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Cocrystallization of curcumin–isonicotinamide with ultrasonic wave treatment to increase solubility

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ABSTRACT: Curcumin is a polyphenol compound with various biological activities, but its solubility in water is very low (4-8 µg/mL). This research aims to increase the solubility of curcumin through cocrystallization with isonicotinamide coformer. Cocrystallization was carried out using solvent evaporation, which was treated with ultrasonic waves. Cocrystal characterization was carried out using light microscopy, PXRD, DSC, and FTIR. The cocrystal solid was evaluated for solubility using the shaking method, while the dissolution test was carried out in a phosphate buffer medium, pH 6.8, with type II equipment. The results show that cocrystallization with ultrasonic wave treatment produces solid cocrystals (CICoc-Ult) with different solid properties than those without ultrasonic wave treatment (CICoc). CICoc-Ult showed higher solubility and dissolution compared to initial curcumin and CICoc cocrystals. Therefore, ultrasonic wave treatment in the cocrystallization process of curcumin using the solvent evaporation method can be used as a potential strategy to overcome the problem of the solubility properties of curcumin.

KEYWORDS: Cocrystallization; curcumin; isonicotinamide; solubility; ultrasonic wave.

INTRODUCTION

Curcumin is a polyphenolic compound proven to have various biological activities such as antioxidant, antibacterial, antifungal, antiviral, anti-inflammatory, anti-cancer, and anti-atherosclerosis [1]. However, the formulation of curcumin into drug preparations faces obstacles, namely its very low solubility in water (around 4-8 µg/mL), so that its oral bioavailability is <1% [2]-[4]. Therefore, the solubility of curcumin needs to be improved to increase its bioavailability and therapeutic effectiveness.

Cocrystallization is often used to increase the solubility of active pharmaceutical ingredients [5]. This technique is used to create a new crystalline form that has different physical properties from the original components by combining a drug molecule with a coformer through non-covalent intermolecular interaction such as hydrogen bonds, Van der Waals interactions, and phi-phi interactions without changing their chemical composition [6]. Cocrystals can increase solubility by reducing the crystal lattice energy so solvent molecules can more easily hydrate the solid [7]. One of the advantages of the cocrystallization method is that the resulting solid is thermodynamically stable, and the pharmacological effects of the active pharmaceutical ingredients do not change [8].

Curcumin possesses a distinct molecular structure featuring two aromatic rings that contain an O-methoxy phenolic group, connected by a seven-carbon chain with a beta-diketol group [9]. Crucially, the phenolic and beta-diketol groups are highly reactive, which allows them to readily form hydrogen bonds [10]. This characteristic makes curcumin an ideal candidate for forming cocrystals with suitable coformers.

To optimize and accelerate this process, ultrasound-assisted cocrystallization has been explored as an effective means of process intensification [11]-[14]. This method works by utilizing ultrasonic waves to induce cavitation within the solution, a mechanism that effectively promotes nucleation even at temperatures lower than the supercritical temperature. Thus, ultrasonic wave treatment in cocrystallization can increase the nucleation rate and reduce the induction time [14]. In addition, cavitation energy from ultrasonic waves is known to reduce the size and prevent aggregation of cocrystal particles so that the solubility and dissolution rate of cocrystal solids increase [14],[15]. Currently, no research has been conducted on increasing the solubility of curcumin through cocrystallization using the solvent evaporation method with ultrasonic wave

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treatment. This research aims to cocrystallize curcumin using the solvent evaporation method with ultrasonic wave treatment to improve its solubility properties. This research's novelty is using ultrasonic waves in the curcumin cocrystallization process so that curcumin cocrystals are produced with increased solubility properties.

MATERIALS AND METHODS

Materials

The ingredients used were curcumin with a purity of >99.8% (Tokyo Chemical Industry, Japan), isonicotinamide (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany), dipotassium hydrogen phosphate (Merck, Germany), methanol (PT. Smart Lab Indonesia, Indonesia), and distilled water.

Equipment

The main tools used were a mini rotator (Thermo Scientific 100-240 VAC, USA), ultrasonic bath 40 kHz (GT Sonic, China), optical microscope equipped with a camera (Olympus BX41-Olympus DP21, Japan), differential scanning calorimeter (DSC) (Thermo plus EVOII 8231, Japan), powder X-ray diffractometer (PXRD) (Panalytical X'Pert Pro PW3373, Netherlands), Fourier transform infrared (FTIR) spectrophotometer (Bruker Alpha II, Germany), dissolution tester (Logan UDT 804, USA) and UV-Vis spectrophotometer (Thermo Scientific Genesys, USA).

Methods

Cocrystallization

Cocrystallization of curcumin was carried out with isonicotinamide coformer using the solvent evaporation method. Curcumin (0.3755 mg) and isonicotinamide (0.1245 mg) were put into a beaker in an equimolar ratio, and then 5.0 mL of methanol was added. The mixture of curcumin and isonicotinamide in a glass beaker was then stirred with a magnetic stirrer at 300 rpm for 30 minutes to dissolve curcumin-isonicotinamide. Cocrystallization without ultrasonic wave treatment was carried out by heating the curcumin-isonicotinamide solution at a temperature of 50 °C while stirring with a magnetic stirrer (100 rpm) until all the solvent evaporated to produce a solid curcumin-isonicotinamide cocrystal (CICoc). Meanwhile, cocrystallization using ultrasonic wave treatment was carried out, referring to previous research with modifications. The curcumin-isonicotinamide solution in a glass beaker was stirred with a magnetic stirrer at 100 rpm at a temperature of 50 °C and then treated with ultrasonic waves so that all the solvent evaporated and a solid curcumin-isonicotinamide cocrystal (CICoc-Ult) was produced [16].

Micrographs analysis

Micrograph analysis was conducted with an optical microscope (Olympus BX 41) equipped with a camera (Olympus DP21). The sample powder was placed evenly on the object glass and then covered with a cover glass. The glass object was then placed on the microscope board, and observations were made at the appropriate magnification.

PXRD analysis

Diffractogram analysis was carried out using PXRD with a Cu Kα radiation source (λ=1.54060 Å). The sample was inserted into the sample holder cavity of the equipment and leveled with a spatula. Measurements were taken at an angle of 2θ with a range of 5-50°. The equipment settings were a voltage of 40 kV, a current of 30 mA, and a measurement speed of 10°/minute [17].

DSC analysis

The thermal properties of the samples were tested with a DSC. Samples of around 2 mg were placed in aluminum hermetic sample pans and sealed tightly. The sample pans were then placed into the sample chamber of the equipment, and measurements were carried out under dry airflow conditions at a temperature range of 50 -250 °C with a heating rate of 10 °C/minute [17].

FTIR spectroscopy analysis

FTIR spectroscopy analysis aims to detect intermolecular interactions, especially hydrogen bonds between molecules in the sample. Testing was carried out using an FTIR spectrophotometer. Samples of

approximately 5 mg were placed evenly on the sample board of the apparatus. Spectra measurements were carried out in the 600-4000 cm-1 wavenumber range using a resolution of 4 cm^{-1} [17].

Solubility test

The solubility test was carried out in distilled water using the shaking method. Excess sample powder was placed into a 100 mL Erlenmeyer flask, and 10 mL of distilled water was added. The Erlenmeyer flask was tightly covered with an aluminum sheet and shaken using an orbital shaker (30 °C, 175 rpm) for 24 hours. The supernatant was filtered using a 0.45 µm filter membrane, and the curcumin content in the supernatant was determined using a UV-Vis spectrophotometer [18].

Dissolution test

An *in vitro* dissolution test was carried out with type II testing equipment using procedures listed in the literature with slight modifications. The equipment was set at a temperature of 37±0.5 °C and a stirring speed of 100 rpm. A sample equivalent to 20 mg of curcumin was placed in an equipment chamber containing 900 mL of phosphate buffer, pH 6.8. Dissolution solution (5 mL) was withdrawn at specific intervals for 2 hours, and new dissolution medium (5 mL) was added after each withdrawal. Samples of the dissolution solution were filtered with 0.45 µm membrane filter and then the filtrate of approximately 3 mL was determined for dissolved curcumin concentration using a UV-Vis spectrophotometer [19].

Statistical analysis

Statistical data analysis was carried out using significance tests with one-way ANOVA and Post-Hoc LSD. Data were considered significantly different if the p-value was < 0.05 and not significantly different if the p-value was > 0.05.

▪ RESULTS

Micrographs of cocrystal

Micrographs of curcumin, isonicotinamide and cocrystallization results are shown in Figure 1. Curcumin had a rectangular plate shape, while isonicotinamide had an irregular shape. The particles of CICoc were irregularly shaped, while CICoc-Ult appeared to have such small particle sizes that their shape was unidentifiable.

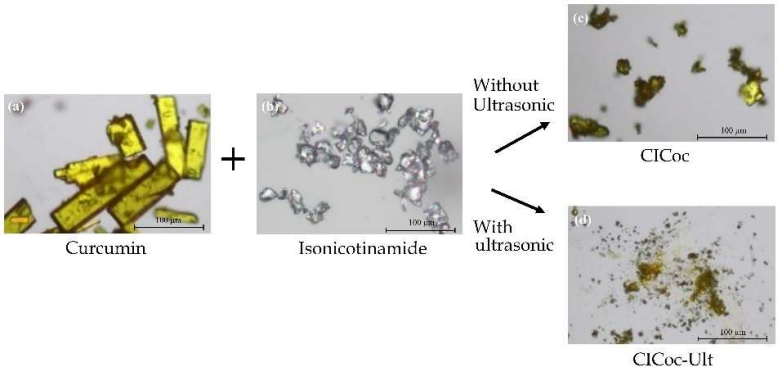

Figure 1. Micrographs of (a) curcumin, (b) isonicotinamide, (c) CICoc, and (d) CICoc-Ult (200x).

PXRD diffractogram

The PXRD diffractogram is shown in Figure 2. Curcumin showed a diffractogram at 2θ with diffraction peaks at 7.7, 8.7, 15.7, 17.1, and 20.9°, while the diffractogram of isonicotinamide showed diffraction peaks at 2θ of 17.5, 20.5, 23.1, 25.6, and 30.6°. CICoc and CICoc-Ult solids showed diffractogram patterns with diffraction peaks different from those of curcumin and isonicotinamide. New diffraction peaks in the CICoc and CICoc-Ult diffractograms appeared at 12.1, 14.4, 17.1, 20.9, and 25.2°.

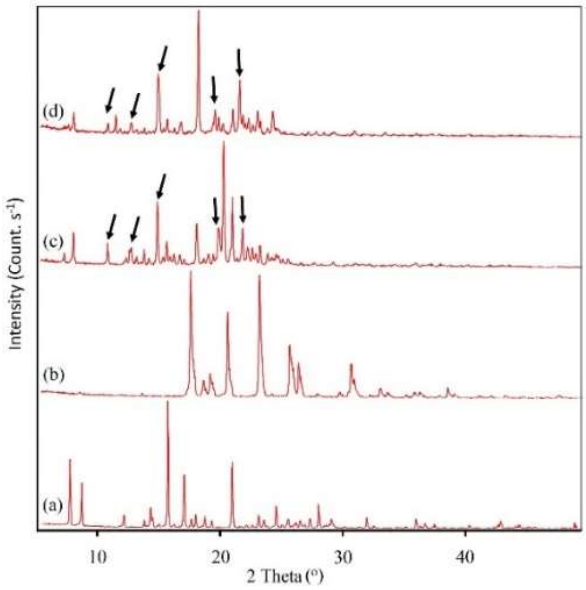

Figure 2. PXRD diffractogram of (a) curcumin, (b) isonicotinamide, (c) CICoc, and (d) CICoc-Ult.

DSC thermogram

The DSC thermograms of curcumin, isonicotinamide, CICoc, and CICoc-Ult are shown in Figure 3. Curcumin showed a sharp endothermic peak at a temperature of 186.1 °C (ΔH=199.254J/g), while isonicotinamide showed a sharp endothermic peak at a temperature of 156.9 °C (ΔH=175.237J/g). Each DSC thermogram of the CICoc and CICoc-Ult solids showed one sharp endothermic peak at 160.6 °C (ΔH=119.021J/g) and 160.5 °C (ΔH=102.891J/g), respectively.

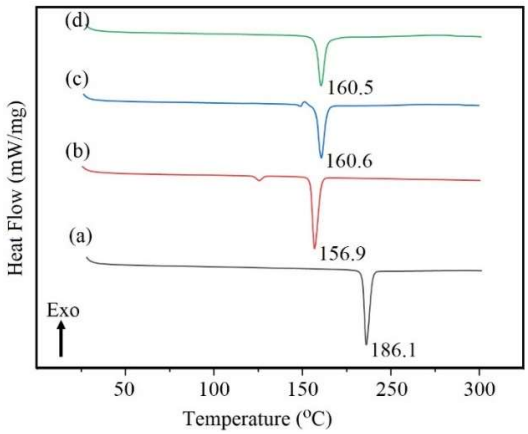

Figure 3. DSC thermograms of (a) curcumin, (b) isonicotinamide, (c) CICoc, and (d) CICoc-Ult.

FTIR spectra

The results of characterization using FTIR are shown in Figure 4. The FTIR spectra of curcumin showed specific absorption peaks at 3500 cm^{-1} (phenolic O–H stretching), 1626 cm^{-1} (C=O stretching), 1601 cm^{-1} (stretching vibrations of the aromatic ring), 1262 cm^{-1} (stretching vibrations of aromatic C–O of enol groups), and 1026 cm^{-1} (vibrations of C–O–C). Isonicotinamide showed spectra with specific absorption peaks at 3362 and 3177 cm^{-1} (stretching vibrations of N–H), 1657 cm^{-1} (stretching vibrations of C=O amide), 1621 cm^{-1} (bending vibrations of amide N–H), and 1408 cm^{-1} (stretching vibrations of C–N amide). The FTIR spectra of CICoc and CICoc-Ult appeared as a combination of the absorption peaks of curcumin and isonicotinamide. However, several absorption peaks of CICoc and CICoc-Ult shifted compared to the individual absorption peaks of curcumin and isonicotinamide. The absorption peak of curcumin showed a shift in CICoc, the vibrations of aromatic C–O shifted from 1262 to 1277 cm^{-1}, while in CICoc-Ult it shifted from 1262 to 1272 cm^{-1}. The absorption peaks of isonicotinamide also showed shifts; the stretching vibrations of N–H in CICoc shifted from 3362 to 3340 cm^{-1}, while in CICoc-Ult, it shifted from 3362 to 3400 cm^{-1}. The stretching vibrations

of C=O amide in CICoc shifted from 1657 cm^{-1} to 1678 cm^{-1}, while in CICoc-Ult, there was no shift. The stretching vibrations of C–N amide in both CICoc and CICoc-Ult shifted from 1408 cm^{-1} to 1427 cm^{-1}.

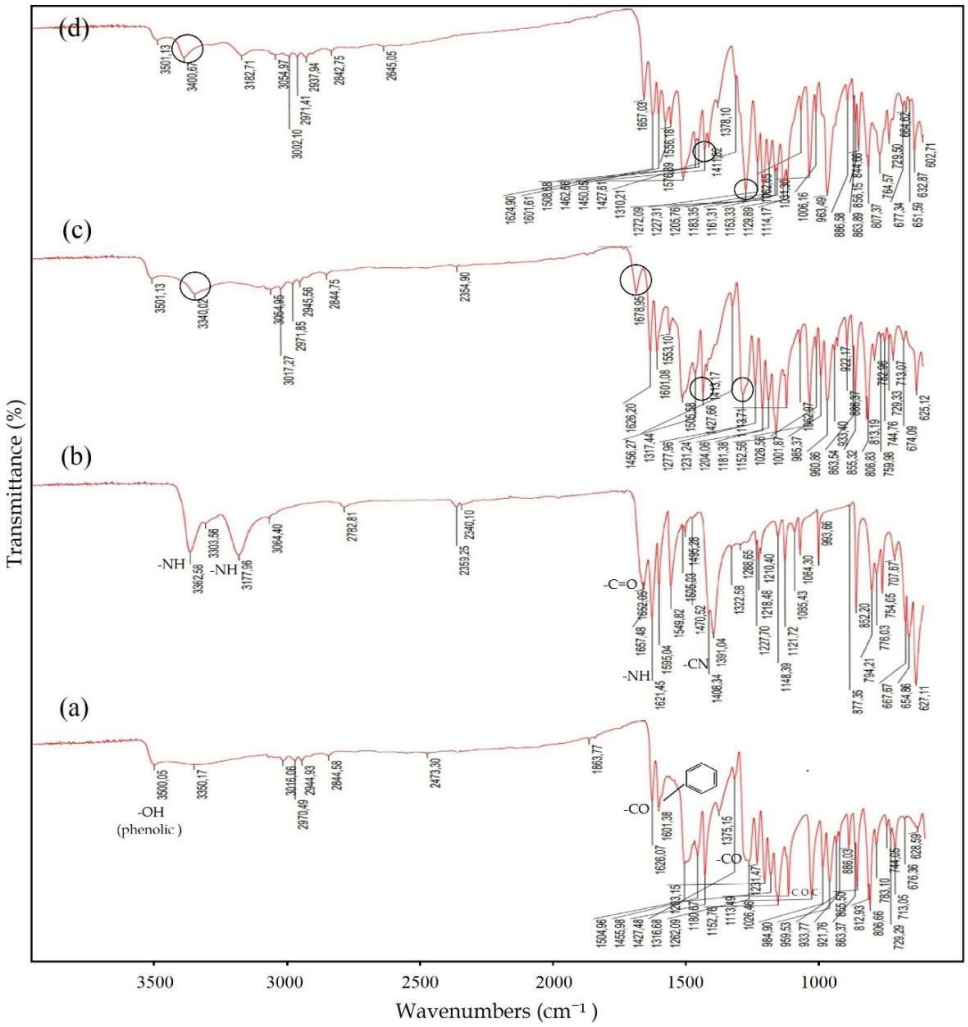

Figure 4. FTIR spectra of (a) curcumin, (b) isonicotinamide, (c) CICoc, and (d) CICoc-Ult.

Solubility

The result of solubility testing in distilled water, curcumin showed a solubility of 13.81±0.75 mg/L. Meanwhile, cocrystallization of curcumin with the isonicotinamide coformer produced CICoc and CICoc-Ult cocrystal solids with water solubilities of 35.44±0.32 and 38.40±0.28 mg/L, respectively. The formation of cocrystals showed a significant increase in curcumin solubility ($p<0.05$) compared to pure curcumin.

Dissolution

Dissolution profiles in phosphate buffer pH 6.8 of curcumin, CICoc, and CICoc-Ult are shown in Figure 5. During the 60-minute dissolution test, curcumin showed a % dissolution of 11.27±0.27%, while CICoc and CICoc-Ult showed % dissolution of 15.58±0.49 and 49.31±0.46%, respectively. At the end of the test (120 minutes), the % dissolved of curcumin was only 19.43±0.35%, while the CICoc and CICoc-Ult were 27.17±0.37% and 69.22±0.15%, respectively.

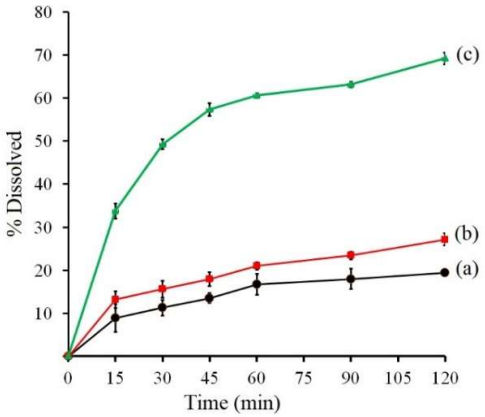

Figure 5. Dissolution profiles in phosphate buffer pH 6.8 of (a) curcumin, (b) CICoc, and (c) CICoc-Ult.

DISCUSSION

The solubility of active pharmaceutical ingredients in water greatly determines their bioavailability and therapeutic effectiveness. In this study, curcumin co-crystallization was carried out using the solvent evaporation method with ultrasonic wave treatment to increase the solubility properties of curcumin. Ultrasonic wave treatment during the cocrystallization of curcumin and isonicotinamide coformer produced cocrystals (CICoc-Ult) with smaller particle sizes than cocrystallization without ultrasonic wave treatment (CICoc). In solution cocrystallization, ultrasonic waves induced the formation of cavities within the solution, which acted as nucleation sites, leading to nucleation events at lower supersaturations. Thus, ultrasonic wave treatment increased the nucleation rate and reduced the induction time for cocrystal formation [14],[20]. An increase in the nucleation rate during the cocrystallization process caused the number of crystal nuclei of the cocrystal to increase, ultimately reducing the particle size of the final cocrystal product [21],[22]. Additionally, ultrasonic waves are known to cause fragmentation of existing crystals due to crystal collisions and prevent agglomeration [14].

The diffractogram of curcumin and isonicotinamide showed diffraction peaks that similar to those reported in the literature, which the curcumin indicated polymorph I with a monoclinic structure [18],[23],[24]. The new diffraction peaks in the diffractograms of CICoc and CICoc-Ult solids indicated that curcumin and isonicotinamide in the solid were not present as a physical mixture, but had formed a new crystalline phase that was different from the individual crystalline phases of curcumin and isonicotinamide [24]. Previous studies showed that the cocrystallization of curcumin with L-carnitine and cinnamic acid coformers produced cocrystalline solids with diffractogram patterns different from the individual diffractograms of curcumin and the coformers [25],[26].

The CICoc-Ult diffractogram showed diffraction peaks with different intensities compared to the CICoc diffractogram. The increase or decrease in the intensity of the diffraction peaks showed that ultrasonic waves affected certain aspects of the growth of curcumin–isonicotinamide cocrystals during the cocrystallization process, thereby altering the crystallinity of the cocrystal product. Higher intensity indicated greater crystallinity or more uniformly oriented crystals, caused by different nucleation and growth rates. In this study, the diffractogram of the CICoc-Ult cocrystal showed diffraction peaks at the same 2θ positions as the CICoc cocrystal, indicating that the ultrasonic wave treatment during the cocrystallization process did not affect the structure of the cocrystal product, so CICoc-Ult and CICoc had the same crystal form [27].

The sharp endothermic peaks in the DSC thermograms of curcumin and isonicotinamide indicated the melting points, which agreed with the literature [18],[28]. Each DSC thermogram of the CICoc and CICoc-Ult solids also showed one sharp endothermic peak at 160.6 °C (ΔH=119.021J/g) and 160.5 °C (ΔH=102.891J/g), respectively, indicating their melting points. The sharpness of the peaks indicated well-defined melting points, characteristic of pure crystalline materials [27]. Curcumin and isonicotinamide molecules interacted intermolecularly in the CICoc and CICoc-Ult solids to produce a single-phase solid. The solid phases of CICoc and CICoc-Ult showed melting points between those of curcumin and isonicotinamide. CICoc and CICoc-Ult exhibited nearly identical melting points, indicating that the ultrasonic treatment during curcumin–isonicotinamide cocrystallization did not significantly affect the crystal structure of the product. The results of

the DSC test confirmed the results of the PXRD test, namely that ultrasonic waves affected certain aspects of the growth of curcumin–isonicotinamide cocrystals but did not alter the structure of the cocrystal product. Crystallization of paracetamol also showed that ultrasonic wave treatment of the crystallization solution did not affect the structure of the crystal product, as indicated by the unchanged thermal behavior [27].

The FTIR spectra of curcumin and isonicotinamide were in agreement with the literature [18],[28],[29]. The shifts of the absorption peaks of curcumin and isonicotinamide in CICoc and CICoc-Ult occurred at the absorption peaks of the donor/acceptor groups of the hydrogen bonds, indicating the occurrence of hydrogen bonding interactions between curcumin and isonicotinamide that formed cocrystalline solids [18]. The shifts of the absorption peaks in CICoc and CICoc-Ult appeared different, notably in the aromatic C–O group of curcumin and the N–H and C=O (amide) groups of isonicotinamide. The ultrasonic wave treatment during the cocrystallization process affected the strength of hydrogen bond interactions in the crystal product [30]. In the crystallization of mefenamic acid, ultrasonic wave treatment caused a shift in the absorption peak from N–H stretching due to internal hydrogen bonding between the amino and carboxylic groups. The higher wavelength values for mefenamic acid's N–H stretching suggested a weaker hydrogen bonding interaction between the amino group and the carboxylic group [30]. Thus, ultrasonic wave treatment in curcumin–isonicotinamide cocrystallization indicated a change in the strength of intermolecular hydrogen bonds in the cocrystal product of CICoc and CICoc-Ult.

Curcumin is a hydrophobic compound whose molecular structure consists of hydrophobic groups, primarily two phenyl rings linked by a diketone moiety. The hydrophobic groups and the formation of intramolecular hydrogen bonds contributed to the hydrophobic nature of curcumin molecules, which promoted compact molecular packing and thus resulted in low water solubility [31]. In the cocrystallization process, curcumin and isonicotinamide formed non-covalent intermolecular interactions (primarily hydrogen bonds), creating a cocrystal with a new crystal lattice structure. The constituent components in the cocrystal were arranged by lattice energy that could be weaker than the lattice energy of the pure form. Thus, CICoc and CICoc-Ult cocrystals indicated weaker crystal lattice energy and also lower solvation energy compared to pure curcumin crystals, making them more easily hydrated by water molecules, resulting in increased solubility [7],[32],[33].

CICoc-Ult showed significantly higher solubility ($p<0.05$) than cocrystals produced from cocrystallization without ultrasonic wave treatment (CICoc). Ultrasonic wave treatment affected the strength of intermolecular interactions such as hydrogen bonds between functional groups. Ultrasonic wave treatment in the cocrystallization process between curcumin and isonicotinamide was thought to affect the strength of intermolecular interactions, which could reduce the crystal lattice energy [30]. Crystalline solids with lower hydrogen bond strength have lower crystal lattice energies, so water molecules more easily hydrate them, causing higher solubility [32],[33]. In addition, ultrasonic wave treatment showed a reduction in the particle size of the cocrystal product, thus also contributing to the increase in solubility of CICoc-Ult [34].

Dissolution testing showed that CICoc and CICoc-Ult cocrystals had a higher % dissolved than pure curcumin at all time points. The dissolution rate of a solid substance is influenced, among other factors, by its solubility [35],[36]. CICoc and CICoc-Ult cocrystals had higher solubility than pure curcumin solids, so CICoc and CICoc-Ult showed higher dissolution rates than pure curcumin. These results concluded that cocrystallization of curcumin with isonicotinamide increased the dissolution rate of curcumin. The CICoc-Ult cocrystal dramatically showed a higher % dissolution than CICoc at all time points. Increased % dissolution of CICoc-Ult indicated that ultrasonic wave treatment in the cocrystallization process increased the dissolution rate of curcumin cocrystal products. CICoc-Ult cocrystals showed higher solubility than CICoc cocrystals, thus causing a higher dissolution rate [35],[36]. Moreover, the CICoc-Ult cocrystal solid showed a smaller particle size than the CICoc cocrystal, resulting in a larger active surface area. A larger active surface area allowed more interactions between solute and solvent molecules simultaneously, thus accelerating the dissolution process. Therefore, it was concluded that ultrasonic wave treatment in the cocrystallization process dramatically increased the dissolution rate of curcumin by increasing the solubility and reducing the particle size of the CICoc-Ult cocrystal [34],[35],[37].

▪ CONCLUSION

Cocrystallization of curcumin with isonicotinamide coformer using the solvent evaporation method resulted in cocrystals with increased solubility and dissolution rate. Ultrasonic wave treatment during the cocrystallization process resulted in CICoc-Ult cocrystals with a dramatically increased dissolution rate

compared to cocrystallization without ultrasonic treatment (CICoc). Therefore, the formation of curcumin-isonicotinamide cocrystals using ultrasonic treatment can be used as a potential strategy to overcome solubility and bioavailability issues in curcumin therapeutic applications. Further testing, such as stability and *in vivo* bioavailability tests, is essential for developing curcumin cocrystal formulations into pharmaceutical dosage forms.

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