EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 8
59-66
Year: 2024

# A COMPREHENSIVE REVIEW ON PHARMACOLOGICAL, PHARMACEUTICAL AND ANALYTICAL PROFILE OF RITONAVIR

**S. K. Rafath Sulthana[1], M. Lakshmikanth[1], K. Sushma[1], B. Baji[1], P. Jahanavi Devi[1], P. Siva Krishna[1]*, M. M. Eswarudu[1] and P. Srinivasa Babu[2]**

[1]Department of Pharmaceutical Analysis, Vignan Pharmacy College, Vadlamudi, Guntur, 522213, Andhra Pradesh, India.
[2]Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur, 522213, Andhra Pradesh, India.

***Corresponding Author: P. Siva Krishna**
Department of Pharmaceutical Analysis, Vignan Pharmacy College, Vadlamudi, Guntur, 522213, Andhra Pradesh, India.

**Article Received on 03/06/2024** **Article Revised on 23/06/2024** **Article Accepted on 13/07/2024**

## ABSTRACT
The present study interplay between ritonavir's analytical, pharmacological, and pharmaceutical attributes, emphasizing its pivotal role in combating HIV/AIDS and its ongoing evolution in the realm of antiretroviral therapy. Ritonavir's analytical properties encompass its chemical structure, molecular weight, and spectral characteristics, which have been extensively studied using various analytical techniques, including spectroscopy, chromatography, and mass spectrometry. These methods have contributed significantly to its identification, quantification, and purity determination, ensuring reliable pharmaceutical formulations. Ritonavir is pharmacologically a protease inhibitor, it exhibits potent antiviral activity by inhibiting HIV-1 protease, a crucial enzyme for viral replication. Its pharmacokinetic profile involves rapid absorption, extensive metabolism via the cytochrome P450 system, and significant protein binding, influencing its bioavailability and half-life. Ritonavir's role as a booster for other antiretroviral drugs has revolutionized combination therapy, enhancing their efficacy by inhibiting drug-metabolizing enzymes. Pharmaceutical formulations, ritonavir presents challenges due to its low aqueous solubility and susceptibility to degradation. Formulation strategies involving solid dispersion, lipid-based formulations, and nanotechnology have been explored to enhance its solubility, stability, and overall bioavailability. Additionally, various dosage forms, including tablets, capsules, and oral solutions, have been developed to cater to different patient populations.

**KEYWORDS:** Ritonavir, Cytochrome P450 system, HIV-1 protease, Bioavailability, High-performance liquid chromatography, Liquid chromatography–mass spectrometry.

## INTRODUCTION
Ritonavir, marketed under the name Norvir, is an antiretroviral employed in tandem with other drugs to combat HIV/AIDS, forming the basis of highly active antiretroviral therapy (HAART). Functioning as a protease inhibitor, it collaborates with other inhibitors and can also be part of treatments for hepatitis C and COVID-19. Administered orally, it's important to note that ritonavir tablets and capsules differ in their impact on peak plasma concentrations. Originally patented in 1989 and introduced for medical use in 1996, ritonavir has secured its place on the World Health Organization's essential medicines list. Capsules of ritonavir gained generic medication approval in the United States in 2020. Initially conceived as a standalone antiviral, ritonavir has displayed remarkable synergy in combination with low-dose ritonavir and other protease inhibitors. Its role has shifted, becoming more prevalent as a booster for other protease inhibitors, available in liquid forms and capsules alike.[1] Even though ritonavir doesn't actively combat hepatitis C virus (HCV) infection, it serves as a critical component in combination therapies for treating HCV infections by amplifying their effectiveness. Acting as a potent CYP3A inhibitor, ritonavir elevates both peak and trough plasma drug concentrations of other protease inhibitors like Paritaprevir, thereby enhancing overall drug exposure. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) guidelines advocate for ritonavir-boosted combination therapies as the primary treatment for HCV Genotype 1a/b and 4 in treatment-naïve patients, regardless of cirrhosis presence.[2] and its structural formula is given in figure 1.[3] Drug profile[4,6], Chemical taxonomy[7] and predicted properties[8] of ritonavir was given in Table 1, 2, 3.

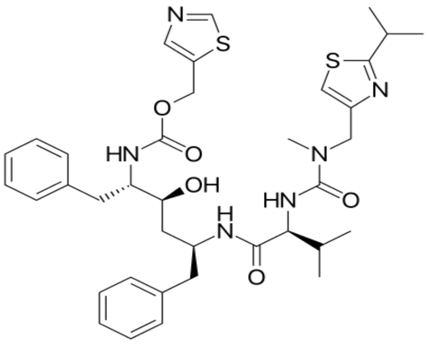


**Figure 1: Chemical Structure of ritonavir.**

**Table 1: Drug profile of ritonavir.**

| **Drug** | **Ritonavir** |
|---|---|
| IUPAC Name | 1,3-thiazol-5-ylmethyl *N*-[(2*S*,3*S*,5*S*)-3-hydroxy-5-[(2*S*)-3-methyl-2-{[methyl({[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl})carbamoyl]amino}butanamido]-1,6-diphenylhexan-2-yl]carbamate |
| Chemical Formula | $C_{37}H_{48}N_6O_5S_2$ |
| Molecular mass | 720.95 g·mol$^{-1}$ |
| Melting point | 126-132°C |
| Physical state | Solid |
| Solubility | DMSO: 20mg/mL; H2O: <1mg/mL; EtOH: <1mg/mL |
| LogP | 3.9 |
| Colour | White to light tan powder |
| *t1/2* | 3-5 hours |

**Table 2: Chemical Taxonomy.**

| | |
|---|---|
| **Description** | This compound belongs to the class of organic compounds known as n-carbamoyl-alpha amino acids and derivatives. These are compounds containing an alpha amino acid (or a derivative thereof) which bears an carbamoyl group at its terminal nitrogen atom. |
| **Kingdom** | Organic compounds |
| **Super Class** | Organic acids and derivatives |
| **Class** | Carboxylic acids and derivatives |
| **Sub Class** | Amino acids, Peptides and Analouges |
| **Direct Parent** | N-carbamoyl-alpha amino acids and derivatives |
| **Alternative Parents** | Valine and derivatives/Alpha amino acid amides\2,4-disubstituted thiazoles etc… |
| **Substituents** | 2,4-disubstituted 1,3-thiazole / Alcohol / Alpha-amino acid amide / Amphetamine or derivatives / Aromatic heteromonocyclic compound / Azacycle / Azole / Benzenoid / Carbamic acid ester / Carbonic acid derivative |
| **Molecular framework** | Aromatic heteromonocyclic compounds |
| **External Descriptors** | carbamate ester, ureas, 1,3-thiazole, carboxamide, L-valine derivative (CHEBI:45409) |

**Table 3: Predicted Properties.**

| **PROPERTY** | **Value** |
|---|---|
| Water solubility | 0.00126 mg/mL |
| LogP | 4.24 |
| LogP | 5.22 |
| logS | -5.8 |
| Pka | 13.68 |
| Pka | 2.84 |
| Physiological charge | 0 |
| Hydrogen acceptor count | 6 |
| Hydrogen donor count | 4 |
| Polar surface area | 145.78 A$^2$ |

| | |
|---|---|
| Rotatable bond count | 18 |
| Refractivity | 194.59 $M^3$- MOL $^{-3}$ |
| Polarizability | 76.23 $A^3$ |
| Number of rings | 4 |
| Bioavailability | 0 |
| Rules of five | NO |
| Ghose filter | NO |
| Vebers rule | NO |
| MDDR like rule | Yes |

**Pharmacological Properties**

**Pharmacodynamic Properties**

Research on how Ritonavir affects the body in relation to its proposed use reveals some compelling findings. It appears to be markedly more targeted toward inhibiting HIV protease (about 500 times more specific) compared to any human aspartyl protease, as evidenced by its inhibition constant equivalent to 15 pM. When investigating its impact on HIV-1 and HIV-2 in laboratory settings using various human cell lines, Ritonavir displayed antiviral activity. It inhibited 50% and 90% of viral replication at concentrations approximately around 0.02 µM and 0.11 µM, respectively. The potency against HIV-1 was notably higher (about 6-to-40-fold) compared to HIV-2. Additionally, it exhibited equal effectiveness against both pre-ZDV sensitive and post-ZDV resistant HIV-1 in MT2 cells.

However, Ritonavir's binding to plasma proteins significantly increased its EC50 value by more than tenfold, indicating a possible attenuation of its in vivo antiviral activity due to this binding. In terms of safety, Ritonavir demonstrated minimal cytotoxicity relative to its antiviral properties. It established an impressive therapeutic index of over 1000 in vitro. Regarding combination therapy with reverse transcriptase inhibitors, experiments indicated an additive effect when Ritonavir was combined with either ZDV or ddI, showing promise for potential combined treatments. Nevertheless, this observation was based on results obtained with a single laboratory HIV strain, and the impact of the biological phenotype of HIV from patients on monotherapy remains unclear. In summary, Ritonavir's antiviral effects have been convincingly demonstrated in vitro, although the submitted virology data were limited, necessitating the use of additional bibliographical references to supplement the assessment of its virological aspects.

Experiments aimed at exploring additional pharmacological effects of ritonavir unveiled limited impact on the central nervous systems of mice and rats when administered doses ranging from 5 to 50 mg/kg. Similarly, minimal influence was observed on the cardiovascular systems of conscious rats and anesthetized dogs. In isolated guinea pig ileum, ritonavir exhibited neither antagonist nor agonist effects. However, the relatively low exposure levels of ritonavir in these tests, compared to doses used in human patients, severely restrict the extent to which conclusions can be drawn. Unfortunately, no further tests were conducted to delve into other potential pharmacodynamic actions of ritonavir.[9]

**Pharmacokinetic Properties**

The estimated oral bioavailability of Ritonavir falls within the range of 60% to 80%. When compared to the fasting state, the capsule formulation shows an approximate 15% increase in the AUC of ritonavir when taken with food. Conversely, the oral solution experiences a 7% decrease in AUC when administered alongside a meal.

**Absorption**

The precise absolute bioavailability of ritonavir remains undetermined. After oral intake, peak concentrations typically occur around 2 hours under fasting conditions and approximately 4 hours when taken without fasting (Tmax). Notably, it's important to highlight that ritonavir capsules and tablets aren't deemed bioequivalent.

**Protein binding**

Ritonavir is highly protein-bound in plasma (~98-99%), primarily to albumin and alpha-1 acid glycoprotein over the standard concentration range.

**Metabolism**

Ritonavir primarily circulates in the plasma in its original, unchanged form. Among the five identified metabolites, the isopropyl thiazole oxidation metabolite (M-2) holds prominence at low plasma levels and maintains a comparable antiviral potency to the unchanged ritonavir. The metabolic breakdown of ritonavir primarily involves the cytochrome P450 enzymes CYP3A and CYP2D6.

**Elimination**

The primary route of elimination for Ritonavir is through fecal excretion. After oral administration of a single 600mg dose of radiolabelled ritonavir, roughly 11.3 ± 2.8% of the dose was eliminated via urine, with 3.5 ± 1.8% being the unchanged parent drug. In the same study, approximately 86.4 ± 2.9% of the administered dose was excreted in the feces, with 33.8 ± 10.8% being the unchanged parent drug.[10]

**Mechanism of action**

Ritonavir functions by binding to HIV-1 protease, disrupting its ability to cleave protein precursors and impeding the generation of new viral particles. However, its significance in treating HIV and HCV often stems from another crucial mechanism: inhibiting the liver enzyme cytochrome P450 3A4 (CYP450-3A4). This particular pathway is responsible for metabolizing various protease inhibitors. By inhibiting CYP450-3A4, ritonavir boosts the bioavailability of other antiretroviral drugs. This inhibition also reduces the breakdown of ARVs, thereby elevating serum drug levels. Caution should be exercised when using ritonavir alongside medications metabolized through this pathway, such as statins, anti-arrhythmic agents, anti-epileptic drugs, and anti-fungal agents.[11] The mechanism of action of ritonavir is depicted in Figure 2.

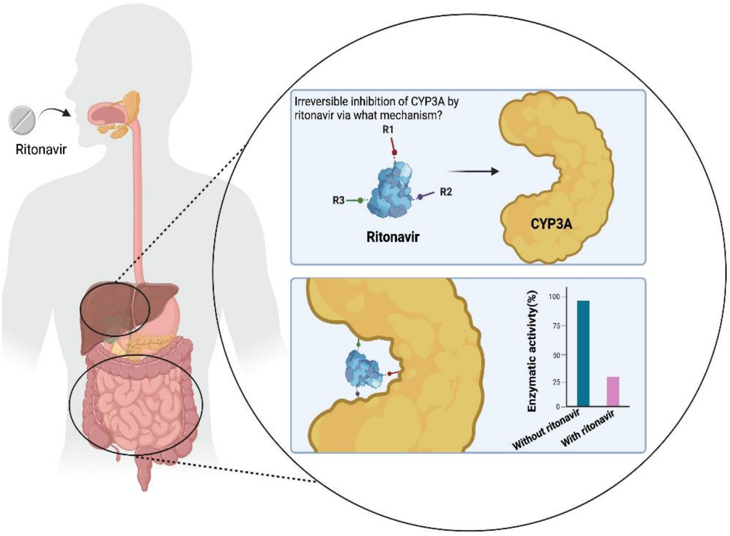


**Figure 2: Mechanism of action of Ritonavir.**

**Indication:** Treatment of HIV infection ass part of combination boosted protease inhibitor (PI).

**Containdications:** Hypersensitivity; Caution if hepatic impairment, HBV or HCV co-infection, structural heart diseases, cardiac conduction disturbance, ischemic heart disease, cardiomyopathy, diabetes melllitus, haemophilia.[12]

**Table 4: List of available marketed brand names for Ritonavir.**

| S. No | Trade name | Company name | Formulation | Dosage form |
|---|---|---|---|---|
| 1 | Norvir | Abbvie inc | Tablet, Oral Solution, Oral powder | 100mg<br>80mg/mL<br>100mg/packet |
| 2 | kaletra | Abbvie inc | Oral solution/Tablet | 100mg/25mg<br>200mg/50mg<br>(400mg/100mg)/5mL |
| 3 | Aluvia | Abbvie inc | film-coated tablets | 200 mg/50 mg |
| 4 | Technivie | Abbvie inc | Tablets | 12.5 mg / 75 mg/ 50 mg |
| 5 | Viekira Pak | Abbvie inc | Tablets | 50 mg |
| 6 | Avikivir | Cipla | Chewable Tablet | 40 mg/600 mg/700 mg and 20 mg/600 mg/700 mg, |
| 7 | Lopimune | Cipla | Chewable Tablet | 20 to 250 mg,<br>40 to 240 mg |
| 8 | Ritonavir Mylan | Mylan | film-coated tablets | 100 mg |
| 9 | Ritocom | Emcure pharmaceuticals | Tablet | 200 mg/50 mg |
| 10 | Darunavir/Ritonavir | Janssen pharmaceuticals | Tablet,oral suspension | 75 mg,150 mg,600 mg,800 mg,100 mg/mL |

**Table 5: List of UV methods reported for Ritonavir.**

| S. No | Wavelength (nm) | Linearity range (µg/mL) | LOD (µg/mL) | LOQ (µg/mL) | Correlation coefficient |
|---|---|---|---|---|---|
| 1[13] | Method (A) 271<br>Method(B) 258 | 10-50 | Method I 0.24 (µg/ml) | Method I 0.75<br>Method II 1.42 | (A) 0.9994<br>(B) 0.9989 |

| | | | | | |
|---|---|---|---|---|---|
| | Method(C) 260-281 | | Method II 0.45 (µg/ml)<br>Method III 0.38 (µg/ml) | Method III 1.14 | (C) 0.9999 |
| 2[14] | 239 | Method I 15-90<br>Method II 15-75 | Method I 0.08314(µg/ml)<br>Method II 0.1493(µg/ml) | Method I 0.25198<br>Method II 0.4525 | Method I 0.99996<br>Method II 0.9987 |
| 3[15] | 260 | 5-100 | - | - | 0.999 |
| 4[16] | 255 | 30-210 | 0.495 | 1.502 | 0.999 |
| 5[17] | 256.75 | 10-20 | 0.595 | 1.804 | 0.994 |
| 6[18] | 266 | 10-30 | 2.62 | 7.96 | 0.9961 |
| 7[19] | 222.3 | 10-30 | - | - | 0.9995 |

**Table 6: List of HPLC methods reported for Ritonavir.**

| S. No | Column type | Mobile phase | Run time (min) | Retention time(min) | Flow rate (mL/min) | Wavelength (nm) | Linearity range (µg/mL) | LOD (µg/mL) | LOQ (µg/mL) | Correlation coefficient |
|---|---|---|---|---|---|---|---|---|---|---|
| 1[20] | $RPC_{18}$ Column (150×4.5 mm, 3.5µ) | 10mM phosphate buffer and acetonitrile (35:65, v/v) | - | 6.3 | 1 | 254 | 1.7 – 40 | 0.0521 | 0.1042 | 0.9996 |
| 2[21] | BDS Hypersil C18 column (250×4.6 mm, 5 µm) | Ethanol: water (80:20, v/v) | - | 6.8 | 1 | 215 | 1 – 20 | 0.32 | 0.96 | 0.9998 |
| 3[22] | C18 Column (Shim-pack) 250 ×4.6 mm, 5 µm | Methanol: water (80:20) | 15 min | 7.7 | 1 | 251 | 50 – 100 | 8.9 | 27.2 | 0.9993 |
| 4[23] | RP-C18 Kinetix column (5 mm, 150 mm 4.6 mm ID) | (0.15 M sodium lauryl sulfate and 0.01 M sodium dihydrogen phosphate, pH 6.2) and ethanol (56:44) | - | 4.5 min | 1 mL/min | 254 nm | 3-100 mg/mL | 0.9 mg/mL | 2.6 mg/mL | 0.999 |

**Table 7: List of LC-MS methods reported for Ritonavir.**

| S. No | M/Z Value | Capillary temperature ($^0$C) | Ionization voltage (V) | Column type | Solvent mixture | Mass Spectroscopy used | Run time (min) | Retention time (min) |
|---|---|---|---|---|---|---|---|---|
| 1[24] | 629.3 | - | 5,000 V | Inertsil ODS column (50 9 4.6 mm,) | 5 mM ammonium acetate buffer (adjusted to pH 3.5) mixed with acetonitrile (20:80 v/v buffer: acetonitrile) | electro spray ionization chamber | 2 min | 1.20 ± 0.50 |
| 2[25] | 721.3 to 296.1 | - | - | Synergi Polar-RP column (100 by 2.0 mm, 4 m) (Phenomenex, Torrance, CA) with a C8 guard column (4 by 2.0 mm) (Phenomenex). | A: water B:acetonitrile C: both with 0.1% acetic acid | liquid chromatography-tandem mass spectrometry (LC-MS/MS) | - | - |
| 3[26] | 721.4→ 296.3 | - | - | hypersil hypurity C18 (4.6 X 50 mm) | 2% formic acid with acetonitrile in the ratio of 20:80(v/v) | Biosystems Sciex API 2000 Mass Spectrometer | - | - |
| 4[27] | 140.2 | - | - | Oasis HLB Direct Connect HP column (30 | A:water | Triple quadrupole | 5 min | 3.37 min |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | mm x 2.1 mm, 20 M, Waters) | B:acetonitrile | mass spectrometer Xevo TQ-S (Waters, Milford, MA, USA) | | |
| 5[28] | 721.4→ 296.3 | - | - | Agilent Zorbax SB-C18 column (150 2.1 mm; 5-m particle size), an Agilent Zorbax SB-C8 column (150 2.1 mm; 5-m particle size), a Waters Acquity phenyl column (100 2.1 mm; 1.7-——m particle size), a Thermo Scientific Hypersil Gold aQ column (100 2.1 mm; 3-m particle size), and a Phenomenex Synergi Polar-RP column | buffers A (water with 0.1% HAc) and B (acetonitrile with 0.1% HAc) | liquid chromatography-mass spectrometry | 4.97 min | - |
| 6[29] | 721.3→ 296.1 | - | - | Hypurity Advance C18 column (50 mm × 4.6 mm, 5 µm; Thermo Scientific Corporations) | 85:15 (v/v) mixture of methanol and 5mM ammonium acetate | MDS Sciex API-3000 mass spectrometer (Foster City, CA, USA) | 2 min | 0.8 min |
| 7[30] | 721.3204 | 320 ◦C | 3.2 kV | Thermo Hypersil GOLD C18 (2.1 mm × 100 mm, 3 µm, Thermo, USA) | 0.1 % formic acid-water and methanol | Q-Exactive™ Orbitrap™ mass spectrometer (Thermo Fisher, USA) | | 3.83 min |
| 8[31] | 727.330 → 274.100 | 300°C, 350°C | - | ZORBAX Eclipse XDB-C8 (4.6 x 150 mm, 5 µm) analytical column | 2 mM ammonium formate (pH 4.5) and organic mixture (10% methanol in acetonitrile) (25:75) | TSQ Quantum Ultra (USA) triple quadrupole mass spectrometer | 4.3 min | - |
| 9[32] | 721.3/296.1 | 320°C | 4500 V | (ZORBAX SB-C8, Agilent Poroshell 120 SB-C18, Atlantis T3-C18) | Acetonitrile and 0.1% formic acid in water (52:48, V:V) | Agilent 6460A triplequadrupole mass spectrometer | 3.65 min | 2.62 min |

## CONCLUSION

Ritonavir's multifaceted profile underscores its significance in HIV/AIDS treatment regimens. Its analytical characterization ensures accurate quantification, while its pharmacological actions and pharmaceutical formulations contribute to its efficacy and patient compliance. Further research in formulation technologies and pharmacokinetics continues to refine its therapeutic potential and broaden its clinical applications.

## CONFLICT OF INTEREST

All the authors have no conflict of interest.

## REFERENCES


1. https://en.wikipedia.org/wiki/Ritonavir Last accessed on 16 Dec. 23.
2. https://go.drugbank.com/drugs/DB00503 Last accessed on 16 Dec. 23.
3. https://en.wikipedia.org/wiki/File:Ritonavir_structure.svg Last accessed on 16 Dec. 23.
4. https://en.wikipedia.org/wiki/Ritonavir Last accessed on 16 Dec. 23.
5. https://go.drugbank.com/drugs/DB00503 Last accessed on 16 Dec. 23.
6. https://aksci.com/item_detail.php?cat=E144 Last accessed on 16 Dec. 23.
7. https://go.drugbank.com/drugs/DB00503 Last accessed on 16 Dec. 23.
8. https://pubchem.ncbi.nlm.nih.gov/compound/Ritonavir Last accessed on 16 Dec. 23.
9. https://www.ema.europa.eu/en/documents/scientific-discussion/norvir-epar-scientific-discussion_en.pdf Last accessed on 16 Dec. 23.
10. https://go.drugbank.com/drugs/DB00503 Last accessed on 16 Dec. 23.
11. https://www.ncbi.nlm.nih.gov/books/NBK544312/ Last accessed on 16 Dec. 23.
12. https://www.pediatriconcall.com/drugs/ritonavir/927 Last accessed on 16 Dec. 23.
13. Gurram Sai Venkata Nagendra Abhay Raj1, Sumanta Mondal*, Subhadip Chakraborty1 And Moumita Ghosh1, Development And Validation Of An Innovative Stability Indicating Method Using Uvspectroscopy Techniques For Ritonavir In Bulk Drug And Pharmaceutical Dosage Forms, International Journal Of Life Science And Pharma Research, (November), 2023; 13(6): 154-169.
14. Pallavi Patil*, Sneha Kannapurkar, Shivani Kalokhe, Validated Stability Indicating Assays Of Atazanavir Sulphate And Ritonavir In Bulk Drug And Marketed

Formulation By Uv Spectrophotometry And Hplc, Current Trends In Pharmacy And Pharmaceutical Chemistry, 2019; 1(1): 48-61.
15. Rochele Cassanta Rossi1,2, Patrícia Weimer1*, Josué Guilherme Lisbôa Moura3, Letícia Lenz Sfair3 And Pedro E. Fröehlich, Development And Validation Of A Dissolution Method For Ritonavir Soft Gelatin Capsules Using Uv-Derivative Spectroscopy, Ex@Tas Online, Dez., 2019; 10(2): 83-94.
16. Mohammad Yasir Peerzade, Shakeel Memon, Dr. Kiran Bhise And Ansari Irfan Aamer , Development And Validation Of Uv-Visible Spectrophotometric Method For Estimation Of Ritonavir In Bulk And Formulation, The Pharma Innovation Journal, 2019; 8(4): 30-34.
17. Sathis Kumar Dinakaran1*, Durga Naga Prashanthi Botla1, Anusha Pothula1, Kamala Kassetti1, Harani Avasarala1 And Ravishankar Kakaraparthy2, Spectrophotometric Method Development And Validation For Valacyclovir Hydrochloride Monohydrate And Ritonavir In Bulk And Tablet Dosage Form Using Absorption Ratio Method, Malaysian Journal Of Pharmaceutical Sciences, 2013; 11(2): 21–29.
18. C.D. Trivedi*, R. B. Mardia, B.N. Suhagia And S.P. Chauhan, Development And Validation Of Spectrophotometric Method For The Estimation Of Ritonavir In Tablet Dosage Form, International Journal Of Pharmaceutical Sciences And Research, 2013; 4(12): 4567 4572.
19. Carolina Lupi Dias, Ana Maria Bergold, And Pedro Eduardo Fro¨Ehlich, Uv-Derivative Spectrophotometric Determination Of Ritonavir Capsules And Comparison With Lc Method, Taylor & Francis Group, 2009; 42: 1900–1910.
20. Nourah Zoman Al-Zoman, Hadir Mohamed Maher and Amal Al-Subaie, Simultaneous determination of newly developed antiviral agents in pharmaceutical formulations by HPLC-DAD Chemistry central Journal, 2017; 11: 1.
21. Mohamed S. Imam, Afnan S. Batubara, Mohammed Gamal, Ahmed H. Abdelazim, Ahmed A, Almrasy & Sherif Ramzy, Adjusted green HPLC determination of nirmatrelvir and ritonavir in the new FDA approved co-packaged pharmaceutical dosage using supported computational calculations Scientific reports, 2023; 13: 137.
22. Aman Kapoor, Amar Deep Ankalgi, Upasana Thakur, Vinay Pandit, Mahendra Singh Ashawat, Method Development and Validation for Multicomponent Analysis of Emtricitabine and Ritonavir in bulk drug by RP-HPLC, Journal of Drug Delivery and Therapeutics, 2020; 10(6): 137-144.
23. Adel Ehab Ibrahim, Roshdy E. Saraya, Hanaa Saleh, Magda Elhenawee, Development and validation of eco-friendly micellar-HPLC and HPTLC-densitometry methods for the simultaneous determination of paritaprevir, ritonavir and ombitasvir in pharmaceutical dosage forms, Heliyon, 2019; 5: e01518.
24. Rajasekhar Damaramadugu1,2, Jaswanthkumar Inamadugu1,2, Ravi Kanneti3, Srinivasulu Polagani2 , Venkateswarlu Ponneri1, Simultaneous Determination Of Ritonavir And Lopinavir In Human Plasma After Protein Precipitation And Lc-Ms-Ms, Springer Fachmedien Wiesbaden Gmbh, 23 February, 2010; 71: 815–824.
25. Josefin Koehn, Yue Ding, Jennifer Freeling, Jinghua Duan, Rodney J. Y. Ho, A Simple, Efficient, And Sensitive Method For Simultaneous Detection Of Anti-Hiv Drugs Atazanavir, Ritonavir, And Tenofovir By Use Of Liquid Chromatography-Tandem Mass Spectrometry, Aac.Asm.Org Journal, November, 2015; 59: 6682-6688.
26. G. A. Temghare*, S. S. Shetye And S. S. Joshi, Rapid And Sensitive Method For Quantitative Determination Of Lopinavir And Ritonavir In Human Plasma By Liquid Chromatographytandem Mass Specrtometry, E-Journal Of Chemistry, 2009; 6(1): 223-230.
27. Katharina Habler A, Mathias Brügel A, Daniel Teupser A, Uwe Liebchenb, Christina Scharf B, Ulf Schönermarckc, Michael Vogeser A, Michael Paal A, Simultaneous Quantification Of Seven Repurposed Covid-19 Drugs Remdesivir (Plus Metabolite Gs-441524), Chloroquine, Hydroxychloroquine, Lopinavir, Ritonavir, Favipiravir And Azithromycin By A Two-Dimensional Isotope Dilution Lc–Ms/Ms Method In Human Serum, Journal Of Pharmaceutical And Biomedical Analysis, 24 January, 2021; 1-8.
28. Josefin Koehn, Rodney J. Y. Ho, Novel Liquid Chromatography-Tandem Mass Spectrometry Method For Simultaneous Detection Of Anti-Hiv Drugs Lopinavir, Ritonavir, And Tenofovir In Plasma, Aac.Asm.Org, May, 2014; 58: 2675–2680.
29. Laxminarayana Burugula 1*, Nageswara Rao Pilli 1, Ajitha Makula 1, Durga Srinivas Lodagala 2, Rajnarayana Kandhagatla 3, Simultaneous Determination Of Ritonavir And Atazanavir In Human Plasma By Lc-Ms/Ms And Its Pharmacokinetic Application, Am. J. Pharmtech Res., 2012; 2(4): 558-571.
30. Fenglun Zhao 1, Zheng Xiang 1, Junping Han, Jie Pan, Yuchen Qu, Kai Fan, Zhiqiang Wu, Delai Xu, Yunli Yu, Zhu Shen*, Cunjin Su* Simultaneous Quantification Of Nirmatrelvir/Ritonavir In Human Serum By Lc–Hrms, Journal Of Pharmaceutical And Biomedical Analysis, 11 October, 2023; 237: 1-6.
31. Pahweenvaj Ratnatilaka Na Bhuket1, Polsak Teerawonganan1, Ekawan Yoosakul1, Wiwat Supasena1, Chotika Watananikorn1, Bancha Chuasuwan1, Piengthong Narakorn1, Isariya Techatanawat1,*, Punnee Pitisuttithum2, Validation Of Liquid Chromatography– Tandem Mass Spectrometric Method For Simultaneous Determination Of Lopinavir And Ritonavir In Human Plasma, And Its Application In A

Bioequivalence Study In Thai Volunteers, J Health Res, December, 2015; 29: 417-424.
32. Xiujing Zhu1,2#, Lin Li3#, Bin Dai3#, Zhijun Liu1,2, Zhipeng Wang1, Lili Cui1, Shouhong Gao 1,2*, Wansheng Chen1*, Xia Tao 1,2*, Deduo Xu 1*, A Simple And Rapid Lc-Ms/Ms Method For The Quantification Of Nirmatrelvir/Ritonavir In Plasma Of Patients With Covid-19.