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Original Article

SOLID DISPERSION OF ETHYL P-METHOXYCINNAMATE (EPMC) FROM *KAEMPFERIA GALANGA* RHIZOME BY FREEZE-DRYING METHOD

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ABSTRACT

Objective: To increase the dissolution rate of Ethyl p-methoxycinnamate (EPMC), which was isolated from *Kaempferia galanga* rhizome, this study aimed to prepare and characterize a Solid Dispersion (SD) system using the hydrophilic polymer Hydroxypropyl Methylcellulose (HPMC) K4M.

Methods: EPMC was isolated from the rhizome of *Kaempferia galanga* and identified using a melting point instrument (Differential Scanning Calorimetry) and Thin Layer Chromatography (TLC). Three distinct EPMC and HPMC K4M ratios-1:1, 1:2, and 1:3 (w/w)-were freeze-dried to prepare the SD. Fourier Transform Infrared (FT-IR) spectroscopy, Scanning Electron Microscopy (SEM), Powder X-ray Diffraction (PXRD), and Differential Scanning Calorimetry (DSC) were used to characterize the SD. For 60 min, the dissolution test was carried out in distilled water free of CO_2 and with an extra 0.1% Sodium Lauryl Sulfate (SLS).

Results: The characterization of SD systems showed a decrease in the endothermic peak and melting point in the DSC analysis, decreased peak intensity in the PXRD patterns, unchanged chemical structure in FT-IR analysis, and pores formation on the surface in SEM analysis. A significant increase in dissolution rate ($p<0.05$) was observed, with a 3.63-fold improvement for the 1:3 SD (60.603±1.163%) compared to intact EPMC (16.684±1.352%).

Conclusion: The SD of EPMC-HPMC K4M was successfully formed, and a higher dissolution rate was achieved than that of the intact EPMC.

Keywords: Ethyl p-Methoxycinnamate, *Kaempferia galanga,* HPMC K4M, solid dispersion, dissolution rate, freeze-drying

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INTRODUCTION

Rheumatism, asthma, digestive issues, headaches, colds, toothaches, and coughs with phlegm have all been traditionally treated with the rhizome of *Kaempferia galanga*. Additionally, it improves blood circulation and regulates internal heat. The pharmacological activity of *Kaempferia galanga*, such as its anti-inflammatory, anti-apoptotic, anti-carcinogenic, soothing, and wound-healing qualities, have been shown in recent studies [1]. Ethyl p-Methoxycinnamate (EPMC), which makes up around 80% of the extract from *Kaempferia galanga* rhizome, is the main chemical found there [2]. However, the main component, EPMC, is only 3 µg/ml soluble in water [3]. Its molecular structure, which consists of a carbonyl group bound to an ethyl group, a nonpolar methoxy group, and an ester group joined to a benzene ring, is probably the cause of its poor solubility [4].

Several methods have been used to modify the solubility and dissolution rate of EPMC. However, the enhancement is still insignificant. The rate of dissolution of EPMC was markedly improved through the process of co-crystallization with tartaric acid, resulting in an enhancement of water solubility by factors of 1.39, 1.50, and 1.44 for cocrystal ratios of 1:1, 1:2, and 1:3, respectively [5]. In other research, the solubility of EPMC when combined with citric acid just demonstrated an increase of 44.19% compared to the untreated EPMC [3]. This research used the Solid Dispersion (SD) technique to increase the EPMC dissolution rate further. Generally, SD is defined as dispersing active substances into a hydrophilic carrier or matrix in a solid state. This technique enhances drug dissolution and solubility by improving the surface area for dissolution, converting the crystalline of the drug into an amorphous phase, and allowing better drug wettability [6–8]. SD can be prepared using spray drying, freeze drying, hot-melt extrusion, melt agglomeration, electrostatic spinning, supercritical anti-solvent, solvent evaporation, cryogenic processing, etc [9]. Freeze-drying is one of the preferred methods that provides advantages over others. Unlike methods that involve high temperatures, freeze drying operates at low temperatures, making it suitable for thermolabile drugs that may degrade under heat [10]. As EPMC undergoes decomposition through hydrolysis and is relatively unstable at high temperatures, its melting point is 48 – 50 °C; the freeze-drying method is an appropriate technique for SD formation in this study [11]. Previous studies have also supported the idea that SD prepared using the freeze-drying method presented positive results regarding the physiochemical properties. A freeze-dried ginger extract showed improved solubility, dissolution rate, and stability [12].

Hydroxypropyl Methylcellulose (HPMC) K4M, a cellulose derivative, is considerable for its abundant availability, ease of use, excellent film-forming ability, and biocompatibility. It is commonly utilized as a matrix in drug delivery systems and as a film-forming agent, emulsifier, stabilizer, or thickener in food applications [13]. As a non-ionic, water-soluble polymer, HPMC K4M is prominent for SD, offering physical stability due to its high glass transition temperature, which limits drug molecular mobility in the amorphous matrix [14]. Moreover, interactions of drug-polymer help maintain homogeneity, prevent phase separation, and reduce moisture absorption. Research has shown that SD with HPMC can significantly enhance solubility, as demonstrated with *Kaempferia parviflora* extract, where solubility increased nearly threefold compared to non-dispersed extracts [15]. These results suggest that HPMC K4M is a promising carrier polymer for this study.

Based on previous studies, SD has significantly enhanced the dissolution rates of poorly water-soluble drugs. The highest dissolution increase reported is a 361-fold enhancement in solubility for aceclofenac [16]. The dissolution rate of glibenclamide increased 20-fold when formulated as a SD with HPMC compared to the pure drug [17]. In other research, incorporating piperine into a SD system with HPMC using freeze-drying resulted in a 7.88-fold increase in solubility and a significant improvement in the dissolution rate [18]. Therefore, this research aims to enhance the dissolution rate of EPMC derived from the rhizome of *Kaempferia galanga* through SD techniques, particularly utilizing the freeze-drying method combined with HPMC K4M as a carrier polymer. Physicochemical characterizations of SD involve several predominant solid-state analyses, including powder X-ray Diffraction (PXRD), Differential

Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), and Fourier Transform Infrared (FT-IR) spectroscopy. The dissolution rate profile is also carried out to evaluate the effect of SD on the enhancement of EPMC's dissolution rate.

MATERIALS AND METHODS

Materials

The *Kaempferia galanga* rhizome simplicia was bought from Rumah Rempah Lestari in Indonesia. Japan's Tokyo Chemical Industry provided the EPMC standard. Shidley Chem (China) provided the medium-viscosity HPMC K4M. The following chemicals and solvents were of analytical grade: Sodium Lauryl Sulfate (SLS), distilled water, n-hexane, ethyl acetate, and 96% ethanol.

Isolation of EPMC from *Kaempferia galanga* rhizome

After being macerated for three days with 96% ethanol, two hundred grams of dried *Kaempferia galanga* rhizome simplicia were filtered and macerated twice more. A rotary evaporator (Buchi Rotavapor R-210, Switzerland) was then used to concentrate the filtrates at 40 °C and 50 rpm. After that, the filtrates had to remain at room temperature for 12 h to recrystallize with n-hexane and ethyl acetate, producing white crystals. The initial simplicia weight was used to compute the yield.

Identification of EPMC from *Kaempferia galanga* rhizome

Ten milligrams of standard and isolated EPMC were dissolved in ethanol and spotted onto a 2×6 cm silica gel F254 TLC plate (Merck, Germany), with a 0.5 cm separation between spots. The plate was developed in a chamber with n-hexane: ethyl acetate (9:1) until the solvent front passed the samples, and the spots were visualized under UV light at λ 254 nm. Melting point determination was then performed by weighing 4-5 mg of each isolated and standard EPMC, which was analyzed using Differential Scanning Calorimetry (Shimadzu DSC-60 Plus, Japan).

Preparation of solid dispersion by freeze-drying

The SD of EPMC with HPMC K4M was prepared using the freeze-drying method using a freeze dryer (Buchi Lyovapor L-200, Switzerland). HPMC K4M was dissolved in distilled water (80-90 °C) and stirred until homogeneous (200 rpm for 10–15 min). EPMC, which dissolved in ethanol, was mixed with the HPMC K4M solution in various ratios, as shown in table 1, and stirred continuously for 2 h. Then, this mixture was frozen for approximately 24 h under a freezing temperature of-50 ºC and then subjected to sublimation for 10 h with chamber pressures maintained below 0.056 atm. The dried sample was stored in an airtight container and placed in a desiccator.

Table 1: Ratios of EPMC to HPMC K4M in solid dispersions

Materials	Weight (mg) (w/w)		
	SD 1:1	SD 1:2	SD 1:3
EPMC	100	100	100
HPMC K4M	100	200	300

SD: solid dispersion

Differential scanning calorimetry (DSC)

A differential scanning calorimeter (Shimadzu DSC-60 Plus, Japan) was used for the thermal analysis of EPMC, HPMC K4M and SD at ratios of 1:1, 1:2, and 1:3. Around 4 milligrams of each sample were placed in aluminum pans, sealed, and heated from 10 to 200 °C at a rate of 1 °C per minute.

Powder X-ray diffraction (PXRD)

EPMC and SDs at ratios of 1:1, 1:2, and 1:3 were placed in an X-ray diffractometer (PAN analytical MPD PW3040/60 type X'pertama Pro, Netherland) holder under the following conditions: Cu metal target, Kα filter, 40 kV voltage, and 30 mA current. Diffraction patterns were measured at 2θ angles ranging from 5 to 50°. The analysis provided a curve showing the relationship between peak intensity and the 2θ angle.

Fourier transform infrared (FT-IR)

The FT-IR spectra EPMC and the SDs were analyzed using an FT-IR spectrometer (Shimadzu IRTracer-100 AH, Japan). About two to three milligrams of each sample were placed in an Attenuated Total Reflectance (ATR) holder, and the absorbance spectra were measured in the wavenumber range of 4000 to 600 cm^{-1}.

Scanning electron microscopy (SEM)

The morphology of EPMC and the SDs were analyzed using a scanning electron microscope (SEM) (Hitachi Flexsem 100, Japan). Samples were placed on aluminum plates and coated with gold. The voltage was set to 20 kV with a current of 12 mA. The samples were then observed at various magnifications using the SEM.

Dissolution studies

The dissolution profile of the EPMC-HPMC K4M SD was analyzed using a USP type II dissolution tester (SR8 Plus Dissolution Test Station Hanson IRTracer-100 AH, US) in 900 ml of CO_2-free distilled water with an additional 0.1% sodium lauryl sulfate, at 75 rpm and 37±0.05 °C. Five milliliters of sample were pipetted at specific time intervals: 5, 10, 15, 30, 45, and 60 min. Each sample withdrawal was replaced with an equal volume of fresh medium. The amount of dissolved sample was measured using a UV-Vis spectrophotometer (Shimadzu UV-1900, Japan) at the maximum wavelength.

Data analysis

Dissolution rates of EPMC and the SD were analyzed using an independent sample T-test with SPSS 29, comparing the percentage of dissolved samples at each time point.

RESULTS AND DISCUSSION

Identification of EPMC from *Kaempferia galanga* rhizome

Thin layer chromatography (TLC) analysis

Analysis through TLC was done for confirming of the isolated EPMC from rhizomes of *Kaempferia galanga* by comparing the spot of the isolated compound with that of the EPMC standard. TLC is a simple and inexpensive technique for the separation of the components of mixture, which are monitored according to their polarity and adsorption onto stationary phase [19]. The results showed that the isolated compound and the standard produced identical retention factor (Rf) values of 0.5. The isolated compound gave a single spot-on TLC plate corresponding to the standard is taken confirmation of purity of EPMC. It confirms the purity and identity of the isolated EPMC as well as emphasizes the efficiency of TLC in qualitative compound analysis.

Melting point determination

Melting point determination using DSC analysis is an effective method for assessing crystal purity [20]. As shown in fig. 1, the crystal isolated from *Kaempferia galanga* rhizomes exhibited a sharp peak at 51.99 °C, indicating high purity. It aligns closely with the standard EPMC, which shows a sharp peak at 51.57 °C, confirming the isolated crystal as EPMC. The DSC results are further supported by previous TLC analysis, reinforcing the purity and identity of the compound. Minor differences in peak temperature may be due to slight variations in experimental conditions, but overall, these findings strongly confirm the isolated crystal as EPMC.

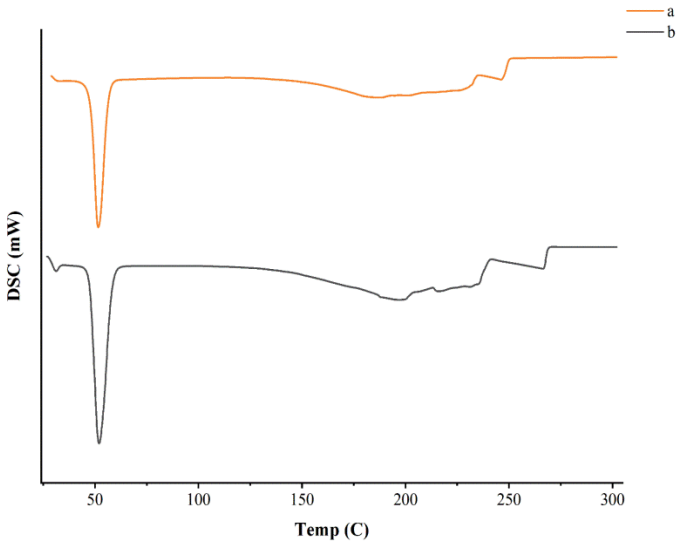


Fig. 1: DSC thermograms of a) standard EPMC and b) isolated EPMC

Solid state characterization of EMPC-HPMC K4M solid sispersion

Differential scanning calorimetry (DSC) analysis

DSC analysis was carried out to confirm the formation of SDs and changes in the solid state [15]. Thermal analysis using DSC on the isolated EPMC formed into SD with HPMC K4M at ratios of 1:1, 1:2, and 1:3 (fig. 2) revealed a decrease in the intensity of the endothermic peak, with corresponding enthalpy reductions to 38.15 J/g, 30.93 J/g, and 26.92 J/g, indicating reduced crystallinity of the isolated EPMC after forming the SD. Additionally, a shift in the melting point from 51.99 °C to 48.71 °C (SD 1:1), 48.20 °C (SD 1:2), and 48.29 °C (SD 1:3) suggests a transition from the crystalline form to an amorphous or semi-amorphous state within the HPMC K4M matrix. This observation is by previous studies using curcumin and HPMC K4M, where significant reductions in DSC thermogram peak intensity and enthalpy were observed, along with a melting point shift, indicating a similar transformation from crystalline to amorphous form in the SD system [21].

Powder X-ray diffraction (PXRD) analysis

The data in table 2 showed that the isolated EPMC exhibited sharp peak intensities at 2θ positions of 26.5074 and 27.3596. These peak intensities decreased following the formation of SDs of EPMC with HPMC K4M at ratios of 1:1, 1:2, and 1:3 (fig. 3). Specifically, at the SD 1:3, the peak intensity significantly dropped from 8155.75 to 1038.77. These results indicated that the degree of crystallinity of the drug decreased with a higher concentration of the hydrophilic polymer, suggesting that the polymer effectively encapsulates the drug, transforming the crystalline phase to a partial amorphous state [22]. Additionally, as seen in table 3, the relative crystallinity index (RCI) of SD 1:3 was the lowest at 33.82. RCI is derived from X-ray diffraction patterns and measures crystallinity relative to amorphous and highly crystalline samples [23]. Crystallinity is crucial in determining the solubility of both natural and pharmaceutical compounds, with lower crystallinity generally associated with higher solubility and dissolution rates [24]. Therefore, this ratio was selected for further characterization and dissolution tests. These results suggest changes in the crystallinity of isolated EPMC can enhance its solubility and dissolution rate. Similar findings have been reported in studies involving the SD of hesperidin with HPMC K4M, which significantly increased the dissolution rate, more than two times higher than that of intact hesperidin [25].

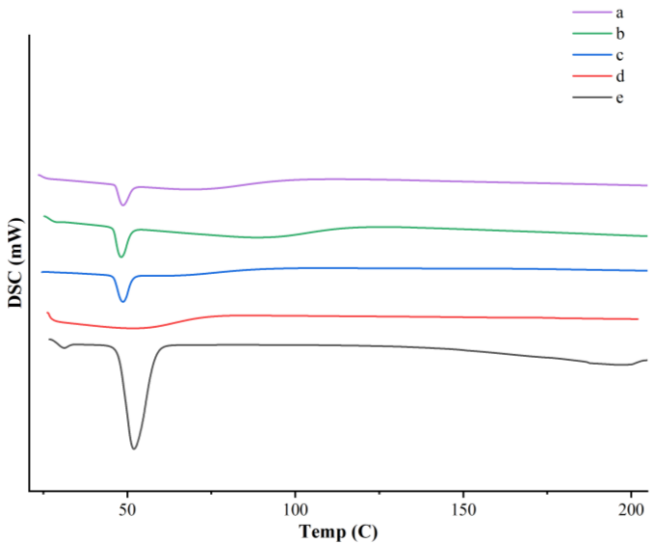


Fig. 2: DSC thermograms of a) SD 1:3, b) SD 1:2, c) SD 1:1, d) HPMC K4M, and e) isolated EPMC

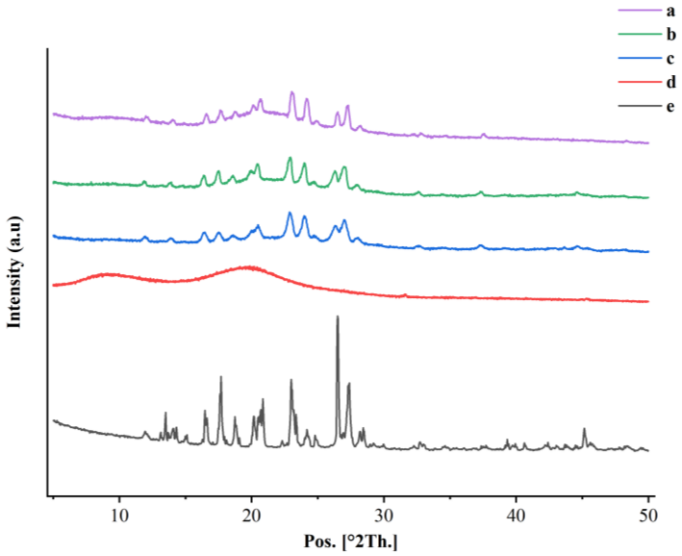


Fig. 3: X-ray diffraction patterns of a) SD 1:3, b) SD 1:2, c) SD 1:1, d) HPMC K4M, and e) EPMC

Table 2: Peak intensity data of EPMC and SDs

Pos. 2θ	Intensity			
	EPMC	SD 1:1	SD 1:2	SD 1:3
16.4684	2088.32	-	693.84	-
16.6351	1625.56	608.05	-	644.72
17.6604	2926.07	618.37	997.57	961.71
18.731	1749.6	475.6	763.65	900.57
20.1655	1863.89	704.76	1081.1	1344.27
20.4936	1334.06	1089.89	-	-
20.8632	2916.94	-	1408.21	1500.26
22.3233	397.73	-	-	-
23.0037	4167.68	1937.26	1907.02	2091.15
23.3869	1569.53	1639.42	-	-
24.1852	1090.74	-	1631.22	1741.43
24.8076	755.11	515.95	492.04	558.7
26.5074	8155.75	1152.81	1148.9	1038.77
27.3596	3917.4	1491.92	1447.04	1464.28
28.192	1052.36	400.76	388.2	352.45
28.4687	975.35	-	-	-
28.9473	239.05	-	-	-
29.2334	327.42	-	-	-
29.9901	256.45	-	-	-

Table 3: The relative crystallinity index of SDs

Area	SD 1:1	SD 1:2	SD 1:3
Crystal Area (a)	5997.34	7606.81	7034.52
Total Area (b)	7757.02	13828.79	20801.04
Relative Crystallinity Index ($\frac{a}{b}$)	77.32	55.01	33.82

Fourier transform infrared (FT-IR) spectroscopy analysis

FTIR spectroscopy analysis aims to identify the sample's chemical functional groups. In this study, drug-polymer interactions are assessed using FTIR analysis. FTIR can identify variations in the vibrational frequencies of functional groups, which could indicate interactions between the drugs and the polymer, including hydrogen bonding or other molecular interactions. Understanding the SD's stability and solubility is important [26]. The FT-IR spectrum (fig. 4) of EPMC displays characteristic peaks at 2981.72–2937.07 cm^{-1} (aliphatic C-H), 1511.58 cm^{-1} (aromatic C=C), 1170.60 cm^{-1} (C-O attached to an aromatic ring), 1024.13 cm^{-1} (C-O in ester group), and 828.21 cm^{-1} (para-substituted aromatic ring). Meanwhile, HPMC K4M shows distinctive peaks at 3435.28 cm^{-1} (O-H), 1640.49 cm^{-1} (C-O), and 2900.02 cm^{-1} (C-H). The FT-IR spectrum of the EPMC-HPMC K4M (1:3) exhibits peaks corresponding to both EPMC and HPMC K4M, with slight shifts observed in functional groups: aliphatic C-H (2939.07 to 2936.02 cm^{-1}), aromatic C=C (1511.58 to 1512.46 cm^{-1}), C-O in ester (1170.60 to 1169.60 cm^{-1}), and para-substituted aromatic (828.21 to 829.52 cm^{-1}). These shifts suggest hydrogen bonding between EPMC and HPMC K4M, which weakens the bonds and lowers the vibrational energy, leading to lower wavenumber values in the FT-IR spectrum [5].

Scanning electron microscopy (SEM) analysis

SEM analysis provides high-resolution images of the surface morphology of SD. It allows us to observe the particles' shape, size, and surface characteristics, which can influence the dissolution and bioavailability of the drug [26]. EPMC's surface

morphology (fig. 5) reveals a variety of forms, sharp edges, and a rough texture, whereas HPMC K4M, which is amorphous, displays fibrous particles. The formation of a porous surface morphology upon dispersing EPMC with HPMC K4M by freeze drying suggests a change in the drug's physical state when mixed with the hydrophilic polymer, which may accelerate the rate at which the isolated EPMC dissolves [18]. A rough, uneven surface with sharp edges appears by SEM analysis of the EPMC-HPMC K4M (1:3), indicating that HPMC K4M has not fully covered EPMC. It is in line with the results of DSC and PXRD, which show that although EPMC is dispersed throughout HPMC K4M, its crystalline form can still be found, although it has a lower peak intensity. It suggests that some crystalline structures remain after the dispersion process does not entirely convert EPMC to an amorphous form. Similar results were obtained in earlier research on quercetin SDs using HPMC K4M, which revealed a porous shape and markedly enhanced dissolving rates, nearly eight times higher after 360 min than intact quercetin [27].

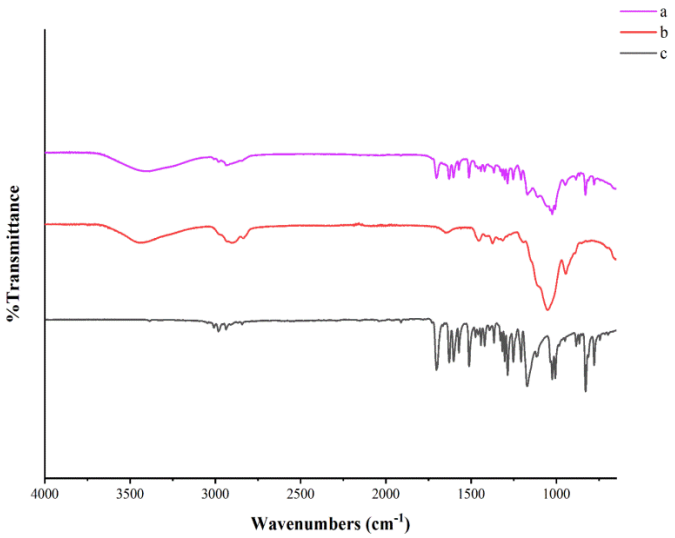
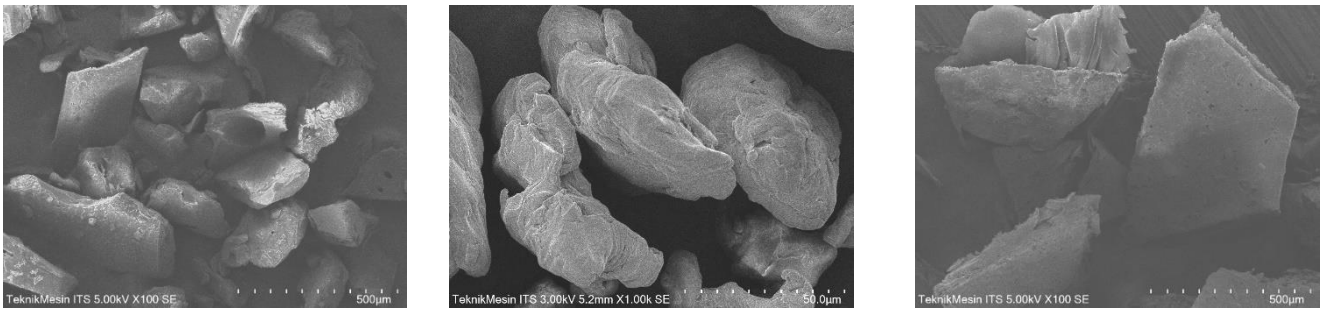


Fig. 4: FT-IR spectra of a) SD 1:3, b) HPMC K4M, and c) isolated EPMC



a) **b)** **c)**

Fig. 5: Surface morphology of a) EPMC, b) HPMC K4M, c) SD 1:3

Dissolution studies

Isolated EPMC exhibited a low dissolution rate in CO_2-free distilled water, reaching only 2.932% in the first 5 min and increasing to 16.684% after 60 min (fig. 6). However, this dissolution rate significantly improved when EPMC was dispersed with HPMC K4M at a 1:3 ratio. Within the first 5 min, the dissolution rate increased 6.3 times, from 2.932% to 18.557%, and after 60 min, it increased approximately 3.6 times, from 16.684% to 60.603%. This increase is much higher compared to other methods previously reported. For instance, the cocrystallization technique could only enhance EPMC solubility by about 1.5 times, and the formation of an inclusion complex with hydroxypropyl-β-cyclodextrin only increased solubility up to 26% [28, 29]. These results are consistent with previous studies showing that dispersing tenoxicam with HPMC K4M through freeze-drying can enhance its dissolution rate [30]. Other research also demonstrated higher solubility of telmisartan SDs with HPMC E5 lV compared to intact telmisartan and its physical mixture, attributed to partial amorphization of the crystalline phase [31].

Statistical analysis using an independent samples t-test confirmed a significant difference in dissolution rates between pure EPMC and the SD ($p<0.05$), indicating that forming a SD of EPMC with HPMC K4M improves the dissolution rate compared to pure EPMC. The use of hydrophilic carriers like HPMC K4M can lead to the formation of amorphous SD, confirmed by reduced peak intensities in PXRD analysis. This amorphous state generally has higher solubility and dissolution rate compared to the crystalline form because the drug is often in a supersaturated state within the carrier and surface morphology of amorphous state increase the surface area of the drug [32]. Additionally, the hydrophilic nature of HPMC K4M helps to improve the wettability of the drug. HPMC K4M has a rapid hydration property in aqueous solutions, which can help in quick dispersion of the drug. Intermolecular hydrogen bonding between HPMC K4M and EPMC that confirmed by FT-IR spectroscopy analysis also has contribution to improved dissolution through stabilize the amorphous form of the EPMC in the SD system and enhance the wettability of the EPMC [33].

However, this study also showed that EPMC's crystalline structure is still observable, indicating incomplete amorphization, which would restrict the maximum increase in dissolution rate. Surface morphology analysis by SEM showed that EPMC was not fully

covered by HPMC K4M, which may also affect the effectiveness of the dissolution rate improvement. To accomplish complete amorphization and improved surface coverage, future studies should investigate other ratios of HPMC K4M and alternate dispersion procedures. It could further increase formulation stability and dissolving rate enhancement.

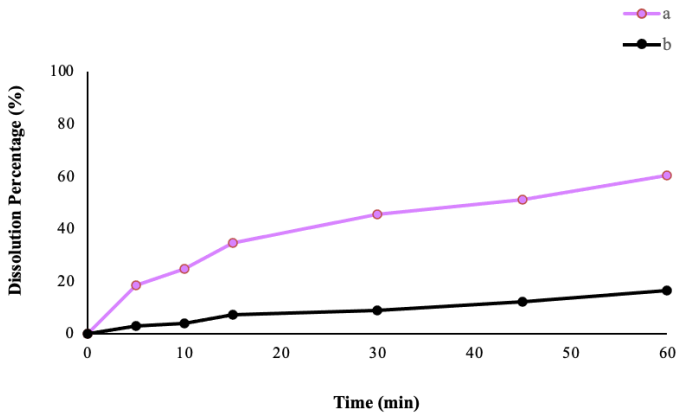


Fig. 6: Dissolution profiles of a) SD 1:3 and b) isolated EPMC

CONCLUSION

The solid dispersion of isolated ethyl p-methoxycinnamate from *Kaempferia galanga* L. rhizomes can be successfully prepared with medium viscosity HPMC K4M as a carrier polymer using the freeze-drying method, as confirmed by DSC, PXRD, FT-IR, and SEM analyses. Solid dispersion EMPC-HPMC K4M at a 1:3 (w/w) ratio resulted in a 3.6-fold increase in the dissolution rate after 60 min compared to the isolated compound.

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AUTHORS CONTRIBUTIONS

Concept: EZ, AJ, LF; Design: EZ, AJ; Data Collection or Processing: ITA, AJ, UH; Analysis or Interpretation: EZ, AJ, LF, UH, ITA; Literature Search: ITA, LF, AJ, EZ; Writing: EZ. AJ, ITA, LF, UH; Approval: EZ.

CONFLICT OF INTERESTS

The authors declare no conflict of interest with the data contained in the manuscript.

REFERENCES

1. Nonglang FP, Khale A, Bhan S. Phytochemical characterization of the ethanolic extract of Kaempferia galanga rhizome for antioxidant activities by HPTLC and GCMS. Futur J Pharm Sci. 2022 Dec 8;8(1):1-12.
2. Adianingsih OR, Widaryanto E, Saitama A, Zaini AH. Analysis of bioactive compounds present in Kaempferia galanga rhizome collected from different regions of east Java, Indonesia. IOP Conf Ser.: Earth Environ Sci. 2021 Nov 1;913(1):1-7. doi: 10.1088/1755-1315/913/1/012074.
3. Rachmaniar R, Riasari H, Fauziah L, Kenti FR, Ferdiansyah R. The effect of cocrystallization method and citric acid as coformer on water solubility of ethyl p-metoxycinnamate particle. AIP Conf Proc. 2020:080013. doi: 10.1063/5.0003178.
4. Rachmaniar R, Warya S, Ferdiansyah R, Riasari H, Gumelar A, Kenti. Pharmaceutical cocrystal of ethyl p-methoxycinnamate: formulation and characterization. In: 2nd Bakti Tunas Husada-Health Science International Conference (BTH-HSIC 2019). Atlantis Press; 2020. p. 96-101. doi: 10.2991/ahsr.k.200523.024.
5. Rachmaniar R, Gozali D, Panatarani C, Legowo WP, Warya S, Rusdiana T. Solubility enhancement of ethyl p-methoxycinnamate under nanoscale confinement. J Chin Pharm Sci. 2022;31(6):461. doi: 10.5246/jcps.2022.06.040.
6. Kumar R, Singh A, Salwan R, Bhanot R, Rahar S, Dhawan RK. An informative review on solid dispersion. GSC Biol Pharm Sci. 2023 Jan 30;23(1):114-21. doi: 10.30574/gscbps.2023.22.1.0498.
7. Mardiyanto M, Untari B, Mara A, Ferdiansyah DF. Formation of hydroxyl-amide solid dispersion involving azithromycin and chitosan-alginate biopolymer to increase the dissolution rate of azithromycin. Sci Technol Indones. 2023 Oct 1;8(4):647-53. doi: 10.26554/sti.2023.8.4.647-653.
8. Butar Butar ME, Wathoni N, Ratih H, Windhu Wardhana Y. Solid dispersion technology for improving the solubility of antiviral drugs. Pharm Sci Res. 2023 Apr 30;10(1):1-19. doi: 10.7454/psr.v10i1.1292.
9. Kaushik R, Budhwar V, Kaushik D. An overview on recent patents and technologies on solid dispersion. Recent Pat Drug Deliv Formul. 2020 Oct 13;14(1):63-74. doi: 10.2174/1872211314666200117094406, PMID 31951172.
10. IS, An R. A review on freeze-drying: a stability enhancement technique. Res J Pharm Technol. 2022 Oct 21;15(10):4841-6.
11. Kamil WM, Mat Jafri MZ, Omar AF, Tan CH. Wan Ahmad [The performance and stability of titanium dioxide and ethylhexyl methoxycinnamate as sunscreen filter: a comparison study]. In: Popp J, Tuchin VV, Pavone FS, editors. Biophotonics. Photonic Solutions for Better Health Care VI. SPIE; 2018. p. 153.
12. Sato H, Ogino M, Yakushiji K, Suzuki H, Shiokawa KI, Kikuchi H. Ginger extract-loaded solid dispersion system with enhanced oral absorption and antihypothermic action. J Agric Food Chem. 2017 Feb 22;65(7):1365-70. doi: 10.1021/acs.jafc.6b04740, PMID 28132501.
13. Da Silva Junior WF, de Oliveira Pinheiro JG, Moreira CD, de Souza FJ, de Lima AA. Alternative technologies to improve solubility and stability of poorly water-soluble drugs. In: Multifunctional systems for combined delivery, Biosensing and diagnostics. Elsevier; 2017. p. 281-305. doi: 10.1016/B978-0-323-52725-5.00015-0.
14. Chavan RB, Rathi S, Jyothi VG, Shastri NR. Cellulose based polymers in development of amorphous solid dispersions. Asian J Pharm Sci. 2019 May;14(3):248-64. doi: 10.1016/j.ajps.2018.09.003, PMID 32104456.
15. Weerapol Y, Tubtimsri S, Jansakul C, Sriamornsak P. Improved dissolution of Kaempferia parviflora extract for oral administration by preparing solid dispersion via solvent evaporation. Asian J Pharm Sci. 2017 Mar;12(2):124-33. doi: 10.1016/j.ajps.2016.09.005, PMID 32104321.
16. Alezzy AA. Solubility and dissolution rate enhancement of aceclofenac by solid dispersion employing kneading and solvent evaporation techniques. Tikrit J Pharm Sci. 2024 Jun 25;18(1):22-30. doi: 10.25130/tjphs.2024.18.1.3.22.30.
17. Budiman A, Sopyan I, Riyandi DS. Enhancement of glibenclamide dissolution rate by solid dispersion method using HPMC and

PVP. Int J App Pharm. 2019 Jun 12:11(5):19-24. doi: 10.22159/ijap.2019v11i5.34137.

18. Fitriani L, Tirtania S, Umar S, Zaini E. Enhancing the solubility and dissolution rate of piperine via preparation of piperine-hydroxypropyl methylcellulose 2910 solid dispersion system using freeze-drying method. J Pharm Pharmacogn Res. 2024 Jan 1;12(1):175-83. doi: 10.56499/jppres23.1734_12.1.175.
19. Ciesla L, Waksmundzka Hajnos M, Sherma J. Thin layer chromatography. In: Grinberg N, editor. Ewing's analytical instrumentation handbook. 4th ed. CRC Press; 2019. p. 921-42. doi: 10.1201/9781315118024-30.
20. Nara O. Automatic twin vessel recrystallizer. Effective purification of acetaminophen by successive automatic recrystallization and absolute determination of purity by DSC. Anal Chim Acta. 2011 Jan;685(1):91-102. doi: 10.1016/j.aca.2010.11.011, PMID 21168556.
21. Ishtiaq M, Asghar S, Khan IU, Iqbal MS, Khalid SH. Development of the amorphous solid dispersion of curcumin: a rational selection of polymers for enhanced solubility and dissolution. Crystals. 2022 Nov 10;12(11):1606. doi: 10.3390/cryst12111606.
22. Yuliandra Y, Fitriani L, Kurniawan R, Yasardi F, Zaini E. Solid dispersions of famotidine: physicochemical properties and *in vivo* comparative study on the inhibition of hyperacidity. Chemistry Select. 2020 Aug 7;5(29):9218-25. doi: 10.1002/slct.202001796.
23. Statton WO. An X-ray crystallinity index method with application to poly(ethylene terephthalate). J Appl Polym Sci. 1963 May 9;7(3):803-15. doi: 10.1002/app.1963.070070302.
24. Colombo M, Orthmann S, Bellini M, Staufenbiel S, Bodmeier R. Influence of drug brittleness, nanomilling time, and freeze-drying on the crystallinity of poorly water-soluble drugs and its implications for solubility enhancement. AAPS Pharm Sci Tech. 2017 Oct 6;18(7):2437-45. doi: 10.1208/s12249-017-0722-4, PMID 28168626.
25. Rosiak N, Wdowiak K, Tykarska E, Cielecka Piontek J. Amorphous solid dispersion of hesperidin with polymer excipients for enhanced apparent solubility as a more effective approach to the treatment of civilization diseases. Int J Mol Sci. 2022 Dec 2;23(23):15198. doi: 10.3390/ijms232315198, PMID 36499518.
26. Jermain SV, Miller D, Spangenberg A, Lu X, Moon C, Su Y. Homogeneity of amorphous solid dispersions-an example with KinetiSol®. Drug Dev Ind Pharm. 2019 May 4;45(5):724-35. doi: 10.1080/03639045.2019.1569037, PMID 30653376.
27. Park SH, Song IS, Choi MK. Preparation and characterization of quercetin-loaded solid dispersion by solvent evaporation and freeze-drying method. Mass Spectrom Lett. 2016 Sep 30;7(3):79-83. doi: 10.5478/MSL.2016.7.3.79.
31. Rachmaniar R, Warya S, Ferdiansyah R, Riasari H, Gumelar A, Kenti. Pharmaceutical cocrystal of ethyl p-methoxycinnamate: formulation and characterization. In: The proceedings of the 2nd bakti tunas husada-health Science International Conference (BTH-HSIC 2019). Paris, France: Atlantis Press; 2020. doi: 10.2991/ahsr.k.200523.024.
32. Ekowati J, Widyowati RR, Isadiartuti D. Preparation of an inclusion complex system of ethyl p-methoxycinnamate-hydroxypropyl-β-cyclodextrin: characterization and solubility evaluation. Res J Pharm Biol Chem Sci. 2017;8(1):1486-94.
33. Umar S, Usman H, Salsabila H, Zaini E. Solid dispersion of tenoxicam-HPMC by freeze-drying: solid-state properties, dissolution study, and analgesic activity in mice. Open Access Maced J Med Sci. 2022 Apr 25;10(A):800-6. doi: 10.3889/oamjms.2022.9553.
34. Zaini E, Fitriani L, Effendy S, Noviza D, Halim A. Preparation and characterization of solid dispersion telmisartan-hydroxypropyl methyl cellulose(HPMC) E5 lV by co-grinding method. Orient J Chem. 2017 Apr 28;33(2):873-8. doi: 10.13005/ojc/330236.
35. Minhaz MA, Rahman MM, Ahsan MQ, Khalipha AB, Chowdhury MR. Dissolution enhancement of poorly soluble drug by solvent evaporation method using hydrophilic polymer: a solid dispersion technique. Int J Pharma Life Sci. 2012 Dec 14;1(2):1-18. doi: 10.3329/ijpls.v1i2.12952.
36. Xu WJ, Xie HJ, Cao QR, Shi LL, Cao Y, Zhu XY. Enhanced dissolution and oral bioavailability of valsartan solid dispersions prepared by a freeze-drying technique using hydrophilic polymers. Drug Deliv. 2016 Jan 2;23(1):41-8. doi: 10.3109/10717544.2014.903012, PMID 24735247.