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Molecular Interaction and Solubility Enhancement of Ketoconazole through Co-Amorphisation with Oxalic Acid

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ABSTRACT

Introduction*: In the modern pharmaceutical field, enhancing the solubility and bioavailability of poorly water-soluble drugs remains a key challenge in formulation. Ketoconazole, a weakly soluble antifungal agent, serves as a model compound in this study.* ***Aims:*** *This research aims to develop and characterise a co-amorphous system of ketoconazole with oxalic acid to enhance solubility and dissolution behaviour.* ***Result:*** *The co-amorphous system was prepared using solvent evaporation and evaluated using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA), and construction of a binary phase diagram. Dissolution studies were performed under biorelevant pH conditions, and equilibrium solubility was assessed using standard shake-flask methods. The co-amorphous ketoconazole–oxalic acid system exhibited a single glass transition and absence of sharp PXRD peaks, confirming successful amorphisation. FTIR analysis indicated intermolecular hydrogen bonding, while thermal analysis demonstrated enhanced physical stability. Dissolution studies revealed significantly improved drug release across pH 1.2, 4.5, and 6.8, and equilibrium solubility increased more than threefold compared to the crystalline form.* ***Conclusion:*** *Co-amorphous formulation with oxalic acid markedly enhances ketoconazole solubility and dissolution, offering a promising strategy for improving the performance of poorly soluble drugs through molecular-level interaction and amorphisation.*

KEYWORDS*: Amorphous solid dispersion, ball milling, co-amorphous system, dissolution enhancement, ketoconazole.*

INTRODUCTION

Ketoconazole, a broad-spectrum antifungal agent, has been widely used for treating systemic and superficial mycoses. Despite its effectiveness, its clinical application is hindered by poor oral bioavailability. This limitation primarily arises from its low aqueous solubility, as ketoconazole is classified as a Biopharmaceutical Classification System (BCS) class II drug. Such compounds exhibit low solubility and high permeability, where dissolution becomes the rate-limiting step for absorption (Ajaz et al., 2024; Lisă et al.,

2022). In its crystalline form, ketoconazole dissolves poorly in gastrointestinal fluids, leading to insufficient drug levels for optimal absorption (Martin et al., 2020).

Moreover, the solubility of ketoconazole is pH-dependent. It is more soluble in acidic environments such as the stomach, but its solubility decreases at the higher pH of the intestine. This behaviour often results in drug precipitation as it passes through the gastrointestinal tract, further limiting its absorption (Rathi et al., 2019). Conventional formulations, such as tablets and granules, typically do not address this issue effectively (Adachi et al., 2016). Alternative strategies like solid dispersions and cocrystals have shown promise, but often suffer from physical instability or are challenging to scale up (Ajaz et al., 2024; Mistry et al., 2017).

In recent years, co-amorphous systems have emerged as a compelling approach to enhance the solubility and stability of poorly soluble drugs. These systems consist of an active pharmaceutical ingredient (API) and a low-molecular-weight co-former that form a homogeneous amorphous phase through molecular interactions. Compared to traditional amorphous solid dispersions that rely on polymers, co-amorphous systems offer lower excipient content, improved molecular homogeneity, and greater physical stability due to stronger intermolecular bonding (J.-H. An et al., 2018; Karagianni et al., 2018). These characteristics often translate into superior dissolution profiles and enhanced bioavailability (Aragón-Aburto et al., 2022).

The choice of co-former plays a crucial role in the performance of a co-amorphous system. Dicarboxylic acids like oxalic acid are particularly effective due to their ability to form strong hydrogen bonds and ionic interactions with basic drugs. Oxalic acid, owing to its low molecular weight and dual carboxyl groups, helps reduce molecular mobility and elevate the glass transition temperature (Tg), thereby stabilising the amorphous form (Fung et al., 2018). This stabilisation helps maintain a supersaturated state in aqueous environments, thereby enhancing drug dissolution.

One efficient technique for generating co-amorphous systems is ball milling. This solvent-free method uses mechanical energy to disrupt the crystalline structure of a drug and its co-former, promoting intimate molecular mixing and amorphisation (Oliveira et al., 2018; Ueda et al., 2018). Ball milling is advantageous in pharmaceutical development due to its simplicity, environmental friendliness, and scalability. It also eliminates the need for solvents, thus reducing safety and regulatory concerns (Jensen et al., 2016; Wang et al., 2023).

Effective formulation requires careful preformulation analysis. Solubility phase studies and binary phase diagrams are essential tools for evaluating the miscibility and interaction potential of drug–co-former systems. These studies provide insights into eutectic points, solubility limits, and optimal molar ratios that favour stability and prevent recrystallization (Kissi et al., 2019; Singh et al., 2021). Understanding these parameters helps optimise drug loading while maintaining the stability of the amorphous phase.

While previous research has explored various strategies to enhance KTZ solubility, these studies often present notable limitations. For instance, traditional approaches using polymeric amorphous solid dispersions frequently suffer from high excipient bulk, hygroscopicity, and physical instability upon storage. Furthermore, although some studies have successfully developed co-amorphous formulations using different drugs and acid co-formers (such as valsartan–nicotinamide or clozapine–carboxylic acid) (Ali et al., 2015; Turek et al., 2021), The application of these systems to KTZ is still limited. Existing KTZ formulations often require hazardous solvents during preparation, posing environmental and regulatory concerns. More importantly, previous studies frequently overlook the critical evaluation of how co-amorphous interactions can specifically mitigate the problematic pH-dependent precipitation of KTZ in the gastrointestinal tract.

Therefore, a clear research gap exists regarding the development of a stable, solvent-free co-amorphous system for KTZ that comprehensively addresses its pH-dependent solubility issues. This study addresses this gap by evaluating the formulation, characterisation, and performance of a novel ketoconazole–oxalic acid co-amorphous system prepared via a green, mechanochemical ball milling approach. Emphasis is placed on understanding physicochemical interactions, thermal behaviour, and structural characteristics using DSC, PXRD, FTIR, and HSM. Additionally, solubility and dissolution studies conducted under various pH conditions will assess the formulation's potential for enhanced oral bioavailability.

This research proposes a novel strategy for improving the solubility and absorption of ketoconazole through a rational co-amorphous design. The insights gained will contribute to advancing formulation techniques for poorly soluble drugs, offering valuable perspectives for future oral antifungal therapies.

METHODS

Material

Ketoconazole (KTZ) (purity 99%) was obtained from PT Dexa Medica (Indonesia).

Oxalic acid dihydrate (OA) (analytical grade, ≥99% purity) was purchased from Merck (Germany). Potassium dihydrogen phosphate, sodium hydroxide, and hydrochloric acid (all analytical grade) were sourced from Emsure®, Merck (Germany). Distilled water used throughout the study was produced in-house using a Millipore system.

Binary Phase Diagram and Preformulation

The binary phase diagram was constructed to evaluate the thermal behaviour and miscibility of ketoconazole and oxalic acid. Physical mixtures of the two components at different molar ratios (10–90% w/w) were analysed using hot-stage microscopy (HSM). Each sample was placed between a coverslip and a microscope slide and gradually heated on a temperature-controlled stage. The appearance of melting, recrystallisation, or eutectic events was recorded visually. HSM enables direct observation of phase transitions and supports the determination of eutectic points and solid-state compatibility (D'Angelo et al., 2018).

Preparation of Co-Amorphous System

A co-amorphous ketoconazole–oxalic acid system was prepared at a 1:1 molar ratio, selected based on preliminary preformulation optimization to ensure optimal stoichiometric interactions**.** The mixture was ball-milled in a planetary mill (Pulverisette 7, Fritsch, Germany) for 90 minutes at 350 rpm. The components were weighed accurately and milled in a 45 mL stainless steel jar with two 10 mm balls. Milling parameters were based on prior studies indicating that 60 minutes and 300 rpm effectively induce amorphisation (Jensen et al., 2015). Intermittent pauses were used to prevent overheating. The process disrupts crystalline structures, facilitating molecular interactions crucial for forming a stable amorphous phase (Mañosa et al., 2024). After milling, the powder was stored in a desiccator to prevent moisture-induced recrystallisation. This solvent-free technique offers an efficient, scalable approach for co-amorphous system preparation while preserving drug stability (Wang et al., 2023).

Thermal Characterization

The thermal behaviour of the co-amorphous ketoconazole–oxalic acid system was evaluated using DSC and TGA. DSC analysis was performed on 3–5 mg samples sealed in aluminium pans and heated from 25 °C to 200 °C at 10 °C/min under nitrogen flow. A single Tg and the absence of melting endotherms indicated an amorphous nature and miscibility (Aragón-Aburto et al., 2022). TGA was employed to assess the thermal stability and decomposition profile of the samples.

Approximately 5–10 mg of each sample was heated from 25 °C to 400 °C at a rate of 10 °C/min under nitrogen purge. Weight loss patterns were recorded to identify degradation events and assess the relative stability of the co-amorphous system compared to the individual components (J.-H. An et al., 2018).

FTIR Analysis

Fourier-transform infrared spectroscopy (FTIR) was used to investigate molecular interactions between ketoconazole and oxalic acid in the co-amorphous system. Samples were analysed using an FTIR spectrophotometer (Shimadzu IRSpirit, Japan) in the range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1}. Spectra were obtained using the KBr pellet method. Shifts or broadening in key functional group peaks (e.g., O–H, C=O, N–H) were assessed to identify hydrogen-bonding or ionic interactions, which are critical for stabilising the amorphous state (J.-H. An et al., 2018). The formation of such interactions confirmed successful co-amorphisation and provided insights into the structural integrity and compatibility of the drug–co-former mixture (Fung et al., 2018; Ueda et al., 2018).

X-ray Diffraction (PXRD)

PXRD was employed to assess the solid-state characteristics of the co-amorphous ketoconazole–oxalic acid system. Analyses were performed using a Rigaku MiniFlex 600 diffractometer (Cu Kα, λ = 1.5406 Å) operated at 40 kV and 15 mA. The scanning was conducted over a 2θ range of 5° to 40° with a 0.02° step size. PXRD is a sensitive method for distinguishing between crystalline and amorphous states, capable of detecting crystallinity levels as low as 5% (Ainurofiq, Mauludin, Mudhakir, & Soewandhi, 2018). This technique plays a pivotal role in confirming structural disorder following ball milling and complements thermal analysis results (Jensen et al., 2015; Martínez et al., 2022).

Solubility Test

Solubility tests were conducted by adding 50 mg of ketoconazole or its co-amorphous formulation into 10 mL of distilled water in screw-capped glass vials. The vials were shaken at 250 rpm using a water bath shaker (Memmert WNB 22, Germany) maintained at 25 ± 0.5°C for 24 hours to reach equilibrium. Afterwards, the suspensions were filtered through 0.45 µm membrane filters and analysed using UV-visible spectrophotometry at 225 nm. Co-amorphous systems typically improve solubility due to the absence of a crystal lattice and enhanced molecular mobility, supporting better dissolution and bioavailability (Baghel et al., 2016).

Dissolution Test

Dissolution studies were performed

using USP Apparatus II (paddle method) at 50 rpm in 900 mL of buffer media (pH 1.2, 4.5, and 6.8) maintained at 37 ± 0.5°C. Samples containing 50 mg ketoconazole or equivalent co-amorphous formulations were introduced into the press. Aliquots were withdrawn at 5, 10, 15, 20, 25, and 30 minutes, filtered through 0.45 µm membranes, and analysed using UV spectrophotometry at 225 nm. The withdrawn volume was replaced with fresh medium to maintain sink conditions. Co-amorphous systems are known to enhance dissolution due to their higher molecular mobility and absence of a crystalline lattice (Baghel et al., 2016), potentially improving bioavailability.

Statistical Analysis

All experiments were performed in at least triplicate (n=3), and the results are expressed as the mean ± standard deviation (SD). Statistical significance was determined using an independent Student's t-test, with a p-value < 0.05 considered statistically significant.

RESULTS AND DISCUSSION

The primary strategy to address the poor aqueous solubility of ketoconazole (KTZ) in this study was to disrupt its rigid crystalline lattice by forming a co-amorphous system. In this context, oxalic acid was strategically selected as the crucial co-former due to its low molecular weight and dual carboxylic acid functional groups. These functional groups act as potent hydrogen-bond donors and can form strong, specific intermolecular interactions with the basic nitrogen atoms on the imidazole and piperazine rings of KTZ. This specific chemical interaction is essential, as it restricts the molecular mobility of the drug, thereby stabilizing the high-energy amorphous state and preventing subsequent recrystallization.

During the preformulation stage, the formulation was optimized to determine the most effective stoichiometric ratio. A 1:1 equimolar ratio of KTZ to oxalic acid was selected as the optimal formula. This ratio was chosen because it provides the most balanced hydrogen-bonding network between the drug and the co-former, ensuring maximum amorphization without leaving an excess of unreacted crystalline components that could otherwise act as nucleation sites for premature recrystallization.

Binary phase diagram

The binary phase diagram constructed for ketoconazole (KTZ) and oxalic acid (AO) (Figure 1) reveals a pronounced eutectic-like behaviour, with a minimum melting point observed at a mole fraction of KTZ close to 0.4–0.5. This significant melting point depression, relative to the pure components, is a key indication of favourable interactions between KTZ and AO that promote disruption of their

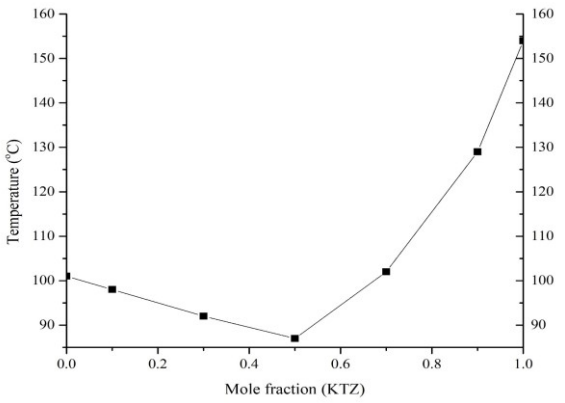


Figure 1. Binary phase diagram of KTZ and OA constructed using hot-stage microscopy.

respective crystal lattices. According to Joos et al. (2020) and Kissi et al. (2019), such a thermal behaviour suggests the potential formation of a co-amorphous phase at or near the eutectic composition.

In the constructed diagram, the temperature continuously decreases from the pure AO (mole fraction 0.0) until it reaches its lowest point at approximately a mole fraction of 0.4–0.5, followed by a sharp increase toward the melting point of pure KTZ. This characteristic "V-shaped" profile is consistent with eutectic systems, where the minimum represents the optimal ratio for molecular miscibility and the highest likelihood of glass formation upon rapid quenching. The one-phase region implied by the diagram suggests good miscibility in the molten state and an increased potential for forming a homogeneous amorphous matrix upon cooling, as described by Valenti et al. (2023) and Wünsche et al. (2022).

The use of Hot Stage Microscopy (HSM) further supported these interpretations by providing real-time visual evidence of thermal transitions. Samples at intermediate compositions exhibited congruent melting without visible phase separation, and no signs of recrystallisation were observed upon cooling, indicating compatibility and potential stability of the co-amorphous form. These observations align with reports by Aucamp et al. (2015), who emphasised the utility of HSM in confirming homogeneity and thermal behaviour of amorphous formulations.

Therefore, the binary phase diagram, supported by HSM, not only confirms the formation of a eutectic mixture between KTZ and AO but also highlights the optimal composition range for achieving a kinetically stabilised co-amorphous system. These findings are crucial for rational co-amorphous design and provide a foundation for further evaluations of physical stability and performance.

Thermal Analysis

Thermal analysis was conducted using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) to evaluate the thermal behaviour and stability of the co-amorphous ketoconazole (KTZ)–oxalic acid (OA) system. As illustrated in Figure 2, the DSC thermogram of pure KTZ (curve a) showed a sharp endothermic peak around 148 °C, corresponding to its melting point. In

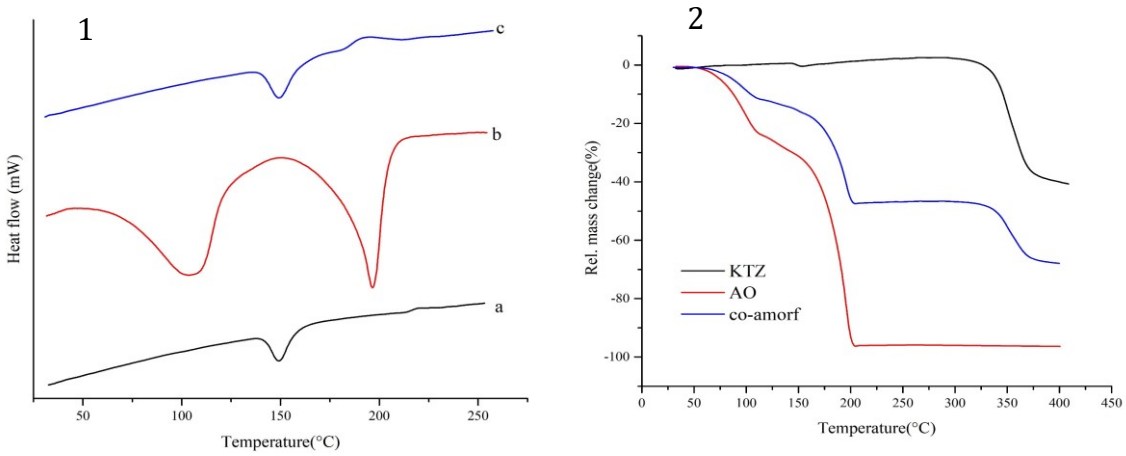


Figure 2. DSC (1) and TGA (2) thermograms of (a) ketoconazole, (b) oxalic acid, and (c) co-amorphous KTZ-OA.

comparison, OA (curve b) exhibited a melting endotherm at approximately 189 °C. Notably, the DSC curve for the co-amorphous system (curve c) displayed a single thermal event as a broad transition near 135–145 °C, without evidence of crystalline melting. This observation strongly suggests the formation of a homogeneous amorphous matrix, supported by the absence of individual melting endotherms and the presence of a single thermal transition, indicating molecular miscibility between KTZ and OA. The appearance of a single thermal event is consistent with prior studies that report single Tg values as markers of successful co-amorphous formation (Ainurofiq, Mauludin, Mudhakir, Umeda, et al., 2018; Kissi et al., 2019).

TGA analysis, shown in Figure 2, further supports these findings. Pure OA exhibited significant mass loss beginning around 150 °C, attributed to thermal decomposition, while KTZ showed decomposition above 300 °C. The co-amorphous system displayed a two-step degradation profile, with an initial weight loss corresponding to OA degradation, followed by further decomposition above 300 °C associated with KTZ. This shift in thermal degradation profile implies molecular interaction between the components, resulting in modified thermal stability. Overall, the integration of DSC and TGA data confirms the successful formation of a thermally stable co-amorphous system with improved thermal characteristics.

FTIR Spectroscopy

FTIR spectroscopy was employed to investigate the molecular interactions between ketoconazole (KTZ) and oxalic acid (OA) within the co-amorphous formulation. Figure 3 displays the FTIR spectra of pure KTZ, OA, and the co-amorphous KTZ–OA system. Ketoconazole exhibits characteristic bands at approximately 1685 cm^{-1} (C=O stretching), 1230 cm^{-1} (C–O),

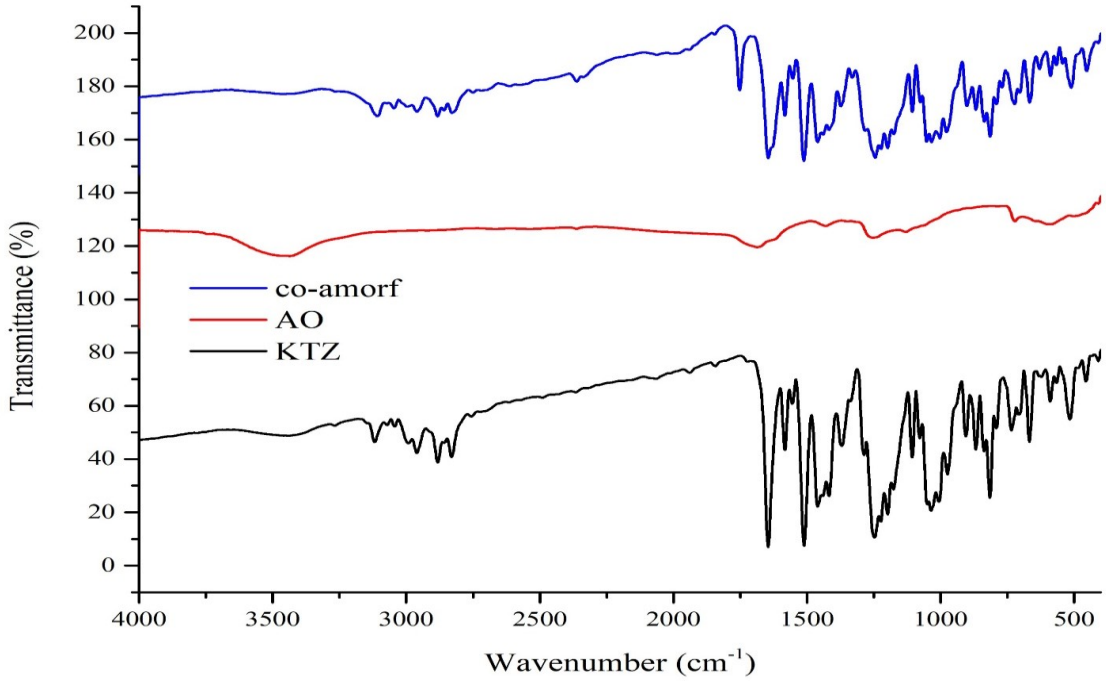


Figure 3. FTIR spectra of ketoconazole, oxalic acid, and co-amorphous KTZ–OA.

and 3110 cm^{-1} (aromatic C–H). Oxalic acid displays strong absorptions in the region of 1700 cm^{-1} (C=O stretching of carboxylic acid) and a broad O–H stretching band between 2500–3500 cm^{-1}.

In the co-amorphous spectrum, notable shifts and modifications are observed. The C=O stretching band of OA shifts to lower wavenumbers, indicating hydrogen bond formation between the carbonyl group of OA and basic nitrogen atoms of KTZ. Simultaneously, the broad O–H band becomes further broadened and less intense, suggesting the involvement of hydroxyl protons in hydrogen bonding. These changes are consistent with literature reports, where such red shifts are indicative of strong molecular interactions in amorphous phases (Chen et al., 2020).

Compared to the simple superposition observed in physical mixtures, these spectral changes confirm that KTZ and OA interact at the molecular level. The absence of characteristic sharp peaks and the emergence of new or shifted bands support the formation of a single-phase amorphous matrix. This interaction contributes significantly to the physical stability and solubility enhancement of the formulation (Ainurofiq, Mauludin, Mudhakir, Umeda, et al., 2018; Oyama et al., 2024).

Structural Characterization (PXRD)

Powder X-ray diffraction (PXRD) analysis was conducted to confirm the solid-state transformation of the binary system of ketoconazole (KTZ) and oxalic acid (OA) following co-amorphisation. Figure 4 presents the PXRD patterns of pure

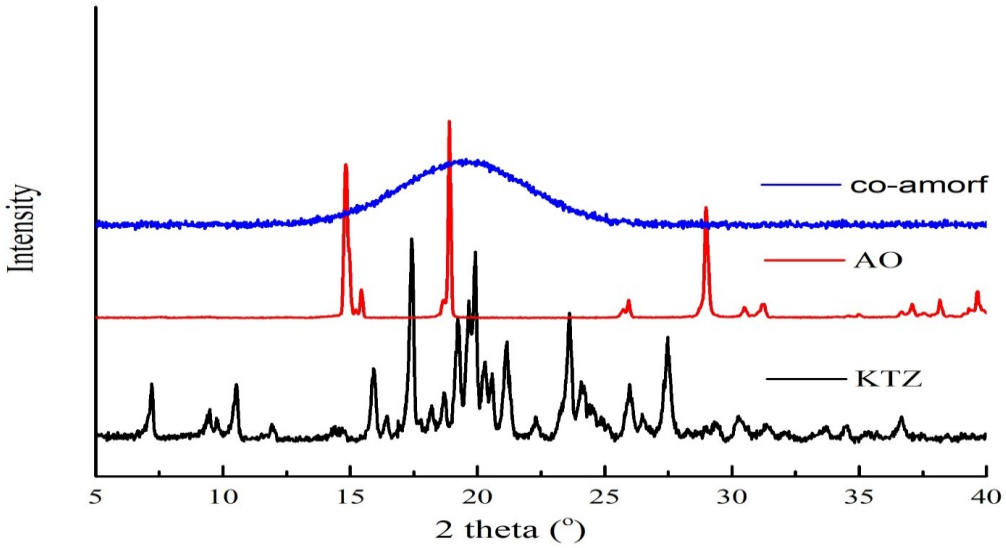


Figure 4. PXRD diffractograms of ketoconazole, oxalic acid, and their co-amorphous system.

KTZ, pure OA, and the co-amorphous KTZ-OA system. Both KTZ and OA exhibited sharp, well-defined peaks in their respective diffractograms, consistent with their crystalline nature. KTZ showed intense reflections predominantly between 10° and 30° 2θ, while OA displayed its distinct peaks within a similar range, indicating long-range molecular order and lattice periodicity.

In contrast, the PXRD pattern of the co-amorphous formulation showed the disappearance of these characteristic Bragg peaks and the emergence of a broad diffuse halo, centred around 15° to 25° 2θ. This absence of sharp reflections confirms the loss of crystallinity, suggesting the formation of a single-phase amorphous system (Hosmani et al., 2024; Velhal & Salunkhe, 2023). The lack of residual peaks further implies that no physical mixture or unconverted crystalline fractions remain in the sample, ruling out incomplete amorphisation.

These observations are in line with previous studies where the co-amorphous phase formation was characterised by similar broad halos, indicating homogeneous molecular dispersion and miscibility of the drug and co-former (Ishii et al., 2021; Kissi et al., 2019). This structural transition is critical for enhancing the dissolution behaviour and physical stability of the formulation, particularly when corroborated by thermal analysis data such as a single Tg in DSC thermograms. PXRD thus serves as definitive evidence of successful co-amorphisation.

Solubility Test

To accurately evaluate the intrinsic enhancement of physicochemical properties driven by the co-amorphization process, pure, untreated crystalline KTZ

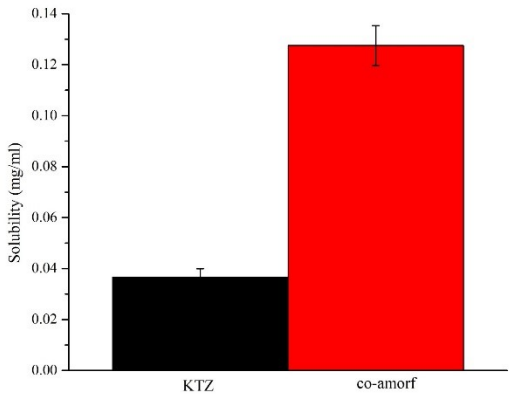


Figure 5. Equilibrium solubility of pure ketoconazole and co-amorphous KTZ-OA system in distilled water at 25 ± 0.5 °C.

process, pure, untreated crystalline KTZ and its physical mixture were used as baseline standards. Comparing the co-amorphous system directly to a commercially formulated product at this fundamental solid-state preformulation stage could introduce confounding variables due to pharmaceutical excipients (e.g., binders, surfactants, or disintegrants). Therefore, using pure KTZ as the control allows for a direct assessment of the solubility and dissolution improvements attributable solely to amorphization and specific drug-co-former interactions.

Solubility evaluation is crucial in assessing the effectiveness of co-amorphous formulations in enhancing the aqueous solubility of poorly water-soluble drugs, such as ketoconazole (KTZ). The results of the equilibrium solubility test (Figure 5) demonstrate a statistically significant enhancement ($p < 0.05$) in the solubility of KTZ when formulated as a co-amorphous system with oxalic acid. The solubility of pure crystalline KTZ was recorded at 0.037 ± 0.003 mg/mL, whereas the co-amorphous formulation exhibited a markedly higher solubility of 0.127 ± 0.008 mg/mL, representing a more than threefold increase.

This enhancement in solubility can be primarily attributed to the amorphous nature of the formulation, which eliminates the long-range order of the crystalline lattice, thereby increasing the free energy and molecular mobility of the drug. According to Yamamoto et al. (2016), The lack of crystalline structure facilitates more efficient water penetration and rapid molecular dispersion, enabling the drug to reach a higher thermodynamic solubility. The intimate molecular mixing of KTZ and oxalic acid in the co-amorphous matrix promotes strong intermolecular interactions, such as hydrogen bonding, which prevent recrystallisation and further stabilise the amorphous form (J.-H. An et al., 2018).

Furthermore, the co-amorphous system helps maintain a supersaturated state by increasing the glass transition temperature (Tg) and reducing molecular mobility below Tg, which is crucial for preserving solubility and preventing precipitation over time (Baghel et al., 2016). This is especially advantageous during drug absorption in the gastrointestinal tract, where maintaining a high concentration gradient can directly

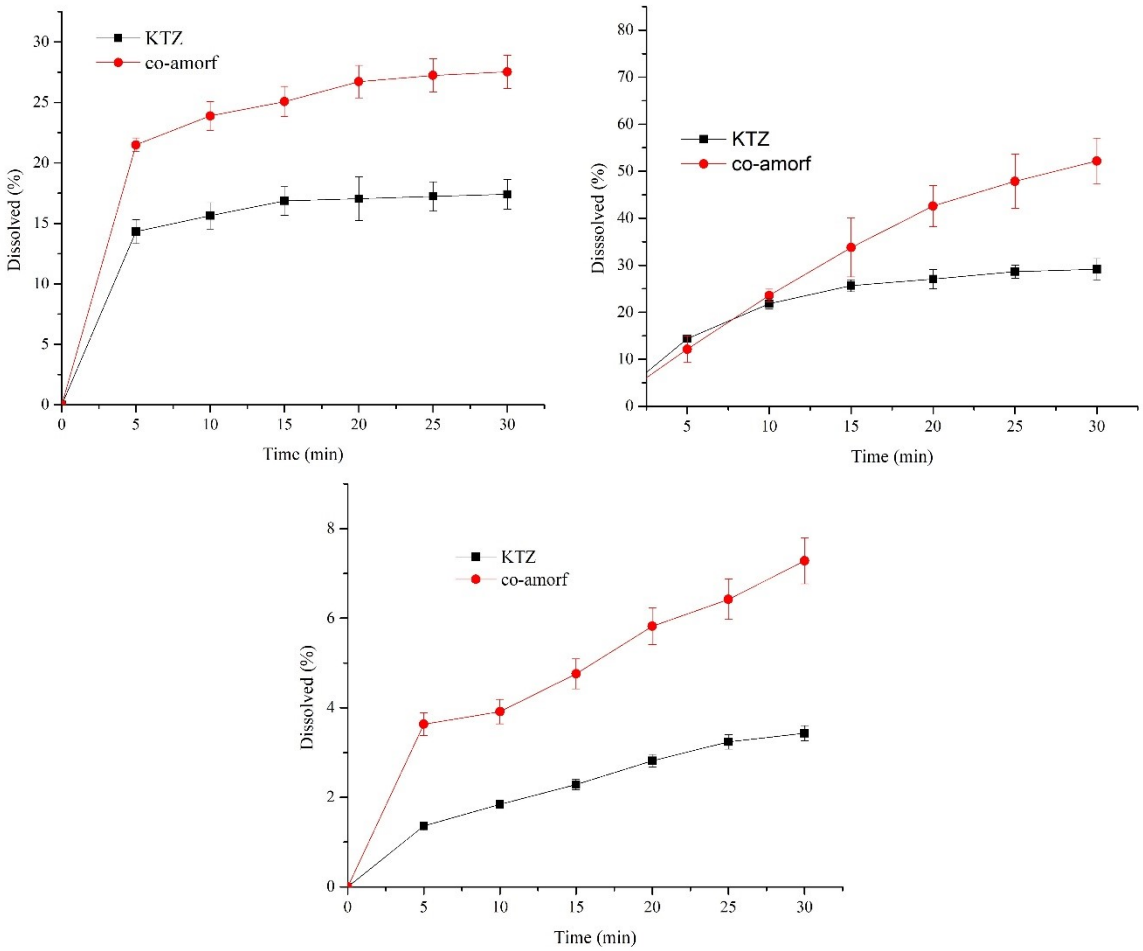


Figure 6. Dissolution profiles of ketoconazole and co-amorphous formulations in media at pH 1.2 (a), pH 4.5 (b), and pH 6.8 (c).

impact bioavailability. Collectively, the improved solubility observed in the co-amorphous ketoconazole formulation underscores the effectiveness of this strategy in overcoming solubility-limited drug delivery.

Dissolution Test

The dissolution profiles of ketoconazole (KTZ) and its co-amorphous formulation with oxalic acid were assessed in biorelevant media at pH 1.2, 4.5, and 6.8 (Figure 6a-c). Across all pH conditions, the co-amorphous system exhibited superior dissolution performance compared to crystalline KTZ. At pH 1.2 (Figure 6a), the co-amorphous formulation displayed a rapid initial dissolution, reaching over 25% dissolved drug within 5 minutes, in contrast to approximately 14% for KTZ. This "spring-parachute" profile suggests effective amorphisation, facilitating supersaturation and maintaining solubility over time, consistent with previous findings by (Vasilev et al., 2023).

At pH 4.5 (Figure 6b), a condition where polymer-based ASDs often underperform due to limited polymer solubility, the co-

amorphous system retained its dissolution advantage. The co-amorphous KTZ exhibited a gradual and sustained increase in dissolution, surpassing 50% within 30 minutes, while crystalline KTZ remained below 30%. This supports the hypothesis that co-amorphous systems, which rely on molecular dispersion rather than matrix solubility, are less sensitive to pH variations (Zhuo et al., 2022).

At pH 6.8 (Figure 6c), mimicking distal intestinal conditions, the dissolution from the co-amorphous system continued to exceed that of KTZ, reaching over 7% compared to only 4% from the crystalline form. The stability of supersaturation across pH environments reflects the strong intermolecular interactions between KTZ and oxalic acid, preventing crystallisation during dissolution (J. An et al., 2018). These results validate the co-amorphous approach as a robust strategy for enhancing dissolution and potential bioavailability of poorly soluble drugs across physiological pH ranges.

Overall, the significance of this research lies in providing a stable, solvent-free platform to effectively overcome the inherent solubility limitations and pH-dependent precipitation of KTZ. By employing a green mechanochemical approach (ball milling), this study provides a scalable method to improve the solid-state properties of poorly water-soluble drugs. In the future, the developed co-amorphous KTZ-oxalic acid system can be utilized as an optimized intermediate raw material for the development of advanced oral solid dosage forms, such as capsules or tablets. These future formulations have the potential to deliver KTZ at lower effective doses, with enhanced bioavailability and minimized food-effect variability, ultimately improving clinical outcomes in antifungal therapy.

CONCLUSION

This study confirms that the co-amorphous formulation of ketoconazole (KTZ) with oxalic acid significantly improves its solubility and dissolution behaviour under biorelevant pH conditions. Solid-state analyses verified the amorphous nature and molecular interactions between components, while dissolution and solubility tests demonstrated a notable enhancement compared to crystalline KTZ. The increased molecular mobility and absence of a crystal lattice facilitated faster and sustained drug release. These results highlight the potential of co-amorphous systems to overcome solubility-limited bioavailability in poorly soluble drugs. This work contributes to advancing co-amorphous formulation strategies in pharmaceutical development. Further studies on physical stability and *in vivo* performance are recommended to support

clinical application and feasibility of scale-up.

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