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IMPROVING THE BIOPHARMACEUTICAL PERFORMANCE OF AZOLE ANTIFUNGALS: A COMPARATIVE STUDY OF SOLID DISPERSION AND CO-CRYSTALLIZATION OF KETOCONAZOLE AND ITRACONAZOLE

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ABSTRACT

Background: Oral bioavailability of BCS class II azole antifungals, ketoconazole and itraconazole, is hampered by low aqueous solubility. Improving solubility and dissolution is necessary for greater therapeutic efficacy. This research compared two approaches: solid dispersion and pharmaceutical co-crystallization to improve their biopharmaceutical properties. **Methodology:** Solid dispersions were prepared using the organic solvent evaporation technique with PEG-10000 for ketoconazole and HPMCE50 for itraconazole. Co-crystals with benzoic and tartaric acids were studied by FT-IR, DSC, and PXRD. Optimized formulations were compressed into tablets and analyzed for pharmacopoeial parameters, dissolution, release kinetics, and ICH stability. **Results and Discussion:** Saturation solubility investigations revealed that, compared to amorphization, solid dispersions exhibited more efficient enhancement due to the combined effect of amorphous enrichment and polymer solubilization. Tartaric acid co-crystals could increase solubility by crystal lattice modification. cc-Tabs showed burst release profiles, while SDs gave controlled drug release. The release of drug was in accordance with the first-order and Korsmeyer–Peppas models with anomalous transport, and was sustained for six months. The low aqueous solubility of azole antifungals restricts their oral bioavailability. The solubility and dissolution of ketoconazole and itraconazole were enhanced by solid dispersion and co-crystallization. Solid dispersions provided superior amorphous stability and extended-release, while co-crystals led to faster initial dissolution and better early drug availability. **Conclusion:** Both approaches were successful in improving solubility, dissolution, and stability. Both SDs modulated drug-release kinetics; sustained-release profiles were obtained from the solid dispersions, and fast dissolution was favored by co-crystallization, thus providing viable approaches for oral delivery of poorly soluble azole antifungals.

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INTRODUCTION

Fungal diseases are still a major public health problem worldwide, especially in immunosuppressed patients and those with underlying conditions. Azoles such as ketoconazole (KTZ) and itraconazole (ITZ) have been used extensively for systemic and superficial mycoses because of their broad antifungal spectrum and clinical effectiveness. These medications act by inhibiting fungal cytochrome P450–dependent enzymes, specifically lanosterol 14-α-demethylase, thus preventing ergosterol biosynthesis and compromising the integrity of the fungal cell membrane. However, these antifungals have relatively low therapeutic efficacy due to limited water solubility and poor dissolution, resulting in reduced absorption after oral administration [1]. Oral administration of drugs remains the most popular route of drug delivery primarily for its ease of use, patient compliance, noninvasiveness, and cost.

However, the efficiency of oral medication is critically dependent on the solubility and dissolution behavior of the active pharmaceutical ingredient (API) in gastrointestinal fluids. In the last decade, a large number of advanced water-insoluble drug molecules, many of which are currently approved or under research, have been discovered and designed in the water-insoluble solid state. According to the Biopharmaceutics Classification System (BCS), approximately 40% of drug products on the shelves and a vast number in development are BCS Class II drugs, which possess low solubility and high permeability. For these drugs, dissolution is the rate-limiting process of drug absorption, and formulations must be developed to improve solubility and dissolution rate [2]. The triazole antifungal agent itraconazole (ITZ) can be considered a representative of BCS class II drugs, possessing very poor aqueous solubility and high lipophilicity. Due to its well-ordered crystalline system and hydrophobic properties, it exhibits dissolution-limited absorption and variable oral bioavailability.

Also, ketoconazole, a known imidazole antifungal and one of the earliest orally active azoles in systemic mycoses, also employs low aqueous solubility despite its high membrane permeability. Ketoconazole has diverse therapeutic uses, including antifungal therapy and endocrine treatments; its oral bioavailability remains strongly influenced by formulation design and gastrointestinal factors. These physicochemical constraints underscore the need for novel formulation approaches to enhance the biopharmaceutical performance of antifungal azoles [3]. Various formulation approaches have been used to overcome solubility-related problems associated with poorly water-soluble drugs. Traditional approaches include particle size reduction, salt formation, complexation, and lipid-based drug delivery systems; advanced strategies include crystal engineering and amorphous drug delivery systems. These methods focus on changing the physicochemical properties of drug(s) without altering their chemical identity to enhance dissolution behavior and, hence, oral bioavailability. Solid-state modification methods are particularly attractive strategies in pharmaceutical development, as they offer a simple and versatile approach to create new solid forms [4]. Development of solid dispersions, especially amorphous solid dispersions (ASDs), is one such promising strategy for solubility enhancement. In this approach, the low-solubility drug is solubilized in a hydrophilic polymer carrier. This transformation of the drug from crystalline to amorphous form reduces its lattice energy and improves wettability, thereby promoting dissolution and better bioavailability.

Moreover, polymeric carriers also stabilize the amorphous state and prevent recrystallization during storage and dissolution. The solid dispersion technique has already been successfully used with various BCS class II drugs to enhance dissolution rates and therapeutic efficacy [5]. Pharmaceutical co-crystallization is another developing complementary approach, grounded in crystal engineering. Pharmaceutical cocrystals are crystalline porous complexes that form between an API and a pharmaceutically acceptable coformer in a well-defined stoichiometry, within which the components are linked by non-covalent intermolecular interactions like hydrogen bonding, π–π stacking, or van der Waals forces. In contrast to salt formation, the generation of cocrystals does not depend on ionizable functionalities and can thus be applied to a wider range of drug molecules. Co-crystals can alter salient physicochemical properties such as solubility, dissolution rate, stability, hygroscopicity, and mechanical behavior of the API while conserving its pharmacological activity. Regulatory approval of pharmaceutical cocrystals has increased over the past few years, with several cocrystal-based drug therapies approved [6]. Ketoconazole has been found to coform with several dicarboxylic acids using crystal engineering tactics, leading to notable amplifications in aqueous solubility. For instance, cocrystals with fumaric acid as the pharmaceutically acceptable coformer have exhibited more than a 35-fold increase in solubility relative to ketoconazole alone. Such results highlight the potential of cocrystal technology to enhance the dissolution

properties of poorly soluble antifungal drugs. Similarly, itraconazole solid dispersion systems have been reported to increase drug wettability, reduce crystallinity, and enhance dissolution behavior [7]. Although these methods have been widely used to enhance solubility, comparative investigations to assess their performance for azole antifungal drugs remain underdeveloped. Knowledge of the advantages and limitations of these strategies is crucial when rationally designing formulations and selecting drug delivery systems for poorly water-soluble antifungal drugs. In fact, comparative assessment may provide valuable information on how different solid-state modification approaches affect drug dissolution behavior in distilled water as well as the overall biopharmaceutical performance of the administered drugs [8]. The present investigation was therefore designed to compare solid dispersion and co-crystallization techniques to enhance the solubility and dissolution of ketoconazole and itraconazole. This investigation systematically evaluated these two formulation methods to establish a scientific foundation for selecting suitable solubility enhancement techniques for BCS Class II antifungal drugs. It is anticipated that the results of this study will provide a basis for the discovery of more potent oral formulations with improved bioavailability, treatment efficacy, and patient outcomes.

MATERIALS AND METHODS

Materials

Ketoconazole and Itraconazole (from Ajanta Pharmaceuticals Pvt. Ltd., Guwahati, India. Polyethylene glycol 10000 (PEG 10000), hydroxypropyl methylcellulose (HPMC E50), Eudragit®S100, guar gum, modified guar gum, and chitosan as hydrophilic carriers for preparation of solid dispersions were purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Benzoic acid and tartaric acid (coformer), selected for co-crystal development, were procured from Northeast Chemicals, Panbazar, Guwahati, Assam, India. All reactants and solvents in this study were of analytical grade and used as received without further purification.

Preparation of Solid Dispersions

The solvent evaporation method was used to prepare solid dispersions of ketoconazole and itraconazole. The precise weights of drug and hydrophilic polymer were dissolved in a denaturing solvent comprising ethanol or an ethanol–acetone blend at various concentrations of drug-to-polymer ratio (1:1, 1:1.5, and 1:2) **(Table 1).** Stirring was continued until all the powder had dissolved and a homogeneous solution was obtained, after which the solvent was removed under reduced pressure to give a dry mass. The dried physical mixture was ground, then sieved through a 60-mesh screen to achieve uniform particle size and stored in a desiccator for further characterization and evaluation [9, 10].

Preparation of Pharmaceutical Co-crystals

The solvent evaporation method was employed to prepare co-crystals of ketoconazole and itraconazole. Both drugs were co-crystallized independently with appropriate hydrogen-bond-forming coformers, benzoic acid and tartaric acid, at molar ratios of 1:1, 1:2, and 1:3 (Table 2). The accurately weighed ingredients were dissolved in ethanol with constant stirring to produce a transparent solution. The resulting solution was left to slowly evaporate at room temperature to encourage the formation of co-crystals. The crystalline mass obtained was isolated, dried, powdered, and sieved to a uniform particle size, then stored in airtight containers for characterization and evaluation studies [10, 11].

Solubility study of solid dispersions

The solubility of ketoconazole from the solid dispersion systems prepared with various hydrophilic carriers (HPMC E50, Eudragit S100, PEG 10000, modified guar gum and chitosan) was evaluated in distilled water. A solid dispersion equivalent to 20 mg was placed in test tubes and then added to 20 mL of distilled water. After 24 h, the samples were sonicated for 30 minutes to ensure good dispersion, then shaken in a thermostatic water bath at 25°C for 24 h until equilibrium solubility was reached. 10 mL of the supernatant was collected, decanted after equilibration, and centrifuged at 2200 rpm for 20 minutes. The resulting clear solution was filtered through a 0.45 µm membrane filter and centrifuged twice at 7000 rpm for 10 min to remove undissolved particles.

Then, 1mL of the clear supernatant was further diluted with methanol to a final volume of 9 mL, and the drug content was estimated by UV-Visible spectrophotometry at 246 nm. The solubility measurement of Itraconazole was performed as described above for Ketoconazole, using 20 mg-equivalent solid dispersion samples [11, 12]. The drug content was estimated spectrophotometrically at λmax (262 nm) for ITZ. The solubility is obtained by:

$$\%\ \boldsymbol{Increase\ in\ solubility} = \frac{\boldsymbol{SD\ solubility\ -\ Original\ drug\ solubility}}{\boldsymbol{Original\ drug\ solubility}} \times \mathbf{100}$$

Solubility study of co-crystals

The saturation solubility of ketoconazole and itraconazole cocrystals, which are prepared with benzoic acid and tartaric acid as the coformers, was also calculated in distilled water. The co-crystal samples corresponding to 20 mg of drug were placed in test tubes with 20 mL of distilled water. The samples were sonicated for 30 min to ensure complete dispersion and then shaken in a water bath at 25°C for 24 h until equilibrium solubility was reached. After equilibrium, the supernatant was extracted with 10 mL and centrifuged at 2200 rpm for 20 min to remove unagitated particles. The supernatant was filtered through a 0.45 µm membrane filter and then centrifuged twice at 7000 rpm for 10 min, yielding a clear solution. 1 mL of the clear solution was transferred to a 10 mL volumetric flask and diluted with methanol. The concentration was determined using a UV-Visible spectrophotometer at 262 nm for itraconazole and the specific λmax for ketoconazole [12,13]. All experiments were conducted in triplicate and presented as the mean ± SD.

Solid State Characterization

Equilibrium solubility and in vitro dissolution rates of prepared solid dispersion and co-crystal formulations of KTZ and ITZ were carried out to assess drug-excipient compatibility, thermal analysis, crystal habit modification, crystallinity alteration, PXRD patterns as well as confirmation for the formation of co-crystals [14, 15].

Fourier Transform Infrared (FT-IR) Spectroscopy

Drug-carrier compatibility and intermolecular interactions present in ketoconazole (KTZ) and itraconazole (ITZ) solid dispersions, as well as co-crystal formulations, were studied using Fourier Transform Infrared (FT-IR) spectroscopy. The FT-IR spectra of the pure drugs, coformers, physical mixtures, solid dispersions, and co-crystals were obtained using the KBr pellet method with an FT-IR spectrophotometer (PerkinElmer Spotlight 400/Aurora). In brief, samples were ground with powdered potassium bromide (KBr) and pressed into transparent pellets using a hydraulic press. The spectra were obtained over the range 4000 – 400 cm^{-1} at room temperature with sufficient resolution. The spectra were analyzed for the characteristic peaks of functional groups and for peak shifts, disappearance, or broadening suggesting hydrogen bonding, drug-polymer interaction, and co-crystal formation [15, 16].

Differential Scanning Calorimetry (DSC) Analysis

Differential scanning calorimetry (DSC 200; Germany) was used to analyze the solid dispersions and co-crystal formulations of ketoconazole (KTZ) and itraconazole (ITZ). About 5 mg of drug, accurately weighed, was placed in a sealed aluminum pan, and a reference was taken with an empty aluminum pan. DSC measurements were performed with a nitrogen flow rate of 20 mL/min and a heating rate of 10°C/min over the temperature range of 30-200°C [17, 18]. Thermograms were obtained to study melting behavior, drug-carrier interactions, and changes in crystallinity resulting from the formation of the solid dispersion and co-crystal.

Powder X-ray Diffraction (PXRD) Analysis

Powder X-ray diffraction (PXRD) was carried out to determine the crystallinity of ketoconazole (KTZ) and itraconazole (ITZ) in solid dispersions and co-crystal forms. X-ray powder diffraction patterns of pure drugs, coformers, physical mixtures, solid dispersions, and cocrystals were collected on an X-ray powder diffractometer (Bruker D8 Venture 2015). Slightly powdered samples were deposited on the sample holder, and measurements were conducted using Cu-Kα radiation (λ = 1.5406 Å) under appropriate voltage and current conditions. The data were collected over the 2θ range of 5°–50° at room temperature in continuous-scan mode. The diffraction patterns were analyzed to detect characteristic peaks of pure drugs and changes in peak intensities, disappearance or appearance of new diffraction peaks, revealing a lower crystallinity state in solid dispersions and co-crystalline phase formation [19, 20].

Preparation of Solid Dispersion and Co-crystal Tablets for two Azole drugs

The tablets of ketoconazole-PEG 1000 solid dispersion and itraconazole-HPMC E50 solid dispersion were prepared by direct compression to achieve a drug content of 200 mg. The drug amount equivalent to 200 mg was then precisely weighed and mixed with appropriate direct-compressing excipients, including microcrystalline cellulose (diluent), croscarmellose sodium (superdisintegrant), talc (glidant), and magnesium stearate (lubricant) [20, 21]. All excipients, excluding talc and magnesium stearate, were sieved through a #60 sieve and then blended for 10–15 minutes to obtain a homogeneous powder blend. Lubricant and glidant were compounded during mixing for 2–3 min. The blended mass was compressed into tablets (450 mg each) on a single-station tablet compression machine using flat-faced punches to ensure consistent compression force and die fill volume, resulting in tablets with consistent weight and hardness. The prepared tablets were packed in airtight containers and stored at room temperature for further studies. Tablets based

on KTZ-TA and ITZ-TA were also formulated with a similar excipient.

Evaluation of Tablets

All the compressed tablets were evaluated for post-compression parameters, including physical appearance, weight variation, thickness, hardness, friability, disintegration time, and drug content uniformity, using standard pharmacopeial methods. Weight variation was calculated by weighing 20 tablets, and hardness was determined with a Monsanto hardness tester. Tablet friability was measured according to the European Pharmacopeia on a Roche friabilator rotating at 25 rpm for 100 revolutions. The disintegration time was measured using a USP disintegration apparatus at 37 ± 0.5 °C. The drug concentration was estimated at a suitable dilution using UV–visible spectrophotometry after trituration of patients' powdered tablets [22, 23]. All measurements were done in triplicate, and values were expressed as Mean ± SD.

In vitro Drug Release Study

In vitro drug release of ketoconazole–PEG 1000 SD tablets and itraconazole–HPMC E50 SD tablets (both containing 200 mg drug) was evaluated using a USP dissolution test apparatus II (paddle method). Dissolution testing was conducted in 900 mL of 0.1 N HCl (pH 1.2) at 37 ± 0.5°C with a hull speed of the paddles at 50 rpm. 5 mL portions of the dissolution medium were withdrawn and replaced with an equal volume of fresh, preheated dissolution medium at sink conditions; removed samples were collected at 30 min intervals. The withdrawn samples were filtered through a 0.45 µm membrane filter, appropriately diluted if needed, and analyzed by UV–Visible spectrophotometry at 262 nm for itraconazole and at the λmax for ketoconazole [22, 23]. All experiments were performed in triplicate, and the cumulative percentage drug release versus time was plotted.

Drug Release Kinetics

The drug release mechanism of ketoconazole and itraconazole in vitro dissolution from solid dispersion tablets (KTZ–PEG 10000 and ITZ–HPMC E50) and cocrystal tablets (KTZ–TA and ITZ-TA) was evaluated by mathematical kinetic model analysis. The cumulative drug release data were analyzed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models by linear regression. The release model that best fit each formulation was determined based on R^2. The Korsmeyer-Peppas equation release exponent (n) was employed to describe the drug release mechanism of the prepared tablet formulation [23, 24].

Stability studies

The optimization of formulation, ketoconazole-PEG 10000 solid dispersion tablets, itraconazole–HPMC E50 solid dispersion tablets, ketoconazole-tartaric acid co-crystal tablet (KTZ-TA) and itraconazole–tartaric acid co-crystal tablet (ITZ-TA), were subjected to accelerated stability studies as per ICH Q1A (R2) guidelines. The tablets were stored in a moisture-protective pack under accelerated conditions (40±2°C, 75±5% RH) for 6 months. Samples were taken at 0, 1, 3, and 6 months and analyzed for appearance, hardness, friability, actual drug content, and in vitro drug release. The hardness, the friability, and the drug content of KTZ–PEG 10000 SD tablets, ITZ–HPMC E50 SD tablets, and the tartaric acid co-crystal formulations of KTZ and ITZ were measured using a tablet hardness tester, a Roche friabilator, and a validated UV spectrophotometric method, respectively. In vitro dissolution studies were performed under previously optimized conditions using a USP Type II (paddle) dissolution rate test apparatus. The stability of these formulations was evaluated by comparing the storage data with those obtained from fresh samples [24, 25].

RESULTS AND DISCUSSION

Solubility Analysis of Ketoconazole and Itraconazole Solid Dispersions

The improved aqueous solubility of ketoconazole is 87 µg/mL (0.087 mg/mL), as reported in Table 1, which is the same concentration expressed in different units. With respect to comparison with Itraconazole, solubility in water is extremely low, occurring at roughly 1–4 ng/mL in neutral aqueous media. Thus, the solubility of Ketoconazole (87 µg/mL) is several orders of magnitude higher than that of Itraconazole. Notably, despite these differences in absolute values, both drugs fall within the parameters of BCS Class II antifungal agents, since their absorption in oral dosage forms is limited by dissolution rate over permeability. Ketoconazole is a pH-dependent solubility compound that dissolves better in acidic media, whereas itraconazole remains almost insoluble over the physiological pH range; formulation approaches such as solid dispersions and co-crystallization techniques are needed to increase its bioavailability. The saturation solubility studies indicated a notable increase in the aqueous solubility of ketoconazole when formulated as a solid dispersion with selected hydrophilic polymers. Solubility studies revealed that

the pure drug had a solubility of 87 µg/mL, indicating that it was insoluble or sparingly soluble in water. The solubility of all solid dispersion formulations noticeably increased, which demonstrates the retarded drug release efficiency by polymeric drug dissolution.

Table 1: Solubility of Ketoconazole in solid dispersions with hydrophilic polymers tested in aqueous medium (drug: polymer ratio, 1:1 to 1:2)

Formulation Code	Drug (mg)	Polymer	Polymer Qty (mg)	Drug: Polymer Ratio	Solvent Used	Solubility of Pure Drug (µg/mL)	Solubility of Solid Dispersion (µg/mL) ±SD	% Increase in Aqueous Solubility
SD-HPMC-1	100	HPMC E50	100	1:1	Ethanol	87	420 ± 12	382%
SD-HPMC-2	100	HPMC E50	150	1:1.5	Ethanol	87	690 ± 18	693%
SD-HPMC-3	100	HPMC E50	200	1:2	Ethanol	87	910 ± 20	945%
SD-PEG-1	100	PEG 10000	100	1:1	Ethanol	87	510 ± 15	486%
SD-PEG-2	100	PEG 10000	150	1:1.5	Ethanol	87	880 ± 22	912%
SD-PEG-3	100	PEG 10000	200	1:2	Ethanol	87	1210 ± 30	1290%
SD-GG-1	100	Eudragit S100	100	1:1	Ethanol	87	290 ± 10	233%
SD-GG-2	100	Eudragit S100	150	1:1.5	Ethanol	87	470 ± 14	440%
SD-GG-3	100	Eudragit S100	200	1:2	Ethanol	87	640 ± 18	636%
SD-MGG-1	100	Mod. Guar Gum	100	1:1	Ethanol	87	210 ± 8	141%
SD-MGG-2	100	Mod. Guar Gum	150	1:1.5	Ethanol	87	360 ± 12	314%
SD-MGG-3	100	Mod. Guar Gum	200	1:2	Ethanol	87	540 ± 16	520%
SD-CH-1	100	Chitosan	100	1:1	1% Acetic Acid + EtOH	87	330 ± 11	279%
SD-CH-2	100	Chitosan	150	1:1.5	1% Acetic Acid + EtOH	87	520 ± 14	497%
SD-CH-3	100	Chitosan	200	1:2	1% Acetic Acid + EtOH	87	750 ± 20	762%

Solid dispersions with PEG 10000 as the selected polymer achieved one of the highest increases in solubility, especially at a drug-polymer ratio of 1:2, with a solubility enhancement of about 1210 ± 30 µg/mL, which was also the maximum achievable among all formulations. The HPMC E50 formulation also showed a marked improvement, with a solubility of approximately 910 ± 20 µg/mL at the same ratio (Table 1). Eudragit S100, modified guar gum, and chitosan solid dispersion systems showed a steady moderate increase in solubility. The increased solubility was believed to result from reduced drug crystallinity, enhanced wettability, larger surface area, and molecular dispersion of ketoconazole in hydrophilic polymer matrices. These results suggest that solid dispersion technology can be a powerful tool for improving the solubility and possibly the oral bioavailability of the poorly water-soluble antifungal drug ketoconazole. Based on physicochemical compatibility and preliminary carrier screening, PEG-10000 and HPMC E50 were selected as optimized carriers for solid dispersions of Ketoconazole and Itraconazole. Ketoconazole is a weakly basic BCS Class II drug with intermediate lipophilicity. When PEG-10000, known for its high aqueous solubility and low melting point, was formulated with ketoconazole, it improved the wettability of the solid form, reduced interfacial tension between the solvent and insoluble substrate, and decreased drug crystallinity, ultimately leading to better dissolution properties. Itraconazole has very low aqueous solubility and high lipophilicity, with a strong tendency to recrystallize; thus, HPMC E50 was chosen for its hydrogen-bonding and precipitation-inhibiting properties, which stabilize supersaturation. Initial tests indicated enhanced dispersion stability and improved dissolution, thus suggesting their role as optimized carriers. Ethanol was chosen because of its sufficient solubilizing power for ketoconazole and its compatibility with polymers such as PEG 10000, HPMC E50, and Eudragit S100, while the ethanol–acetic acid mixture was used to improve the solubility of polymers such as chitosan.

Ethanol provided good internal solubilization of the systems due to its moderately polar structure and its removability by solvent evaporation. For polymers such as chitosan, the ethanol–acetic acid mixture improved solubility and ensured homogeneous mixing with the drug before evaporation.

Table 2: Solubility of Itraconazole in solid dispersions with hydrophilic polymers tested in pH 1.2 simulated gastric juice (drug: polymer ratio, 1:1 to 1:2)

Formulation Code	Drug (ITZ)	Polymer	Polymer Quantity (mg)	D/P Ratio	Solvent Used	Solubility of ITZ (µg/mL) in 0.1 M HCl	Solubility of SDs (µg/mL) in 0.1 M HCl	% increase in solubility
SD-HPMC-1	100 mg	HPMC E50	100 mg	1:1	Ethanol	1.8	54.1±3.4	2905.56%
SD-HPMC-2	100 mg	HPMC E50	150 mg	1:1.5	Ethanol	1.8	62.5±4.1	3372.22%
SD-HPMC-3	100 mg	HPMC E50	200 mg	1:2	Ethanol	1.8	48.4±3.7	2588.89%
SD-PEG-1	100 mg	PEG 10K	100 mg	1:1	Ethanol	1.8	14.2±1.5	688.89%
SD-PEG-2	100 mg	PEG 10K	150 mg	1:1.5	Ethanol	1.8	18.7±1.3	938.89%
SD-PEG-3	100 mg	PEG 10K	200 mg	1:2	Ethanol	1.8	11.5±1.2	538.89%
SD-GG-1	100 mg	Guar Gum	100 mg	1:1	Ethanol	1.8	2.0±0.5	11.11%
SD-GG-2	100 mg	Guar Gum	150 mg	1:1.5	Ethanol	1.8	2.4±0.2	33.33%
SD-GG-3	100 mg	Guar Gum	200 mg	1:2	Ethanol	1.8	1.8±0.5	0.00%
SD-MGG-1	100 mg	Mod. Guar Gum	100 mg	1:1	Ethanol	1.8	11.4±1.3	533.33%
SD-MGG-2	100 mg	Mod. Guar Gum	150 mg	1:1.5	Ethanol	1.8	14.6±1.4	711.11%
SD-MGG-3	100 mg	Mod. Guar Gum	200 mg	1:2	Ethanol	1.8	9.5±1.1	427.78%
SD-CH-1	100 mg	Chitosan	100 mg	1:1	1% AA +EtOH	1.8	38.1±2.1	2016.67%
SD-CH-2	100 mg	Chitosan	150 mg	1:1.5	1% AA +EtOH	1.8	44.5±1.8	2372.22%
SD-CH-3	100 mg	Chitosan	200 mg	1:2	1% AA +EtOH	1.8	35.4±2.0	1866.67%

Table 2 shows that for HPMC and PEG, the 1:1.5 ratio often outperformed the 1:2 ratio. While increasing polymer concentration consistently improves wettability and amorphous stabilization, excess polymer could increase microenvironmental viscosity around dissolving particles and ultimately impede drug diffusion into the dissolution media. The best solubility was observed at the optimal 1:1.5 ratio, with reduced drug crystallinity and uniform molecular dispersion contributing to enhanced solubility. However, excessive increases in polymer content can lead to partial entrapment of the drug within the polymeric matrix. This non-linear behavior has already been well documented for known hydrophilic carrier-based solid dispersions. It confirms that an optimal carrier concentration exists at which maximum dissolution enhancement can be achieved. Cumulative percent release of itraconazole from the marketed tablet and prepared formulations was determined in 0.1 M HCl (pH 1.2 simulated gastric fluid). A saturation solubility study was also conducted in this medium, indicating improved dissolution properties for Itraconazole when formulated as solid dispersions with hydrophilic polymers. The drug itself was highly insoluble in water, with a saturation solubility of about 1.8 µg/mL. The solid dispersion formulations exhibited higher solubility than the pure drug, indicating that polymeric carriers effectively improve dissolution in an acidic medium. HPMC E50-based solid dispersions exhibited the maximum enhancement in solubility of all the polymers studied, especially at a drug: polymer ratio (1:1.5), due to which the solubility was increased up to 62.5 ± 4.1 µg/mL (Table 2). Chitosan formulations also showed significant improvement, with solubility values ranging from 35 to 44 µg/mL, likely due to chitosan protonation at acidic pH. PEG 10000 formulations demonstrated a moderate enhancement, and guar gum/modified guar gum dispersions showed lower improvement. As a result, the higher the polymer content, the greater the solubility enhancement of itraconazole, leading to better amorphization and wettability of the drug. Overall, the results supported the effectiveness of solid dispersion technology in enhancing the solubility of itraconazole, as well as its dissolution and oral bioavailability. In the current work, the solubility of Itraconazole was measured in solid dispersion formulations using a simulated gastric fluid (pH 1.2) system to mimic its pH-dependent solubility better and enhance physiological relevance. In contrast, equilibrium solubility for pure drugs and co-crystal systems was determined in distilled water for comparison purposes only. Even though solubility studies of ketoconazole & itraconazole were performed in media mimicking their respective physicochemical characteristics at the same time, future comparative studies should involve standardized evaluation in a single medium (e.g., distilled water; pH 1.2, pH 4.5 & pH 6.8 buffers) to allow direct comparison of formulation performance under various GI pH conditions.

Solubility studies of ketoconazole and itraconazole co-crystals

Co-crystallization with benzoic acid and tartaric acid significantly improved the aqueous solubility of ketoconazole across all drug:co-former ratios (1:1–1:3 w/w). A concentration-dependent increase in solubility was observed as co-former content increased, indicating modification of the drug crystal lattice and a reduction in lattice energy. Among the co-formers investigated, tartaric acid co-crystals consistently exhibited greater solubility enhancement than benzoic acid systems (Table 3). This improvement may be attributed to the higher intrinsic solubility of tartaric acid, its stronger hydrogen-bonding ability due to multiple hydroxyl and carboxyl groups, and the possible formation of a salt–co-crystal continuum with the basic ketoconazole molecule.

The solvent evaporation method successfully produced reproducible and stable co-crystal systems, as indicated by low variability in solubility values. The 1:3 drug:co-former ratio was identified as the optimized composition for both co-formers, showing maximum solubility enhancement. Overall, the findings demonstrate that co-crystallization is an effective solid-state approach to enhancing ketoconazole solubility, with ketoconazole–tartaric acid co-crystals showing strong potential to improve dissolution and oral bioavailability. Co-crystallization with benzoic acid and tartaric acid resulted in a substantial enhancement of the solubility of itraconazole at all drug:co-former ratios (1:1–1:3 w/w). A ratio proportional to the solubility enhancement as co-former concentration increased was observed, suggesting lattice modification and improved drug–water interactions. Of all the co-formers investigated, tartaric acid co-crystals always demonstrated greater solubilization as compared to the benzoic acid system; this was attributed to the stronger hydrogen bonding potential of the former and higher intrinsic solubility thereof.

The maximum solubility improvement was observed at a 1:3 drug:co-former ratio**.** Collectively, these results indicate that co-crystallization is a promising approach to enhance itraconazole solubility and that tartaric acid may be the most suitable co-former, with distinct potential for dissolution and anticipated oral bioavailability. Co-crystallization is intrinsically a stoichiometric process that relies on particular intermolecular interactions (for example, hydrogen bonding), and as such, molar ratios are usually taken into account during experimental preparations.

In this study, the drug and co-formers were initially selected from a stoichiometric (molar) perspective to enable the formation of stable supramolecular synthons. For practical formulation manipulation and reproducibility in solvent-evaporation processing, however, the compositions are expressed as weight ratios (w) in Table 3. The weight ratios chosen (1:1, 1:2, and 1:3), which imply proportional escalations in co-former content relative to the drug, were derived from their respective molar equivalents, based on molecular weight differences between the drug and co-formers. These weight ratios were represented in Table 3 for experimental convenience; however, the formulation design was guided by stoichiometric principles consistent with co-crystal engineering approaches.

Table 3: Aqueous solubility of ketoconazole and itraconazole co-crystals prepared with benzoic acid and tartaric acid by solvent evaporation technique

Drug	F. Code	Drug (mg)	Co-former	Co-former (mg)	Drug: Co-former Ratio (w:w)	Solvent Used	Solubility of Pure Drug (µg/mL)	Solubility of Co-crystal (µg/mL ± SD)	% Increase in Aqueous Solubility
Ketoconazole	CC-BA-1	100	Benzoic acid	100	1:1	Ethanol	87	156 ± 4.8	79.3
Ketoconazole	CC-BA-2	100	Benzoic acid	200	1:2	Ethanol	87	212 ± 6.1	143.7
Ketoconazole	CC-BA-3	100	Benzoic acid	300	1:3	Ethanol	87	268 ± 7.4	208.0
Ketoconazole	CC-TA-1	100	Tartaric acid	100	1:1	Ethanol	87	182 ± 5.3	109.2
Ketoconazole	CC-TA-2	100	Tartaric acid	200	1:2	Ethanol	87	248 ± 6.9	185.1
Ketoconazole	CC-TA-3	100	Tartaric acid	300	1:3	Ethanol	87	315 ± 8.2	262.1
Itraconazole	CC-BA-1	100	Benzoic acid	100	1:1	Ethanol	1.8	5.2 ± 0.4	188.9
Itraconazole	CC-BA-2	100	Benzoic acid	200	1:2	Ethanol	1.8	7.8 ± 0.6	333.3
Itraconazole	CC-BA-3	100	Benzoic acid	300	1:3	Ethanol	1.8	10.6 ± 0.9	488.9
Itraconazole	CC-TA-1	100	Tartaric acid	100	1:1	Ethanol	1.8	6.4 ± 0.5	255.6
Itraconazole	CC-TA-2	100	Tartaric acid	200	1:2	Ethanol	1.8	9.6 ± 0.7	433.3
Itraconazole	CC-TA-3	100	Tartaric acid	300	1:3	Ethanol	1.8	13.9 ± 1.1	672.2

The systems were designed using stoichiometric molar ratios to govern supramolecular interactions and hydrogen-bond formation between the co-former and the drug. For practical formulation processing and experimental reproducibility, the compositions are presented in Table 3 as weight-to-weight (w:w) ratios, based on molar equivalents derived from molecular weight differences between components. Solid dispersion (SD) formulations exhibit a more pronounced improvement in solubility than co-crystal (CC) systems; this finding may be explained by intrinsic differences in solid-state characteristics and, consequently, in transition pathways during dissolution. In SDs, the drug is mostly present in a dispersed or amorphous state, distributed in co-solvent-hydrophilic polymers such as PEG-10000 and HPMC E50, leading to higher free energy and rapid supersaturation of the solution ("spring effect"). These polymers subsequently stabilize supersaturation and prevent recrystallization ("parachute effect"). By contrast, an ordered crystalline structure exists under the lattice-modified state in CCs to a larger extent than in amorphous SD systems, thus restricting solubility enhancement.

FT-IR Studies

The potential molecular interactions and compatibility between azole antifungal drugs and hydrophilic carriers in physical mixtures and solid dispersion systems were studied using FT-IR spectroscopy. The FT-IR spectrum of pure KTZ exhibited the characteristic absorption bands due to, N–H stretching (3400–3200 cm^{-1}), aliphatic C–H stretching (2960–2850 cm^{-1}), C=N and aromatic C=C stretching (1640–1500 cm^{-1}) and C–O–C/C-C-N vibrations (1250–1020 cm^{-1}), which confirms the integrity of the drug structure. The PEG 10000 spectrum shows characteristic peaks at about 2880 cm^{-1} (C–H stretching), 1465 cm^{-1} (CH_2 bending), and around 1100 cm^{-1} (C–O–C stretching). The physical mixture of KTZ and PEG 10000 showed the principal peaks of both the crystalline and molecular backgrounds, which, without appreciable shifts or changes in their patterns, developed new bands characteristic of both components, indicating that there is no chemical interaction between them. In the solid dispersion spectrum, peaks of ketoconazole can still be identified; however, it was found to be broadened with decreased intensity, particularly in the fingerprint region, indicating hydrogen bonding and enhanced molecular-level dispersion of the drug by chemical stability in the PEG matrix (Figure 1A). FT-IR spectroscopy was also performed on the itraconazole–HPMC E50 systems, as HPMC E50 exhibited the greatest increase in solubility. Pure itraconazole exhibited peaks due to O–H/aromatic C–H stretching (3400–3200 cm^{-1}), aliphatic C–H stretching (2950–2850 cm^{-1}), C=O and aromatic C=C stretching (1700–1500 cm^{-1}) and C–O–C stretching for ether groups at 1100~1000 cm^{-1}. HPMC E50 showed characteristic bands of cellulose-ether type polymer: O–H stretching around 3400 cm^{-1}, C–H stretching about 2900 cm^{-1}, and C–O–C stretching at 1050 – 1100 cm^{-1}. The absence of a peak shift in the physical mixture and the slight band broadening and decrease in peak intensity observed for the solid dispersion confirmed hydrogen bonding as well as molecular dispersion, which supports drug stability (Figure 1B). FT-IR spectroscopy was also performed to evaluate intermolecular interactions between ketoconazole (KTZ) and tartaric acid (TA) in physical mixture and co-crystal formulations. Pure ketoconazole showed characteristic peaks such as an N–H stretching band at 3400–3200 cm^{-1}, aliphatic C–H (2900 and 2850 cm^{-1}) stretching bands, C=N and aromatic C=C stretches at 1650–1500 cm^{-1} , and those due to the C–O–C/C–N vibrations from 1250 to1020 cm^{-1}. Tartaric acid exhibited a wide O–H stretching band in the region 3500–3200 cm^{-1}, a strong C=O stretching peak at 1700 cm^{-1}, and C–O stretching bands between 1200 and 1000 cm^{-1}. The physical mixture showed superimposed peaks for both components without shifts, indicating that no interaction occurred during mixing. In contrast, the co-crystal exhibited peak broadening and slight shifts, particularly in the O–H/N–H and carbonyl regions, indicating the formation of a hydrogen bond between KTZ and TA. No new degradation peaks were noted, indicating chemical stability and successful co-crystallization (Figure 1C). Among the co-formers, itraconazole showed the maximum solubility in the tartaric acid co-crystal system; hence, compared to the physical mixture, other formulations with tartaric acid were also screened by FT-IR for drug–co-former compatibility studies and to predict any intermolecular interactions between the drug and the co-former. Characteristic peaks of pure itraconazole showed a broad band at 3400–3200 cm^{-1} (O–H and aromatic C–H stretching), peak values at 2950–2850 cm^{-1} (aliphatic C–H stretching) and bands in the range of 1700–1500 cm^{-1} (C=O, aromatic C=C stretching), as well as intense vibrations from stretching of the C–O–C bond couples medium strength in the ranges between 1100 and 1000 cm^{-1}. The O–H stretching vibration band of the tartaric acid was detected as a wide one at 3500–3200 cm^{-1}, the carbonyl (C=O) group was observed around 1700 cm^{-1}, and C–O stretching bands were found from 1200 to 1000 cm^{-1}. The physical mixture of the two components

showed superimposed peaks with minimal alterations, indicating compatibility between them. However, the co-crystal was found to undergo a small peak shift and broadening of peaks in the hydrogen-bonding-sensitive area, which implied the existence of intermolecular hydrogen bonding [17]. These spectral changes confirm successful co-crystal formation and the chemical stability of itraconazole in the ITZ–TA system (Figure 1D).

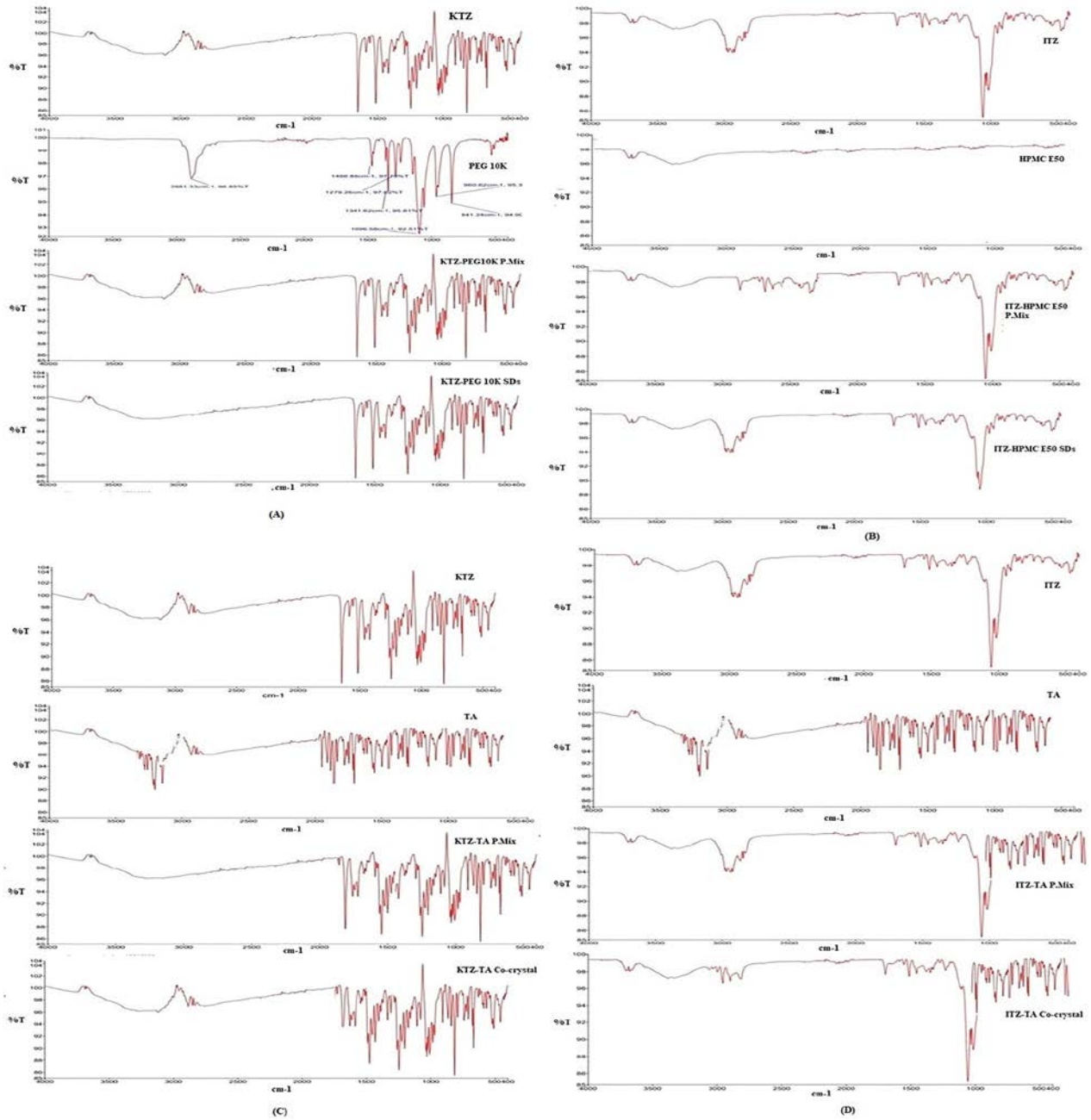

Figure 1: Comparative FT-IR analysis of (A) KTZ SDs, (B) ITZ SDs, (C) KTZ Co-crystals, (D) ITZ Co-crystals

For Ketoconazole, the stretching band of C=O (1645–1655 cm^{-1}) exhibited slight shifting and broadening, which suggests the formation of a hydrogen bond between ketoconazole and the hydroxyl group from PEG and co-formers. The C–N stretching region, at 1500–1550 cm^{-1}, showed changes that also supported molecular interaction in the carrier matrix. Likewise, given that it indicated the physical interactions of the formation of hydrogen bonds with polymer molecules (HPMC), where principal band shifts at around 1500–1600 cm^{-1} and broadening of bands (3200–3500 cm^{-1}) were seen for O-H stretching material from all HPMC-containing preparations and confirmed hydrogen-bonding interactions contributing to enhanced solubility improvement and amorphization.

Differential Scanning Calorimetry (DSC) Studies

Pure DSC thermogram of ketoconazole (KTZ) exhibited a sharp endothermic melting peak at 148–150°C, indicating the crystalline nature and stability of the drug. The thermogram of PEG 10000 showed a typical endothermic peak at around 60–65°C, indicating the polymer's melting point and semi-crystalline nature. For the KTZ-PEG10000 SDs, this melting peak was either markedly decreased in intensity or absent for ketoconazole, while the PEG 10000 remained visible with some broadening. This shift demonstrates the conversion of ketoconazole from a crystalline to an amorphous or molecularly dispersed state in the PEG matrix.

The absence of a separate drug melting endotherm indicates successful solid dispersion and enhanced ketoconazole wettability/dissolution relative to the physical mixture, resulting from polymer-assisted amorphization (Figure 2A). The DSC thermogram of pure ITZ exhibited a sharp endothermic melting peak around 166–170 °C, indicating its crystalline nature. HPMC E50 had a broad endothermic peak in the temperature range of approximately 50–120 °C due to loss of physically absorbed water, suggesting the polymer was amorphous rather than having any well-defined melting point.

The physicochemical changes induced by the incorporation of guar gum, the resulting association between the itraconazole polymer, and changes in form with respect to molecular weight, for example, yielded good solubility when incorporated with substituents at lower concentrations. However, native guar gum swells within a few minutes to form an extremely viscous gel layer surrounding drug particles, thereby slowing their diffusion in the dissolution medium. In contrast to both HPMC E50 and PEG-10000, guar gum has a comparatively weaker hydrogen-bonding strength with azole antifungals, thereby providing less efficient molecular dispersion and short-range amorphous stabilization. PEG-10000 and HPMC E50 both improve wettability and reduce interfacial tension, whereas guar gum is a weak surface-active agent.

If excess guar gum is present, it likely forms a swollen polymeric matrix in which hydrophobic drug particles are entrapped, thereby hindering diffusion and limiting any enhancement of apparent solubility. Polymer selection in solid dispersion systems should be based not only on hydrophilicity but also on intermolecular compatibility between the drug and the polymer, viscosity, and the ability to stabilize supersaturation. The characteristic melting peak of itraconazole was suppressed or absent, but the polymer-related thermal transition was still observed in ITZ–HPMC E50 SDs. This indicates molecular dispersion of itraconazole within the HPMC matrix and the drug's amorphization. Loss of the melting endotherm for the drug indicates that a solid dispersion has been successfully formed, which is expected to improve the wettability and dissolution of itraconazole (Figure 2B).

DSC analysis confirmed co-crystal formation for both ketoconazole (KTZ) and itraconazole (ITZ) with tartaric acid (TA). Pure KTZ showed a sharp melting peak at about 150–155 °C, while TA exhibited characteristic thermal events near 205–210 °C and around 245–250 °C (Figure 2C). Similarly, pure ITZ displayed a melting peak at 165–170 °C, and TA showed its typical melting transition around 205–210 °C followed by a secondary event near 250–260 °C (Figure 2D).

Physical mixtures retained individual melting peaks of the components, indicating no significant interaction. In contrast, co-crystals showed the disappearance of drug and co-former melting peaks and the emergence of a new thermal transition, confirming the formation of a new crystalline phase. DSC analysis was conducted to assess alterations in the crystallinity and solid-state properties of the drugs within SD and CC systems.

In the optimized solid dispersion formulations, the characteristic melting endothermic peak of the pure drug was either eliminated or significantly reduced, indicating conversion of crystalline drug into an amorphous/molecularly dispersed state within the hydrophilic polymer matrix. The disappearance of the melting endotherm supports the formation of a true amorphous dispersion and correlates with the improvements in solubility and dissolution performance observed with SDs. In contrast, the optimized co-crystal formulations demonstrated either a shifted melting endothermic peak or the development of a new thermal event differing from those of the parent drug and co-former melting temperatures. Such thermal behavior is representative of co-crystal formation, during which a new crystalline supramolecular structure forms without complete amorphization. The retention of crystallinity in the CC systems also accounts for their comparatively modest yet stable improvement in solubility. Overall, these DSC results confirm the distinct solid transformations occurring in the SD and CC formulations.

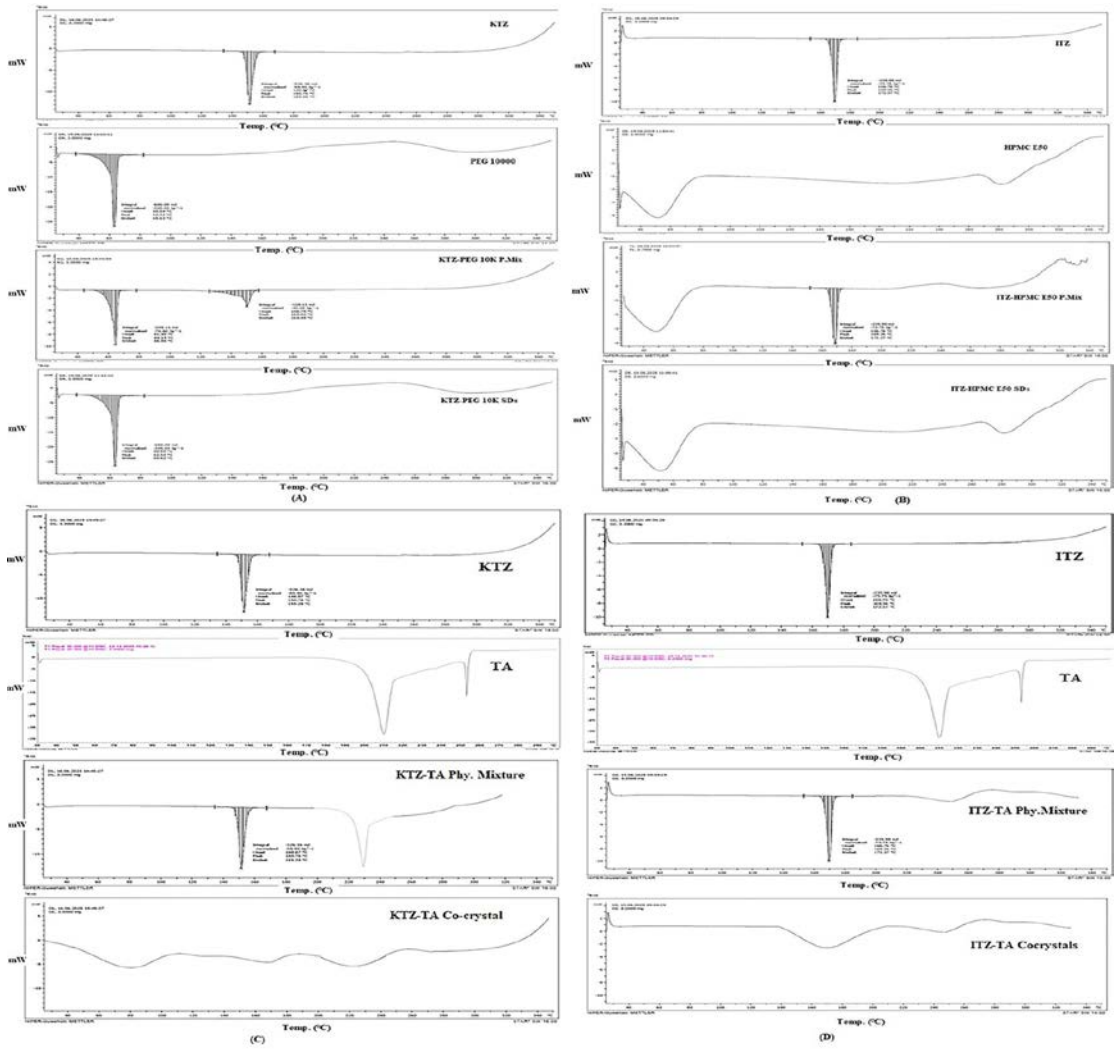

Figure 2: Comparative DSC analysis of (A) KTZ-PEG10K SDs (B) ITZ-HPMC E50 SDs (C) KTZ-TA Co-crystals (D) ITZ-TA Co-crystals

Powder X-ray diffraction

X-ray diffraction (XRD) analysis was carried out to examine the solid-state properties of ketoconazole–PEG and itraconazole–HPMC E50 solid dispersion systems. Pure ketoconazole exhibited sharp, intense diffraction peaks across the 2θ range, confirming its highly crystalline nature, whereas PEG displayed characteristic reflections consistent with its semi-crystalline structure. In the ketoconazole–PEG solid dispersion, a marked reduction in peak intensity, broadening of peaks, and partial disappearance of characteristic drug reflections were observed, along with a diffuse halo pattern, indicating transformation of ketoconazole into an amorphous or partially amorphous form within the polymer matrix (Figure 3A). Similarly, pure itraconazole exhibited distinct crystalline peaks, whereas HPMC E50 showed a broad amorphous halo typical of cellulose-based polymers. The itraconazole–HPMC E50 solid dispersion demonstrated a near-disappearance of the drug's crystalline peaks, confirming molecular dispersion and loss of crystallinity. The absence of new diffraction peaks in both systems indicates drug- polymer compatibility. These structural changes are expected to enhance solubility & dissolution performance (Figure 3B). For Co-crystal formulations, PXRD analysis revealed distinct differences between the individual components and the ketoconazole–tartaric acid cocrystal system. Pure ketoconazole (KTZ) and tartaric acid (TA) exhibited sharp, intense diffraction peaks within the 2θ range of 5–30°, confirming their highly crystalline nature and well-ordered lattice structures. In contrast, the ketoconazole–tartaric acid cocrystal (KTZ-TA) showed significant peak broadening, reduced intensity & disappearance of the characteristic peaks of both components, with the pattern dominated by a diffuse halo. These changes indicate disruption of the parent crystal lattices and formation of a new solid-state phase stabilized by intermolecular hydrogen bonding. The reduced crystallinity

suggests improved molecular disorder, which is expected to enhance solubility and dissolution behavior of ketoconazole through cocrystal formation (Figure 3C). PXRD analysis demonstrated clear distinctions between the individual components and the itraconazole–tartaric acid cocrystal. Pure itraconazole (ITZ) and tartaric acid (TA) exhibited sharp, intense diffraction peaks within the 2θ range of 6–30°, confirming their highly crystalline nature and ordered lattice structures. In contrast, the cocrystal (ITZ-TA) showed marked reduction in peak intensity, significant broadening, and disappearance of characteristic reflections of both components, with a dominant diffuse halo pattern. These findings confirm disruption of the parent crystal lattices and formation of a new solid-state phase stabilized by intermolecular hydrogen bonding. The reduced crystallinity and increased molecular disorder are expected to enhance solubility and dissolution, supporting the effectiveness of tartaric acid in itraconazole cocrystal engineering (Figure 3D). Nevertheless, one cannot exclude amorphization in solid dispersion (SD) formulations solely based on qualitative and semi-quantitative analyses of PXRD peak height reduction and broadening, even when supported by FTIR data or superior dissolution profiles, as these are commonly used measures of amorphization. However, the crystallinity fraction activity of biopharmaceuticals in SD and co-crystal systems is needed due to the major focus on comparative evaluation between both systems. Conversely, the reduced intensity of specific peaks is indirect evidence of significant amorphous conversion for SD drugs.

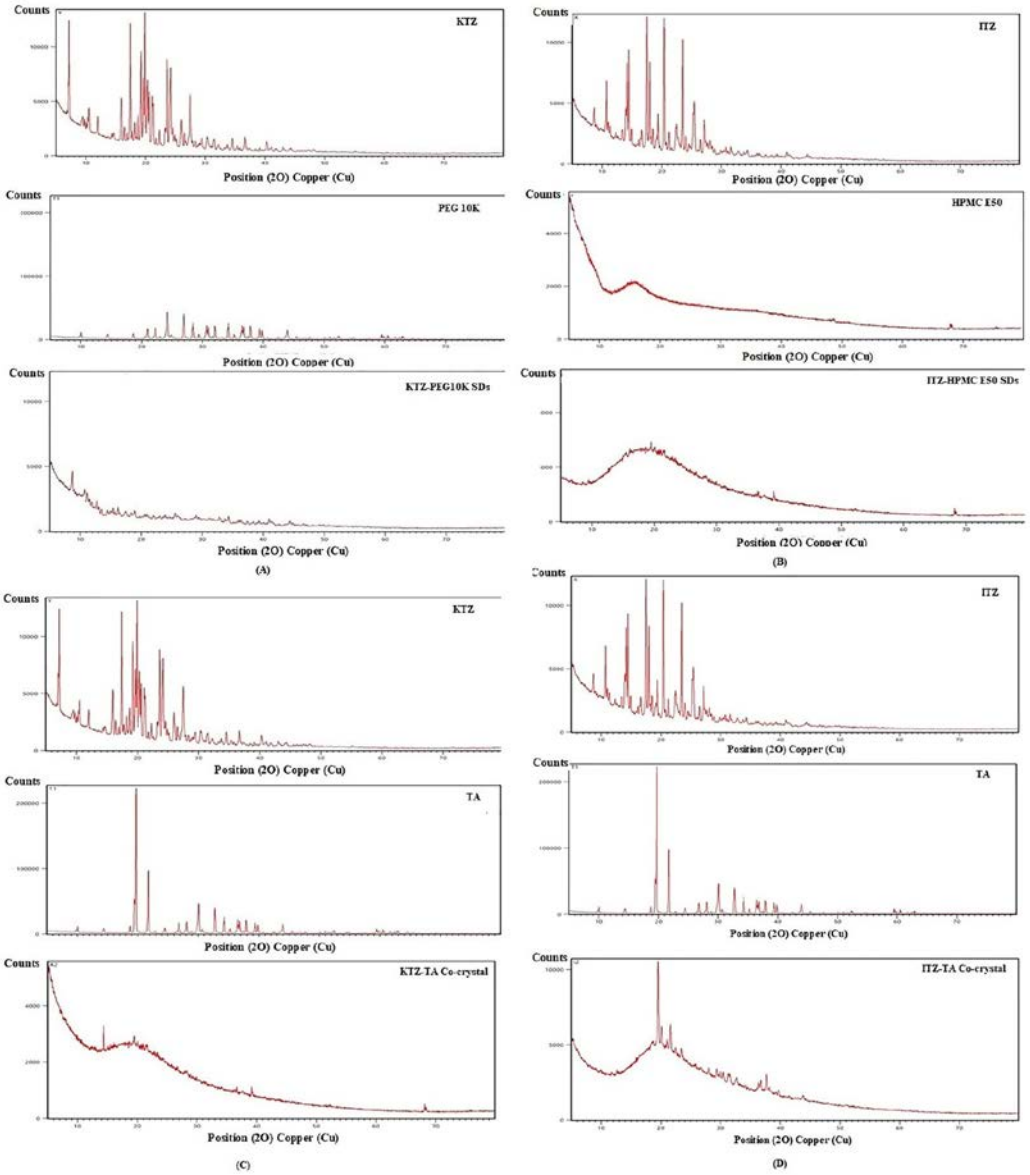

Figure 3: Comparative XRD analysis of (A) KTZ-PEG 10K SDs (B) ITZ-HPMC E50 SDs (C) KTZ-TA Cocrystal (D) ITZ-TA Cocrystal

Table 4: Formulation composition of solid dispersion and co-crystal tablets and their evaluation results

Parameter / Ingredient	% w/w	KTZ Solid Dispersion Tablet	ITZ Solid Dispersion Tablet	KTZ Co-crystal Tablet	ITZ Co-crystal Tablet
Formulation Composition					
Solid dispersion / Co-crystal (equiv. to 200 mg drug)	69.3	312 mg	312 mg	320 mg	320 mg
Microcrystalline cellulose (MCC)	—	120 mg	120 mg	110 mg	110 mg
Croscarmellose sodium	4	20 mg	20 mg	20 mg	20 mg
Talc	1	5 mg	5 mg	5 mg	5 mg
Magnesium stearate	1	5 mg	5 mg	5 mg	5 mg
Total weight (mg)	100	450	450	460	460
Evaluation Results	----	------	------	------	-------
Appearance	—	Smooth, uniform	Smooth, uniform	Smooth, uniform	Smooth, uniform
Average weight (mg)	—	449.6 ± 2.8	450.8 ± 3.1	459.2 ± 2.5	460.4 ± 2.7
Thickness (mm)	—	4.52 ± 0.06	4.48 ± 0.05	4.60 ± 0.07	4.58 ± 0.06
Hardness (kg/cm²)	—	5.4 ± 0.3	5.2 ± 0.4	5.8 ± 0.2	5.6 ± 0.3
Friability (%)	—	0.62	0.58	0.55	0.60
Disintegration time (min)	—	6.2 ± 0.4	6.5 ± 0.5	5.8 ± 0.3	6.0 ± 0.4
Drug content (%)	—	98.6 ± 0.9	99.1 ± 0.8	99.4 ± 0.7	98.9 ± 0.6

Solid Dispersion and Cocrystal Tablets Development

Solid dispersion tablets of ketoconazole–PEG 10000 and itraconazole–HPMC E50, as well as KTZ–TA and ITZ–TA cocrystal tablets corresponding to 200 mg of drug, were also obtained by direct compression (Table 4). The powder mixes showed good flow and compressibility, indicating that no granulation is necessary for direct compression. The solid dispersions or cocrystals were uniformly mixed with microcrystalline cellulose and crosscarmellose sodium to achieve uniform drug distribution. The overall conclusion is that the direct compression technique was found to be time-saving and reproducible for the development of either solid dispersion- or cocrystal-based tablets. All tablet formulations met the pharmacopeial limits for Uniformity of weight, hardness, friability (not more than 1), drug content (95-105%), and disintegration time (Table 4). Formulated co-crystal tablets showed marginally higher hardness and faster disintegration compared with solid dispersion tablets, suggesting satisfactory compressibility and homogeneous blending of excipients

Tablet Dissolution Profile of Solid Dispersion and Co-crystal Tablets

The solid dispersion tablets of ketoconazole-PEG 10000 and itraconazole-HPMC E50 exhibited faster, higher drug release in an acidic medium. Drug release was above 80% within an hour, and almost complete release took place at the end of two hours, showing enhanced dissolution characteristics of the solid dispersion formulations. As observed with tartaric acid co-crystals of ketoconazole and itraconazole, the tartaric acid co-crystal tablets of ketoconazole and itraconazole quickly dissolved in acidic conditions. Over 70% drug release was obtained within 30 min, and complete drug release was achieved within 90–120 min (Table 5). The enhanced dissolution characteristics of the co-crystal tablets could be attributed to increased solubility, decreased lattice energy, and improved wettability in a co-crystalline system. A rapid increase in the initial concentration of the drug in the systemic circulation is often desirable to achieve an early therapeutic effect, which has advantages over standard applications for acute infections with fungal elements that require a timely onset of antifungal action, in which burst release from co-crystal (CC) formulations could be beneficial. Conversely, SD formulations exhibited a relatively controlled drug-release profile (mediated by polymer-matrix diffusion), which would ensure sustained plasma levels and possibly minimize dosing frequency.

This release behavior confers unique clinical advantages for both CC and SD formulations. Thus, both release modalities have distinct clinical advantages: CC formulations particularly favor rapid therapeutic onset, whereas SD formulations maintain high drug exposure and enhanced antifungal efficacy. The co-crystal and solid dispersion systems exhibited distinct release profiles that could translate into formulation-specific therapeutic advantages; e.g., co-crystals may be well-suited for rapid-onset antifungal therapy, while solid dispersions support sustained systemic exposure and prolonged in vivo efficacy.

Table 5: In vitro drug release profile of ketoconazole–PEG 1000, itraconazole–HPMC E50 solid dispersion tablets, KTZ–tartaric acid, ITZ–tartaric acid co-crystal tablets in 0.1 N HCl (pH 1.2) (mean ± SD, n = 3)

Time (min)	% DR (KTZ–PEG 10000 SD Tablets)	% DR (ITZ–HPMC E50 SD Tablets)	% DR (KTZ–Tartaric Acid Co-crystal Tablets)	% DR (ITZ–Tartaric Acid Co-crystal Tablets)
0	0.00	0.00	0.00	0.00
5	18.42 ± 0.85	15.76 ± 0.72	25.18 ± 0.92	22.64 ± 0.88
10	32.15 ± 1.02	28.43 ± 0.94	41.76 ± 1.15	38.12 ± 1.02
15	45.87 ± 1.20	40.62 ± 1.10	58.34 ± 1.28	53.47 ± 1.19
30	63.24 ± 1.35	58.18 ± 1.28	76.92 ± 1.10	71.83 ± 1.26
45	74.91 ± 1.18	70.05 ± 1.22	88.15 ± 0.94	84.26 ± 1.05
60	84.36 ± 1.05	80.74 ± 1.14	94.72 ± 0.76	91.38 ± 0.88
90	93.12 ± 0.92	90.21 ± 0.96	98.21 ± 0.52	96.84 ± 0.64
120	98.45 ± 0.64	96.87 ± 0.72	99.12 ± 0.41	98.35 ± 0.55

Drug Release Mechanism of Tablet Formulations of Solid Dispersion and Co-crystal

The kinetic studies revealed that the first-order and Korsmeyer–Peppas models had higher correlation coefficients than the zero-order model. The diffusional release exponents (n) values were found to be in the range of 0.736- 0.828, indicating an anomalous (non-Fickian) pattern of drug release, implying that both diffusion and polymer chain relaxation imposed the release of drug from the solid dispersion matrix. The release data for ketoconazole–tartaric acid and itraconazole–tartaric acid co-crystal tablets were fitted to various kinetic models to determine the highest R2 value. The value of release exponent (n=0.76–0.78) indicates anomalous transport, which means the drug release from co-crystal tablets occurred through a combined diffusion/dissolution mechanism (Table 6). The Korsmeyer-Peppas model results for the release exponent (n) of all optimized formulations ranged from 0.736 to 0.828, confirming a non-Fickian (anomalous) transport mechanism in which coupled diffusion and dissolution processes occur. This indicates that drug release from SD and co-crystal tablets occurred via a combination of diffusion of drug molecules through a hydrated polymer matrix and polymer relaxation/erosion. Longer polymer chains that control release via matrix swelling resulted in higher n values in SD tablets, whereas co-crystal tablets exhibited comparably diffusion-dominated release patterns.

Table 6: Release kinetic parameters of tablets containing KTZ–PEG 10000 SDs, ITZ–HPMC E50 SDs, KTZ–TA Co-crystals and ITZ–TA Co-crystals.

Model	Parameter	KTZ–PEG 1000 SD Tab	ITZ–HPMC E50 SD Tab	KTZ–TA Co-crystal Tab	ITZ–TA Co-crystal Tab
Zero-order	k_0 (% min^{-1})	0.753	0.758	0.716	0.730
	R^2	0.811	0.845	0.689	0.731
First-order	k_1 (min^{-1})	0.032	0.027	0.0398	0.0342
	R^2	0.987	0.993	0.986	0.990
Higuchi	kH (% $min^{-½}$)	9.214	9.404	8.427	8.741
	R^2	0.949	0.965	0.862	0.894
Korsmeyer–Peppas	n	0.828	0.736	0.761	0.779
	R^2	0.999	0.984	0.999	0.999

Accelerated Stability Results of Tablet Formulations

Six-month accelerated stability studies conducted at 40 ± 2°C and 75 ± 5% RH demonstrated that ketoconazole–PEG 10000 solid dispersion tablets, itraconazole–HPMC E50 solid dispersion tablets, and the tartaric acid co-crystal formulations of ketoconazole and itraconazole remained stable under the applied stress conditions. There were no apparent changes in appearance and hardness , and friability remained within acceptable limits, suggesting mechanical integrity had been preserved. The drug content was found to be more than 97% and confirmed the chemical stability. Dissolution profiles were similar, indicating limited recrystallization or phase transformation. Overall, the formulations demonstrated acceptable physical and mechanical properties and chemical stability under accelerated storage conditions. Although accelerated storage did not significantly alter dissolution performance or drug content, minor recrystallization events in amorphous solid dispersions cannot be ruled out, even with advanced solid-state analytical techniques.

CONCLUSION

Both solid dispersion and co-crystallization approaches improved the solubility and dissolution of the poorly water-soluble azole antifungals, ketoconazole and itraconazole. Tartaric acid co-crystals showed good solubility improvement by tailoring the crystal lattice via intermolecular hydrogen bonding. FT-IR, DSC, and PXRD data confirmed a solid-state transformation without chemical degradation during processing. Dissolution profiles revealed enhanced and comparable release in both systems, while stability studies confirmed satisfactory physical and chemical stability. Nevertheless, the research was limited to in vitro testing and short-term stability, whereas in vivo bioavailability should be assessed for clinical significance. In today's pharmaceutical environment, with multiple emerging drug candidates exhibiting low solubility, this work underscores the applicability of solid dispersion and co-crystallization as feasible, scalable techniques for enhancing the oral delivery and therapeutic efficacy of BCS class II antifungal drugs. Selection between solid dispersion and co-crystallization strategies should ideally be based on therapeutic targets, physicochemical properties of the drug candidate, the desired release profile, and long-term stability requirements. Co-crystals may be preferable for rapid therapeutic onset and enhanced crystalline stability, while solid dispersions could improve dissolution and provide longer exposure to very poorly soluble antifungal drugs.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Payal Dasgupta conducted the experimental work, including preparation of solid dispersions/co-crystals and data collection. Bipul Nath conceived, designed, supervised the study, interpreted results, and finalized the manuscript. Apurba Talukdar contributed to data interpretation, manuscript writing, and critical review. Atanu Sarma assisted in formulation optimization, characterization, and data validation. Sidhartha Jyoti Bora performed statistical analysis and literature review. All authors reviewed, approved, and are accountable for the final manuscript.

DECLARATION OF USE OF AI TOOLS

The authors used the HIX AI tool to assist with language editing and readability improvement. All content, analysis, and conclusions were reviewed and verified by the authors. The authors take full responsibility for the originality, accuracy, and integrity of the work.

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