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Research Paper

A Comparison Study between Green Synthesis of Microwave Irradiation and Solvent Evaporation Methods in The Formation of *p*-Methoxycinnamic Acid-Succinic Acid Cocrystals

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Abstract
Cocrystal of *p*-Methoxycinnamate acid-succinic acid has been produced by microwave irradiation and solvent evaporation methods. Cocrystals are formed using succinic acid as the coformer at a molar ratio of 1:1. The formation of cocrystal can be done by solvent evaporation method and microwave radiation method. Physicochemical properties have been studied by FT-IR, DSC, PXRD, and SEM analysis. The solubility test was carried out with pH 6.8 phosphate buffer at a temperature of 25±0.5°C for 5 hours and the dissolution test was carried out with 900 mL pH 6.8 phosphate buffer at a temperature of 37±0.5°C with the speed of 75 rpm using a paddle-type dissolution test apparatus. The solubility of PMCA has increased its solubility in cocrystals by the solvent evaporation method by 1.19 times and by the microwave radiation method by 1.16 times compared to PMCA. The dissolution rate of the cocrystals of the solvent evaporation method increased by 3.50 times and the cocrystals of the microwave radiation method increased by 2.29 times compared to PMCA.

Keywords
p-Methoxycinnamic Acid, Succinic Acid, Cocrystal, Green Synthesis, Solubility, Dissolution Rate

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1. INTRODUCTION

Cocrystallization is also physic modification which is often used to improve drugs with poor solubility, low dissolution rate, and absorption problems (Karimi-Jafari et al., 2018; Liu et al., 2022). Cocrystal was formed by the combination of two or more active compounds with non-covalent bonds such as hydrogen bonds, lipophilic-lipophilic interactions, $\pi-\pi$ interactions, and Van der Waals forces (Guo et al., 2021). Cocrystals can increase the hygroscopicity, chemical stability, compressibility, and flow properties of the compound (Dhondale et al., 2023). Coformer also has an important role in crystal production via the optimization of active ingredient properties such as solubility, dissolution rate, and permeability (Tan et al., 2021).

Coformer selection must refer to several important parameters such as the supramolecular synthon approach, Cambridge Structural Parameter Database (CSD), hydrogen bonding, and Hansen solubility, no toxicity and generally regarded as safe (GRAS) status (Buddhadev and Garala, 2021). This study uses succinic acid as a coformer which has two carboxylic groups that can act as hydrogen bond donors and acceptors.

Cocrystallization can be formed by several methods such as solvent evaporation, hot melt extrusion, spray drying, supercritical fluid technology, laser irradiation, and microwave irradiation (Pawar et al., 2021). The solvent evaporation method is often used for the cocrystallization process (Thayyil et al., 2020). In this method, both coformer and active compounds were dissolved in the solvent and allowed to slow the evaporation of the solvent. The evaporation process that takes place will produce supersaturation leading to nucleation for the formation of cocrystals. This method utilizes hydrogen bonding in active compounds and coformer to form cocrystals (Karimi-Jafari et al., 2018). Solvent evaporation methods tend to produce cocrystals with lower energies and are homogeneous in the composition of crystals (Guo et al., 2021).

Microwave irradiation methods can provide an efficient energy source and minimize the use of solvents. This method

also produces cocrystals in a short time without changing the formation of crystals. This method works by extracting rotational energy using wavelengths on the micrometer scale. Microwaves are able to increase the mobility of molecules due to the interaction between microwave radiation and dipole spins of molecules. Microwave heating depends on the dielectric properties of the material (Palma et al., 2020). The dielectric properties of materials include dielectric constant, dielectric loss, and polarity (Pagire et al., 2013). Several studies showed a solvent evaporation method for the formation of cocrystals. However, the study about microwave irradiation methods still lacks information.

Kaempferia galanga L. is part of the Zingiberaceae family and is often used as a medicinal plant. *Kaempferia galanga* L. was known as an anti-diarrhea, anti-inflammatory, anti-asthma, anti-cancer, antioxidant, analgesic, and immunomodulator (Dwita and Hikmawanti, 2021; Harmayani et al., 2019; Wang et al., 2021). The major compound from kencur is ethyl *p*-methoxy-cinnamate (EPMC) which has *p*-methoxycinnamate acid (PMCA) as a derivative compound (Dwita and Hikmawanti, 2021). Bioavailability is related to the amount and rate of drug entry into the systemic circulation by crossing a barrier from the intestine, until entering the target of action. Moreover, bioavailability is also influenced by the physicochemical properties of drugs such as drug solubility (Alqahtani et al., 2021; Stillhart et al., 2020). The PMCA solubility in distilled water is 0.712 mg/mL at 25°C which still needs modification to gain better solubility such as micronization, chemical modification, pH adjustment, solid dispersion, complexation, micelle dissolving and hydrotrope (Abdullah Ali and Kamal Omer, 2022; de Souza de Bustamante Monteiro et al., 2012).

This study aims to determine the effect of PMCA-succinic acid cocrystals with a molar ratio of 1:1 through solvent evaporation and microwave irradiation methods on the solubility and dissolution rate of PMCA. This research is very effective in increasing the solubility of an active pharmaceutical ingredient through the cocrystal formation method. From the results of this research, it's confirmed that the formation of cocrystals significantly increased the solubility of *p*-methoxynamic acid, both by the solvent evaporation and the microwave irradiation. Even though both methods provide gave insignificantly different, but the microwave irradiation method is favorable. Microwave irradiation is environmentally friendly because it does not employ harmful organic solvents in the forming of PMCA-succinic acid cocrystals.

2. EXPERIMENTAL SECTION

2.1 Materials

The materials used in this study were *p*-methoxycinnamic acid ($C_{10}H_{10}O_3$, Tokyo Chemical Industry Co., Ltd., Japan, Lot: 2BI8N), succinic acid ($C_4H_6O_4$, E. Merck, Germany, Lot: K48212482 708), ethanol (C_2H_5OH, E. Merck, Indonesia, Lot: M1009832500), potassium bromide (KBr, E. Merck, Germany, pro spectroscopy) and phosphate buffer pH 6.6 (Sigma Aldrich, Singapore, Lot: P8165).

2.2 Sample Preparations

2.2.1 Preparation of PMCA-Succinic Acid Physical Mixture

The physical mixture of PMCA and succinic acid was prepared by sifting the two samples using a mesh of 60-80. To prepare a physical mixture of PMCA-succinic acid at a molar ratio of 1:1 in 2 g. Furthermore, each sample was mixed until homogeneous (Setyawan et al., 2014).

2.2.2 Preparation of PMCA-Succinic Acid Cocrystal by Solvent Evaporation

1,202.84 mg of PMCA and 797.16 mg of succinic acid were dissolved using 15 mL ethanol until dissolved in a beaker, then the two solutions were mixed at a molar ratio of 1:1. The mixture was stirred with a magnetic stirrer and evaporated at room temperature. The cocrystals that had been formed were stored in a desiccator for 48 hours or until dry cocrystals were obtained. The cocrystals were sieved with a mesh of 60-80. After that, cocrystals were stored at room temperature (Setyawan et al., 2018).

2.2.3 Preparation of PMCA-Succinic Acid Cocrystal by Microwave Irradiation

The PMCA-succinic acid cocrystal was prepared by microwave irradiation method at a molar ratio of 1:1 in 2 g. The PMCA-succinic acid was mixed homogeneously in a porcelain cup, followed by the addition of 10% w/w methanol and mixed in a porcelain cup. The mixture was placed in the microwave at 540 W for 20 min (Setyawan et al., 2018).

2.3 Characterizations

2.3.1 Fourier Transform Infrared (FT-IR)

The FT-IR analysis was obtained by a Fourier transform infrared spectrometer. PMCA and succinic acid were weighed for 10 mg of each. Furthermore, each sample was mixed homogeneously with 10 mg potassium bromide (KBr) and then pressed using a KBr plate press to produce a pellet disk. The disk was placed in a sample holder to be analyzed at wavenumbers of 4000-400 cm^{-1} (Setyawan et al., 2017).

2.3.2 Differential Scanning Calorimetry (DSC)

The DSC test was performed to determine the thermal behavior of samples by differential scanning calorimeter. Firstly, the instrument was calibrated by Indium for temperature and heat flow accuracy. Each PMCA powder and succinic acid were accurately weighed for 2-3 mg and placed in a hermetic aluminum pan. Measurements were made at a temperature range of 30-300°C with a heating rate of 10°C/min (Wicaksono et al., 2018).

2.3.3 Powder X-Ray Diffraction (PXRD)

Diffractograms of co-crystal, physical mixture, and pure PMCA were analyzed by X-ray diffractometer. The radiation source was Cu-K$\alpha\lambda$ = 1.54 Å. PXRD test was carried out by adjusting the voltage and electric current at 40 kV and 30 mA. The samples with 2-3 mg were placed in an aluminum sample

container. Data was collected by continuous scanning with a diffraction angle at 5-50° in 2θ and a heating rate at 10°/min (Setyawan et al., 2014).

2.3.4 Scanning Electron Microscopy (SEM)

The characterization of morphology and shape from co-crystal, physical mixture, and pure was analyzed by scanning electron microscope. The samples were 10 mg placed in the sample holder and coated with gold aluminum with a thickness of 10 nm. The samples were then observed at 600× and 2500× magnification using a SEM instrument with a voltage set at 20 kV and 12 mA (Setyawan et al., 2017).

2.4 Solubility and *In vitro* Dissolution Test

2.4.1 Solubility Test

Solubility test in distilled water was tested by the shake flask method. The 25 mg of each sample including PMCA, physical mixture, and cocrystals was dissolved in 25 mL of phosphate buffer pH 6.6 medium and stirred using a magnetic stirrer at 600 rpm and a temperature of 25±0.5°C for 5 hours. Samples were taken in the amount of 5.0 mL and then filtered with a 0.45 µm filter membrane. Analysis of the screening results using a UV-Vis spectrophotometer at a wavelength of 300 nm. The test was carried out in three repetitions (Wicaksono et al., 2018).

2.4.2 *In vitro* Dissolution Test

The dissolution test was carried out using the paddle method with a type II USP dissolution test apparatus. 50 mg of each PMCA, physical mixture, and cocrystals was dissolved in 900 mL of phosphate buffer pH 6.6 medium and then stirred at 75 rpm with 37±0.5°C. A total of 5 mL of dissolution media was taken in 5 min, 10 min, 15 min, 30 min, 45 min, and 60 min after the end of stirring and replaced with the same media and volume. The sample was then filtered through a 0.45 μm filter membrane and observed for its absorbance with a UV-Vis spectrophotometer at a wavelength of 300 nm. The dissolution test was replicated three times (Setyawan et al., 2018).

All of the data measured were displayed in mean±SD and analyzed by SPSS 21 software with the least significant difference test. The significant difference was considered at $p<0.05$ (Wicaksono et al., 2018).

3. RESULTS AND DISCUSSION

3.1 Fourier Transform Infrared Spectroscopy

FT-IR is widely used to determine the vibrational spectrum of molecules, thus it can predict the structure of chemical compounds by identifying functional groups from the compound (Nandiyanto et al., 2019). This method is often used to observe chemical interactions in cocrystals (Setyawan et al., 2018).

The formation of cocrystals has the potential to shift peaks, reduce peak intensity, reduce peaks, and produce new peaks in the FT-IR spectrum. The formation of crystalline phase in IR spectra of cocrystal was characterized by the shift and disappearance of absorption peaks of functional groups that

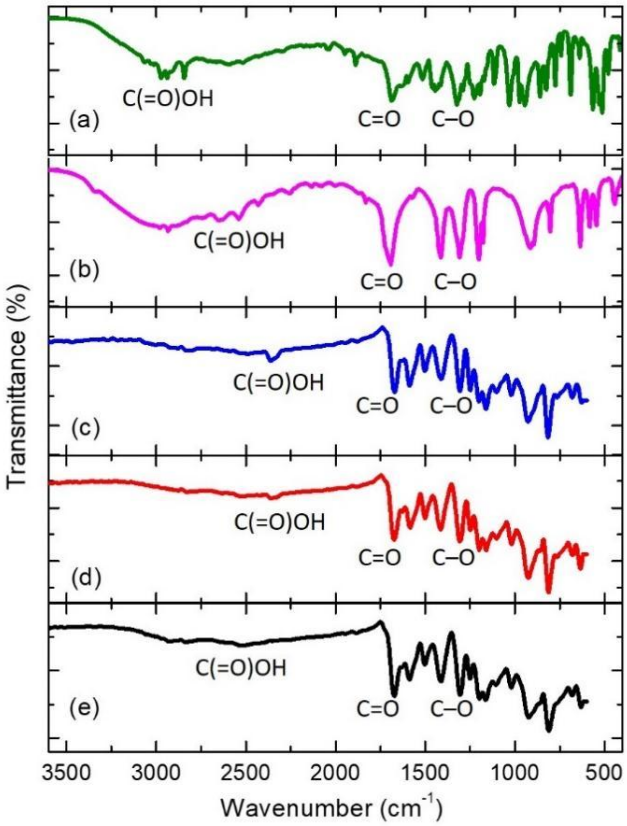

Figure 1. Figure 1. FT-IR Analysis. (a). PMCA, (b). Succinic Acid, (c). Physical Mix, (d). Solvent Evaporation Cocrystal, (e). Microwave Irradiation Cocrystal

interact to form hydrogen bonds as shown in Figure 1. The IR spectra of the physical mixture, solvent evaporation cocrystal, and microwave irradiation cocrystal showed shifts and loss of absorption peaks when compared to PMCA. The loss of absorbance peak occurs in the carboxylic OH group (C=(O)OH) at 3024 cm^{-1} and the shift of absorbance peak occurs in the C=O group at 1678 cm^{-1}. These two groups are predicted to form hydrogen bonds in PMCA with succinic acid (Wicaksono et al., 2018).

3.2 Differential Scanning Calorimetric

DSC can be used to detect the formation of new crystals, where the formation of cocrystals is indicated by a different melting point from the starting material due to the influence of differences in crystal lattice and arrangement (Buddhadev and Garala, 2021; Guo et al., 2021; Nijhawan et al., 2022). Identification of cocrystals from DSC thermograms is generally when the melting point of the cocrystal is located between or below the original compound. The results of DSC analysis showed that the melting point of PMCA was 173.56°C and that of succinic acid was 189.31°C. According to Figure 2, The physical mixture shows a shift in the melting point at 159.98 °C. The

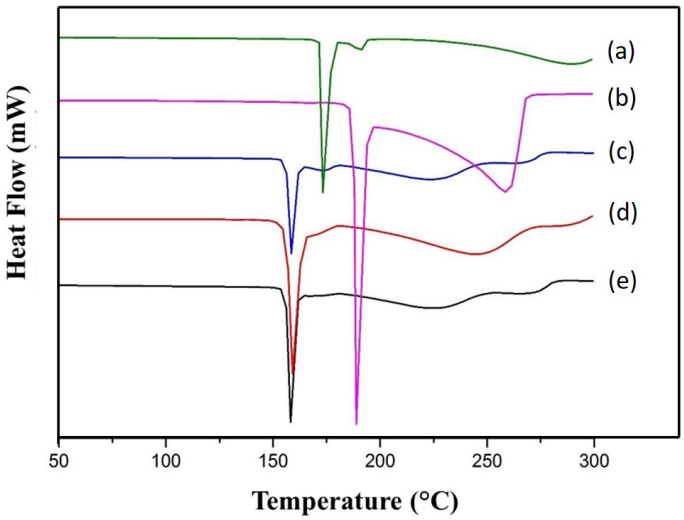

Figure 2. DSC Thermogram. (a). PMCA, (b). Succinic Acid, (c). Physical Mix, (d). Solvent Evaporation Cocrystal, (e). Microwave Irradiation Cocrystal

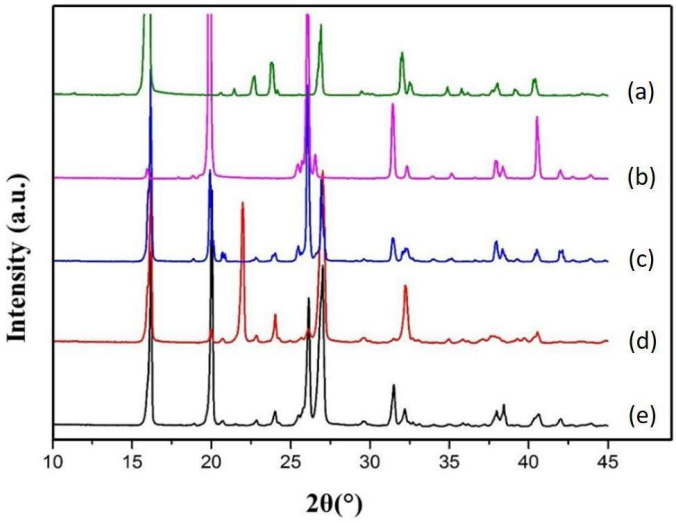

Figure 3. PXRD Analysis. (a). PMCA, (b). Succinic Acid, (c). Physical Mix, (d). Solvent Evaporation Cocrystal, (e). Microwave Irradiation Cocrystal

physical mixture also has an endothermic peak at 174.05°C which coincides with constituent components. This indicates that the physical mixture has not yet formed a homogeneous cocrystal and there are still components that have not reacted completely. The solvent evaporation cocrystal and microwave irradiation cocrystal had a new endothermic peak below the melting point of PMCA and succinic acid. The endothermic peak of the solvent evaporation cocrystal was 159.86°C and that of the microwave irradiation cocrystal was 159.50°C. The difference in melting points of solvent evaporation cocrystals and microwave irradiation cocrystals with respect to their constituent components indicates the presence of intermolecular interactions and changes in the crystal lattice which result in the alteration of physicochemical properties of cocrystals. The single endothermic peak shown from DSC analysis indicates that the cocrystal is homogeneous (Bashimam and El-Zein, 2022; Wünsche et al., 2021).

3.3 Powder X-Ray Diffraction

Powder X-ray diffraction can be used to determine crystal structures. Scanning the sample through 2θ angle range causes all lattice diffraction to be achieved (Kumar Bandaru et al., 2021; Vemuri and Lankalapalli, 2021). The new interactions formed in the cocrystal show the results of PXRD characterization with new diffraction peaks when compared to the constituent components. This assay was carried out over a range of 2θ (°) 10-45°

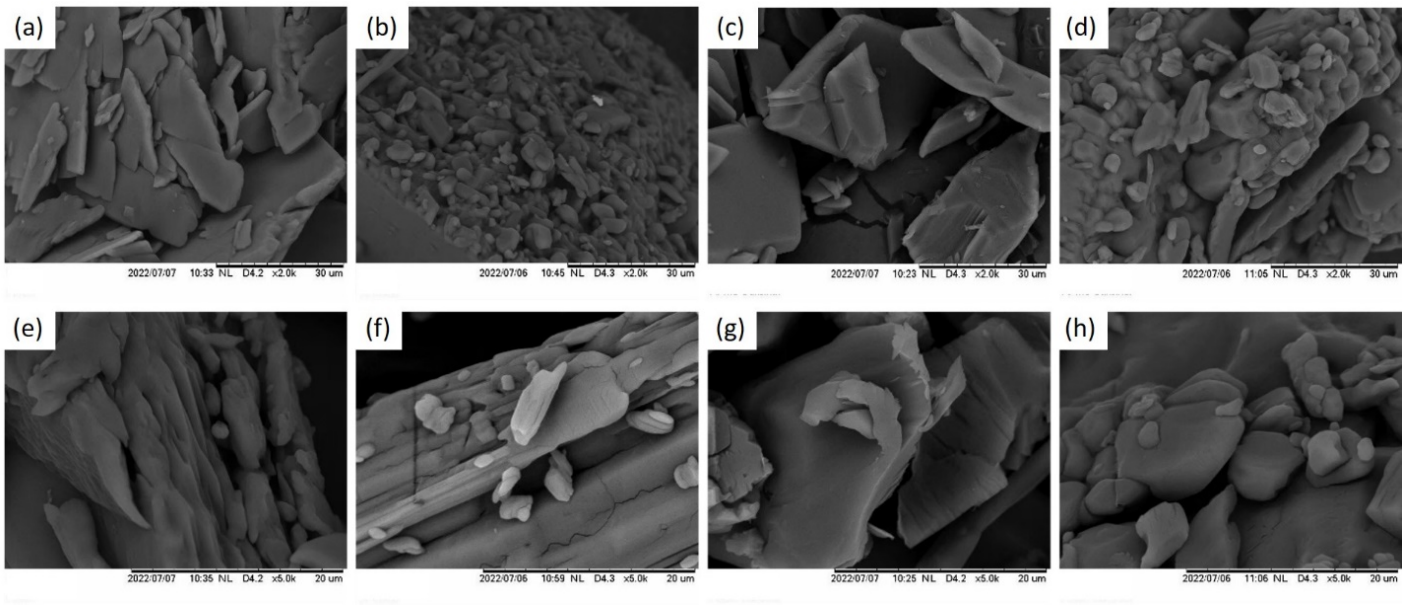

Figure 4. SEM Observation with 2000×. (a). PMCA, (b). Succinic Acid, (c). Solvent Evaporation Cocrystal, (d). Microwave Irradiation cocrystal. SEM Observation with 5000×. (e). PMCA, (f). Succinic Acid, (g). Solvent Evaporation Cocrystal, (h). Microwave Irradiation Cocrystal

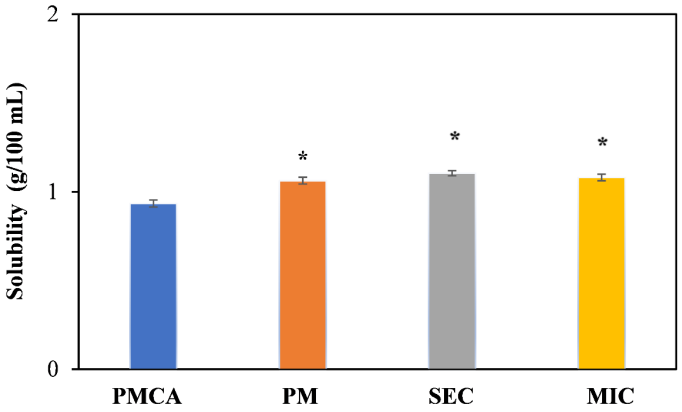

Figure 5. PMCA Solubility Test Profile, Physical Mixture (PM), Solvent Evaporation Cocrystal (SEC), and Microwave Irradiation Cocrystal (MIC). *Significant Difference.

on PMCA, succinic acid, physical mixture, solvent evaporation cocrystal, and microwave irradiation cocrystal. In Figure 3, the results of XRD analysis on PMCA and succinic acid showed a specific and sharp peak indicating the presence of a crystalline phase. The diffractogram of the PMCA shows a specific diffraction peak at an angle of 2θ = 7.85°; 16.00°; 16.11°; 23.74°; 26.89°; 32.09°; and 34.86° while succinic acid at an angle of 2θ = 15.97°; 19.89°; 26.08°; 31.46°; 40.52°. In the physical mixture, the diffractogram did not show any new diffraction peaks and only superimposition of PMCA and succinic acid diffraction peaks. This indicates that there is no interaction between PMCA and succinic acid to form a new crystalline phase. On solvent evaporation cocrystals and microwave irradiation cocrystals, new diffraction peaks appeared which were not found in PMCA, succinic acid, and physical mixtures. The solvent evaporation cocrystal showed new diffraction peaks at angles 2θ = 20.03°, 25.86°, and 39.23° while in the microwave irradiation cocrystal at angles 2θ = 32.71°, 33.13°, and 37, 22°. This diffractogram pattern indicates that a new crystalline phase has formed. This new crystalline phase is the result of the interaction between PMCA and succinic acid through hydrogen bonds (Zaini et al., 2020).

3.4 Scanning Electron Microscopy

SEM is an electron microscope that can be used to observe surface morphology on micro and nanoscale. In general, cocrystals show changes in external structure and crystal morphology (Tan et al., 2021; Witika et al., 2020). SEM testing was carried out on PMCA, succinic acid, PMCA-succinic acid physical mixture, PMCA-succinic acid solvent evaporation cocrystal, and PMCA-succinic acid microwave irradiation cocrystal as shown in Figure 4. Magnification of 2000× showed differences in crystal surface morphology between PMCA, succinic acid, solvent evaporation cocrystal, and microwave irradiation cocrystal. This shape change occurs due to interactions between molecules that result in modifications to the morphology of the crystal surface. The surface morphology of PMCA was bladed and succinic acid was granular. The morphology of solvent evaporation cocrystal had a rectangular prism or rod-shaped surface. Meanwhile, microwave irradiation cocrystals had a massive granular form.

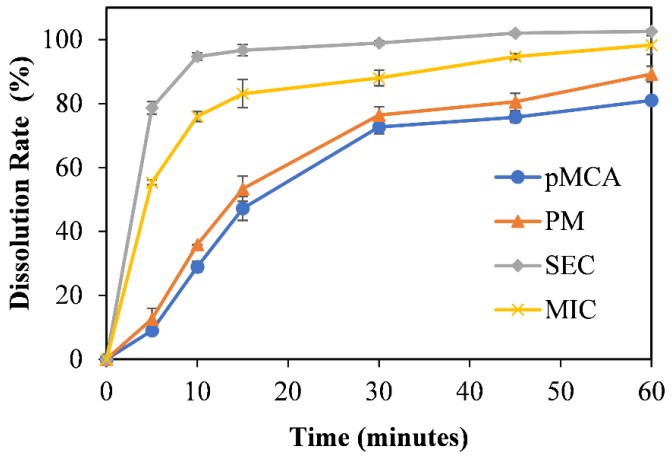

Figure 6. PMCA Dissolution Rate Profile, Physical Mixture (PM), Solvent Evaporation Cocrystal (SEC), and Microwave Irradiation Cocrystal (MIC)

3.5 Solubility Test

The solubility test showed that the solvent evaporation cocrystal and microwave irradiation cocrystal had increased solubility values compared to PMCA. The highest solubility values were sequentially found in solvent evaporation cocrystals, microwave irradiation cocrystals, physical mixtures, and PMCA. As depicted in Figure 5, the solvent evaporation cocrystals could increase PMCA solubility by 1.18 times and microwave radiation cocrystals by 1.16 times. Statistical test results showed that there was a significant difference ($p<0.05$) between PMCA and physical mixture, solvent evaporation cocrystal, and microwave radiation cocrystal. The increase in solubility of the physical mixture is caused by the dissolving effect of succinic acid which can increase the wettability of PMCA in liquid medium. Cocrystals are built from intermolecular interactions such as Van der Waals forces, $\pi-\pi$ interactions, stacking interactions, and hydrogen bonds (Alfuth et al., 2022; Karagianni et al., 2022; Timmer and Mooibroek, 2020). The bond that occurs between PMCA and succinic acid is a hydrogen bond. The formation of hydrogen bonds occurs in the carboxylic group in PMCA and the carboxylic group in succinic acid. The increased solubility of PMCA-succinic acid cocrystal could be due to the succinic acid molecules being more soluble than cocrystal, leaving an empty structure in the crystal (Rai et al., 2020; Ren et al., 2019). Loss of intermolecular interactions between the active ingredient and the conformer leads to low cocrystal stability. This condition leads to the dissolution of active compound molecules and an increase in the solubility of active compounds (Guo et al., 2021).

3.6 Dissolution Rate

The dissolution rate test (Figure 6) showed that solvent evaporation cocrystal had the highest rate followed by microwave irradiation cocrystal, physical mixture, and PMCA, respectively. Dissolution efficiency (DE) was measured to compare PMCA levels in dissolution medium until 15 min. The PMCA levels showed a DE of 22.12±1.16%. The physical mixture exhibited a slight increase with DE of 27.88±1.58%. Solvent evaporation cocrystals exhibited the highest value with DE of 90.59±0.44%. However, microwave irradiation cocrystals displayed a lower value than solvent evaporation cocrystals with DE of 69.71±0.79%. Solvent evaporation cocrystals can increase PMCA dissolution rate by 3.5 times and microwave irradiation cocrystals by 2.29 times. Statistical test results showed that there was a significant difference between PMCA and solvent evaporation cocrystals and microwave radiation cocrystals. In addition, the dissolution rate of a drug is directly proportional to the solubility of the drug (Khan et al., 2015; Soni et al., 2016; Zaini et al., 2020).

4. CONCLUSIONS

The formation of PMCA-succinic acid cocrystal through solvent evaporation method and microwave irradiation method displayed a new crystalline phase according to FT-IR, DSC, PXRD, and SEM analysis. PMCA-succinic acid cocrystals also had better solubility and dissolution rates than PMCA. Solvent evaporation cocrystals could increase PMCA solubility by 1.18 times and microwave radiation cocrystals by 1.16 times. Whereas, solvent evaporation cocrystals can increase PMCA dissolution rate by 3.5 times and microwave irradiation cocrystals by 2.29 times. Although there are no significant solubility and dissolution enhancements, nevertheless, the microwave irradiation method is greener compared to the solvent evaporation method, because no organic solvent is used during synthesis, a rapid and simple process, as well as environmentally benign. We believe that our findings could be used to develop cocrystals of active pharmaceutics ingredients.

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