



Research Article

Development and Evaluation of Ritonavir Co-Crystal for Improved Solubility and Dissolution Profile

Rahul Kumar Soni, Mohan Lal Kori

Faculty of Pharmaceutical Science, Ram KrishnaDharmarth Foundation University, Gandhi Nagar, Bhopal, M.P.

ABSTRACT

Ritonavir is a highly lipophilic antiretroviral drug whose poor aqueous solubility can limit its dissolution and oral drug delivery performance. The present study was designed to develop ritonavir–tartaric acid pharmaceutical cocrystals as a solid-state approach for improving the aqueous solubility and dissolution behavior of ritonavir. Tartaric acid was selected as a hydrophilic coformer, and cocrystals were prepared using co-grinding, solvent evaporation, and liquid-assisted grinding techniques at ritonavir:tartaric acid molar ratios of 1:1, 1:2, and 1:3. The prepared cocrystals were evaluated for saturation solubility, drug content, Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM). The optimized cocrystal system was subsequently incorporated into tablet formulations and evaluated for pre-compression and post-compression characteristics and in-vitro drug release. The saturation solubility study demonstrated a concentration-dependent improvement in ritonavir solubility. Among the tartaric acid cocrystals, RCTS3 prepared by solvent evaporation at a 1:3 molar ratio exhibited the highest solubility of 6.12 mg/mL, compared with 3.02 mg/mL for RCTG1 prepared by co-grinding at a 1:1 ratio. The drug content of the prepared cocrystals ranged from 94.86% to 98.65%, indicating satisfactory drug incorporation. FTIR and thermal studies demonstrated changes in the molecular environment of ritonavir after cocrystallization, supporting intermolecular interactions between ritonavir and tartaric acid. The prepared tablet blends exhibited acceptable flow and compression characteristics. Among the ritonavir–tartaric acid tablet formulations, RCTG3T exhibited the highest cumulative drug release of 99.70% at 12 h, followed by RCTG2T (97.70%) and RCTG1T (96.60%). The study demonstrated that cocrystallization with tartaric acid is a promising strategy for enhancing the solubility and dissolution performance of ritonavir, while maintaining satisfactory pharmaceutical processing characteristics.

Keywords: Ritonavir; Tartaric acid; Pharmaceutical cocrystal; Solubility enhancement; Dissolution; Solvent evaporation; Co-grinding; Solid-state characterization; Sustained release.

ARTICLE INFO: Received 22 June 2026; Review Complete 16 July 2026; Accepted 26 August 2026; Available online 15 Oct. 2026



Cite this article as:

Soni RK, Kori ML, Development and Evaluation of Ritonavir Co-Crystal for Improved Solubility and Dissolution Profile, Asian Journal of Pharmaceutical Research and Development. 2026; 14(5): 37-43 DOI: <http://dx.doi.org/10.22270/ajprd.v14i5.1868>

*Address for Correspondence:

Prof. (Dr.) Mohan Lal Kori, Faculty of Pharmaceutical Science, Ram Krishna Dharmarth Foundation University, Gandhi Nagar, Bhopal, M.P.

INTRODUCTION:

Ritonavir is a potent antiretroviral drug belonging to the protease inhibitor class and has been widely used in the management of human immunodeficiency virus infection. In addition to its antiviral activity, ritonavir has an important role as a pharmacokinetic enhancer because of its ability to inhibit cytochrome P450 3A-mediated metabolism. Despite its pharmacological importance, the physicochemical properties of ritonavir present challenges for the development of efficient oral dosage forms [1].

One of the major factors influencing the oral bioavailability of a drug is its aqueous solubility. Poorly water-soluble drugs frequently exhibit dissolution-limited absorption, resulting in variable and sometimes inadequate systemic

exposure. Ritonavir is highly lipophilic and possesses poor aqueous solubility, making improvement of its dissolution characteristics an important formulation objective. Conventional approaches such as particle-size reduction, salt formation, solid dispersions, surfactant-based systems, and lipid formulations can improve drug dissolution; however, these approaches may be associated with limitations related to physical stability, manufacturing complexity, or formulation compatibility [2].

Pharmaceutical cocrystallization has emerged as an attractive solid-state strategy for modifying the physicochemical properties of active pharmaceutical ingredients without altering their covalent molecular structure. A pharmaceutical cocrystal consists of an active pharmaceutical ingredient and one or more suitable

coformers arranged within a common crystalline lattice through non-covalent interactions such as hydrogen bonding, π - π interactions, and van der Waals forces. The resulting crystal may exhibit physicochemical properties that differ substantially from those of the individual components.

The selection of an appropriate coformer is a critical step in cocrystal development. Tartaric acid is a multifunctional organic acid containing hydroxyl and carboxylic acid groups capable of participating in intermolecular hydrogen bonding. Its hydrophilic nature makes it an attractive candidate for modifying the aqueous dissolution behavior of poorly soluble drugs. Interaction between ritonavir and tartaric acid may alter the crystal packing, molecular interactions, wettability, and apparent solubility of ritonavir [3].

Different preparation methods can produce cocrystals with different physicochemical characteristics. Co-grinding is a simple and solvent-minimized technique in which mechanical energy facilitates molecular interaction between the drug and coformer. Liquid-assisted grinding involves the addition of a small quantity of solvent during grinding and can improve molecular mobility and cocrystal formation. Solvent evaporation involves dissolving the drug and coformer in a suitable solvent system followed by controlled evaporation, allowing formation of a new crystalline phase [4].

The present study was therefore undertaken to design and develop ritonavir-tartaric acid cocrystals using different cocrystallization techniques and drug:coformer molar ratios. The prepared systems were investigated for their ability to enhance the aqueous solubility of ritonavir. The optimized cocrystal was further incorporated into tablet formulations and evaluated for pharmaceutical quality and in-vitro drug release [5].

Materials and Methods

Materials: Ritonavir was used as the active pharmaceutical ingredient and tartaric acid was selected as the coformer. Pharmaceutical excipients required for preparation of tablet formulations were selected according to their functional characteristics and compatibility with the cocrystal system. Analytical-grade solvents and reagents were used throughout the study.

Preformulation characterization of ritonavir: Prior to cocrystal development, ritonavir was subjected to preformulation characterization. Organoleptic characteristics, density, particle size, flow properties, pH-dependent solubility, partition coefficient, melting point, and FTIR spectroscopy were evaluated [6-7].

Organoleptic properties: Ritonavir was examined for color, odor, and taste. The drug was observed as a yellowish cream-colored powder with characteristic odor and slightly bitter taste.

Density: Bulk and tapped densities were determined using a tapped-density apparatus. The bulk density of ritonavir was found to be 0.762 g/cm³, while the tapped density was 0.798 g/cm³.

Particle size: The mean particle size of the untreated ritonavir powder was found to be approximately 104 μ m.

Flow properties: Flow characteristics were evaluated using Carr's compressibility index, Hausner's ratio, and angle of repose. Ritonavir exhibited a Carr's index of $11.03 \pm 0.011\%$, Hausner's ratio of 1.11 ± 0.102 , and angle of repose of $28.2 \pm 0.103^\circ$, indicating satisfactory flow properties.

Solubility study: The solubility of ritonavir was determined in different aqueous media. The drug demonstrated solubility of 1.021 ± 0.101 mg/mL in water, 1.131 ± 0.124 mg/mL in 0.1 N HCl, 0.123 ± 0.113 mg/mL in phosphate buffer pH 4.5, and 2.103 ± 0.116 mg/mL in phosphate buffer pH 6.8.

Partition coefficient: The partition coefficient of ritonavir was found to be approximately 5.6 ± 0.012 , confirming its highly lipophilic character.

Melting point: The melting point of ritonavir was determined by the capillary tube method and was found to be $115 \pm 0.102^\circ\text{C}$.

Preparation of Ritonavir-Tartaric Acid Cocrystals: Ritonavir-tartaric acid cocrystals were prepared using three different cocrystallization techniques: co-grinding, solvent evaporation, and liquid-assisted grinding. Ritonavir and tartaric acid were combined at 1:1, 1:2, and 1:3 molar ratios. The formulations prepared by co-grinding were coded RCTG1, RCTG2, and RCTG3 for 1:1, 1:2, and 1:3 molar ratios, respectively. The solvent evaporation formulations were coded RCTS1, RCTS2, and RCTS3, while the liquid-assisted grinding formulations were designated RCTL1, RCTL2, and RCTL3 [8-9]. The prepared products were collected, dried appropriately, and stored in tightly closed containers until further characterization.

Characterization of Ritonavir-Tartaric Acid Cocrystals

Saturation solubility: Saturation solubility was determined in 0.1 N HCl (pH 1.2) at 37°C after 24 h equilibration. The samples were filtered and the amount of ritonavir dissolved was quantified using an appropriate UV spectrophotometric method [10].

Drug content: Drug content was determined to evaluate the amount and uniformity of ritonavir incorporated within the prepared cocrystals. All formulations were analyzed using the validated analytical procedure [11].

FTIR spectroscopy: FTIR spectroscopy was performed to investigate possible intermolecular interactions between ritonavir and tartaric acid. The spectra of pure ritonavir, pure tartaric acid, and selected cocrystal formulations were compared with respect to characteristic functional-group absorption bands.

Powder X-ray diffraction: PXRD analysis was performed to compare the crystalline characteristics of pure ritonavir with those of the prepared cocrystals. Changes in the intensity and position of characteristic diffraction peaks were used to assess modification of the crystal lattice [12-13].

Scanning electron microscopy: SEM was used to investigate the surface morphology and particle characteristics of pure ritonavir and the prepared cocrystals.

Development and Evaluation of Ritonavir–Tartaric Acid Cocrystal Tablets: The selected ritonavir–tartaric acid cocrystals were incorporated into tablet formulations. The powder blends were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose before compression. The compressed tablets were subsequently evaluated for weight variation, thickness, diameter, hardness, friability, drug content, and in-vitro drug release [14-15].

Results and Discussion

Preformulation characterization of ritonavir: The preformulation study confirmed the physicochemical characteristics of ritonavir relevant to cocrystal development. Ritonavir was obtained as a yellowish cream-colored powder with characteristic odor and slightly bitter taste. The bulk and tapped density values were 0.762 and 0.798 g/cm³, respectively. The mean particle size was 104 µm. The Carr's index of 11.03 ± 0.011%, Hausner's ratio of 1.11 ± 0.102, and angle of repose of 28.2 ± 0.103° indicated satisfactory flow characteristics of the untreated drug. These characteristics were favorable for subsequent processing and formulation development. The solubility study demonstrated pronounced pH-dependent behavior. The highest solubility was observed in phosphate buffer pH 6.8 (2.103 ± 0.116 mg/mL), whereas the lowest solubility was observed in phosphate buffer pH 4.5 (0.123 ± 0.113 mg/mL). The partition coefficient of approximately 5.6 confirmed the highly lipophilic nature of ritonavir. The poor aqueous solubility combined with high lipophilicity justified the selection of cocrystallization as a strategy for modifying the solid-state and dissolution properties of the drug.

Saturation solubility of ritonavir–tartaric acid cocrystals: The saturation solubility results demonstrated a substantial improvement in ritonavir solubility following cocrystal formation. The magnitude of enhancement depended on both the preparation method and ritonavir: tartaric acid molar ratio. Among the co-ground formulations, RCTG1, RCTG2, and RCTG3 exhibited

solubilities of 3.02, 3.87, and 4.02 mg/mL, respectively. Thus, increasing the tartaric acid ratio from 1:1 to 1:3 progressively improved the apparent solubility. The solvent evaporation method produced greater enhancement. RCTS1 showed a solubility of 5.01 mg/mL, while RCTS2 and RCTS3 demonstrated values of 5.97 and 6.12 mg/mL, respectively. RCTS3, containing ritonavir and tartaric acid at a 1:3 molar ratio, exhibited the highest solubility among the investigated tartaric acid cocrystals. The liquid-assisted grinding formulations showed solubilities of 4.02, 4.74, and 5.08 mg/mL for RCTL1, RCTL2, and RCTL3, respectively. The overall improvement may be attributed to modification of the crystal lattice, increased wettability, and formation of intermolecular interactions between ritonavir and tartaric acid. The solvent evaporation process may have facilitated more effective molecular association between the drug and coformer, resulting in a more favorable cocrystalline structure.

The order of solubility according to preparation technique was:

Solvent evaporation > Liquid-assisted grinding > Co-grinding

The results further indicated that increasing the tartaric acid ratio from 1:1 to 1:3 generally increased the solubility of the resulting cocrystals.

Drug content of ritonavir–tartaric acid cocrystals: The drug-content analysis showed satisfactory incorporation of ritonavir into the cocrystal systems. The drug content of the co-ground formulations ranged from 95.23% to 96.24%. The solvent evaporation formulations showed values ranging from 94.86% to 97.02%, while the liquid-assisted grinding formulations exhibited drug content between 97.52% and 98.65%.

The results indicate that the cocrystallization process produced formulations with acceptable drug content and relatively low variation. Among the liquid-assisted grinding formulations, RCTL2 showed the highest drug content of 98.65%.

Table 1: Saturation solubility of ritonavir–tartaric acid cocrystals

Formulation	Ratio	Method	Solubility (mg/mL)	Drug content (%)
RCTG1	1:1	Co-grinding	3.02	95.23
RCTG2	1:2	Co-grinding	3.87	96.04
RCTG3	1:3	Co-grinding	4.02	96.24
RCTS1	1:1	Solvent evaporation	5.01	97.02
RCTS2	1:2	Solvent evaporation	5.97	94.86
RCTS3	1:3	Solvent evaporation	6.12	95.21
RCTL1	1:1	Liquid-assisted grinding	4.02	97.52
RCTL2	1:2	Liquid-assisted grinding	4.74	98.65
RCTL3	1:3	Liquid-assisted grinding	5.08	97.65

FTIR characterization: FTIR spectroscopy was employed to investigate the molecular interactions responsible for cocrystal formation. Pure ritonavir exhibited characteristic absorption bands associated with its major functional groups, including amide, carbonyl, N–H, aromatic, and other characteristic vibrations. Following cocrystallization

with tartaric acid, changes in the position, intensity, and shape of characteristic absorption bands were observed. Such modifications suggest a change in the molecular environment of the functional groups participating in intermolecular interactions. The presence of hydroxyl and carboxylic acid groups in tartaric acid provides suitable

hydrogen-bonding sites for interaction with functional groups of ritonavir. The observed spectral modifications therefore support the formation of intermolecular hydrogen bonds between ritonavir and tartaric acid. Importantly, the absence of evidence for new covalent functional groups

suggests that the interaction was predominantly supramolecular rather than the result of chemical degradation or covalent reaction. These findings support the formation of a pharmaceutical cocrystal through non-covalent molecular interactions.

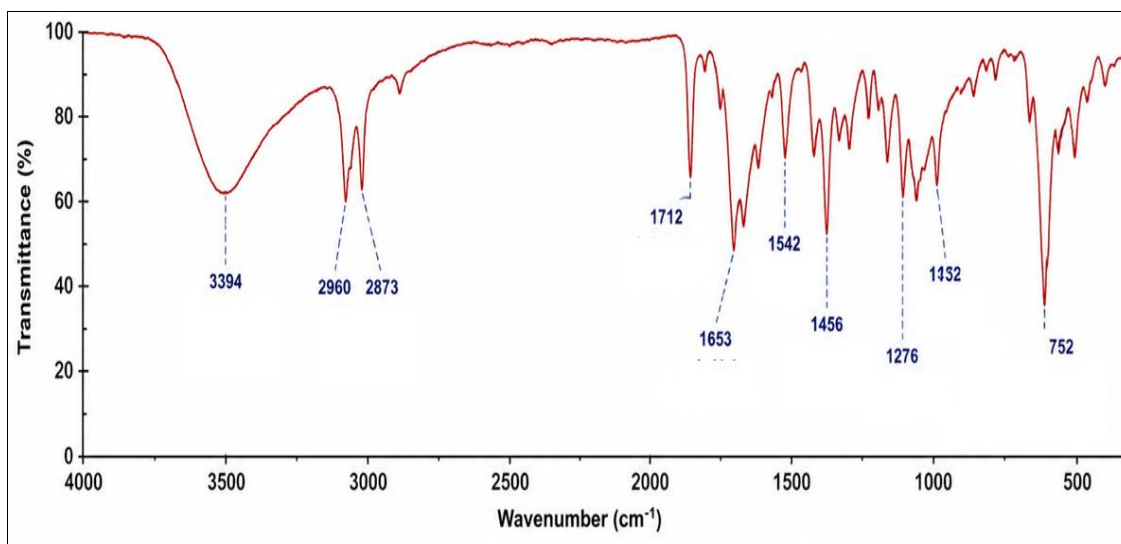


Figure 1: FTIR spectrum of ritonavir cocrystal with tartaric acid conformer

Powder X-ray diffraction analysis: PXRD analysis was used to compare the crystalline structure of pure ritonavir with the prepared cocrystals. Pure ritonavir exhibited characteristic sharp diffraction peaks corresponding to its crystalline structure.

The cocrystal formulation demonstrated changes in diffraction peak intensities and/or positions compared with

the parent drug. Such changes are indicative of modification of the crystal lattice and formation of a different solid-state structure.

The PXRD findings, when considered together with FTIR and DSC observations, support the formation of a new crystalline phase rather than a simple physical mixture of ritonavir and tartaric acid.

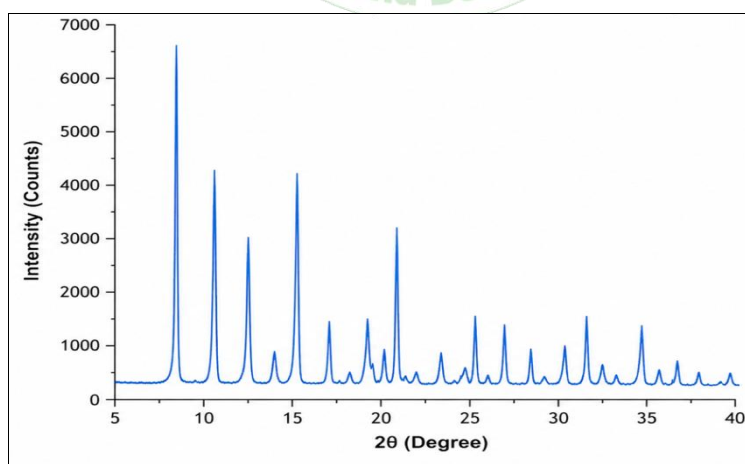


Figure 2: X-ray diffraction pattern of ritonavir cocrystal

Scanning electron microscopy: SEM examination demonstrated differences in the morphology of the cocrystal material compared with the parent drug. Pure ritonavir exhibited its characteristic crystalline morphology, whereas the prepared cocrystal showed

altered particle shape and surface characteristics. The morphological transformation can be attributed to the crystallization process and the formation of a new crystal lattice. Such changes may also contribute to improved wettability and dissolution performance of the cocrystal.

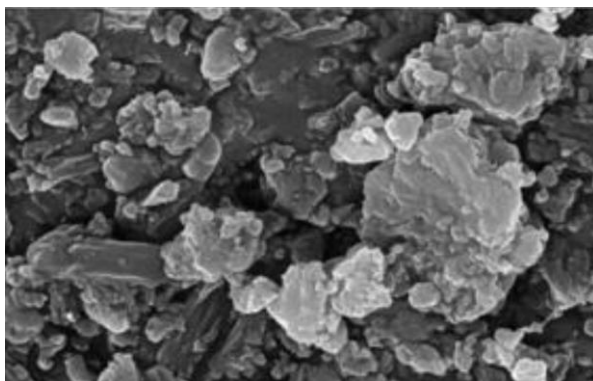


Figure 3: SEM images of RCRS3; ritonavir cocrystal with resorcinol conformer with Solvent evaporation method

Evaluation of Ritonavir–Tartaric Acid Cocrystal Tablets

Pre-compression characteristics: The pre-compression properties of the ritonavir–tartaric acid cocrystal tablet blends were evaluated using bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. For the tartaric acid formulations, bulk density values ranged approximately from 0.298 to 0.358 g/cm³, while tapped density values ranged from 0.321 to 0.473 g/cm³. Carr's

index values were generally within the range indicating fair to good flow characteristics. Hausner's ratio values ranged from approximately 1.19 to 1.58. The angle of repose values were generally below 30°, indicating acceptable flowability of the prepared blends. RCTS3T showed an angle of repose of 21.14°, demonstrating particularly favorable flow behavior. Overall, the pre-compression data indicated that the cocrystal-containing blends possessed adequate flow and packing properties for tablet compression.

Table 2: Pre-compression characterization of ritonavir tartaric acid cocrystal tablet

Formulation code	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's index (%)	Hausner's Ratio	Angle of Repose (°)
RCTG1T	0.299	0.473	22.78	1.58	22.62
RCTG2T	0.315	0.417	21.25	1.26	25.75
RCTG3T	0.335	0.423	20.81	1.26	26.13
RCTS1T	0.332	0.401	20.11	1.21	23.18
RCTS2T	0.312	0.415	20.04	1.25	22.05
RCTS3T	0.308	0.411	21.11	1.34	21.14
RCTL1Y	0.298	0.321	21.45	1.25	21.34
RCTL2T	0.308	0.337	23.14	1.19	21.24
RCTL3T	0.317	0.346	22.98	1.24	21.43

Post-compression Evaluation

Weight variation: The prepared tablets demonstrated satisfactory weight uniformity. The average weights of the ritonavir–tartaric acid cocrystal tablets ranged from 487.11 ± 0.04 mg to 508.14 ± 0.04 mg depending on the formulation and preparation technique. The relatively low standard deviations indicated consistent die filling and reproducible tablet compression. The satisfactory weight variation further demonstrated the suitability of the powder blends for tablet manufacturing.

Thickness and diameter: The thickness of the ritonavir–tartaric acid tablets ranged from approximately 2.51 to 2.59 mm, while tablet diameter ranged from 7.8 to 8.2 mm. The low variation in tablet dimensions indicated uniform compression and consistent tablet formation.

Hardness: The hardness values of the ritonavir–tartaric acid cocrystal tablets were within the acceptable range for conventional compressed tablets. The formulations exhibited sufficient mechanical strength to withstand handling, packaging, and transportation. The low variation in hardness among batches indicated good reproducibility of the compression process.

Friability: The friability values of the prepared ritonavir–tartaric acid cocrystal tablets were below 1%. Values ranged approximately from 0.75% to 0.83% for the tartaric acid formulations. The results demonstrated adequate resistance to mechanical abrasion. The acceptable friability may be attributed to effective interparticulate bonding and suitable compression characteristics of the cocrystal-containing blends.

Drug content: The ritonavir–tartaric acid tablets demonstrated satisfactory drug content. For the tartaric acid formulations, drug content values ranged from 96.16 ± 1.44% to 99.34 ± 1.11%. The relatively narrow variation in drug content indicated uniform distribution of the cocrystal within the tablet matrix and reproducible manufacturing.

In-vitro Drug Release Study: The in-vitro drug release profiles of the ritonavir–tartaric acid cocrystal tablets were evaluated for 12 h. All formulations demonstrated a gradual increase in cumulative drug release throughout the dissolution period. Among the co-ground formulations, RCTG1T, RCTG2T, and RCTG3T showed cumulative drug releases of 96.60%, 97.70%, and 99.70%, respectively, at 12 h. The progressive increase in drug release with increasing tartaric acid ratio suggests a

favorable effect of cocrystal composition on dissolution behavior. The solvent evaporation formulations RCTS1T, RCTS2T, and RCTS3T exhibited 12-h drug release values of 89.65%, 91.23%, and 95.37%, respectively. The release increased with increasing coformer ratio. The liquid-assisted grinding formulations RCTL1T, RCTL2T, and RCTL3T demonstrated 12-h releases of 87.23%, 91.87%, and 98.09%, respectively. Among all investigated formulations, RCTG3T exhibited the highest cumulative drug release of 99.70% at 12 h, followed by RCTL3T (98.09%) and RCTG2T (97.70%). The improved dissolution behavior can be attributed to the enhanced solubility of the ritonavir–tartaric acid cocrystal, altered crystal packing, improved wetting of the drug particles, and increased interaction between the cocrystal surface and dissolution medium.

The order of drug release at 12 h was:

RCTG3T > RCTL3T > RCTG2T > RCTG1T > RCTS3T > RCTL2T > RCTS2T > RCTS1T > RCTL1T

Therefore, RCTG3T was identified as the best-performing formulation on the basis of cumulative drug release.

Drug Release Kinetics: The dissolution data were subjected to different mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The zero-order model was used to investigate the release of a constant amount of drug per unit time, whereas the first-order model evaluated release as a function of the remaining drug concentration. The Higuchi model was applied to investigate diffusion-controlled release from the matrix. The Korsmeyer–Peppas model was used to assess the mechanism of drug release based on the release exponent. The comparative model fitting indicated that the ritonavir–tartaric acid cocrystal tablets exhibited controlled release behavior involving diffusion and/or matrix-related drug transport. The exact dominant model should be assigned according to the experimentally obtained regression coefficients (R^2) for each formulation.

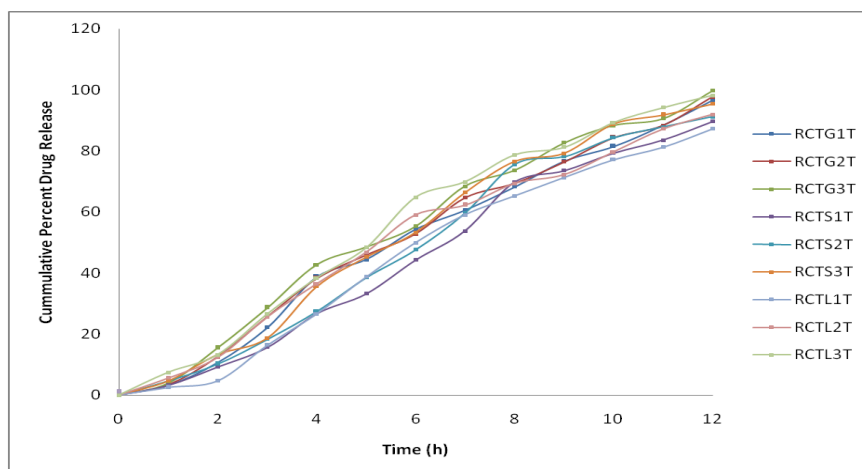


Figure 4: Zero-order release of ritonavir tartaric acid cocrystal tablet

DISCUSSION:

The present investigation demonstrated the potential of pharmaceutical cocrystallization to improve the physicochemical and dissolution characteristics of ritonavir. The initial preformulation studies confirmed that ritonavir possessed high lipophilicity and limited aqueous solubility, supporting the need for a solubility-enhancement strategy. Tartaric acid was selected as the coformer because of its hydrophilic nature and ability to participate in hydrogen bonding. Cocrystallization resulted in a considerable increase in the saturation solubility of ritonavir. The maximum solubility among the tartaric acid systems was obtained with RCTS3, prepared by solvent evaporation at a 1:3 ritonavir:tartaric acid ratio, with a solubility of 6.12 mg/mL. Compared with the untreated ritonavir solubility in water of approximately 1.02 mg/mL, the RCTS3 system represented an approximately six-fold increase in apparent solubility. This improvement indicates that modification of the solid-state structure through cocrystallization can substantially alter the aqueous behavior of the drug. The preparation method also had a significant influence on solubility. Solvent evaporation produced greater solubility enhancement than liquid-

assisted grinding and co-grinding in the saturation-solubility study. This may be associated with improved molecular mixing and crystal growth during controlled solvent removal. Interestingly, the formulation exhibiting the highest saturation solubility, RCTS3, was not the formulation exhibiting the highest 12-h drug release. RCTG3T demonstrated the highest cumulative drug release of 99.70%. This observation highlights the fact that tablet dissolution is influenced not only by intrinsic cocrystal solubility but also by tablet composition, porosity, compression characteristics, wetting, and matrix structure. The solid-state characterization results further supported the formation of a modified crystalline phase. FTIR changes suggested intermolecular interactions, while DSC and PXRD demonstrated changes in the thermal and crystalline behavior of the drug following cocrystallization. SEM further indicated morphological modification of the crystalline material. The tablet evaluation showed satisfactory pharmaceutical properties, including acceptable weight uniformity, dimensions, hardness, friability, and drug content. Thus, the improved dissolution characteristics were achieved without compromising the basic quality attributes required for tablet manufacture. Overall, the findings demonstrate that ritonavir–tartaric acid

cocrystallization represents a promising approach for modifying the physicochemical behavior of ritonavir and improving its dissolution performance.

CONCLUSION:

The present study successfully demonstrated the development of ritonavir–tartaric acid pharmaceutical cocrystals as a strategy for enhancement of solubility and dissolution. Ritonavir exhibited poor aqueous solubility and high lipophilicity, making it a suitable candidate for solid-state modification. Cocrystals prepared using co-grinding, solvent evaporation, and liquid-assisted grinding showed improved solubility compared with the parent drug. Among the investigated systems, RCTS3 prepared by solvent evaporation at a 1:3 ritonavir:tartaric acid molar ratio exhibited the highest saturation solubility of 6.12 mg/mL. The FTIR, DSC, PXRD, and SEM findings collectively supported the formation of a modified crystalline phase and the presence of intermolecular interactions between ritonavir and tartaric acid. The resulting cocrystals were successfully incorporated into tablet formulations with satisfactory pre-compression and post-compression properties. Among the prepared tablet formulations, RCTG3T exhibited the highest cumulative drug release of 99.70% after 12 h, followed by RCTL3T (98.09%) and RCTG2T (97.70%). The results demonstrate that cocrystallization with tartaric acid can substantially improve the dissolution performance of ritonavir while maintaining acceptable tablet quality. Therefore, ritonavir–tartaric acid cocrystallization may be considered a promising formulation strategy for overcoming the solubility and dissolution limitations of ritonavir and warrants further investigation with respect to solid-state stability, scale-up, biopharmaceutical performance, and in-vivo evaluation.

REFERENCES

- Kempf DJ, Marsh KC, Denissen JF, McDonald E, Vasavanonda S, Flentge CA, et al. ABT-538 is a potent inhibitor of the human immunodeficiency virus protease and has favorable pharmacokinetic properties. *Antimicrob Agents Chemother.* 1995;39(1):24-30.
- Flexner C. HIV-protease inhibitors. *N Engl J Med.* 1998;338(18):1281-1292.
- Koudriakova T, Iatsimirskaia E, Utkin I, Gangl E, Vouros P, Storozov M, et al. Metabolism of the human immunodeficiency virus protease inhibitor ritonavir by human liver microsomes and identification of the major metabolites. *Drug Metab Dispos.* 1999;27(11):1369-1379.
- Gupta E, Barza M, O'Brien P, Chan M, Spector SA, Fennelly G, et al. Pharmacokinetic interactions between protease inhibitors and other anti-HIV drugs. *Clin Pharmacokinet.* 1999;37(4):289-298.
- Dressman JB, Reppas C. In vitro-in vivo correlations for lipophilic, poorly water-soluble drugs. *Eur J Pharm Sci.* 2000;11 Suppl 2:S73-S80.
- Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Adv Drug Deliv Rev.* 2007;59(7):617-630.
- Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. *Cryst Growth Des.* 2009;9(6):2950-2967.
- Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: an overview. *Int J Pharm.* 2011;419(1-2):1-11.
- Gadade DD, Pekamwar SS. Pharmaceutical cocrystals: regulatory and strategic aspects, design and development. *Adv Pharm Bull.* 2016;6(4):479-494.
- Anand R, Kumar A, Nanda A. Pharmaceutical co-crystals—design, development and applications. *Drug Deliv Lett.* 2020;10(3):169-184.
- Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: a review of preparations, physicochemical properties and applications. *Acta Pharm Sin B.* 2021;11(8):2537-2564. doi:10.1016/j.apsb.2021.03.030.
- Kumar A, Nanda A. In-silico methods of cocrystal screening: a review on tools for rational design of pharmaceutical cocrystals. *J Drug Deliv Sci Technol.* 2021;63:102527. doi:10.1016/j.jddst.2021.102527.
- Pantwalawalkar J, Kale N, Nangare S, Patil S, Pawar S, Jadhav N. Pharmaceutical cocrystals: unlocking the potential of challenging drug candidates. *J Drug Deliv Sci Technol.* 2024;95:106572. doi:10.1016/j.jddst.2024.106572.
- Yadav V, Kumar R, Sharma M, Dhir A, Bhardwaj VK. Pharmaceutical cocrystals: an overview of synthesis, characterization, and applications. *J Mol Struct.* 2026;1349:143682. doi:10.1016/j.molstruc.2025.143682.
- Aakerøy CB, Salmon DJ. Building co-crystals with molecular sense and supramolecular sensibility. *CrystEngComm.* 2005;7:439-448.