablets

General Notices

Action and use

Protease inhibitor; antiviral (HIV).

DEFINITION

Ritonavir Tablets contain Ritonavir.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ritonavir, $C_{37}H_{48}N_6O_5S_2$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions prepared in a mixture of equal volumes of *acetonitrile* and *water*.
(1) Shake a quantity of the powdered tablets containing 20 mg of Ritonavir with 10 mL. Centrifuge and use the supernatant liquid.
(2) 0.2% w/v of *ritonavir BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 2 µL of each solution.
(d) Develop the plate to 6 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

5 volumes of *glacial acetic acid*, 6 volumes of *n-heptane* and 18 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the principal peak in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the requirements in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.
(b) Use 900 mL of 0.06M *polyoxyethylene 10 lauryl ether*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions
(1) After 120 minutes withdraw a sample of the medium and filter. Use the filtered medium, diluted with dissolution medium if necessary, expected to contain 0.011% w/v of Ritonavir.
(2) 0.11% w/v of *ritonavir BPCRS* in *methanol R1*. Dilute 1 volume to 10 volumes with dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 25 µL of each solution.

MOBILE PHASE

45 volumes of 0.03M *potassium dihydrogen orthophosphate*, adjusted to pH 4.0 using *orthophosphoric acid*, and 55 volumes of *acetonitrile R1*.

DETERMINATION OF CONTENT

Calculate the total content of ritonavir, $C_{37}H_{48}N_6O_5S_2$, in the medium from the chromatograms obtained and using the declared content of $C_{37}H_{48}N_6O_5S_2$, in *ritonavir BPCRS*.

LIMITS

The amount of ritonavir released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Pre-rinse all glassware with *water*.

Solution A Equal volumes of *acetonitrile* and a 0.38% w/v solution of *potassium dihydrogen orthophosphate*.

Solution B 10 volumes of a 0.38% w/v solution of *potassium dihydrogen orthophosphate*, 10 volumes of *water*, 15 volumes of *butan-1-ol* and 65 volumes of *acetonitrile*.

Solution C 5 volumes of *butan-1-ol*, 15 volumes of *acetonitrile* and 80 volumes of a 0.38% w/v solution of *potassium dihydrogen orthophosphate*.

(1) Shake a quantity of powdered tablets containing 0.5 g of Ritonavir with 250 mL of solution B, shake and then mix with the aid of ultrasound. Add sufficient solution B to produce 500 mL and stir. Centrifuge and dilute 1 volume of the supernatant liquid to 2 volumes with solution C. Filter through a 0.2-µm nylon filter and use the filtrate.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution C.
(3) Dilute 1 volume of solution (2) to 10 volumes with solution C.
(4) 0.1% w/v of *ritonavir for peak identification EPCRS* in solution A. Dilute 1 volume to 2 volumes with solution C.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped butylsilyl silica gel for chromatography* (3 µm) (YMC C4 is suitable).

(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 60°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 5 volumes of *butan-1-ol*, 8 volumes of *tetrahydrofuran, stabiliser-free*, 18 volumes of *acetonitrile* and 69 volumes of a solution containing 0.025% w/v of *dipotassium hydrogen orthophosphate* and 0.38% w/v of *potassium dihydrogen orthophosphate*. Adjust to pH 6.3 using 1M *orthophosphoric acid* or 1M *potassium hydroxide*.

Mobile phase B 8 volumes of *butan-1-ol*, 13 volumes of *tetrahydrofuran, stabiliser-free*, 30 volumes of *acetonitrile* and 49 volumes of 0.38% w/v of *potassium dihydrogen orthophosphate*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-80	100	0	isocratic
80-80.1	100→0	0→100	linear gradient
80.1-115	0	100	isocratic column wash
115-115.1	0→100	100→0	linear gradient
115.1-145	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to ritonavir (retention time about 31 minutes) are; impurity E, about 0.39; impurity F, about 0.41; impurity 1, about 0.7; impurity L, about 0.9 and impurity O, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *peak to valley ratio* is at least 1.2, where *Hp* is the height above the baseline of the peak due to impurity E and *Hv* is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity F.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities E, F, L and O using solution (4) and multiply the areas of these peaks by the corresponding correction factors: impurity F, 1.4 and impurity L, 1.9.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than 2.6 times the area of the principal peak in the chromatogram obtained with solution (2) (2.6%)

the area of any peaks corresponding to impurities E, O or L is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3% of each);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the sum of the area of any *secondary peaks*, excluding impurity F, is not greater than 0.9 times the area of the principal peak in the chromatogram obtained with solution (2) (0.9%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. Pre-rinse all glassware with *water*.

Solution D Equal volumes of *acetonitrile* and 0.03M *potassium dihydrogen orthophosphate*.

Solution E 10 volumes of 0.03M *potassium dihydrogen orthophosphate*, 10 volumes of *water*, 15 volumes of *butan-1-ol* and 65 volumes of *acetonitrile*.

(1) To a number of whole tablets containing 1 g of Ritonavir, add 500 mL of solution E. Add sufficient solution E to produce 1000 mL and stir. Centrifuge and dilute 1 volume of the supernatant liquid to 10 volumes with solution D.
(2) 0.01% w/v solution of *ritonavir BPCRS* in solution D.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octylsilyl silica gel for chromatography* (5 µm) (Hypersil C8 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 240 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

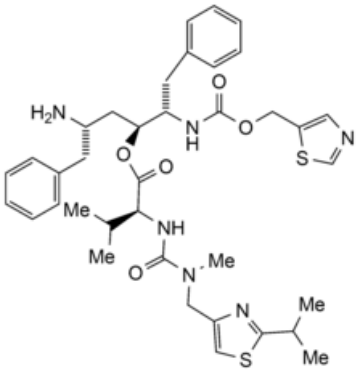
10 volumes of *methanol*, 10 volumes of *tetrahydrofuran, stabiliser-free*, 17.5 volumes of *acetonitrile* and 62.5 volumes of 0.03M *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Calculate the content of ritonavir, $C_{37}H_{48}N_6O_5S_2$, in the tablets from the chromatograms obtained and using the declared content of $C_{37}H_{48}N_6O_5S_2$, in *ritonavir BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B to S listed under *Ritonavir* and:



1. (1,3-thiazol-5-yl)methyl (5*S*,8*S*,9*S*)-8-[(2*S*)-2-amino-3-phenylpropyl]-9-benzyl-2-methyl-3,6-dioxo-5-(propan-2-yl)-1-[2-(propan-2-yl)-1,3-thiazol-4-yl]-7-oxa-2,4,10-triazaundecan-11-oate (geo isomer)