Journal for Educators, Teachers and Trainers
The PROFESIOLab electronic, peer-reviewed, open-access Magazine

ISSN 1989-9572

DOI:10.47750/jett.2023.14.05.068

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Journal for Educators, Teachers and Trainers, Vol.14(5)

https://jett.labosfor.com/

Date of Reception: 12 Aug 2023

Date of Revision: 05 Sep 2023

Date of Publication : 16 Oct 2023

1 R.Vijay Kumar, 2 Ch Laxmi Manasa, 3 R Shiva Kumar (2023). INVESTIGATION OF CO-SOLVENTS' IMPACT ON THE SOLUBILITY OF FUROSEMIDE. *Journal for Educators, Teachers and Trainers*,Vol.14(5)741-754

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ISSN1989 –9572

https://jett.labosfor.com/

INVESTIGATION OF CO-SOLVENTS' IMPACT ON THE SOLUBILITY OF FUROSEMIDE

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ABSTRACT

Background: The low water solubility of furosemide, a popular loop diuretic, restricts its bioavailability and therapeutic effectiveness. Improving furosemide's solubility is essential to increasing its efficacy and absorption. Co-solvents can improve the solubility of medications like furosemide that are not very soluble in water when combined with water.

The purpose of this study is to determine the best co-solvent combinations that increase the solubility and dissolution rate of furosemide by examining the effects of various co-solvents on its solubility.

Methods: Using ethanol, propylene glycol, and polyethylene glycol in varying proportions with water, the solubility of furosemide was assessed in a variety of co-solvent systems. By creating saturated solutions and utilising UV spectrophotometry to measure the concentration of furosemide, the solubility was ascertained. The solubility in pure water was compared to the results.

Results: The investigation showed that the addition of co-solvents greatly enhanced the solubility of furosemide, with ethanol having the most noticeable effect. It was discovered that the solubility was directly correlated with the mixture's co-solvent content. The combination of ethanol and polyethylene glycol (PEG) produced the greatest solubility improvement among the co-solvents that were evaluated.

In conclusion, co-solvents greatly increase furosemide's solubility, which may increase its bioavailability. This study sheds light on how furosemide should be formulated for improved therapeutic results, particularly when taken orally. It is necessary to do more research on the pharmacokinetic and clinical implications of these results.

Keywords: ethanol, polyethylene glycol, bioavailability, co-solvents, solubility augmentation, weakly water-soluble medications, and furosemide.

1. INTRODUCTION

Drug effectiveness is significantly impacted by solubility. One fundamental characteristic that needs to be taken into account is a drug's solubility in water. For medications with poor solubility in particular, the pharmacokinetic profile is crucial.[1] Orally administered drugs with low solubility will have less active drug molecules in the systemic circulation, which also impacts the medicine's bioavailability. According to the United States Pharmacopoeia [USP] classification, around 30–40% of the medications that have been created to date fall into the category of medications that are extremely difficult to dissolve in water (0.1 mg/mL).[2] Drugs with limited solubility include those in class II of the Biopharmaceutics Classification System (BCS), such as phenytoin, danazol, and nifedipine, and class IV of the BCS, such as hydrochlorothiazide, furosemide, and taxol.[3,4] To solve particular drug formulation issues like solubility, there are a number of ways to alter the physical characteristics of medications. These techniques include hydrotropy, solid dispersion, cocrystal, amorphous compound synthesis, inclusion complexes, particle size reduction, nanosuspension, surfactants, salt production, and pH control.[5,6] In order to serve as a guide for creating drug formulations and resolving concerns with medication bioavailability, we will describe in this review how to increase the solubility of pharmaceuticals, particularly those with low solubility.

Particle Size Reduction

Since drug solubility and drug particle size are inherently correlated, decreasing particle size can increase drug solubility. The drug's surface area with a volume ratio rises when the particle size falls.[7] More surface area promotes solubility by enabling more contact with the solvent. Micronization and nanonization are the two main methods used to reduce particle size.[8] Submicron-sized drug particles, often known as nanoparticles, are a type of chemical. This is due to a decrease in size to

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

where is the surface tension of solids, V is the molar particle volume, R is the gas constant, T is the absolute temperature, is the density of a solid body, r is the particle radius, and Cs is saturated solubility and C is solid solubility made up of big particles.

The two mechanisms that underpin nanoparticles are top-down and bottom-up. Mechanical milling is one top-down approach of creating nanoparticles. Ball milling and mechanochemical synthesis are the two types of mechanical milling. Metal powder is put in a container with heavy balls to be ground in a ball mill. The balls then process the powder using a lot of mechanical energy while spinning quickly. Low-energy tumble mills, vibrating ball mills, planetary ball mills, high-energy ball mills, and attrition ball mills are some of the different methods of milling that reduce particle size.[11] Repetitive welding and deformation from the reactant mixture are the foundation of mechanochemical synthesis. The initial material is ground after being

stoichiometrically combined. Chemical interactions between the reagent and the substrate take place on the surface layer during grinding, requiring only modest temperatures. Following their dispersion in the salt matrix, the generated nanoparticles will be cleaned using a suitable solvent and dried for 12 hours at 105°C.[12] Combining tiny particles (atoms, molecules, or complex molecules) is the foundation of bottom-up nanoparticle production. Hydrolysis, condensation, particle size growth, and particle agglomeration are the four steps of the sol–gel process. Alcohol is the most often used solvent. A catalyst is added to a homogenous alkoxide solution to initiate the reaction at a regulated pH in order to generate nanoparticles.[11] One example of a nanoparticle created using precipitation processes is Sandoz's Hydrosol. After dissolving the medication in a solvent, the solvent solution is added to the nonsolvent solution. After then, there is extremely high saturation, rapid nucleation, and the formation of numerous tiny nuclei. The dispersion can be filtered and lyophilised to produce highly soluble nanocrystals once the solvent has been eliminated.[13] There are already many pharmaceutical items made from nanoparticles on the market; a few examples are shown in Table 1.[5] The benefits of using nanoparticle techniques include improved compatibility with various drug solubility profiles, good reproducibility with large-scale production, and a low risk of increasing the solubility of drug substances without altering the drug's chemical properties. On the other hand, because particle size reduction does not alter the solid-state nature of the particles, needs a significant energy input, and is not appropriate for cytotoxic medications with a low therapeutic index, it has a negligible impact on the solubility of the drug substances.[8,14]

2. Nanosuspension

A nanosuspension is a submicron colloidal dispersion system stabilised by surfactants and containing pure medication particles with diameters ranging from 10 to 1000 nm.[15] If the volume diameter of a system's formulation is 90% undersize (D90), it can be categorised as a nanosuspension. Nanoparticles, which are typically found in the form of a polymeric colloidal carrier system, are not the same as nanosuspensions. On the other hand, the solid medication is stabilised by surfactants and kept in the necessary crystalline condition with smaller particles in nanosuspensions.[17] Efforts to improve the solubility of nanosuspensions are, in theory, similar to those made for nanoparticles, which employ the Ostwald–Freundlich equation. This method can be applied to medications that have limited permeability, are poorly soluble in water, or both. As a result, when a drug becomes more soluble, its rate of dissolution likewise rises, resulting in a quicker reach of the drug's maximum plasma concentration.[18].

Generally speaking, the size of the drug particle and its rate of solubility are correlated. Smaller drug particles have a higher surface area–volume ratio and a larger surface area, which improves their interaction with the solvent and speeds up the drug's rate of dissolution.[19] Micronization is one of the traditional methods for lowering particle size. Drugs with high dosages should not be micronised because it does not alter the solubility of drug saturation, and the

increase in oral bioavailability that micronization provides is insufficient because micronised products have a tendency to aggregate. Micronization is accomplished by milling the drug using rotor-stator colloid mills or jet mills.[20] As a result, the system is stabilised when a stabiliser called a surfactant is added to nanosuspensions. The ability of surfactants to stabilise nanosuspension has been explained by a number of hypotheses, including (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

decrease of interfacial tension, (ii) the steric stabilisation theory, and (iii) the Overbeek (DLVO) theory.

There are two ways to prepare nanosuspensions: top-down and bottom-up. Drug particles are dissolved in an organic solvent using the bottom-up method, also known as the precipitation method, which creates a nanosuspension. The drug particles are then precipitated by adding a separate solvent in which they are insoluble. When making nanosuspensions, the top-down procedures are preferable since they reduce the size of the drug particles to the nanometre range.[21] There are several ways to implement the bottom-up approach: (i) emulsion solvent, (ii) spray drying, (iii) supercritical fluid process, and (iv) solvent–antisolvent method. The top-down approach, on the other hand, uses (i) medium milling, (ii) high-pressure homogenisation, and (iii) microfluidization to break down big particles into smaller ones.[22] Crystal growth and agglomeration are the outcomes of the particle size reduction in the top-down approach. Stabilisers are therefore utilised to stabilise the system in order to stop this phenomena. Polymers such as hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP K30) as well as surfactants like ionic sodium lauryl sulphate (SLS) and nonionic polysorbate (Tween 80) can be used as stabilisers.[23] However, bottom-up techniques like solvent-antisolvent precipitation are straightforward, reasonably priced, and easily scalable for the manufacturing of industrial nanosuspensions. By increasing the concentration gradient, height supersaturation can be accomplished using this technique. Furthermore, the saturation solubility is increased when the drug crystals are interfered with by nanoparticles. Ostwald ripening occurs when small particles with higher concentrations have a higher saturation solubility and diffuse into the vicinity of larger particles with lower drug concentrations. For the particle size to be uniform and to prevent significant size variations, which can prevent Ostwald ripening, it is therefore essential to avoid various concentration gradients and saturation solubility.

One medication whose solubility, dissolution, and oral bioavailability can be enhanced by nanosuspension is itraconazole. According to a recent study, the optimised Itraconazole nanosuspension formulation, which was made by media milling with glycerol as a wetting agent and poloxamer 407 as a stabiliser, had a greater in vitro dissolution profile in terms of drug release than both the pure drug and the commercial formulation.[24] However, compared to raw furosemide powder, the dissolution rate of furosemide nanosuspension, which was made by

antisolvent precipitation, was noticeably greater. In addition, as compared to pure pharmaceuticals, nanosuspensions exhibit better oral bioavailability and in vivo pharmacokinetic characteristics including Cmax (highest concentration) and AUC(0-t) [rise in the area under the curve (AUC) from drug administration to the final quantifiable sample].[25] The following other nanosuspension medication products have been studied: omeprazole, budesonide, spironolactone, naproxen, budesonide, danazol, and tarazepide. Increased solubility, a higher rate of dissolution because of the bigger surface area, the lack of Ostwald ripening because of the uniform particle size, and a narrow range of particle sizes that eliminates the concentration gradient factor are the benefits of employing nanosuspension. This method's drawback is that after the particle size is reduced, the polymorphs change into different crystalline polymorphs, which could not have any therapeutic benefits.

Surfactant

Surfactants are molecules with polar (hydrophilic) and nonpolar (hydrophobic) groups in their structure. Amphiphilic compounds with a single structure that combines hydrophilic and hydrophobic elements are known as surfactants. Surfactants can increase the solubility of chemicals that are hard to dissolve because of their activity in surface regions or two-phase interfaces. The majority of surfactants are made up of segments of hydrocarbons joined to the polar group. Along with functional groups like sulphates, amides, amines, alcohol, thiol, esters, acids, sulfonates, and phosphates, polar groups are made up of heteroatoms like N, P, S, or O groups.

The following describes the various forms of surfactants.

Anionic

In water, this surfactant separates into amphiphilic cations and anions. The most common kind of surfactant is this one, like SLS.

Cationic

Amphiphilic cations and anions can be created when this kind of surfactant dissociates in water. Because they include quaternary ammonium compounds and have a bactericidal effect, cationic surfactants are typically utilised as disinfectants and preservatives. Benzalkonium chloride and cetrimide are two examples of these surfactants.

Not ionic

Because its hydrophilic group has a nondissociable kind, such as amide, ester, ether, alcohol, and phenol, this type of surfactant does not dissociate in water. When polyethylene glycol chains are present, the majority of nonionic surfactants become hydrophilic. Moreover, these surfactants are less irritating than cationic or anionic ones. Polysorbate and poloxamer are two types of nonionic surfactants.

Amphoteric

Depending on the water's pH, this kind of surfactant can be cationic, anionic, or nonionic. Alkyl betaine is an illustration of this type of surfactant.

Surfactants can boost a drug's solubility in organic solvents while decreasing surface tension. The molecules of the surfactant will be drawn to the surface area when it dissolves in a liquid, and its presence can alter the surface tension. When surfactants

are positioned on the surface area, they will adsorb at low concentrations, changing the free energy considerably.[30] The surfactant will aggregate to create micelles once it has taken up the full surface area or interface. Micelles are a type of surfactant nanosystem in which the outer shell is made up of hydrophilic components and the nucleus is made up of hydrophobic ones. The diameter of this structure is typically between 20 and 80 nm.[31] Drugs that are hard to dissolve in water are dissolved by this structure. Micelle formation, also referred to as micellar solubilisation, traps medications within micelles.[32] The selfassembling system not only solubilises micelles from less soluble drugs but also offers a number of benefits, including ligand-mediated targeting, cellular internalisation, subcellular localisation, high drug dissolving capacity, protection against enzymatic hydrolysis, and increased oral bioavailability and drug loading capacity.[31] Micelles also have a number of drawbacks. Long-term chronic administration of synthetic surfactants may not be tolerable; dilution with aqueous media or physiological liquids may result in uncontrolled precipitation; deposits may vary in size and be either crystalline or amorphous; and dissolving other materials together, such as preservatives, may alter the stability and efficacy of the drug.[5] Glimepiride, gliclazide, repaglinide, pioglitazone, glipizide, and rosiglitazone are a few examples of antidiabetic medications that are challenging to dissolve in water utilising the micellar solubility technique.[33] Additional instances and the surfactants used to improve a drug's solubility are shown in Table 2.

Formation of Salt A neutralisation reaction between bases and acids produces salt. For medications that can be ionised to improve solubility, salt production is utilised. Protons are transferred from acids to bases to generate salt. If the difference in the ionisation constant (ΔpKa) between bases and acids is more than 3, then ionic bonds from salts can form and remain stable.[37] A counter ion, a stoichiometric molar ratio, and an appropriate solvent are necessary for the creation of salt by this process. Since the salt choice can affect the pre-formulation assessment of medications, choosing the appropriate salt structure for active components in pharmaceuticals must be effective and logical. The route of drug administration, biological variables, pKa, biopharmaceutical factors, ionic factors, and the organic solvents chosen are only a few of the many elements that must be taken into account when salt compounds are formed.[38] By calculating the relative position of equilibrium, the pKa value in the drug's active ingredient becomes a crucial metric for figuring out the compound's acidity and base levels, which can then be used to assess a salt compound's efficiency. If the ionisation process is lower than the pKa of a weak base and the pH is greater than the pKa of a weak acid, the degree of solubility of an active pharmacological agent may increase. The right salt for a therapeutic ingredient can be chosen by altering the solubility principle.[7] The pharmacodynamics of the medication salt compound may be impacted by the method of drug administration. Complex metal ions including Cu2+, Fe2+, Zn2+, and Mg2+ are typically added to salt production to improve drug absorption; nevertheless, they can also create a chelate that has serious negative effects. Additionally, salt compounds can lessen

the negative effects of pure drug compounds or increase the bioavailability of medications within the body. Because different administration routes need distinct salt compound formations, drug administration methods can also have an impact on salt compounds through their functions. In general, organic solvents speed up the pace at which compounds crystallise, altering the solubility and dissolution of drugs.[38] By making the substance more soluble, salt production may be advantageous if the original compound's inherent solubility was between 1 and 10 mg/mL. Seldom are compounds with inherent solubility greater than 10 mg/mL changed to their saline form unless their physical characteristics make the existing therapeutic formulation unfeasible.

An alternate method of improving medication solubility is salt production. It is regarded as an inexpensive way to improve the solid-state characteristics of the medication and is highly effective.[40] Active pharmacological components must or are protonated from an ionisable functional group structure in order to create salt.[41] Isoniazid (INH) is one medication that can undergo salt formation modification. According to a study, INH was screened using a succession of acids that the drug got, including methane sulfonic acid, oxalate, and maleic acid. In order to lessen INH degradation, these salts were made to produce a new solid form that is more soluble and thermally stable than the original INH. With the exception of mesylated isoniazid salts, the crystalline structure revealed that the salt had a layered structure that was mostly stabilised by the C-H... OH and N-H... O bonds as well as by π... π stacking interactions. Calculations using four dissolution media (clean water and acidic media) revealed that mesylate and maleic salts were roughly three times more soluble than INH.[42].

ACLPPZ-H2 O salt and ACL-THP cocrystal are two solid forms of the BCS class IV medication acetazolamide (ACL), which serves as another example. Its permeability and solubility are increased by the creation of cocrystals and salts, according to in vitro permeation comparison experiments and powder dissolution using different techniques. In contrast to ACL-THP cocrystals, ACL-PPZ-H2 O has higher ACL solubility, and the cocrystalline form has superior permeability. The concurrent rise in ACL can also be connected to the formation of salt.

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]

Understanding the structure of drug-related activities requires knowledge of permeability and solubility.[43] The benefits of salt production include improved drug solubility, enhanced stability against hydrolysis, photolysis, or thermolysis, improved tabletability, and favourable organoleptic characteristics.[44] There are certain drawbacks to the salt production approach for active pharmaceutical ingredients. The resulting salt may undergo disproportionation or a hydrolysis event to change into its nonionic state. The physicochemical properties of active pharmaceutical ingredients can be altered via disproportionation. Drugs that have been altered by salt production become less soluble as a result.[45]

Adjusting the pH

Almost all medications are ionised. Another strategy for improving the solubility of ionised medications is pH alteration. The saturation solubility of ionised medicines with dissociation is strongly impacted by pH changes. medications that dissolve in water when the pH changes and can be ionised with protonated (basic) or deprotonated (acid) molecules. A stable ionised molecule that dissolves in water is produced following the most appropriate pH adjustment. Weak acid medications dissolve more readily at pH > pKa while weakly basic drugs dissolve at pH < pKa due to pH-dependent solubility. [46] In order to treat insoluble medications, this pH-dependent solubility is investigated. Consideration should be given to buffer capacity and pH tolerance in order to overcome the solubility approach.[6] In tablet and capsule dosage forms, excipients are also utilised to modify pH. Quick development and ease of production are features of pH-adjusted formulations. The drug's solubility in the body in relation to the organ system in which it is absorbed or a varied, purposefully maintained pH are the basis for the pH adjustment.[47].

The rate of medication dissolution will be impacted by solubility, dissolution, and pKa as a result of pH variations. The pH of the dissolving medium, which influences the ability of tablets to break down into drug particles until the medication is fully dissolved, should always be referred to in the dosage form's whole drug dissolution profile. The dissolution of medications from solid dosage forms with pH modifications is significantly influenced by excipients and manufacturing processes.[6].

substances known as hydrotropes, which have a structure made up of both hydrophilic and hydrophobic groups, are employed in hydrotropic solubilisation to dissolve hydrophobic substances in aqueous solutions. Therefore, the equilibrium between a hydrotrope's hydrophilic and hydrophobic components determines its efficiency.[52] A good hydrotrope should ideally be both hydrophobic and very soluble in water. In the case of nicotinamide, for instance, the rate of increase in solubility is typically the most researched hydrotrope.

Hydrotropes are amphiphilic organic compounds that have structural characteristics with surfactants. If the level is higher than the minimal hydrotropic concentration (MHC), hydrotropes may aggregate in aqueous solution. It's interesting to note that molecules that are intractable or only weakly soluble in water can be dissolved by hydrotropes.[55] Hydrotropy is suggested as a superior

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

approach is superior to other solubilisation techniques including co-solvency, salting in, miscibility, and micellar solubilisation because the solvent's properties are high selectivity, non-pH-dependent, and emulsification-free. All that has to be done is combine the medication and hydrotrope with water.

Because the solvent's nature is not pH-dependent, it does not require chemical modification, it has high selectivity, and it does not require emulsification; the drug is only mixed with hydrotrope compounds in water solvents, and organic solvents are not used. This makes hydrotropy superior to other methods like micellar solubility, miscibility, co-solvency, and salting-in.

The hydrotrope method's drawback is that it may collect by itself in solution, losing its capacity to make the medicine more soluble in water.[56,57].

Dispersion of Solids

One of the most popular techniques for enhancing medications' poor water solubility is solid dispersion. Dispersing one or more medications into a solid matrix or inert polymer is known as solid dispersion.[58] Because they inhibit crystallisation and maintain the saturation level in the dissolution media by preventing crystallisation from the solvent, polymers play a crucial role in solid dispersion, which helps to keep the medicine stable during storage.[59].

When creating solid dispersions, choosing the right polymers is a crucial step. A number of factors can be taken into account when choosing polymers, including the assessment of the polymer's physicochemical characteristics, including its glass transition temperature (Tg), hygroscopicity, solid solution capacity, and solubilisation.[60] Additionally, if the solid dispersion is created using the fusion process, the polymer that is utilised needs to be drug compatible, inert, nontoxic, and thermostable with a low melting point.[61]. The melting technique

Because the melting procedure is simpler, less expensive, and solvent-free, it is employed. The medication and polymers used in this process need to get along and be able to mix.[59] Melting the polymer and then combining it with the medication is how the melting process is carried out. A cooling procedure, which can be carried out with ice cubes, comes after this phase.[62] Examples of medications modified using the solid suspension technique are displayed in Table 4.

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

The initial stage in solvent evaporation is dissolving the medication and polymers in volatile solvents. Low temperatures are used during evaporation to reduce the possibility of medication and polymer thermal breakdown.[65] Examples of medications altered by solvent evaporation are displayed in Table 5.

By decreasing particle size, improving wetting ability, and decreasing agglomeration, the solid dispersion method can increase the bioavailability of medications with poor solubility conditions. When the system comes into contact with water, it increases drug dissolution and supersaturation by enabling conformation of molecular dispersion between insoluble medicines and hydrophilic carriers. Solid dispersion's drawbacks include manufacturing challenges, issues with scaling up and improving manufacturing processes, physical instability of the dispersion primarily caused by temperature and humidity, the need for a large amount of polymer to facilitate an increase in dissolution rate, easy transformation into crystals and implications for decreasing solubility as they increase over time, and the difficulty of handling certain solid dispersions due to their adhesiveness.[70]

Cocrystal

The effectiveness of cocrystal technology in solving the issue of insoluble pharmaceuticals led to its emergence as a novel strategy.[71] Cocrystals are solid

materials made up of two or more distinct components bound by noncovalent bonds, often hydrogen bonds, with a stoichiometric ratio at room temperature.[72] "Cocrystalline" was formerly referred to as "molecular complex" or "intermolecular complex" in pharmaceutical science.[73] New crystalline structures created by cocrystallization are frequently better than those created by each individual component. Because cocrystals have a higher solvent affinity and a lower lattice energy, they are more soluble in drugs.[71].

Cocrystallization formers, also known as coformers, are neutral guest compounds that are present in the same crystal lattice as API to create cocrystals. The elements in the crystal lattice are ionised when salt is created, and 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 P188 PVP K25	Ethanol	[67]
Febuxostat	d-α-Tocopherol polyethylene glycol succinate (TPGS) P188	Ethanol	[68]
Valsartan	Soluplus® PVP K25	Acetone Ethanol	[69]

It interacts through nonionic interactions while in a neutral state. For coformers, the US Food and Drug Administration (FDA) has released guidelines. Coformers must be deemed safe for human ingestion and pharmaceutically acceptable in order to transform into nontoxic compounds with no negative side effects. Collections listed on the Generally Recognised as Safe (GRAS) list are available for selection. Organic acids (such as citric acid, glutamic acid, gallic acid, ascorbic acid, histidine, glycine, nicotinamide, valine, tyrosine, urea, and saccharine) and nutraceuticals (such as p-coumaric acid, quercetin, pterostilbene, and saccharine) are examples of coformers that are listed on the GRAS list. The choice of coformer types has a significant impact on the success of cocrystal formation because of the increased likelihood of hydrogen bonds forming with API.[74].

Cocrystal formation is explained in the current study as a well-known method of altering a drug's physicochemical characteristics. Pharmaceutical cocrystals can improve an API's solubility, hygroscopicity, chemical stability, physical stability, bioavailability, compressibility, and rate of dissolution.[75] Cocrystals can be created using a variety of methods. Solution evaporation is the longest procedure. Solution evaporation, solid-state co-grinding (with or without solvent), co-melting, co-sublimation, and co-heating are traditional methods for creating cocrystals. Maintaining saturated conditions increases the possibility that solvents may mediate cocrystal formation [39]. Cocrystallization by extrusion, sonococrystallization, electrochemically induced cocrystallization, cocrystallization from suspensions, cocrystallization from supercritical fluids, cocrystallization by laser irradiation, freeze-drying cocrystallization, spray-drying cocrystallization, and cocrystallization from polymers, ionisation, and polymer gels are some of the more advanced methods for creating cocrystals.

Cocrystals are superior to salt formation in a number of ways. The application of cocrystallization to API under acidic, basic, and nonionized molecules is possible.[80] Cocrystals are of interest in pharmaceutical production for two reasons: first, the nonpermanent modification interaction between the API and its coformers is guaranteed to be completely separated before reaching the site of action, ensuring that the drug

molecule's pharmacological activity stays unchanged; second, the use of cocrystals in pharmaceutical products can prolong the API's storage life. The inability to guarantee cocrystal formation is a drawback of cocrystallization. In other words, it is impossible to forecast the possibility of API cocrystallization.[81].

Amorphous

API can generally be either crystalline or amorphous. One strategy to increase solubility is to try to change crystalline substances into amorphous forms. In general, amorphous products can be categorised as pure substances or solid dispersions, where drug molecules may be distributed within a carrier. Better oral absorption results from amorphous particles' high dissolving rates and water solubility, which are caused by their thermodynamic characteristics. One example of an amorphous commercial drug product is zafirlukast (Accolate®).[82].

Inclusion Complexes

One plausible method for enhancing the drug's physicochemical characteristics, such as its bioavailability, solubility, and rate of dissolution, is the inclusion complexation of drug molecules as the guest and cyclodextrins (CDs) as the host. CDs are cyclic oligosaccharides that function as solubilising and complexing agents because of their hydrophilic surface and hydrophobic inner cavity.[85] α-1,4-linked glucose units create CDs, which can be referred to as γ-CD, β-CD, or α-CD depending on how many d-glucopyranose units they contain (6, 7, and 8 units, respectively). Because of its cavity size for encapsulating medicinal molecules, β-CD is most frequently utilised in medicines. The price of β-CD is quite low, and it is not very soluble in water. Glucosyl-β-CD, sulfobutylether-β-CD, methyl-β-CD, and hydroxypropyl-β-CD are among the β-CD derivatives.[86] Because CDs can form inclusion complexes with a variety of guest molecules by stabilising the polar portion via their polar surface and encasing the nonpolar portion in their hydrophobic cavity, they are used for the controlled delivery of pharmaceutical molecules that are inorganic, organic, and biological.[87] Drug molecules bound in the CD inclusion complex encounter dynamic equilibrium with free drug molecules; noncovalent bonds can be broken or generated in aqueous solution during complex formation. Drug molecules can form complexes with one or more CD molecules, and CD molecules can create complexes with one or more drug molecules.[88] Examples of medications with enhanced solubility after inclusion complex modification are displayed in Table 6.

Table 6: Examples of inclusion complex methods

Drug	Complex	Method	Source
Triptonide	2,6-Dimethyl-β-CD	Saturated aqueous solution	[83]
Nystatin	β-CD	Spray drying Freeze-drying	[90]
Dronedarone	2-Hydroxypropyl-β-CD β-CD	Kneading Freeze-drying 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]

When compared to host molecules alone, inclusion complexes containing guest-host molecules may exhibit superior biological

or chemical characteristics.[92] Converting liquid medications into amorphous powders or microcrystalline form, altering the time profile and/or drug delivery site, extending the drug's shelf life and enhancing its physicochemical stability, removing or lessening offensive flavours and odours, enhancing bioavailability, dissolution, and aqueous solubility, and avoiding drug–excipient or drug–drug interactions are just a few benefits of the inclusion complex.[93] The primary drawback of employing CDs is the requirement to get past complex medications' stability, which makes them challenging to ionise. The stability of the nonionized form is four times that of the ionised form. Determining the dose size and modifying the amount of CD with appropriate drug administration is another drawback of challenging drug formulations with CDs; the least amount of CD must be utilised to prevent the medication's bioavailability from declining because of the excessively large particles. To establish the right amount of CD to employ, the drug's solubility in the final formulation must also be ascertained.[94]

3. Table 7 provides an example of a drug from each approach by quickly going over the relevant variables pertaining to the drug's solubility, which are based on the previous description of the solubility improvement method.

4. Conclusion

Numerous solubility enhancement approaches are available to alter the solubility of drugs that are poorly soluble in water. In this overview, we describe ten of these methods, each with pros and cons. Since we have just discussed the most important aspects of the approaches discussed in this study, a more in-depth analysis is required to help readers better understand them. Each approach requires more investigation.

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