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Solubility and Dissolutıon Improvement of Paramethoxycinnamic Acid (PMCA) Induced by Cocrystal Formation using Caffeine as a Coformer

(Penambahbaikan Keterlarutan dan Pelarutan Asid Parametoksisinamik (PMCA) Teraruh oleh Pembentukan Hablur menggunakan Kafein sebagai Pembentuk)

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ABSTRACT

Para-methoxy cinnamic acid (pMCA) is a derivative compound of ethyl p-methoxycinnamate that could be obtained in nature. pMCA has excellent pharmacological properties. However, in their application as a drug, pMCA has poor water solubility. In this present research, we try to increase the water solubility of pMCA using the cocrystal formation (cocrystallization) strategy. Here, we use caffeine as a coformer that can interact very well with pMCA *via* non-covalent bonding and Van der Waals interaction to achieve cocrystal formation. The cocrystal samples were successfully synthesized using various synthesis techniques; physical mixture, solvent evaporation, and microwave radiation methods. It shows that the solubility of the samples synthesized using microwave-assisted and solvent evaporation increases about 3.30 and 3.12 times, respectively, whereas the dissolution rate profile increases 2.50 and 2.39 times, respectively, compared to pure APMS. Our findings explain the importance of the cocrystal formation strategy to enhance the solubility of active material pMCA. This strategy can also be used as a standard formulation of a new drug system with excellent solubility and dissolution which is very important for the pharmaceutical industry.

Keywords: Caffeine; cocrystal; dissolution; drugs; para-methoxy cinnamic acid; solubility

ABSTRAK

Asid sinamik para-metoksi (pMCA) ialah sebatian terbitan etil p-metoksisinamat yang boleh didapati secara semula jadi. pMCA mempunyai sifat farmakologi yang sangat baik seperti sifat analgesik, anti-radang, anti-diabetes, anti-kanser, hepatopelindung dan neuropelindung. Walau bagaimanapun, dalam penggunaannya sebagai ubat, pMCA mempunyai keterlarutan air yang lemah. Manakala, keterlarutan dadah merupakan aspek penting yang perlu dimiliki oleh sesuatu ubat untuk mencapai kesan yang dikehendaki. Dalam penyelidikan ini, kami cuba meningkatkan keterlarutan air pMCA menggunakan strategi pembentukan hablur (penghabluran). Di sini, kami menggunakan kafein sebagai pembentuk yang boleh berinteraksi dengan baik dengan pMCA melalui ikatan bukan kovalen dan interaksi Van der Waals untuk mencapai pembentukan hablur. Sampel hablur telah berjaya disintesis menggunakan pelbagai teknik sintesis; campuran fizikal, penyejatan pelarut dan kaedah sinaran gelombang mikro. Semua sampel hablur mempunyai keterlarutan yang sangat baik berbanding dengan keadaan murni atau pMCA tulen. Sampel yang disediakan menggunakan sinaran gelombang mikro mempunyai keterlarutan yang paling tinggi berbanding sampel yang disediakan menggunakan kaedah campuran fizikal dan penyejatan pelarut. Penemuan kami menerangkan kepentingan strategi pembentukan hablur untuk meningkatkan keterlarutan bahan aktif pMCA. Strategi ini juga boleh digunakan sebagai formulasi standard sistem ubat baharu dengan keterlarutan dan pembubaran yang sangat baik yang sangat penting untuk industri farmaseutik.

Kata kunci: Asid sinamik para-metoksi; dadah; kafein; keterlarutan; hablur; pembubaran

INTRODUCTION

Para-methoxy cinnamic acid (pMCA) is a derivative compound of ethyl p-methoxycinnamate that could be found in nature (Isadiartuti et al. 2021). pMCA has analgesic and anti-inflammatory effects by inhibiting the activity of cyclooxygenase enzymes (COX-1 and COX-2) to prevent the overproduction of prostaglandins (Dwita et al. 2021). pMCA also possesses pharmacological properties such as anti-diabetic, anti-cancer, hepatoprotective, and neuroprotective properties (Płowuszyńska & Gliszczyńska 2021). However, pMCA as pharmaceutical active material has poor water solubility, which poses a significant obstacle to their use as drugs (Isadiartuti et al. 2021). Solubility and dissolution are fundamental parameters in the process of regulating the absorption rate and bioavailability of an oral drug (Khadka et al. 2014). The low dissolution rate caused by poor solubility could reduce the oral drug's bioavailability, resulting in a suboptimal therapeutic effect (Tambosi et al. 2018). More than 40% of the pharmaceutical industry produced and distributed drugs that fall into the category of drugs with poor or insoluble solubility. In addition, approximately 80-90% of currently being developed drugs contain drug ingredients with poor solubility in water, which contributes to their failure in clinical trials (Padrela et al. 2018).

Increasing the solubility and dissolution rate of drugs can be achieved through a variety of structural developments using physical or chemical modification techniques. These strategies include several techniques namely micronization, nanosuspension, particle size reduction, eutectic mixtures, solid dispersion, cryogenic, and cocrystal formation techniques (Savjani, Gajjar & Savjani 2012). In the pharmaceutical industry, cocrystal formation techniques have become widespread in recent years (Biscaia et al. 2021; Mehta et al. 2023). The cocrystallization technique is one of the dependable methods for modifying the physical properties of pharmaceutical active ingredients (API), such as increasing their solubility, dissolution rate, stability, hygroscopicity, and compressibility, without altering their pharmaceutical function (Ancheria et al. 2019; Zhang et al. 2019). Cocrystal is a crystalline material composed of two or more different molecules with similar crystal lattices, in this case, API and the so-called coformers. In the cocrystal system, the energy of the crystal grid decreases, as a consequence, the covalent bond of the API molecules is easy to break due to the existence of coformers, therefore, the water solubility of the cocrystal increases (Thakuria et al. 2013; Yadav et al. 2023).

Coformers are one of the key factors that facilitate cocrystallization and influence the formation of cocrystals (Aghara & Dudhat 2023; Buddhadev & Garala 2021; Sopyan et al. 2021). The combination of API and coformers in the form of cocrystal should be in the specific stoichiometric ratio which is mixed via non-ionic or non-covalent bonds (Li & Matzger 2016). The stoichiometric ratio between API and coformers is generally 1:1, 1:2, or 2:1 (Korotkova & Kratochvíl 2014; Sopyan et al. 2021). Moreover, predicting the formation of cocrystals can be done through a calculation using ΔpKa equation. pKa indicates the ability of an acid to give protons, when ΔpKa = pKa (API) – pKa (coformer) is negative then the proton donor process does not occur and cocrystals are most likely to be formed. However, if ΔpKa > 3 then it is most likely that salt is formed, instead (Sathisaran & Dalvi 2018). According to the Food and Drug Administration (FDA), salt will also be formed if the value of ΔpKa ≥ 1, and if ΔpKa ≤ 1 then a cocrystal will be formed. Another indication is that if ΔpKa ≥ 2.7-3, then the possibility of salt formation is higher than the cocrystal formation (Cerreia Vioglio, Chierotti & Gobetto 2017). In this study, the formation of pMCA-caffeine cocrystals should satisfy the aforementioned criteria. Wherein, the pKa of pMCA was 3.887 and the pKa of caffeine was 10.4, yielding ΔpKa = - 6.51.

The coformer must be non-toxic and included on the list of Generally Recognized as Safe (GRAS). According to the United States Food and Drug Administration (USFDA), caffeine is safe and can be used in drug production (Sanphui, Kumar & Nangia 2012; Sopyan et al. 2021). Caffeine has been extensively used as a coformer, and it has been combined with a variety of API, including Paracetamol, Furosemide, Quercetin, Niclosamide, Myricetine, and Hesperetin (Chaudhari et al. 2018; Guo et al. 2021; Ren et al. 2019; Sanphui, Kumar & Nangia 2012). The use of caffeine as a coformer in quercetin at a stoichiometric ratio of 1:1 can increase solubility 14 times higher and oral bioavailability 2.6 times higher than pure quercetin (Ren et al. 2019). The solubility of niclosamide-caffeine cocrystal at 37 °C was determined to be 56.7 mg/L, which is greater than the solubility of pure niclosamide, which is only about 42.8 mg/L. The dissolution rate of niclosamide-caffeine cocrystal is also three times greater than that of pure niclosamide (Sanphui, Kumar & Nangia 2012).

For the preparation of cocrystals, several methods are available *via* both chemical and physical synthesis techniques (Pagire et al. 2013; Panzade, Shendarkar & Kulkarni 2022; Sathisaran & Dalvi 2018). In this study, solvent evaporation and microwave radiation methods will be employed, while a physical mixture-prepared sample will serve as the control. Typically, the solvent evaporation method is the most common way to produce cocrystals. The solvent evaporation method is simple and could obtain high purity and high homogeneity of cocrystal (Pawar et al. 2021). Nevertheless, the evaporation method also has several drawbacks, including the need for large quantities of solvent precursors and small-scale cocrystal production (Karagianni, Malamatari & Kachrimanis 2018; Karimi-Jafari et al. 2018). In another case, the microwave radiation-assisted synthesis method offers other advantages, such as rapid cocrystal formation induced by microwave radiation,

high yield, and environmental friendliness (Pagire et al. 2013). We also use water as solvent media in the microwave radiation synthesis method which offer the advantage of being cost-effective compared to the solvent evaporation method which typically using ethanol as a solvent media. Water is one of the best non-toxic polar solvents which is highly suitable for the microwave-assisted synthesis (Gawande et al. 2014; Pagire et al. 2013).

According to the preceding explanation, here, we analyze the solubility and dissolution profiles of the 1:1 ratio of pMCA-caffeine cocrystal synthesized using solvent evaporation and microwave radiation methods, while preparing a control sample synthesized using the physical mixture. We analyze the phase, structure, and morphology of the samples, as well as their solubility and dissolution rates, using various methods of characterization. The results indicate that the sample was successfully synthesized. The solubility and dissolution rate of cocrystals were found to be significantly higher than in their pristine state. We believe that this discovery could shed light on how to increase the solubility and dissolution rates of active materials pMCA *via* the cocrystals strategy. Thus, further can be used as a standard formulation of any drug system having excellent solubility and dissolution which is very important for the pharmaceutical industry.

MATERIALS AND METHODS

MATERIALS

This study utilized the following materials: pMCA (*Tokyo Chemical Industry Co., Ltd., Japan, Lot:* 2BI8N), caffeine *base* (*Tokyo Chemical Industry Co., Ltd., Japan, Lot:* M88JN), 96% absolute ethanol (Merck, *Germany*), $NaH_2PO_4.H_2O$ (Merck, *Germany*, *Lot*: AM1680746108), $Na_2HPO_4.2H_2O$ (Merck, *Germany*, *Lot*: K51201280913), and NaOH (Merck, *Germany*, *Lot*: B0986198345), and distilled water.

SYNTHESIS OF pMCA-CAFFEINE COCRYSTALS

A total of 478.50 mg of pMCA and 521.50 mg of caffeine precursors were carefully weighed (Mettler Toledo AL 2014) to satisfy the 1:1 pMCA-caffein ratio. The precursors were then combined and synthesized using three synthesis techniques; physical mixture, solvent evaporation, and microwave radiation. (i) The cocrystal samples were synthesized using a physical mixture method carried out by physically combining the precursors *via* a stirring process without solvent. The mixture was then sieved with an ASTM Restch 60-80 mesh sieve to achieve a uniform particle size. (ii) For the sample synthesized by using the solvent evaporation method, the precursors were dissolved in ethanol in a beaker glass and stirred with a magnetic stirrer (Setyawan et al. 2017). Under an acidic cabinet, the precursor solvent was stirred until completely evaporated and dry. The sample was then sieved using mesh sieve numbers 60-80 to achieve a uniform size. (iii) For the microwave radiation method, the precursors were first mixed until uniform by manual stirring in a porcelain cup. The water then was added until a uniform mixture of precursor and water is found. The mixture was then placed in a microwave oven using 450 Watts of radiation power (Sharp R-728 (W) -IN). The microwave radiation process is set for 15 min. Before using the microwave oven, it is essential to ensure that it is in its initial condition and that there is no residual thermal energy by allowing it to stand for at least 5 h in an open state and unplugged from the power source.

PHASE AND MICROSTRUCTURE CHARACTERIZATIONS

The infrared spectrum (FTIR) characterization of pure pMCA and caffeine, as well as the resulting cocrystal samples, were prepared using the KBr pellet method and they analyzed using a ShimadzuIRTracer-100 FTIR spectrophotometer at a wavelength of 400 to 4000 cm^{-1}. X-ray Diffraction (XRD) (PANalytical X 'Pert3 Powder) also was performed using scanning range of 5-50° in increments of 0.017° and a scanning speed of 10°/min. A scanning electron microscope (SEM) was also utilized to understand the microstructures of the samples. To produce a high-quality image, the sample was coated with a 10 nm thick aluminum layer. The sample was observed at 600x and 2500x magnification using a Hitachi TM3000 SEM instrument with 20 kV and 12 mA voltage. The samples were also examined using differential scanning calorimetry (DSC) (Mettler Toledo). Before the test was conducted, the temperature calibration with indium was performed, thus, the observations were conducted in the temperature range of 30-300 °C at an increment rate of 5 °C per minute.

SOLUBILITY TEST

The solubility test utilizes 25.0 mg of pure pMCA and 52.25 mg of pMCA-caffeine cocrystal sample (equivalent to 25.0 mg of pure pMCA). Each sample was put into a solubility vessel containing 25 mL of a 6.8 pH phosphate buffer medium. The mixture was then continuously stirred at 250.5 °C to obtain a homogeneous liquid mixture. Upon saturation of the liquid mixture, 5.0 mL of the total liquid phase sample was filtered through a 0.45 m filter membrane. Thus, 2.0 mL of the obtained filtrate was diluted with 6.8 pH of phosphate buffer in a 5.0 mL volumetric flask as a sample solution for the solubility test. Furthermore, to determine the solubility, we observe the absorbance behavior of the aforementioned solution samples with a UV-Vis spectrophotometer (Hitachi UH5500, Japan) at the maximum wavelength of pMCA. Three separate solubility

tests were conducted. The solubility test would obtain a percentage of solubility (%b/v) of pure pMCA and pMCA-caffeine cocrystal samples.

DISSOLUTION TEST

We use 50.0 mg of pure pMCA and 104.50 mg of pMCA-caffeine cocrystals samples for the dissolution test (equivalent to 50.0 mg of pure pMCA). The dissolution test was conducted in a 6.8 pH phosphate buffer dissolution medium containing 500 mL. Our dissolution apparatus is an agitator of type II (paddle). In this measurement, the temperature of the dissolution medium was maintained at 37 0.5 °C, and the stirrer rotates at 75 revolutions per minute. 5 mL samples were collected every 5, 10, 15, 20, 30, 45, and 60 min. The sample fragment was then extracted using a filter holder containing 0.45 millipore filter paper. The dissolution medium was replaced whenever the sampling volume reached the predetermined quantity. Furthermore, the absorbance of each fragment was measured using a UV-Vis spectrophotometer at the maximum wavelength of pMCA. In this study, the dissolution test was performed three times for each tested sample. The dissolution test profiles of pure pMCA and pMCA-caffeine cocrystals could be determined based on the results of the dissolution test. To obtain the actual concentration of dissolved pMCA, it is necessary to account for the 5.0 mL dilution of dissolution media added to each sample. Using the correction factor with the Wurster equation, one can determine the actual concentration of pMCA.

RESULTS AND DISCUSSION

The obtained samples were characterized using FTIR to determine the intermolecular interaction that occurs between cocrystallized pMCA and caffeine, as shown in Figure 1. The cocrystal formation can be detected through peak shifts, decreased intensity, peak loss, and the appearance of new peaks in infrared spectrum results (Veverka et al. 2015). Based on the FTIR results, the presence of the C=N (2361.59) group in the samples indicates the presence of the caffeine phase. Due to the non-covalent interaction between the imidazole ring along with the methoxy group and the aromatic ring in the pMCA, the C=N group of the caffein imidazole ring experienced a significant shift in the cocrystal samples. Changes in the wave number of the C-H in the samples (from 857.7 to 819.82 (solvent evaporation) and 817.54 (microwave-assisted)) and C=C (from 1426.84 to 1501.95 (solvent evaporation) and 1499.86 (microwave-assisted)) aromatic groups suggest a non-covalent interaction between the aromatic ring of pMCA, whereas, the C=N (from 2361.59 to 2318.42 (solvent evaporation) and 2325.84 (microwave-assisted)) and C-H alkanes (from 2951.3 to 2947.83 (solvent evaporation) and 2944.81 (microwave-assisted)) indicates the existence effect of caffeine in the samples. In general, the results of the FTIR spectra suggest that the cocrystal sample synthesized *via* physical mixture, solvent evaporation, and microwave radiation methods is distinct from the constituent materials indicating the cocrystal phase is formed. The result also suggests that pMCA and caffeine are mixed with intermolecular non-covalent interactions such as hydrogen bonds and Van der Waals forces.

Figure 2(a) shows the XRD result containing information about solid systems related to the interaction between pMCA and caffeine. The presence of new diffraction peaks compared to the constituent materials indicates that pMCA and caffeine interact to form a cocrystal. The sharp and high-intensity of XRD peaks indicate that pMCA and caffeine are in the crystalline phase (Kakran, Sahoo & Li 2011). The specific XRD peaks of pMCA appeared at angles of 2θ = 7.85°, 16°, 23.75°, 26.89°, 32.09°, 32.49°, and 38.03°. While for caffeine appear at 8.29°, 11.77°, 11.97°, 12.45°, 14.41°, 15.74°, 19.68°, 20.55°, 22.23°, 23.66°, 24.03°, 25.93°, 26.40°, 27.05°, 28.34°, and 30.28°. In Figure 2(b), it is evident that the diffraction peaks of the sample produced by a physical mixture are well superimposed with the two constituent phases, and no new crystalline phase is formed. This is in contrast with the FTIR result, but we speculated that the FTIR results only describe the interaction between pMCA and caffeine is indeed occurs in the sample fabricated using a physical mixture but without any formation of new phase.

In contrast, the new peaks were formed in the sample created by solvent evaporation and microwave radiation methods. The XRD results of cocrystals synthesized by solvent evaporation and microwave radiation methods differ from their constituent phase and, those of the sample prepared by the physical mixture method. This result indicates that a new crystalline phase formed which presumably originated from crystalline changes of pMCA due to bonding with caffein. Strong interactions between the two constituents; pMCA and caffeine, may result in decreased crystal lattice energy of pMCA induce by caffeine. In addition, Figure 2(c) and 2(d) show the XRD peak of the pMCA phases (16.0° and 26.90°) which is shifted to a larger degree (16.10° and 26.92° and 16.15° and 26.93°, respectively) in the samples prepared by solvent evaporation and microwave radiation methods, indicating the crystal lattice parameter of pMCA decrease due to its strong interaction with caffeine.

To further understand the nanostructure of the samples, here we use Williamson-Hall analysis (Mote, Purushotham & Dole 2012) by evaluating the pMCA peak in XRD data using Equation (1). The calculated slope obtained from the Williamson-Hall equation implicitly indicates the samples have different grain sizes and microstrains, as shown in Figure 3(a). Here, the intercept of the slope describes the relation of $K\lambda/D$, wherein D is the grain size information of the samples. Whereas, the slope describes the strain (ε)

information of the sample. The calculated grain size and microstrain in the samples are shown in Figure 3(b). It shows that the cocrystals have larger grain sizes compared to their pristine state or pure pMCA. The trend modulation of the strain in the samples is also linearly similar to the grain size. The analysis using Williamson-Hall strongly indicates that the addition of coformer could increase the grain size and strain, though the grain size is not always sufficiently related to the solubility (Cappelletto et al. 2017). Especially, the increase of microstrain of pMCA could be originated due to its interaction with caffeine as a coformer. Large microstrain indicate a large lattice distortion (Qin et al. 2008), which further affect the crystal lattice energy and further the solubility behaviour (Chaturvedi et al. 2020).

$$\beta_{hkl} cos\theta = \frac{K\lambda}{D} + 4\varepsilon sin\theta \quad (1)$$

We also use SEM measurements to provide visual information on the samples (Pawar et al. 2021). The SEM results of pMCA, caffeine, and cocrystal samples fabricated via physical mixture, solvent evaporation, and microwave radiation methods are depicted in Figure 4(a)-4(d), respectively. The SEM results demonstrate that the cocrystals synthesized via solvent evaporation and microwave radiation have a distinct morphology from their constituent components. It demonstrates that pMCA has a bladed structure, whereas caffeine has a lamellar or multilayered structure. In contrast, cocrystals produced by solvent evaporation and microwave radiation have a columnar structure. These results demonstrate conclusively that cocrystals are successfully formed by solvent evaporation and microwave radiation techniques. Both methods produce cocrystals with smaller particle sizes (red circles in the SEM images) than those of pure pMCA crystals. Cocrystals' small particle size influences the contact area with the solvent. The smaller particle size of the cocrystal implies a larger contact surface area; consequently, the cocrystal has superior solubility and dissolution in comparison to pure pMCA (Karimi-Jafari et al. 2018). From Williamson-Hall analysis, the pMCA in the cocrystal synthesized using solvent evaporation and microwave radiation methods also have larger grain sizes compared to their pristine state. This is indicated that a more uniform grain size in the cocrystal may further support the increasing surface contact area and enhances the solubility and dissolution.

Figure 5 depicts the comparison of DSC measurements for pMCA, caffeine, and cocrystals fabricated by physical mixtures, solvent evaporation, and microwave radiation methods, respectively. The melting points of pMCA and caffeine are indicated by an endothermic peak at 173.56 °C and 235.87 °C, respectively. In contrast to their constituents, the cocrystals produced by physical mixture, solvent evaporation, and microwave radiation had lower melting points. The shift or change in melting point indicates that pMCA and caffeine interact during cocrystallization which may also affect the solubility (Setyawan et al. 2018).

Figure 6(a) shows the solubility test results of the cocrystal form of pMCA synthesized using microwave-assisted, solvent evaporation and physical mixture methods which found increases approximately 3.30, 3.12, and 2.67 times, respectively, compared to pure pMCA. These results are in line with previous microstructural analysis, wherein, caffeine as coformer could induce the modulation of crystal and nanostructure of pMCA. Due to the decreased crystal lattice energy of pMCA when bonded to caffeine, its solubility increases (Chaturvedi et al. 2020). The non-covalent bonds between PMCA and caffeine are easier to break, and thus the crystal lattice energy decreases (Thakuria et al. 2013). When the non-covalent bond between pMCA and caffeine is broken, the detachment of the caffeine bond from pMCA causes a change in the cocrystal structure. Due to the 'spring' effect, the solubility of pMCA rapidly increases under crystallization disorder conditions with caffeine as a conformer (Babu & Nangia 2011; Guzmán et al. 2007). The dissolution test was also conducted, which was also linear with solubility test results, as shown in Figure 6(b). The samples produced by solvent evaporation and microwave radiation exhibit excellent dissolution properties compared to their pristine state.

The API of pMCA that very important in the medical treatment of any disease can have a proper function when they have excellent solubility and dissolution. Our strategy is much more simple compared to other strategies that have previously been reported; just by only mixed it with caffeine as a coformer to induce cocrystallization (Cao et al. 2022; Sıdır & Sıdır 2018). Not only known as a good coformer that could be used to obtain cocrystals (Guo et al. 2021; Syed, Gaikar & Mukherjee 2019) but caffeine is also relatively cheap and largely abundant which support for their implementation and commercialization in the drug industry.

Furthermore, it shows that cocrystal sample synthesized using the microwave radiation method provides the highest solubility and dissolution because the microwave radiation during synthesis process could induce better formation of cocrystals; for instance, the crystallization of cocrystals fabricated using microwave radiation was found much more improved compared to other synthesis methods. In addition, the microwave radiation method is more environmentally friendly. When we consider the high product yields, the microwave-assisted methods that we use in this study are very suitable, which indicated that our strategy is also industrial-suited. We believe that our strategy not only could shed light on how to increase the API of pMCA but also could be used for other drug systems that suffer from their poor solubility which is then important for their commercialization.

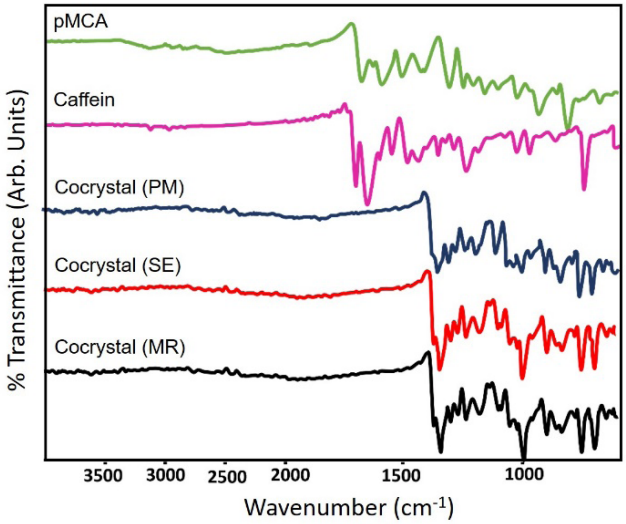

FIGURE 1. FTIR result of pMCA (green line) and caffeine (magenta line), as well as cocrystal sample synthesized using a physical mixture (PM) (blue line), solvent evaporation (SE) (red line), and microwave radiation (MR) (black line) methods

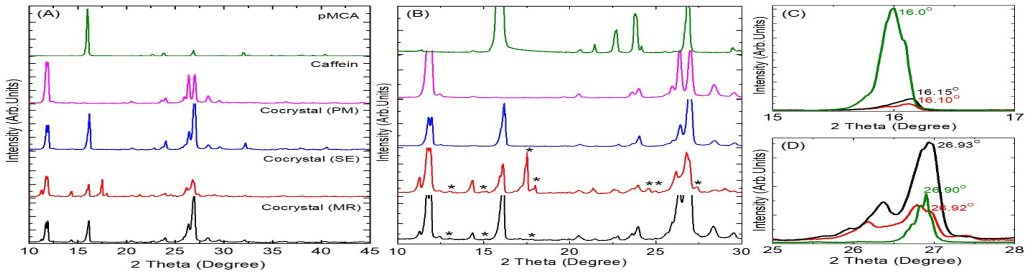

FIGURE 2. XRD result of pMCA (green line) and caffeine (magenta line), as well as cocrystal sample synthesized using a physical mixture (PM) (blue line), solvent evaporation (SE) (red line), and microwave radiation (MR) (black line) methods. (a) Full XRD scan from 10-45 degrees and magnify from (b) 10-30, (c) 15-27, and (d) 25-28 degrees

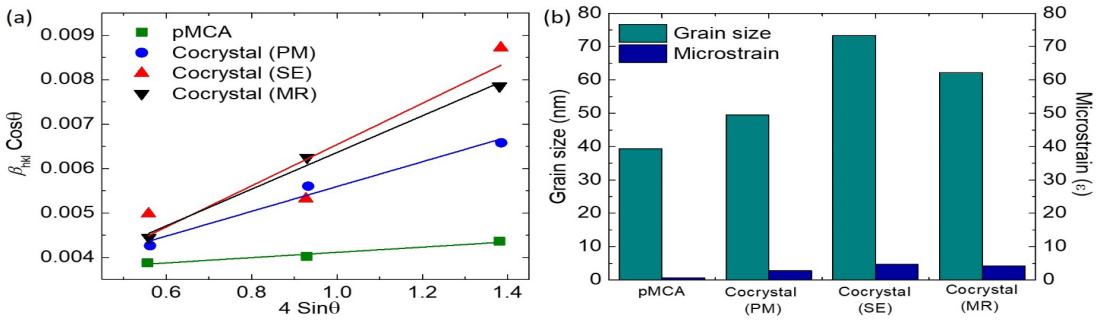

FIGURE 3. (a) The plot of β_{hkl} cosθ vs sinθ of the samples; pMCA (green line) and cocrystal samplesynthesized using a physical mixture (PM) (blue line), solvent evaporation (SE) (red line), and microwave radiation (MR) (black line) methods.(b) The corresponding grain size and microstrain of the samples obtained β_{hkl} cosθ vs sinθ plot

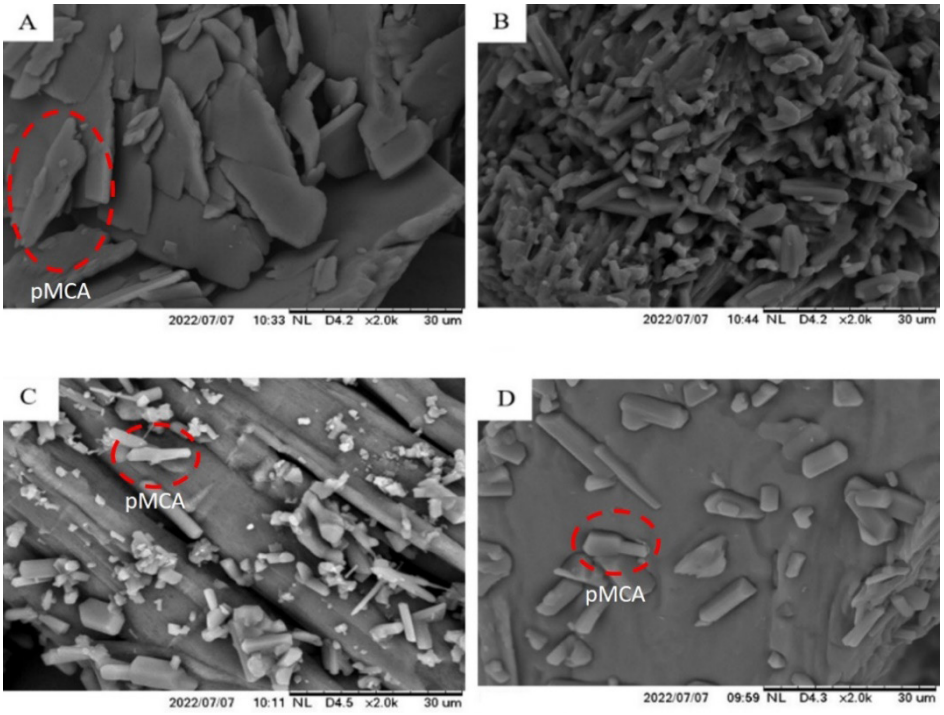

FIGURE 4. (A) Microphotographs from pMCA, (B) caffeine, and (C) cocrystal fabricated using solvent evaporation (SE), and (D) microwave radiation (MR) methods with 2000x magnification

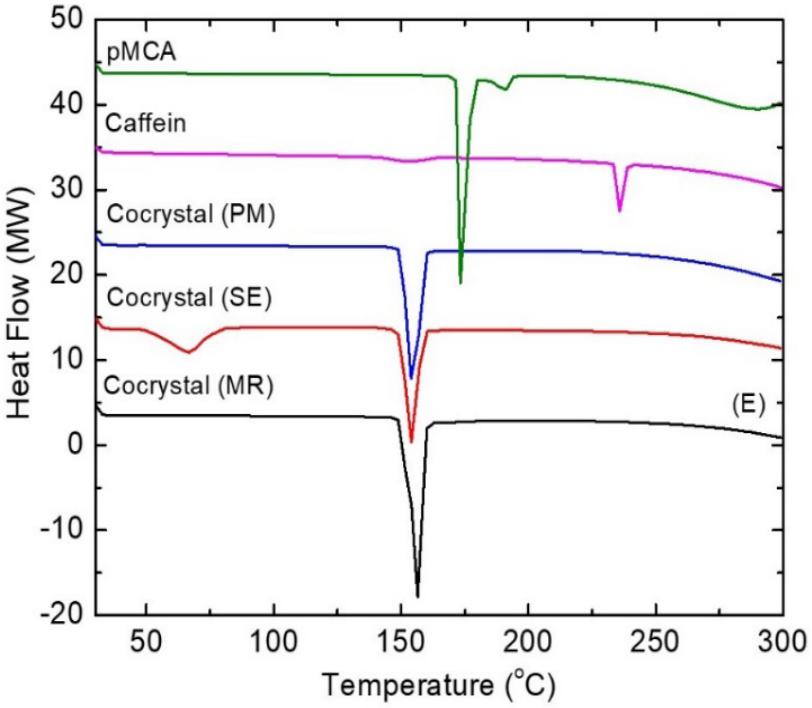

FIGURE 5. DSC result of pMCA (green line) and caffeine (magenta line),as well as cocrystal sample synthesized using a physical mixture (PM) (blue line), solvent evaporation (SE) (red line), and microwave radiation (MR) (black line) methods

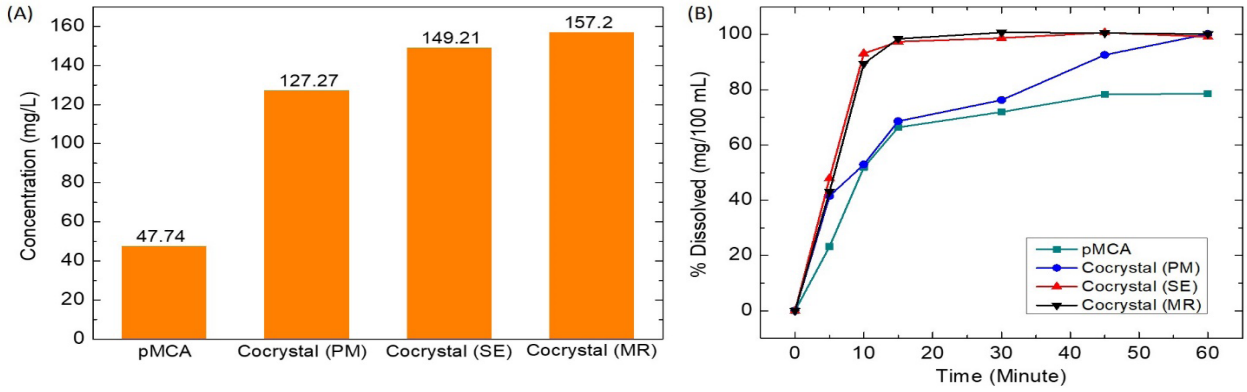

FIGURE 6. (a) Solubility and (b) dissolution tests profile of pMCA constituent and cocrystal fabricated using a physical mixture (PM), solvent evaporation (SE), and microwave radiation (MR) methods

CONCLUSIONS

According to the study's findings, cocrystal formation via solvent evaporation and microwave radiation methods has a higher solubility and dissolution rate than pure pMCA. Caffeine modulates the crystal structure of pMCA (grain, crystallization order, and size) thus increasing solubility and dissolution rate. Our finding could shed light on the importance of cocrystal formation to enhance the solubility and dissolution of any drugs, not only pMCA. Thus, we believe that new kinds of drug drugs that suffer from their solubility and dissolution could be realized in the market shortly using this strategy.

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