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Review Article

Solubility Enhancement Strategies for Poorly Soluble Drugs: Recent Trends

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Abstract

Pharmaceutical development is severely hampered by poor drug solubility; over 40% of medications on the market and about 90% of drugs in development pipelines have inadequate solubility. Which also reduces bioavailability and therapeutic effectiveness. This review thoroughly investigates a range of methods, including physical alterations, chemical approaches, and innovative formulation techniques, for enhancing the solubility of poorly soluble drugs. Important techniques are covered in detail, including lipid-based formulations, solid dispersions, complexation with cyclodextrins, particle size reduction, and nanotechnology-based carriers. The mechanisms behind solubility enhancement, the benefits and drawbacks of each strategy, and their effects on drug absorption and clinical outcomes are also highlighted in the review. Recent developments and cutting-edge technologies that present viable ways to get around solubility-related obstacles in drug delivery are highlighted. For researchers and formulators looking to maximize drug solubility and enhance therapeutic results, this synthesis offers a useful framework.

Keywords: Solubility, Poor Soluble drugs, Bioavailability, Solid Dispersion, Nanotechnology, Solubility Enhancement.

INTRODUCTION

Solubility is the greatest quantity of solute that may dissolve in a certain volume of solvent at a particular temperature and pressure, resulting in a saturated solution. In pharmaceutical sciences, aqueous solubility is particularly critical as it directly influences drug dissolution, absorption, and ultimately bioavailability following oral administration. Solubility is a critical characteristic for attaining the required drug concentration in systemic circulation for pharmacological efficacy. The solubility criteria as per I. P. is given in Table Ⅰ.

Table Ⅰ: - Solubility criteria a per I.P.

Descriptive Term	**Approximate volume of solvent in millilitres per gram of solute**
Very Soluble	Less than 1
Freely Soluble	From 1 o 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly Soluble	From 1000 to 10000
Practically Insoluble	Above 10000

The drug molecules in solid dosage forms taken orally dissolve first into smaller pieces or even primary particles, which allows them to dissolve more readily in the gastrointestinal tract (GIT) fluids than they would in an intact tablet. The drug's molecular dissolution is then followed by its passage through the intestinal barrier. In

order for the medication molecules to reach the proper quantities in the systemic circulation and provide the necessary therapeutic effectiveness, solubility is a crucial need. Since permeability and bioavailability are strongly correlated with medication solubility, a drug molecule with extremely poor solubility cannot dissolve in the GIT fluids, which impairs permeability. Poorly soluble medications with low bioavailability result in costly final formulations since high dosages are required to provide therapeutic benefits and occasionally they may be harmful. There are several variables that can impede medication absorption from the GI tract, but the two most important drug's inadequate water solubility and membrane permeability are significant limitations. An active ingredient that is taken orally must dissolve in the stomach and/or intestinal fluids before it can pass through the GIT membranes and enter the bloodstream. As a result, two areas of pharmaceutical research concentrate on increasing the oral bioavailability of active agents: boosting the solubility and rate of dissolution of medications that are not very water soluble. The BCS is a scientific framework for grouping pharmacological substances according to intestinal permeability and aqueous solubility. [1,2] The solubility and permeability of pharmacological compounds in the GIT determine their classification into four BCS classes as shown in Table Ⅱ.

Table Ⅱ: - Biopharmaceutical Classification System.

Class	Solubility	Permeability	Example
I	High	High	Mefloquine hydrochloride, Nelfinavir mesylate, Quinine sulphate
II	Low	High	Ibuprofen, Nifedipine, Loratadine, Desloratadine
III	High	Low	Amiloride hydrochloride, Amoxicillin, Ethosuximide, Fluconazole
IV	Low	Low	Acetazolamide, Doxycycline

As drug release from the dosage form and solubility in gastric fluid, rather than absorption, constitute the rate-limiting factors for BCS class II and IV drugs, enhancing solubility will increase drug bioavailability. A formulation development process failure may result from poor aqueous solubility. The drug's poor rate of dissolution and low solubility in aqueous media are the primary causes of its insufficient bioavailability. [3]

Many hydrophilic carriers that have demonstrated notable improvements in solubility are now being investigated. The majority of drug substances have been innovated in recent years, but one of the most challenging jobs in drug research is still trying to increase the solubility and dissolution of hydrophobic therapeutic substances. For an oral medication to have improved absorption and bioavailability, it must dissolve in an aqueous media, such as stomach fluid. Therefore, polymer matrices of different origins can be employed to advance the bioavailability of weakly water-soluble substances, such as biopharmaceutical classification system class II and IV medications. In essence, a drug's therapeutic efficacy is determined by its solubility and bioavailability. The majority of newly discovered chemical entities have low water solubility and are lipophilic. Since over 40% of drugs have low water solubility, new chemical entities created in the pharmaceutical business are lipophilic and do not make it to market because of this. There are several ways to alter a drug's physical characteristics in order to solve certain formulation issues, such solubility. These techniques include hydrotropy, cocrystal, amorphous compound creation, inclusion complexes, particle size reduction, nanosuspension, surfactants, salt formation, pH modification, and solid dispersion. In order to serve as a guide for creating drug formulations and resolving concerns with drug bioavailability, we will describe in this study the techniques for improving drug solubility, particularly for medications with poor solubility. [1,3,4]

Theoretical Framework of Solubility Enhancement

Fundamental Principles:

The enhancement of drug solubility relies on modifying either the drug itself or its immediate environment to favour dissolution. The Noyes-Whitney equation describes the dissolution process:

$dM/dt = DA (Cs - C)/h$

Where dM/dt represents the dissolution rate, D is the diffusion coefficient, A is the surface area, Cs is the saturation solubility, C is the concentration in the bulk solution, and h is the diffusion layer thickness.

METHODS

Classification of Solubility Enhancement Strategies. [5-7]

I. Physical Approach:

1. Particle size reduction
   a. Micronization
   b. Conventional Methods
   c. Nanosuspension
2. Complexation
   a. Physical mixture
   b. Kneading method
   c. Co-precipitation method
3. Modification of crystal habit
   a. Polymorphs
   b. Pseudo polymorphs

4. Solubilization by surfactants
   a. Self-micro emulsifying drug delivery system.
   b. Microemulsions
5. Inclusion Complex Formulation Based Techniques
   a. Lyophilization/ Freeze- drying Technique
   b. Microwave irradiation method
6. Drug dispersion in carriers
   a. Solid solutions
   b. Solid dispersions

- Solvent Method
- Fusion solvent method
- Fusion Process
- Hot melt Extrusion
- Dropping Method
- Lyophilization (Freeze Drying Method)
- Spray drying

II. Chemical Approach:

- Co-crystallization
- Salt Formation
- Co-solvency
- Nanotechnology
- Hydrotropy
- Use of novel solubilizer

III. Miscellaneous:

- Supercritical Fluid Process
- Liquisolid technique
- Polymeric alteration

The pictorial representation of classification is shown in fig1.

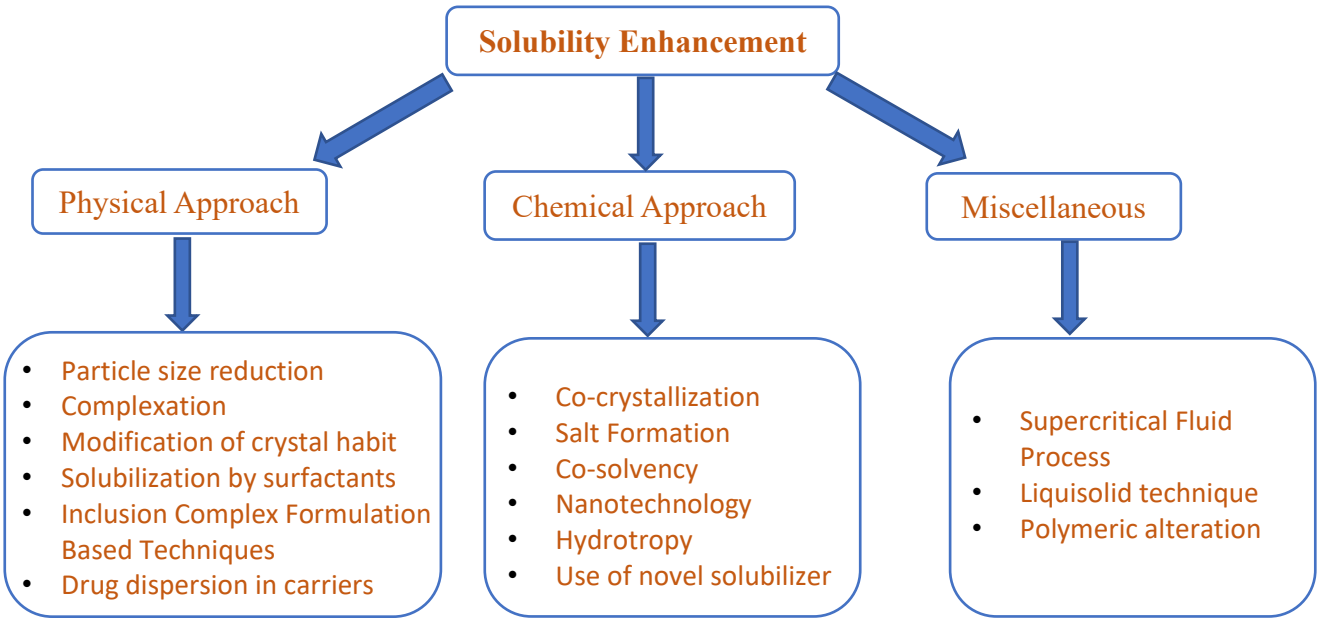

Figure 1: Classification of solubility enhancement methods.

Physical Approach:

Physical methods of solubility enhancement are key strategies in pharmaceutical formulation to improve the dissolution rate and bioavailability of poorly soluble drugs.

Particle size reduction:

Drug solubility and particle size are often inherently connected; when particle size decreases, surface area increases. A stronger contact with the solvent is made possible by the bigger surface area, leading to an increase in solubility. Augmented surface area improves solubility by reducing particle size. The active component is broken down by mechanical stress in conventional particle size reduction techniques like comminution and spray drying. However, when using spray drying to thermosensitive materials, thermal stress should be considered. There are various ways of particle size reduction other than conventional method, this are micronization and nanosuspension. Micronization uses a high energy particle size reduction approach, coarse particles may be reduced to particles with a diameter that is smaller than 5 µ. In order to provide a homogeneous dosage form, micronization produces a uniform and narrow particle size distribution. Surface area grows as particle size decreases and solubility rises when micronization takes place. The most widely used methods for creating micronized particles include mechanical communication, spray drying, and supercritical fluid (SCF) technologies. Drugs with a high dosage number should not be micronized since it does not alter the drug's saturation solubility. Micronization is performed via milling methods such as rotor stator

colloid mills, jet mills, and so on. Progesterone, fenofibrate, spironolactone diosmin, and griseofulvin are some example that are subjected to these procedures for solubility enhancement. A nanosuspension is a submicron colloidal dispersion system stabilized by surfactants and containing pure medication particles with diameters ranging from 10 to 1000 nm. A pharmaceutical nanosuspension is a biphasic system made up of drug particles that are nanosized and stabilized by surfactants. It can be administered parenterally and pulmonary or orally and topically. The solid particles in nanosuspension typically have an average particle size of 200–600 nm, with a particle size dispersion of less than one micron. There are two ways to prepare nanosuspensions: top-down and bottom-up. Drug particles are dissolved in an organic solvent using the bottom-up approach, 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 creating nanosuspensions, top-down techniques are recommended since they reduce the size of the drug particles to the nanometer range. Itraconazole is example whose solubility and dissolution are increased by nanosuspension. [3,5,8]

Complexation:

Complexation is the interaction of two or more molecules to generate a standalone entity with a specific stoichiometry. London forces, hydrogen bonds, and hydrophobic interactions are examples of relatively weak forces that are involved in complexation.

There are two different kinds of complexes:

1. Stacking Complex: - Stacking complexes are fueled by the interaction between the complexing agent and the drug's non-polar region. Because of this, the non-polar region is kept from coming into touch with water, which lowers the system's overall energy. Both mixed and homogeneous stacking provide a transparent solution.
2. Inclusion Complex: - More precisely than any other solubility improvement technique, the inclusion complex formation strategy has been utilised to improve the bioavailability, rate of dissolution, and aqueous solubility of drugs that are poorly soluble in water. Adding a nonpolar molecule or the nonpolar part of a single molecule (called the guest) to the cavity of another molecule or collection of molecules creates inclusion complexes (known as host). In complexation, cyclodextrin and its derivatives are often utilized. A class of cyclic oligosaccharides known as cyclodextrins (CD) is produced when starch is broken down by enzymes. The three primary cyclodextrins, ß, γ-CD, and α-CD, are made up of six, seven, and eight D- (+) glucopyranose units, respectively. The outside of cyclodextrins is hydrophilic, whereas the inside cavity is hydrophobic. They combine with the medication to enhance its solubility and bioavailability in poorly soluble drugs. The most widely used R cyclodextrin derivatives with higher water solubility are found in pharmaceutical formulations, such as (hydroxypropyl-R-cyclodextrin HP-R-CD). [9]

The many techniques used to produce inclusion complexes of poorly soluble drugs in an attempt to improve their water solubility are outlined below:

- Physical Mixture: - To achieve the required particle size in the finished product, the CDs or equivalent polymer and drug are fully combined by trituration in a mortar and then passed through the proper sieve. It is a straightforward trituration technique.
- Kneading Method: - This process involves turning CDs or an appropriate polymer into a paste by soaking them in a little quantity of hydroalcoholic solutions and water. After that, the medicine is added to the paste mentioned above and kneaded for a predetermined amount of time. After being kneaded, the mixture is desiccated and sieved.
- Co-precipitation: - At normal temperature, the active medication dissolves in ethanol, while the appropriate polymer dissolves in distilled water. The active medication and appropriate polymers are combined in varying molar ratios. After an hour of stirring at room temperature, the solvent is removed from the mixture. After being ground up and sent through sieve number 80, the resulting material is kept in desiccators. [10]

Modification of Crystal Habit:

Crystal habit polymorphism refers to the capacity of an element or compound to form crystals in multiple distinct structures. In addition to polymorphism, pseudo polymorphs, or co-crystals are solid crystalline solids made up of two or more molecules or atoms in the identical crystal lattice. Co-crystals can also be broadly classified as clathrates (trapped molecules), hydrates (trapped solvent), and solvates (present solvent). The co-crystals of quinone and hydroquinone were the first to be documented in 1844 by Friedrich Wöhle. Co-crystals have a direct impact on the solubility and bioavailability of solid-state characteristics. Co-crystals are commonly used in pharmaceutical formulations, and the co-crystal phenomenon has previously been used in the design of several medicinal products, including tropomyosin and troponin. [11]

Solubilization By Surfactants:

The polar and non-polar parts of surfactant molecules are separate. A polar group is joined to a hydrocarbon segment to form the majority of surfactants. Anionic, cationic, zwitterionic, or nonionic polar groups are all possible. This solubilization process is crucial to both natural and industrial processes. The drug's solubility in an organic solvent may be improved and surface tension reduced by the addition of surfactants. Perhaps the most basic, important, and traditional technique for enhancing the dissolving performance of poorly soluble medicinal compounds is the use of surfactants.

Self-micro emulsifying systems work on the basis of the idea that emulsions occur in the gastrointestinal tract. In the absence of an external phase (water), the mixture of oil, surfactant, co-surfactant, one or more hydrophilic

solvents, and co-solvent forms a transparent isotropic solution known as the self-emulsifying drug delivery system (SMEDDS). When diluted by the aqueous phase in the GIT, the mixture spontaneously forms fine o/w emulsions or micro-emulsions, which are used to improve lipophilic drug absorption and dissolution. The fact that SMEDDS are thermodynamically stable and form spontaneously when their constituents are mixed under mild agitation is one of its benefits with regard to manufacturing and scaling up. High surfactant concentrations and medication chemical instability are among this system's disadvantages. One type of self-micro emulsifying medication delivery device is the Neoral-R. (SMEDDS). [12]

Micro emulsions are optically clear pre-concentrates, isotropic, thermodynamically stable, transparent, and translucent systems that dissolve poorly water-soluble drugs by combining hydrophilic solvent, hydrophilic surfactant, and oil. The determining criteria for surfactants are HLB and non-toxicity. The formulations self-emulsify when they come into contact with water, forming a highly clear emulsion of uniformly sized, tiny oil droplets that contain the poorly soluble medication that has been solubilized. [13]

Inclusion Complex Formulation Based Techniques:

Inclusion complexes are created when a nonpolar molecule or nonpolar portion of one molecule (referred to as the guest) lodges into the cavity of another molecule or collection of molecules (known as host). Cyclodextrins are frequently utilized host molecules. The host's cavity has to be both big enough to fit the visitor and tiny enough to get rid of water. Numerous techniques, including co-precipitation, neutralization, co-grinding, spray drying, microwave irradiation, and kneading, are used to create solid inclusion complexes. [14-16]

Lyophilization: This method involves first freezing the solution containing the medication and CDs or an appropriate polymer at low pressure, followed by drying the solution to remove the solvent system. Water's special qualities and its functions as a solvent, gas, diluent, plasticizer, and stabilizer are crucial to lyophilization. Drug and carrier molecules are mixed in a common solvent as an alternative to solvent evaporation. [17]

Microwave Irradiation Method: It involves the complexing agent and medication undergoing a microwave irradiation process in a microwave oven. A certain amount of water and organic solvent is used to dissolve the medication and CD in a given molar ratio in a round-bottom flask. In the microwave oven, the mixture is reacted for a brief period of one to two minutes at 60°C. To get rid of the remaining, uncompelled free drug and CD, a sufficient amount of solvent mixture is added to the reaction mixture above once it is finished. Whatman filter paper is used to separate the precipitate, which is then dried for 48 hours at 40°C in a vacuum oven.

Drug Dispersion in Carriers

Two crystalline solids combined to form a new crystalline solid is called a solid solution. When the two components crystallize together in a homogeneous one-phase solution, a mixed crystal is created. Therefore, compared to simple eutectic systems, it is anticipated to produce significantly greater rates of dissolution.

Solid Dispersion: Sekiguchi and Obi first introduced the idea of solid dispersions in the early 1960s when they studied the formation and dissolving characteristics of eutectic melts of a sulphonamide medication and a water-soluble carrier. One practical pharmaceutical method for improving the therapeutic effectiveness, absorption, and dissolution of medications in dose forms is the use of solid dispersions. A collection of solid goods made up of at least two distinct components—typically a hydrophilic matrix and a hydrophobic drug—is referred to as a solid dispersion. The most popular hydrophilic carriers for solid dispersions are Plasdone-S630, polyethylene glycols (PEGs), and polyvinylpyrrolidone (Povidone, PVP). [18-21]

The following list includes many methods for creating a solid dispersion of hydrophobic medications that will increase their solubility in water[22,23]:

- Solvent Evaporation Method: A suitable organic solvent is used to dissolve the active substance and the carrier. Either a high temperature or a vacuum is used to evaporate this solvent. Super saturation happens during solvent removal, and the contents precipitate simultaneously, leaving behind a solid residue. To remove any solvent that may have readily adhered to the particle, the co-precipitate is then vacuum-dried. It is indicated that even minute quantities of the solvent have been removed. Complete solvent removal may be demonstrated using fewer sensitive methods like spectroscopy and gravimetry as well as more sensitive ones like differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA).
- Fusion Solvent Method: The drug(s) is/are incorporated as a solution after the carrier(s) is/are melted. There is no need to remove the solvent if the liquid is safe and the carrier can contain a specific amount of liquid while keeping its solid qualities. The approach works effectively for drugs that are thermolabile or have high melting points.
- Fusion Process: The drug is added to the matrix after the carrier is heated to a temperature slightly over its melting point. To evenly distribute the medication throughout the matrix, the mixture is chilled while being continuously stirred.
- Hot Melt Extrusion: In the polymer sector, it is a widely utilized technique. However, the first people to apply this technique for pharmacological purposes were Speiser and Huttenrach. The following sections make up a melt extrusion: An exit port with an optional die to shape the extruding mass, a heated barrel with extruder screws to transport and mix the supplied ingredients, and an aperture to supply raw materials. The carrier and active chemicals are continuously delivered into the heated extruder barrel. The mixture of the carrier and active component is changed into its "fluid like condition"

when it is passed through heated screws. This condition enables close and even mixing due to the extruder screws' strong shear. The melt is shaped into the desired form, such as granules, pellets, films, or powder, using an exit port that includes an optional die. [24]

- Dropping Method: A melting drug carrier fluid is pipetted into a solid dispersion, which is then deposited onto a plate to solidify into spherical particles.
- Lyophilization (Freeze Drying Method): After adding the necessary stoichiometric amounts of host and guest to an aqueous cyclodextrin solution, the suspension was magnetically agitated for 24 hours and then freeze-dried for 24 hours at 60 °C.
- Spray Drying: In an appropriate solvent, the active component and the carrier are suspended and dissolved. By drying it and then applying a stream of warm air, this solvent is evaporated. The solvent evaporates fast and solid dispersion forms soon because of the droplets' enormous surface area. [25]

Chemical Approach:

Co-crystallization:

Co-crystallization is thought to be a possible substitute for optimizing drug characteristics since it modifies molecular interactions. Multi-component crystal that is created between two substances that are solids under ambient circumstances, where at least one component is an appropriate ion or molecule, which is an accurate description of a co-crystal. A number of an API's physical, chemical, or physiological shortcomings are addressed via co-crystallization. By reducing the interfacial tension, the co-solvency mechanism promotes the dissolving of a non-polar solute. The solubility of additional medications, including carbamazepine, itraconazole, paracetamol, piroxicam, gabapentin, and caffeine, has been investigated in relation to cocrystal formation. The following medications are available on the market as cocrystals: carbamazepine (Tegretol®), fluoxetine hydrochloride (Prozac®), etc.[26-28]

Salt Formation:

For many years, a method to improve solubility has been the salt production of weakly soluble therapeutic candidates (weak acids and bases). Ionization of a chemical in solution results in the formation of salts. It functions well for parenteral and other liquid formulations as well as solid dosage forms. A salt that is more soluble than the corresponding medicine is created when an acidic or basic substance is transformed. For example, theophylline, and barbiturates. Progesterone is a commercially available example of this strategy; it is a water-insoluble steroid that dissolves in peanut oil. [29]

Co-solvency:

It is possible to boost the solubility of drug that are weakly soluble in water by combining them with a water-miscible solvent that the drug dissolves well in. Co-solvency is the term for this technique, and cosolvent refers to the solvent employed in conjunction. The way a cosolvent system functions is by lowering the interfacial tension between the hydrophobic solute and the aqueous solution. Another name for it is solvent blending. Commonly used cosolvents are ethanol, glycerol, PEG-400, etc.[30]

Nanotechnology:

In addition to revolutionary therapeutic breakthroughs employing components in the 1–100 nanometer range, nanotechnology offers the ability to rejuvenate badly performing commercial pharmaceuticals and many of those pre-clinically promising candidates that were "beached" due to inadequate water solubility. Researchers have been addressing this issue by creating medications with the help of nanocarriers as a result of recent advancements in nanotechnology. Nano emulsions, carbon nanotubes, nanosuspension, dendrimers, micelles, solid lipid nanoparticles, polymeric nanoparticles, inorganic nanoparticles, MOFs, liposomes, niosomes and so on are the most widely used nanotechnology-based techniques for creating drug delivery systems. One drug whose solubility, dissolution, and oral bioavailability can be enhanced by nanosuspension is itraconazole. [31-33]

Hydrotropy:

Hydrotropy is a solubilisation process in which a considerable quantity of a second solute is added, enhancing the solute water solubility. Numerous medications with low water solubility have been shown to have their aqueous solubilities improved by concentrated aqueous hydrotropic solutions of sodium benzoate, urea, sodium citrate, nicotinamide, and sodium salicylate. [34]

Use of Novel Solubilizer:

Different solubilizing compounds can help increase the solubility of poorly soluble drugs. Examples of conventional solubilizers that increase the solubility of hydrophobic APIs include PEG 400, Soluplus, polysorbates and Povacoat. A new Solubilizer: Sepitrap, 80% of the solubilizers from SepitrapTM (Microencapsulated Solubilizer for Solid Dosage Application) are desorbed in less than five minutes, making them available to solubilize the medicinal component. [35]

Miscellaneous:

Supercritical Fluid Process:

The drug particles may re-crystallize at much smaller particle sizes after being soluble in SCF. SCF techniques' accuracy and adaptability enable the micronization of medication particles within very specific particle size ranges, frequently down to sub-micron levels. Nitrous oxide, propane, n-pentane, ethanol, ethylene, ammonia, and water are examples of supercritical solvents that are often employed. A number of SCF processing techniques, including gas antisolvent recrystallization, rapid expansion of supercritical solutions, and precipitation with compressed antisolvents process (PCA), have been developed. [36]

Liquisolid Technique:

The liquisolid technique is a new idea that allows a liquid to be physically blended with a chosen carrier and coating material to create a free-flowing, easily compressible, and seemingly dry powder. The liquid component is integrated into the porous carrier material and can take the form of a liquid medication, drug suspension, or drug solution in appropriate non-volatile liquid vehicles. The tiny coated particles immediately adsorb the liquid layer that forms on the particle surface once the carrier is saturated with liquid. Consequently, a powder that seems dry, free-flowing, and compressible is produced. [37]

Polymeric Alteration:

Polymorphs are several crystalline forms of a medication that may have distinct characteristics. Physical and chemical stability, vapor pressure, rate of dissolution, density, inherent solubility, melting point, and bioavailability are only a few examples of the physicochemical characteristics that might differ amongst polymorphs. Among the crystalline polymorphs that are stable, unstable, and metastable, metastable forms are associated with higher energy and greater surface area, solubility, bioavailability, and efficiency. [38]

CASE STUDIES:

Kureshi et al. (2024)- Formulation and Evaluation of rapid release system of Irbesartan by liquisolid technology. The liquisolid tablet technique had been an effective way to improve the dissolution rate of water-insoluble drugs such as Irbesartan. This novel approach to formulation had been helpful in improving oral bioavailability. [39]

Nair et al. (2023) had enhanced solubility of loratadine by forming amorphous solid dispersion of drug in Soluplus®. The result of present research showed that the excipient Soluplus® was appropriate for creating solid loratadine dispersions. It was discovered that the dispersions significantly increased loratadine's solubility in aqueous media by 130-fold. [40]

Nayyer Islam et al. (2023)- Loratadine oral bioavailability enhancement via solid dispersion loaded oro-dispersible films. The result of present research showed that the when compared to pure LRD, LRD-SDs-ODFs demonstrated better solubility and in-vitro dissolution outcomes. In aqueous solutions, the LRD-SD coded as LTS-4 was 190 times more soluble than the pure medication. In general, LRD-SDs-ODFs significantly improved the antihistaminic effectiveness, bioavailability, dissolution rate, and solubility of LRD. [41]

Rao et al. (2023)- Solubility Enhancement of Nevirapine Using B-Cyclodextrin Nano sponges. The result of present research showed that the Compared to other binary combinations, the NVP-SDNS binary mixture exhibited better saturation solubility and a higher rate of dissolution. It was concluded that using β-Cyclodextrin Nano sponges improved the solubility of NVP. [42]

Chauhan et al. (2025)- Solubility Enhancement of Brexpiprazole for Schizophrenia using HPβ Cyclodextrin Ternary Complexation. The result of present research showed that the Brexpiprazole solubility was improved by the ternary complex, which led to a faster rate of dissolution and an earlier start of action. It was believed that succinic acid was a potential solubilizer for the development of a ternary complex, and that solvent evaporation was one of the favoured complexation techniques. [43]

RECENT RESEARCH TRENDS IN SOLUBILITY ENHANCEMENT:

Recent research in solubility enhancement is shifting toward nanotechnology-based systems, deep eutectic solvents, and data-driven/ML-supported formulation design for poorly water-soluble drugs. Some of them are shown in Table Ⅲ. [44-50]

Table Ⅲ: - Recent research trends.

Technology	Primary Focus	Key outcomes	Ref
Deep Eutectic System	This are green solvent systems that significantly reduce the melting points of their constituent parts to produce liquids with special processing and solvation capabilities.	Therapeutic deep eutectic system and deep eutectic system are viable solvents to improve both the solubility and chemical stability of APIs Example: Menthol – camphor system Enhanced percutaneous delivery of tacrolimus for atopic dermatitis	44,45
Magnetic Nano Particles	By inhibiting aggregation and increasing the wettability of hydrophobic drug molecules, these nanoparticles can serve as carriers that distribute the medication throughout the gastrointestinal system.	MNPs can help pharmaceuticals amorphized, a process that transforms a poorly soluble drug's crystalline structure into an amorphous form with greater solubility. Example: A study on curcumin-loaded MNPs functionalized with sodium alginate and chitosan revealed a notable increase in drug release and solubility, resulting in improved therapeutic effectiveness against breast cancer cells.	46

Amorphous Solid Dispersion	Polyvinyl Pyrrolidone (PVP)-Based Amorphous Solid Dispersion	Drug crystallization is inhibited by PVP-based ASDs, keeping the drug amorphous. By enhancing wettability, creating hydrogen bonds or other interactions with the drug, boosting drug solubility, and encouraging drug–carrier complexation, they improve drug dissolution. Example: ASD has been successful in increasing the solubility and bioavailability of lopinavir in Kaletra® for HIV/AIDS.	47
	PROTAC-ASDs	By adding surfactants, ternary ASDs were effectively created, improving PROTAC-ASDs' dissolving performance and acting as a model for future oral PROTAC formulations.	48
Dual Drug Co-Amorphous System	CAMs are made by combining two or more substances, usually a drug, and a co-former, to produce a co-amorphous form.	By combining two or more drugs, the CAMs strategy improves oral bioavailability, solubility, and dissolution. Example: Pioglitazone–rosuvastatin	49
Artificial Intelligence/ Machine Learning	AI/ML models, such as LASSO, MLP, and SVR, for correlating medication solubility and solvent density in the supercritical state with model inputs of temperature and pressure	For modelling, MLP (Multilayer Perceptron), SVR (Support Vector Regression), and LASSO were used; Tabu Search was used for hyper-parameter tuning. After that, the models were contrasted to see which one best correlated density and solubility.	50

NOTABLE PATENTS FILED:

Some of the recently filed patents on solubility enhancements strategies are shown in Table Ⅳ.

Table Ⅳ: - Notable filed patents.

Patent	Assignee	Key Innovation	ID
Composite comprising amorphous solid dispersion (2025).	Shin-Etsu Chemical Co., Ltd.	The invention describes a composite containing a medication, Hypromellose Acetate Succinate (HPMCAS), and Methyl Cellulose. This unique mixture and processing approach inhibit the recrystallization of the amorphous drug, hence retaining high solubility and stability substantially better than typical ASDs employing HPMCAS alone.	US20250319029A1
Polymer Salts for Improved Drug Delivery from Amorphous Solid Dispersions (2025).	Purdue Research Foundation	A novel method for amorphous solid dispersions using polymer salts (ASDs). Instead of employing standard polymers like HPMCAS, this invention employs polymeric salts that give greater drug dispersion and enable higher solubility improvement across a range of pH conditions.	US20250242031A1
Process for continuous hot melt granulation of low soluble pharmaceuticals (2024).	Merck Patent GmbH, Merck KGaA, Merck Life Science KGaA	Allows homogeneous dispersion of API within PVA polymer matrix while preventing API degradation from excessive heat exposure	US20240189239A1
Pharmaceutical composition (2022).	Astellas Pharma Inc	When compared to traditional polymers, PVA exhibits greater solubility enhancement at this particular saponification degree.	US11376328B2

FUTURE ASPECTS:

Future developments in improving the solubility of medications that are poorly soluble will probably concentrate on combining innovative formulation methods with state-of-the-art technology. Novel strategies like nanotechnology, which includes lipid-based nanoparticles and nanocrystals, provide encouraging paths to improve medication bioavailability and dissolution rates. Development will be further

accelerated by the use of artificial intelligence and machine learning to forecast solubility behavior and improve formulation parameters. Drug delivery may be revolutionized by personalized medicine techniques that adjust solubility augmentation tactics to the demands of specific patients. In general, resolving solubility issues and enhancing treatment results will need integrating interdisciplinary ideas.

CONCLUSION:

To sum up, improving the solubility of poorly soluble medications is still a significant issue in pharmaceutical research, since it has a direct bearing on the therapeutic efficacy and drug bioavailability. Particle size reduction, solid dispersions, complexation, and innovative formulation procedures are just a few of the tactics that have shown great promise in enhancing solubility and dissolving rates. A customized strategy that considers the drug's physicochemical characteristics, the planned method of administration, and patient-specific variables is necessary for the best results.

Conflicts of Interest: The authors declare no conflicts of interest

REFERENCES:

1. Ainurofiq A, Putro DS, Ramadhani DA, Putra GM, Do Espirito Santo LDC. A review on solubility enhancement methods for poorly water-soluble drugs. Journal of Reports in Pharmaceutical Sciences. Wolters Kluwer Medknow Publications; 2021. p. 137–47. doi:10.4103/jrptps.JRPTPS_134_19
2. Jagtap M. Recent Trends in Solubility Enhancement Techniques for Poorly Water-Soluble Drugs. International Journal of Scientific Research and Technology. 2025 Aug 11.
3. Kumari L, Choudhari Y, Patel P, Gupta G Das, Singh D, Rosenholm JM, et al. Advancement in Solubilization Approaches: A Step towards Bioavailability Enhancement of Poorly Soluble Drugs. Life. MDPI; 2023. doi:10.3390/life13051099
4. Bhalani D V., Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines. MDPI; 2022. doi:10.3390/biomedicines10092055
5. Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research. 2018 Sep 1;10(9):2205-11.
6. Gajanan Bajait M, Ghatmale R, mundhe B. IMPORTANCE OF SOLUBILITY AND SOLUBILITY ENHANCEMENT TECHNIQUES. Journal of Medical Pharmaceutical and Allied Sciences [Internet]. 2019;6:2403–16. Available from: www.jmpas.com
7. Godase CB, Babar AL, Gopal AB. A concise review on methods of solubility enhancement. Int Pharm Sci 2020; 11: 109. doi: 10.31531/2231. 2020;5896(2).
8. Nurul Batrisyia R, Kumar Janakiraman A, Chiau Ming L, Helal Uddin A, Islam Sarker Z, Kai Bin L. A Review On The Solubility Enhancement Technique For Pharmaceutical Formulations. Volatiles & Essent. Oils. 2021. Report.
9. Aiassa V, Garnero C, Zoppi A, Longhi MR. Cyclodextrins and Their Derivatives as Drug Stability Modifiers. Pharmaceuticals. Multidisciplinary Digital Publishing Institute (MDPI); 2023. doi:10.3390/ph16081074
10. Deshmukh AS, Tiwari KJ, Mahajan VR. Solubility Enhancement Techniques for Poorly Water-Soluble Drugs. International Journal of Pharmaceutical Sciences and Nanotechnology. 2017 May 31;10(3):3701–8. doi:10.37285/ijpsn.2017.10.3.1
11. Chettri A, Subba A, Singh GP, Bag PP. Pharmaceutical co-crystals: A green way to enhance drug stability and solubility for improved therapeutic efficacy. Journal of Pharmacy and Pharmacology. Oxford University Press; 2024. p. 1–12. doi:10.1093/jpp/rgad097 PubMed PMID: 37934904.
12. Sapra K, Sapra A, Singh SK, Kakkar S. Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs. Indo Global Journal of Pharmaceutical Sciences. 2012. Report.
13. Yadav KS, Soni G, Choudhary D, Khanduri A, Bhandari A, Joshi G. Microemulsions for enhancing drug delivery of hydrophilic drugs: Exploring various routes of administration. Medicine in Drug Discovery. Elsevier B.V.; 2023. doi:10.1016/j.medidd.2023.100162
14. dos Santos Lima B, Shanmugam S, de Souza Siqueira Quintans J, Quintans-Júnior LJ, de Souza Araújo AA. Inclusion complex with cyclodextrins enhances the bioavailability of flavonoid compounds: a systematic review. Phytochemistry Reviews. Springer; 2019. p. 1337–59. doi:10.1007/s11101-019-09650-y
15. Kim DH, Lee SE, Pyo YC, Tran P, Park JS. Solubility enhancement and application of cyclodextrins in local drug delivery. Journal of Pharmaceutical Investigation. Springer; 2020. p. 17–27. doi:10.1007/s40005-019-00434-2
16. Saha S, Roy A, Roy K, Roy MN. Study to explore the mechanism to form inclusion complexes of β-cyclodextrin with vitamin molecules. Sci Rep. 2016 Oct 20;6. doi:10.1038/srep35764 PubMed PMID: 27762346.
17. Abhijeet S, Ganesh S, Jadhav P, Atish V, Ashish B, kumar Redasani V. A Review on Solid Dispersion and Polymers Used For Solubility Enhancement Through Lyophilization Technique. Asian Journal of Pharmaceutical Research and Development. 2025;13(3):108–13. doi:10.22270/ajprd.v13i3.1563
18. Tekade AR, Yadav JN. A review on solid dispersion and carriers used therein for solubility enhancement of poorly water soluble drugs. Advanced Pharmaceutical Bulletin. Tabriz University of Medical Sciences; 2020. p. 359–69. doi:10.34172/apb.2020.044 PubMed PMID: 32665894.
19. Losada-Barreiro S, Celik S, Sezgin-Bayindir Z, Bravo-Fernández S, Bravo-Díaz C. Carrier Systems for Advanced Drug Delivery: Improving Drug Solubility/Bioavailability and Administration Routes. Pharmaceutics. Multidisciplinary Digital Publishing Institute (MDPI); 2024. doi:10.3390/pharmaceutics16070852
20. Sharma A, Chaudhary A, Singh B. A Review on Solubility Enhancement by Solid Dispersion Technique. J Pharm Res Int. 2021 Dec 29;77–87. doi:10.9734/jpri/2021/v33i63a35217
21. Malkawi R, Malkawi WI, Al-Mahmoud Y, Tawalbeh J. Current Trends on Solid Dispersions: Past, Present, and Future. Advances in Pharmacological and Pharmaceutical Sciences. Hindawi Limited; 2022. doi:10.1155/2022/5916013
22. Verma S. Solid Dispersion: Different methods of enhancing solubility and classification of solid dispersion. International Journal of Advance Research [Internet]. 2019. Report. Available from: www.IJARIIT.com
23. Sareen S, Joseph L, Mathew G. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012;2(1):12. doi:10.4103/2230-973x.96921
24. Patil H, Vemula SK, Narala S, Lakkala P, Munnangi SR, Narala N, et al. Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation—Where Are We Now? AAPS PharmSciTech. Springer Science and Business Media Deutschland GmbH; 2024. doi:10.1208/s12249-024-02749-2 PubMed PMID: 38355916.
25. Wang B, Liu F, Xiang J, He Y, Zhang Z, Cheng Z, et al. A critical review of spray-dried amorphous pharmaceuticals: Synthesis, analysis and application. International Journal of Pharmaceutics. Elsevier B.V.; 2021. doi:10.1016/j.ijpharm.2020.120165 PubMed PMID: 33309835.
26. Dhondale MR, Thakor P, Nambiar AG, Singh M, Agrawal AK, Shastri NR, et al. Co-Crystallization Approach to Enhance the Stability of Moisture-Sensitive Drugs. Pharmaceutics. MDPI; 2023. doi:10.3390/pharmaceutics15010189

27. Patole T, Deshpande A. CO-CRYSTALLIZATION-A TECHNIQUE FOR SOLUBILITY ENHANCEMENT. Int J Pharm Sci Res. 2014;5(9):3566. doi:10.13040/IJPSR.0975-8232.5(9).3566-76

28. Dumda AK, Tidke VN, Rawat S, Tigote RM. Advanced co-crystal technologies for effective solubility enhancement in BCS Class II and IV drugs. PEXACY International Journal of Pharmaceutical Science. 2024 Feb 15;3(02):86-106.

29. Serajuddin ATM. Salt formation to improve drug solubility. Advanced Drug Delivery Reviews. 2007. p. 603–16. doi:10.1016/j.addr.2007.05.010 PubMed PMID: 17619064.

30. Vishwanath Doke V, Sunder Kunwarpuriya A, Gupta K, Khutle NM. CO-SOLVENCY AND ANTI-SOLVENT METHOD FOR THE SOLUBILITY ENHANCEMENT: AN OVERVIEW. World J Pharm Res. 2020;9. doi:10.20959/wjpr20205-17317

31. Sharma M, Sharma R, Jain DK. Nanotechnology Based Approaches for Enhancing Oral Bioavailability of Poorly Water Soluble Antihypertensive Drugs. Scientifica. Hindawi Limited; 2016. doi:10.1155/2016/8525679

32. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. Journal of advanced pharmaceutical technology & research. 2011 Apr 1;2(2):81-7.

33. Liu Y, Liang Y, Yuhong J, Xin P, Han JL, Zhu R, et al. Advances in Nanotechnology for Enhancing the Solubility and Bioavailability of Poorly Soluble Drugs. Drug Design, Development and Therapy. Dove Medical Press Ltd; 2024. p. 1469–95. doi:10.2147/DDDT.S447496 PubMed PMID: 38707615.

34. Kim JY, Kim S, Papp M, Park K, Pinal R. Hydrotropic solubilization of poorly water-soluble drugs. J Pharm Sci. 2010;99(9):3953–65. doi:10.1002/jps.22241 PubMed PMID: 20607808.

35. Pignatello R, Corsaro R, Bonaccorso A, Zingale E, Carbone C, Musumeci T. Soluplus® polymeric nanomicelles improve solubility of BCS-class II drugs. Drug Deliv Transl Res. 2022 Aug 1;12(8):1991–2006. doi:10.1007/s13346-022-01182-x PubMed PMID: 35604634.

36. Tran P, Park JS. Application of supercritical fluid technology for solid dispersion to enhance solubility and bioavailability of poorly water-soluble drugs. International Journal of Pharmaceutics. Elsevier B.V.; 2021. doi:10.1016/j.ijpharm.2021.121247 PubMed PMID: 34740762.

37. Priya C, Kumari R, Ankita K. LIQUISOLID TECHNIQUE: AN APPROACH FOR ENHANCEMENT OF SOLUBILITY INTRODUCTION. Journal of Drug Delivery & Therapeutics [Internet]. 2011;2013(3):131–7. Available from: http://jddtonline.info

38. Chauhan J, Gupta D, Shah C, Upadhyay U. SOLUBILITY ENHANCEMENT TECHNIQUES. European Journal of Biomedical and Pharmaceutical Sciences [Internet]. 2024. Report. Available from: www.ejbps.com

39. Kureshi JB, Gupta VP, Tiwari B. FORMULATION AND EVALUATION OF RAPID RELEASE SYSTEM OF IRBESARTAN BY LIQUISOLID TECHNOLOGY. Current Research in Pharmaceutical Sciences. 2024 Oct 8;14(3):36–40. doi:10.24092/CRPS.2024.140302

40. NAIR HA, GADHIRAJU G, SUNNY G. DEVELOPMENT OF ORODISPERSIBLE TABLETS OF LORATADINE CONTAINING AN AMORPHOUS SOLID DISPERSION OF THE DRUG IN SOLUPLUS® USING DESIGN OF EXPERIMENTS. Int J Pharm Pharm Sci. 2023 Aug 1;19–27. doi:10.22159/ijpps.2023v15i8.47750

41. Islam N, Khan NU, Razzaq A, Menaa F, Khan ZU, Hussain A, et al. Loratadine oral bioavailability enhancement via solid dispersion loaded oro-dispersible films: Formulation, characterization and pharmacokinetics. Colloids Surf B Biointerfaces. 2023 Oct 1;230. doi:10.1016/j.colsurfb.2023.113526 PubMed PMID: 37647750.

42. Rao MRP, Pawar JA. Solubility Enhancement of Nevirapine Using B-Cyclodextrin Nanosponges. Int J Pharm Investig. 2023 Jul 8;13(3):496–502. doi:10.5530/ijpi.13.3.061

43. Chauhan N, Patel A, Patel R. Solubility Enhancement of Brexpiprazole for Schizophrenia using HPβ Cyclodextrin Ternary Complexation. Ars Pharmaceutica (Internet). 2025 Mar 19;66(2):126–38. doi:10.30827/ars.v66i2.32043

44. Sharma A, Park YR, Garg A, Lee BS. Deep Eutectic Solvents Enhancing Drug Solubility and Its Delivery. Journal of Medicinal Chemistry. American Chemical Society; 2024. p. 14807–19. doi:10.1021/acs.jmedchem.4c01550 PubMed PMID: 39185938.

45. Javed S, Mangla B, Sultan MH, Almoshari Y, Sivadasan D, Alqahtani SS, et al. Pharmaceutical applications of therapeutic deep eutectic systems (THEDES) in maximising drug delivery. Heliyon. Elsevier Ltd; 2024. doi:10.1016/j.heliyon.2024.e29783

46. Zhuo Y, Zhao YG, Zhang Y. Enhancing Drug Solubility, Bioavailability, and Targeted Therapeutic Applications through Magnetic Nanoparticles. Molecules. Multidisciplinary Digital Publishing Institute (MDPI); 2024. doi:10.3390/molecules29204854 PubMed PMID: 39459222.

47. Rusdin A, Mohd Gazzali A, Ain Thomas N, Megantara S, Aulifa DL, Budiman A, et al. Advancing Drug Delivery Paradigms: Polyvinyl Pyrolidone (PVP)-Based Amorphous Solid Dispersion for Enhanced Physicochemical Properties and Therapeutic Efficacy. Polymers. Multidisciplinary Digital Publishing Institute (MDPI); 2024. doi:10.3390/polym16020286

48. Zhang H, Wu H, Wang L, Gao Y, Galarza LM, Zhao Y, et al. Preparation and characterization of ASDs improves the solubility and dissolution performance of a PROTAC drug. J Drug Deliv Sci Technol. 2025 May 1;107. doi:10.1016/j.jddst.2025.106837

49. Shelke R, Velagacherla V, Nayak UY. Recent advances in dual-drug co-amorphous systems. Drug Discovery Today. Elsevier Ltd; 2024. doi:10.1016/j.drudis.2023.103863 PubMed PMID: 38141778.

50. Chen C. Artificial Intelligence aided pharmaceutical engineering: Development of hybrid machine learning models for prediction of nanomedicine solubility in supercritical solvent. J Mol Liq. 2024 Mar 1;397. doi:10.1016/j.molliq.2024.124127