

Original Research Article

Preparation and physicochemical characterization of para-methoxycinnamic acid cocrystals using *in silico* method

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Abstract

Purpose: To predict *in silico* bond formation between para-methoxycinnamic acid (PMCA) and coformers, using Autodock software.

Methods: Cocrystals were synthesized with microwave irradiation so as to support green chemistry. Cocrystal characterization was performed using Fourier-Transform Infrared Spectroscopy (FTIR), Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), and Scanning Electron Microscopy (SEM).

Results: *In silico* analysis showed the presence of non-covalent bonds such as hydrogen bonds, π - π bonds, and Van der Waals bonds, with binding energy values of -3.70, -2.63, -2.38, -1.96, -1.86, and -1.70 kcal/mol for L-glutamine, saccharin, nicotinamide, benzoic acid, malic acid and tartaric acid, respectively. The smaller the binding energy, the easier it is to form interactions between PMCA and coformers. Characterization with FTIR showed decreases in intensity, loss, and peak absorption in cocrystals, when compared to PMCA and coformers. The PXRD diffractogram also showed new diffraction peaks in the cocrystals when compared to PMCA and coformers. Results from DSC indicated changes in the melting points of cocrystals, while SEM results showed differences in crystal surface structures between PMCA cocrystals and coformers.

Conclusion: *In silico* analysis of cocrystal formation is the initial stage in choosing an efficient and effective coformer. Characterization using FTIR, XRD, DSC, and SEM indicates that the cocrystals formed with the coformers met the characteristics of cocrystals.

Keywords: Cocrystal, *In silico*, Microwave, Physicochemical characterization, Para-methoxy cinnamic acid

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INTRODUCTION

Three factors impact the effectiveness of a drug: permeability, solubility, and potency (dose). Solubility and permeability are aspects that are modifiable and controllable, whereas the dose is not [1]. Poorly soluble drugs (less than 10 mg/mL) lead to incomplete absorption and long

absorption times, thereby resulting in low therapeutic effects [2]. When administered orally, a medicine with poor solubility results in low dissolution rate and limited bioavailability, leading to a less-than-ideal therapeutic effect [3]. Aqueous solubility is the key factor that determines the rate of absorption and bioavailability of an oral preparation [4]. The solubility of pharmaceutically active compounds

may be increased using techniques such as addition of surfactants and hydrotropic agents, cocrystallization, solid dispersion, salt formation, inclusion complexes, and salt formation. Cocrystallization results from noncovalent bonds between coformers and pharmaceutically active ingredients, as well as intermolecular connections in the form of hydrogen bonds, Van der Waals bonds, phi-phi links, and halogen bonds in a particular stoichiometric ratio [1,5-7].

Cocrystal production is a commonly used technique in both studies and pharmaceutical sector [6,7]. The concept of cocrystallization was created in the pharmaceutical industry in order to enhance the physicochemical characteristics of pharmaceutically active compounds without changing their crystal structures or pharmacological activities. All molecules, including non-ionized and medicinally active substances with poor ionization potential, undergo cocrystal formation [6,8].

The formation of cocrystals requires the addition of coformers which must be safe for use in medicinal products that are generally recognized as safe (GRAS). The most crucial stage in cocrystal formation is coformer selection. Prediction of the right coformer for cocrystal formation prior to manufacturing in the laboratory will save time, cost and effort. One may use the difference in pKa values (ΔpK_a) between parmethoxycinnamic acid (PMCA) and coformer to forecast the formation of cocrystallates. When the value of ΔpK_a , i.e., $[pK_a(\text{API}) - pK_a(\text{coformer})]$ is negative, there is probably no proton donor present, and a cocrystal will form. The pKa value indicates the capacity of an acid to supply protons. On the other hand, salt formation is most likely if $\Delta pK_a > 3$ [9]. The FDA classifies new crystal forms [10]. However, there are several generally accepted definitions of salt forms, cocrystals, and their combinations [10].

The next step in optimizing the selection of coformers is the *in silico* approach which utilizes the AutoDock Tools software. The *in silico* approach calculates the difference in pKa values between binding affinity (BAF) and the coformer, and uses the binding energy value as a reference to predict the formation of cocrystals. The presence of noncovalent bonds such as hydrogen bonds, phi-phi bonds, and Van der Waals bonds indicates cocrystal formation [11]. With the *in silico* approach, there is hope for reduction in the use of laboratory experiments for identifying the potential of coformers to form cocrystals [12,13].

Green chemistry approach uses fewer organic solvents than other methods. Like microwave method, it is an environmentally benign procedure for producing cocrystals [14]. Microwave radiation results in faster and more uniform heat transmission when compared to traditional methods of conduction and convection. Additionally, radiation accelerates the production of crystals. As in conventional methods, the production of cocrystals is accelerated by microwave radiation, which transmits heat more quickly and more uniformly than conduction and convection [7,15].

The present study was aimed at predicting formation of cocrystals between PMCA and coformers through *in silico* analysis, and characterization of the cocrystals using PXRD, DSC (for melting temperature and enthalpy), FTIR (for functional groups), and SEM (for crystal surface morphology) [16].

EXPERIMENTAL

Design of study

This study was done in 4 stages. The first stage involved calculation of the difference in pKa between PMCA and each coformer in order to select coformers based on ΔpK_a value < 3 . The next stage was to conduct *in silico* tests between PMCA and coformers from the acidic group and basic group.

The third involved using microwave irradiation to make cocrystals between PMCA and coformers with the least binding energy values, namely benzoic acid (from the acidic group) and L-glutamine (from the basic group). In the 4th and final stage, the physicochemical characteristics of the cocrystals were determined using FTIR, DSC, XRD and SEM.

In silico screening of coformer

Ligand preparation

The tested ligands employed were L-glutamine, saccharin, nicotinamide, benzoic acid, malic acid, and tartaric acid. The two-dimensional image was created using ChemDraw structure of the ligand analogue (PerkinElmer ChemOffice Suite) before making a copy. Then, MMFF94 was utilized to quantify the lowest energy, after which it was stored as .mol2 (a file format used to store molecular structures). The docking software used was AutoDock. One of the benefits of AutoDock lies in its capacity to predict binding energy, thereby demonstrating cocrystal formation between PMCA and coformers.

Receptor preparation

In silico analysis of the development of the cocrystals predicted that PMCA, a compound with large molecules, was a likely receptor. Water molecules and other unnecessary parts were removed, non-polar hydrogen was added and charged, and the coordinate grid and size were arranged. The size and coordinates of the grid box were automatically adjusted to the position of each receptor ligand by making the center of the grid box the location of the ligand.

Validation of docking protocol

The validation procedure was completed through re-docking of cocrystal ligands isolated from active-site receptors. A ligand cocrystal was validated at a selected binding location using the Root Mean Square Deviation (RMSD) metric. In molecular docking, RMSD is a metric used to measure the difference in atomic positions between two molecular structures. The RMSD is often used to assess the quality of docking results, i.e., how well the docked molecule (ligand) matches the target or predicted position. Results of RMSD are said to be valid if they are less than 2 Å [17].

Molecular docking

The AutoDock docking program of Scripps Research Institute was utilized [17]. One of the benefits of AutoDock lies in its capacity to forecast binding energy and hence demonstrate the development of a cocrystal between PMCA and coformer [18].

To ensure that the tested ligand was bound to the ideal position for each ligand, the binding site orientation was determined using the blind docking method, and the results for each of the tested ligands showed a cavity with the highest affinity equal to the comparative ligand [17,18]. For this reason, the same grid box size was used for the docking process and the validation process. With a total of 100 genetic algorithm runs, a population size of 150, a moderate number of maximum energy evaluations (2,500,000), and with 27,000 as the maximum number of generations, this study used the Lamarckian genetic algorithm docking search settings [18]. The main variables employed in the docking method were binding affinity (ΔG) and inhibition constant (K_i). Values of binding affinity (ΔG) and inhibition constant (K_i) are usually used to determine the strength of ligand-ligand binding. A stronger ligand-ligand connection is indicated by a greater negative binding affinity (ΔG) value and a lower value of inhibition

constant (K_i). To determine the potential of the tested ligands, the results obtained for the tested ligands were compared with those from cocrystal ligand validation. The ligand-ligand interaction was visualized using the BIOVIA Discovery Studio Visualizer.

Solid-state characterization for the detection of cocrystal formation

Sample preparation

The conformer and PMCA were prepared at a 1:1 ratio (1 gram) plus 10 % Aquades (100 μ L). The mixture was placed in a porcelain cup and put in a microwave at 450 watts for 10 min, after which it was placed in a desiccator for 72 h.

Fourier Transform Infrared (FT-IR)

The FTIR analysis was carried out at wave numbers between 4000 and 500 cm^{-1} , with the sample in a sample holder.

Differential Scanning Calorimetry (DSC)

The DSC test was used to ascertain the thermal behavior of samples. Firstly, an Indium test method was used for accurate temperature and heat flow calibration on the device. Then, 2 - 3 mg of PMCA, coformer, physical mixture, and cocrystal were placed in a hermetic aluminum pan, and the DSC measurement was made at a temperature range of 30 – 300 $^{\circ}\text{C}$ at a heating rate of 10 $^{\circ}\text{C}/\text{min}$ [19].

Powder X-Ray Diffraction (PXRD)

Diffractionograms of pure PMCA, coformers, physical mixture and cocrystal were analyzed using an X-ray diffractometer. The radiation source was $\text{Cu-K}\alpha$ $\lambda = 1.54$ Å. The PXRD test was carried out at adjusted voltage and current values of 40 kV and 30 mA, respectively, on 2 - 3 mg samples placed in an aluminium sample container. Data was collected through continuous scanning at diffraction angles of 5° - 50° in 2θ , and at a heating rate of 100 $^{\circ}\text{C}/\text{min}$ [5].

Scanning Electron Microscopy (SEM)

The characterization of morphology and shape of the co-crystals, physical mixtures, and pure samples was done with scanning electron microscope [20]. In this process, 10 mg of each sample was placed in the sample holder and coated with gold and aluminium to a thickness of 10 nm. The sample was then examined at x640 magnification using a SEM instrument (Thermo

Fisher Scientific, US), with voltage set at 20 kV and 12 Ma.

RESULTS

The results of *in silico* autodocking between PMCA and coformer are presented in Table 1, while the type and number of bonds formed are shown in Figure 1. The overlay of RMSD: PMCA-benzoic acid is presented in Figure 2. The FTIR analysis revealed that the carboxylate group of PMCA at 2835 cm^{-1} was not lost. Spectral results showed the formation of new peaks from the cocrystals formed with benzoic acid and glutamine at wavelength of 3550 cm^{-1} , indicating the presence of O-H, as shown in Figure 3. Results from DSC (Figure 4) indicated that the melting point of PMCA was $174.17\text{ }^{\circ}\text{C}$. However,

there were decreases in the melting points of the cocrystal PMCA-benzoic acid and cocrystal PMCA-glutamine, with values of 104.50 and $172.40\text{ }^{\circ}\text{C}$, respectively. Results from X-ray diffraction revealed the formation of new diffraction peaks at angles $2\theta = 8.07^{\circ}$, 8.22° , and 13.85 due to the cocrystal PMCA-benzoic acid, as well as new diffraction peaks at angles $2\theta = 31.80^{\circ}$, 32.40° and 32.79° corresponding to the cocrystal PMCA-glutamine. These results are shown in Figure 5. The surface structures of the formed cocrystals were examined with SEM, and the results are shown in Figure 6. The cocrystals had different crystal shapes and sizes, with cocrystal PMCA-benzoic acid having irregular granular shape and small size, while cocrystal PMCA-glutamine was slab-shaped and smaller in size.

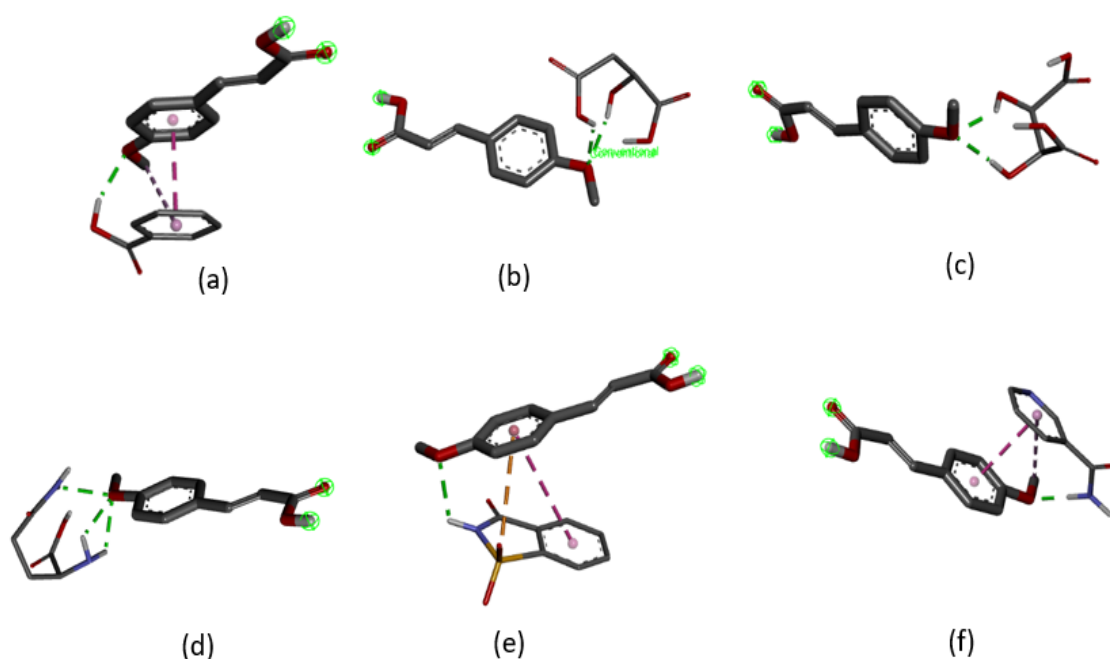


Figure 1: Results of *in silico* analyses: (a) PMCA-benzoic acid, (b) PMCA-malic acid (c) PMCA-tartaric acid, (d) PMCA-glutamine, (e) PMCA-saccharin, (f) PMCA-nicotinamide

Table 1: Binding energy values and noncovalent bonds formed *in silico*

Co-crystal	Noncovalent bond	Binding energy (kcal/mol)
PMCA-benzoic acid	Hydrogen bonds, phi-pi bonds, Van der Waals bonds	-1,96
PMCA-malic acid	Hydrogen bonds	-1,86
PMCA-tartaric acid	Hydrogen bonds	-1,70
PMCA-glutamine	Hydrogen bonds	-3,70
PMCA-Saccharin	Hydrogen bonds	-2,63
PMCA-nicotinamide	Hydrogen bonds, phi-pi bonds, Van der Waals bonds	-2,38

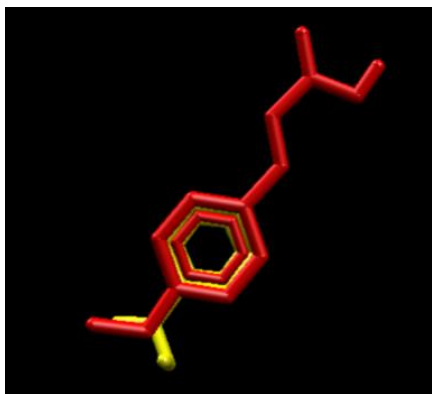


Figure 2: The overlay of RMSD: PMCA-benzoic acid

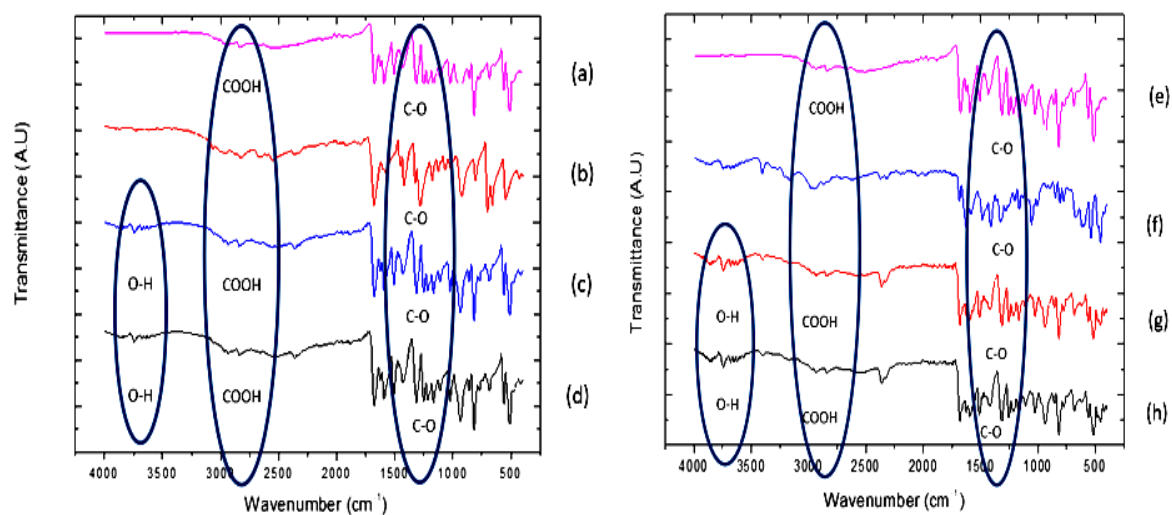


Figure 3: Results of FTIR analyses: (a) PMCA, (b) Benzoic acid, (c) Physical mixture of PMCA-benzoic acid, (d) Cocrystal of PMCA-benzoic acid, (e) PMCA, (f) L-glutamine, (g) Physical mixture of PMCA-glutamine, (h) Cocrystal PMCA-glutamine

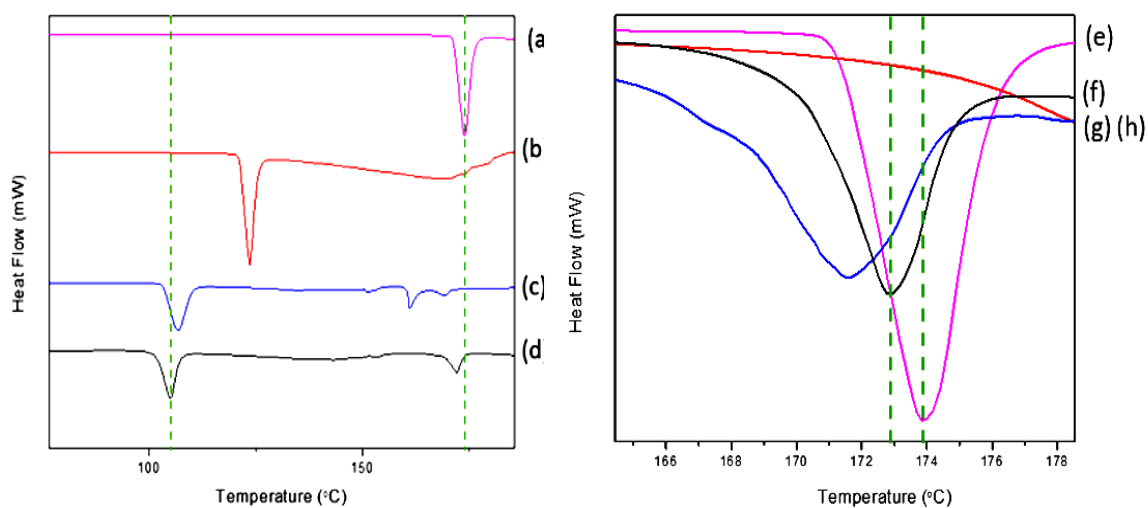


Figure 4: Results of DSC analyses: (a) PMCA, (b) Benzoic acid, (c) Physical mixture of PMCA-benzoic acid, (d) Cocrystal of PMCA-benzoic acid, (e) PMCA, (f) L-glutamine, (g) Physical mixture of PMCA-glutamine, (h) Cocrystal of PMCA-glutamine

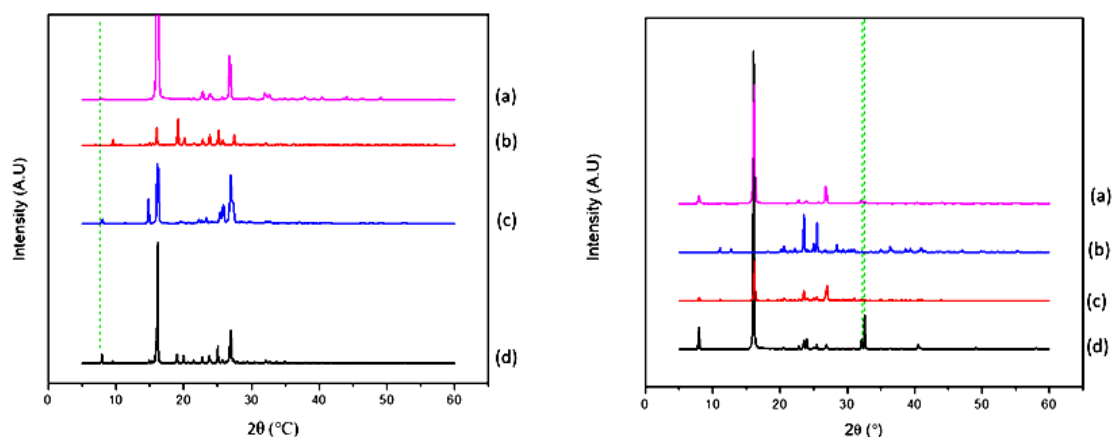


Figure 5: Results of XRD analyses: (a) PMCA, (b) Benzoic acid, (c) Physical mixture of PMCA-benzoic acid, (d) Cocrystal of PMCA-benzoic acid, (e) PMCA, (f) L-glutamine, (g) Physical mixture of PMCA-glutamine, (h) Cocrystal of PMCA-glutamine

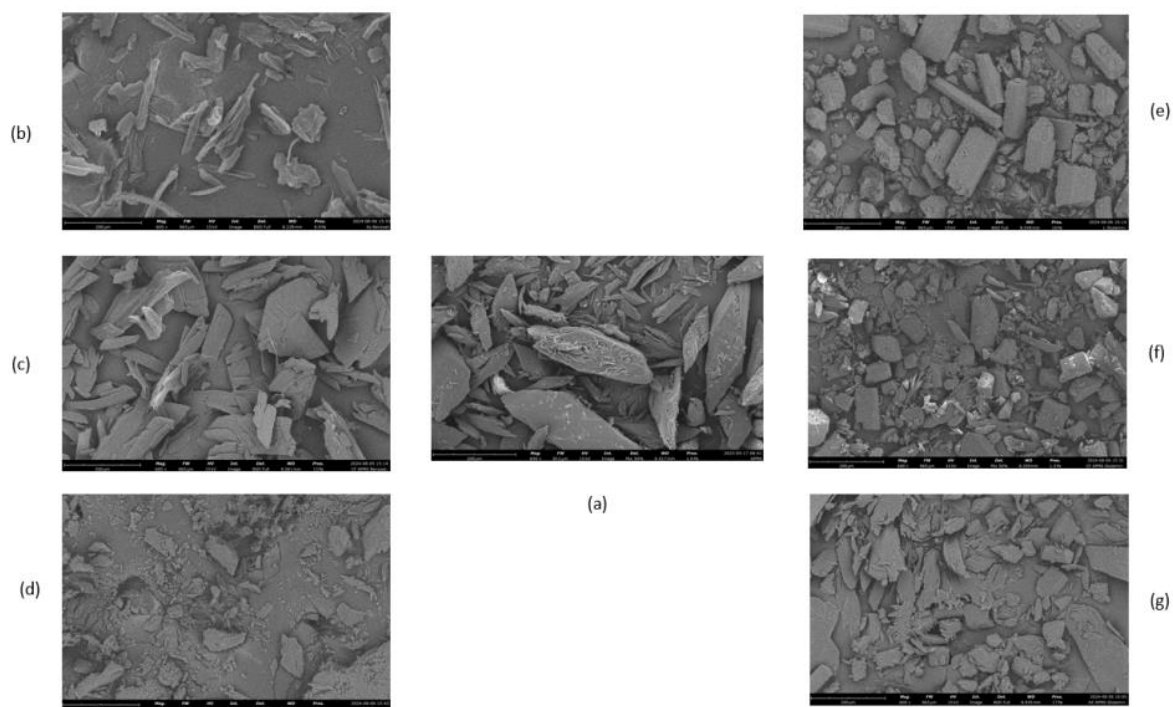


Figure 6: Results of SEM analyses: (a) PMCA, (b) Benzoic acid, (c) Physical mixture of PMCA-benzoic acid, (d) Cocrystal of PMCA-benzoic acid, (e) PMCA, (f) L-glutamine, (g) Physical mixture of PMCA-glutamine, (h) Cocrystal of PMCA-glutamine

DISCUSSION

The calculated differences in pKa values (ΔpK_a) between PMCA and the cofomers L-glutamine, saccharin, nicotinamide, benzoic acid, malic acid and tartaric acid were less than 3. This implies that cocrystals with non-covalent bonds were formed, instead of salts. The ΔpK_a rule serves as guide for differentiating between salt and cocrystals, based on the proton transfer and ionic interaction between the cocrystal-forming components [13]. From the docking results using Autodock apparatus and visualization with

Discovery Studio, non-covalent bonds were formed, i.e., hydrogen bonds, in all cocrystals, and phi-phi bonds in cocrystals formed with nicotinamide and saccharin. The H atom of the cofomer and the methoxy group of PMCA established hydrogen bonds. The energy needed to form a bond between PMCA and the cofomer is reflected in the binding energy value: the lower the binding energy, the easier the bond formation between the two.

The results from prediction of cocrystal formation using Autodock showed low binding energy

values, with a free binding energy of -3,70 kcal/mol for PMCA-glutamine, and -1.96 kcal/mol for PMCA-benzoic acid. Visually, hydrogen bonds were formed between PMCA and the coformer on the methoxy group of PMCA. This was further proven *via* results from analyses using FT-IR, DSC, XRD and SEM.

Infrared spectroscopy is the most practical method for solid-state material characterization and determination of intermolecular interactions [21,22]. This method is often used to examine noncovalent interactions in cocrystals. The IR spectra in Figure 3 show that the -COOH group of PMCA appeared at 2843 cm^{-1} . At this position, the hydrogen bonds formed were indicated by the new peak at 3741 cm^{-1} , and the shifts in PMCA methoxy group spectra from 1274 to 1258 cm^{-1} (PMCA-benzoic acid) and from 1274 to 1266 cm^{-1} (PMCA-glutamine). In the DSC thermogram, there was a decrease in melting point of the cocrystal formed when compared to that of PMCA. The melting point of PMCA was 174.17 $^{\circ}\text{C}$, while the melting points of PMCA-benzoic acid cocrystal and PMCA-glutamine cocrystal were 104.50 $^{\circ}\text{C}$ and 172.40 $^{\circ}\text{C}$, respectively. The noncovalent linkage between PMCA and each coformer caused the formation of a new crystal structure, leading to a rise in entropy value and a reduction in melting point.

The XRD technique may be used to identify the phase or type of crystal in a sample [22]. The formation of a new crystal lattice gives rise to a new diffractogram [22]. In the present study, there was a new diffraction pattern that differed between cocrystals and PMCA, i.e., the presence of new peaks at angles $2\theta = 8.07^{\circ}$, 8.22° , and 13.85° from cocrystal PMCA-benzoic acid, as well as the new diffraction peaks at angles $2\theta = 31.80^{\circ}$, 32.40° and 32.79° from cocrystal PMCA-glutamine. These features indicate that new crystal lattices had been formed due to non-covalent bonds between PMCA and the coformers. Results from SEM showed differences in crystal surface structures between PMCA cocrystals and coformers. The size of the cocrystals formed was smaller and more uniform due to the interactions of additional molecules in their crystal structure, leading to smoother appearance and more blunt edges than PMCA. These smaller and more uniform cocrystal particles are also beneficial in improving dispersibility and dissolution properties [3,4].

CONCLUSION

The findings in this study have demonstrated that the selection of coformers in cocrystal formation through *in silico* methods is an effective and

efficient technique for improving some drug physicochemical properties. The formation of cocrystals is an effort to enhance the solubility of poorly soluble drugs, thereby potentially increasing their therapeutic effects.

DECLARATIONS

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Use of Artificial intelligence/Large language models

We also declare that we did not use generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript

Availability of data and materials

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request

Conflict of interest

No conflict of interest is associated with this work.

Authors' contributions

We declare that this research was carried out by the authors named in this article, and that all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Ninis Yuliati and Dwi Setiawan conceived and designed the study. Retno Sari collected and analyzed the data. Ninis Yuliati wrote the manuscript. Dwi Setiawan and Retno Sari reviewed and edited the manuscript. All authors reviewed the results of this research and approved the final version of the manuscript.

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