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Ritonavir Tablets

DEFINITION
Ritonavir Tablets 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

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

Solution B: Acetonitrile, butyl alcohol, water, and *Buffer* (65:15:10:10)

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

Standard solution: 0.1 mg/mL of USP Ritonavir RS in *Solution A*

Sample stock solution: Nominally 1 mg/mL of ritonavir prepared as follows. Transfer Tablets (NLT 5) equivalent to 500 mg of ritonavir into a 500-mL volumetric flask. Fill the flask half full with *Solution B*, and mechanically shake for at least 60 min or until the Tablets have visually disintegrated. Dilute with *Solution B* to volume, and stir for 30 min. Transfer a sufficient quantity of this solution to a centrifuge tube, and centrifuge for about 15 min. Use the supernatant to prepare the *Sample solution*.

Sample solution: Nominally 0.1 mg/mL of ritonavir in *Solution A* from the supernatant of *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

Capacity factor: 15–24

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 Tablets 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

• **Dissolution ⟨711⟩**

Medium: 0.06 M polyoxyethylene 10 lauryl ether; 900 mL

Apparatus 2: 75 rpm

Time: 120 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: 1.11 mg/mL of USP Ritonavir RS in methanol

Standard working solution: 111 µg/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.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 215 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: 0.9–1.5

Capacity factor: Greater than 3.5

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 = label claim for ritonavir (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 75% (*Q*) of the labeled amount of ritonavir ($C_{37}H_{48}N_6O_5S_2$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

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, butyl alcohol, water, and *Buffer A* (65:15:10:10)

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

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

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

Standard stock solution: 0.05 mg/mL of USP Ritonavir RS in *Solution A*

Standard solution: 2.5 µg/mL of USP Ritonavir RS in *Solution C* from *Standard stock solution*

System suitability stock solution: 1 mg/mL of USP Ritonavir Related Compounds Mixture RS in *Solution B*

System suitability solution: 0.5 mg/mL of USP Ritonavir Related Compounds Mixture RS in *Solution C* from *System suitability stock solution*

Sample stock solution: Nominally 1 mg/mL prepared as follows. Transfer Tablets (NLT 5) equivalent to 500 mg of ritonavir into a 500-mL volumetric flask. Fill the flask half full with *Solution B*, and mechanically shake for at least 60 min or until the Tablets have visually disintegrated. Dilute with *Solution B* to volume, and stir for 30 min. Transfer a sufficient quantity of this solution to a centrifuge tube, and centrifuge for 15 min. Use the supernatant to prepare the *Sample solution*.

Sample solution: Nominally 0.5 mg/mL of ritonavir in *Solution C* from the supernatant of *Sample stock 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 after each injection of the *Sample solution* with *Cleaning solution* for about 26 min, and equilibrate with *Mobile phase* for about 30 min. Store in *Cleaning solution* after the analysis is completed.

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: 2.4 times the retention time of ritonavir

System suitability

Samples: *Standard solution* and *System suitability solution*

See *Table 1* for relative retention values. Disregard all peaks occurring before the *N*-deacylvaline ritonavir peak.

Suitability requirements

Resolution: Greater than 0.7 between the hydroxyritonavir and hydantoin aminoalcohol peaks, *System suitability solution*

Capacity factor: Greater than 10.8, *Standard solution*

Tailing factor: 0.8–1.2, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets 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)

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

F = relative response factor *(See Table 1)*

Acceptance criteria: See *Table 1*. Disregard peaks less than 0.05%.

Table 1

Name	Relative Retention	Relative Response Factor	Acceptance Criteria, NMT (%)
N-Deacylvaline ritonavir[a,b]	0.11	1.0	0.2
Acetamidoalcohol[c,d]	0.15	—	—
2,5-Thiazolylmethyldicarbamate[d,e]	0.24	—	—
Hydroxyritonavir[b,f]	0.36	1.0	0.3

Name	Relative Retention	Relative Response Factor	Acceptance Criteria, NMT (%)
Hydantoin aminoalcohol[b,g]	0.39	0.73	2.6
Ritonavir hydroperoxide[b,h]	0.44	1.0	0.2
Hydantoin-oxazolidinone derivative[d,i]	0.50	—	—
Ethyl analog[d,j]	0.64	—	—
Geo-isomer[b,k]	0.74	1.0	0.2
BOC-aminoalcohol[d,l]	0.81	—	—
Isobutoxycarbonyl aminoalcohol[d,m]			
Oxazolidinone derivative[b,n]	0.87	0.53	0.3
Ureidovaline isobutyl ester[d,o]	0.94	—	—
Ritonavir	1.00	—	—
4-Hydroxy isomer[d,p]	1.05	—	—
3*R*-Epimer[d,q]	1.11	—	—
Aminoalcohol urea derivative[d,r]	1.14	—	—
3*R*,5*R*-Diastereomer[d,s]	1.23	—	—
5*R*-Epimer[d,t]	1.32	—	—
Diacyl valine urea[d,u]	1.70	—	—
Any individual unspecified degradation product	—	1.0	0.2
Total impurities	—	—	3.5

[a] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-[(*S*)-2-amino-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

[b] Degradation product.

[c] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-acetamido-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

[d] Process impurity included in this table for peak identification only. This impurity is controlled in the drug substance. It is not to be reported for the drug product nor included in the total impurities.

[e] Bis(thiazol-5-ylmethyl) (2*S*,3*S*,5*S*)-3-hydroxy-1,6-diphenylhexane-2,5-diyldicarbamate. (Two peaks may be detected with a relative retention value of 0.24. The first peak is considered as an unknown impurity and the second as 2,5-thiazolylmethyldicarbamate.)

[f] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-3-hydroxy-5-[(*S*)-2-(3-{[2-(2-hydroxypropan-2-yl)thiazol-4-yl]methyl}-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

[g] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-3-hydroxy-5-[(*S*)-4-isopropyl-2,5-dioxoimidazolidin-1-yl]-1,6-diphenylhexan-2-ylcarbamate.

[h] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-[(*S*)-2-(3-{[2-(2-hydroperoxypropan-2-yl)thiazol-4-yl]methyl}-3-methylureido)-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

[i] (4*S*,5*S*)-Thiazol-5-ylmethyl 4-benzyl-5-{(*S*)-2-[(*S*)-4-isopropyl-2,5-dioxoimidazolidin-1-yl]-3-phenylpropyl}-2-oxooxazolidine-3-carboxylate.

[j] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-[(*S*)-2-{3-[(2-ethylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

[k] (*S*)-{(2*S*,3*S*,5*S*)-5-Amino-1,6-diphenyl-2-[(thiazol-5-ylmethoxy)carbonylamino]hexan-3-yl} 2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanoate.

[l] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-(5-*t*-butoxycarbonylamino)-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate (may co-elute with isobutoxycarbonyl aminoalcohol).

[m] Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-(5-isobutoxycarbonylamino)-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate (may co-elute with BOC-aminoalcohol).

[n] (*S*)-*N*-[(*S*)-1-[(4*S*,5*S*)-4-Benzyl-2-oxooxazolidin-5-yl]-3-phenylpropan-2-yl]-2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamide.

[o] (*S*)-Isobutyl 2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanoate.

[p] Thiazol-5-ylmethyl (2*S*,4*S*,5*S*)-4-hydroxy-5-[(*S*)-2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

[q] Thiazol-5-ylmethyl (2*S*,3*R*,5*S*)-3-hydroxy-5-[(*S*)-2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

[r] Bis(thiazol-5-ylmethyl) (2*S*,2'*S*,3*S*,3'*S*,5*S*,5'*S*)-5,5'-carbonylbis(azanediyl)bis(3-hydroxy-1,6-diphenylhexane-5,2-diyl)dicarbamate.

[s] Thiazol-5-ylmethyl (2*S*,3*R*,5*R*)-3-hydroxy-5-[(*S*)-2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

[t] Thiazol-5-ylmethyl (2*S*,3*S*,5*R*)-3-hydroxy-5-[(*S*)-2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

[u] (3*S*,4*S*,6*S*,10*S*,13*S*,15*S*,16*S*)-Bis(thiazol-5-ylmethyl)-4,15-dihydroxy-10-isopropyl-8,11-dioxo-3,6,13,16-tetrabenzyl-2,7,9,12,17-pentaazaoctadecanedioate.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at or below 30°.
- **USP Reference Standards** ⟨11⟩
  USP Ritonavir RS
  USP Ritonavir Related Compounds Mixture RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
RITONAVIR TABLETS	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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