



## Technique Development in Improving the Solubility of Poorly Water Soluble Drugs (BCS II and IV): a Review Study

*(Pengembangan Teknik dalam Meningkatkan Kelarutan Obat yang Larut Buruk dalam Air (BCS Kelas II dan IV): Studi Review)*

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### ABSTRACT

Orally active drugs are currently available on the market. API should have adequate solubility and permeability to enhance its therapeutic efficacy when administered orally and obtain optimum bioavailability. Almost 40% of New Chemical Entities had limited solubility or fell into BCS class II and IV. Our review aims to summarize and discuss the development of methods and characterization for increasing the solubility of poorly aqueous drugs from papers published in Google Scholar, NCBI, Science direct, Researchgate, and MDPI. We checked that the methods used such as solid dispersion, cocrystal formation, and coamorphous can increase the solubility of API which has an impact on increasing bioavailability. The successful formation of solid dispersions, cocrystals and coamorphs can be confirmed by the characterization of PXRD, DSC and SEM. In conclusion, drug solubility is an important aspect of pharmacological effects. Drugs with high solubility can provide fast solubility rates and high bioavailability, reducing the dose administered. Solid dispersion, cocrystals, and coamorphous techniques, have succeeded in increasing the solubility of BCS class II and IV drugs.



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## INTRODUCTION

Oral administration has become the most popular and convenient treatment method for patients. Hence oral dosage forms are of significant importance to the pharmaceutical industry. The nature of Active Pharmaceutical Ingredients (API) is a factor to be considered in the manufacture of pharmaceutical preparations, particularly in terms of solubility and permeability. API is intended to have good solubility and permeability (Ghadi & Dand, 2017). Solubility is the phenomenon whereby a solid dissolve in a liquid to form a homogenous system. In the pharmaceutical industry, solubility is among the essential criteria. Because the drug will enter the systemic circulation in a dissolved condition and produce a pharmacological reaction, solubility is important in determining the concentration, dose, and efficacy of medicine (Savjani *et al.*, 2012). The degree of solubility is affected by the temperature, pressure, and kind of solvent (Humayun *et al.*, 2016). Low solubility drugs result in a suboptimal dissolution rate, which might affect the absorption process, affect bioavailability, and ultimately generate a suboptimal pharmacological effect (Duggirala *et al.*, 2016). In general, chemical substances employed as medications are weak acids or weak bases with poor water solubility (Savjani *et al.*, 2012). Nearly 40% of New Chemical Entities have poor solubility in water. More than one-third of the drugs listed in the US Pharmacopeia are insoluble in water (Williams *et al.*, 2013).

The Biopharmaceutical Classification System (BCS) classifies drug solubility and permeability into four classes, namely Class I, II, III, and IV. Class II and IV drugs in the BCS have poor water solubility. Moreover, natural compounds can also exhibit low solubility in water (Gupta *et al.*, 2020). There are numerous issues with unprocessed dry extracts, including wetness and water solubility. Occasionally, the resulting dry extract has poor stability, which hinders the preservation of its functional properties and complicates preparation and manufacturing (Esposito *et al.*, 2014). In formulation development, low water solubility is a significant obstacle. Oral administration of medication with low water solubility frequently necessitates high doses to achieve therapeutic concentrations (Fernandes *et al.*, 2018).

Pharmaceutical research has developed various methods to improve drug solubility, resulting in enhanced bioavailability and therapeutic efficacy at lower dose concentrations. Particle size reduction, solid dispersion, complexation, nanoparticles, liquisolid, microencapsulation, nanosuspension, nanoemulsion, nanocrystal, Self Microemulsion Drug Delivery System (SMEDSS), cocrystal, and coamorphous construction are all methods used to significantly boost the solubility of drugs (Bhardwaj *et al.*, 2016; Katiyar *et al.*, 2018; Kumar & Nanda, 2017; Li *et al.*, 2017; Patel *et al.*, 2018). In recent years more and more methods have been developed to improve the solubility properties of APIs. The previous articles have provided a brief description, advantages and disadvantages of methods of increasing solubility (Kadam *et al.*, 2013; Shalu, 2020). In this article, we examine techniques that can

improve the solubility of APIs such as solid dispersions, cocrystals and coamorphous. This article has the latest information regarding the mechanism of increasing the solubility of the solid dispersion, cocrystal and coamorphous methods, the results of characterization using X-Ray Diffraction (XRD), Differential Scanning Calorimetry (DSC), Fourier-Transform Infrared (FTIR), and Scanning Electron Microscope (SEM) of each method as a parameter for the success of cocrystal, solid dispersion, and coamorph formation in increasing API solubility, besides that this article provides several examples of API that have been applied in solid dispersion, coamorphous, and cocrystal methods to improve API solubility.

## **METHODOLOGY**

The journals used for this review were international journals. This article used Internet-based primary data sources accessed through online search engines such as Google, NCBI, Sciencedirect, Researchgate, and MDPI with the keywords "Enhancement Solubility, Improvement Solubility." The used journal articles were from 2009 to 2021.

## **RESULTS AND DISCUSSION**

Display with the system all research data in this section in the form of paragraphs, tables and figures. In this section, if there are tables and figures that require additional information, the sentences are presented briefly, clearly and easily understood.

### **Dispersion of Solids**

Solid dispersion is a concentrated shape comprising at least two distinct substances, typically a hydrophilic polymer and a hydrophobic drugs. The polymers can be crystalline or amorphous. The drug may be molecularly distributed in amorphous or crystalline particles (Dhirendra *et al.*, 2009). Solid dispersions can increase the solubility water and the dissolution of poorly soluble API through several mechanisms. Reducing the particle size is the easiest way to increase the solubility of API by producing a wider particle surface so that the contact of the particles with the dissolution medium increases. The presence of a second compound in the dissolution medium which plays a role in separating the particles physically can reduce API agglomeration and increase dissolution. PEG 6000 carrier increases the wettability of diazepam and temazepam API in solid dispersions by the formation of a micro-environment on the surface of API crystals after dissolution of the polymer and causes an increase in the solubility and dissolution rate of API. Certain carriers can form complexes with API which have very high solubility thereby increasing the dissolution of API. Some carrier polymers increase the solubility and dissolution rate by forming the metastable polymorph API which has a higher solubility than the previous polymorph. The most common mechanism for increasing the solubility of poorly soluble API by solid dispersion is by changing the crystalline phase to become amorphous. In terms of

thermodynamics, the amorphous phase exhibits higher transient solubility, dissolution rate, vapor pressure, and molecular mobility. The dissolution of the amorphous phase does not require the high energy required for the crystalline phase to break up the crystal lattice. In addition, the formation of solid dispersions can inhibit the formation of crystals which can reduce the rate of dissolution. Polymers in solid dispersion may interfere with either or both steps by interacting with API or changing the character of the solvent medium. Some polymers can suppress the nucleation process, other polymers are adsorbed on the surface of API crystals to prevent the attachment of API molecules so that crystal growth is inhibited. The polymer-API interactions are mainly formed through hydrogen bonds. HPMC (Hydroxypropyl Methylcellulose) polymer is able to inhibit API nucleation which has a hydrogen bond acceptor in its structure. Hydrogen bonds formed between API and polymer increase the nucleation activation energy and suppress crystal growth. Evaluation and characterization of solid dispersions must be performed to certify the preparation process for the successfully formed solid dispersion. The evaluation was performed in vitro, whereas characterization used PXRD (Powder X-ray Diffraction), DSC (Differential Scanning Calorimetry), SEM (Scanning Electron Microscope) and FTIR.

Characterization using PXRD is the detection of crystalline phases in hybrid systems that PXRD can analyze. The crystalline form gives narrow and sharp diffractogram peaks, and the amorphous form shows broad peaks. The ratio between these intensities can be used to calculate the crystallinity in the material. PXRD can also be used to confirm the presence of phase transitions (from crystalline to amorphous form) in a sample. The decrease in peak height and the lack of several prominent peaks in the PXRD solid dispersion pattern indicated a reduction in crystallinity and the transformation of crystalline polymorphs into amorphous solid dispersions (Krishnamoorthy *et al.*, 2011). For instance, the PXRD pattern of pure carvedilol gives peaks at  $2\theta$  5.75°, 11.57°, 12.92°, 13.52°, 14.78°, 17.42°, 18.38°, 20.21°, 24.26° and 26.18°. In solid dispersion, the lack of peaks in the PXRD pattern with PVP (polyvinylpyrrolidone) polymer illustrates that carvedilol turns into an amorphous form, and no recrystallization occurs (Krstić *et al.*, 2020). Changes in the peak pattern of the diffractogram indicate changes in the arrangement of the crystal lattice. Drugs that have many sharp peaks indicate that the drug is in crystal form and has limited solubility. In solid dispersions, there was a decrease in sharpness and even a loss of peaks, this indicated that the drug changed into an amorphous form that had better solubility.

DSC is a thermal process characterization to determine the heat flow and temperature associated with the transition of substances. DSC can provide melting point temperature information in various substances. The interaction between drug and polymer generally causes changes in exothermic and endothermic peaks. The absence of an endothermic peak indicates the transformation to an amorphous form, this of course can increase the solubility due to the irregular arrangement of the crystal lattice.

From a thermodynamic point of view, it is generally considered that recrystallization is possible at temperatures above Transition Glass ( $T_g$ ). This condition will cause the appearance of an endothermic peak in the thermogram. Pure haloperidol (HP) thermogram showed a single characteristic rise at 150 °C, indicating a crystalline form. The solid dispersion DSC curve shows a more expansive and decreasing melting peak due to a rise in the amount of polymer in the solid dispersion. There is no melting rise of haloperidol in the solid dispersion with PVP: HP (5:1), PEOZ (poly(2-ethyl-2-oxazoline)) : HP (15:1), PnPOZ (poly(2-propyl-2-oxazoline)) : HP (15:1), and PiPOZ (poly(2-isopropyl-2-oxazoline)) : HP (20:1), suggesting that the drug was in amorphous form. Nevertheless, HP remained as crystalline in dispersion with PMOZ Poly(2-methyl-2-oxazoline), even PMOZ: HP (25:1) (Shan *et al.*, 2020).

SEM was used to observe the morphological characteristics of solid dispersions (Afifi, 2015). ASD<sub>1</sub> (Amorphous solid dispersions), ASD<sub>2</sub>, and ASD<sub>3</sub> show smooth surfaces and ball dents that the solvent's rapid evaporation can cause during the spray drying process. Those ASDs indicated irregular, quasispherical, or broken sphere shapes (Muqtader Ahmed *et al.*, 2020). In addition, infrared (IR) spectroscopy is a type of vibrational spectroscopy that analyzes the frequency at which a sample absorbs different types of radiation. The vibration happens when the dipole moment undergoes a shift. Also, Fourier Transform Infra Red (FTIR) provides information on possible interactions between APIs and polymers. The presence of a new functional group formed indicates a simple physical interaction (Siahi-Shadbad *et al.*, 2014; Yang *et al.*, 2012). For instance, the FTIR spectrum of carvedilol powder has the characteristics of an absorption band on carvedilol crystals. N-H undergoes stretching 3346  $\text{cm}^{-1}$ , C-H undergoes stretching 2933  $\text{cm}^{-1}$ , and C-O undergoes stretching 1091  $\text{cm}^{-1}$ . In the solid dispersion FTIR spectrum with PVP/VA (vinylpyrrolidone-vinyl acetate) polymer, a typical carvedilol crystalline absorption band at 3346  $\text{cm}^{-1}$  was not appeared, resulting in a molecular interaction with the PVP/VA polymer. Moreover, on wavenumbers between 2930  $\text{cm}^{-1}$  and 2850  $\text{cm}^{-1}$ , are characteristic for the previously identified carvedilol crystals, but no separate absorption bands are appeared in the solid dispersion, but one broadband over the range of numbers original waveform, which also suggested that there was an interaction between carvedilol and PVP/VA. According to the characteristics of a single, less intense and slightly shifted absorption band and the similarity between the solid dispersion spectra and the amorphous carvedilol spectra found in the previous studies, it was determined that carvedilol transitions to an amorphous state and can form hydrogen bonds with polymers (Krstić *et al.*, 2020).

Table 1. Examples of Active Pharmaceutical Ingredients and Coformers in Solid Dispersions

No.	API	Polymer	Preparation of Methods	Objective	Reference
1	Apixabane	HPMC & PEG 6000	Solvent Evaporation	Increases solubility and bioavailability	(Amit <i>et al.</i> , 2020)
2	Atorvastatine	Poloxamer	Solvent Evaporation	Increases solubility and bioavailability	(Wenxaing <i>et al.</i> , 2018)
3	Carvedilol	Soluplus	Supercritical CO <sub>2</sub>	Increases solubility and bioavailability	(Marko <i>et al.</i> , 2020)
4	Haloperidole	PVP	Solvent Evaporation	Increases solubility and bioavailability	(Shan <i>et al.</i> , 2020)
5	Lumefantrine	Hydroxypropyl methylcellulose phthalate (HPMCP),	Spray Antisolvent	Increases solubility and bioavailability	(Sonal <i>et al.</i> , 2021)
6	Progesterone	Brij35 dan Pluronic F-127	Solvent evaporation	Increases solubility and bioavailability	(Hassan <i>et al.</i> , 2018)
7	Praziquantel	Sodium CMC dan Sodium Alginate	Solvent evaporation	Increases solubility and bioavailability	(Marquesa <i>et al.</i> , 2018)
8	Metformin HCl	Compritrol 888 ATO	Solvent evaporation	Increases solubility and bioavailability	(Jagdale <i>et al.</i> , 2011)
9	Amlodipine	Dextrine	Spray drying	Increases solubility and bioavailability	(Jang <i>et al.</i> , 2013)
10	Diazepam	Mannitol	Spray drying	Increases solubility and bioavailability	(Kauppinen <i>et al.</i> , 2018)

### Co-crystal

Cocrystallization is one of the strategies or approaches that can enhance the physicochemical properties of Active Pharmaceutical Ingredients (API) (Wicaksono *et al.*, 2017). Cocrystals are characterized as

multi-component systems that create non-covalent bonds, like hydrogen bonds, aromatic-aromatic interactions, and van der Waals bonds, and produce room-temperature solids. Increased solubility with the cocrystal technique by lowering the lattice energy and or increasing the affinity for the solvent. The interaction between API and the coformer will form a crystal lattice with a lower energy than the previous crystal lattice. The presence of functional groups that can interact with water molecules in the coformer plays a role in increasing the solubility of API. The solubility of the coformer will affect the solubility of the cocrystal. Coformers that have high solubility will provide a high level of solubility in cocrystals. The cocrystal solubility is also affected by the stoichiometry formed by the API-coformer. The presence of polar functional groups in API molecules or coformers allows specific interactions with water so that solubility can be increased. Cocrystals will have different solubility with each component component due to changes in the crystal lattice structure. Dissolution rate of quercetin cocrystal which is a secondary metabolite of the flavonoid group. Quercetin has a solubility of 0.3 g/ml in water, quercetin cocrystals were prepared by the solvent evaporation method with malonic acid coformer. The results showed that the dissolution rate of the quercetin-malonic acid cocrystal was 95.30% in the 60<sup>th</sup> minute, higher than the solubility of pure quercetin and also the physical mixture of aquercetin-malonic acid which had a dissolution rate of less than 60% in the 60<sup>th</sup> minute. Several mechanisms are thought to be involved in increasing the dissolution rate of quercetin in cocrystals, such as the solubility of the coformer malonic acid which is a water-soluble compound, as well as decreasing the crystal lattice energy and increasing the affinity of the solvent for the cocrystal. Evaluation and characterization of cocrystals must be performed to confirm the successful preparation of cocrystals.

The evaluation was conducted in vitro, whereas XRD, DSC, SEM, and FTIR were used for the characterization. Specifically, the X-ray diffraction (XRD) technique is employed to determine the crystal structure of cocrystals. Comparisons are made between the diffractogram patterns. Cocrystals are formed when the XRD patterns of cocrystals and their constituent components differ. Sharp peaks on the diffractogram show that the two compounds between the Active Pharmaceutical Ingredients (API) and coformers include cocrystals. New peaks formed on the cocrystals signal the formation of the cocrystal phase and the molecular interaction between the two materials to form cocrystals (Najih *et al.*, 2018). Figure 1 illustrates the diffractogram pattern of pure piperine, which has prominent and sharp diffraction peaks at 2, namely 14.91, 19.68, 22.50, 25.85, and 28.25°, indicating a solid form with high crystalline characteristics. Pure succinic acid has typical peaks at 16.09, 18.98, 20.06, 26.17, 31.53, 32.52, 38.09, and 38.42°. Different patterns at 2, notably 8.56, 9.92, 12.40, 13.98, 20.91, 24.53, 28.01, and 29.21°, indicated the production of cocrystals (Zaini *et al.*, 2020). Decrease in sharpness or even loss of peaks diffractogram on the cocrystal indicates that the degree of crystallinity has decreased, and

this can increase the solubility of drugs due to the irregular arrangement of the crystal lattice so that with lower energy it can dissolve drugs.

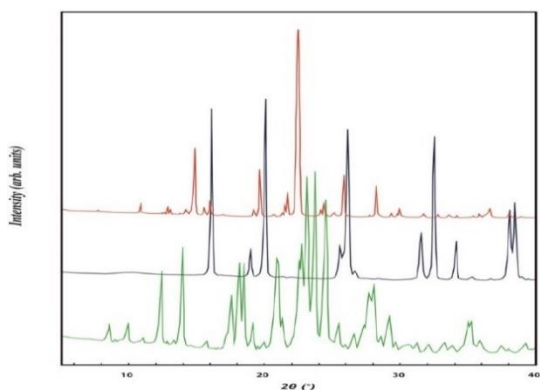


Figure 1. A pattern of Power X-ray Diffraction on Piperine (Red), Succinic Acid (Black), and Cocrystals of Piperine-Succinic Acid with a 2:1 Molar Ratio (Green) (Zaini *et al.*, 2020)

DSC attempts to determine the difference between each sample's melting point and its thermal characteristics. To identify cocrystal formation, an exothermic peak must be followed by an endothermic peak or the melting point alteration of the DSC thermogram. In more than 50% of situations the cocrystal's melting point is lower than the melting point of each active component and coformer or between the melting points of the active ingredient and coformer (Najih *et al.*, 2018). Pure carvedilol and cocrystal formulations utilizing succinic acid, fumaric acid, and oxalic acid exhibited sharp endothermic peaks at 119.5°C, 94°C, 115°C, and 100.5°C, respectively, on DSC thermograms. The endothermic peak of carvedilol is altered. This modification substantiates the creation of a new solid phase. The shift of the endothermic peak to a lower temperature determines the reduction in the drug's cocrystal's melting point. Explain in further detail how a lower melting point might increase solubility. (Thenge *et al.*, 2019). The melting point is the temperature when the solid and liquid phases are in equilibrium. The process takes place thermodynamically where the transition free energy is equal to zero, this value is determined by the ratio between the fusion enthalpy to the fusion entropy change. There are several factors that affect the melting point of cocrystals such as the arrangement of the molecules in the crystal lattice, the symmetry of the molecules, the degree of conformational freedom of the molecules and the interactions between the molecules. Generally a high melting point is desirable but can adversely affect solubility. Conversely, a low melting point can increase solubility, because the energy required to break bonds between molecules is lower.

Using a Scanning Electron Microscope (SEM), cocrystal and amorphous morphological properties were observed (Wicaksono *et al.*, 2021). Pure Karvedilol, for instance, has plate-shaped crystals, but cocrystals formed with coformers have variable crystal forms. This alteration in crystal habit suggests the creation of cocrystals (Thenge *et al.*, 2019). In addition, FTR is used to determine alteration in the



cocrystal lattice's chemical structure and molecular interactions. Hydrogen bonding is one of the connections that contribute to creating cocrystals, and this interaction can be identified via peaks in the infrared spectrum. In the infrared spectrum, the development of cocrystals can result in peak shifts, a drop in peak intensity, or the appearance of additional peaks (Najih *et al.*, 2018). Figure 2 illustrates the FTIR spectrum of MA (Mefenamic Acid), and the MA-MG (N-methyl d-glucamin) cocrystal exhibits a strong and sharp band at  $1643\text{ cm}^{-1}$  in the FTIR spectrum; in MA, the vibration of the carboxylate band results in the stretching of the functional group (COOH). In the MA-MG cocrystal phase, the stretching band on the carboxylate group moved to a lower wavenumber at  $1569\text{ cm}^{-1}$ . In addition, a significant shift at  $3306\text{ cm}^{-1}$  in the N-H or O-H band experienced stretching. The MA-MG cocrystal exhibited stretching of the N-H or O-H band at around  $3439\text{ cm}^{-1}$ , showing the presence of intermolecular hydrogen bonds between MA and MG that lead to the generation of a new crystalline phase (Erizal *et al.*, 2019).

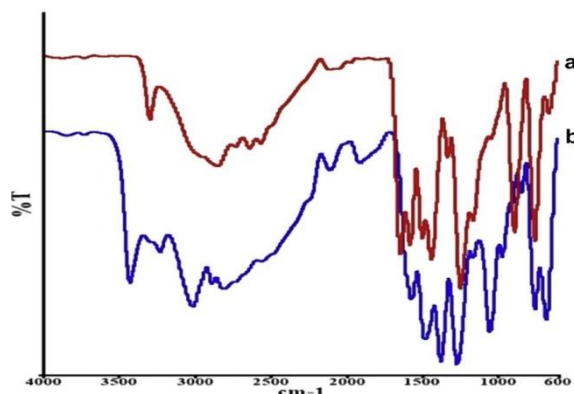


Figure 2. FT-IR Spectrum (a) Mefenamic Acid and (b) MA-MG Multicomponent Crystals (Zaini *et al.*, 2019)

Table 2. Examples of Active Pharmaceutical Ingredients and Coformers in Cocrystal

No.	API	Cofomer	Preparation of Methods	Obejctive	Reference
1	Atorvastatin	Isonicotinamide	Solvent Evaporation	Increases solubility and bioavailability	(Wicaksono <i>et al.</i> , 2017)
2	Ketoconazole	Carboxylic Acid	Slurry	Increases solubility and bioavailability	(Hiendrawan <i>et al.</i> , 2015)
3	Tadalafil	Salicylic Acid	Solvent Evaporation	Increases solubility and bioavailability	(103) (Vinesha <i>et al.</i> , 2013)
4	Carbamazepine	Saccharin	Anti Solvent	Increases solubility and bioavailability	(In CW <i>et al.</i> , 2013)
5	Diklofenak	Proline	Grinding	Increases solubility and bioavailability	(Nugrahani <i>et al.</i> , 2020)

No.	API	Cofomer	Preparation of Methods	Obejctive	Reference
6	Hydrochlortiazide	Sucralose	Wet Grinding	Increases solubility and bioavailability	(Arafa <i>et al.</i> , 2016)
7	Teophyline	Nicotinamide	Hot Melt Extrusion	Increases solubility and bioavailability	(Priyanka <i>et al.</i> , 2020)
8	Karvedilol	Oxalic Acid	Solvent Evaporation	Increases solubility and bioavailability	(Raju <i>et al.</i> , 2020)
9	Lansoprazole	Nicotinamide	Solvent Evaporation	Increases solubility and bioavailability	(Surini <i>et al.</i> , 2020)
10	Domperidone	Succinic Acid	Solvent Evaporation	Increases solubility and bioavailability	(Mounika <i>et al.</i> , 2016)

### Co-amorphous

Coamorphous is the process of stabilizing a drug in an amorphous state with one or more excipients with a low molecular weight or additional medicinal compounds, such as cofomers, resulting in the generation of a homogenous process in an amorphous system. Compared to solid amorph based on polymers and mesoporous silica, this method has some potential because the drug's weight can grow from 20 to 30% to 50% or even higher in some situations. Cofomers with low molecular weight can be other medicinal components or excipients with a low molecular weight, namely amino acids, organic acids, and other small molecules like nicotinamide. Cofomers can physically stabilize an amorphous drug by engaging with it at the molecular level (e.g., by salt formation, hydrogen bonding, and  $\pi$   $\pi$  interactions, or by simple mixing molecules) (Dengale *et al.*, 2014). Coamorphous provide high drug solubility because of the high energy of the amorphous state and because no energy is required for rearrangement of the crystal lattice during dissolution. In addition, the stability of the coamorphous mixture is due to the increased Tg and the homogeneous molecular level dispersion achieved by high-energy mixing. In most studies, the physical stability of such systems is related to intermolecular interactions such as hydrogen bonds,  $\pi$ - $\pi$  interactions, or even ionics. Changes in Gibbs free energy due to the mixing process can be used to predict the possibility of forming a mixture. The decrease in Gibbs free energy during the mixing process indicates that the mixed state will be more stable than the individual states. Predictability of the formation of coamorphous systems has been carried out and identified two reliable indicators for the formation of coamorphous, namely negative  $\Delta H_{mix}$  (mixing enthalpies) and small  $\Delta \log P$  (lipophilicity differences) between components. In addition, it was found that the stability of the coamorphous system increases when the  $\Delta H_{mix}$  is negative and the amorphous

forms of the constituent compounds are stable. It can be concluded that the coamorphous system with a small  $\Delta H_{mix}$  value (large negative) has a lower hygroscopicity.

Evaluation and characterization of coamorphs must be done to confirm the successful preparation of coamorphs. The evaluation was carried out *in vitro*, while the characterization was carried out by PXRD, DSC, SEM, and FTIR. First, PXRD is a good method for measuring the crystallinity of coamorphs during processing and storage. The degree of crystallization was determined based on the obtained X-ray diffraction pattern. The crystallization degree value was determined as the ratio between the sample's sharp diffraction peaks and the reference crystal samples. An indicator of its amorphous properties is the presence of a halo in the PXRD pattern (Shi *et al.*, 2019). For example, PXRD LH (Lurasidone Hydrochloride) crystal pattern shows diffraction peaks at  $2\theta$  namely 11.56, 14.04, 15.24, 15.64, 16.60, 17.24, 19.64, 20.92, and 22.04°. Meanwhile, CYS (L-cysteine hydrochloride) shows a solid peak at 18.36°  $2\theta$ . In the PXRD pattern of the physical mixture, the overlapping diffraction peaks of LH and CYS crystals were seen. Only halos were appeared in the PXRD pattern in coamorphs with LH than LH crystals. However, CYS shows diffraction peaks that are identical to the crystal form. In LH and CYS, the diffraction of LH and CYS has gone totally in the PXRD pattern (Heng *et al.*, 2020). The results of the coamorph XRD characterization show that it is successful in reducing the degree of crystallinity of the pure drug, and this can increase the solubility of the drug. This decrease in crystallinity indicates that the drug is in an amorphous form which results in an irregular crystal lattice arrangement which only requires less energy to be able to break bonds in the crystal lattice so that the drug dissolves more easily.

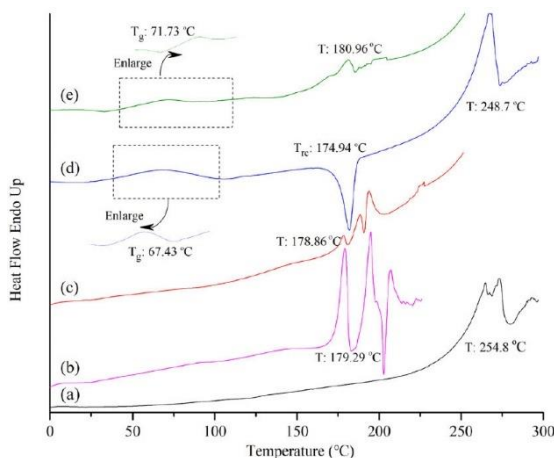


Figure 3. Thermogram of DSC on (a) LH crystal, (b) CYS crystal, (c) Physical mixture of LH and CYS, (d) amorphous LH, and (e) amorphous LH-CYS (Weili *et al.*, 2020)

DSC is a method for analyzing thermal events related to solid phase transitions. Therefore, the phase transition obtained from the DSC thermogram can be used to strengthen the amorphous conjecture. DSC

can also be used to estimate the phase solubility of amorphous materials. The crystal form shows a sharp endothermic peak. Tg coamorph shows a temperature higher than the melting point of the crystal. Therefore, the substantially larger Tg of the amorphous system shows that the drug and cofomers engage in intermolecular interactions like hydrogen bonding. Intermolecular interactions in coamorphous systems generally increase stability and reduce crystallization tendency (Wicaksono *et al.*, 2021). For example, Figure 3 shows the DSC Thermogram of an LH Crystal showing its melting point at 254.8°C, then splitting into two endothermic peaks, primarily due to the thermal degradation of LH. The endothermic melting peak of CYS crystals occurred at 179.3 °C, followed by thermal decomposition. The physical mixture demonstrated a melting peak at 178.9 °C, followed by a degradation peak in CYS crystals. The thermal characteristics of amorphous LH differ significantly from those of its crystalline form. LH in an amorphous state experience a glass transition at 67.4 °C, followed by a change to a crystalline state at 174.9 °C and subsequent deterioration at 248.7 °C. On the LHCYS coamorph thermal curve, a single Tg at 71.7°C was detected. The endothermic peak at 181.0 °C is attributed to the crystallization of CYS solution. The DSC results succeeded in changing from a crystalline to a coamorphous form with a lowering of the melting point and one Tg peak. It can be said that drugs with a low melting point can increase solubility because it only requires a small amount of energy to break bonds in the crystal lattice.

Therefore, SEM was used to explore the morphological properties of crystals and coamorphs (Wicaksono *et al.*, 2021). Figure 4 demonstrates, for instance, that KTZ (Ketoconazole) particles exist to form agglomerates prior to complete formation. Furthermore, KTZ-SUC (succinic acid) particles are significantly larger than other coamorphous systems (Fung, Bērziņš *et al.*, 2018). In the meanwhile, FTIR spectroscopy can be used to uncover potential chemical interactions in coamorphous systems. The FTIR spectrum identifies non-covalent bond interactions, like hydrogen bonds and  $\pi$ - $\pi$  interactions, which shift or broaden the absorption peaks in coamorphous functional groups. Peak enlargement is connected with amorphization resulting from crystal lattice disruption (Wicaksono *et al.*, 2021). Crystals of nifedipine, for example, exhibit characteristic peaks at 1679 and 1728  $\text{cm}^{-1}$  for the carbonyl group and the nitro group, respectively. The crystalline physical combination retains all of the nifedipine's distinctive peaks. In contrast, the characteristic peaks of the carbonyl and amine groups migrated to a higher wavenumber (1703  $\text{cm}^{-1}$ ) in the coamorphous system, showing a molecular interaction between the carbonyl groups of nifedipine and valsartan (Lodagekara *et al.*, 2019).

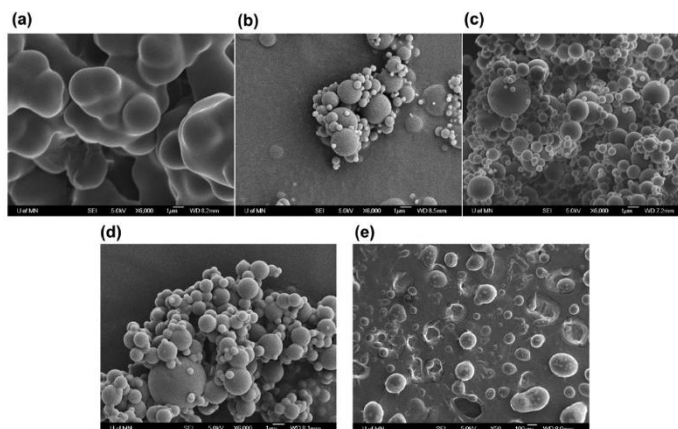


Figure 4. SEM images of (a) amorphous KTZ, (b) coamorphous KTZ-OXA, (c) coamorphous KTZ-TAR, (d) coamorphous KTZ-CIT, (e) coamorphous KTZ-SUC (Fung, Bērziņš, *et al.*, 2018)

Table 3. Examples of Active Pharmaceutical Ingredients and Coformers in Coamorphous

No.	API	Cofomer	Preparation of Methods	Objective	Reference
1	Cimetidine	Naproxen	Ball Milling	Increases solubility and bioavailability	(Alleso <i>et al.</i> , 2009)
2	Repaglinide	Saccharine	Solvent Evaporation	Increases solubility and bioavailability	(Gao <i>et al.</i> , 2013)
3	Lurasidone hydrochloride	Saccharine	Solvent Evaporation	Increases solubility and bioavailability	(Qian <i>et al.</i> , 2015)
4	Naproxen	Proline	Ball Milling	Increases solubility and bioavailability	(Jensen <i>et al.</i> , 2014)
5	Indomethacin	Arginine	Spray Drying	Increases solubility and bioavailability	(Lenz <i>et al.</i> , 2015)
6	Indomethacin	Ranitidine Hydrochloride	Ball Milling	Increases solubility and bioavailability	(Chieng <i>et al.</i> , 2009)
7	Indomethacin	Naproxen	Quench Cooling	Increases solubility and bioavailability	(Lobmann <i>et al.</i> , 2013)
8	Ritonavir	Indomethacin	Solvent Evaporation	Increases solubility and bioavailability	(Dengale <i>et al.</i> , 2014)

## CONCLUSION

Drug solubility is a crucial aspect of pharmacological effects. Drugs with high solubility can give a rapid dissolving rate and high bioavailability, reducing the provided dose. Various strategies, such as solid dispersion, cocrystal formation, and coamorphous formation, have been successful in improving the solubility drugs of BCS class II and IV compared to pure drugs. Evaluation and characterization can be used to confirm the technique employed to improve solubility. In vitro evaluation and characterization with PXRD, DSC, SEM, and FTIR are possible.

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## CONFLICT OF INTEREST

All authors declare no conflict of interest.

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