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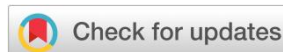
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Research Article

Formulation of Co-crystals of Lopinavir using Co-former to Enhance Solubility and Bioavailability

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Abstract

The poor aqueous solubility and limited oral bioavailability of many antiviral drugs, particularly lopinavir, present major challenges to effective oral drug delivery. Lopinavir exhibits low solubility, poor intestinal permeability, and variable absorption, resulting in reduced therapeutic efficacy. The present study aimed to develop and evaluate pharmaceutical cocrystals of lopinavir using pharmaceutically acceptable coformers to enhance its physicochemical and biopharmaceutical properties without altering its pharmacological activity. Cocrystals were prepared using crystal engineering techniques, including solvent evaporation, slurry conversion, and solvent-assisted grinding. The prepared formulations were characterized by Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM), to confirm cocrystal formation and investigate structural modifications. Solubility, dissolution, and stability studies were conducted to compare the optimized cocrystals with pure lopinavir. The results demonstrated a marked improvement in aqueous solubility and dissolution rate, attributed to the formation of a modified crystal lattice and intermolecular hydrogen-bonding interactions between lopinavir and the selected coformer. The optimized cocrystals also exhibited satisfactory physicochemical stability while maintaining the therapeutic integrity of the drug. These findings suggest that pharmaceutical cocrystal engineering is a promising, scalable, and regulatory-acceptable approach for enhancing the oral bioavailability and therapeutic performance of poorly soluble antiviral drugs such as lopinavir. Improved dissolution characteristics may contribute to reduced dose variability, enhanced patient compliance, and better clinical outcomes.

Keywords: Pharmaceutical cocrystals; Antiviral drugs; Solubility enhancement; Bioavailability; Coformers; Dissolution rate; Drug delivery; Crystal lattice modification.

INTRODUCTION:

The development of pharmaceutical dosage forms with enhanced therapeutic performance remains a major focus of modern pharmaceutical research. Despite significant advances in drug discovery and medicinal chemistry, the clinical effectiveness of many newly developed drug molecules is often limited by poor aqueous solubility ¹. It is estimated that approximately 40–70% of newly discovered drug candidates and nearly 90% of compounds identified through high-throughput screening exhibit poor water solubility and are classified under the Biopharmaceutics Classification System (BCS) Class II or IV. These drugs exhibit dissolution-rate-limited absorption, leading to poor oral bioavailability, variable therapeutic response, and reduced clinical efficacy. Consequently, improving the solubility and dissolution characteristics of poorly water-soluble drugs has become a critical objective in pharmaceutical formulation development. Oral drug delivery remains the most preferred route of administration because of its convenience, patient compliance, cost-effectiveness, and ease of manufacturing ². However, successful oral absorption

depends on the dissolution of the drug in gastrointestinal fluids before permeation across the intestinal membrane. According to the Noyes–Whitney equation, the dissolution rate is directly proportional to the surface area of the drug particles and the concentration gradient between the drug surface and dissolution medium. Drugs with poor aqueous solubility dissolve slowly, resulting in inadequate absorption, low bioavailability, inconsistent plasma drug concentrations, and considerable interpatient variability. In many cases, higher doses are required to achieve therapeutic efficacy, increasing the risk of adverse effects and reducing patient compliance. Crystal engineering has emerged as an important multidisciplinary field that focuses on the rational design of crystalline materials by manipulating intermolecular interactions such as hydrogen bonding ³, van der Waals forces, π - π interactions, and electrostatic forces. Within pharmaceutical sciences, crystal engineering has gained considerable attention because it enables modification of drug properties while preserving molecular identity and pharmacological activity. Among crystal engineering approaches, pharmaceutical

cocrystallization has become one of the most promising techniques for enhancing the pharmaceutical performance of poorly soluble drugs. Pharmaceutical cocrystals are crystalline solids composed of an API and one or more pharmaceutically acceptable neutral coformers in a definite stoichiometric ratio ⁴. These components are held together through non-covalent intermolecular interactions, predominantly hydrogen bonding, without complete proton transfer as observed in pharmaceutical salts. Consequently, cocrystals retain the chemical identity of the parent drug while significantly improving important physicochemical properties. Numerous studies have demonstrated that cocrystals can enhance aqueous solubility, dissolution rate, oral bioavailability, mechanical strength, compressibility, flowability, thermal stability, hygroscopicity, and chemical stability. Furthermore, cocrystal technology provides opportunities for intellectual property protection because novel cocrystal forms may be patented independently, thereby extending product life cycles and promoting pharmaceutical innovation ⁵. Pharmaceutical cocrystallization provides an effective solution to these challenges by modifying crystal packing and intermolecular interactions without altering the molecular structure of the drug. The incorporation of suitable coformers into the crystal lattice disrupts strong intermolecular forces within the parent crystal, resulting in improved wettability, higher saturation solubility, faster dissolution, and enhanced oral bioavailability. The selection of an appropriate coformer is critical for successful cocrystal formation. Generally, coformers are selected from compounds recognized as safe for pharmaceutical use, including substances classified as Generally Recognized as Safe (GRAS). Frequently used coformers include nicotinamide, saccharin, caffeine, succinic acid, fumaric acid, citric acid, tartaric acid, malic acid, benzoic acid, urea, and amino acids, all of which possess functional groups capable of forming predictable hydrogen-bonding networks with drug molecules ⁶.

Antiviral drugs play a crucial role in controlling viral replication, reducing disease progression, and improving patient survival. However, many clinically important antiviral agents, including acyclovir, ritonavir, efavirenz, darunavir, lopinavir, fampiravir, remdesivir, atazanavir, and telaprevir, exhibit poor aqueous solubility and limited oral bioavailability ⁷. Their highly crystalline structures and hydrophobic characteristics contribute to slow dissolution and incomplete gastrointestinal absorption. As a result, these drugs often require high doses or prolonged treatment regimens, increasing the risk of adverse effects, poor patient adherence, treatment failure, and the development of antiviral resistance. Improving the solubility and dissolution behavior of antiviral drugs is therefore essential for enhancing therapeutic efficacy and optimizing clinical outcomes ⁸. The pharmaceutical cocrystallization represents an innovative and effective crystal engineering strategy for overcoming poor aqueous solubility and limited oral bioavailability of antiviral drugs. By enhancing dissolution, stability,

manufacturability, and therapeutic performance while preserving the molecular structure of the API, cocrystals offer considerable potential for the development of next-generation antiviral formulations with improved efficacy, safety, and patient compliance. Lopinavir is an important protease inhibitor used in combination antiretroviral therapy for HIV infection. Co-administration with ritonavir improves its bioavailability and therapeutic effectiveness. Despite gastrointestinal and metabolic side effects, lopinavir remains useful in HIV management when used under appropriate clinical monitoring ⁹. The present study aims to develop, optimize, and evaluate cocrystals of lopinavir to improve their aqueous solubility, dissolution rate, and oral bioavailability. Lopinavir, a Biopharmaceutics Classification System (BCS) Class II drug, exhibits high permeability but poor solubility. The study focuses on employing pharmaceutical cocrystallization with suitable pharmaceutically acceptable co-formers to modify the crystal lattice through non-covalent interactions without altering the molecular structure of the active pharmaceutical ingredients.

MATERIAL AND METHODS

Determination of Absorption Maxima (λ_{max}): The analytical method for the quantitative estimation of lopinavir was developed using UV-visible spectrophotometry. Accurately weighed 100 mg of drug was transferred separately into 100 mL volumetric flasks and dissolved in 0.1 N hydrochloric acid (HCl). Calibration curves were constructed in 0.1 N HCl over the concentration range of 10–50 $\mu\text{g/mL}$. A primary stock solution (1000 $\mu\text{g/mL}$) was prepared by dissolving 100 mg of each drug separately in 100 mL of 0.1 N HCl. Secondary stock solutions containing 10 $\mu\text{g/mL}$ were prepared by suitable dilution of the primary stock solution. Aliquots equivalent to 10, 20, 30, 40 and 50 $\mu\text{g/mL}$ were prepared in 10 mL volumetric flasks using 0.1 N HCl as the diluent. The absorbance of each solution was measured at 215 nm for lopinavir against the reagent blank ¹⁰.

Preparation of Cocrystals

Dry Grinding Method: Cocrystals of Lopinavir were prepared by the dry grinding technique using tartaric acid, hydroquinone, and resorcinol as coformers in stoichiometric ratios of 1:1, 1:2, and 1:3, as presented in Tables 1. Accurately weighed quantities of the drug and coformer were thoroughly blended in a mortar and ground manually with a pestle for 45 minutes to facilitate cocrystal formation. The resulting powder was dried overnight at room temperature and stored in airtight containers until further characterization ¹¹.

Solvent Evaporation Method: For the solvent evaporation method, accurately weighed amounts of Lopinavir and the selected coformers were mixed in the required stoichiometric ratios (1:1, 1:2, and 1:3). Each component was dissolved separately in ethanol, and the resulting solutions were combined and sonicated briefly to obtain a homogeneous mixture. The solution was transferred to a Petri dish and allowed to evaporate at

ambient temperature until complete solvent removal. The dried cocrystals were collected and preserved in tightly sealed containers for subsequent evaluation.

Liquid-Assisted Grinding Method: In the liquid-assisted grinding technique, Lopinavir and the selected coformers were mixed in stoichiometric ratios of 1:1, 1:2, and 1:3. The components were ground in a mortar

and pestle for 30 minutes with the gradual addition of 2.5 mL of ethanol. The resulting wet mass was dried in a hot air oven and stored in airtight containers. In this method, ethanol served as a catalytic grinding aid by enhancing molecular mobility and promoting intermolecular interactions essential for cocrystal formation without being incorporated into the final crystalline product¹².

Table 1: Preparation of lopinavir cocrystal with various Coformer

F. Code			Lopinavir: Tartaric acid, hydroquinone, resorcinol molar ratio	Cocrystallization methods
LCTG1	LCHG1	LCRG1	01:01	Co grinding
LCTG2	LCHG2	LCRG2	01:02	Co grinding
LCTG3	LCHG3	LCRG3	01:03	Co grinding
LCTS1	LCHS1	LCRS1	01:01	Solvent evaporation
LCTS2	LCHS2	LCRS2	01:02	Solvent evaporation
LCTS3	LCHS3	LCRS3	01:03	Solvent evaporation
LCTL1	LCHL1	LCRL1	01:01	Liquid assisted grinding
LCTL2	LCHL2	LCRL2	01:02	Liquid assisted grinding
LCTL3	LCHL3	LCRL3	01:03	Liquid assisted grinding

Characterization of Cocrystals: The prepared cocrystals were comprehensively characterized to confirm successful cocrystal formation and to evaluate their physicochemical properties. Preliminary confirmation of cocrystal formation was achieved by comparing the analytical characteristics of the optimized formulations with those of the pure drug and coformers (tartaric acid, hydroquinone, and resorcinol). Characterization techniques included scanning electron microscopy (SEM), Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD). Furthermore, in vitro dissolution and ex vivo permeation studies were performed to assess the improvement in drug release and permeation behavior of the developed cocrystals¹³.

Saturation Solubility: The saturation solubility of pure drugs and the prepared cocrystals was determined by the equilibrium solubility method. An excess amount of each sample was added separately to 10 mL of distilled water in sealed glass vials. The vials were placed in a thermostatically controlled shaker water bath and agitated continuously for 24 hours to attain equilibrium. After equilibration, the samples were filtered, suitably diluted, and analyzed using a UV-Visible double-beam spectrophotometer. The absorbance was measured at 215 nm for Lopinavir and the saturation solubility was calculated from the corresponding calibration curves.

Drug Content: Drug content was determined to evaluate the uniformity and accuracy of drug incorporation into the cocrystals. A quantity of cocrystal powder equivalent to 10 mg of the pure drug was

accurately weighed and dissolved in approximately 60 mL of 0.1 N hydrochloric acid. The solution volume was adjusted to 100 mL with the same solvent and filtered through Whatman No. 41 filter paper. The absorbance of the filtrate was recorded at 215 nm for Lopinavir using a UV-Visible double-beam spectrophotometer, and the drug content was calculated accordingly.

Scanning Electron Microscopy (SEM): The surface morphology of the pure coformers and the optimized cocrystal formulation was examined using a Nova Nano SEM 450 scanning electron microscope. The powder samples were mounted on double-sided conductive adhesive tape fixed to aluminum stubs and sputter-coated with a thin platinum layer (approximately 5 nm) to enhance electrical conductivity. The coated samples were maintained under vacuum for 100 seconds at 30 W prior to analysis. Micrographs were recorded at different magnifications to evaluate changes in particle shape, surface characteristics, and crystal morphology¹⁴.

Fourier Transform Infrared (FTIR) Spectroscopy: FTIR spectroscopy was employed to investigate possible intermolecular interactions between the drug and coformers. The samples were finely mixed with potassium bromide (KBr), compressed into pellets, and analyzed using a PerkinElmer FTIR spectrophotometer over the spectral range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1} . The obtained spectra were compared to identify any shifts or changes in characteristic functional group vibrations indicative of cocrystal formation.

Differential Scanning Calorimetry (DSC) Thermal analysis of the prepared cocrystals was carried out using a Shimadzu DSC-60 differential scanning calorimeter equipped with TA-60 software. Samples were placed in sealed aluminum pans, while an empty aluminum pan served as the reference. Thermograms were recorded over a temperature range of 30–300°C at a heating rate of 10°C/min. The thermal behavior of the cocrystals was compared with that of the pure components to confirm the formation of a new crystalline phase ¹⁵.

Powder X-ray Diffraction (PXRD): The crystalline characteristics of the pure coformers and the optimized cocrystal formulations were analyzed using a Bruker D8 Advance Powder X-ray Diffractometer equipped with a fine-focus X-ray tube. The powdered samples were mounted on a motorized goniometer and rotated during data acquisition to ensure uniform diffraction. The obtained diffraction patterns were compared with those

of the pure drug and coformers to identify changes in crystallinity and the emergence of new diffraction peaks, thereby confirming successful cocrystal formation.

Preparation of Cocrystal Tablets: Tablets containing optimized cocrystals equivalent to 200 mg drug were prepared by wet granulation. Cocrystals were blended with microcrystalline cellulose, dibasic calcium phosphate, lactose and potato starch. Polyvinylpyrrolidone K-30 (10% w/v in isopropyl alcohol) was used as the granulating binder. The wet mass was passed through sieve No. 10 and dried at 60°C for 1 h. The dried granules were resized through sieve No. 14 and lubricated with talc and magnesium stearate. Compression was carried out using a single-punch tablet compression machine equipped with 8 mm flat-faced punches to obtain tablets having a hardness of approximately 5 kg/cm² ¹⁶.

Table 2: Preparation of lopinavir various cocrystal containing tablets

Ingredients	Amount (mg /tablet)								
	LCTG1T	LCTG2T	LCTG3T	LCTS1T	LCTS2T	LCTS3T	LCTL1T	LCTL2T	LCTL3T
	LCHG1T	LCHG2T	LCHG3T	LCHS1T	LCHS2T	LCHS3T	LCHL1T	LCHL2T	LCHL3T
	LCRG1T	LCRG2T	LCRG3T	LCRS1T	LCRS2T	LCRS3T	LCRL1T	LCRL2T	LCRL3T
Lopinavir coformer cocrystal	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
Microcrystalline cellulose (Avicel PH - 102)	140	140	140	140	140	140	140	140	140
Sodium starsh glycollate	15	15	15	15	15	15	15	15	15
Di-basic calcium phosphate dihydrate (DBP)	55	55	55	55	55	55	55	55	55
Lactose	50	50	50	50	50	50	50	50	50
Starch (Potato)	30	30	30	30	30	30	30	30	30
Talc (Purified)	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Polyvinyl pyrrolidone K-30	10 % w/v in iso-propyl alochol								
Total weight of tablet	500 mg								

Evaluation of Tablet Formulations: Prepared tablets were evaluated for both pre-compression and post-compression parameters.

Flow Properties of Granules: The flow characteristics of the prepared granules were evaluated to determine their suitability for tablet compression. Flow behavior

was assessed by measuring bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose. Bulk and tapped densities were determined using standard pharmacopeial procedures, and Carr's index and Hausner's ratio were calculated using established equations. The angle of repose was

measured by the fixed funnel method, where granules were allowed to flow freely through a funnel to form a conical heap. The angle formed between the surface of the heap and the horizontal plane was calculated to evaluate the flowability of the granules¹⁷.

Weight Variation Test: The weight variation test was carried out to assess the uniformity of tablet weight within each formulation batch. Twenty tablets were randomly selected and individually weighed using a calibrated digital analytical balance. The average tablet weight was calculated, and the percentage deviation of each tablet from the mean weight was determined. The results were evaluated according to pharmacopeial specifications to ensure compliance with the prescribed limits for weight uniformity.

Thickness Measurement: Tablet thickness was measured to ensure dimensional consistency among the compressed tablets. Twenty tablets from each formulation were selected randomly, and the thickness of each tablet was determined using a calibrated Vernier caliper. The average thickness and standard deviation were calculated to evaluate the uniformity of tablet dimensions and the consistency of the compression process.

Hardness Test The mechanical strength of the tablets was evaluated by determining their hardness using a Monsanto hardness tester. Individual tablets were placed between the anvils of the instrument, and pressure was gradually applied until tablet fracture occurred. The force required to break each tablet diametrically was recorded as the tablet hardness or crushing strength, indicating the ability of the tablets to withstand handling, packaging, and transportation.

Friability Test: The resistance of tablets to abrasion and mechanical stress was evaluated using a Roche friabilator. Ten tablets were accurately weighed and subjected to 100 revolutions at a rotational speed of 25 rpm. After completion of the test, the tablets were dedusted and reweighed. The percentage friability was calculated from the weight loss, and tablets exhibiting a weight loss of not more than 1.0% were considered to possess acceptable mechanical integrity¹⁸.

In Vitro Dissolution Study: The in vitro dissolution study was performed using a USP Type II (paddle) dissolution apparatus to evaluate the drug release characteristics of the prepared tablets. The dissolution medium consisted of 900 mL of 0.1 N hydrochloric acid maintained at $37 \pm 0.5^\circ\text{C}$, with the paddle rotation speed set at 100 rpm. At predetermined time intervals, 1 mL aliquots were withdrawn, filtered through a 0.45 μm membrane filter, and replaced immediately with an equal volume of fresh dissolution medium to maintain constant volume and sink conditions. The filtered samples were analyzed using a UV-Visible spectrophotometer at 215 nm for Lopinavir. The cumulative percentage of drug released was calculated and used to compare the dissolution profiles of the different tablet formulations¹⁹.

RESULTS AND DISCUSSION

The developed UV spectrophotometric method was found to be simple, rapid, accurate, and reproducible for the quantitative estimation of lopinavir. The linear calibration curve obtained over the concentration range of 2–10 $\mu\text{g/mL}$ confirms the suitability of the method for routine pharmaceutical analysis and for evaluating the performance of the developed formulations. The results indicate that the method is appropriate for further analytical applications, including dissolution profiling, assay determination, and stability studies.

The solubility study demonstrated that the preparation method and coformer significantly influenced the physicochemical properties of lopinavir cocrystals. Among all formulations, cocrystals prepared with resorcinol exhibited the highest solubility compared to those prepared with tartaric acid and hydroquinone. The LCRS3 formulation, prepared by the solvent evaporation method, showed the maximum solubility of 15.02 mg/mL with a satisfactory drug content of 97.02%, indicating efficient incorporation of the drug into the cocrystal lattice. In comparison, formulations prepared by grinding and liquid-assisted grinding exhibited relatively lower solubility values, suggesting that solvent evaporation promoted better crystal organization and intermolecular interactions.

The FTIR spectrum of LCRS3 showed characteristic peak shifts and broadening compared with pure lopinavir, confirming the formation of intermolecular hydrogen bonding between lopinavir and resorcinol without any chemical degradation. The DSC thermogram revealed the appearance of a new melting endotherm with the disappearance of the individual component peaks, demonstrating the formation of a distinct crystalline phase. X-ray diffraction analysis exhibited new diffraction peaks and changes in peak intensity, confirming the generation of a novel cocrystalline structure. SEM images further supported cocrystal formation by revealing uniformly shaped crystals with a morphology distinctly different from the parent drug. These findings collectively confirm successful cocrystal formation and demonstrate that the LCRS3 formulation effectively enhanced the aqueous solubility of lopinavir while maintaining excellent drug content, making it the optimized formulation for further pharmaceutical evaluation.

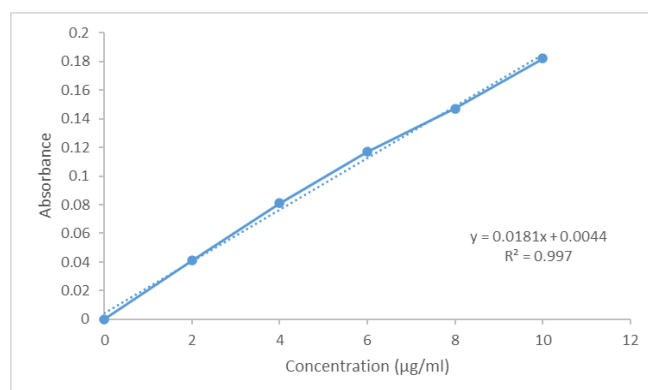
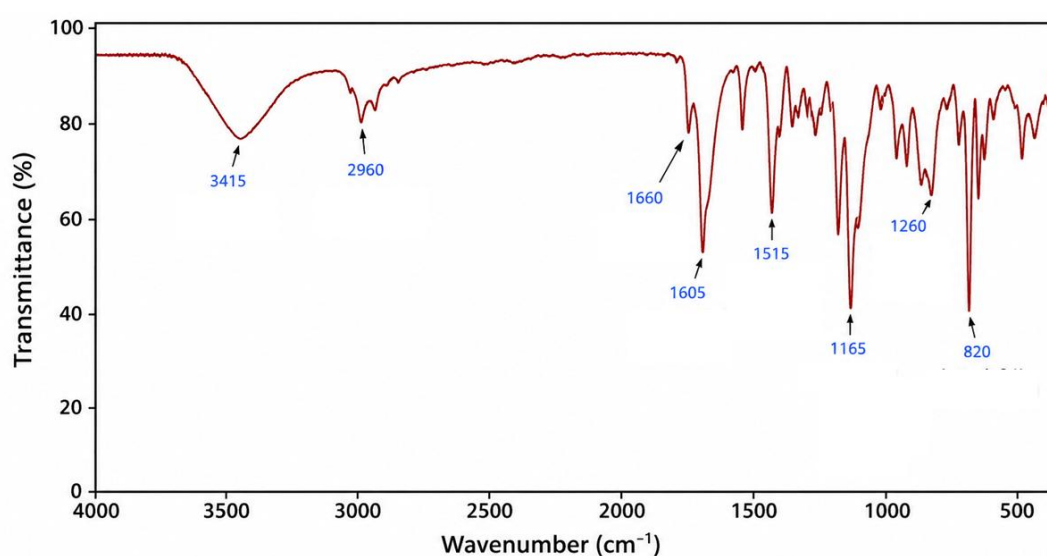
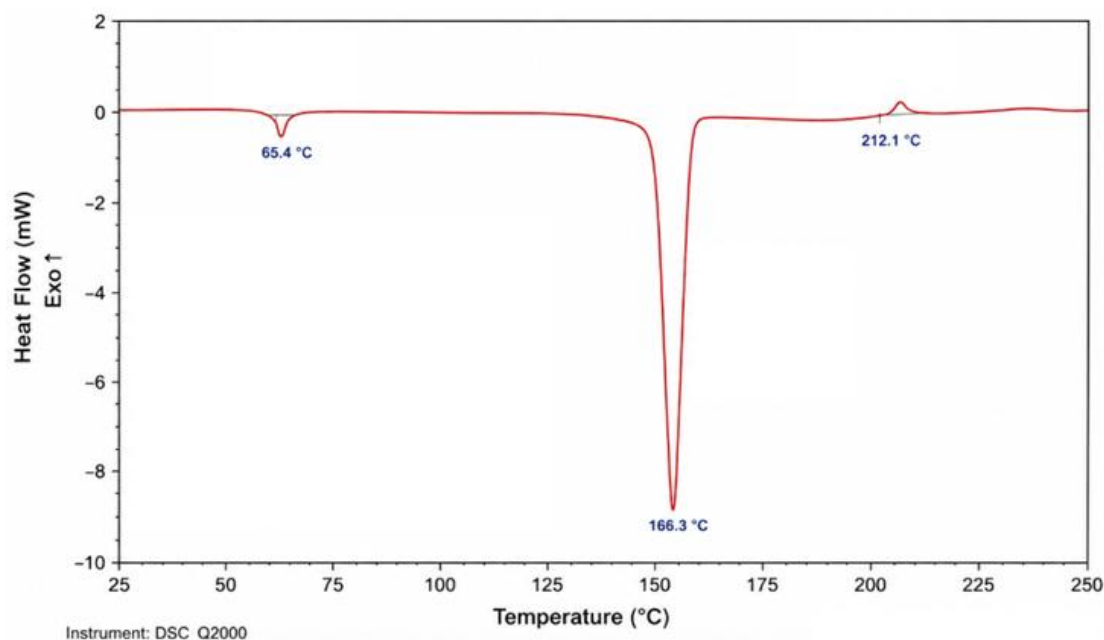


Figure 1: Standard curve of lopinavir in 0.1 N HCl solution (215 nm)

Table 3: Solubility of lopinavir cocrystal with tartaric acid Coformer in 0.1 N HCl (pH 1.2) at 37°C and after 24 hours equilibration

F. Code	Solubility (mg/ml)	Drug content (%)	F. Code	Solubility (mg/ml)	Drug content (%)	F. Code	Solubility (mg/ml)	Drug content (%)
LCTG1	2.08	95.14	LCHG1	6.04	96.26	LCRG1	10.14	97.45
LCTG2	2.74	95.32	LCHG2	6.47	97.04	LCRG2	10.54	98.01
LCTG3	2.89	95.47	LCHG3	7.02	97.34	LCRG3	11.21	98.47
LCTS1	4.78	96.01	LCHS1	9.14	98.04	L CRS1	13.05	99.02
LCTS2	5.02	94.25	LCHS2	10.01	96.06	L CRS2	14.11	96.48
LCTS3	5.63	95.03	LCHS3	11.12	96.34	L CRS3	15.02	97.02
LCTL1	3.04	96.25	LCHL1	7.98	98.65	LCRL1	11.54	98.78
LCTL2	3.87	97.65	LCHL2	8.45	97.65	LCRL2	12.11	99.85
LCTL3	4.02	98.45	LCHL3	9.03	98.36	LCRL3	13.08	98.48

**Figure 2:** FTIR spectrum of LCRS3; lopinavir cocrystal with resorcinol Coformer with Solvent evaporation method**Figure 3:** DSC thermogram of LCRS3; lopinavir cocrystal with resorcinol Coformer with Solvent evaporation method

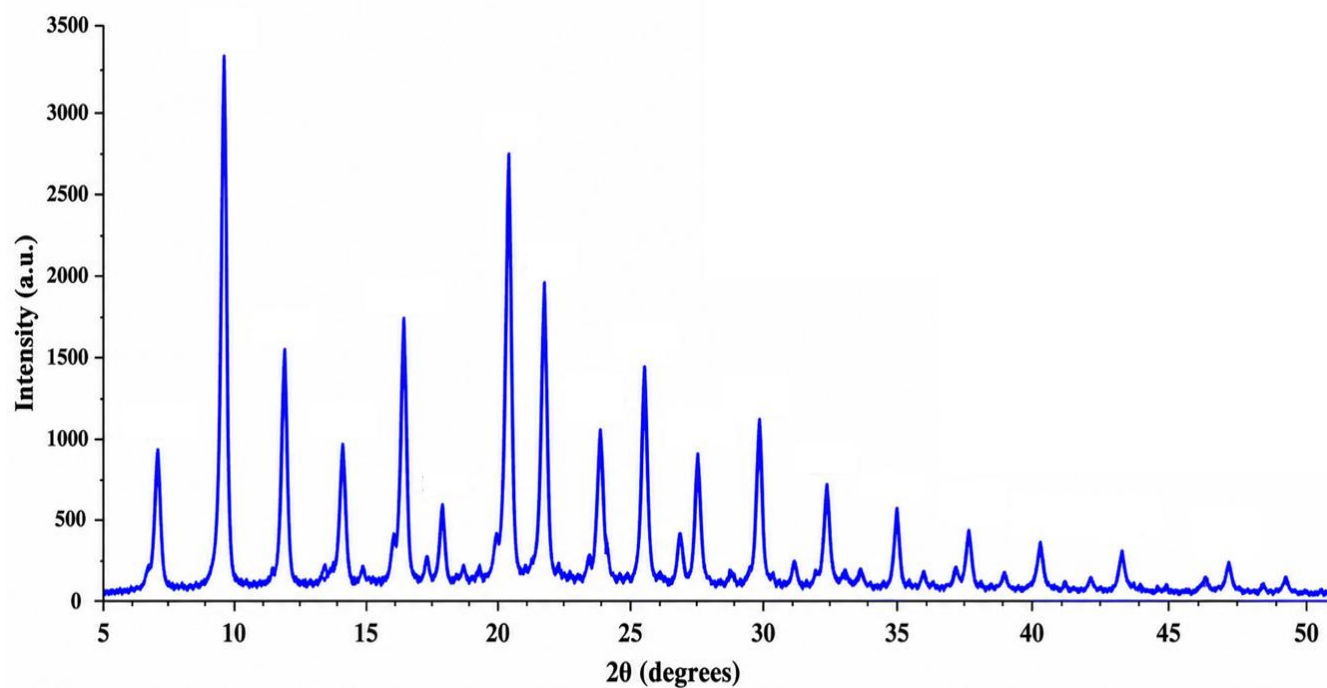


Figure 4: X-ray diffraction pattern of LCRS3; lopinavir cocrystal with resorcinol Coformer with Solvent evaporation method

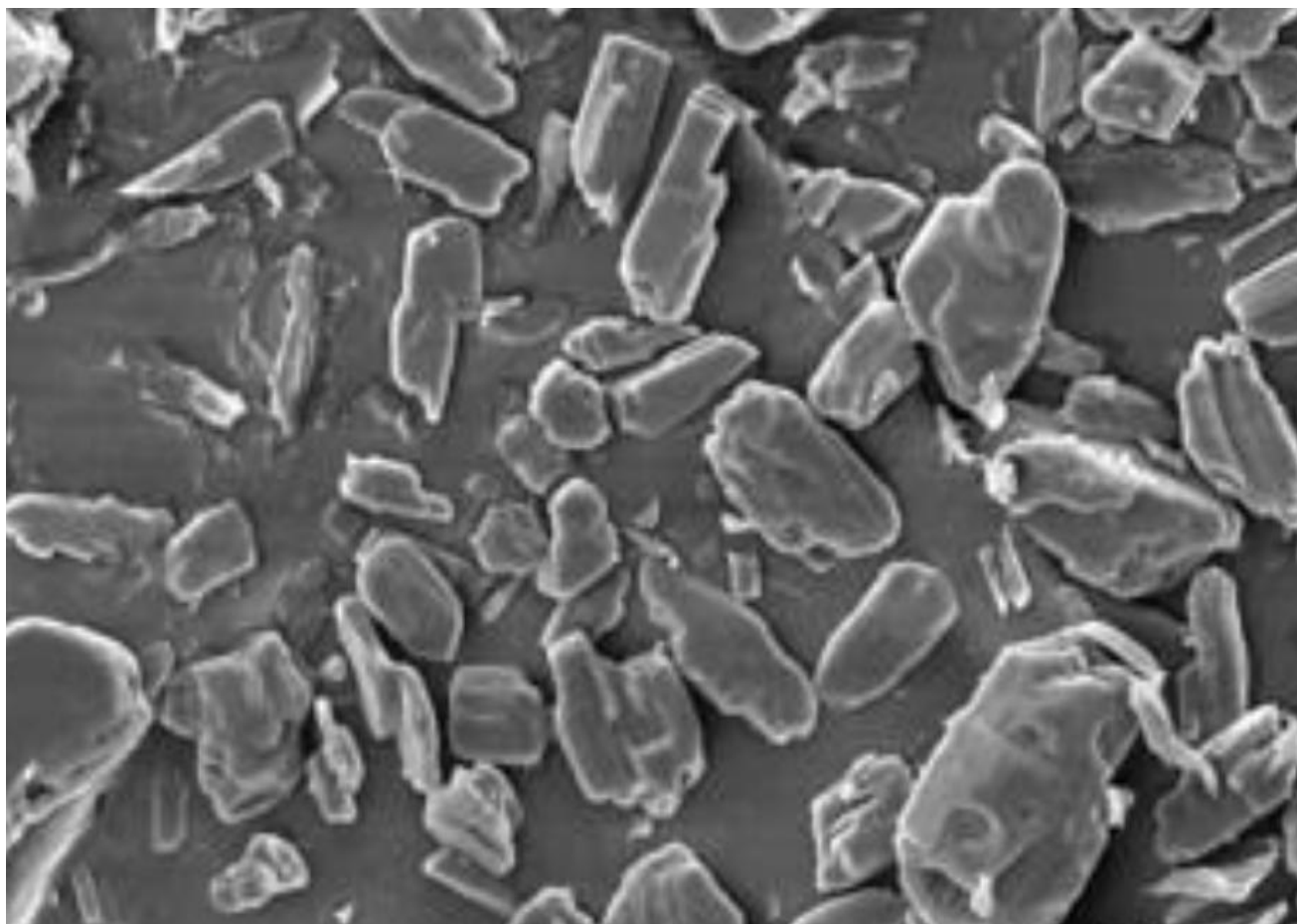


Figure 5: SEM images of LCRS3; lopinavir cocrystal with resorcinol Coformer with Solvent evaporation method

Table 4: Pre-compression characterization of lopinavir 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 (θ)
LCTG1T	0.358	0.433	23.32	1.21	26.77
LCTG2T	0.365	0.464	21.33	1.27	22.33
LCTG3T	0.385	0.449	14.25	1.16	26.18
LCTS1T	0.343	0.437	21.51	1.27	24.88
LCTS2T	0.369	0.465	20.64	1.26	21.65
LCTS3T	0.278	0.421	23.81	1.51	27.64
LCTL1T	0.299	0.473	36.78	1.58	22.62
LCTL2T	0.315	0.417	21.25	1.26	25.75
LCTL3T	0.335	0.423	20.81	1.26	26.13

Table 5: Pre-compression characterization of lopinavir hydroquinone cocrystal tablet

Formulation code	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's index (%)	Hausner's Ratio	Angle of Repose (θ)
LCHG1T	0.302	0.452	22.02	1.18	24.12
LCHG2T	0.298	0.446	21.35	1.16	23.05
LCHG3T	0.296	0.448	22.23	1.13	25.13
LCHS1T	0.302	0.456	21.96	1.12	24.28
LCHS2T	0.308	0.452	22.04	1.19	23.12
LCHS3T	0.296	0.442	22.46	1.15	22.11
LCHL1T	0.298	0.424	21.98	1.14	21.41
LCHL2T	0.305	0.431	22.04	1.16	22.18
LCHL3T	0.291	0.429	21.87	1.15	21.97

Table 6: Pre-compression characterization of lopinavir resorcinol cocrystal tablet

Formulation code	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Carr's index (%)	Hausner's Ratio	Angle of Repose (θ)
LCRG1T	0.311	0.321	24.96	1.14	24.56
LCRG2T	0.308	0.331	23.84	1.13	24.34
LCRG3T	0.315	0.321	24.04	1.14	24.31
LCRS1T	0.311	0.311	24.14	1.15	24.25
LCRS2T	0.312	0.322	24.84	1.16	24.32
LCRS3T	0.307	0.318	24.23	1.15	24.05
LCRL1T	0.311	0.329	23.14	1.15	23.87
LCRL2T	0.308	0.319	24.15	1.14	24.01
LCRL3T	0.314	0.328	23.87	1.16	23.87

Table 7: Post compression characterization of lopinavir tartaric acid cocrystal tablet

Formulation code	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
LCTG1T	494.59±0.04	2.54±0.09	8.1±0.02	6.14±0.18	0.91±0.89	97.52±1.26
LCTG2T	501.07±0.01	2.51±0.04	8.2±0.01	6.24±0.42	0.81±0.46	97.08±1.08
LCTG3T	495.28±0.04	2.59±0.01	8.1±0.02	6.11±0.41	0.86±0.43	95.29±1.98
LCTS1T	493.27±0.01	2.53±0.01	8.1±0.02	6.04±0.41	0.71±0.67	97.15±1.45
LCTS2T	502.73±0.03	2.59±0.01	8.1±0.01	6.11±0.27	0.82±0.43	95.65±1.14
LCTS3T	510.24±0.06	2.56±0.02	8.1±0.01	6.10±0.28	0.75±0.23	96.91±1.82
LCTL1T	508.15±0.07	2.56±0.03	8.1±0.02	6.09±0.25	0.79±0.15	95.11±1.14
LCTL2T	511.24±0.06	2.51±0.02	8.1±0.01	6.04±0.14	0.75±0.24	97.01±1.15
LCTL3T	508.14±0.04	2.56±0.06	8.1±0.01	6.12±0.17	0.80±0.31	94.13±1.12
LCHG1T	508.02±0.04	2.56±0.03	8.0±0.02	5.87±0.44	0.84±0.64	93.25±1.12
LCHG2T	504.02±0.01	2.51±0.02	8.0±0.02	5.91±0.10	0.75±0.46	94.32±1.16
LCHG3T	492.08±0.03	2.56±0.06	8.1±0.03	5.24±0.23	0.63±0.56	97.15±1.24
LCHS1T	498.07±0.03	2.53±0.05	7.9±0.02	5.82±0.44	0.81±0.75	98.12±1.34
LCHS2T	491.03±0.03	2.52±0.02	8.0±0.02	5.93±0.10	0.76±0.85	97.24±1.31
LCHS3T	502.14±0.02	2.53±0.02	8.1±0.03	5.92±0.23	0.84±0.46	94.13±1.24
LCHL1T	498.12±0.04	2.58±0.01	8.0±0.02	5.67±0.21	0.73±0.27	96.12±1.21
LCHL2T	492.08±0.03	2.56±0.02	8.1±0.01	5.78±0.24	0.79±0.45	98.13±1.14
LCHL3T	498.07±0.03	2.56±0.02	7.9±0.01	5.73±0.14	0.82±0.27	99.04±1.16
LCRG1T	494.12±0.03	2.51±0.03	7.9±0.02	5.92±0.07	0.84±0.46	92.41±1.12
LCRG2T	493.11±0.02	2.49±0.01	8.1±0.02	6.02±0.03	0.78±0.61	97.08±1.08
LCRG3T	489.08±0.02	2.50±0.03	8.1±0.02	5.91±0.04	0.79±0.75	95.02±1.28
LCRS1T	492.07±0.03	2.51±0.02	8.1±0.02	5.94±0.04	0.69±0.45	98.09±1.15
LCRS2T	495.03±0.02	2.51±0.02	7.9±0.03	5.96±0.05	0.84±0.63	96.15±1.14
LCRS3T	496.24±0.03	2.53±0.01	8.0±0.03	5.93±0.07	0.75±0.58	98.09±1.22
LCRL1T	481.23±0.01	2.48±0.02	8.1±0.01	5.96±0.02	0.81±0.23	99.18±1.12
LCRL2T	488.11±0.03	2.52±0.02	7.8±0.01	5.92±0.07	0.76±0.21	97.14±1.10
LCRL3T	492.01±0.03	2.48±0.02	8.1±0.03	5.99±0.03	0.78±0.23	99.19±1.12

In-vitro drug release study:

The zero-order release profiles of lopinavir tartaric acid, hydroquinone, and resorcinol cocrystal tablets are presented in Figures 6, 7 and 8, respectively. The plots demonstrate the cumulative amount of lopinavir released as a function of time. The linearity of the profiles indicates that drug release from the cocrystal tablets occurred at a relatively constant rate over the investigated period. A good linear relationship between cumulative drug release and time suggests that the formulations were capable of maintaining a controlled and predictable release pattern.

The lopinavir tartaric acid cocrystal tablet (Figure 6) exhibited a progressive increase in cumulative drug

release with time. The comparatively linear profile suggests that the release of lopinavir was sustained throughout the dissolution study. The incorporation of tartaric acid into the cocrystal lattice may have modified the physicochemical characteristics of lopinavir, resulting in a controlled dissolution behavior. The zero-order pattern indicates that the amount of drug released per unit time remained relatively consistent, which is desirable for maintaining uniform drug availability.

The lopinavir hydroquinone cocrystal tablet (Figure 7) also demonstrated an approximately linear increase in drug release with time. The observed zero-order behavior indicates a controlled release mechanism in which the drug was released at a nearly constant rate. Formation of the hydroquinone cocrystal may have

altered the crystal packing wettability, dissolution characteristics, and drug-excipient interactions of lopinavir, thereby influencing its release from the tablet matrix. The sustained and relatively uniform release profile suggests improved control over the dissolution of the drug compared with an immediate-release system.

Similarly, the lopinavir resorcinol cocrystal tablet (Figure 8) showed a gradual and nearly linear increase

in cumulative drug release. The zero-order release pattern indicates that the cocrystal tablet provided a relatively constant drug-release rate throughout the study period. The modified crystal structure produced by resorcinol may have contributed to controlled hydration, dissolution, and diffusion of lopinavir from the tablet formulation.

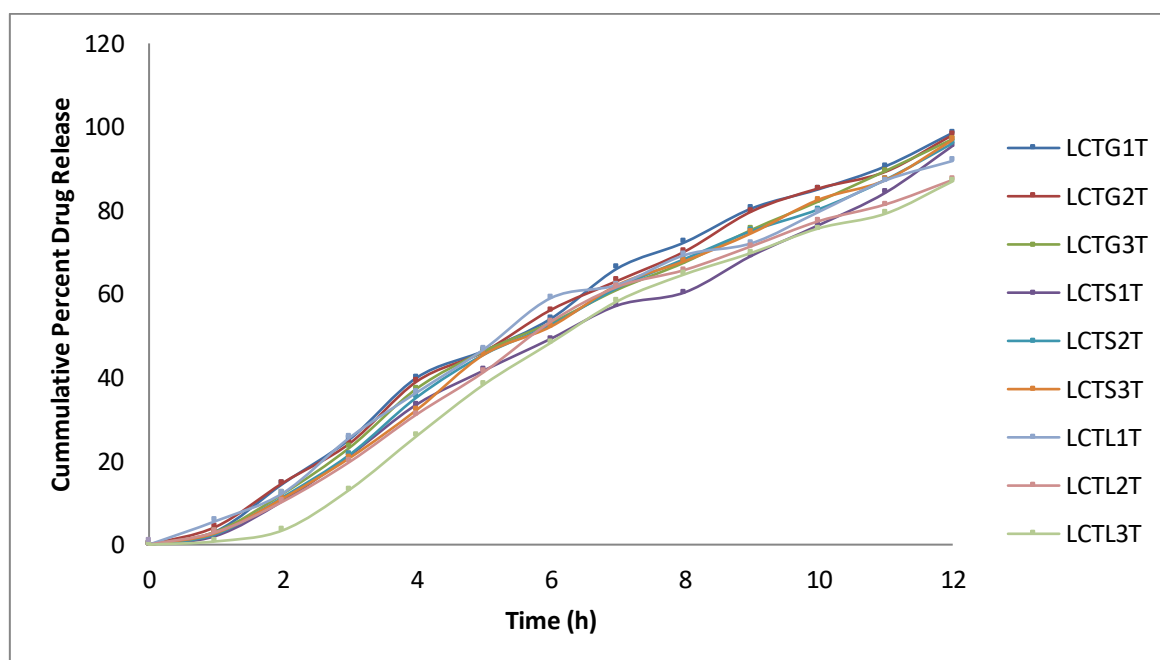


Figure 6: Zero-order release of lopinavir tartaric acid cocrystal tablet

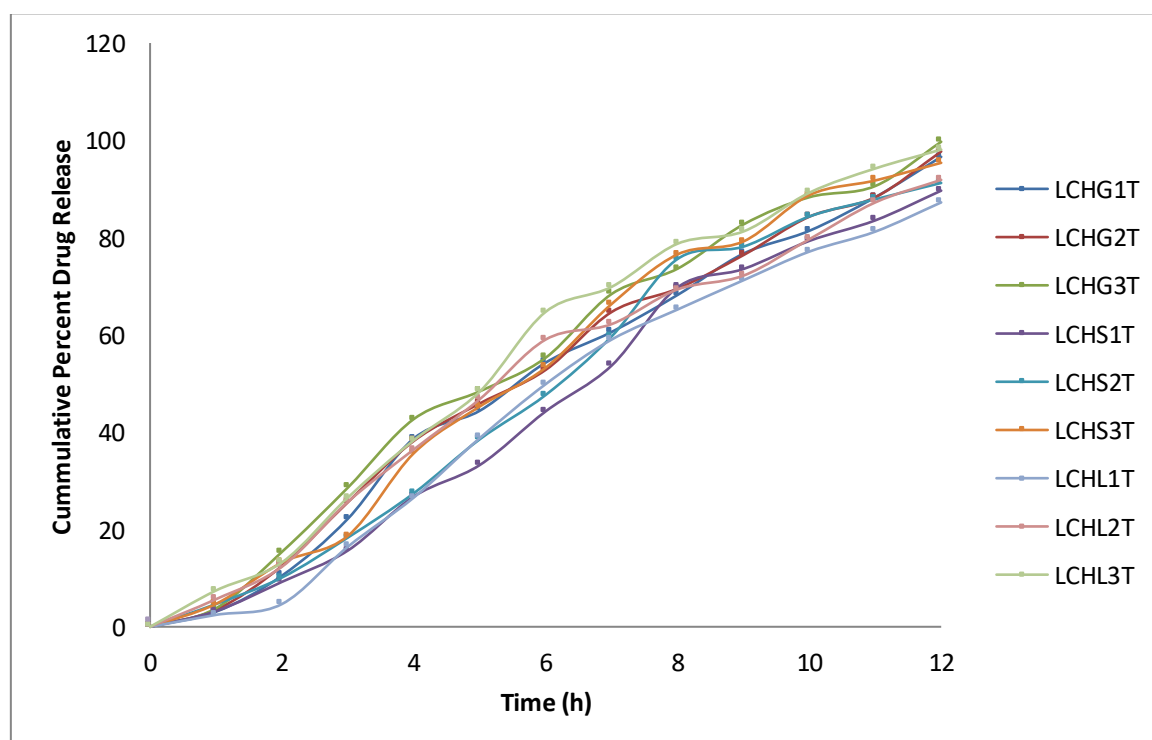


Figure 7: Zero-order release of lopinavir hydroquinone cocrystal tablet

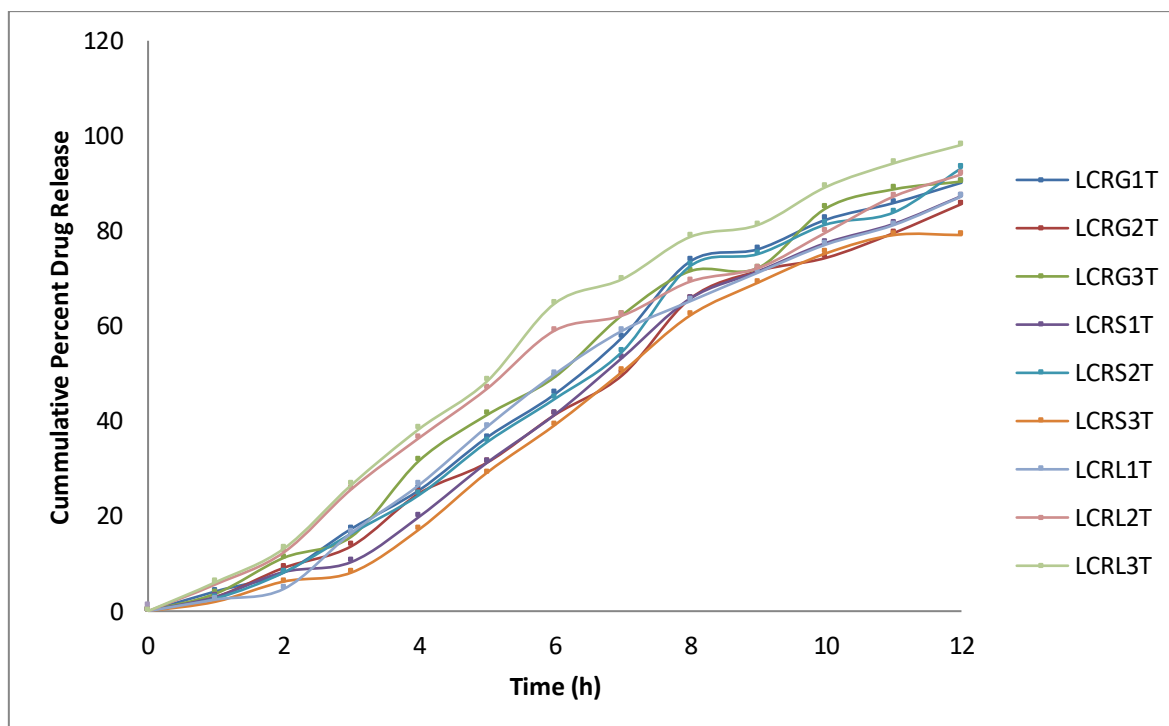


Figure 8: Zero-order release of lopinavir resorcinol cocrystal tablet

The zero-order plots for all three lopinavir cocrystal tablets indicate controlled and relatively constant drug-release behavior. The differences in slope and linearity among the tartaric acid, hydroquinone, and resorcinol cocrystals may be attributed to differences in crystal packing, intermolecular interactions, aqueous solubility, wettability, and dissolution characteristics of the respective cocrystals. These findings demonstrate that cocrystal formation can significantly influence the release characteristics of lopinavir and may provide a useful approach for modulating its dissolution behavior. The formulation exhibiting the highest linearity (R^2 value closest to 1.0) can be considered to have the best fit to the zero-order release model and, consequently, the most consistent release rate among the investigated cocrystal tablets.

CONCLUSION

The present study successfully demonstrated the potential of pharmaceutical cocrystallization as an effective crystal-engineering approach for improving the physicochemical and biopharmaceutical properties of poorly water-soluble lopinavir. Cocrystals of lopinavir were prepared using tartaric acid, hydroquinone, and resorcinol as pharmaceutically acceptable coformers through dry grinding solvent evaporation, and liquid-assisted grinding techniques. The developed cocrystals exhibited improved aqueous solubility and satisfactory drug content compared with the parent drug, confirming the beneficial influence of coformer selection and cocrystallization method on the performance of lopinavir. Among the investigated formulations, LCRS3, consisting of lopinavir and resorcinol prepared by the solvent evaporation method, demonstrated the highest solubility (15.02 mg/mL) with a drug content of 97.02% and was therefore identified as the optimized cocrystal

formulation. FTIR, DSC, PXRD, and SEM studies collectively supported the formation of a new crystalline phase and indicated the presence of intermolecular interactions between lopinavir and resorcinol. These structural modifications were associated with enhanced solubility and improved dissolution characteristics without compromising the chemical identity of the drug.

The optimized cocrystal was successfully incorporated into tablet formulations using conventional wet granulation. The prepared tablets exhibited satisfactory pre-compression flow properties and acceptable post-compression characteristics, including uniform weight, thickness, hardness, friability, and drug content. In vitro dissolution studies demonstrated progressive and relatively controlled drug release from the developed cocrystal tablets, with the release profiles showing a satisfactory fit to the zero-order model. The findings establish that pharmaceutical cocrystallization, particularly with resorcinol, can be a promising strategy for overcoming the solubility and dissolution limitations of lopinavir. The developed approach may improve the consistency of oral drug absorption and potentially enhance bioavailability. Further in vivo pharmacokinetic and bioavailability studies are warranted to confirm whether the observed improvements in solubility and dissolution translate into enhanced systemic exposure and therapeutic performance.

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References

- Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to address low drug solubility in discovery and development. *Pharmacol Rev.* 2020;72(2):491-541.
- Thipparaboina R, Kumar D, Chavan RB, Shastri NR. Multidrug cocrystals: a novel approach to reduce polypharmacy. *Trends Pharmacol Sci.* 2020;41(1):20-32.
- Pani NR, Nath LK, Acharya S, Bhuyan B. Pharmaceutical cocrystals: a review of preparation, characterization and applications. *J Pharm Bioallied Sci.* 2020;12(3):216-227.
- Javadzadeh Y, Shadbad M, Adibkia K, Barzegar-Jalali M. Recent advances in improving oral drug bioavailability by cocrystals. *Bioimpacts.* 2020;10(2):95-106.
- Wouters J, Quéré L, editors. Pharmaceutical salts and cocrystals: current trends in pharmaceutical solid-state development. *Pharmaceutics.* 2021;13(10):1611.
- Thakuria R, Delori A, Jones W, Lipert MP, Roy L, Rodríguez-Hornedo N. Pharmaceutical cocrystals and their physicochemical properties. *Int J Pharm.* 2021;592:120038.
- Kumari P, Kaur S, Kumar S, Nanda A. Pharmaceutical cocrystals: a review of preparations, physicochemical properties and applications. *Crystals.* 2021;11(8):876. <https://doi.org/10.1016/j.apsb.2021.03.030> PMID:34522597 PMCID:PMC8424375
- Xia M, Zhu BQ. Superior dissolution behavior and bioavailability of pharmaceutical cocrystals and recent regulatory issues. *ACS Med Chem Lett.* 2022;13(1):29-37. <https://doi.org/10.1021/acsmedchemlett.1c00478> PMID:35059121 PMCID:PMC8762724
- Bolla G, Sarma B, Nangia AK. Crystal engineering of pharmaceutical cocrystals in the discovery and development of improved drugs. *Chem Rev.* 2022;122(13):11514-11603. <https://doi.org/10.1021/acs.chemrev.1c00987> PMID:35642550
- Mathdevru B, Sharma P, Kore SD, Sharma J, Dumbre R, Singhal NK. Cocrystals of lopinavir: effect on drug release and hygroscopicity characteristics. *J Pharm Negat Results.* 2022;13(Special Issue 8):5016-5024. doi:10.47750/pnr.2022.13.S08.658.
- Malik J, Khatkar A, Nanda A. A comprehensive insight on pharmaceutical co-crystals for improvement of aqueous solubility. *Curr Drug Targets.* 2023;24(2):157-170. <https://doi.org/10.2174/1389450124666221114095400> PMID:36380409
- Zilpe RD, Mulla JAS. Pharmaceutical co-crystals: a concise review on traditional and novel techniques for preparation, their physicochemical properties and applications. *Indian J Novel Drug Deliv.* 2023;15(3):1-10.
- Patil R, Patil S, Mali S. Unlocking potential: cocrystals as catalyst for heightened solubility and dissolution of low solubility pharmaceuticals. *Int J Res Pharm Allied Sci.* 2024;3(4):73-88.
- 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;97:106572. <https://doi.org/10.1016/j.jddst.2024.106572>
- Tamboli SS, Rathod KB, Raut DP, Timble AN, Panigrahi GK. Enhanced solubility and dissolution by drug-drug cocrystals: a comprehensive review. *Int J Novel Res Dev.* 2024;9(7):1-15.
- Das M, Habibullah S, Das T, Mallick S. Pharmaceutical cocrystals for solubility enhancement of drugs. In: Singh I, Mallick S, Rath R, editors. *Cocrystals in Pharmaceutical Sciences*. Hoboken: Wiley; 2025. <https://doi.org/10.1002/9781394302505.ch9>
- Odeku OA, Akin-Ajani OD. Pharmaceutical cocrystals. In: Singh I, Mallick S, Rath R, editors. *Cocrystals in Pharmaceutical Sciences*. Hoboken: Wiley; 2025. <https://doi.org/10.1002/9781394302505.ch1>
- Nangia AK. Pharmaceutical cocrystals for drug delivery. In: *Methods in Drug Discovery and Discovering Lead Molecules*. Hoboken: Wiley; 2025. <https://doi.org/10.1002/0471266949.bmc310> PMID:40826870
- Alharby TN, Huwaimel B. Machine learning analysis of pharmaceutical cocrystals solubility parameters in enhancing the drug properties for advanced pharmaceutical manufacturing. *Sci Rep.* 2025;15:29970. <https://doi.org/10.1038/s41598-025-12886-8> PMID:40817338 PMCID:PMC12356857
- Sonawane SR, Patil SB. Pharmaceutical cocrystals of nitrendipine with improved solubility and dissolution characteristics. *Adv Pharm Pharmacol.* 2025;13(4A):867-878. <https://doi.org/10.13189/app.2025.130711>