Review Article

# A Review on Solubility Enhancement Methods for Poorly Water-soluble Drugs

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## Abstract

One of the most important parameters in pharmacy is drug solubility. Solubility affects the efficacy of a drug. Drug solubility has an important role in determining the concentration of a drug to achieve the necessary pharmacological response, as all drugs absorbed by the body must be in the form of a solution. Drug solubility is quite a common issue and affects the bioavailability of a drug in the body. Drugs with low solubility are poorly absorbed, resulting in poor bioavailability. Many methods have been developed for increasing the solubility of a drug. In this review, we will describe possible efforts for improving the solubility of a drug, e.g., reducing particle size, surfactants, the use of nanosuspension technology, solid dispersion, salt formation, pH adjustment, hydrotropy, cocrystal, amorphous compound formation, and inclusion complexes. The main objective of this review was to focus on efforts that can increase the solubility of a drug to obtain good drug efficacy.

**Keywords:** *Poor soluble drug, solubility, solubility enhancement method*

**Key Messages:** *Solubility in water is a basic property of active pharmaceutical ingredients (API) that must be considered. API with good solubility can be absorbed into the body properly, having a therapeutic effect. Not all API have good solubility, requiring solubility enhancement method treatment.*

## Introduction

Solubility has a significant effect on drug efficacy. The solubility of a drug in water is a basic property that must be considered. The pharmacokinetic profile is important, especially for drugs with low solubility.[1] Drugs taken orally will have a lower number of active drug compounds in the systemic circulation if the drug has low solubility, which also affects the bioavailability of the drug. About 30–40% of the drugs that have been developed to date are included in the category of drugs that are very difficult to dissolve in water (<0.1 mg/mL according to the United States Pharmacopeia [USP] definition).[2]

Drugs that have low solubility are biopharmaceutics classification system (BCS) class II drugs, e.g., phenytoin, danazol, nifedipine, and BCS class IV drugs, e.g., hydrochlorothiazide, furosemide, and taxol.[3,4] There are several methods for modifying the physical properties of drugs to address specific drug formulation problems such as solubility. These methods include particle size reduction, nanosuspension, surfactants, salt formation, pH adjustment, hydrotropy, solid dispersion, cocrystal, amorphous compound formation, and inclusion complexes.[5,6] In the present review, we will explain the methods for increasing drug solubility, especially drugs with low solubility, to provide a reference for developing drug formulations and for addressing issues regarding drug bioavailability.

## Particle Size Reduction

Drug solubility can be increased by reducing particle size, as drug solubility is intrinsically related to drug particle size. If the particle size decreases, the surface area of the drug with a volume ratio increases.[7] A greater surface area allows greater interaction with the solvent, which increases solubility. There are two principal approaches to reducing particle size: micronization and nanonization.[8] Drug particles in the submicron range, referred to as nanoparticles, are <1 μm in size. Particle size that can increase solubility is in the nano range. Nanoparticle technology is an approach for improving the solubility of drugs that are less soluble in water, namely BCS class II and class IV drugs. The reduction in particle size affects the kinetic solubility of

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a compound. This is because a reduction in size to <1 mm increases the pressure of the solvation, which increases solubility and also disrupts the interaction of the solute, which facilitates solubilization.[9] Reduction in particle size to <1 µm significantly increases the saturation solubility, as explained by the Ostwald-Freundlich equation (equation 1):[10]

$$\log \frac{C_S}{C_\infty} = \frac{2\sigma V}{2.303RT\rho r} \quad (1)$$

where $C_s$ is saturated solubility, $C_\infty$ is solid solubility consisting of large particles, σ is the surface tension of solids, $V$ is the molar particle volume, $R$ is the gas constant, $T$ is the absolute temperature, ρ is the density of a solid body, and $r$ is particle radius.

Nanoparticles are based on two processes: top–down and bottom–up. One top–down nanoparticle synthesis method involves mechanical milling. There are two kinds of mechanical milling: ball milling and mechanochemical synthesis. With ball milling, metal powder is placed in a container with heavy balls. The powder is then processed with high mechanical energy from the balls, which rotate at high speed. There are several types of particle size reduction by milling: low-energy tumbling mill, vibrating ball mill, planetary ball mill, high-energy ball mill, and attrition ball mill.[11] Mechanochemical synthesis is based on the repetition of welding and deformation from the reactant mixture. The starting material is stoichiometrically mixed and processed by grinding. When grinding, chemical reactions occur on the surface layer between the substrate and the reagent so that the chemical reaction uses only low temperatures. The nanoparticles produced will be dispersed in the salt matrix and subsequently washed using a good solvent and dried at 105°C for 12 h.[12] Bottom–up nanoparticle synthesis is based on the combination of small particles (atoms, molecules, or compound molecules). One method is the sol–gel method, which involves four stages: hydrolysis, condensation, particle size growth, and particle agglomeration. The most common solvent used is alcohol. A homogeneous solution of alkoxide is prepared for the formation of nanoparticles with the addition of a catalyst to start the reaction at a controlled pH.[11] Hydrosol developed by Sandoz is an example of nanoparticles made with precipitation techniques. The drug is dissolved in a solvent, and this solution is then added to the nonsolvent solution. Then, super-high saturation occurs, followed by fast nucleation, and many small nuclei are formed. After the solvent is removed, the dispersion can be filtered and lyophilized to obtain nanocrystals, which have high solubility.[13] Pharmaceutical products from nanoparticles are already widely available on the market; Table 1 presents some examples of products.[5] The advantages of nanoparticle methods are that they are safe methods with little risk of increasing the solubility of drug substances without changing the chemical properties of the drug, good reproducibility with large-scale production, and good compatibility with different drug solubility profiles. Conversely, the drawback is that the particle size reduction has a relatively small effect on the solubility of the drug substances, as it does not change the solid-state nature of the particles, requires high energy input, and is not suitable for cytotoxic drugs with a low therapeutic index.[8,14]

## Nanosuspension

A nanosuspension is a submicron colloidal dispersion system with pure drug particle sizes of 10–1000 nm and that is stabilized by surfactants.[15] A system can be classified as a nanosuspension if its formulation has a volume diameter of 90% undersize ($D_{90}$) of <2.5 µm and a volume median diameter ($D_{50}$) of <1 µm.[16] Nanosuspensions are different from nanoparticles, where nanoparticles are commonly found in the form of a polymeric colloidal carrier system. In contrast, in nanosuspensions, the solid drug is maintained in the required crystalline state with reduced particle size and is stabilized by surfactants.[17] In principle, efforts to increase nanosuspension solubility are the same as that for nanoparticles, which uses the principle of the Ostwald–Freundlich equation. This approach can be used to improve the solubility of poorly water-soluble drugs, have poor permeability, or both. Therefore, when drug solubility increased, its dissolution rate also increases, and the maximum plasma concentration of the drug is reached faster.[18]

In general, the rate of drug solubility correlates with the drug particle size. When the drug particle becomes smaller, the surface area–volume ratio increases and the surface area of the drug particle increases, which allows better interaction with the solvent and increases the dissolution rate of the drug.[19] There are many conventional techniques for reducing particle size, one of which is micronization. Drug micronization is done by milling using rotor-stator colloid mills or jet mills; micronization is not suitable for drugs with high doses because it does not change the solubility of drug saturation, and the increase in oral bioavailability with micronization is insufficient, as micronized products tend to agglomerate.[20] Therefore, the addition of a stabilizer known as a surfactant in nanosuspensions stabilizes the system. Several theories have been suggested to explain how surfactant can stabilize nanosuspension, i.e., (i) the Derjaguin–Landau–Verwey–

**Table 1: Examples of marketed nanoparticle products**

| Drug | Indication | Trade name | Innovator company |
|---|---|---|---|
| Fenofibrate | Hypercholesterolemia | Tricor® | Abbott Laboratories |
| Aprepitant | Anti-emetic | Emend® | Merck & Co. |
| Tizanidine hydrochloride | Muscle relaxant | Zanaflex capsule | Acorda Therapeutics |
| Megestrol | Anti-anorexic | Megace ES® | Par Pharmaceutical |

Overbeek (DLVO) theory, (ii) the steric stabilization theory, and (iii) the lowering of interfacial tension.[16]

Nanosuspensions can be prepared using two methods: bottom–up and top–down. The bottom–up method, or the precipitation method, is a nanosuspension preparation in which drug particles are dissolved in an organic solvent and then precipitated by adding a different solvent in which the drug particles are not soluble. The top–down methods are more preferred approaches for preparing nanosuspensions and cause reduction in the drug particle size to the nanometer range.[21] The bottom–up method can be executed in different forms: (i) solvent–antisolvent method, (ii) spray drying, (iii) supercritical fluid process, and (iv) emulsion solvent. In contrast, the top–down method involves breaking down large particles to smaller particles by: (i) media milling, (ii) high-pressure homogenization, and (iii) microfluidization.[22] In the top–down method, the particle size reduction results in crystal growth and agglomeration. Therefore, to prevent this phenomenon, stabilizers are used to stabilize the system. Stabilizers can be polymers, including polyvinylpyrrolidone (PVP K30), hydroxypropyl methylcellulose (HPMC), and surfactants, including ionic sodium lauryl sulfate (SLS) and nonionic polysorbate (Tween 80).[23] On the other hand, bottom–up methods such as solvent–antisolvent precipitation are relatively cost-effective, simple, and can be easily scaled-up for industrial nanosuspension production. In this method, height supersaturation can be achieved by increasing the concentration gradient. In addition, interference with the drug crystals to nanoparticles increases the saturation solubility. The higher saturation solubility of small particles with higher concentrations diffusing into the area around larger particles of lower drug concentration is called Ostwald ripening. So, it is necessary to avoid different concentration gradients and saturation solubility, for the particle size to be homogeneous and to avoid large differences between its sizes, which can inhibit Ostwald ripening.[22]

Itraconazole is one example of a drug whose solubility as well as dissolution and oral bioavailability can be improved by nanosuspension. A recent study showed that the *in vitro* dissolution profile of the optimized Itraconazole nanosuspension formulation, prepared by media milling using poloxamer 407 as a stabilizer and glycerol as a wetting agent, showed higher drug release compared to the pure drug and marketed formulation.[24] On the other hand, furosemide nanosuspension, prepared by antisolvent precipitation, had a significantly higher dissolution rate than raw furosemide powder. Nanosuspensions also show improved *in vivo* pharmacokinetic parameters such as $C_{max}$ (maximum concentration) and $AUC_{(0-t)}$ [increase in the area under the curve (AUC) from drug administration to the final quantifiable sample] as well as oral bioavailability compared to pure drugs.[25] Other nanosuspension drug products that have been researched are danazol, budesonide, tarazepide, spironolactone, naproxen, paclitaxel, and omeprazole. The advantages of using nanosuspension are the increased solubility, increased dissolution rate due to the larger surface area, the absence of Ostwald ripening due to homogeneous particle size, and narrow range of particle size obtained, which eliminates the concentration gradient factor. The disadvantage of this method is that the particle size reduction is followed by the transformation of polymorphs into other crystalline polymorphs, which may not have a therapeutic effect.[26,27]

## Surfactant

Surfactants are molecules whose structure has hydrophilic (polar) and hydrophobic (nonpolar) groups. Surfactants are amphiphilic molecules that contain both hydrophilic and hydrophobic portions in one structure. Surfactants have activity in the surface areas or two-phase interfaces and can improve the solubility of difficult-to-dissolve compounds. Most surfactants consist of hydrocarbon segments that are connected to the polar group. Polar groups consist of heteroatoms such as N, P, S, or O groups; there are also functional groups such as sulfates, amides, amines, alcohol, thiol, esters, acids, sulfonates, and phosphates.[28]

Surfactants are grouped into several types as described subsequently.[29]

### Anionic

This surfactant dissociates in water in the form of amphiphilic anions and cations. This type of surfactant is most often used, e.g., SLS.

### Cationic

This type of surfactant can dissociate in water to form amphiphilic cations and anions. Cationic surfactants are usually used as disinfectants and preservatives because these surfactants have a bactericidal effect and include quaternary ammonium compounds. Examples of these surfactants are cetrimide and benzalkonium chloride.

### Non-ionic

This type of surfactant is not dissociated in water, as its hydrophilic group has a nondissociable type, such as amide, ester, ether, alcohol, and phenol. Most nonionic surfactants are made hydrophilic in the presence of polyethylene glycol chains. Such surfactants also have a less irritating effect than anionic or cationic surfactants. Examples of nonionic surfactants are poloxamer and polysorbate.

### Amphoteric

This type of surfactant can be nonionic, anionic, or cationic depending on the pH conditions of the water. An example of this surfactant is alkyl betaine.

The presence of surfactants can reduce surface tension but increase the solubility of drugs in organic solvents. When a surfactant is dissolved in a liquid, the surfactant molecules will be attracted to the surface area and its presence can change the surface tension. Surfactants in a position in the surface area will experience adsorption in low concentrations, which significantly changes the free energy.[30] After occupying the

entire interface or surface area, the surfactant will undergo aggregation to form micelles. Micelles are a nanosystem of surfactants with hydrophobic portions that comprise the nucleus, and hydrophilic parts that form the outer shell of the system. This structure has a diameter that is usually 20–80 nm.[31] This structure dissolves drugs that are difficult to dissolve in water. The formation of micelles traps drugs in micelles, known as micellar solubilization.[32] Along with the solubilization of micelles from less soluble drugs, the self-assembling system also has various advantages such as cellular internalization, subcellular localization, ligand-mediated targeting, high drug dissolving capacity, protecting drugs from enzymatic hydrolysis, and increasing oral bioavailability and drug loading capacity.[31] Micelles also have several disadvantages: tolerability of synthetic surfactants can be bad in long-term chronic administration, uncontrolled precipitation can occur with dilution with aqueous media or physiological liquids, deposits may vary in size and can be amorphous or crystalline, and dissolving other materials together such as preservatives can cause changes in drug effectiveness and stability.[5] Examples of antidiabetic drugs that are difficult to dissolve in water using the micellar solubility system are glimepiride, gliclazide, repaglinide, pioglitazone, glipizide, and rosiglitazone.[33] Table 2 presents some other examples and the surfactants used to increase the solubility of a drug.

## Salt Formation

Salt formation is a neutralization reaction between acids and bases. Salt formation is used for drugs that can be ionized so that solubility increases. Salt is formed by the transfer of protons from acids to bases. Ionic bonds from salts can form and are stable if the difference in the p$K_a$ (ionization constant) between acids and bases ($\Delta pK_a$) is >3.[37] Through this reaction, salt formation requires a counter ion, stoichiometric molar ratio, and a suitable solvent. The selection of the proper salt structure of active drug ingredients must be efficient and rational, as the salt selection can influence the pre-formulation evaluation of drugs. Many criteria must be considered in the formation of salt compounds: the route of drug administration, biological factors, p$K_a$, biopharmaceutical factors, ionic factors, and organic solvents selected.[38] The determination of the p$K_a$ value in the active substance of the drug becomes an important parameter for determining the acidity and base levels of the compound, which can then be used to determine the efficiency of a salt compound by determining the relative position of equilibrium. The level of solubility of an active drug agent may increase depending on the ionization process being lower than the p$K_a$ of a weak base and pH higher than the p$K_a$ of a weak acid. The principle of solubility can be changed to determine the appropriate salt of a medicinal compound.[7] The drug administration route can affect the pharmacodynamics of the drug salt compound. In general, complex metal ions such as $Cu^{2+}$, $Fe^{2+}$, $Zn^{2+}$, and $Mg^{2+}$ are added in salt formation to increase drug absorption, but these metal ions can form a chelate that causes major adverse effects. Salt compounds can also work by increasing the bioavailability of drugs inside the body or reducing the adverse effects of pure drug compounds. Drug administration routes can also affect salt compounds through their function, where different administration routes need a different salt compound formation. Organic solvents generally increase the rate of compound crystallization, which results in changes in drug dissolution and solubility.[38] If the intrinsic solubility of the original compound is 1–10 mg/mL, salt formation could provide an advantage by increasing the solubility of the compound. Compounds with intrinsic solubility of >10 mg/mL are rarely converted to their saline form unless their physical properties do not support the current drug formulation.[39]

Salt formation is an alternative technology for increasing drug solubility. It is very effective and is considered a low-cost method for enhancing the drug's solid-state properties.[40] To produce salt, active pharmaceutical ingredients are protonated or must protonate from an ionizable functional group structure.[41] One example of a drug that can be modified with salt formation is isoniazid (INH). A study reported the screening of INH with a series of acids received by the drug (maleic acid, oxalate, and methane sulfonic acid). These salts were prepared to yield a new solid form with higher solubility and thermal stability than the original INH, which can help reduce INH degradation. The crystalline structure showed that the salt exhibited a layered structure mainly stabilized by the C-H ... OH and N-H ... O bonds, and also with π ... π stacking interactions, except with mesylated isoniazid salts. Calculations from four dissolution media (acidic media and pure water) showed that mesylate and maleic salts had considerably increased solubility compared to INH by about three times.[42]

Another example is the BCS class IV drug acetazolamide (ACL), which in this case is modified into two solid forms: ACL-PPZ-$H_2O$ salt and ACL-THP cocrystal. *In vitro* permeation comparison tests and powder dissolution using various methods show that the formation of cocrystals and salts increases its permeability and solubility. ACL-PPZ-$H_2O$ shows increased ACL solubility compared to ACL-THP cocrystals, while the cocrystalline form has better permeability. The formation in salt can also be linked to the simultaneous increase in ACL

**Table 2: Examples of surfactant methods**

| Drug | Surfactant | Type of surfactant | Source |
|---|---|---|---|
| Sodium diclofenac | • *n*-Heptadecyl-3-methyl pyridinium bromide | Cationic | [34] |
| Ketoprofen | • *n*-Hexadecyl-3-methyl pyridinium bromide | | |
| Diphenhydramine hydrochloride | Sodium deoxycholate transglycosylate | Anionic nonionic | [35] |
| Tolfenamic acid | Didodecyldimethylammonium bromide | Cationic | [36] |

permeability and solubility; this is important information for understanding the structure of drug-related activities.[43]

The advantages of salt formation include increased drug solubility; increased stability against thermolysis, photolysis, or hydrolysis; good organoleptic properties; and increased tabletability.[44] The salt formation method for active drug compounds also has some weaknesses. The salt that forms can transform into its nonionic state from hydrolysis reaction or disproportionation. Disproportionation can change the physicochemical aspect of active drug compounds. The result is decreased solubility of drugs that have been modified by salt formation.[45]

## pH Adjustment

Nearly all drugs can be ionized. pH modification is considered an alternative means for increasing the solubility of ionized drugs. Changes in pH significantly affect the saturation solubility of ionized drugs with dissociation. Water-soluble drugs that can be ionized with protonated (basic) or deprotonated (acid) molecules that can dissolve in water with changes in pH. After the most suitable pH adjustment, a stable ionized compound that is soluble in water is obtained. The pH-dependent solubility means that weak acid drugs dissolve more easily at pH > p$K_a$ and weakly basic drugs dissolve at pH < p$K_a$.[46] This pH-dependent solubility is explored to treat insoluble drugs. Overcoming the solubility approach with buffer capacity and pH tolerability are important aspects to consider.[6] Excipients are also used to adjust pH in tablet and capsule dosage forms. pH-adjusted formulations are easy to produce and develop quickly. The pH adjustment is based on the solubility of the drug in the body according to the organ system in which the drug is absorbed or based on a different, deliberately maintained pH.[47]

Solubility, dissolution, and p$K_a$ due to pH changes will affect the rate of drug dissolution. The complete drug dissolution profile from the dosage form should always refer to the pH of the dissolution medium, which affects the ability of tablets to disintegrate to form drug particles until the drug is completely dissolved. Excipients and manufacturing methods greatly affect the dissolution of drugs from pH-modified solid dosage forms.[6]

Many insoluble drugs on the market are designed with pH modification. For example, ciprofloxacin is a weakly basic drug and is practically insoluble in water under neutral pH conditions.[5] The compound exhibits high pH-dependent solubility under acidic conditions. The poorly water-soluble repaglinide is formulated with meglumine as a pH modifier. Most intravenous formulations contain lactic acid as a pH modifier to increase solubility.[48] Aspirin is another example whose solubility is pH dependent. The currently available soluble effervescent tablets contain aspirin; effervescence in favorable pH conditions is needed for the solubility of aspirin in the presence of sodium bicarbonate and citric acid in the formulation.[5]

The advantage of using pH modification to increase solubility is a low risk of failure of formulation, and it does not require complicated formulation equipment. The disadvantages of this method are tolerability and toxicity due to the use of nonphysiological pH. Drugs in formulations with pH adjustment can become difficult to dissolve and settle when diluting in aqueous media or can cause embolism if given intravenously. The drug is also less stable under water conditions, as hydrolysis or other degradation can increase.[49]

## Hydrotropy

Hydrotropy is one of many methods for enhancing the solubility of poorly soluble solutes by the addition of a large amount of a second solute (hydrotrope). Mechanistically, hydrotropic drug solubilization is different from co-solvency, where the hydrotrope concentrates the drug molecules, but co-solvency improves drug solubility by minimizing the polarity gap between the drug and the solvent.[50] The solubility of various poorly water-soluble drugs can be increased by using hydrotropic solubilization, e.g., ketoprofen, aceclofenac, salicylic acid, cefixime, tinidazole, frusemide, and amoxicillin. Hydrotropic solubilization is a promising strategy for increasing the solubility of drugs that do not dissolve properly, as it does not require chemical modification of the drug, or both the use of organic solvents and the preparation of an emulsion system.[51]

Hydrotropes used in hydrotropic solubilization are compounds that solubilize hydrophobic compounds in aqueous solutions, where their structure consists of hydrophilic and hydrophobic groups. Thus, the efficiency of a hydrotrope depends on the balance between its hydrophilic and hydrophobic portions.[52] Ideally, a good hydrotrope must have high water solubility while maintaining hydrophobicity. Nicotinamide, for example, is the most widely studied hydrotrope, where the rate of increase in solubility is usually <500-fold. This is insufficient for increasing the solubility of less soluble hydrophobic drugs. Nevertheless, a water-insoluble drug model, i.e., paclitaxel, has shown that nicotinamide derivatives are excellent hydrotropes. That study found that *N*,*N*-diethylnicotinamide (DENA) is the best hydrotrope, where 3.5 M DENA increased the solubility of paclitaxel 5-fold.[53] Hydrotropes and surfactants both contain hydrophilic and hydrophobic parts, but the hydrophilic portion in hydrotropes is very small when compared to that of surfactant. The greater the hydrophobic portion of the hydrotrope, the better the hydrotropic efficiency, while the charge function in the hydrophilic portion is less significant. Hydrotropic agents can be cationic, anionic, or neutral; inorganic or organic; and solid or liquid. Table 3 lists some examples of hydrotropic agents.[54]

Hydrotropes are organic amphiphilic molecules with similar structural features to surfactants. Hydrotropes can aggregate in aqueous solution if the level is above the minimum hydrotropic concentration (MHC). Interestingly, hydrotropes can dissolve molecules that are slightly soluble or insoluble in water.[55] Hydrotropy is recommended as an excellent

**Table 3: Examples of hydrotropic agents**

| Type | Example |
|---|---|
| Aromatic anionics | Sodium salicylate, sodium benzoate, *N*,*N*-dimethyl benzamide, sodium benzene sulfonate, sodium benzene disulfonate, sodium *para*-toluene sulfonate, sodium cumene sulfonate, DENA, sodium cinnamate, sodium 3-hydroxy-2-naphthoate, nicotinamide |
| Aromatic cationic | Caffeine, *para*-aminobenzoic acid hydrochloride, procaine hydrochloride |
| Aliphatics and linear compounds | Urea, *N*,*N*-dimethyl urea, sodium alkanoate |

technique compared to other solubilization methods, such as co-solvency, salting in, miscibility, and micellar solubilization, as the characteristics of solvent are not pH-dependent, does not require emulsification, and has high selectivity. This only requires mixing the drug with the hydrotrope in water.[56]

The advantage of hydrotropy is that it is considered to be better than other methods such as micellar solubility, miscibility, co-solvency, and salting-in, because the nature of the solvent is not pH-dependent, does not require chemical modification, has high selectivity, does not require emulsification; the drug is mixed only with hydrotrope compounds in water solvents, and organic solvents are not used. The disadvantage of the hydrotrope method is that it can gather alone in solution and lose the ability to increase the solubility of the drug in water.[56,57]

## Solid Dispersion

Solid dispersion is one of the most widely used methods for improving the poor solubility of drugs in water. Solid dispersion is carried out by dispersing one or more drugs into an inert polymer or solid matrix.[58] Polymers in the function of solid dispersion are for maintaining the stability of the drug during storage, as it inhibits crystallization and maintains the saturation level in the dissolution media because it prevents crystallization from the solvent.[59]

The selection of polymers is an important step in making solid dispersions. Polymers can be selected based on several considerations, namely evaluation of the polymer's physicochemical properties such as glass transition temperature ($T_g$), hygroscopicity, as well as the solid capacity of solutions and solubilization.[60] Besides, the polymer used must be inert and nontoxic, drug compatible, and thermostable with a low melting point if the solid dispersion is made by the fusion method.[61]

The commonly used methods for making solid dispersions are melting and solvent evaporation.

### Melting method

The melting method is used because it is cheaper, easier, and does not require solvents. In this method, the drug and polymers must be compatible and can be intermingled.[59] The melting method is performed by melting the polymer first and then mixing it with the drug. This step is followed by a cooling process, which can be performed using ice cubes.[62] Table 4 shows examples of drugs that are modified by the solid suspended method.

**Table 4: Examples of the melting method**

| Drug | Polymer | Source |
|---|---|---|
| Troglitazone | PVP K30 | [63] |
| Curcumin | HPMC 6 | [64] |
| | HPMC 6000 | |
| | Polyethylene oxide (PEO) | |

### Solvent evaporation

Solvent evaporation consists of several steps: the first is dissolving the drug and polymers in volatile solvents. Evaporation is carried out under low-temperature conditions to minimize the risk of thermal decomposition of the drug and polymers.[65] Table 5 shows examples of drugs that are modified by solvent evaporation.

The solid dispersion method has several advantages, including increasing the bioavailability of drugs with poor solubility conditions by reducing particle size, increasing wetting ability, and reducing agglomeration. It allows conformation of molecular dispersion between insoluble drugs and hydrophilic carriers, thereby increasing drug dissolution and supersaturation when the system comes into contact with water. The disadvantages of solid dispersion include the difficulty of manufacturing, problems in improving manufacturing methods and scaling up, physical instability of the dispersion mainly due to humidity and temperature, the requirement of a large amount of polymer to facilitate an increase in dissolution rate, easy change into crystals and implications for decreasing solubility as they increase in time, and some solid dispersions are difficult to handle due to adhesiveness.[70]

## Cocrystal

Cocrystal technology emerged as a new approach because of its success in overcoming the problem of insoluble drugs.[71] Cocrystals are solid materials formed from two or more different components with a stoichiometric ratio at room temperature that are bound by noncovalent bonds, usually hydrogen bonds.[72] In terms of pharmaceutical science, "co-crystalline" was previously known as "molecular complex" or "intermolecular complex."[73] Cocrystallization produces new crystalline shapes that are often superior to each separate component. Cocrystals have increased drug solubility because of the lower lattice energy and higher affinity of the solvent.[71]

Cocrystals consist of API with a neutral guest compound termed cocrystallization formers (coformers) in the same crystal lattice. When salt is formed, the components in the crystal lattice are in an ionized state, the cocrystal component is

**Table 5: Examples of the solvent evaporation method**

| Drug | Polymer | Solvent | Source |
|---|---|---|---|
| Atorvastatin | Poloxamer 188 (P188) | Methanol | [66] |
| Pyrimethamine | Polyethylene glycol (PEG) 6000<br>P188<br>PVP K25 | Ethanol | [67] |
| Febuxostat | d-α-Tocopherol polyethylene glycol succinate (TPGS)<br>P188 | Ethanol | [68] |
| Valsartan | Soluplus®<br>PVP K25 | Acetone<br>Ethanol | [69] |

in a neutral state, and it interacts through nonionic interactions. The US Food and Drug Administration (FDA) has published guidelines for coformers. Coformers must be pharmaceutically acceptable and declared safe for human consumption into nontoxic substances without adverse effects. They can be selected from collections that appear on the Generally Recognized as Safe (GRAS) list. Examples of coformers that are included in the GRAS list are organic acids (e.g., citric acid, glutamic acid, gallic acid, ascorbic acid, histidine, glycine, nicotinamide, valine, tyrosine, urea, and saccharine) and nutraceuticals (e.g., p-coumaric acid, quercetin, pterostilbene, and saccharine). The selection of coformer types is such that there is a high possibility of hydrogen bonds being formed with API, which affects the success of cocrystal formation.[74]

The cocrystal design approach can be considered $\Delta pK_a$. In principle, salt and cocrystals differ based on the absence of proton transfer in cocrystals. $\Delta pK_a$ is a reliable indicator for distinguishing salts and cocrystals; it can be defined as a cocrystal when the $\Delta pK_a$ between the API and coformers is <0. Salt formation requires a difference in $pK_a$ of at least two units (between the acid and base). When the $\Delta pK_a$ is between 0 and 2, they can be either a salt or cocrystal in an ionized mixture.[37]

In current work, cocrystal formation is described for a familiar approach in modifying a drug's physicochemical properties. Cocrystals in pharmaceuticals can increase the dissolution rate, solubility, hygroscopicity, chemical stability, physical stability, bioavailability, and compressibility of API.[75] Several techniques can be used for synthesizing cocrystals. The longest method is solution evaporation. Classic techniques for making cocrystals include solution evaporation, solid-state co-grinding (without or with solvent), co-melting, co-sublimation, and co-heating. The likelihood of cocrystal formation being mediated by solvents is greater if saturated conditions are maintained[39]. The more sophisticated techniques for making cocrystals include cocrystallization by extrusion; sonococrystallization; cocrystallization from suspensions; electrochemically induced cocrystallization; cocrystallization from supercritical fluids; cocrystallization by laser irradiation; freeze-drying cocrystallization; spray drying cocrystallization; and cocrystallization from polymers, ionization, and polymer gels.[76,77]

A drug included in the BCS class IV category is furosemide, which has low solubility and permeability.[78] High-dose furosemide at a dose of 80 mg is an accepted approach for increasing furosemide solubility and can be classified into two categories: the formulation process with added excipients, and by changing physicochemical properties such as cocrystallization.[79] Another study showed that fluoxetine hydrochloride formed cocrystals with succinic acid, showing approximately doubled water solubility. Cocrystal formation has been explored to increase the solubility of other drugs such as itraconazole, carbamazepine, paracetamol, gabapentin, piroxicam, and caffeine. Products on the market in the form of cocrystals include carbamazepine (Tegretol®), fluoxetine hydrochloride (Prozac®), and itraconazole (Sporanox®).[71]

Cocrystals have several advantages compared to salt formation. Cocrystallization has the potential to be applied to API under acidic, basic, and nonionized molecules.[80] In pharmaceutical production, there is interest in cocrystals because, first, the interaction of nonpermanent modification between the API and its coformers is guaranteed to be complete separation before reaching the site of action, so that the pharmacological activity of the drug molecule remains the same, and the storage age of the API can be extended by using cocrystals in pharmaceutical products. The disadvantage of cocrystallization is that cocrystal formation is not guaranteed. That is, the potential for API cocrystallization cannot be predicted.[81]

## Amorphous

In general, API can be amorphous or crystalline. Efforts to convert crystalline compounds into amorphous form are one means of improving solubility. Generally, products in amorphous form can be classified as solid dispersions or pure substances, where drug molecules can be dispersed in a carrier. Due to their thermodynamic properties, amorphous particles exhibit water solubility and high dissolution rates, resulting in better oral absorption. Zafirlukast (Accolate®) is an example of an amorphous commercial drug product.[82]

Although the benefits including increasing drug solubility and relatively small manufacturing failure conditions, the disadvantage of using amorphous active substances is the possibility of recrystallization during manufacturing, storage, and use. One common means of overcoming these limitations is to form amorphous particles into solid dispersion forms, namely by reducing the mobility of amorphous particle molecules through intermolecular interactions to reduce

recrystallization. However, the disadvantages of the solid dispersion method include toxicity and high hygroscopic properties of polymers used in large quantities, and the mixing of drugs with polymers. Thus, another method that can be used is the co-amorphous technique, which combines two relevant active substances to produce a very stable co-amorphous mixture while still improving its dissolution properties.[83] Amino acids are excipients that have been used extensively in co-amorphous techniques because they are nontoxic and inexpensive.[84]

## Inclusion Complexes

The inclusion complexation of drug molecules as the guest and cyclodextrins (CDs) as the host is a likely technique for improving the physicochemical properties of the drug, such as bioavailability, solubility, and dissolution rate. CDs are cyclic oligosaccharides that have a hydrophilic surface and hydrophobic inner cavity, which makes them solubilizing and complexing agents.[85] CDs are formed by α-1,4-linked glucose units and take the form of γ-CD, β-CD, and α-CD based on the number of d-glucopyranose units (6, 7, and 8, respectively). β-CD is most used in pharmaceuticals because it has the cavity size for drug molecule encapsulation. β-CD has relatively poor water solubility and a relatively economic price. The β-CD derivatives include glucosyl-β-CD, sulfobutylether-β-CD, methyl-β-CD, and hydroxypropyl-β-CD.[86]

CDs are used for controlled delivery of inorganic, organic, and biological pharmaceutical molecules due to their ability to form inclusion complexes with various guest molecules by stabilizing the polar portion via their polar surface and encapsulating the nonpolar portion in their hydrophobic cavity.[87] During complex formation, noncovalent bonds can be broken or are formed in aqueous solution; the drug molecules bound in the CD inclusion complex experience dynamic equilibrium with free drug molecules. One or more CD molecules can complex with one drug molecule, and one or more drug molecules can form a complex with one CD molecule.[88]

Table 6 shows examples of drugs with improved solubility following modification by inclusion complexes.

**Table 6: Examples of inclusion complex methods**

| Drug | Complex | Method | Source |
|---|---|---|---|
| Triptonide | 2,6-Dimethyl-β-CD | Saturated aqueous solution | [89] |
| Nystatin | β-CD | Spray drying<br>Freeze-drying | [90] |
| Dronedarone | 2-Hydroxypropyl-β-CD<br>β-CD | Kneading<br>Freeze-drying<br>Co-lyophilization | [91] |

**Table 7: Drugs from each method with variables related to solubility**

| Formulation strategy | Technique | Drug | BCS class | Comment | Source |
|---|---|---|---|---|---|
| Particle size reduction | Wet-milling | Tranilast | II | Hydroxypropyl cellulose and sodium dodecyl sulfate (SDS) stable redispersible systems experience increased solubility under acidic conditions | [95] |
| Nanosuspension | Antisolvent precipitation | Carvedilol | II | Nanosuspension-stabilized SDS showed increased $C_{max}$ and AUC, and decreased $T_{max}$ (time to maximum), compared to coarse suspension. | [96] |
| Solid dispersion | Solvent evaporation | Pioglitazone | II | Solid dispersion was prepared by amorphous polymers (PVP K30 and PVP K90) and semi-crystalline polymers (PEG 6000 and F68). Amorphous polymers become more stable because they are more effective in inhibiting the rate of crystallization | [97] |
| Cocrystal | Anti-solvent crystallization | Indomethacin | II | Saccharin-indomethacin cocrystal has a significantly higher solubility profile compared to pure indomethacin | [98] |
| Inclusion complex | Kneading | Ibuprofen | II | Tablets and pellets formulated by drug–CD complexes show a high level of solubility and dissolution when compared with pure ibuprofen | [99] |
| Surfactant | Thin film hydration | Amphotericin | II | Self-assembled, lecithin-based mixed polymeric micelle containing Pluronic, Kolliphor RH40, tocopherol PEG succinate, and PEG 2000. | [100] |
| Amorphous nanoparticle | Controlled precipitation | Aprepitant | II | Soluplus and SDS are used as secondary stabilizers that have a particle size of <100 nm. Solubility increased dramatically | [101] |
| Salt formation | Solvent evaporation | Piroxicam | II | Piroxicam-ethanolamine salt can improve the solubility of piroxicam | [102] |
| Hydrotropic | Solubilization | Carbamazepine | II | Urea and nicotinamide are used to see the effect of hydrotropic agents on solubility of carbamazepine | [50] |

Inclusion complexes with guest–host molecules can show better biological or chemical properties compared to host molecules only.[92] The advantages of the inclusion complex include the conversion of liquid drugs into amorphous powders or microcrystalline form; modification of the time profile and/or drug delivery site; improving the drug's shelf life and increasing its physicochemical stability; eliminating or reducing unpleasant smell and taste; improving bioavailability, dissolution, and aqueous solubility; and preventing drug–excipient or drug–drug interactions.[93] The main disadvantage of using CDs is the need to overcome the stability of complex drugs, which are relatively difficult to ionize. The nonionized form has four times the stability of the ionized form. Another disadvantage of difficult drug formulations with CDs is determining the size of the dose and adjusting the amount of CD with proper drug administration; the least amount of CD must be used so that the bioavailability of the drug does not decrease due to the particles being too large. The solubility of the drug must also be determined in the final formulation to be able to determine the appropriate amount of CD to be used.[94]

Based on the description of the solubility improvement method above, Table 7 presents an example of a drug from each method by briefly reviewing the commentary variables related to the solubility of the drug.

## Conclusion

There are many kinds of solubility enhancement methods for modifying the solubility of poorly water-soluble drugs. In this review, we describe 10 such methods, each with their own pros and cons. Here, we have only explained the basic information for the methods, and deeper analysis is required for each method; therefore, a more specific review is needed to provide better understanding of the methods included in the present review.

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### Conflicts of interest

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