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RESEARCH ARTICLE

Synthesis, Characterization and Dissolution Performance of Cocrystal of Cinnamic Acid with Nicotinamide: Experimental and Computation Investigation

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ABSTRACT:
Cinnamic acid cocrystals have been synthesized with nicotinamide coformers using the solvent evaporation method to produce white crystals. Characterization results with DSC show that cinnamic acid cocrystals have different endothermic peaks of 110°C, cinnamic acid (136°C), and individual nicotinamide (127°C). PXRD results where cinnamic acid cocrystals have different diffractogram patterns with individual cinnamic acid, namely diffractogram peaks at 6.7°, 13.4°, and 20.2°. The FTIR characterization results also indicate that cinnamic acid cocrystals exhibit distinct FTIR spectra. Specifically, there is an absence of twin peaks in the wave number range of 3400-3000 cm^{-1} corresponding to the -NH group, and absorption peaks resembling fusion appear at wave numbers around 1600 cm^{-1} and 1500 cm^{-1}, corresponding to -C=O and -C=C alkene groups. Additionally, SEM analysis reveals that while cinnamic acid has an irregular plate-like shape, the formed cocrystals exhibit a smooth surface morphology and an irregular block-like shape. Furthermore, the solubility test demonstrates that the solubility of cinnamic acid increases from 0.57 g/100 ml to 1.09 g/100 ml after cocrystallization, indicating a proportional enhancement in Dissolution Efficiency (DE) from 80.104% to 96.021%. The bond formation in the cocrystal is a hydrogen bond, as indicated by the isosurface map and the RDG Scatter Plot. This bond occurs between the carboxylic group of cinnamic acid and the amide group of nicotinamide in the $C{=}O_{CA}\cdots_{NIC}H\text{-}N$ synthon, as well as between the hydroxide group of cinnamic acid and the carboxylic group of nicotinamide in the $O\text{-}H_{CA}\cdots_{NIC}O{=}C$ synthon. The hydrogen bond is represented by a blue spike at sign(λ_2)ρ around -0.04 a.u.

KEYWORDS: Cocrystals, Cinnamic acid, Nicotinamide, Dissolution, QTAIM.

INTRODUCTION:

Cinnamic acid is a secondary metabolite compound that is widely found in typical Indonesian plants such as frankincense sap (Styrax Benzoin)[1] and Laja Gowah (Alpinia malaccensis (Burm.f.))[2,3]. Cynamic acid is found in nature generally in a transform derived from the conversion of phenylalanine through the deamination reaction of the phenylalanine ammonium lyase enzyme on the shikimate pathway[4]. Sinamic acid has many biological activities as antimicrobial[5], antifungal[6], antioxidant[7], and antidiabetic[8]. In addition to its many biological activities, cinnamic acid also has low toxicity[9]. However, cinnamic acid has a significant limitation in being developed as a candidate for new drug compounds: its low water solubility of 0.5 mg/L[8]. This makes it necessary to improve the water solubility value of the cinnamic acid.

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Their lipophilicity and intermolecular bonds generally influence the solubility of active pharmaceutical ingredients[10]. Efforts made to increase solubility due to high lipophilicity properties are solvency, micelle formation, and complexation, whilst, for compounds like cinnamic acid, whose viscosity problems are caused by strong intermolecular forces in the crystal lattice, the technique that can be used is the solid state technique[11] Solid-state techniques can be carried out in several ways, such as forming salts, polymorphs, hydrates, solvates, and cocrystals[12]. A potential solid-state technique to be developed is cocrystallization. Cocrystals have advantages over salts (only for ionic molecules) because they can be used for ionic and non-ionic molecules; compared to salts, hydrates, and solvents, the structure of cocrystals can be modified without changing their pharmacological properties, and when compared to polymorphs, cocrystals have higher stability[13,14]. Cocrystal is a crystal engineering technique between Pharmaceutical Active Ingredients (BAF) and former through intermolecular bonds such as van der Waals, π-π, and hydrogen interactions[15–17].

Research on cocrystal to improve drug solubility has been widely conducted. Fael's[18] research on synthesizing floxacin cocrystals with resorcinol conformers showed that the solubility of cocrystals was ten times greater than that of norfloxacin. Duan's research[19] also showed that palbociclib cocrystals with resorcinol coformers showed thirteen times greater solubility than palbociclib. The research of Sabouri and Shayanfar[20] synthesizing carbamazepine cocrystals with succinic acid coformers showed a ten-fold increase in solubility compared to carbamazepine. On the other hand, cinnamic acid has been used to manufacture cocrystals. However, it is still a coformer as researchers Hiendrawan et al.[21] showed that itraconazole cocrystals with cinnamic acid coformers have the highest solubility when compared to coformers of suheic acid, sebatic acid, benzamide, and 1-hydro-2-naphthoic acid.

Currently, cocrystal research is being conducted by combining experimental and computational results to confirm the structure and intermolecular bonds in cocrystals[22,23]. One of the computational methods currently used in cocrystals is Quantum Theory Atoms in Molecules (QTAIM) of Bader[24–27]. QTAIM allows for quantitative analysis of bond strength by identifying Bond Critical Points (BCPs), which are points in space where electron density is at a maximum along the bond path between two atoms. This helps in understanding the strength and nature of intermolecular interactions, including hydrogen and halogen bonds[28,29]. Furthermore, QTAIM provides an analysis of electron density topology, which assists in identifying atomic basins and their properties. This topological approach allows for a detailed understanding of how atoms interact within molecules or cocrystals, including the identification of hydrogen bond donors and acceptors[26,30,31]

The Huang et al.[28] QTAIM study has been utilized in a systematic investigation of cocrystals, including sulfonamides such as sulfaguanidine. The analysis involves Hirshfeld surface, molecular electrostatic potential surface (MEPS), and QTAIM, providing a comprehensive understanding of hydrogen bond interactions in co-crystals. This aligns with Yadav et al.'s[32] research, which combines spectroscopy and quantum chemistry studies on the hydrochlorothiazide-nicotinamide cocrystal to confirm intermolecular hydrogen bonding that enhances the pharmacological properties of the cocrystal. Based on this background, this study combines experimental and computational results of cinnamic acid and nicotinamide cocrystals synthesized using the slow solvent evaporation method. The resulting cocrystals are further characterized by DSC, PXRD, ATR-FTIR, SEM, and computational analysis using QTAIM to determine the strength and nature of intermolecular bonding responsible for cocrystal formation. Additionally, in this study, solubility and dissolution rate analyses are conducted to assess pharmacological property enhancements.

MATERIALS AND METHODS:

Materials:

Trans-sinnamic acid (CA) (≥99%), Nicotinamide (NIC) (≥98%), and acetonitrile (≥99%) were purchased from Sigma-Aldrich.

Cocrystalline CA-NIC synthesis:

The cocrystallization in this study uses a slow solvent evaporation method[32]. First, 0.2mmol of cinnamic acid is added with 10ml of acetonitrile dissolved in a stirring hot plate for 20 minutes. On the other hand, 0.2mmol of nicotinamide is added, and 10ml of acetonitrile is dissolved in a stirring hotplate for 20minutes. Next, solution of cinnamic acid and nicotinamide is mixed on a stirring hot plate for 2hours. The solution was aged in a desiccator for five days to obtain white cinnamic acid and nicotinamide cocrystals (CA CC).

Differential Scanning Calorimetry (DSC) Analysis:

DSC analysis uses a Mettler Toledo instrument to analyze CA, NIC, Physical Mixture of cinnamic acid and nicotinamide (CA PM), and CA CC. The instrument is calibrated by Indium for temperature and heat flow accuracy. Measurements were carried out in the temperature range of 30°C - 300°C with a heating rate of 10°C/min.

Powder X-ray Diffraction (PXRD) Analysis:

PXRD analysis uses the PANanalytic X'Pert PRO X-ray powder diffractometer to scan CA, NIC, CA PM, and CA CC. West Sumatra X-Raay is Cu-Kα with a

wavelength of 1.540598 Å. The divergence and scattering slit were set to 1°, and receiving slit was set to 12.75mm. PXRD is performed by adjusting the voltage and current at 40kV and 30mA, respectively. The sample was placed in a quart glass sample slide plane with an etched square and measured. Angular range (2θ) is 5.0084°-59.98614° at step times 10.1500 s and step size 0.0170°.

Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FTIR) Analysis:

The ATR-FTIR analysis uses Shimadzu IR-Prestige-21 with a horizontal Golden-Gate MKII single reflection ATR system equipped with ZnSe lenses to analyze CA, NIC, CA PM, and CA CC. The cocrystals' FT-IR spectra were collected in the range from 400 to 4000 cm^{-1}.

Scanning Electron Microscopy (SEM) Analysis:

Morphological analysis of CA and CA CC using SEM HITACHI FLEXSEM 100. A 10mg sample is placed in a sample holder and coated with gold aluminum with a thickness of 10nm. The sample was then observed at a range of 500-5000 x with a voltage set at 20.0 kV.

Solubility Test:

The solubility test is conducted in distilled water using the shaking flask method. 25mg of CA, CA PM, and CA CC samples are dissolved in 25ml of phosphate buffer media (pH = 6.6) and stirred on a hot plate for 5 hours at 25±0.5°C. The subsequent screening results are analyzed using a UV-VIS spectrophotometer. The test is repeated three times.

Dissolution Test:

The dissolution test uses the paddle method with a USP type II dissolution apparatus. 50mg of CA, CA PM, and CA CC samples are dissolved in 900ml of phosphate buffer media (pH = 6.6) and stirred at 75 rpm at a temperature of 37±0.5°C. A total of 5 mL of dissolution media is collected at 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45minutes, and 60minutes after the end of stirring and replaced with the same volume of fresh media. The subsequent screening results are analyzed using a UV-VIS spectrophotometer. The test is repeated three times.

Computation Investigation Using QTAIM of Bader:

Optimization of molecular geometry for active pharmaceutical ingredients (APIs), coformers, and co-crystals is computed using Density Functional Theory (DFT) method with Gaussian16 program, employing Becke-Yang-Parr exchange correlation functional theory (B3LYP) and basis set 6-311++*G*(d,p)[28]. The results of this optimization are then used to determine topology and non-covalent interaction energies using Multiwfn 3.8, which are subsequently visualized using Visual Molecular Dynamics (VMD) 1.9.4.

RESULT:

Cocrystalline CA-NIC synthesis:

The slow solvent evaporation method has successfully synthesised cinnamic acid and nicotinamide cocrystals, as shown in Figure 2.

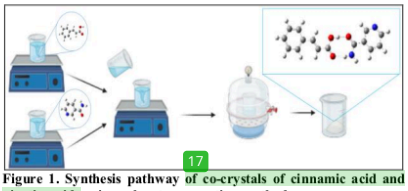

Figure 1. Synthesis pathway of co-crystals of cinnamic acid and nicotinamide using solvent evaporation method.

Figure 1 shows that the cocrystal synthesis process begins with dissolving cinnamic acid and nicotinamide in acetonitrile in a ratio of 1:1, respectively. Next, the two solutions were mixed with a stirring hot plate for 2 hours. The mixture was left in a desiccator for five days, and the solvent was slowly evaporated to reduce the concentration of the solution so that white crystals formed.

Differential Scanning Calorimetry (DSC) Analysis:

DSC is used to identify properties of cocrystals where melting point changes indicate the formation of new phases or interactions between components of cocrystals. The results of the characterization of cinnamic acid and its cocrystals using DSC can be seen in Figure 2.

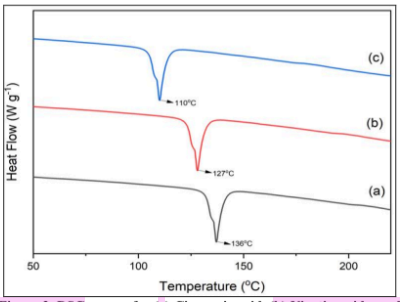

Figure 2. DSC curves for (a) Cinnamic acid, (b) Nicotinamide, and (c) Cocrystal of cinnamic acid

Figure 2 shows that cinnamic acid has endothermic peak was 136 °C, according to the research of Kopjar[33], while nicotinamide conformer shows an endothermic peak was 127 °C, according to the research of Ding[34]. The cinnamic acid cocrystal showed the shift endothermic peak was 110°C.

Powder X-ray Diffraction (PXRD) Analysis:

Powder XRD is used to identify the phase of the cocrystal by detecting changes in the crystal lattice. Various cocrystals exhibit different characteristic peaks due to their unique crystal structures. The formation of cocrystals often leads to changes in the dimensions of the unit cell compared to the individual components. These changes are reflected in the PXRD pattern, which causes the appearance of new peaks or shifts in existing peaks[35]. PXRD results of cinnamic acid and its cocrystal can be seen in Figure 3.

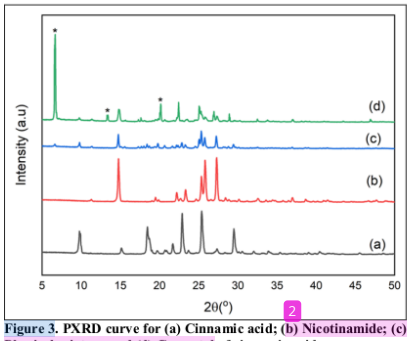

Figure 3. PXRD curve for (a) Cinnamic acid; (b) Nicotinamide; (c) Physical mixture and (d) Cocrystal of cinnamic acid

The results of XRD analysis in Figure 3 show that cinnamic acid has characteristic peaks at 9.8°, 14.8°, 18.5°, 22.9°, 25.4° and 29.5° as in the research of Trivedi[36]. Nicotinamide has characteristic peaks at 14.8°; 22.2°; 23.3°; 25.4°; 25.8°; and 27.3° as reported by Junior[37]. On the other hand, the physical mixture between cinnamic acid and nicotinamide showed peaks at 9.8°, 22.9° and 25.4° from the characteristic peak of cinnamic acid and 14.8°, 22.2°, 23.3°, 25.8° and 27.3° from nicotinamide. This shows that no new crystalline phase is formed in the physical mixture, and only a mixture of cinnamic acid and nicotinamide is formed individually. The cocrystal shows a new crystalline phase formation indicated by characteristic peaks at 6.7 °, 13.4° and 20.2°. In comparison, there are peaks of individual cinnamic acid that are lost at 9.8° and 18.5°, and the peaks of the missing individual nicotinamide are 22.2° and 23.3°.

Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FTIR) Analysis:

The cocrystallization was characterized using ATR-FTIR due to its ability to provide detailed information about the molecular structure and intermolecular interactions within the cocrystal lattice. The results of ATR-FTIR characterization of cinnamic acid and its cocrystals can be seen in Figure 4.

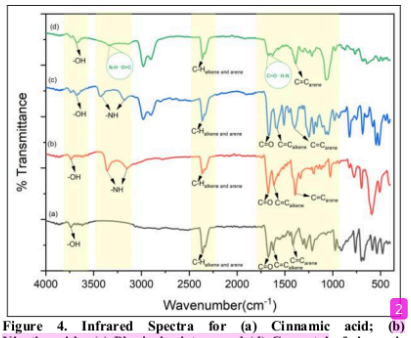

Figure 4. Infrared Spectra for (a) Cinnamic acid; (b) Nicotinamide; (c) Physical mixture and (d) Cocrystal of cinnamic acid

The FTIR characteristic results of cinnamic acid showed the stretching vibration of -OH, -CH, -C=O, $C=C_{alkene}$ and $C=C_{arene}$ at 3739 cm^{-1}, 2361 cm^{-1}, 1669 cm^{-1}, 1620 cm^{-1} and 1414 cm^{-1}, respectively, as in previous studies[8,36,38] On the other hand, nicotinamide showed stretching vibration of -OH, -NH, -CH, -C=O, $C=C_{alkene}$ and $C=C_{arene}$ at wavelengths of 3736 cm^{-1}; 3426 cm^{-1} and 3182 cm^{-1}, 2361 cm^{-1}; 1674 cm^{-1}; 1614cm^{-1} and 1391 cm^{-1}, respectively, as in previous studies[37]. In addition, the physical mixture between cinnamic acid and nicotinamide shows absorption peaks which are a combination of individuals, stretching vibration of -OH, -NH, -CH -C=O, $C=C_{alkene}$ and $C=C_{arene}$ at wavelengths of 3677 cm^{-1}, 3426 cm^{-1} and 3182 cm^{-1}, 2361 cm^{-1}, 1668 cm^{-1}, 1585 cm^{-1}, and 1398 cm^{-1}. The cocrystal shows the same peaks as API and coformers, stretching vibration of -OH, -CH, and $C=C_{arene}$ at wavelengths of 3674 cm^{-1}; 2361 cm^{-1}; and 1389 cm^{-1} but there is a missing stretching vibration of -NH and fusion-like absorption peaks of -C=O and -C=C alkene.

Scanning Electron Microscopy (SEM) Analysis:

SEM characterized the cocrystals to understand their morphology, which is essential for assessing their physical and behavioural properties. The results of the characterization of cinnamic acid and its cocrystals by SEM can be seen in Figure 5. Figure 6 shows that SEM results indicate that cinnamic acid has an irregular plate-like shape, as in Batista[39] and Silva[38] studies. On the other hand, the cocrystals that are formed have a smooth surface morphology and regular block-like shape, which differs from the individual API. In addition, SEM results show a difference in crystal size; for cinnamic acid,, the size is 44.93 mm and the cocrystal is 20.18 mm.

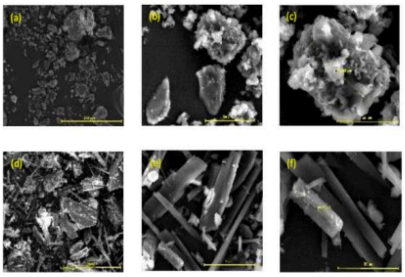

Figure 5. SEM morphology for synamic acid (above) observation with: (a) 500x (b) 2500x (c) 5000x and cocrystallization (below) observation with: (c) 500x (d) 2500x (f) 5000x

Solubility Test:

Solubility tests showed that the solvent-evaporated cocrystals had higher solubility values than cinnamic acid and the physical mixture, as shown in Figure 6.

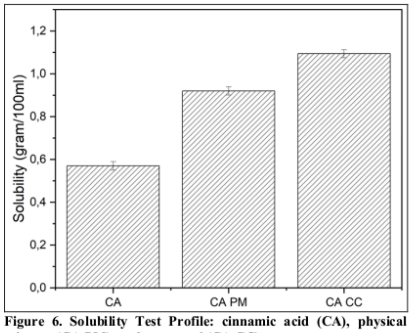

Figure 6. Solubility Test Profile: cinnamic acid (CA), physical mixture (CA PM), and co-crystal (CA CC)

Figure 6 shows that the highest solubility in order was found in cocrystals, physical mixture, and cinnamic acid. The solubility of cinnamic acid was 0.57 g/100 ml, the physical mixture was 0.92 g/100 ml, and the cocrystal was 1.09 g/100 ml.

Dissolution Test:

Dissolution tests showed that the cocrystals had a higher dissolution rate than cinnamic acid and the physical mixture, as shown in Figure 7. Figure 6 shows that the dissolution test results indicate that the cocrystal of cinnamic acid with nicotinamide by solvent evaporation has the highest rate compared to the physical mixture and individual cinnamic acid. Cinnamic acid showed a DE of 80.104%, while the physical mixture showed a slight increase with a DE of 87.284%. The cocrystal had the highest DE value of 96.021%.

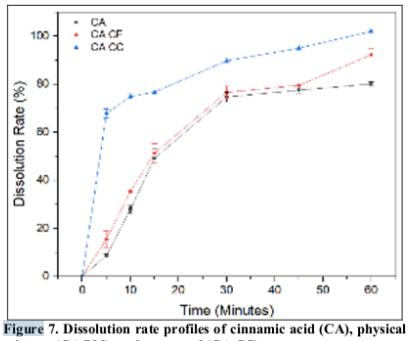

Figure 7. Dissolution rate profiles of cinnamic acid (CA), physical mixture (CA PM), and co-crystal (CA CC)

Computation Investigation Using QTAIM of Bader:

Topology and noncovalent interaction energy analysis tests of cinnamic acid and Nicotinamide cocrystals were performed using the Quantum Theory Atom In Molecules of Bader (QTAIM) method. The use of such QTAIM method to analyze the topology and energy of noncovalent interactions in cocrystals is driven by its ability to provide a detailed, quantitative, and comprehensive understanding of intermolecular interactions, which is important for fundamental research and practical applications in crystal engineering e.g. solubility properties[32]. The results of topological analysis of cinnamic acid and Nicotinamide cocrystals are shown in Figure 8.

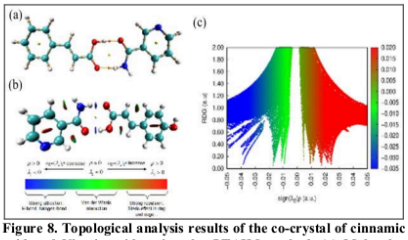

Figure 8. Topological analysis results of the co-crystal of cinnamic acid and Nicotinamide using the QTAIM method: (a) Molecular Geometry, (b) Isosurface Map, (c) Reduced Density Gradient (RDG) (blue = hydrogen bond; green = van der Waals bond; Red = Steric Effect)

Figure 8 (a) shows that the topological results of QTAIM analysis indicate that cocrystals of cinnamic acid and nicotinamide are formed with the presence of intermolecular bonds between the carboxylic group of cinnamic acid with the amide group of nicotinamide and between the hydroxide group of cinnamic acid with the carboxylic group of nicotinamide. On the other hand, the isosurface map in Figure 9 (b) shows that the bonds that

occur in the formation of cocrystals are hydrogen bonds indicated by blue chips. This result is also supported by Figure 9 (c), where there is a blue spike in sign(λ_2)ρ around -0.04 a.u, which indicates the presence of hydrogen bonds[31]. The topology results are also supported by quantitative QTAIM analysis in Table 1.

Table 1 shows that the cocrystals of cinnamic acid and nicotinamide ∇2ρ(r) of 0.1195 a.u and 0.1282 a.u, H(r) of 0.0092 a.u and 0.0201 a.u, and |V(r)|/G(r) of 0.0599 a.u and 0.1004 a.u which indicates the interactions that occur are intermolecular hydrogen bonds. The hydrogen bond has an interaction energy of -76.0833kcal/mol and an intermolecular hydrogen bond energy of -63.525 kJ/mol and -95.025kJ/mol.

DISCUSSION:

In this study, cocrystallization has been carried out with the active ingredients ferulic acid and nicotinamide as coformers through the methanol solvent evaporation method. As shown in Figure 1, the cocrystal synthesis process begins with dissolving cinnamic acid and nicotinamide in acetonitrile until a clear solution is formed. Next, the two solutions were mixed and stirred for 2 hours, forming a clear solution. The mixture was left in a desiccator for five days to form white crystals. The white crystals were formed because as the solvent evaporated, the supersaturated solution finally reached the point where the first nucleation was formed. The subsequent growth of these nuclei into larger crystals is driven by the continued evaporation of the solvent and the ongoing intermolecular interactions between the drug molecules and the coformer[40–42]. On the other hand, at the supersaturated state, the API molecules and the coformer interact through intermolecular forces such as hydrogen bonding, ionic interactions, or π-π stacking. These interactions facilitate the formation of a stable cocrystal lattice structure, i.e., white crystals[43–46]. The crystals were further characterized for their thermal properties by DSC, crystal structure by PXRD, functional groups by FTIR and morphology by SEM.

The DSC results in Figure 3 show that the melting temperature of the formed cocrystals is lower than that of the API and individual conformers. This is due to stronger intermolecular interactions and supramolecular heterosinones, and the increased thermodynamic stability of the cocrystals contributes to the formation of more stable cocrystals with lower melting points[44,47]. The lower melting point indicates that the cocrystal has a lower energy level than the individual components, which is due to stronger intermolecular interactions in the cocrystal lattice[48–50]. This is also supported by the difference in PXRD diffractogram patterns between cinnamic acid and its cocrystal, as shown in Figure 4. The characteristic diffractogram patterns observed in the XRD results of the samples at 6.7°, 13.4°, and 20.2° result from the unique crystal lattice structure and intermolecular interactions in the cocrystal. The formation of new peaks indicates a change in the dimensions of the unit cell and the appearance of new intermolecular interactions not seen in the individual components[47,51–54].

The FTIR characterization also supports the PXRD and DSC results in Figure 5. The formation of cocrystals from FTIR results occurs due to the disappearance of twin peaks at wave numbers around 3400-3000 cm^{-1} of the -NH group caused by strong hydrogen bonds between the amide group of nicotinamide and the carboxyl group of cinnamic acid while the appearance of fusion-like peaks at wavenumbers around 1600 cm^{-1} and 1500cm^{-1} indicating of -C=O and -C=C_{alkene} is caused by the formation of new bonds and changes in the bonding environment in the cocrystal lattice as the results of PXRD[47,54–57]. The results of these characterizations are also supported by SEM morphology and the size of solids that differ between cinnamic acid and cocrystals, as shown in Figure 6. SEM results show that cinnamic acid has an irregular plate-like shape, as in the studies of Batista[39] and Silva[38], while the cocrystals formed have a smooth surface morphology and a regular block-like shape. On the other hand, the size of the cinnamic acid crystal is 44.93mm, and the cocrystal is 20.18mm. This is due to the new intermolecular interactions introduced by the coformer, which result in changes in particle shape and size so that the morphology of the cocrystal is different from that of individual cinnamic acid[24,58].

Table 1. The topological parameters obtained from the QTAIM analysis

Material	E_{int} (Kcal/mol)	†BCP	ρ (a.u)	$\nabla^2\rho$ (a.u)	G (a.u)	H (a.u.)	V (a.u)	$E_{H\cdots O}$ (kJ/mol)	ε (a.u)
CA CC	-76,083	$C{=}O_{CA}\cdots_{NIC}H{-}N$	0,0383	0,1195	0,0391	0,0092	-0.0484	-63,525	0.0054
		$O{-}H_{CA}\cdots_{NIC}O{=}C$	0,0562	0,1282	0,0522	0,0201	-0.0724	-95,025	0.0021

†Bond Critical Point (BCP), energy interaction (Eint)electron density (ρ), Laplacian of electron density (∇2ρ), Lagrangian kinetic energy (G), Hamiltonian kinetic energy (H), Potential energy density (V), Hydrogen bond Energy (EH···O), and eliplicity of electron density

Previous research[8,35,59,60] showed that cocrystals can increase solubility and dissolution compared to API due to differences in structure and physicochemical properties between cocrystals and API. This is in line with this study in Figure 7, where the solubility of cinnamic acid is 0.57g/100 ml. After being synthesized into cocrystals, the solubility increases 1.91 times to 1.09g/100 ml due to strong intermolecular interactions and a denser and more ordered cocrystal lattice structure. These interactions increase solubility by improving the interaction with the solvent and reducing the energy required for dissolution[8,45,61,62]. This is by the parachute spring effect, whereby when a drug forms a cocrystal with a conformer, new intermolecular interactions are introduced that can loosen or alter the crystal lattice. These changes in intermolecular bonds increase the solubility of the drug by making it easier for the solvent to penetrate and dissolve it like a spring. The stability of the cocrystal will make the solubility stability sustainable, like a parachute, to increase the effectiveness of the drug in the body[46,63]. On the other hand, the dissolution rate of cocrystals, as shown in Figure 8, is higher when compared to individual cinnamic acid and its physical mixture, where cinnamic acid shows a Dissolution Efficiency (DE) of 80.104% after becoming a cocrystal, the DE value increases to 96.021%. This is because cocrystals are formed through intermolecular interactions that stabilize the cocrystal lattice and create a more regular structure. This increased orderliness increases the rate at which the cocrystal solubilizes by providing a more favourable environment for the solvent molecules to interact with the drug molecules. This result is also proven by the magnitude of the drug dissolution rate, which is directly proportional to the solubility of the drug[60].

The intermolecular bonds of the cocrystals were predicted using the QTAIM method, as shown in Figure 9 and Table 1. The use of such a method is because it provides a detailed and quantitative analysis of the noncovalent interactions that stabilize these complexes and can gain a thorough understanding of the intermolecular interactions that stabilize the cocrystals, which is crucial for predicting their solubility, dissolution rate and overall stability [28,31,64,65]. Figure 9 shows that the cocrystals of cinnamic acid and nicotinamide are formed by the intermolecular bond between the carboxylic group of cinnamic acid with the amide group of nicotinamide on the $C{=}O_{CA}\cdots_{NIC}H{-}N$ synthon and between the hydroxide group of cinnamic acid with the carboxylic group of nicotinamide on the $O{-}H_{CA}\cdots_{NIC}O{=}C$ synthon. On the other hand, based on the isosurface map shows that the bonds that occur in the cocrystal formation are hydrogen bonds indicated by blue colour chips supported by the RDG Scatter Plot where there is a blue spike at sign $(\lambda_2)\rho$ around -0.04 a.u as research by Pujiono[31].

The topological parameter results from QTAIM predict that intermolecular hydrogen bonds are formed if $\nabla_2\rho_{(r)} > 0$, $H_{(r)} > 0$, and $|V_{(r)}|/G_{(r)} < 1$ as reported by Hammami and Issaoui[66]. The report supports the results of this study, shown in Table 1, that the interactions that occur in cocrystal formation are intermolecular hydrogen bonds. In addition, these results are also supported by Espinosa's postulates[65–68] where if there is hydrogen bonding, the Laplacian value is 0.024-0.139 a.u while the results of this study are 0.1195 a.u and 0.1282 a.u Laplacian values. Hydrogen bonds between cocrystal molecules and solvents can increase solubility and dissolution because cocrystals containing hydrogen bond acceptors such as oxygen or nitrogen atoms can form hydrogen bonds with water molecules, making it easier for cocrystals to dissolve in water[69–72].

CONCLUSION:

Cinnamic acid cocrystals have been synthesized with nicotinamide conformer by a solvent evaporation method. The synthesis results obtained white crystals, and characterization results show that the crystals are cinnamic acid-nicotinamide cocrystals. Characterization results with DSC show that cinnamic acid cocrystals have an endodermic peak (110°C) in contrast to cinnamic acid (136°C) and individual nicotinamide (127°C). These results are also supported by the results of PXRD, where cinnamic acid cocrystals have different diffractogram patterns with cinnamic acid and individual nicotinamide as well as with physical mixtures, the presence of diffractogram peaks at 6.7°, 13.4° and 20.2 °. On the other hand, the results of FTIR characterization also show that cinnamic acid cocrystals have different FTIR spectra, the disappearance of twin peaks at wave numbers around 3400-3000 cm^{-1} from the -NH group and absorption peaks that are fusion-like at wave numbers around 1600 cm^{-1} and 1500cm^{-1}, indicating -C=O and $-C{=}C_{alkene}$ and SEM results which show different SEM morphology and solid size between cinnamic acid and cocrystals. SEM results show that cinnamic acid has an irregular plate-like shape as the research, while the cocrystals formed have a smooth surface morphology and an irregular block-like shape. On the other hand, the crystal size of cinnamic acid is 44.93mm, and the cocrystal is 20.18mm. The solubility test showed that the solubility of cinnamic acid was 0.57 g/100ml. After being synthesized into cocrystals, the solubility rose 1.91 times to 1.09g/100ml. The solubility test is directly proportional to the dissolution test; cinnamic acid shows a Dissolution Efficiency (DE) of 80.104% after becoming a cocrystal, and the DE value increases to 96.021%. QTAIM topology results, cinnamic acid and nicotinamide cocrystals are formed by the presence of intermolecular bonds between the carboxylic group of cinnamic acid with the amide group of nicotinamide on the $C{=}O_{CA}\cdots_{NIC}H{-}N$ synthon and

between the hydroxide group of cinnamic acid with the carboxylic group of nicotinamide on the O-$H_{CA}\cdots_{NIC}$O=C synthon. Based on the isosurface map, it shows that the bonds that occur in the cocrystal formation are hydrogen bonds indicated by blue colour chips supported by the RDG Scatter Plot where there is a blue spike at sign(λ_2)ρ around -0.04 a.u.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

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