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Original Research Article

Enhancing Solubility and Dissolution Rate of p-Methoxycinnamic Acid via Multicomponent Crystal Formation with Meglumine

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ABSTRACT

p-Methoxycinnamic acid, a bioactive compound derived from the hydrolysis of ethyl p-methoxycinnamate found in the rhizome of *Kaempferia galanga*, possesses notable pharmacological activity, including analgesic, anti-inflammatory, and antidiabetic properties. However, its poor water solubility limits its effectiveness, necessitating high doses to achieve therapeutic levels. As a Biopharmaceutics Classification System (BCS) class II compound, it has low solubility but high permeability, making solubility and dissolution rate the main barriers to absorption. This study addresses these limitations by forming a multicomponent crystal with meglumine as a coformer to enhance its solubility and therapeutic potential. The multicomponent crystal was prepared in a 1:1 molar ratio using the solvent drop grinding method. Solid state characterization was performed using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FT-IR), and scanning electron microscopy (SEM). PXRD analysis revealed new diffraction peaks, indicating the formation of a distinct crystalline phase, while FT-IR spectra confirmed molecular interactions through wavenumber shifts. SEM analysis illustrated significant morphological changes in the multicomponent crystal compared to the pure constituent. Solubility of the multicomponent crystal showed a 3.4-fold increase, and dissolution studies demonstrated a 2.6-fold enhancement in dissolution efficiency compared to pure p-methoxycinnamic acid. These results highlight the successful formation of a p-methoxycinnamic acid-meglumine multicomponent crystal, classified as a salt. This approach not only improves solubility and dissolution efficiency but also provides a practical strategy for enhancing the formulation of poorly water-soluble drugs. These improvements may lead to better clinical performance and therapeutic outcomes, making it a valuable option in pharmaceutical development.

Keywords: p-Methoxycinnamic acid, Meglumine, Multicomponent crystal, Solubility, Dissolution rate

Introduction

p-Methoxycinnamic acid (p-MCA), a derivative of cinnamic acid, is an aromatic organic compound containing a benzene ring and a carboxylic acid group.[1] It is derived from the hydrolysis of ethyl p-methoxycinnamate, which is isolated from the rhizome of *Kaempferia galanga* L, also known as kenkur, cutcherry, or aromatic ginger, a plant in the ginger family.[2–4] p-MCA exhibits various pharmacological activities, including anti-inflammatory,[3] analgesic, and antidiabetic properties.[2,4] However, despite its therapeutic potential, p-MCA suffers from a poor water solubility of only 0.71 mg/mL at 25 °C.[1] Its low solubility and dissolution rate limit its bioavailability when administered orally, necessitating high doses to achieve therapeutic effects. Improving the solubility and dissolution of p-MCA is therefore crucial for achieving optimal therapeutic efficacy.[2–4]

Various methods have been explored to enhance the solubility of poorly water-soluble drugs, such as solid dispersions, inclusion complexation, prodrug formation, the use of buffer systems, and nanotechnology-based approaches.[5,6]

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Among these, multicomponent crystal formation offers a promising strategy for enhancing the physicochemical properties of a drug without altering its pharmacological effects. Multicomponent crystals form through the molecular interaction of two or more components to create salts, cocrystals, solvates, or hydrates, modifying the drug's crystalline lattice and physicochemical properties.[7] Through the formation of intermolecular bonds like hydrogen bonds or van der Waals interactions, this technique often improves solubility and reduces molecular aggregation.[8] Several methods are available for multicomponent crystal preparation, including solvent evaporation, fusion, grinding, and solvent drop grinding techniques. The latter offers the advantage of being relatively simple and efficient for creating stable multicomponent crystals.[9] N-Acetyl glucosamine, also known as meglumine, is an organic base recognized for its exceptional water solubility (1 g/mL) and melting point range of 128–132 °C. It is widely regarded as a safe, inert, and versatile pharmaceutical excipient.[10] Frequently employed as a coformer, meglumine enhances the solubility of poorly soluble drugs and has been utilized in various formulations, including liposomes,[11] solid dispersions,[12,13] ternary drug systems,[10] microemulsions,[14] and multicomponent crystals. For example, meglumine has been shown to significantly improve the solubility and dissolution rate of sulfamerazine.[12] As a polyhydroxy organic amine, meglumine is particularly effective in forming salts with weakly acidic compounds. Such salts not only enhance solubility but also improve drug release rates and stabilize the physicochemical properties of the molecules. These attributes underscore the critical role of meglumine in pharmaceutical applications, demonstrating its efficacy in addressing solubility and bioavailability challenges in drug development.[13,15]

Previous studies have consistently highlighted the effectiveness of multicomponent crystal formation in improving the solubility and

dissolution rates of poorly soluble compounds. For instance, Melanny et al. demonstrated that the formation of cocrystals with succinic acid via the solvent evaporation method significantly reduced lattice energy, leading to enhanced solubility of p-MCA.[3] Similarly, Dwi et al. reported the successful formation of cocrystals using caffeine as a coformer through solvent evaporation, further supporting the potential of this approach in optimizing drug solubility and dissolution profiles.[4] Inspired by these findings, this study aimed to develop a multicomponent crystal of p-MCA with meglumine using the solvent drop grinding method. The resulting multicomponent crystal was characterized using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FT-IR), and scanning electron microscopy (SEM), alongside an evaluation of its solubility and dissolution rate profile to evaluate its potential for improving the bioavailability of p-MCA.

Materials and Methods

Materials

The materials utilized in this study included p-methoxycinnamic acid (TCI, Japan), meglumine (TCI, Japan), sodium lauryl sulfate (Brataco Chemika, Indonesia), ethanol of analytical grade, and CO_2-free distilled water. All additional chemical reagents met pharmaceutical-grade standards.

Preparation of multicomponent crystal

The multicomponent crystal of p-MCA and meglumine was prepared in a 1:1 molar ratio. p-MCA (0.178 g) and meglumine (0.195 g) were accurately weighed and ground together with two drops of ethanol in a mortar for 30 minutes. The mixture was then stored in a tightly sealed container and placed in a desiccator for further characterization.[16]

Differential scanning calorimetry (DSC) analysis

DSC analysis was conducted using a differential scanning calorimeter (Shimadzu DSC-60Plus, Japan) on p-MCA, meglumine, and the multicomponent crystal of p-MCA and meglumine. A sample weighing 1−4 mg was placed in a crucible pan, sealed with a cover, and pressed. The sample was then introduced into the instrument, with nitrogen gas flowing at 25 mL/min. The temperature range for heating was set from 30 °C to 250 °C, with a heating rate of 10 °C per minute.

Powder X-ray diffraction (PXRD) analysis

PXRD analysis of the sample was conducted at room temperature using a diffractometer (PANalytical MPD PW3040/60 X'Pert Pro, The Netherlands). The analysis was performed under the following conditions: Cu metal target, Kα filter, 40 kV voltage, 40 mA current, with data collected over a 2-theta range of 5° to 50°. The sample was placed on a glass holder and leveled to avoid any particle orientation during storage.

Fourier transform infrared (FT-IR) spectroscopy analysis

The samples, directly placed on the sample holder, were analyzed using an FT-IR spectrophotometer (Thermo Fisher Scientific, USA). Absorption spectra were recorded in the wavenumber range of 4000–500 cm^{-1}. The analysis was performed on p-MCA, meglumine, and the p-MCA-meglumine multicomponent crystal.

Scanning electron microscopy (SEM) analysis

For SEM analysis, the sample was placed on an aluminum sample holder and examined under various magnifications using a scanning electron microscope (JEOL JSM-6360 LA, Japan). The voltage was set between 15−20 kV, and the current was adjusted to 12 mA.

Solubility test

Solubility tests were performed by preparing saturated solutions. An excess of p-MCA or the multicomponent crystal was suspended in 100 mL CO_2-free distilled water in a 100 mL Erlenmeyer flask and mixed under continuous agitation on an orbital shaker at RT for 48 h. The resulting mixture was filtered through Whatman 0.45 µm filter paper and the filtered solution was analyzed for absorbance using a UV-Vis spectrophotometer (Shimadzu UV-1900i, Japan) at the wavelength of maximum absorbance of p-MCA. The concentration was calculated using the regression equation from the calibration curve. The solubility test was repeated three times to ensure accuracy.[16]

Dissolution rate profile

Dissolution profiles were determined using the paddle method (Type II USP). The dissolution flask was filled with 900 mL of CO_2-free distilled water, to which 0.1% sodium lauryl sulfate (SLS) and p-MCA (50 mg) or p-MCA-meglumine multicomponent crystal (corresponding to 50 mg of p-MCA) were added. The solution was maintained at a temperature of 37 ± 0.5 °C with stirring at 50 rpm. At predetermined intervals (5, 10, 15, 30, 45, and 60 minutes), 5 mL aliquots were withdrawn, filtered, and the test solution was replenished with 5 mL of fresh dissolution medium. The absorbance of the filtered solution was measured using a UV-Vis spectrophotometer (Shimadzu UV-1900i, Japan) at a wavelength of 286 nm. The concentration of the sample was calculated based on the regression equation derived from the calibration curve. The dissolution test was repeated three times to ensure reproducibility.[2]

Results and Discussion

Solid state characterization

DSC analysis

The DSC thermograms of p-MCA, meglumine, and the p-MCA-meglumine multicomponent crystal are provided in Figure 1a. Melting points for p-MCA, meglumine, and the multicomponent crystal at 172.89, 132.28, and 118.44 °C, respectively, indicate a reduction in the melting point for the multicomponent crystal compared to the individual components. A significant decrease in the melting point was observed for the multicomponent crystal, suggesting the formation of physical interactions between p-MCA and meglumine, and weakened lattice energy relative to the individual components, facilitating crystal disintegration and solubilization.[17,18] DSC analysis provides critical insights into the solid-state physical interactions between active pharmaceutical ingredients and coformers. These interactions can be indicated by shifts, often reductions, in melting points.[17] This finding highlights the potential of multicomponent crystal formation to improve the dissolution properties of poorly soluble compounds.

PXRD analysis

PXRD patterns for p-MCA, meglumine, and the multicomponent crystal are presented in Figure 1b. Characteristic peaks for p-MCA appear at 2θ values of 7.9706°, 16.2256°, and 26.9116°, with intensities of 5876.89, 53126.4, and 15014.8, respectively. Characteristic peaks for meglumine are observed at 2θ values of 8.9522°, 12.428°, 17.9428°, and 21.9870°, with intensities of 15556.9, 2166.37, 3576.21, and 5086.43, respectively. These individual component peaks are absent in the PXRD of the multicomponent crystal, which exhibits unique peaks at 2θ values of 9.7357°, 15.345°, 19.2727°, 21.9127°, 22.5727°, 23.3977°, 26.9287°, and 27.9517°, with intensities of 4633.52, 10154.02, 6428.94, 9026.19, 6098.74, 4338.07, 4450.95, and 3900.51, respectively. PXRD analysis confirmed the formation of a new crystalline phase, as evidenced by distinct peaks in the multicomponent crystal diffractogram compared to those of the pure components. The multicomponent crystal exhibited unique peaks, such as those at 2θ values 9.7357° and 26.9287°, absent in the pure components and affirming a new crystalline structure (Figure 1).[19] Enhanced crystallinity, indicated by increased peak intensity, contributes to improved solubility and dissolution. PXRD identifies crystalline phases through diffraction patterns expressed as angles (θ and 2θ).[20]

FT-IR spectroscopic analysis

The FT-IR spectra of the multicomponent crystal showed shifts of several wavenumbers, indicating potential hydrogen bonding interactions between the carboxyl group of p-MCA and the secondary amino group of meglumine[3] (Figure 1c). The broader OH band at 3269.58 cm^{-1} compared to the individual components supports this interaction, enhancing solubility and dissolution without chemically modifying the functional groups.[2,21]

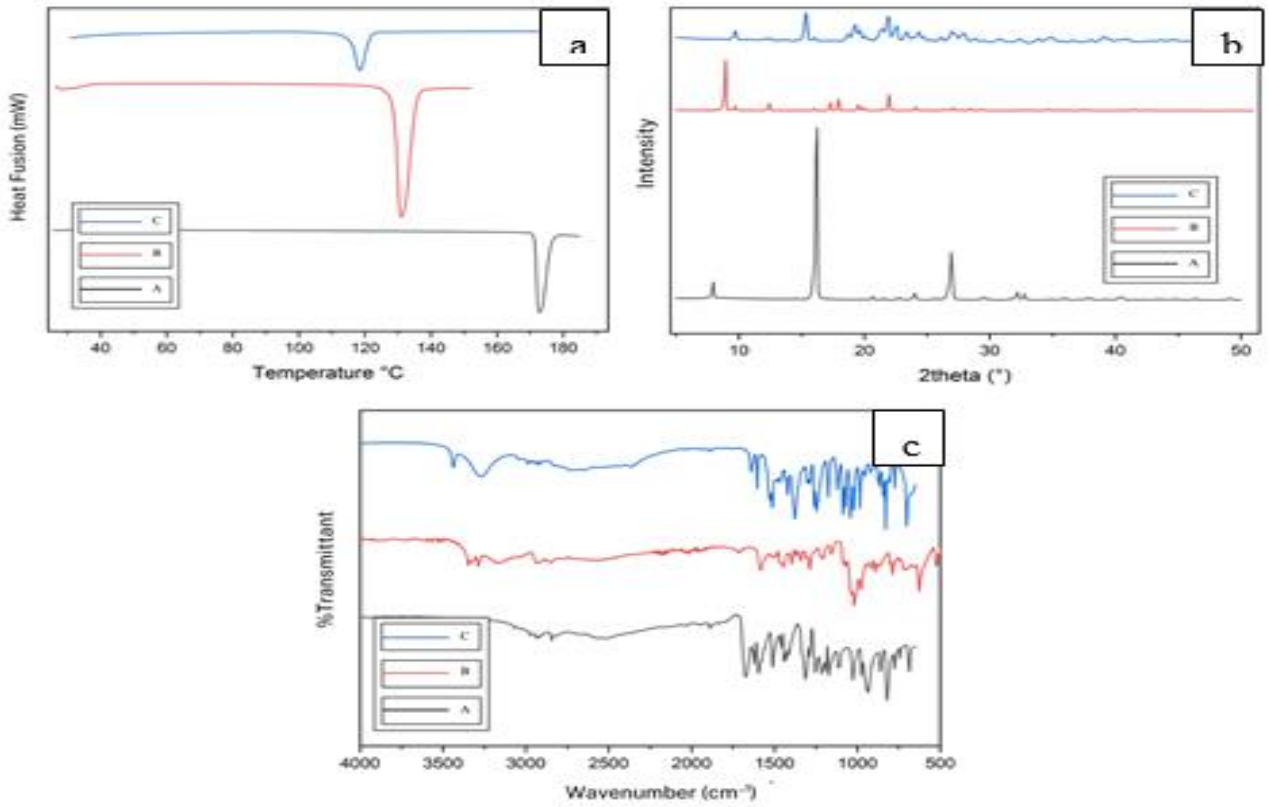

Figure 1: Solid state characterization. **(a)** DSC thermogram of (A) p-MCA, (B) meglumine, and (C) p-MCA-meglumine multicomponent crystal. **(b)** PXRD patterns of (A) p-MCA, (B) meglumine, and (C) p-MCA-meglumine multicomponent crystal. **(c)** FT-IR spectra of (A) p-MCA, (B) meglumine, and (C) p-MCA-meglumine multicomponent crystal.

SEM analysis

SEM analysis revealed significant changes in crystal morphology. p-MCA is observed as large, irregularly shaped crystals, and meglumine crystals exhibit a rod-like structure. The multicomponent crystal formed needle-like agglomerates, with a smaller and more uniform particle size compared to the pure components (Figure 2).[22] These changes can be attributed to the solvent drop grinding method, which reduces particle size, increasing surface area and improving solubility.[23]

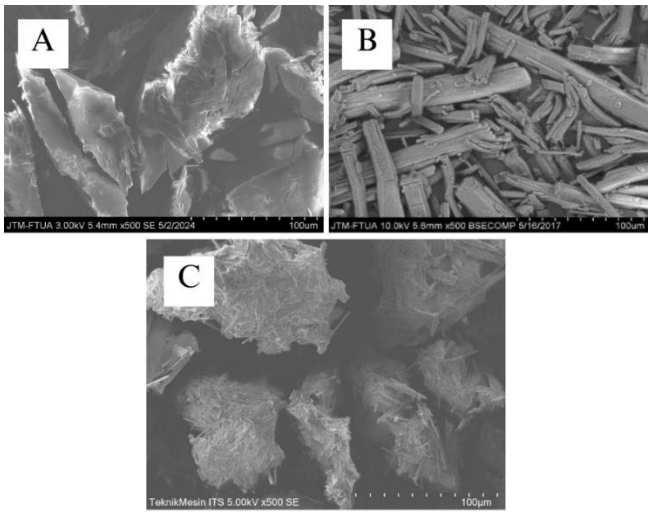

Figure 2: SEM morphologies of (A) p-MCA, (B) meglumine, and (C) p-MCA-meglumine multicomponent crystal.

Solubility test

The solubility test showed a 3.40-fold increase in p-MCA solubility after multicomponent crystal formation with meglumine (Table 1). This enhancement aligns with the observed reduction in melting point and crystallinity from DSC analysis, suggesting improved molecular mobility.[9] Additionally, the ΔpKa between p-MCA and meglumine supports the likelihood of salt formation, which may contribute to enhanced solubility through ionization in aqueous media. This is consistent with Zaini et al., who reported that salt-type multicomponent crystals dissociate into cations and anions, increasing water affinity.[24] Therefore, both reduced crystallinity and potential salt formation may synergistically improve solubility, supporting the strategic value of salt-type multicomponent crystals in developing formulations for poorly water-soluble drugs.[25,26]

Table 1: Solubility data.

Material	Solubility (mg/100 mL)	± SD
Pure p-MCA	7.9903	± 0.6020
p-MCA-meglumine multicomponent crystal	27.2410	± 2.8967

Dissolution rate profile

Dissolution tests revealed a 2.6-fold increase in dissolution efficiency for the multicomponent crystal, with 56.41% dissolution after 60 minutes compared to 21.73% for pure p-MCA (Figure 3). This improvement is linked to reduced melting point and particle size, as indicated by SEM analysis. The addition of 0.1% sodium lauryl sulfate prevented hydrophobic behavior, while CO_2-free distilled water at pH

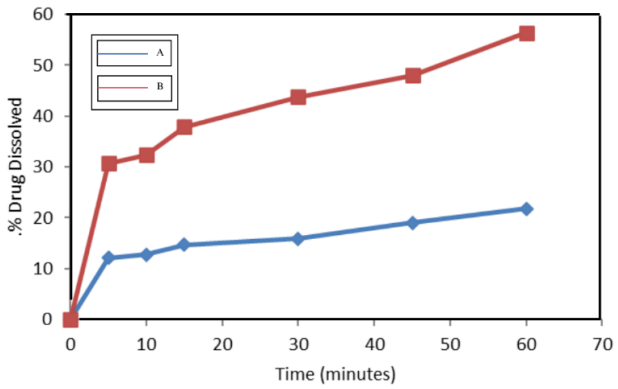

Figure 3: Dissolution profiles of (A) p-MCA and (B) p-MCA-meglumine multicomponent crystal.

7 facilitated dissolution.[27] According to the Noyes-Whitney equation, a smaller particle size enhances surface area, improving dissolution and absorption rates.[28]

Conclusion

The formation of a multicomponent crystal between p-methoxycinnamic acid and meglumine markedly enhanced the drug's solubility and dissolution rate, achieving a 3.4-fold and 2.6-fold increase, respectively, compared to the pure compound. These improvements are attributed to reduced crystallinity and the possible formation of ionic interactions, supported by physicochemical characterization. The findings highlight the formation of multicomponent crystals, particularly with hydrophilic coformers like meglumine, as a promising strategy to improve the oral bioavailability of poorly water-soluble drugs. Moving forward, this approach holds considerable potential for broader application in pharmaceutical development, especially for BCS Class II compounds. Further studies involving in vivo evaluation and scale-up feasibility are recommended to support translation into clinical settings.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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