

Development of Ethyl p-Methoxycinnamate – Benzoic Acid Nanoconfined Coamorphous System to Enhance Solubility and Dissolution

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ABSTRACT

Ethyl p-methoxycinnamate (EPMC) is the major bioactive compound of *Kaempferia galanga* L., yet its application is restricted by very low solubility and dissolution rate. This study aimed to develop a nanoconfined coamorphous (NCA) EPMC–benzoic acid system and assess its impact on solubility and dissolution behaviour. A binary EPMC–benzoic acid system (1:1) was prepared using the solvent evaporation method and subsequently loaded into mesoporous silica nanoparticles (MSN) at a 3:7 ratio (binary system:MSN) to obtain the NCA system. Characterization was performed using FT-IR, and evaluations included EPMC content determination, aqueous solubility testing, and dissolution studies in simulated gastrointestinal media (pH 1.2, 4.5, and 6.8). FT-IR results showed shifts in the C=O and –OH absorption bands, indicative of intermolecular interactions between EPMC and benzoic acid without the formation of new chemical species, suggesting successful NCA formation. The EPMC content in the NCA system was 9.5%. Solubility testing demonstrated a 1.05-fold increase in NCA (38.275 mg/L) compared with pure EPMC (36.364 mg/L). Dissolution testing also showed substantial enhancement, with increases of 2,81-fold at pH 1.2, 3,78-fold at pH 4.5, and 4,13-fold at pH 6.8. Overall, the NCA EPMC–benzoic acid system improved EPMC solubility and dissolution, demonstrating its potential to enhance oral bioavailability.

Keywords: Benzoic Acid; Dissolution; Ethyl p-Methoxycinnamate; Nanoconfined Coamorphous; Solubility.

INTRODUCTION

Ethyl p-methoxycinnamate (EPMC) is a major natural compound isolated from *Kaempferia galanga* L. and has been reported to exhibit various pharmacological activities. However, its potential application remains limited due to its extremely low aqueous solubility. Rachmaniar et al. (2020) reported that the solubility of EPMC is only 0.0301 mg/mL, which may hinder its absorption and consequently reduce its biological effectiveness (1). This limitation highlights the need for formulation strategies capable of significantly enhancing the solubility and dissolution performance of EPMC.

Initial efforts to overcome this limitation have been conducted through the development of a coamorphous EPMC–benzoic acid system, which demonstrated improved solubility and dissolution behavior, although the results were not yet optimal (2). This limitation is mainly attributed to the metastable nature of amorphous forms, which are prone to recrystallization due to their high free energy and increased molecular mobility (3). Therefore, a formulation approach that not only enhances solubility and dissolution but also provides improved physical stability is required.

In response to this challenge, nanoconfined coamorphous (NCA) technology has emerged as a promising strategy. The NCA system incorporates a binary drug–coformer mixture into mesoporous matrices, resulting in a more physically stable amorphous form that is less susceptible to temperature

and humidity fluctuations. Mesoporous silica, characterized by pore sizes ranging from 2 to 50 nm and thermal stability up to 500°C, effectively protects drug molecules from recrystallization and aggregation (2). The advantages of this technology have been demonstrated in several studies, including a reported twelve-fold increase in the dissolution rate of ritonavir (4). In the case of EPMC, the NCA approach has also been shown to provide superior dissolution enhancement compared to other techniques (2), indicating its strong potential for further application.

The successful formation of an NCA system is highly dependent on the selection of an appropriate coformer, as the coformer plays a crucial role in establishing specific intermolecular interactions that govern the stability and performance of the drug. Benzoic acid has been identified as a suitable coformer for EPMC due to its ability to form favorable interactions that improve physicochemical properties and enhance the dissolution profile (2). Therefore, the use of benzoic acid as a coformer provides a strong rationale for the development of an EPMC-based NCA system.

Based on the above considerations, this study aims to develop an EPMC–benzoic acid nanoconfined coamorphous system to achieve a more significant enhancement in solubility and dissolution performance. Dissolution evaluation was conducted using three buffer media simulating physiological conditions, namely hydrochloric acid pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8, allowing a comprehensive assessment of EPMC dissolution behavior across different gastrointestinal pH conditions. This approach is expected to provide a thorough understanding of the potential application of EPMC in the development of more effective and physically stable pharmaceutical formulations.

METHODS

Materials

The materials used in this study included ethyl p-methoxycinnamate (EPMC) isolated from *Kaempferia galanga* L. rhizomes by Sekolah Tinggi Farmasi Indonesia (STFI); mesoporous silica nanoparticles (MSN) (Jiangsu XFNANO Materials Tech. Co., Ltd.); benzoic acid (Wuhan Youji Industries Co., Ltd.); ethanol 96% (Acidatama); hydrochloric acid (PT IAI); acetic acid (Foodchem International Corp., China); sodium acetate (PT IAI); potassium dihydrogen phosphate (Foodchem International Corp., China); sodium hydroxide (Asahi); 0.45 µm membrane filters (ANPEL Laboratory Technologies); and distilled water (PT Amidis Tirta Mulia®).

Detailed Procedure

Preparation of Binary System

The binary system was prepared using the solvent evaporation method. EPMC and benzoic acid were dissolved in 60 mL of 96% ethanol at an equimolar ratio of 1:1. The solution was stirred using a magnetic stirrer at 150 rpm and 60°C until complete solvent evaporation. After evaporation, the resulting residue was cooled at 16°C (5).

Preparation of Nanoconfined Coamorphous System

The binary system particles were used as the starting material for NCA formation. A total of 3 g of EPMC–benzoic acid binary system was dissolved in 150 mL of 96% ethanol, followed by the dispersion of 7 g of mesoporous silica nanoparticles into the solution. The mixture was stirred using a magnetic stirrer at 100 rpm for 4 × 24 h. After dispersion, the NCA suspension was centrifuged at 3500 rpm for 20 min. The obtained precipitate was then dried in an oven at 50°C for 24 h (2). The equimolar (1:1) ratio of EPMC to benzoic acid was selected based on previous coamorphous studies reporting that an equimolar composition provides the most favorable intermolecular interactions between the drug and coformer, thereby maximizing amorphous-phase stability and solubility

enhancement (5) (6). The 3:7 (binary system:MSN) loading ratio was chosen to keep the drug-coformer payload below the estimated pore-filling capacity of the mesoporous silica carrier, ensuring that the binary system is confined within the mesopores rather than deposited on the external particle surface, which is critical for preserving the amorphous state and preventing recrystallization (4) (7).

Characterization of EPMC–Benzoic Acid NCA

The EPMC–benzoic acid NCA system was characterized to identify functional group interactions. Functional group analysis was performed using Fourier transform infrared (FT-IR) spectroscopy (Thermo Scientific Nicolet iS5). Samples were scanned over a wavenumber range of 500–4000 cm^{-1} with a resolution of 2 cm^{-1} (5).

Evaluation of EPMC–Benzoic Acid NCA

Assay Determination

Quantitative analysis was carried out using a UV–Vis spectrophotometer (Thermo Scientific), with mandatory instrument validation performed prior to analysis. A total of 50 mg of EPMC was accurately weighed and dissolved in 96% ethanol in a 100 mL volumetric flask to obtain a stock solution. The stock solution was subsequently diluted to obtain concentrations of 2, 3, 4, 5, and 6 ppm. All diluted solutions were analyzed at the maximum absorption wavelength (8), (9), (10) A total of 50 mg of EPMC–NCA was weighed and dissolved in 96% ethanol using a 10 mL volumetric flask. The solution was sonicated for 30 min and subsequently centrifuged at 4000 rpm for 20 min. The resulting supernatant was analyzed using a UV–Vis spectrophotometer at the maximum absorption wavelength (2).

Solubility Determination

An amount of particles equivalent to 50 mg of EPMC was weighed and dispersed in 100 mL of distilled water. The mixture was agitated using an orbital shaker at 400 rpm for 24 h at 25°C. After agitation, the solution was filtered through a 0.45 μm membrane filter, and the obtained filtrate was analyzed using a UV–Vis spectrophotometer at the maximum absorption wavelength of EPMC (11).

Dissolution Profile in Simulated Gastrointestinal Media

Particles equivalent to 50 mg of EPMC were weighed and subjected to dissolution testing using a USP dissolution apparatus type II (paddle). The dissolution study was conducted in 500 mL of dissolution media consisting of 0.1 N hydrochloric acid, acetate buffer pH 4.5, and phosphate buffer pH 6.8, maintained at a controlled temperature of $37 \pm 0.5^\circ\text{C}$. The paddle rotation speed was set at 50 rpm. Aliquots of 5 mL were withdrawn at 5, 10, 15, 30, 60, 90, and 120 min using a syringe fitted with a 0.45 μm membrane filter. After each sampling, the withdrawn volume was immediately replaced with an equal volume (5 mL) of fresh dissolution medium maintained at the same temperature. The filtered samples were subsequently analyzed using a UV–Vis spectrophotometer at the maximum absorption wavelength of EPMC (12).

RESULT AND DISCUSSION

The preparation of the EPMC–benzoic acid binary system using the solvent evaporation method successfully produced a dry powder with a pale yellowish-white appearance and a characteristic EPMC odor, as shown in Figure 1(a). Following the formation of the binary system, the process was continued with the fabrication of the EPMC–benzoic acid nanoconfined coamorphous (NCA) system through the loading of binary particles into mesoporous silica nanoparticles. This step resulted in a fine white powder exhibiting physical characteristics distinct from those of the original binary system.

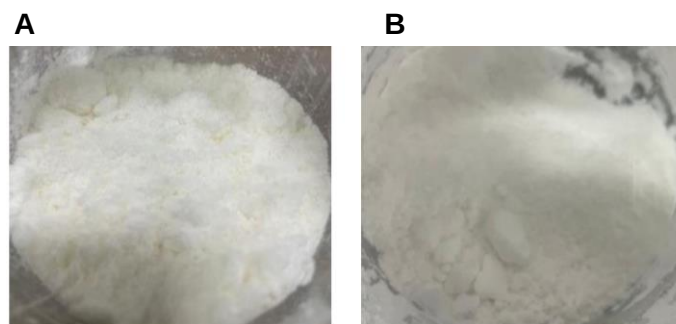


Figure 1. (A) EPMC–benzoic acid binary system powder; (B) EPMC–benzoic acid nanoconfined coamorphous (NCA) powder.

The UV–Vis spectrophotometric analytical method used for EPMC assay determination was validated in accordance with the guidelines of the International Council for Harmonisation (ICH) and pharmacopoeial requirements. Validation parameters included the evaluation of linearity, accuracy, precision, as well as the determination of the limit of detection (LOD) and limit of quantitation (LOQ). The obtained correlation coefficient (R) was 0.9998, with a regression equation of $y = 0.0907x + 0.0845$. A regression coefficient exceeding 0.9 indicates an excellent linear relationship between concentration and absorbance, confirming that the selected concentration range is valid for quantitative analysis. The EPMC calibration curve is shown in Figure 2.

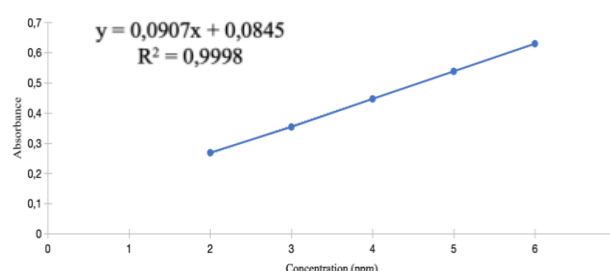


Figure 2. Calibration curve of EPMC obtained by UV–Vis spectrophotometry.

The acceptable recovery range was set at 98–102%. The results demonstrated that the percentage recovery values of EPMC were 101.33%, 99.83%, and 100.18%, all of which met the specified criteria, indicating good accuracy of the method. The percentage relative standard deviation (%RSD) values obtained from the precision study were 0.272%, 0.159%, and 1.010%, all below the acceptance limit of <2%, confirming that the method fulfills the established precision requirements. The LOD value of 0.076 $\mu\text{g/mL}$ indicates that the instrument is capable of detecting EPMC at this concentration with acceptable sensitivity. Meanwhile, the LOQ value of 0.253 $\mu\text{g/mL}$ suggests that quantitative analysis of EPMC can be reliably performed at this concentration with adequate accuracy and precision.

The preparation of the EPMC–benzoic acid binary system using the solvent evaporation method was intended to transform EPMC from its crystalline form into an amorphous state through a crystal disruption mechanism facilitated by benzoic acid as a coformer. The coformer acts as a recrystallization inhibitor, suppressing the tendency of EPMC to revert to its crystalline form. The transition to the amorphous state increases the specific surface area and the free energy of the system, which thermodynamically favors enhanced solubility and dissolution of EPMC.

Following the formation of the binary system, the nanoconfined coamorphous (NCA) system was designed to provide comprehensive protection through a nanoconfinement mechanism. The mesoporous structure, with pore sizes ranging from 2 to 50 nm, functions as a physical barrier that shields the coamorphous system from moisture-induced recrystallization, while simultaneously offering thermal stability up to 500°C, thereby preventing the amorphous phase from readily reverting to the crystalline state. This mechanism is particularly important because coamorphous systems inherently possess high molecular mobility and elevated free energy, making them susceptible to recrystallization. Consequently, nanoconfinement within mesoporous matrices effectively preserves the stability and advantages of the amorphous phase for long-term pharmaceutical applications.

To confirm the presence of EPMC within the NCA system, functional group analysis was performed using FT-IR spectroscopy. As shown in Figure 3, the spectrum of benzoic acid exhibited characteristic vibrations of the carboxyl (-COOH) functional group, including C=O stretching around 1700 cm^{-1} , a broad O-H stretching band at $2500\text{--}3300\text{ cm}^{-1}$, and aromatic absorption bands in the range of $700\text{--}900\text{ cm}^{-1}$. Shifts observed in the C=O and O-H bands after combination with EPMC indicate the formation of intermolecular hydrogen bonding.

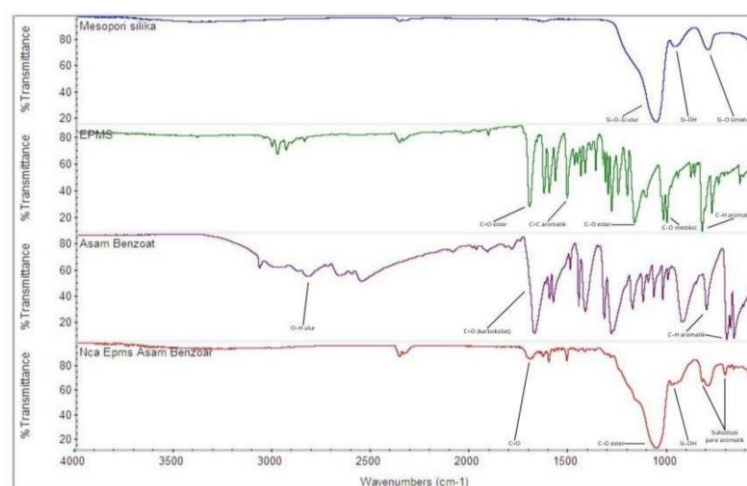


Figure 3. FT-IR spectra of EPMC, benzoic acid, mesoporous silica nanoparticles (MSN), and EPMC–benzoic acid nanoconfined coamorphous (NCA) system for functional group identification and confirmation of hydrogen bonding interactions.

The FT-IR spectrum of mesoporous silica nanoparticles (MSN) displayed major peaks at $1080\text{--}1100\text{ cm}^{-1}$ corresponding to Si-O-Si asymmetric stretching, a peak at approximately 800 cm^{-1} associated with symmetric Si-O stretching, and bands at $960\text{--}980\text{ cm}^{-1}$ attributed to surface silanol (Si-OH) groups. The presence of these surface hydroxyl groups enables potential interactions with both EPMC and benzoic acid. Meanwhile, the FT-IR spectrum of the EPMC–benzoic acid NCA system exhibited a combination of characteristic features from all components, confirming the successful incorporation of the binary system into the mesoporous silica matrix.

The absorption peaks at 980.18 and 709.43 cm^{-1} indicate the presence of Si–OH groups originating from the mesoporous structure, while the peak at 826.28 cm^{-1} reflects para-aromatic substitution. The absorption region at 1288.91–1064.99 cm^{-1} corresponds to the ester C–O stretching vibrations of EPMC, and the peak at 1690.76 cm^{-1} represents the C=O stretching vibration that is shifted, indicative of intermolecular interactions with benzoic acid. The observed shifts in wavenumber and the reduction in intensity of several absorption bands are suggestive of changes in the molecular environment consistent with a transition toward an amorphous phase, while simultaneously verifying the successful formation of a stable nanoconfined coamorphous system within the mesoporous matrix. It should be noted, however, that FT-IR analysis alone is not sufficient to unambiguously confirm either the formation of specific hydrogen bonds or the full crystalline-to-amorphous transition of EPMC. Complementary techniques such as X-ray diffraction (XRD), differential scanning calorimetry (DSC), and solid-state nuclear magnetic resonance (ss-NMR) are required to directly verify the loss of crystalline long-range order and the specific nature of the drug–coformer interactions.

Table 1. Results of EPMC content determination in the EPMC–benzoic acid NCA system.

Sample	Weight (mg)	Absorbance	Measured Content (mg)	Content (%)	Mean (%)	SD
EPMC – benzoic acid NCA system	50	0.793 0.788 0.786	4.764 4.732 4.719	9.5 9.5 9.4	9.5	0.07

To further evaluate the amount of EPMC successfully incorporated into the NCA structure, an assay determination was performed show in table 1. The analysis revealed that only approximately 9.5% of EPMC was detected from a nominal 50 mg sample, corresponding to about ± 4.75 mg of EPMC. Although this value appears relatively low, it is fundamentally consistent with the intrinsic characteristics of nanoconfined coamorphous (NCA) systems, which are primarily designed to enhance physical stability and inhibit recrystallization rather than to maximize drug loading capacity (4,5). Consequently, the amount of EPMC that can be accommodated within the mesoporous pores is inherently limited. This observed loading is broadly consistent with the range typically reported for drug–coformer systems confined in mesoporous silica, where drug loadings generally fall between approximately 5% and 30% (w/w) depending on pore volume, drug–coformer ratio, and surface chemistry (4,12). For example, Budiman et al. reported ritonavir–saccharin coamorphous loadings of similar magnitude when confined in mesoporous silica of comparable pore size (4). The 9.5% EPMC content obtained here therefore reflects a typical loading profile for NCA systems rather than an anomalously low value, and it remains sufficient for meaningful dissolution enhancement studies.

Table 2. Results of Solubility determination of EPMC and EPMC–benzoic acid NCA Systems

Sample	Weight (mg)	Absorbance	Measured Content (mg)	Content (%)	Mean (%)	SD
EPMC–benzoic acid NCA system	50	0.430	19.046	38.092	38.275	0.114
		0.431	19.101	38.202		
		0.434	19.266	38.532		
EPMC	50	0,413	18.109	36.218	36.364	0.084
		0.414	18.164	36.328		
		0,416	18.274	36.548		

In addition, the use of benzoic acid as a coformer in an equimolar ratio further influences the apparent EPMC content in the total formulation. Since both components are present in equal proportions, the fraction of EPMC in the coamorphous mixture is inevitably reduced. Considering these aspects, the relatively low EPMC content observed in the EPMC–benzoic acid NCA system represents a logical outcome of the physicochemical properties of the active compound, the coformer proportion, and the finite pore capacity of the mesoporous carrier. Therefore, this result should not be interpreted as a methodological failure, but rather as an inherent characteristic of the NCA system, which is specifically engineered to prioritize amorphous stability over high drug loading.

Subsequently, aqueous solubility analysis was conducted, as this parameter plays a critical role in determining drug bioavailability. EPMC is known to exhibit extremely low intrinsic solubility; therefore, The formation of a nanoconfined coamorphous (NCA) system using benzoic acid was expected to improve the solubility profile of EPMC. As shown in Table 2, the aqueous solubility of EPMC was 1:5499, whereas the solubility of the EPMC–benzoic acid NCA system was 1:5225, corresponding to an increase of only approximately 1.05-fold.

This modest improvement is consistent with the inherent characteristics of the amorphous state, which increases the free energy of the system but does not necessarily result in a substantial enhancement of equilibrium solubility, as solubility remains strongly governed by the intrinsic molecular properties of the compound and its interactions with the solvent (3). In NCA systems, mesoporous silica primarily functions to maintain the physical stability of the amorphous phase rather than to significantly increase solubility capacity. Moreover, non-covalent interactions such as hydrogen bonding contribute only marginally to improved particle wettability (5,6). Therefore, although a slight improvement was observed, the solubility of the EPMC–benzoic acid NCA system did not increase significantly, as the saturated solubility is predominantly determined by the inherent chemical characteristics of EPMC itself.

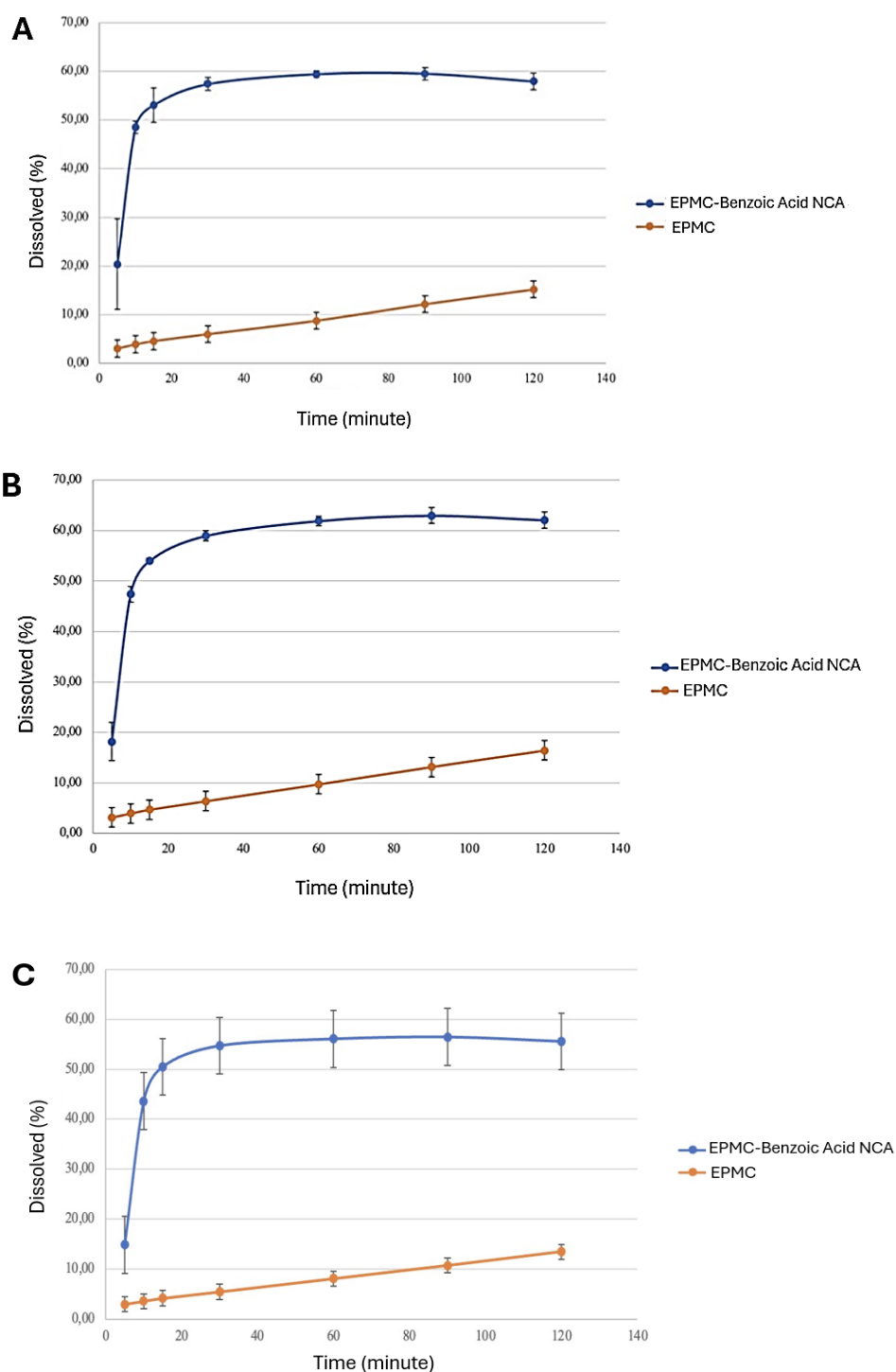


Figure 4. Dissolution profiles of pure EPMC and EPMC–benzoic acid nanoconfined coamorphous (NCA) system in (A) pH 1.2, (B) pH 4.5, and (C) pH 6.8 media up to 120 min.

Dissolution testing was conducted to compare the drug dissolution rate under controlled and reproducible conditions. The dissolution media were selected to simulate gastrointestinal pH environments, namely pH 1.2 to represent gastric conditions, pH 4.5 to mimic the duodenum as a transitional region from acidic to basic environments, and pH 6.8 to represent intestinal conditions. The dissolution temperature was maintained at $37 \pm 0.5^\circ\text{C}$ to simulate physiological body

temperature. The results are presented in Figures 4 and 5, illustrating the dissolution profiles of EPMC and the EPMC–benzoic acid nanoconfined coamorphous (NCA) system across the three of pH media.

The dissolution results demonstrated that the EPMC–benzoic acid NCA system provided a markedly enhanced drug release compared to pure EPMC. These findings confirm that the synergistic effects of coamorphization and nanoconfinement effectively improve both the dissolution rate and the extent of drug release. This enhancement can primarily be attributed to the transformation of EPMC from its crystalline form into an amorphous state, which reduces crystallinity and increases the free energy of the system, thereby facilitating molecular transfer into the dissolved phase. In addition, mesoporous silica plays a crucial role in maintaining the stability of the amorphous phase by suppressing recrystallization, as EPMC molecules are molecularly dispersed within pores ranging from 2 to 50 nm (7). This condition allows supersaturation to be sustained for a longer duration during the dissolution process, leading to improved kinetic solubility even though the equilibrium solubility does not change significantly.

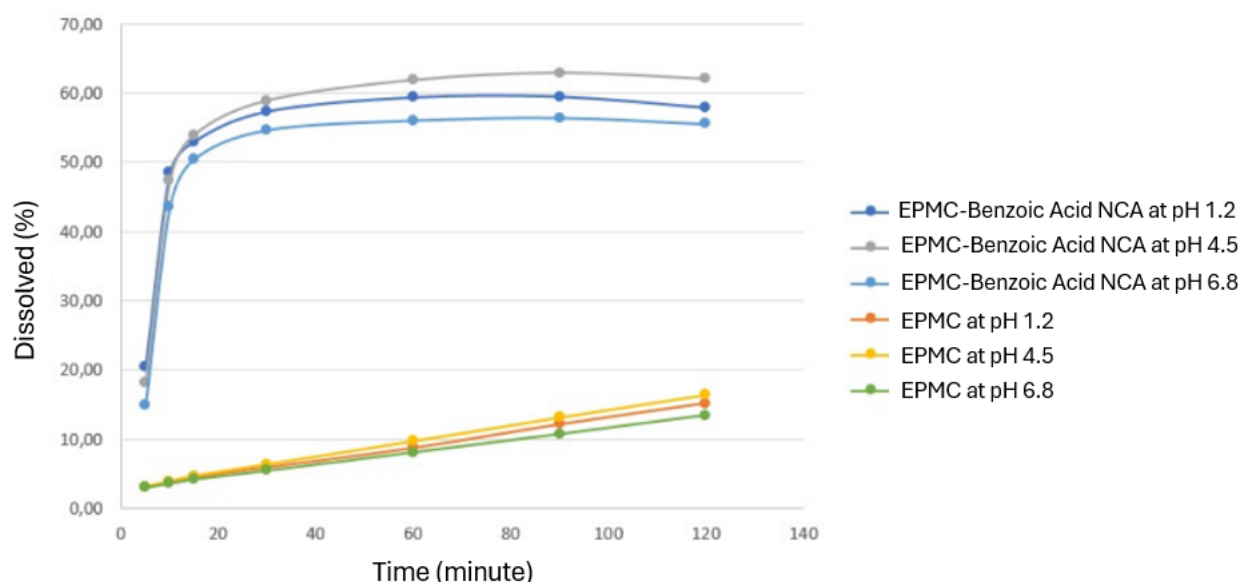


Figure 5. Comparative dissolution profiles of pure EPMC and EPMC–benzoic acid nanoconfined coamorphous (NCA) system at pH 1.2, 4.5, and 6.8 up to 120 min

Benzoic acid as a coformer also contributes through the formation of hydrogen bonds with EPMC, which act as recrystallization inhibitors and improve particle wettability (6). Mesoporous silica, with its high surface area, increases the contact area between the NCA matrix and the dissolution medium, thereby accelerating solvent penetration and facilitating drug diffusion into the solution (7). The combination of these mechanisms results in a markedly superior dissolution performance compared to that of pure EPMC.

The dissolution profiles were strongly influenced by the pH of the medium. At pH 1.2, pure EPMC achieved 15.2% dissolution, whereas the NCA system exhibited approximately 57.94% drug release, which was approximately 2,81-fold higher than that of pure EPMC. The improvement under acidic conditions remained limited because benzoic acid predominantly exists in its non-ionized form ($-\text{COOH}$), which is more hydrophobic and less effective in enhancing particle wettability.

At pH 4.5, pure EPMC achieved 16.42% dissolution, whereas the NCA system reached its highest drug release, namely 62.10%, which was approximately 3,78-fold higher than that of pure EPMC. This condition is considered optimal, as the pH is close to the pKa of benzoic acid (~4.2), leading to partial ionization that increases system polarity and strengthens non-covalent interactions, thereby stabilizing supersaturation (6).

At pH 6.8, pure EPMC achieved 13.45% dissolution, whereas the NCA system reached its highest drug release, namely 55.57%, which was approximately 4,13-fold higher than that of pure EPMC the dissolution of the NCA system remained higher than that of pure EPMC, but showed a slight decrease compared to pH 4.5. This phenomenon can be attributed to an increased tendency toward reprecipitation under basic conditions, where higher molecular mobility facilitates partial recrystallization. Although nanoconfinement helps preserve the amorphous phase, the stability of the supersaturated state decreases at higher pH values.

Overall, the formation of the NCA system was shown to significantly enhance EPMC dissolution through complementary mechanisms, including amorphization, hydrogen bond formation, improved wettability, increased surface contact with the dissolution medium, and stabilization of the amorphous phase via nanoconfinement (6,7). This study demonstrates that the NCA system effectively overcomes the dissolution limitations of pure EPMC. The observed enhancement is not solely attributable to amorphization, but rather to the synergistic contribution of multiple mechanisms. Therefore, the NCA approach can be considered a promising formulation strategy for improving the bioavailability of poorly water-soluble compounds such as EPMC.

CONCLUSION

Based on the results of this study, an EPMC–benzoic acid nanoconfined coamorphous (NCA) system was successfully developed using benzoic acid as a coformer and mesoporous silica nanoparticles as the nanoconfinement matrix. FT-IR analysis revealed shifts in the C=O and –OH absorption bands and changes in peak intensity, which are indicative of intermolecular interactions between EPMC and benzoic acid without the formation of new chemical species; however, unambiguous confirmation of hydrogen bonding and the full crystalline-to-amorphous transition will require complementary analyses such as XRD and DSC in future work. The EPMC–benzoic acid NCA system showed only a modest improvement in aqueous solubility, approximately 1.05-fold compared to pure EPMC. In contrast, a more pronounced enhancement in dissolution performance was observed, with increases of approximately 2.81-fold in HCl buffer pH 1.2, 3.78-fold in acetate buffer pH 4.5, and 4.13-fold in phosphate buffer pH 6.8 relative to pure EPMC. As no inferential statistical testing was performed in this study, these enhancements are described as observed differences rather than statistically significant effects; future work incorporating replicate experiments and statistical analysis is needed to quantitatively confirm the magnitude of improvement.

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