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Original Research Article

Enhancement of Aceclofenac Dissolution Rate via Solid Dispersion with Hydroxypropyl Methylcellulose

Doddy Rusli[1,2], Salman Umar[1], Yufri Aldi[3], Hendrizal Usman[1], Muhammad N Siregar[1] and Erizal Zaini[1]*

[1]*Department of Pharmaceutics, Faculty of Pharmacy, Universitas Andalas, Padang, West Sumatera, Indonesia.*
[2]*School of Pharmacy Bhakti Pertiwi Palembang, South Sumatera, Indonesia.*
[3]*Department of Pharmacology, Faculty of Pharmacy, Universitas Andalas, Padang, West Sumatera, Indonesia*.

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ABSTRACT

Aceclofenac, a widely used NSAID for managing osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, faces bioavailability challenges due to its poor water solubility, classifying it as a BCS Class II drug. This limits its dissolution and absorption, necessitating higher doses, which increase the risk of side effects. This study aimed to enhance aceclofenac's solubility and dissolution rate by formulating solid dispersions with hydroxypropyl methylcellulose (HPMC), a hydrophilic polymer. Solid dispersions were prepared via freeze-drying at drug-to-polymer ratios of 1:1, 1:2, and 2:1 Solid-state characterization was performed using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier transform infrared spectroscopy (FTIR). Solubility and *in vitro* dissolution profiles were compared to those of pure aceclofenac. DSC and PXRD analyses confirmed a significant reduction in crystallinity, evidenced by the absence of characteristic crystalline peaks and endothermic transitions, indicating transformation into an amorphous state. Reduced crystallinity is associated with weaker lattice energy, which enhances the dissolution process. FTIR analysis revealed no chemical interactions between aceclofenac and HPMC. The solubility of the 1:2 solid dispersion formulation was significantly higher ($p < 0.001$), achieving a 2.73-fold increase compared to pure aceclofenac. Dissolution testing showed almost complete drug release within 60 minutes, highlighting the formulation's superior performance. These findings suggest that the 1:2 aceclofenac-HPMC solid dispersion holds promise for improving the solubility, dissolution rate, and overall bioavailability of aceclofenac, thereby enhancing its therapeutic efficacy.

Keywords: Aceclofenac, Hydroxypropyl Methylcellulose, Solid Dispersions, Solubility, Dissolution Rate.

Introduction

Poorly water-soluble drugs present a significant challenge in the development of pharmaceutical formulations, especially for drugs with high therapeutic potential but limited dissolution rates.[1–3] Aceclofenac, a nonsteroidal anti-inflammatory drug (NSAID), is a derivative of phenyl-acetic acid and has anti-inflammatory, analgesic, and antipyretic action.[4,5] The molecular structure of aceclofenac is shown in Figure 1. It falls under the Biopharmaceutics Classification System (BCS) Class II, characterized by low solubility but high permeability.[1,4–6] This classification underscores the need to enhance its water solubility to improve absorption. Its therapeutic effectiveness is often compromised by poor water solubility, which leads to slow and erratic absorption in the gastrointestinal tract, delaying the onset of therapeutic action.[1,4]

*Corresponding author. E mail: erizal.ffua@gmail.com
Tel: +62 813-9502-9297

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In addition to these challenges, aceclofenac and other nonsteroidal drugs tend to exhibit high degrees of crystallinity, further impeding their absorption and reducing overall bioavailability.[4]

Therefore, addressing both its low solubility and high crystallinity is crucial for enhancing its therapeutic performance. A variety of strategies have been developed to enhance the dissolution rate of poorly water-soluble drugs, with solid dispersion techniques standing out as among the most effective. Solid dispersions involve embedding the drug in a hydrophilic carrier matrix, which modifies its physicochemical properties, leading to significant improvements in both solubility and dissolution rates.[2] In the case of aceclofenac, different approaches have been utilized, such as salt formation,[7] solid dispersions,[2] and multicomponent crystals with various coformers.[8,9] Salt forms, such as aceclofenac potassium with lysine, are designed to enhance solubility and dissolution by altering the drug's solubility profile and stability, thereby improving pharmacokinetic and pharmacodynamic outcomes. However, while salt formation can offer substantial benefits, its application requires careful counterion selection and characterization, and its effectiveness may be limited in certain cases.[7] To overcome these limitations, other methods such as micronization, complexation, spray drying, nano-particulate technologies, and the use of hydrophilic carriers in solid dispersions have been developed to enhance the solubility and bioavailability of poorly soluble drugs like aceclofenac.[5,10]Among these approaches, solid dispersions offer a distinct advantage for enhancing the solubility and dissolution of aceclofenac.[2,3] By dispersing the drug in a hydrophilic carrier polymer like hydroxypropyl methylcellulose (HPMC), the solid dispersion effectively reduces the crystallinity of aceclofenac, transforming it into an amorphous or partially amorphous state and improving wettability of the hydrophobic drug.[11,12] HPMC is a promising candidate for solid dispersion systems due to its advantageous properties, including low glass transition temperature, low melt viscosity, and reduced hygroscopicity compared to other

HPMC grades, which often require plasticizers for solid dispersion formation.[13] Additionally, HPMC, as a cellulose derivative, is well known for its low toxicity and safe use in pharmaceutical applications. Drug release from HPMC-based matrices occurs through diffusion or polymer erosion, making it particularly effective in hydrophilic systems.[14] As a polymer used in spray drying for amorphous solid dispersions (ASD), HPMC has gained popularity in the pharmaceutical industry for its low water sorption, its ability to maintain supersaturation in dissolution processes, and its high miscibility with drugs.[15,16] Furthermore, HPMC's ability to inhibit crystal growth and prolong supersaturated conditions enhances the stability and bioavailability of drugs and underlies its role in improving *in vivo* drug absorption.[16–18]The novelty of this study lies in formulating aceclofenac solid dispersions using HPMC via freeze-drying, a method less explored for this drug-polymer combination. This research aims to characterize the physicochemical properties of the resulting solid dispersions and evaluate their solubility and dissolution profiles compared to pure aceclofenac, offering insights into an optimized therapeutic formulation.

Material and Methods

Materials
The materials used were as follows: aceclofenac (Bocsci Inc, USA), HPMC, ethanol pro analysis, methanol, and CO_2-free water (Chemistry Laboratory, Andalas University, Indonesia). All other chemical reagents were of pharmaceutical grade.

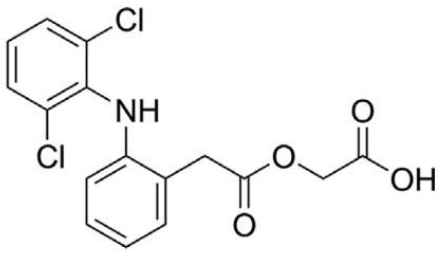

Figure 1: Molecular Structure of Aceclofenac

Preparation of solid dispersion
Aceclofenac and HPMC were mixed in ratios of 1:1, 1:2, and 2:1 (w/w). Aceclofenac was moistened with 96% ethanol, while HPMC was swollen in distilled water up to 200 mL. Both materials were then mixed and homogenized on a magnetic stirrer at 60 °C until a paste was formed. After homogenization, the mixture was frozen in a freezer. The frozen mixture was dried using a freeze dryer apparatus (Christ Alpha 1-2 LD Plus, Germany). The solid dispersion was stored in a sealed container in a desiccator.

Differential scanning calorimetry (DSC) analysis
Thermal analysis of the sample was performed using a DSC instrument (Shimadzu DSC-60 Plus, Japan) with calibrated temperature. A 5 mg sample was placed in a sealed aluminium pan. The DSC was programmed with a temperature range of 30 to 160 °C at a heating rate of 10 °C per minute.

Powder X-ray diffraction (PXRD) analysis
Powder X-ray diffraction analysis of the sample was performed at room temperature using a Rigaku diffractometer (PANalytical MPD PW3040/60 type X'Pert Pro, the Netherlands). The measurement conditions were as follows: Cu metal target, Kα filter, 40 kV voltage, 40 mA current, with analysis conducted in the 2-theta range of 5° to 50°. The sample was placed on a glass sample holder and leveled to prevent particle orientation during sample storage.

Fourier transform infrared (FT-IR) spectroscopy analysis
Samples were analyzed using an infrared spectrophotometer (Thermo Fisher Scientific, USA) by directly placing them on the sample holder. Absorption spectra were recorded with FT-IR in the wavenumber range of 4000–500 cm^{-1}. The analysis was performed for aceclofenac, HPMC, and the solid dispersions of aceclofenac and HPMC.

Scanning electron microscopy (SEM) analysis
The sample placed on an aluminium sample holder was observed at various magnifications using SEM (JEOL JSM-6360 LA, Japan). The voltage was set to 15−20 kV and the current to 12 mA.

Solubility test
The solubility of pure aceclofenac and its solid dispersions was evaluated using an orbital shaker (Memmert WNB 29, Germany). Samples equivalent to 20 mg of aceclofenac were combined with 100 mL of CO_2-free distilled water in Erlenmeyer flasks and shaken for 24 hours at 25 °C. The solutions were then filtered through Whatman filter paper (0.45 µm) and analyzed for absorbance using a UV-Vis spectrophotometer (Shimadzu UV-1900i, Japan) at a wavelength of 275 nm. Solubility values were determined using a calibration curve prepared from standard aceclofenac solutions. Each test was conducted in triplicate to ensure precision and accuracy. The solubility data were statistically analyzed using IBM SPSS Statistics software (version 26.0, IBM Corp., Armonk, NY, USA). A one-way ANOVA was performed to identify significant differences between the solubility of pure aceclofenac and solid dispersion formulations (SD 1:1, SD 1:2, and SD 2:1). A p-value < 0.05 was considered statistically significant. This approach follows established protocols for assessing solubility enhancement in pharmaceutical research.

Dissolution rate profile
The dissolution flask was filled with 900 mL of CO_2-free distilled water and maintained at 37 ± 0.5 °C with a stirring speed of 50 rpm using a Type II dissolution apparatus (Hanson SR8 Plus, USA). Prior to establishing the dissolution profile, the lag time of the capsules was determined using empty capsule shells. The samples were placed inside the capsules and immersed in the medium. At 5, 10, 15, 30, 45, and 60 minutes, 5 mL aliquots were pipetted from the dissolution solution, replacing the removed volume with fresh medium at the same volume and temperature. The experiments were repeated three times. Each aliquot was transferred to a glass container and analyzed using a UV-Vis spectrophotometer (Shimadzu UV-1900i, Japan) at a wavelength of 275 nm. The dissolution rate profile was conducted on pure aceclofenac, its physical mixtures, and its solid dispersion powders.

Results and Discussion

Differential scanning calorimetry analysis
DSC characterizes the thermal properties of solids by measuring energy absorbed or released as a function of temperature or time. DSC provides insights into thermal transitions in solid dispersions, indicated by endothermic peaks in the thermogram which represent processes like melting, phase transitions, and recrystallization.[19] In this study, DSC analysis was conducted from 30 to 160 °C at a heating rate of 10 °C per minute. The overlay of the DSC thermograms of the solid dispersions is shown in **Figure 2**.
Aceclofenac (**Figure 2A**) displayed a sharp and distinct endothermic peak characteristic of its crystalline phase.[11] In contrast, HPMC (**Figure 2B**) did not exhibit any sharp peaks but showed a broad and shallow decline, confirming its amorphous state.[20] The endothermic peaks in the solid dispersions were also broader than that of aceclofenac, suggesting that the system had transitioned into an amorphous or partially amorphous state.[11] The reduction in melting points reflects a decrease in crystallinity, which could enhance the solubility of aceclofenac.[8,19,21]In addition to the disappearance of melting points and endothermic peaks, the aceclofenac-HPMC solid dispersions (**Figure 2C**, **2D**, and **2E**) also showed a complete loss of fusion enthalpy, indicating the transformation into an amorphous state. Enthalpy represents the amount of energy required for the melting of a substance, which decreases with a reduction in crystallinity of the substance.[22]
The decrease in enthalpy aligns with the decrease in crystallinity observed in the diffractogram, suggesting that the aceclofenac-HPMC solid dispersion may potentially enhance the solubility of aceclofenac.

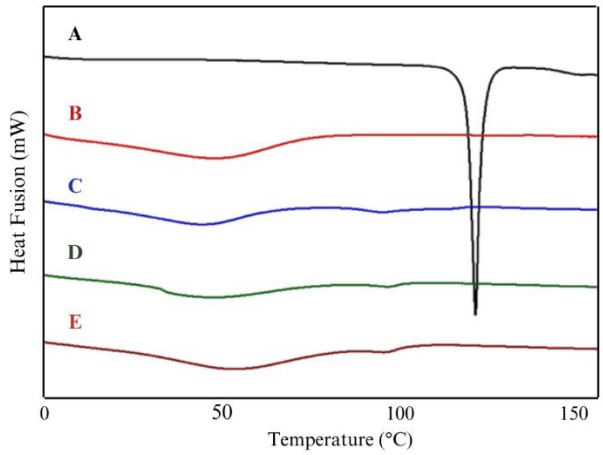

Figure 2: DSC Thermograms of (A) Aceclofenac, (B) HPMC, (C) SD 1:1, (D) SD 1:2, and (E) SD 2:1

Powder X-ray diffraction analysis

Aceclofenac and HPMC were mixed in ratios of 1:1, 1:2, and 2:1 (w/w). Aceclofenac was wetted with 96% ethanol, while HPMC was dispersed in distilled water. Both components were combined and homogenized using a magnetic stirrer at 60 °C until a paste formed. Once homogenized, the mixture was frozen in a freezer and then dried using a freeze dryer apparatus. The resulting solid dispersion was stored in a sealed container and placed in a desiccator. The aceclofenac-HPMC solid dispersions showed a significant decrease in diffraction peak characteristics (**Figure 3**). From the PXRD pattern, it is evident that the crystalline phase of aceclofenac underwent partial amorphization within the hydrophilic polymer matrix. As a result, characteristic peaks of aceclofenac were still observed, but with reduced peak intensity and a decrease in the total number of peaks. The higher the ratio of HPMC used in the solid dispersion, the lower the peak intensity. In the amorphous state, the active pharmaceutical ingredient's molecules are randomly arranged in the crystal lattice, and the intermolecular bonds are weaker compared to those in its crystalline phase. Therefore, the amorphous state has higher solubility and dissolution rates than the crystalline state.[23] PXRD analysis can be used to estimate the degree of crystallinity of the solid dispersion powder in comparison to pure aceclofenac.

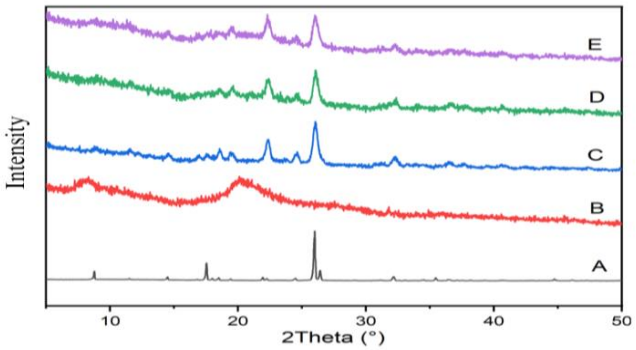

Figure 3: XRD Patterns of (A) Aceclofenac, (B) HPMC, (C) SD 1:1, (D) SD 1:2, and (E) SD 2:1

Fourier transform infrared spectroscopy analysis

To support the PXRD and DSC analysis results, FTIR analysis was conducted. This analysis aims to detect any shifts in absorbance of the solid dispersion, which may indicate the formation of hydrogen bonds. FTIR spectroscopy is commonly used to identify interactions between the drug and polymer.[1,12] The FTIR spectra results are shown in **Figure 4**. The spectrum of the solid dispersion shows the same functional groups as those of aceclofenac and HPMC but a shift in wavenumber indicates interactions between the components. The FT-IR spectrum of the solid dispersion powder is a superposition of the transmission peaks from each component. The FT-IR spectrum of the solid dispersion powder in the wavenumber range 3750−3000 cm^{-1} shows the presence of O-H and N-H stretching. The O-H stretching gives a strong absorption band around 3350 cm^{-1}, with a broad spectrum indicating the presence of hydrogen bonding.[1] No new peaks appeared in the FT-IR spectrum of the solid dispersion, nor were there any significant changes or shifts in the peaks. These findings suggest no evidence of specific chemical interactions between aceclofenac and HPMC.

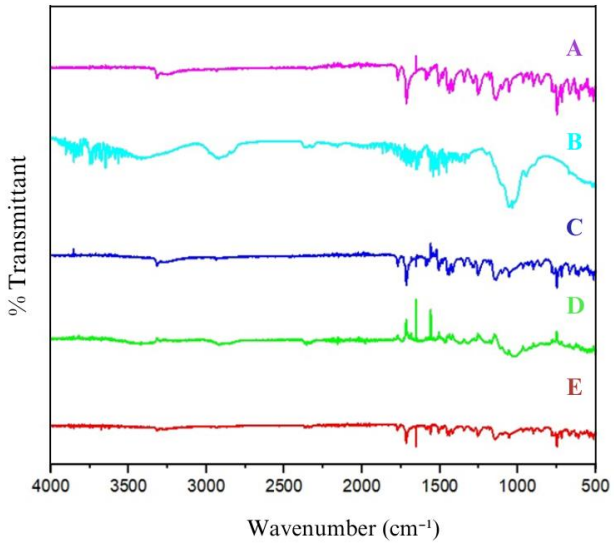

Figure 4: FTIR Spectrum of (A) Aceclofenac, (B) HPMC, (C) SD 1:1, (D) SD 1:2, and (E) SD 2:1

Scanning electron microscopy analysis

To better understand the morphology, shape, and particle size of the samples, SEM analysis was performed. The SEM images of the solid dispersion at a magnification of 10,000x reveal detailed structural features, providing insights into the particle arrangement and surface characteristics. These observations are crucial for correlating the physical properties of the dispersion with its solubility and dissolution rate behavior. Based on the SEM images in **Figure 5**, pure aceclofenac appears in crystalline form, while HPMC has an irregular chunk-like shape with uneven surfaces. In contrast, the aceclofenac-HPMC solid dispersions exhibit a near-spherical shape with smaller particle size distribution. These findings support the PXRD results, which showed a decrease in intensity, indicating the formation of crystal lattices with lower symmetry compared to their individual components. The scale on the SEM images of the solid dispersion, set at 10 µm, reveals a significant reduction in particle size distribution. The application of freeze-drying techniques in the preparation of solid dispersions typically results in porous particles. As a result, the surface area of the solid dispersion is increased compared to pure aceclofenac.

Solubility test

The solubility test results in **Table 1** indicate a significant increase in aceclofenac solubility through the formation of solid dispersions with HPMC. Among the tested formulations, the highest solubility was observed in the SD 1:2 dispersion, which achieved a solubility value of 10.986 mg/100 mL, representing a 2.73-fold increase compared to pure

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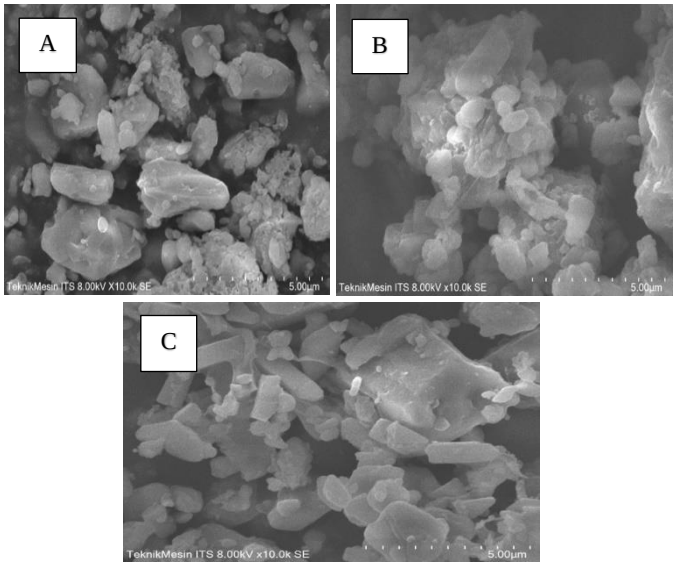

Figure 5: SEM Morphology of (A) SD 1:1, (B) SD 1:2, and (C) SD 2:1

aceclofenac (4.024 mg/100 mL). This substantial improvement is attributed to the higher proportion of polymer, which facilitates drug dispersion and enhances the dissolution process.[24] In contrast, the SD 1:1 formulation exhibited a lower solubility increase, reaching 5.292 mg/100 mL. The equal polymer-to-drug ratio in this formulation may limit the polymer's ability to enhance solubility effectively, possibly due to insufficient disruption of the crystalline structure of aceclofenac. Similarly, the SD 2:1 formulation, with a solubility value of 5.176 mg/100 mL, showed only a slight improvement. The reduced polymer content in this dispersion likely results in incomplete encapsulation of aceclofenac, reducing the polymer's potential to enhance solubility.[23,25] To determine whether the differences in solubility between formulations were statistically significant, a one-way analysis of variance (ANOVA) was conducted. The ANOVA results revealed a significant difference in solubility among the tested groups ($p < 0.001$), as evidenced by an F-value of 77.969. This indicates that the polymer-to-drug ratio has a substantial impact on solubility enhancement, with the 1:2 ratio proving to be the most effective in reducing crystallinity and improving the drug's solubility. The results highlight the importance of incorporating sufficient polymer to effectively disrupt the crystalline structure of aceclofenac.

Dissolution rate profile

Based on the dissolution tests conducted in a phosphate buffer medium at pH 7.4, the aceclofenac-HPMC solid dispersions showed a significant improvement in dissolution rate compared to pure aceclofenac (**Figure 6**). At the 60-minute mark, the percentage of aceclofenac dissolved was 47.977 ± 2.122% for pure aceclofenac, 96.189 ± 0.257% for SD 1:1, 98.871 ± 0.096% for SD 1:2, and 81.273 ± 1.444% for SD 2:1. Among these, the SD 1:2 formulation achieved the highest dissolution, reaching nearly complete drug release within one hour. The superior dissolution of the SD 1:2 formulation can be attributed to the increased proportion of HPMC, which disrupts the crystalline structure of aceclofenac more effectively, promoting a faster release into the medium. In contrast, the SD 1:1 formulation, while showing a marked improvement, exhibited a slightly lower dissolution rate, possibly due to the equal drug-to-polymer ratio limiting the polymer's ability to fully facilitate dissolution.[25] Similarly, the lower polymer content in SD 2:1 may have resulted in incomplete encapsulation of aceclofenac, leading to slower dissolution. These findings suggest that optimizing the polymer-to-drug ratio is crucial for enhancing the dissolution of poorly soluble drugs. The higher dissolution rate of SD 1:2 compared to pure aceclofenac indicates the potential of solid dispersions to improve drug solubility and bioavailability, particularly through partial amorphization of the drug.

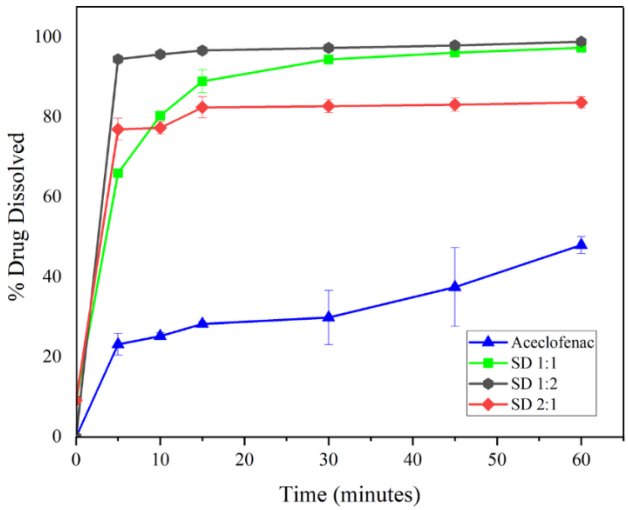

Figure 6. Comparative Dissolution Profile of Aceclofenac, SD 1:1, SD 1:2, and SD 2:1

Table 1: Solubility Test Results for aceclofenac, SD 1:1, SD 1:2, and SD 2:1

Components	Solubility (mg/100mL) ± SD
Aceclofenac	4.024 ± 0.003
SD 1:1	5.292 ± 0.003
SD 1:2	10.986 ± 0.01
SD 2:1	5.176 ± 0.24

Indicated a significant difference in solubility among the tested groups ($p < 0.001$)

Conclusion

The formation of aceclofenac-HPMC solid dispersions significantly enhanced the solubility and dissolution rate of aceclofenac compared to the pure drug. Among the tested formulations, the SD 1:2 ratio exhibited the most notable improvement, with a 2.73-fold increase in solubility and almost complete dissolution within 60 minutes. These results demonstrate the efficacy of HPMC as a hydrophilic polymer for reducing crystallinity and enhancing the bioavailability of poorly water-soluble drugs like aceclofenac. This study underscores the potential of solid dispersion technology as a versatile and effective strategy for addressing solubility challenges in drug development. The use of freeze-drying for solid dispersion preparation could be further explored and optimized for other challenging pharmaceutical compounds. Additionally, investigating alternative hydrophilic polymers or polymer combinations may provide enhanced stability and tailored release profiles for specific therapeutic needs. Future studies should extend to *in vivo* pharmacokinetic evaluations to confirm the clinical relevance of this approach and its potential to improve patient outcomes through better drug absorption and bioavailability.

Conflict of Interest

The authors declares no conflict of interest,

Author's Declaration

The authors declare that the work presented in this article is original and accept responsibility for any claims regarding its content.

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