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Review Article

# SOLID DISPERSION AS A POTENTIAL APPROACH TO IMPROVE DISSOLUTION AND BIOAVAILABILITY OF CURCUMIN FROM TURMERIC (*CURCUMA LONGA* L.)

**RENI AGUSTINA[1,2], DEWI SETYANINGSIH[1*]**

**[1]Faculty of Pharmacy, Sanata Dharma University, Special Region of Yogyakarta-55281, Indonesia. [2]Department of Research and Development, PT. Erlimpex, Semarang, Central Java-50269, Indonesia**
**[*]Corresponding author: Dewi Setyaningsih; [*]Email: dewi@usd.ac.id**

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**ABSTRACT**

This review article attempts to outline techniques and solid dispersion carriers that have been applied to improve curcumin's solubility and bioavailability in turmeric extract. This paper also examines the variables that impact the efficacy of curcumin solid dispersion. Turmeric (*Curcuma longa* L.) contains curcuminoids as bioactive compounds consisting of curcumin, dimethoxy-curcumin, and bis-dimethoxy-curcumin. Curcumin, as the main component, is proven to have several pharmacological effects. However, it has limitations in modern drug development, such as poor stability, solubility, and bioavailability. Many studies have been conducted to overcome these limitations, including the application of solid dispersion. The preparation methods of curcumin solid dispersions are carried out by solvent evaporation, fusion/melting, and co-milling, using various types of carriers. However, the formation of a solid dispersion system only sometimes provides a considerable improvement in solubility, dissolution, and bioavailability. Differences in the selection of preparation methods, carriers, and solvents result in various arrangements of particles in the solid dispersion that may affect the performance of the system. In addition, the type of carrier also has a role in increasing curcumin permeability and bioavailability. Hydrophilic surfactant carriers have inhibitory activity against body transporters, such as P-gp and MRP, that can help to increase curcumin's bioavailability. Natural Deep Eutectic Solvent (NADES) as a novel alternative solvent also has promising opportunities for the development of curcumin solid dispersion. Therefore, selecting appropriate preparation methods, carriers, and solvents should be considered to achieve optimum solubility, dissolution, and bioavailability of curcumin.

**Keywords:** Bioavailability, Carrier, Curcumin, Dissolution, NADES, Solid dispersion


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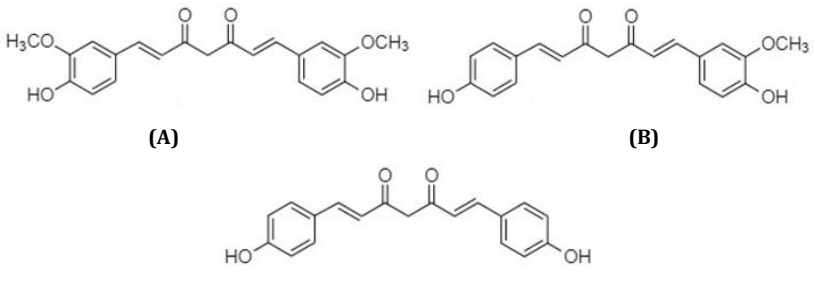
## INTRODUCTION

Oral drug delivery is a preferred route since it is the most accessible and most convenient for patients [1]. However, one of the biggest challenges in the formulation of oral dosage forms has been the problem of low drug solubility and dissolution rate [2, 3]. Solid dispersion technology is one of the most influential and widely used approaches to increasing materials' solubility [4, 5]. This method disperses a lipophilic compound into one or more hydrophilic carriers. The system can form a solid solution (molecular distribution), a eutectic mixture, a glass solution, or a glass suspension as a result of interactions between the lipophilic drug compounds and the carriers via hydrogen bonds, Van der Waals, or electrostatics [4, 6–8]. The solid dispersion approach increases the specific area of the drug and has high energy (amorphous, molecular, or nanocrystal form) to improve the dissolution rate [9]. The mechanisms involved include possible particle size reduction to a nanosize or a molecular level, improved wettability of drug compounds, drug amorphization, and formation of soluble complexes between drug and carrier [8, 10, 11].

Turmeric (*Curcuma longa* L.) ( fig. 1) is a herbaceous plant that has been utilized in traditional medicine, particularly in China, India, and Indonesia [12–14]. Turmeric extract contains curcuminoid consisting of curcumin, bis-demethoxy-curcumin, and demethoxy-curcumin ( fig. 2) [14–16]. Curcumin demonstrates various pharmacological effects, such as antioxidant, anti-inflammation, antiviral, antifungal, antimicrobial, antidiabetic, and anticancer [13, 15].

**(A)** **(B)**

**Fig. 1: (A) Turmeric plant (B) Turmeric rhizome (courtesy of Reni Agustina)**




**(A)** **(B)**

**(C)**

**Fig. 2: Chemical structure of (A) Curcumin, (B) Demethoxy-curcumin, and (C) Bis-demethoxy-curcumin (by Reni Agustina via chemdrawdirect. perkinelmer. cloud)**

Curcumin has low bioavailability problems caused by poor dissolution and is rapidly eliminated from the body [14, 17]. Wahlstrom and Blennow [18] reported that curcumin was excreted in the feces by about 75% at a dose of 1 g/kg in rats after oral treatment. In contrast, plasma levels of curcumin were barely detectable. Other studies conducted by Yang *et al.* [19] demonstrated that curcumin had only 1% oral bioavailability in rats. Since curcumin belongs to Class II Biopharmaceutical Classification System (BCS), its poor oral bioavailability is a factor in its low aqueous solubility [20, 21]. Curcumin has an extremely poor water solubility of only 11 ng/ml [21, 22].

Curcumin was recognized as a "Generally Recognized as Safe" (GRAS) ingredient by The United States Food and Drug Administration (US-FDA) [23, 24], indicating that curcumin is a safe compound to use. In the review of Soleimani *et al.* [25], several studies conducted on rats showed no toxicity up to a dose of 5000 mg/kg for 14 d. The European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) reported that the adequate daily intake (ADI) of curcumin was 0-3 mg/kg [26]. Results of human studies showed that curcumin had shown no toxicity up to doses of 8 grams, with a maximum tolerance of 12 grams per day [27]. However, using large amounts of curcumin also raises problems, such as inconveniences and patient compliance, resulting in therapeutic failures. Therefore, developing a formulation addressing improved curcumin's solubility and oral bioavailability is necessary.

Many studies have been conducted regarding applying solid dispersion techniques for poorly soluble drugs, including curcumin. However, finding a recommended preparation method and carrier to achieve optimum dissolution and bioavailability of curcumin is a challenge. Therefore, optimizing the selected preparation method and carrier is necessary to achieve maximum dissolution and bioavailability. This review describes the method of preparing a solid dispersion of curcumin from various carriers suitable for each preparation method. It explores the factors that affect the performance of the solid dispersion of curcumin, such as solubility, dissolution, and bioavailability. In addition, this article is also expected to be used as a recommendation and consideration in conducting further research related to the solid dispersion of curcumin.

**Methods**

The literature search was done through Google Scholar, PubChem, and Dimensions, using Boolean logic (AND, OR, NOT) with keywords: curcumin, *Curcuma longa* extract, solid dispersion, solubility, dissolution, and oral bioavailability. The literature search for the research study is limited to articles published in the last ten years, from 2012 to 2022. The articles included in this review meet the criteria: 1) reputable international journals included in the Scopus Q1–Q3 index and Web of Science; 2) research articles; 3) display a clear and detailed study design.

The selected articles were then reviewed based on the following parameters: 1) The solid dispersion method; 2) The type of carriers (single or mixture); 3) The particle arrangement of solid dispersion; 4) Increased solubility, dissolution, and bioavailability of curcumin through the formation of solid dispersion.

**RESULTS AND DISCUSSION**

**Preparation method for the solid dispersion of curcumin**

Many methods and types of carriers are available to prepare solid dispersions. Solid dispersion preparation methods can generally be carried out in several ways, e.g., solvent evaporation, melting/fusion, and kneading [9]. Carriers in solid dispersion are categorized into three classes or generations: 1) crystalline carriers of low molecular weights compounds (e.g., urea, sugars, and their derivatives); 2) polymers, both natural and synthetic polymers (e.g., polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG)); 3) surfactants, which can be used alone or in combination with other types of carriers (e.g., Inulin, Poloxamer, Gelucire®, Soluplus®) [4,7,9]. The carrier used must meet the following criteria: 1) soluble or expand in water and dissolve in various other solvents; 2) economical, inert, and non-toxic; 3) stable at high temperature; 4) compatible with the drug used [7].

In the case of curcumin, several preparation methods and carriers can be used to formulate solid dispersions. The results of the studies on the curcumin solid dispersion formulation are presented below and summarized in Table 1.

**Solvent evaporation method**

In this method, the drug and carrier are dissolved in an organic solvent before the solvent is evaporated [28]. The solvents used are methanol, ethanol, acetone, ethyl acetate, methylene chloride, and a mixture of water-organic solvents [10]. This method does not use exposure to high temperatures, so it is suitable for thermolabile materials. Additionally, this method works well for carrier types with high melting points, which the melting method finds challenging to achieve [4, 9].

The polymer carrier often used to manufacture solid dispersions of curcumin is PVP. According to the study of Guo *et al.* [29], the curcumin-PVP solid dispersion with a ratio of 1:6 and 1:8 showed the highest solubility. Incorporating curcumin into PVP could significantly increase the solubility and stability of curcumin. This result follows research conducted by He *et al.* [30], which demonstrated that amorphous solid dispersions with PVP carriers at a ratio of 1:9 were able to produce better solubility, stability, and bioavailability compared to Poloxamer 188 and Hydroxypropyl-β-cyclodextrin (HP-β-CD) carriers. In this case, the solid dispersion of curcumin-PVP increased bioavailability by 11-fold and improved its anti-inflammatory activities by reducing cytokine production (MMP-9, IL-1β, IL-6, VEGF, MIP-2, and TNF-α). Curcumin's solubility and dissolution can be improved due to the presence of two hydroxyl phenolic groups in curcumin, which can form hydrogen bonds with the carbonyl group of pyrrolidone in PVP. The curcumin-PVP solid dispersion can also prevent curcumin from chelating with some metal ions to increase its stability.

Li *et al.* [31] researched the solid dispersion of curcumin using the solvent method with rotary evaporation. This study was carried out with various carriers, including single polymers (PEG, PVP, and Eudragit) and mixtures of polymers (PVP with Eudragit, Eudragit with HPMC). The study showed that the strongest hydrogen bonds formed from amorphous solid dispersion of curcumin in keto form and Eudragit/HPMC (3:1) would be the best compared to other solid dispersion mixtures. The dissolution of curcumin of the solid dispersion formula containing curcumin-Eudragit/HPMC (3:1) was superior compared to curcumin dissolution of pure curcumin (non-formulated), solid dispersion with PEG, PVP, Eudragit, PVP/Eudragit (1:1), PVP/Eudragit (3:1), and Eudragit/HPMC (1:1). The addition of HPMC can improve the dissolution performance of solid dispersion with the Eudragit carrier. A solid dispersion with carriers Eudragit E100 and HPMC at a ratio of 6:1 was reported to achieve the highest solubility compared to other carriers i.e. HPMC and Eudragit E100/HPMC (1:1). The results of this study are according to the study conducted by Fan *et al.* [32], which shows that the use of HPMC can maintain the stability of solid dispersion by avoiding the crystallization of curcumin during storage. In addition, the use of mixed carriers is more stable than single carriers.

HPMC has also been shown to increase curcumin's bioavailability and activities. Shin *et al.* [33] found that curcumin solid dispersion in HPMC carriers at 20% drug load increased oral bioavailability in rat plasma and hepatoprotective activity in assays performed on t-BHP-induced HepG2 cells.

Al-Akayleh *et al.* [22] prepared solid dispersion utilizing Soluplus® to increase curcumin's solubility. The study's findings demonstrated that increasing the concentration of Soluplus® increases curcumin's solubility and dissolution. Soluplus® as a solid dispersion carrier increased the curcumin solubility and dissolution at a high drug load of 50%. The FTIR data suggested that Soluplus® forms intermolecular hydrogen bonding with curcumin. Together with the formation of partial amorphous curcumin in the solid dispersion system of Soluplus-Curcumin as indicated by the DSC dan XRPD pattern, it was suggested that the underlying mechanism of dissolution enhancement was based on the formation of intermolecular hydrogen bonding and the amorphous system.

In their investigation, Al-Taani *et al.* [34] used the freeze-drying method with inulin and Neusilin US2 as carriers. The mixture of

curcumin, inulin, and Neusilin US2 at a ratio of 1:5:1 (14.29% drug load) showed the highest curcumin release profile; nearly 98% of curcumin dissolved after one hour. These data demonstrate a significant improvement over the pure curcumin release, which is only 29% within an hour. Moreover, the solid dispersion technique did not alter the antioxidant activity of curcumin, as confirmed by the DPPH (2,2-Diphenyl-1-picrylhydrazyl) free radical assay.

Song *et al.* [35] also used a freeze-drying method to generate a curcumin solid dispersion utilizing mannitol and D-α-Tocopheryl Polyethylene Glycol 1000 succinate (TPGS) carriers. Solid dispersion containing curcumin, TPGS, and mannitol in the ratio of 1:10:15 released 90% of curcumin within 10 min. Furthermore, pharmacokinetic studies of the selected formulation curcumin-TPGS showed plasma concentrations of Cmax of curcumin 86 times and AUC 65 times higher than pure curcumin.

Another surfactant reported is Gelucire®50/13 in combination with Aerosil, prepared by a melt evaporation method. The study conducted by Teixeira *et al.* [36] showed that solid dispersion with a ratio of 1:1 can increase the solubility of curcumin up to 3600 times and its dissolution up to 7.3-fold. Additionally, a pharmacokinetic study showed that rat blood plasma concentrations were 5.5 times higher than unprocessed curcumin. The highest curcumin dissolution was confirmed by its increased anti-inflammatory activity in the edematous rats model.

In addition to polymers and surfactants, the formulation of curcumin solid dispersion can also be carried out with carriers from the carbohydrate group. Hou *et al.* [37] developed curcumin solid dispersion with a Rebaudioside A (RA) carrier. RA is a steviol glycoside, a diterpene group with the primary structure of steviol and mono-and trisaccharide carbohydrate residues at the $C_{13}$ and $C_{19}$ chain positions. In an aqueous solution, the hydrophilic sugar side chains and hydrophobic diterpene groups of RA can combine to form micelles. However, the drug load of curcumin in RA is relatively low (3.85%), which can provide good stability during storage. A solid dispersion of curcumin/RA can increase curcumin solubility and antioxidant activity. Pharmacokinetic studies have also shown increased oral bioavailability compared to pure curcumin.

**Melting/fusion method**

This method thoroughly mixes the drug and carrier before heating them to a temperature above their melting points [4, 28]. This method is appropriate for thermostable drugs, is easy to carry out, and does not require organic solvents [9]. A carrier with a low melting point is suitable for this method.

Hu *et al.* [21] researched increasing the bioavailability of curcumin with solid dispersion through the melting method. The carrier is a mixture of Cremophor® RH40, Poloxamer 188, and PEG 4000 (3:3:4 w/w). Solid dispersion of curcumin and carrier mixture with a ratio of 1:5 or 1:7 has the highest dissolution profile, which reaches 80% in 60 min compared to solid dispersion with a ratio of 1:3.

Muthu *et al.* [38] also applied the same method to prepare curcumin solid dispersion. In this study, a comparison of solid dispersion characteristics with various carriers, i.e., Poloxamer 407, Poloxamer 188, Gelucire® 50/13, and Mannitol, was carried out in the ratio of 1:3, 1:4, 1:5, 1:6, and 1:7. The study results showed that solid dispersion with the carrier Poloxamer 407 (1:7) could increase the solubility of curcumin up to 14.46-fold. It has the highest solubility enhancement compared to the other carriers.

The use of Soluplus® in the melting method was carried out in the research of Parikh *et al.* [39]. Soluplus® is amorphous and has a low glass transition temperature (Tg). The study results showed that the use of Soluplus® can form a self-nanomicellizing solid dispersion, hydrogen bonding interaction, and amorphization. The ratio of Curcumin to Soluplus® is 1:10, which can increase solubility up to 20.613-fold and bioavailability up to 117-fold. In addition, the formation of self-nanomicellizing solid dispersion also increases the stability of curcumin against exposure to alkaline pH and light.

The application of the melting/fusion method on a commercial scale is carried out using an extruder. This technique is part of the melting method, where the mixture of the melted drug and carrier is then homogenized and expelled through a twin-screw extruder. In this method, exposure to the drug at high temperatures tends to be short, i.e., only for 1-2 min, so it is still possible for thermolabile materials [9]. Fan *et al.* [40] investigated the hot melt extrusion (HME) process for the preparation of curcumin solid dispersion. The carrier used in this study is Eudragit EPO with a 20% drug load (ratio 1:4). The solubility of a solid dispersion of curcumin in Eudragit EPO has increased up to 5-fold compared to pure curcumin. Pharmacokinetic studies showed an increase in Cmax of solid dispersion by 2.6-fold and a bioavailability 1.5-fold higher than pure curcumin.

Critical process parameters that affect the characteristics of solid dispersion using the HME method include 1) temperature; an optimal temperature is needed to be able to change all crystalline forms to amorphous but still maintain drug stability; 2) the speed of the screw extruder, the slow speed of the screw extruder causes the drug contact time to be longer so it has the potential for degradation; 3) cooling method, amorphous solid dispersion can be produced by using the proper cooling method to avoid phase separation and drug nucleation [40, 41].

The development of the melting method was also carried out using a microwave. The use of microwaves helps break down molecules, thereby reducing high temperatures and maintaining the stability of compounds against exposure to high temperatures. Dharmalingam *et al.* [42] studied the solid dispersion formulation of curcumin with an HPMC carrier using the microwave-induced diffusion method. Compared to the ratios 1:1 and 1:2, solid dispersion with a curcumin and HPMC content of 1:4 demonstrated nanoparticle sizes in the 20-40 nm range and more excellent drug release at pH 1.2 and 6.8.

**Co-milling method**

In this method, mechanical energy is used to reduce the size of the particles into fines for a particular time to form amorphization (partial or whole). This technique has several limitations, including the potential for agglomerates to form on particles<30 μm in size and crystallization, reducing the dissolution rate and bioavailability. Crystallization occurs during storage, triggered by moisture absorption from the hydrophilic carrier [43].

The co-milling method used to prepare a solid dispersion of curcumin was carried out by Zhang *et al.* [44] with disodium glycyrrhizin ($NA_2GA$) as a carrier. $Na_2GA$ is the glycyrrhizic acid (GA) salt, a triterpene glycoside extracted from licorice root. It has an amphiphilic characteristic that allows it to form complexes with various hydrophobic molecules. The results of a pharmacokinetic study showed that a solid dispersion containing curcumin and $NA_2GA$ at a ratio of 1:4 increased oral bioavailability in rats by up to 19 times. In addition, a solid dispersion of curcumin-$NA_2GA$ also showed a higher cytotoxicity effect on glioblastoma U-87 MG cells than pure curcumin. In the milling process, the crystal structure of curcumin is destroyed, and the spherical shape of the $NA_2GA$ particles forms irregular polydisperse particles. The longer milling time causes the particle dispersion to be more homogeneous, which increases the surface area of the particles and enhances their solubility [44].

Another study by Zhang *et al.* [45] used a group of polysaccharide macromolecules as carriers, i.e., arabinogalactan (AG). According to the study's findings, a solid dispersion of curcumin and AG at a ratio of 1:10 enhanced curcumin's solubility by 10.5 times when compared to pure curcumin. In addition, there was an increase in *in vitro* permeability studies and stability in accelerated storage. Pharmacokinetic studies have also shown an eight-fold increase in bioavailability in rats compared to pure curcumin.

Lu *et al.* [46] conducted a study using Kolliphor® P407 (Poloxamer 407) and Kolliphor® P188 (Poloxamer 188) as carriers. The study found that the solid dispersion of curcumin with a high drug load (65.5%) could significantly increase the solubility and bioavailability of curcumin. Relative bioavailability increased by 309% for Kolliphor® P407 and 163% for Kolliphor® P188.

The use of the ball milling method was also reported by Mai *et al.* [47], using Hydroxypropyl Cellulose (HPC) and Sodium Dodecyl Sulfate (SDS) as carriers. The results showed that with an increase in

HPC, the solubility of curcumin also increased. Solid dispersions containing 90% HPC can improve the solubility of curcumin up to 1000 times. To achieve the same drug release, the grinding time can be reduced from 60 min to 30 min by adding 25% SDS surfactant to the binary solid dispersion that contains 90% HPC.

**Factors affecting the solubility, dissolution, bioavailability, and stability of solid dispersion**

The formation of a solid dispersion only sometimes has good results regarding solubility, dissolution, bioavailability, and stability. This is due to several factors that have a direct impact on the level of solubility and dissolution of solid dispersion, such as the selection of preparation method, carrier, and solvent ( fig 3). There is no single best method that can be claimed to be the most suitable in improving solid dispersion performance. However, several types of carriers and solvents have specific characteristics that can increase the effectiveness of solid dispersion. These factors are also particular to the features of the Active Pharmaceutical Ingredients (API) used. This implies that the methods, carriers, and solvents appropriate for use with some APIs may not be suitable for use with others. Therefore, exploring and optimizing each of the selected factors is necessary to produce the expected increase in solubility, dissolution, bioavailability, and stability of solid dispersion.

**Selection of preparation method**

Several alternative methods for preparing solid dispersion are described in the previous point. Several studies have shown that different preparation methods will produce solid dispersions with varying levels of solubility and dissolution, even when they use the same carriers.

Gangurde *et al.* [48] researched the solid dispersion of curcumin with Eudragit EPO and HPMC E5 carriers at a ratio of 50:49:1 (50% drug load). The study compared two solvent evaporation methods, i.e., spray drying and rotary evaporation, and also compared two organic solvents, i.e., ethanol and acetone. The solubility of curcumin in a solid dispersion system increased significantly compared to the solubility of pure curcumin, which was 40.29% by spray drying technique and 18.78% by rotary evaporation technique. The dissolution observations found that forming a solid dispersion could increase the dissolution of curcumin within 2 h by 32.00–46.00% with the spray drying technique and by 8.00–18.00% with the rotary evaporation technique. In this investigation, the spray drying technique produced more excellent solubility and dissolution of the curcumin solid dispersion than the rotary evaporation technique. Furthermore, the spray drying technique can achieve higher solubility by using acetone as an organic solvent because curcumin is more soluble in acetone than in ethanol.

Shin *et al.* [33] researched the preparation of curcumin solid dispersion with HPMC carriers using the solvent evaporation method with the rotary evaporation technique. The curcumin-HPMC solid dispersion composition with a ratio of 1:4 showed an increase in the bioavailability of curcumin by 17.5 times, as seen from the AUC value. Dharmalingam *et al.* [42] also studied preparing curcumin solid dispersion using the same carrier with microwave-induced diffusion method. In the same curcumin-HPMC ratio as the previous study, an increase in water solubility of 63 times was obtained. However, Dharmalingam *et al.* did not report the bioavailability data.

In a different instance, Alves *et al.* [49] studied how the solid dispersion method and carrier modification affected the solubility and stability of curcumin. In this study, a comparison was made between the microwave-induced fusion method and co-precipitation with carrier variations of HPMC K4M, Poloxamer 407, and PVP K30 at ratios of 1:2, 1:1, and 2:1. The results showed that solid dispersion of curcumin-Poloxamer 407 (1:2) with the co-precipitation method had the highest solubility compared to pure curcumin and other carriers, up to 755 times. However, in the microwave-induced fusion method, the best solubility of curcumin was achieved by solid dispersion with Poloxamer 407 carrier at a ratio of 1:1, up to 680 times. The study also demonstrated that the chemical stability of curcumin at pH 4.5 and 7.0 increased by forming solid dispersion with the Poloxamer 407 carrier. Poloxamer 407 changes the crystalline form of curcumin to a glass transition, with lower melting energy (ΔH) than pure curcumin. As a result, crystal formation can be decreased, and stability increased in the case of curcumin solid dispersion generated by co-precipitation utilizing the Poloxamer 407 carrier.

Furthermore, another study by Ishtiaq *et al.* [50] investigated the effectiveness of hydrophilic polymers in manufacturing curcumin solid dispersions. This study used polymer carriers such as PEG 6000, HPMC E5, PVP K30, and bovine serum albumin (BSA) polymer-carriers. In addition, a comparison of the preparation method using kneading and solvent evaporation was also carried out. The findings demonstrated that the solubility of curcumin improved with increasing polymer composition to a ratio of 1:4. For dissolution testing, the highest drug release was achieved by solid dispersion curcumin with HPMC carrier (1:4) at 72% in the solvent evaporation method and 57% for solid dispersion with PVP K30 carrier in the kneading process.

**Selection of solvent**

The use of solvents in the preparation of solid dispersion also dramatically affects the dissolution of the APIs. According to the research done by Setyaningsih *et al.* [51], different solvents would result in varying levels of dissolution. In this study, a comparison of the solvents used, i.e., ethanol, ethyl acetate, and a mixture of ethanol and ethyl acetate, was carried out. The study's findings revealed that there was different dissolution of curcumin, as seen from the results of the Dissolution Efficiency (DE) analysis of 38.5% for ethanol, 37.8% for ethyl acetate, and 32.0% for mixed solvents (ethanol and ethyl acetate). This was also demonstrated in a study by Gangurde *et al.* [48], which has also been discussed in the previous point, that the solubility of curcumin in the solid dispersion also varies when employing different solvents.

Inappropriate solvent selection can also affect the stability of the solid dispersion system. Residual solvents can impact the solubility of APIs in polymers, liquid-liquid phase separation, and molecular mobility (via influencing Tg). Increased mobility in solid dispersion systems due to residual solvents will trigger crystallization. Solvents during the solid dispersion manufacturing process will affect the interaction between the API and the polymer, affecting the homogeneity of the final solid dispersion [52–55]. Dohrn *et al.* [54] conducted a study regarding the suitability of ritonavir or naproxen APIs with PVP, polyvinyl-pyrrolidone-co-vinyl acetate (PVPVA), or hydroxypropyl methylcellulose acetate succinate (HPMCAS) polymers using acetone, ethanol, and dichloromethane (DCM) solvents. The suitability of the solid dispersion system is seen from the solubility parameters of the polymer's APIs, the solvent polymer's APIs' influence on the glass transition, and the possibility of forming a liquid-liquid phase separation. The study showed that acetone was inappropriate for solid dispersion with PVPK90 polymer, while ethanol and DCM were unsuitable for solid dispersion with HPMCAS polymer. Acetone can be used in solid dispersion with PVPVA64 polymer, while ethanol and DCM can be used in solid dispersion with PVPK90 and PVPVA64 polymers.

Some of the solvents described above are organic solvents. Several organic solvents are commonly used in solid dispersion technology, especially in solvent evaporation, i.e., solvent class 3 (ethanol, acetic acid) and solvent class 2 (chloroform, dichloromethane, methanol). The use of organic solvents still risks toxicity, and residual evaporation from these solvents causes air pollution and global warming [56]. In addition, it is not easy to find a solvent that can solubilize both hydrophobic drugs and hydrophilic carriers simultaneously [8, 10].

Currently, there is an alternative solvent that is relatively safer and can minimize the risk of using organic solvents, namely NADES. It is an alternative solvent derived from plant metabolites, a mixture of two or three components in a solid form that interacts through hydrogen bonds (donor and acceptor), which at a specific molar ratio forms a eutectic mixture (liquid). The melting point of this mixture is lower than that of each component. NADES is classified as a "green solvent" because it is relatively safe and environmentally friendly. The parameters are safe because they come from natural materials, are easy to prepare, and require low energy while being environmentally friendly because they are biodegradable and can be recycled [56]. NADES can be classified into 1) ionic liquid NADES,

which is composed of a mixture of acids and bases; 2) neutral NADES, which is composed of only sugar or sugar and polyalcohol; 3) neutral NADES with acid, which is composed of sugar or polyalcohol and organic acids; 4) neutral NADES with base, which is composed of sugar or polyalcohol and an organic base; 5) amino acids based on NADES, which are composed of amino acids and organic acids or sugars [57].

NADES has the potential to be an alternative solvent to improve the extraction-ability, solubility, stability, and bioavailability of bioactive components, including curcumin [58, 59]. Jelinski *et al.* [58] conducted a study on using NADES to increase curcumin's solubility, stability, and delivery. In this study, choline chloride and glycerol were used as components of NADES. The system can maintain the stability of curcumin from potential degradation due to light exposure. In addition, there was also a significant increase in the bioavailability of curcumin in small intestinal fluids. This study is corroborated by Huber *et al.* [60], who used a mixture of NADES choline chloride and lactic acid at a ratio of 1:1 as a solvent adjuvant for a mix of ethanol and triacetin to extract curcumin from *Curcuma longa*. The study showed that the solubility of curcumin is increased two-fold and that the extraction power can achieve a yield of ~90%. This proves the efficiency of the extraction process by using less solvent to achieve the same extraction yield.

Recently, NADES began to be developed in the formulation of solid dispersion. NADES inhibits the crystallization process in the solid dispersion system because it can maintain the supersaturation of the drug in its amorphous form without precipitation and increase drug absorption [61]. However, using NADES in solid dispersion is still relatively new, and few studies have been published. In a study by Liu *et al.* [61], solid dispersion RA-XII utilized NADES to improve antitumor activity in rats. The natural cyclopeptide RA-XII was obtained from *Rubia yunnanensis*. Betaine and mandelic acid are the solvents employed in NADES in a 1:1 molar ratio, whereas PVP K30 was selected as the carrier in the solid dispersion of RA-XII. According to the study, the solubility of RA-XII increased up to 17.51 times in 20% NADES solution. In the Franz cell permeability test, there was also an increase of up to 10.35 times. In addition, the oral bioavailability of RA-XII in NADES solid dispersion system (mixture of PVP K30, RA-XII, and NADES at a ratio of 3:1:1) increased by approximately 7.56 times compared with that of pure RA-XII.

**Selection of carrier**

The carriers in solid dispersion vary widely, and each has its characteristics. Therefore, the carrier type factor is also one of the considerations in preparing solid dispersion because it will determine the features of the solid dispersion. Different carriers will affect dissolution mechanisms. Li *et al.* [31] compared the dissolution mechanism of solid dispersion curcumin with various polymers, including PEG 6000, PVP, Eudragit® EPO, Eudragit® EPO/HPMC E50, and PVP/Eudragit® EPO. The results of the dissolution analysis demonstrated that the dissolution mechanism pattern of solid dispersion with a Eudragit carrier was through an erosion process, while solid dispersion with a PVP carrier was through a diffusion process.

In addition, different carrier molecular structures also result in particular interactions with curcumin. Research by Li *et al.* [31] also showed that different carriers would resulted in different interactions with different drugs. This is evidenced by the Raman imaging plus spectroscopy characterization test to observe the molecular and interfacial interactions between curcumin and polymers. Hydrogen bonds are formed between the OH group (PEG, HPMC) and the C=O group (Curcumin) and between the C=O group (PVP, Eudragit) and the OH group (Curcumin). The interaction between Curcumin-PEG produces a keto form, while the interaction between Curcumin-PVP produces an enol form. For Eudragit carriers, interactions with curcumin can produce keto and enol forms. In general, curcumin can form keto-enol tautomers (tautomerism) depending on the pH of the environment because it has two main functional groups, i.e., ketones and phenols. In an acidic environment, curcumin is in the keto form, while in an alkaline environment, it is in the enolate form [15, 16, 62–64]. Therefore, the study results showed that the formation of curcumin tautomers is influenced by pH and the interaction between curcumin and the carrier. This will also impact the dissolution mechanism and stability of the solid dispersion.

These results were confirmed by Fan *et al.* [65], who reported that the keto form of curcumin has stronger interactions with polymers than the enol form. This study compared the binary carriers Eudragit EPO (EuD)-PVP K30 and Eudragit EPO (EuD)-HPMC E50. The Raman Imaging Spectroscopy characterization results showed that solid dispersion Cur/EuD-PVP had lower predicted molecular interactions than solid dispersion Cur/EuD-HPMC. This is due to the bond between curcumin and Eudragit EPO, which causes more curcumin in the enol form.

Additionally, Fan *et al.* [65] showed how specific carrier use impacts drug release. The cumulative release of solid dispersion Cur/EuD-PVP was lower (approximately 15%) than that of solid dispersion Cur/EuD-HPMC (about 48%) in the study. In solid dispersion Cur/EuD-PVP, the drug controlled the wetting rate. Carrier-controlled dissolution occurs when the carrier has a role in the wetting rate of the drug, where at higher percentages of the carrier, the amount of dissolved drug is also higher. In contrast, drug-controlled dissolution occurs when drug release is determined by the characteristics of the drug, such as the size and shape of the drug particles.

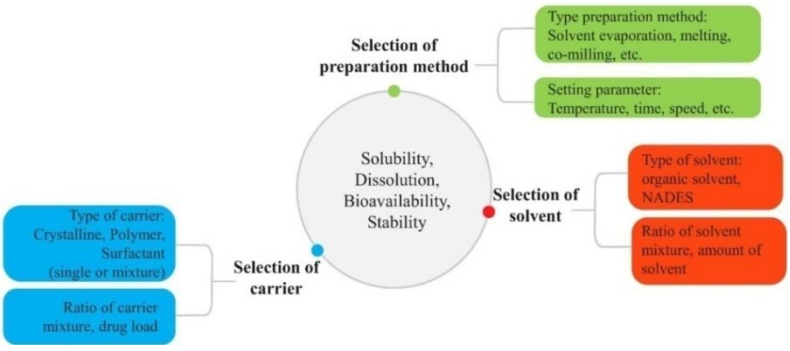



**Fig. 3: Factors affecting the solubility, dissolution, bioavailability, and stability of solid dispersion (courtesy of reni agustina)**

**The role of solid dispersion carriers on the permeability and bioavailability of curcumin**

The process of drug transfer from the absorption site to the blood circulation is assisted by several transporters in the body, such as P-glycoprotein (P-gp or ABCB1) and MRP2 (ABCB2). They are the drug efflux pumps from the ATP-binding cassette (ABC) transporter class, which efficiently remove cytotoxic drugs from the intercellular environment through an ATP-dependent mechanism [66, 67]. P-gp is found in some normal tissues and in large amounts in epithelial cells of the liver, kidney, pancreas, small intestine, colon, and adrenal glands [68–70]. The inhibitory activity on P-gp function and expression will facilitate the transport of the drug from the absorption site into the blood circulation to achieve the target site of action.

The permeability experiment showed that curcumin absorption was inhibited by the presence of P-gp efflux activity [35, 71, 72]. Zhang *et al.* [73] reported that curcumin interacts directly with the drug-binding site of the P-gp transporter. Therefore, other compounds that have inhibitory activity on P-gp function are needed to increase curcumin's absorption.

In the case of solid dispersion, the increase in dissolution is not always followed by an increase in bioavailability. The efflux pump mechanism may influence this affected. Some of the carriers in solid dispersion can inhibit the function of P-gp, thereby improving the permeability and bioavailability of curcumin. An *in vitro* study conducted by Prakash [74] showed that surfactants with optimum hydrophilic-lipophilic balance (HLB) and critical micellar concentration (CMC) values had high efflux pump inhibitory activity. CMC and HLB values can also predict lipophilicity and hydrogen bonding capacity between the APIs and carriers.

Hanke *et al.* [75] investigated the interaction of several non-ionic surfactants on the efflux transporters P-gp and MRP2. The results showed that Cremophor® EL, Vitamin E TPGS 1000, and high concentrations of polysorbate 80 could inhibit the function of both transporters. Pluronic® PE 10300 and sucrose ester L-1695 specifically inhibited P-gp, whereas Chremophor® RH40 inhibited MRP2 activity.

Song *et al.* [35] discovered that a solid dispersion containing curcumin, TPGS, and Mannitol in a ratio of 1:10:15 successfully improved intestinal permeability and inhibited P-gp function to enhance the anti-proliferative effect of curcumin on breast cancer cells MDA-MB-231. This effect is aided by the TPGS carrier, which can hinder P-gp function, enhancing drug absorption and cellular accumulation [76].

Using a carrier mixture with an optimum ratio will result in increased dissolution and bioavailability. Research by Hu *et al.* [21] showed that solid dispersion of curcumin with mixed carriers Cremophor® RH40, Poloxamer 188, and PEG 4000 at a ratio of 3:3:4 could achieve the best dissolution and bioavailability of curcumin. Removing one of the carrier components will affect the percentage of drug dissolution. Cremophor® RH 40 also functions as a permeation enhancer, which can increase drug absorption by increasing paracellular and transcellular transport by modifying cell membranes. In addition, Poloxamer 188 is also an absorption enhancer by slowing peristaltic motion in the gastrointestinal tract, which causes the retention time of curcumin to be longer, resulting in increased absorption and bioavailability of curcumin.

Another surfactant that has been shown to have a role in increasing the bioavailability of curcumin is Solutol® HS15. According to Seo *et al.* [77], a solid dispersion of curcumin and Solutol® HS15 at a 1:10 ratio has an excellent release profile, with 90% of curcumin dissolved within one hour. In addition, the results of pharmacokinetic studies also showed an increase in AUC of up to 5 times. Solutol® HS15 carriers can increase intestinal permeability by opening tight junctions and inhibiting P-gp or CYP450 to improve intracellular concentration and residence duration [77, 78].

Huang *et al.* [79] found that forming a solid dispersion with a chitosan oligosaccharide (COS) carrier increased curcumin solubility and permeability. In pharmacokinetic studies, the $AUC_{0-\infty}$ increased by 1.55-3.01 times compared to pure curcumin. In addition, the permeability test using Caco-2 cells also showed similar results, with an increase in the permeability coefficient of the three solid dispersion formulas at weight ratios of 1:1, 1:2, and 1:4 by 1.71-4.44 times compared to pure curcumin. This is influenced by the function of COS, which can open tight junctions in Caco-2 cells. This activity can increase the permeability of curcumin in the intestine so that curcumin bioavailability also increases.

**Table 1: Summary of curcumin solid dispersion studies**

| Carrier | Method | Drug-carrier ratio | Result | References |
|---|---|---|---|---|
| Cremophor® RH40, Poloxamer 188, PEG 4000 (3:3:4) | Melting/Fusion | 1:5 | Increased dissolution: curcumin was released up to 80% within 60 min in pH 2.0 and 6.8 compared to pure curcumin of about 5%<br>Improved bioavailability: Cmax 4-fold, AUC 2.5-fold | [21] |
| Soluplus® | Solvent evaporation | 1:1 | Curcumin was released almost 100% within two h, compared to pure curcumin, about 30% | [22] |
| PVP | Solvent evaporation | 1:9 | Improved bioavailability: AUC0-t 11.4-fold, Cmax 28.6-fold | [30] |
| HPMC | Solvent evaporation | 1:4 | Improved bioavailability up to 17-fold (AUC) | [33] |
| Inulin/Neusilin US2 | Solvent evaporation | 1:5:1 | Increased dissolution up to 96% compared to pure curcumin by about 2% | [34] |
| TPGS/ Mannitol | Solvent evaporation | 1:10:15 | Increased dissolution: about 90% of curcumin was released within 10 min<br>Improved bioavailability: Cmax 86-fold, AUC 65-fold<br>Increased solubility across a pH range of 1.2-7.4 and decreased the pH-dependent solubility pattern | [35] |
| Gelucire® 50/13 | Solvent evaporation | 2:3 | Increased solubility in aqueous HCl 3600-fold<br>Increased dissolution rate in aqueous HCl 7.3-fold | [36] |
| RA | Solvent evaporation | 1:25 | Improved bioavailability 19.06-fold | [37] |
| Poloxamer 407 | Melting/Fusion | 1:7 | Increased solubility up to 14.16-fold | [80] |
| Soluplus® | Melting/Fusion | 1:10 | Increased aqueous solubility by over 20.000-fold<br>Improved bioavailability: Cmax 26.54-fold, T½ 4-fold (longer), AUC 36.79-fold | [39] |
| Eudragit® E PO | Melting/Fusion | 1:4 | Improved bioavailability: AUC 1.5-fold, Cmax 2.6-fold | [40] |
| HPMC | Melting/Fusion | 1:4 | Increased solubility: 63-fold in water and 50-fold in phosphate buffer pH 6,8<br>Increased dissolution: Drug release achieved 80% in simulated gastric medium (pH 1.2) within 120 min and in simulated intestinal medium (pH 6.8) within 240 min | [42] |
| $Na_2GA$ | Co-milling | 1:4 | Improved bioavailability: Cmax 20-fold, AUC 19-fold | [44] |
| AG | Co-milling | 1:10 | Increased solubility up to 10.5-fold<br>Improved bioavailability 8-fold | [45] |
| Kolliphor® P407 | Co-milling | 2:1 | Improved relative bioavailability 309% | [46] |
| Kolliphor® P188 | | | Improved relative bioavailability 163% | |
| HPC, SDS | Co-milling | 1:9 | Increased solubility up to 1000-fold<br>The addition of SDS can reduce the grinding time from 60 to 30 min | [47] |
| Eudragit® EPO/HPMC E5 | Solvent evaporation-spray drying | 49:50:1 | Increased solubility by 40.29% compared to pure curcumin by about 0.02% in acidic pH 1.2 | [48] |
| Eudragit® EPO/HPMC E5 | Solvent evaporation-rotary evaporation | 49:50:1 | Increased solubility by 18.78% compared to pure curcumin of about 0.02% in acidic pH 1.2 | [48] |
| Poloxamer 407 | Solvent evaporation | 1:2 | Increased solubility 755 times compared to pure curcumin | [49] |
| Eudragit® EPO/PVP | Solvent evaporation | 1:4 | Improved cumulative release 15% | [65] |
| Eudragit® EPO/HPMC | | | Improved cumulative release 48% | |

**The effect of particle arrangement on dissolution and bioavailability of solid dispersion**

Differences in the selection of preparation methods, carriers, and solvents will result in a different arrangement of particles in the solid dispersion system. This will affect the performance of the solid dispersion. In general, there are several types of solid dispersion arrangements: that is 1) solid solution, which is the incorporation of crystalline drug molecules into the carrier crystal lattice; 2) eutectic mixture, which is a mixture of two compounds that can melt in liquid form, and at a particular composition both components will crystallize when there is a decrease in temperature; 3) glass solution, which occurs when the drug is dispersed in an amorphous carrier at the molecular level; 4) glass suspension, which is a suspension containing drug in an amorphous phase dispersed in an amorphous carrier [8, 81, 82].

The formation of solid dispersion can be seen in the characterization of Powder X-ray Diffraction (PXRD), Fourier Transformed Infrared Spectroscopy (FTIR), and Differential Scanning Calorimetry (DSC). PXRD is used to identify the characteristics of the crystal form in solid dispersion. The shape of the sharp peak indicates the presence of a crystalline component in the sample. FTIR is a technique for detecting intermolecular interactions and drug-carrier compatibility. FTIR identifies the physical and chemical interactions between the drug and the carrier. Hydrogen bonding between the drug and carrier is critical for describing the physical form and stability of the drug in solid dispersion [10]. DSC provides information related to the melting point and glass transition temperature, which indicate phase changes such as melting and crystallization processes. The reduction of the solid dispersion peak in the DSC thermogram suggests that the drug is amorphous. The single amorphous phase was characterized by the appearance of a single Tg between the two components, while two Tg indicated the presence of an immiscible phase. The single crystalline phase is indicated by a broad peak between the API peak and the crystal carrier [10, 83].

Table 2 describes the particle arrangement of various solid dispersion curcumin studies. These data show that differences in method, carriers, and drug load can impact the particle arrangement in a solid dispersion system, which can be crystalline or amorphous, either wholly or partially. This affects dissolution and bioavailability.

The interaction between curcumin and carrier is required to improve the solid dispersion system's drug load, solubility, and stability. In solid dispersion, drugs and polymer-carriers can form weak bonds or non-covalent interactions, such as hydrogen, ionic, Van der Waals, dipole-dipole, and acid-base interactions [84]. Curcumin has two hydroxyl phenolic groups that allow hydrogen bonds and form complexes, with carriers having a carbonyl group as a proton acceptor. This bond can prevent aggregation between drug molecules that trigger recrystallization. The molecular interaction between drug and polymer is critical for drug release and the stability of the solid dispersion system. This interaction can keep the drug in an amorphous form during dissolution and storage. As a result, hydrogen bonding is essential in increasing the amorphous form's stability [84].

**Table 2: Dissolution and bioavailability enhancement from particle arrangement in solid dispersion**

| Carrier | Method | Solid dispersion arrangement | Drug load (%) | Increased dissolution* | Dose | Increased bioavailability* | Ref. |
|---|---|---|---|---|---|---|---|
| Cremophor® RH40, Poloxamer 188, PEG 4000 | Melting/Fusion | Glass suspension | 16.67 | 4-fold | 400 mg/kg | Cmax: 4-fold<br>AUC: 2.5-fold | [21] |
| PVP | Solvent evaporation | Homogeneously dispersed in the carriers in the amorphous states | 10 | 33-fold | 100 mg/kg | $AUC_{0-t}$: 11.4-fold<br>Cmax: 28.6-fold | [30] |
| HPMC | Solvent evaporation | Molecularly dispersed in amorphous carriers | 20 | N/A | 250 mg/kg | 17-fold | [33] |
| TPGS/Mannitol | Solvent evaporation | Reducing the crystalline state of curcumin and carriers | 3.8 | 4-fold | 30 mg/kg | Cmax: 86-fold<br>AUC: 65-fold | [35] |
| Gelucire® 50/13 | Solvent evaporation | Molecularly dissolved in the melted carriers | 40 | 7.3-fold | 500 mg/kg | 5.5-fold | [36] |
| RA | Solvent evaporation | Noncrystalline of curcumin in the crystalline state of RA | 3.85 | N/A | 150 mg/kg | 19.06-fold | [37] |
| Soluplus® | Melting/Fusion | Amorphous curcumin in self-nanomicelling solid dispersion | 9.1 | 100-fold | 150 mg/kg | 117-fold | [39] |
| Eudragit® E PO | Melting/Fusion | Amorphous curcumin-EPO | 20 | 2.5-fold | 100 mg/kg | Cmax: 2.6-fold<br>AUC: 1.5-fold | [40] |
| $Na_2GA$ | Co-milling | Amorphous curcumin-GA | 20 | 74-fold | 150 mg/kg | Cmax: 20-fold<br>AUC: 19-fold | [44] |
| AG | Co-milling | Partially amorphous curcumin in amorphous AG | 9.1 | N/A | 150 mg/kg | 8-fold | [45] |

Description: *control: Physical mixture or unformulated curcumin

**Limitations in the application of the solid dispersion technique**

Although many studies have proven that the solid dispersion technique can effectively increase drug solubility and dissolution, this technique has limitations, including those related to physicochemical stability. Solid dispersions can be either amorphous particles or crystals, depending on the drug's and carrier's characteristics. The crystal state has excellent stability but low solubility and bioavailability. On the other hand, amorphous solid dispersions can increase the dissolution rate of poor-soluble drugs due to their high free energy. However, they are thermodynamically unstable and have the potential to form crystals, which can affect drug solubility and bioavailability [85, 86]. The stability of amorphous forms depends on the temperature and humidity of the environment because the amorphous form can easily absorb water and change to a more stable crystalline form [3, 87].

Uncontrolled crystallization can occur in drugs and carriers during manufacturing, dissolution, or storage, leading to decreased dissolution rates [88–90]. This phenomenon can occur in conditions of high drug loads. A high drug load can increase the effectiveness of drug use because of its smaller dose, but it also has the potential for crystallization [91].

In addition, uncontrolled crystallization can also occur with the use of carriers with high hydrophilicity. Van Drooge *et al.* [92] reported that using saccharide carriers (such as sucrose and trehalose), which have fast-dissolving characteristics at high drug loads, causes a decrease in the dissolution rate. This is due to a high supersaturation in the dissolution medium, which causes uncontrolled crystallization. This phenomenon causes the formation of large crystalline particles, thereby decreasing the dissolution rate. Furthermore, it was also found that the drug and carrier in the solid dispersion system did not interact, which also affected the crystallization behavior [92, 93].

Undesirable crystallization can be minimalized for crystalline solid dispersion because it is already stable. However, the drug crystals

must be maintained at the nanoscale to obtain a large surface area to increase the dissolution rate [94]. For amorphous solid dispersion, uncontrolled crystallization is effectively prevented by surfactant incorporated into the solid dispersion system [95]. Surfactants can reduce crystallinity by increasing the solubility of the drug due to the increased contact area between the drug and the solvent. In addition, surfactants can also improve the wettability of the drug and prevent precipitation by adsorbing the surface of the drug particle and forming micelles to encapsulate the drug [2, 3]. When a solid dispersion is prepared without surfactants, it forms a layer rich in drug substances on its surface, hindering drug release. As a result, the presence of surfactant can maintain supersaturation conditions and prevent unwanted crystallization [90, 96].

**Future perspective**

Research related to curcumin solid dispersion can still be developed. The hydrophilic surfactant-type carriers in the manufacture of a solid dispersion of curcumin can be further explored because they can increase the permeability of curcumin through inhibitory activity against body transporters. Surfactants can also maintain supersaturation conditions and prevent uncontrolled crystallization.

Furthermore, NADES, a new alternative solvent, has several advantages, such as improving the effectiveness of extraction and increasing drug absorption and stability by preventing the crystallization in solid dispersion systems. Using NADES in solid dispersion can be an opportunity for further research.

## CONCLUSION

Curcumin solid dispersion can be prepared by several alternative methods proven to increase solubility, dissolution, and bioavailability. Using carriers that can form strong hydrogen bonds with curcumin and form a molecular dispersion system can significantly increase the compound's solubility and dissolution. Interaction between curcumin and carrier is essential for developing particle arrangement in the solid dispersion system. In addition, the formation of curcumin tautomers is influenced by pH and the interaction between curcumin and the carrier. This will also impact the dissolution mechanism and stability of the solid dispersion.

However, not all increases in dissolution are accompanied by increases in bioavailability. This is related to the characteristics of curcumin, which can interact directly with human transporters such as P-gp and MRP2, so carriers that have inhibitory functions on these transporters are needed to assist in increasing the permeability of curcumin, such as the use of hydrophilic surfactants.

In addition, amorphous solid dispersion also has limitations related to uncontrolled crystallization phenomena during the manufacturing process, dissolution, and storage. The crystal growth in the solid dispersion system can decrease the dissolution rate of the drug. As a result, selecting appropriate preparation methods, carriers, and solvents should be considered to achieve optimum solubility, dissolution, and bioavailability of the drug, including curcumin.

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## AUTHORS CONTRIBUTIONS

The contributions from each author are equal.

## CONFLICT OF INTERESTS

The authors state that this paper has no actual, potential, or perceived conflicts of interest.

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