RESEARCH ARTICLE

Multicomponent Crystal of Aceclofenac with Saccharin to Improve Solubility and Dissolution Rate

Hendrizal Usman, Yufri Aldi, Salman Umar, Muhammad Nasrul Siregar, Erizal Zaini*

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Andalas, Padang, West Sumatera, Indonesia

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ABSTRACT

Aceclofenac is a Non-Steroidal Anti-Inflammatory Drug (NSAID) frequently prescribed for managing osteoarthritis and rheumatoid arthritis. It is categorized under the Biopharmaceutics Classification System (BCS) as a Class II compound, characterized by low water solubility but high membrane permeability. This poor solubility presents challenges in dissolution and absorption in gastrointestinal fluid. The objective of this study was to improve the solubility and dissolution behavior of aceclofenac by formulating a multicomponent crystal with saccharin as the selected coformer. The multicomponent crystal was prepared through a solvent-drop grinding technique using a 1:1 molar ratio. To confirm the formation and evaluate the physicochemical properties of the multicomponent system, solid-state characterization was performed using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier-transform infrared spectroscopy (FTIR). Additionally, solubility and in vitro dissolution tests were carried out and compared with those of the unmodified drug. Results from DSC and PXRD demonstrated a substantial decrease in crystallinity, evident by the loss of distinct melting peaks and diffraction signals, indicative of eutectic formation. This structural alteration is associated with a reduction in lattice energy, which contributes to enhanced dissolution. FTIR spectra verified the absence of covalent interactions between the drug and coformer. The optimized multicomponent crystal exhibited a 2.49-fold increase in solubility and a 2.6-fold enhancement in dissolution rate relative to pure aceclofenac. Overall, this study supports the use of multicomponent crystal engineering with saccharin as a feasible approach to improve the biopharmaceutical performance of aceclofenac.

Keywords: Aceclofenac, Saccharin, Multicomponent crystal, Solubility, Dissolution rate

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INTRODUCTION

Aceclofenac is a commonly utilized non-steroidal anti-inflammatory agent (NSAID) that is routinely prescribed for managing conditions such as osteoarthritis and rheumatoid arthritis. Its pharmacological activity involves the inhibition of cyclooxygenase enzymes (COX-1 and COX-2), which leads to a reduction in both inflammation and pain.[1,2] Although aceclofenac is known for its therapeutic effectiveness, it falls under Class II of the Biopharmaceutics Classification System (BCS), which is defined by its poor solubility in water and high permeability across biological membranes.[3] This poor solubility significantly limits its dissolution rate, leading to suboptimal bioavailability and inconsistent therapeutic effects. To compensate for this limitation, higher doses are often required, which increases the risk of gastrointestinal and renal adverse effects, thereby posing safety concerns for long-term use.[4,5]

Improving the solubility and dissolution behavior of drugs with limited water solubility remains a key focus in pharmaceutical formulation. Numerous strategies, including salt modification, nanoparticle-based systems, and the induction of amorphous states have been investigated to enhance the dissolution performance of BCS Class II compounds.[6,7] For aceclofenac, some strategies including salt formation[3], solid dispersions[2], and multicomponent crystal formation with different coformers[1,8] have been investigated to overcome its solubility limitations. Among these approaches, solid dispersions have shown potential in improving dissolution; however, their reliance on polymeric carriers can lead to increased molecular weight and particle size, which may compromise drug bioavailability and therapeutic efficacy.[9] In contrast, multicomponent crystal formation emerges as a superior alternative, enhancing solubility and dissolution without the need for polymeric carriers, thereby avoiding potential pharmacokinetic complications.[5,10] The technique, which utilizes a coformer to adjust the physicochemical characteristics of the active pharmaceutical ingredient (API) without impacting its pharmacological function, has received considerable interest for its effectiveness in improving solubility, dissolution rate, and stability while preserving the molecular structure of the drug.[11,12] Consequently, multicomponent crystal formation represents a promising strategy for optimizing the physicochemical and biopharmaceutical performance of aceclofenac.

In this study, saccharin was selected as the coformer to form a multicomponent crystal with aceclofenac. Saccharin

*Author for Correspondence: erizal@phar.unand.ac.id

Table 1: Solubility data of Aceclofenac and Multicomponent crystal of aceclofenac and saccharin

Sample	Solubility (mg/100mL) ± SD	Solubility enhancing
Aceclofenac	7.699± 0.3103	-
Multicomponent crystal of aceclofenac and saccharin	19.1392± 1.2911	2.49

(SAC), a synthetic sweetening agent, is commonly employed as a coformer in cocrystal engineering owing to its capacity to establish hydrogen bonding interactions.

Several studies have reported that SAC can increase the solubility of various drugs with low aqueous solubility, including carbamazepine, ketoprofen, and gliclazide[13], compared to their pure forms. Its weakly acidic nature (pKa 1.6 at 25°C) and available hydrogen bonding sites make it a suitable candidate for multicomponent crystal formation.[14] Previous studies have demonstrated that cocrystallization with SAC not only improves solubility and dissolution but also enhances the chemical stability of the active pharmaceutical ingredient (API).[12,15] Additionally, SAC has been reported to enhance the solubility of simvastatin, further supporting its potential as an effective coformer in pharmaceutical applications.[16]

The multicomponent crystal was prepared using the solvent-drop grinding method, a widely utilized technique that facilitates intermolecular interactions between the API and coformer. The confirmation of multicomponent crystal formation and evaluation of its physicochemical behavior were carried out using solid-state techniques including differential scanning calorimetry, powder X-ray diffraction, and Fourier transform infrared spectroscopy. In addition, evaluations of solubility and in vitro dissolution rates were performed to determine the extent of improvement in the drug's bioavailability profile.

This study aims to demonstrate that multicomponent crystal formation with saccharin can serve as an effective strategy to increase the solubility and dissolution rate of aceclofenac, potentially leading to improved bioavailability and therapeutic efficacy.

MATERIALS AND METHODS

Materials

The study utilized aceclofenac (Bocsci Inc., USA), saccharin (TCI, Tokyo, Japan), analytical grade ethanol, methanol, and carbon dioxide-free water. All remaining reagents were of pharmaceutical grade quality.

Method

Preparation of Multicomponent Crystal of Aceclofenac and Saccharin using Solvent Drop Grinding Method

Aceclofenac (354.18 mg) and saccharin (183.18 mg) were mixed in an equimolar ratio of 1:1. The components were placed in a mortar and ground manually for 15 minutes, with the gradual addition of ethanol as a grinding solvent. The resulting powder was then stored at room temperature for further characterization.

Differential Scanning Calorimetry (DSC)

The thermal characteristics of the sample were determined via DSC (Shimadzu DSC-60 Plus, Japan), using a pre-calibrated temperature system. A weighed 5 mg portion was enclosed in an aluminum pan, with heating conducted from 25°C to 300°C at a rate of 10°C/min.

Powder X-ray Diffraction (PXRD)

PXRD measurements were conducted under ambient conditions using a PANalytical X'Pert Pro diffractometer (MPD PW3040/60, The Netherlands) equipped with a Cu-Kα radiation source. Operational parameters included a voltage of 40 kV and a current of 40 mA. Data were acquired across a 2θ range of 5° to 50°, following sample placement on a glass sample holder.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectral analysis was carried out using a Thermo Fisher Scientific spectrophotometer (USA), covering a

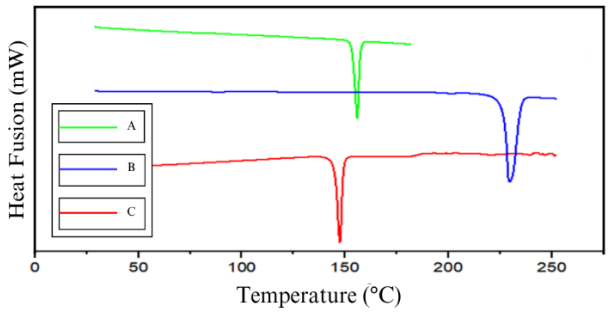

Figure 1: DSC Thermograms of (A) Aceclofenac, (B) Saccharin, and (C) Multicomponent crystal of aceclofenac and saccharin

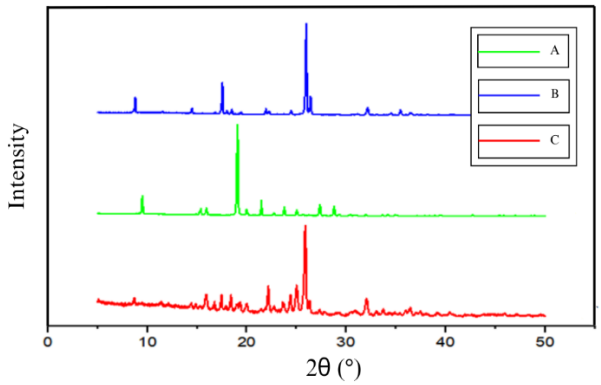

Figure 2: XRD Patterns of (A) Saccharin, (B) Aceclofenac, (C) Multicomponent crystal of aceclofenac and saccharin

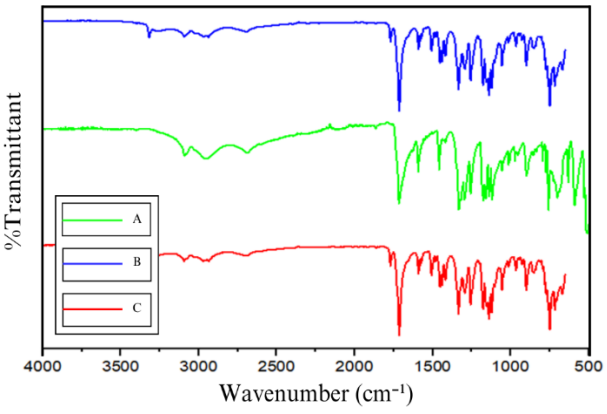

Figure 3: FTIR of (A) Saccharin, (B) Aceclofenac, and (C) Multicomponent crystal of aceclofenac and saccharin

wavenumber range of 4000–500 cm^{-1}. The spectra were recorded for pure aceclofenac, saccharin, and the synthesized aceclofenac-saccharin multicomponent crystal, with each sample properly mounted on the sample holder prior to scanning.

Solubility Study

The solubility assessment of both pure aceclofenac and its multicomponent crystal was performed using an orbital shaker (Memmert WNB 29, Germany). A quantity of sample equivalent to 20 mg of aceclofenac was dispersed in 100 mL of CO_2-free distilled water contained in an Erlenmeyer flask and agitated at 25°C for 24 hours under controlled room temperature conditions. The suspension was subsequently filtered through a 0.45 µm Whatman membrane filter, and the drug concentration was quantified using a UV-Vis spectrophotometer (Shimadzu UV-1900i, Japan) at 275 nm. Solubility was calculated based on a standard calibration curve prepared from known concentrations of aceclofenac. All measurements were conducted in triplicate to ensure precision and reproducibility. Statistical analysis was carried out using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA), employing one-way ANOVA to detect statistically significant differences among the multicomponent crystal formulations, with significance defined at $p < 0.05$. The experimental procedure adhered to established methodologies for investigating solubility enhancement in pharmaceutical formulations.

Dissolution Rate Profile

The dissolution study was performed using a paddle-type apparatus (USP Dissolution Apparatus Type II) (Hanson SR8 Plus, USA). The dissolution vessel was filled with 900 mL of CO_2-free distilled water, maintained at 37°C ± 0.5°C, and stirred at a paddle speed of 50 rpm. Samples of 5 mL were collected at specific time points (5, 10, 15, 30, 45, and 60 minutes) and immediately replaced with an equal volume of fresh dissolution medium preheated to the same temperature to preserve sink conditions. Each experiment was conducted in triplicate to ensure consistency. The withdrawn aliquots were placed in glass vials and analyzed by High-Performance Liquid Chromatography (HPLC). This procedure was applied to both pure aceclofenac and the aceclofenac-saccharin multicomponent crystal to compare their dissolution behaviors.

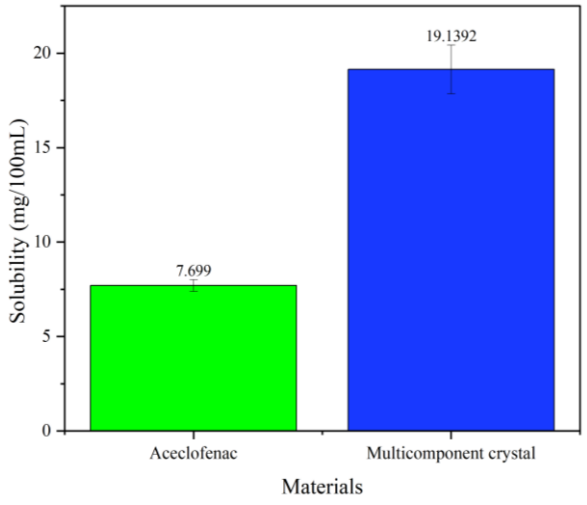

Figure 4: Solubility comparison of aceclofenac and multicomponent crystal of aceclofenac and saccharin

RESULTS

Differential Scanning Calorimetry (DSC)

DSC is a thermal analytical method used to characterize solid-state materials by monitoring heat flow changes related to temperature or time variations. This technique reveals thermal events in multicomponent crystals, including endothermic peaks indicative of melting, phase changes, and crystallization. In the present study, DSC measurements were conducted over a temperature range of 0 to 250°C with a heating rate of 10°C per minute. The superimposed DSC thermograms are illustrated in Figure 1. The DSC thermogram of pure aceclofenac (Figure 1A) exhibited a sharp, single endothermic peak at 155.77 °C, indicative of its crystalline nature. Saccharin (Figure 1B) also showed an endothermic peak at 230 °C; however, it was broader compared to that of aceclofenac, suggesting differences in crystallinity or molecular interactions. In the case of the aceclofenac-saccharin multicomponent crystal (Figure 1C), the endothermic peak remained sharp, similar to pure aceclofenac, but appeared at a lower temperature (146,94 C°) than pure aceclofenac and saccharin. Thermal analysis indicated a reduction in the melting point of the multicomponent crystal compared to pure aceclofenac and saccharin. This decrease in melting point suggests the occurrence of eutectic system formation, where the physical interaction between the two components results in a weaker lattice structure without the generation of a new crystalline structure. A eutectic mixture consists of molecules held together by weak intermolecular forces, leading to a melting point lower than that of either individual component. Consequently, the reduction in melting point observed in this study aligns with the typical characteristics of eutectic systems, which enhance the dissolution rate properties of the drug.[7,18]

Powder X-ray Diffraction (PXRD)

PXRD is a robust analytical method employed to investigate the interactions between two solid components and to identify the emergence of new crystalline phases. The XRD patterns demonstrated that both aceclofenac and

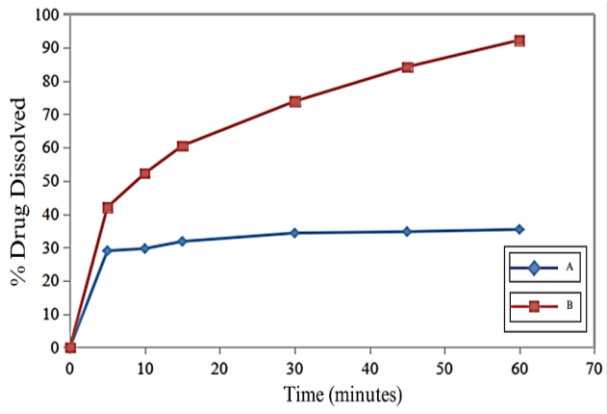

Figure 5: Dissolution rate profile of (A) Aceclofenac and (B) Multicomponent crystal of aceclofenac and saccharin

saccharin retained their crystalline nature, as indicated by the presence of sharp and distinct diffraction peaks, which are illustrated in Figure 2.

The diffractogram of the aceclofenac-saccharin multicomponent crystal exhibited characteristic peaks at specific 2θ values: 8.69°, 15.86°, 18.40°, 22.17°, 24.38°, and 32.03°. However, no additional diffraction peaks appeared in the multicomponent crystal, indicating that the system did not generate a new crystalline phase. Instead, the diffraction pattern suggests that the multicomponent crystal is a physical combination of two distinct crystalline phases, forming a simple eutectic mixture. This implies that aceclofenac and saccharin remain as separate crystalline entities within the system rather than undergoing structural reorganization into a new single-phase crystalline form.[7,15,18] This finding corroborated the thermal analysis of multicomponent crystal of aceclofenac and saccharin.

Fourier Transform Infrared Spectroscopy (FTIR)

To assess possible intermolecular interactions in the multicomponent crystal, FTIR analysis focused on detecting changes in the transmission bands of the infrared spectra.[19] The spectral data of the multicomponent crystal were compared with those of pure aceclofenac and saccharin to identify any potential changes in functional group vibrations. As illustrated in Figure 3, the FTIR spectra of the multicomponent crystal exhibit slight shifts in specific absorption bands when compared to those of pure aceclofenac and saccharin. These shifts, however, remain within the expected range for functional groups present in the individual components, suggesting that no significant chemical transformation has occurred.

The observed spectral shifts are primarily attributed to hydrogen bonding interactions between aceclofenac and saccharin in the solid-state system. Hydrogen bonding can influence molecular vibrations by altering bond strength, leading to minor frequency shifts in the FTIR spectrum. This finding indicates that the formation of the multicomponent crystal involves non-covalent interactions rather than the creation of new chemical bonds, further supporting the conclusion that the system represents a physical modification rather than a chemical alteration.[15]

Solubility Study

The solubility results for pure aceclofenac and its multicomponent crystal are summarized in Table 1. The data reveal that the multicomponent crystal exhibits a 2.49-fold improvement in solubility relative to pure aceclofenac. This enhancement is likely due to the formation of a eutectic mixture, which is characterized by a decreased melting point, indicating lowered lattice energy and a reduction in the enthalpy of fusion. Consequently, this leads to a reduction in crystallinity, making the structure less rigid. The decreased crystal rigidity lowers the energy required to disrupt the molecular arrangement, thereby facilitating a more efficient dissolution process.[1,7]

Dissolution Rate Profile

The dissolution results exhibited a similar trend to the solubility study, as illustrated in Figure 5. The dissolution profiles revealed that after 60 minutes, pure aceclofenac exhibited a dissolution rate of 35.30%, whereas the multicomponent crystal achieved a significantly higher dissolution rate of 92.07%. This substantial enhancement in dissolution can be attributed to the formation of a eutectic mixture, which reduces crystal lattice energy and increases wettability, thereby facilitating faster drug release. Increasing the dissolution rate of drugs with low aqueous solubility is a crucial strategy for enhancing their absorption in the gastrointestinal tract following oral administration.[12] By increasing the dissolution efficiency, multicomponent crystal formation offers a promising approach to overcoming solubility-related bioavailability challenges associated with aceclofenac.[1,2,7]

CONCLUSION

The formation of a multicomponent crystal between aceclofenac and saccharin effectively improved both the solubility and dissolution rate of aceclofenac. Thermal analysis via differential scanning calorimetry (DSC) and structural evaluation through powder X-ray diffraction (PXRD) confirmed decreased crystallinity, indicative of eutectic mixture formation. Fourier-transform infrared spectroscopy (FTIR) revealed hydrogen bonding interactions without the emergence of new chemical bonds. The multicomponent crystal exhibited a 2.49-fold increase in solubility and a significantly enhanced dissolution rate of 92.07% at 60 minutes, compared to 35.30% for pure aceclofenac, an improvement of approximately 2.6-fold. These results highlight that forming a multicomponent crystal is a promising approach to enhance the physicochemical characteristics of aceclofenac, potentially translating to better bioavailability and therapeutic outcomes. Further in vivo investigations are warranted to assess the pharmacokinetic and pharmacodynamic effects of this formulation.

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