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Physicochemical Characterization and Dissolution Enhancement of Mefenamic Acid–Isonicotinamide Crystalline Solid Dispersion

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Abstract

Poor aqueous solubility limits the bioavailability of non-steroidal anti-inflammatory drugs like mefenamic acid. This study aims to improve the solubility and dissolution of mefenamic acid through crystalline solid dispersions using solvent evaporation and co-grinding techniques with selected co-formers. Solid dispersions were formulated at different drug-to-co-former ratios (1:1, 1:2, and 2:1) and characterized using differential scanning calorimetry, Fourier-transform infrared spectroscopy, and powder X-ray diffraction. DSC results revealed reduced crystallinity, indicated by the disappearance of melting peaks and the appearance of a single glass transition temperature. FTIR analysis confirmed hydrogen bonding between the drug and co-former, while PXRD patterns showed a loss of long-range order, supporting the formation of amorphous phases. Dissolution testing demonstrated a significant increase in drug release, particularly in the 1:2 formulation, which outperformed the pure drug and other ratios. These results confirm that the choice of preparation method and co-former ratio critically influence the performance of solid dispersions. This study provides valuable insights into the design of improved oral formulations for poorly soluble drugs, contributing to the advancement of pharmaceutical technology.

Keywords: Crystalline solid dispersion; Dissolution improvement; Drug–co-former interaction; Mefenamic acid.

INTRODUCTION

Oral drug administration remains the most widely adopted route in clinical practice due to its convenience, non-invasiveness, cost-effectiveness, and high patient compliance. However, the therapeutic efficacy of orally delivered drugs is critically dependent on their aqueous solubility and dissolution rate, which directly influence systemic bioavailability. A large proportion of both established pharmaceutical agents and new chemical entities (NCEs) fall into the Biopharmaceutics Classification System (BCS) Class II category, which includes compounds with high membrane permeability but poor water solubility (Mehta et al., 2016; Patel et al., 2015). The dissolution-limited absorption of such drugs often results in low and variable bioavailability, necessitating higher doses that may elevate the risk of side effects and reduce formulation efficiency.

Mefenamic acid, a commonly used non-steroidal anti-inflammatory drug (NSAID), exemplifies these challenges. Despite its therapeutic utility in treating pain and inflammation, mefenamic acid exhibits limited solubility in aqueous environments, leading to erratic absorption profiles and requiring frequent or high-dose administration (Ghyadh & Al-Khedairy, 2023; Vasanani et al., 2016). These limitations not only reduce patient adherence but also raise safety concerns due to potential gastrointestinal and renal adverse effects (Pervaiz et al., 2023; Sanas & Pachpute, 2023).

Several formulation strategies have been explored to address solubility-related issues in BCS Class II drugs, including particle size reduction, lipid-based delivery systems, and solid dispersion techniques (Doshi et al., 2024; Fontana et al., 2018). Among these, solid dispersion technology has shown significant promise by enhancing drug dissolution through alterations in solid-state properties (H. Kumar et al., 2022; Neeharika & Jyothi, 2021). By dispersing a poorly soluble drug in an inert carrier matrix, this approach often facilitates reduced crystallinity or complete amorphization of the active pharmaceutical ingredient (API), thereby improving wettability, surface area, and the thermodynamic driving force for dissolution.

Within the spectrum of solid dispersions, crystalline solid dispersions (CSDs) represent an underexplored yet valuable subclass. Unlike amorphous solid dispersions that eliminate crystallinity, CSDs retain partial or complete crystalline order while achieving improved dissolution through spatial distribution and drug–carrier interactions (Baghel et al., 2016; A. Kumar, 2017). This

partial retention of crystallinity offers greater physical stability, minimizing the risk of recrystallization—a common drawback of amorphous systems (Babu & Nangia, 2011). Although CSDs may not always achieve the same level of solubility enhancement as fully amorphous dispersions, they provide a favorable compromise between performance and shelf stability (Thayyil et al., 2020).

The choice of an appropriate co-former or matrix is central to the success of CSDs. While polymers like polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) are commonly used, low-molecular-weight co-formers such as isonicotinamide (INA) have recently gained attention due to their capacity for hydrogen bonding, GRAS status, and physicochemical compatibility (Garbiec et al., 2023; Turek et al., 2021). INA has been reported to enhance solubility and inhibit recrystallization in co-amorphous systems and co-crystals by stabilizing the high-energy non-crystalline phase of the drug (Suknuntha et al., 2023).

Although several studies have demonstrated the potential of INA in enhancing the solubility of other BCS Class II drugs, limited research has specifically investigated its use in forming crystalline solid dispersions with mefenamic acid—particularly when no new crystalline phase is detectable via PXRD. This presents a unique opportunity to explore whether dissolution enhancement can still occur through molecular-level interactions without visible amorphization or co-crystal formation.

This study aims to investigate the physicochemical characteristics and dissolution behavior of mefenamic acid–isonicotinamide crystalline solid dispersions prepared via solvent evaporation. Through PXRD, DSC, FTIR, and dissolution analysis, this research explores whether such systems can effectively improve solubility, offering a novel strategy for formulating poorly water-soluble NSAIDs.

MATERIALS AND METHODS

Materials

Mefenamic acid (MEFA) was obtained from PT. Kimia Farma Tbk (Indonesia) as the active pharmaceutical ingredient (API). Isonicotinamide (INA), used as a low-molecular-weight co-former, was procured from Merck (Germany). All other solvents and reagents were of analytical grade and used without further purification. Distilled water was used throughout the experiments for solubility and dissolution studies.

Instruments

The solid-state characterization of the samples was conducted using several instruments. Differential scanning calorimetry (DSC) analysis was performed with a Shimadzu DSC-60 Plus (Japan), calibrated using the indium standard, operating in a nitrogen atmosphere. Powder X-ray diffraction (PXRD) was carried out using a PANalytical X'Pert PRO diffractometer (Netherlands) with Cu Kα radiation (λ = 1.5406 Å), operating at 40 kV and 30 mA. Scanning was performed over a 2θ range of 5–40°. Fourier-transform infrared (FTIR) spectroscopy was performed using a Bruker Alpha II FTIR spectrometer (Germany) in the 4000–500 cm^{-1} range using the KBr pellet method. Dissolution testing was conducted using a USP Type II paddle apparatus (Logan Instruments Corp., USA) at 75 rpm. UV-visible spectrophotometry was conducted on a Shimadzu UV-1800 (Japan) for drug quantification at 285 nm.

Preparation of Crystalline Solid Dispersions

CSDs of MEFA and INA were prepared using the solvent evaporation method, which allows for homogeneous mixing and distribution of drug and co-former molecules (Chauhan et al., 2005; Xie et al., 2009). The drug and INA were accurately weighed in molar ratios of 1:1, 1:2, and 2:1, then dissolved in a minimal amount of ethanol as the common solvent. The resulting solutions were stirred magnetically at room temperature for 1 hour to ensure complete mixing. The solvent was evaporated under reduced pressure using a rotary evaporator at 40 °C. The dried residues were further desiccated and pulverized into fine powder using a mortar and pestle, then stored in airtight containers until further analysis. This method was selected due to its ability to promote molecular-level interactions without thermal degradation, which is particularly suitable for thermolabile compounds.

FTIR Analysis

Fourier-transform infrared spectroscopy (FTIR) evaluated the potential intermolecular interactions between MEFA and INA within the solid dispersions. The samples were mixed with potassium bromide (KBr) and compressed into pellets. The FTIR spectra were recorded in the 4000–400 cm^{-1} region. Shifts in characteristic peaks of functional groups were interpreted to detect hydrogen bonding or other non-covalent interactions, which may indicate successful dispersion or complex formation (Liu et al., 2015; Wicaksono et al., 2019).

DSC Analysis

Differential scanning calorimetry (DSC) was employed to investigate the prepared solid dispersions' thermal properties and crystalline behavior compared to the pure drug and co-former. Approximately 2–5 mg of each sample was weighed and placed in sealed aluminum pans. Samples were scanned from 30 °C to 250 °C at a heating rate of 10 °C/min under a nitrogen atmosphere (Alatas et al., 2021; Nandi et al., 2021). The appearance or disappearance of endothermic peaks was used to assess melting point depression, crystalline transitions, and potential amorphization (Wdowiak et al., 2024).

Dissolution Testing

The dissolution rate of MEFA in solid dispersions and pure form was assessed using a USP Type II dissolution apparatus with 900 mL of phosphate buffer (pH 7.4) at 37 ± 0.5 °C and 75 rpm. Samples equivalent to 50 mg of MEFA were placed in the dissolution vessel. At predetermined intervals (10, 20, 30, 45, and 60 minutes), 5 mL aliquots were withdrawn and filtered immediately. The withdrawn volume was replaced with a fresh medium. Drug content was analyzed spectrophotometrically at 285 nm. This test was critical for evaluating the dissolution enhancement resulting from solid dispersion formulation (Miller et al., 2012; Park et al., 2018).

RESULTS AND DISCUSSION

The physicochemical characterization of CSDs of MEFA with INA prepared via the solvent evaporation method was conducted through DSC, FTIR, PXRD, and dissolution testing. These analytical techniques provided critical insights into the solid-state transformations, interactions, and biopharmaceutical behavior of the formulations.

Thermal Behavior (DSC Analysis)

Differential Scanning Calorimetry (DSC) was conducted to investigate the thermal behavior and physical state of MEFA in crystalline solid dispersions formulated with varying molar ratios of the small-molecule co-former INA. As shown in Figure 1, pure MEFA (Sample A) exhibited a sharp endothermic peak at approximately 230 °C, corresponding to its melting point and confirming its crystalline nature, consistent with previously reported data (Nandi et al., 2021). In contrast, solid dispersion samples (B–E) demonstrated a gradual reduction in the intensity and sharpness of this melting endotherm, particularly in Sample C (1:2 ratio), where the peak nearly disappeared.

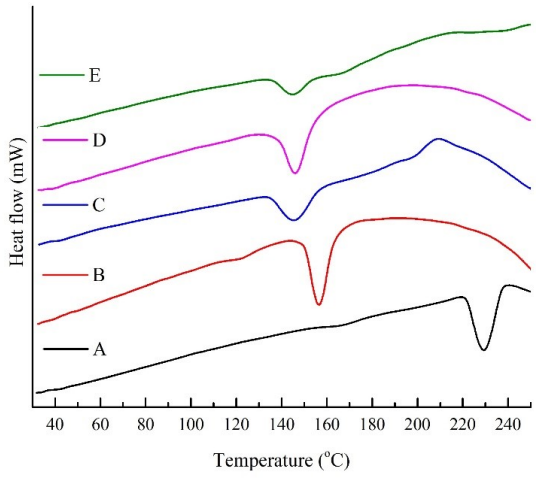

Figure 1. DSC Thermograms of MEFA (A), INA (B), and CSDs with ratios 1:1 (C), 1:2 (D), and 2:1 (E).

The diminished and broadened thermal signals indicate a significant reduction in crystallinity, suggestive of partial amorphization or molecular-level interaction between MEFA and INA. Notably, samples D and E exhibited a single broad glass transition temperature (Tg), indicative of a homogenous molecular dispersion and good miscibility between the drug and the small-molecule co-former. The presence of a single Tg—without any distinct melting peak—suggests the formation of a metastable solid phase, potentially co-amorphous or weakly crystalline, stabilized through intermolecular hydrogen bonding.

This behavior underscores the role of the co-former ratio in modifying solid-state properties. As the proportion of INA increased, the system transitioned from a crystalline to a more amorphous or molecularly integrated state. These findings are consistent with previous reports, such as those by Fitriani et al. (2017), demonstrating that enhanced co-former interaction facilitates the disordering of the drug lattice in non-polymeric matrices.

Intermolecular Interactions (FTIR Analysis)

FTIR spectroscopy assessed the molecular interactions between MEFA and its co-formers. The spectra in Figure 2 show significant shifts and changes in peak characteristics across different formulations. The pure drug (A) exhibited distinct absorption bands corresponding to its functional groups: the N–H stretching band around 3300 cm^{-1}, C=O stretching at ~1650 cm^{-1}, and aromatic C–H bending near 750 cm^{-1}.

Upon forming solid dispersions (samples B through D), notable shifts and reductions in the intensity of the O–H and N–H stretching vibrations were observed. In particular, the broadening and red-shifting of these bands suggest the formation of intermolecular hydrogen bonds between the carboxylic or amine groups of MEFA and the functional groups of the co-former (Liu et al., 2015; Oyama et al., 2024). Such interactions imply that the drug has been effectively incorporated into the polymer matrix at a molecular level.

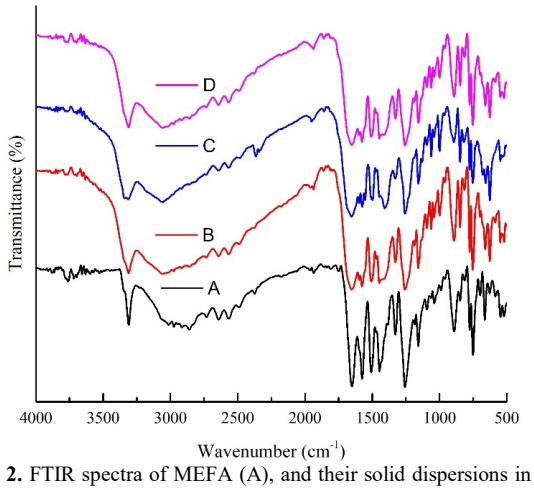

Figure 2. FTIR spectra of MEFA (A), and their solid dispersions in ratios 1:1 (B), 1:2 (C), and 2:1 (D).

Moreover, the disappearance or weakening of sharp carbonyl peaks in the dispersion spectra, particularly in sample C, supports the hypothesis of drug–co-former interaction. This is further corroborated by the appearance of new absorption bands in the fingerprint region (~1000–1500 cm^{-1}), which are absent in the spectra of the physical mixture, indicating that molecular-level interactions—likely hydrogen bonding—occurred during the preparation of the dispersions (Guedes et al., 2011; Qian et al., 2015).

Crystalline Behavior (PXRD Analysis)

PXRD analysis, illustrated in Figure 3, was utilized to investigate the crystallinity of the prepared systems further. The diffractogram of pure MEFA (sample A) shows sharp, intense peaks at characteristic 2θ values, confirming its highly crystalline nature. However, these peaks are markedly diminished or absent in the solid dispersions (samples B to E), particularly in sample C (1:2 ratio), which displays a broad halo pattern instead of defined peaks, indicating a substantial reduction in crystallinity and transformation to an amorphous state.

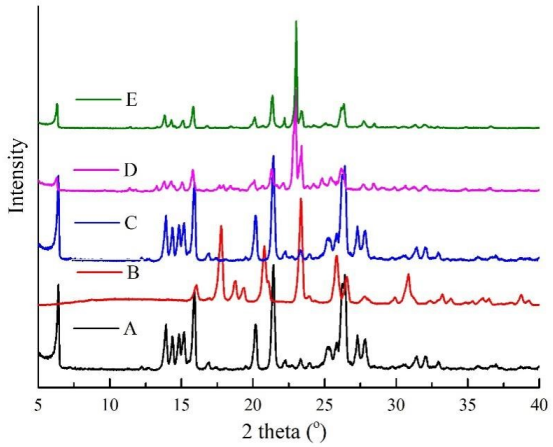

Figure 3. PXRD patterns of MEFA (A), INA (B), and solid dispersions in ratios 1:1 (C), 1:2 (D), and 2:1 (E).

The progressive disappearance of these peaks with increasing co-former ratio reflects the successful formation of amorphous solid dispersions and confirms the DSC findings. According to Sapkal et al. (2018), such reductions in diffraction peak intensity denote the drug's molecular dispersion into the co-former, enhancing its solubility due to the loss of crystal lattice energy. Additionally, the new halo patterns appearing in samples C and D may suggest forming a new amorphous phase or co-amorphous system.

These findings are consistent with previous studies on etoricoxib and famotidine solid dispersions, where reduced or absent PXRD peaks signified enhanced dispersion and amorphization (Chauhan et al., 2005; Fitriani et al., 2017). Furthermore, the presence of only low-intensity broad peaks, without the sharp reflections typical of a crystalline phase, strongly supports the solid-state transformation from a crystalline to an amorphous form.

In Vitro Dissolution Study

The dissolution profiles of pure mefenamic acid (MEFA) and its crystalline solid dispersions with isonicotinamide (INA) in varying molar ratios are illustrated in Figure image.png. Pure MEFA exhibited poor dissolution, reaching only about 23.16% drug release after 60 minutes, consistent with its known low aqueous solubility. In contrast, all MEFA:INA dispersions demonstrated enhanced dissolution, with the 1:2 ratio achieving the highest release, approximately 58.51% within 60 minutes.

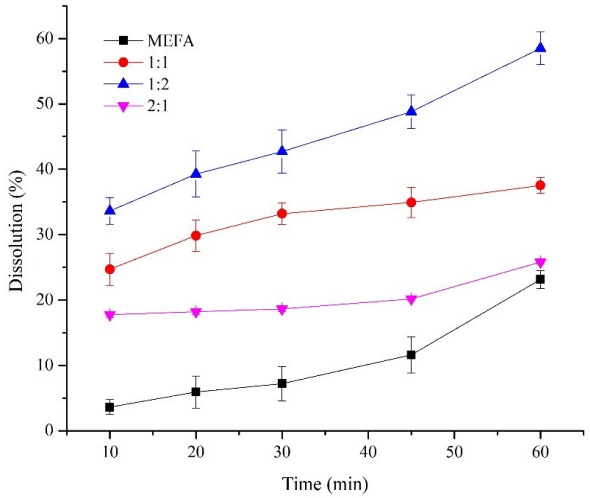

Figure 4. Dissolution profiles of MEFA and its solid dispersions with INA at molar ratios of 1:1, 1:2, and 2:1.

The 1:2 system significantly outperformed the 1:1 (37.53%) and 2:1 (25.80%) ratios, underscoring the importance of co-former concentration in facilitating drug solubilization. This enhancement correlates with findings from PXRD and DSC analyses, which indicated a shift from a crystalline to a more amorphous or molecularly dispersed state. The absence of distinct melting endotherms and the appearance of a broad glass transition in DSC thermograms suggest that the drug is well integrated at the molecular level.

The improved solubility and dissolution profiles observed across the solid dispersions can be attributed to the synergistic effects of molecular dispersion, hydrogen bonding, and reduced crystallinity. The FTIR spectra demonstrated significant intermolecular interactions, particularly in the 1:2 system, where characteristic drug peaks were either shifted or suppressed. DSC confirmed the transition from crystalline to amorphous form through the disappearance of melting endotherms and the appearance of a single Tg. PXRD further corroborated these findings by showing decreased intensity in the same samples.

These solid-state modifications have been shown to contribute to enhanced dissolution rates directly, a trend

consistent with prior studies on poorly soluble NSAIDs, such as etoricoxib, naproxen, and fenofibrate (Liu et al., 2015; Mardiyanto et al., 2020; Sharma et al., 2017). Moreover, the increased dissolution rate observed in the optimal 1:2 formulation illustrates the importance of identifying and applying the appropriate co-former ratio to improve maximal solubility.

Together, these findings substantiate the role of solid dispersion as an effective strategy for enhancing the bioavailability of poorly soluble drugs such as MEFA. They also highlight the necessity of comprehensive solid-state characterization to elucidate the mechanisms behind dissolution enhancement and to inform formulation development decisions.

CONCLUSIONS

This study demonstrates the effectiveness of CSDs using solvent evaporation and co-grinding techniques to enhance the solubility and dissolution rate of MEFA. Among the formulations tested, the 1:2 drug-to-INA ratio produced the most significant improvement in dissolution, supported by comprehensive physicochemical analyses. Differential scanning calorimetry revealed the disappearance of the drug's melting peak and the appearance of a single glass transition temperature, indicating reduced crystallinity and enhanced miscibility. PXRD patterns showed a broad halo, confirming partial or complete amorphization, while FTIR spectra suggested the formation of intermolecular hydrogen bonds between the drug and the co-former.

These findings underscore the critical role of small-molecule co-former ratios in modulating solid-state properties and improving drug performance. Importantly, this study expands the application of CSDs beyond polymeric systems, highlighting the potential of INA as a non-polymeric solubility enhancer. The analytical data collectively confirm the successful formation of molecularly dispersed systems that resist recrystallization and promote rapid dissolution.

Future investigations should evaluate long-term physical stability, in vivo bioavailability, and alternative GRAS-status co-formers or surfactants to further optimize formulation performance for poorly soluble non-steroidal anti-inflammatory drugs such as MEFA.

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