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A review on solubility enhancement technique for pharmaceutical drugs

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Abstract

Solubility, a critical parameter governing the bioavailability and therapeutic efficacy of pharmaceutical compounds, often poses a significant challenge in drug development. This review article offers a thorough examination of several methods used to improve the solubility of medications that have low solubility, in order to overcome their limits. The discussion encompasses both conventional and emerging strategies, highlighting their mechanisms, advantages, and limitations. The study examines conventional methods such as particle size reduction, solid dispersion, and cosolvency, focusing on their historical importance and extensive use. Advances in nanotechnology, including nanosuspensions, nanocrystals, and lipid-based nanocarriers, are discussed for their potential to revolutionize solubility enhancement through improved drug delivery systems. An essential determinant in achieving optimal medication dosage absorption into the circulatory system is the demonstration of a pharmacological action is directly linked to the solubility of a substance. The primary challenge in formulating the new medicinal chemical is its limited water solubility. Medications with low solubility in water need large doses in order to achieve their highest effective concentration in the bloodstream when taken orally. The biopharmaceutical categorization system (BCS) classifies substances according to their solubility and permeability.

Regulatory agencies and health organizations have used this categorization approach to validate bioequivalence for chemicals that are both highly soluble and very permeable by using dissolution as a form of confirmation. Medications that have a poor capacity to dissolve in water have a slow pace of breaking down, which results in a reduction in the amount of the medication that may be absorbed into the bloodstream when taken orally.

Keywords: Solubility enhancement: BCS Classification; Pharmaceutical Drugs

1. Introduction

Solubility is the maximum amount of solute that may be dissolved in a given amount of solvent. It may be characterized both mathematically and qualitatively. Quantitatively, it is precisely defined as the solute's concentration in a saturated solution at a certain temperature. Solubility refers to the inherent tendency of two or more chemicals to form a homogeneous molecular combination [1]. Drug solubility refers to the highest concentration at which the drug solute may be dissolved in a given solvent, taking into account certain conditions such as temperature, pH, and pressure. The solubility of a drug in a saturated solution is a fixed characteristic, whereas the dissolution rate of the medication is a variable characteristic that is more directly associated with the rate at which the drug becomes available for absorption in the body. A solubility chart provides a comprehensive list of ions and their behavior when combined with other ions, indicating whether they will form precipitates or stay in an aqueous state. Solubility is a crucial factor in attaining the appropriate drug concentration in the bloodstream, which is necessary for the pharmacological reaction to occur [2]. Medications that are well soluble show good oral absorption and, as a result, good bioavailability [3].

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Solubility is a crucial pre-formulation attribute that regulates the targeted drug concentration in the systemic circulation. The bulk of newly discovered chemical entities have low solubility, which leads to low bioavailability [4]. The drug's solubility is a crucial characteristic since it influences the drug's release, absorption, rate of dissolution, and ultimately its bioavailability. Therefore, processing is required to enhance the medication's water solubility and dissolution [5].

1.1. Solubility Expressions

In table 1 different solubility expressions were mentioned and following are some properties related to solubility.

- A medicine is considered poorly soluble if its aqueous solubility is less than 100 ug/ml.
- Poor dissolution: < 0.1 mg/cm 2/min for intrinsic dissolution rate
- Molecular weight greater than 500
- A high energy crystal.

Table 1 Different Solubility Expressions

Sr. No.	Descriptive term	Part of solvent required per part of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	from 100 to 1000
6	Very slightly soluble	From 1000 to 10000
7	Insoluble or partially insoluble	More than 10000

1.2. BCS Classification System

The US Food and Drug Administration (FDA) created the Biopharmaceutics Classification System (BCS). categorizes pharmaceuticals into four classes according on their solubility and permeability characteristics. Low solubility causes a soluble obstacle in Classes II and IV of the system, where the medication absorption process's rate-limiting phase is dissolution. The drugs are categorized by the Biopharmaceutical Classification System (BCS) according to their intestinal permeability and intrinsic solubility. Good intestinal permeability and solubility contribute to a drug's high bioavailability. The bioavailability of drugs with low solubility and permeability is dependent on their solubility and permeability, respectively. The majority of medications in the pharmaceutical industry today have poor solubility. Poor solubility has been effectively addressed by a number of solubility enhancement strategies [6].

In Table 2 depicted the BCS Classification of drugs with examples.

Table 2 BCS Classification System of drugs

Sr. No.	BCS Class	Solubility	Permeability	Example
1.	Class I	High	High	Metoprolol, Amlodipine
2.	Class II	Low	High	Ibuprofen, Naproxen
3.	Class III	High	Low	Cimetidine, Ranitidine
4.	Class IV	Low	Low	Furosemide, Nelfinavir

1.3. Importance of Solubility

The oral bioavailability is influenced by several aspects, such as the medication's water solubility, its capacity to pass through membranes, the pace at which it dissolves, its metabolism before reaching the systemic circulation, its metabolism before entering the systemic circulation, and its vulnerability to processes that remove it from the body. Poor solubility and inadequate permeability are the primary factors responsible for low oral bioavailability [7].

Solubility is also significant for various types of dosage forms, such as parenteral formulations. In order to get the proper concentration of a drug in the systemic circulation and trigger the required pharmacological response, solubility is an essential component. Insufficiently soluble medicines may need elevated dosages to achieve therapeutic levels in the bloodstream after oral use. The primary challenge in formulating novel chemical entities and developing generic drugs is the limited solubility in water. In order for a medicine to be absorbed, it must exist in the form of a watery solution at the location where absorption takes place. The ideal solvent for liquid pharmaceutical formulations is water. Most drugs have little solubility in water because they are either weakly basic or moderately acidic. Practically insoluble in water, over 40% of new chemical entities (NCEs) generated in the pharmaceutical sector exhibit this characteristic. The low water solubility of many medications results in sluggish absorption, leading to insufficient and inconsistent bioavailability, as well as potential damage to the gastrointestinal mucosa. The solubility of orally taken medications is the primary factor that determines the pace at which they may reach the target concentration in the bloodstream, thereby affecting their pharmacological effectiveness [8].

1.4. Factors affecting solubility

1.4.1. Particle size

The drug's dissolving rate rose when the size of the particles shrank, leading to a rise in the specific surface area. In their investigations, Chu et al. noticed substantial changes in dissolving rate during the first portion of the dissolution study based on variations in particle size and particular surface areas. Conversely, in the latter phases, the rate at which the surface dissolves remained almost constant, independent of the size of the particles. The mathematical evaluation of these facts indicated a considerable correlation between the particle size distribution and the dissolving rate of poorly soluble medicines [9].

1.4.2. Temperature

The solubility data, which varied with temperature, were used to ascertain the thermodynamic characteristics of dissolution, such as Gibb’s energy, enthalpy, and entropy. The solubility exhibits the anticipated upward trend with temperature [10]. During endothermic dissolution processes, the overall energy change that occurs when bonds are broken and formed leads to the absorption of heat energy into the system when the solute dissolves. Additional thermal energy is added to the system as its temperature increases. Le Chatelier's Principle states that in response to an increase in heat, the system will prefer the dissolving process in order to absorb the extra heat energy. As a result, increasing the temperature will make the solute more soluble. Exothermic reactions include the release of heat energy upon the dissolution of a solute in a solution. Elevating the temperature results in the addition of a greater amount of thermal energy to the system. In accordance with Le Chatelier's Principle, the system will respond to the surplus heat energy by suppressing the dissolution process. Raising the temperature results in a reduction in the solubility of the solute [11].

Elevating the temperature and introducing a pharmacological compound result in an augmentation of The core radius and aggregation number are both, ultimately leading to a more desiccated core [12].

1.4.3. Molecular size

Essentially, as the molecular weight increases, two opposing effects occur: a reduction in the pace at which chains move and an increase in the physical attraction of a polymer. The impact of reducing particle size is more noticeable in systems with smaller molecular weights, and changing molecular weights have less of an impact over time. Higher molecular weight systems exhibit bigger aggregates upon rehydration after the drying process. Our study findings indicate that polymers with lower molecular weight are more optimal than bigger polymers for effective nano comminution. This suggests that the kinetic factors of molecular weight have a significant role [13].

1.4.4. Salt Form

with smaller molecular weights, and changing molecular weights have less of an impact over time. The most favored method for enhancing the solubility of a substance in water for the purpose of creating liquid formulations for injection is via the process of salt creation. In the field of solid dosage forms, Nelson [2], [3] conducted research in the 1950s which showed that the rate at which salt forms of some weakly acidic chemicals dissolve under gastrointestinal (GI) pH circumstances is much greater than that of their corresponding free acid forms. He ascribed the increased rate of dissolution of a salt to its greater solubility (compared to the unbound acid form) in the aqueous diffusion layer surrounding the solid. Significant variations were seen in the absorption rates and levels of novobiocin [4] and tolbutamide [5] in comparison to their corresponding sodium counterparts [14].

1.4.5. Pressure

Changes in pressure almost never affect the solubility of solids or liquid solutes, however for gaseous solutes, a rise in pressure causes an increase in solubility and a reduction in solubility.

1.4.6. Solute and solvent properties

At room temperature, the solubility of lead (II) chloride in water is limited to 1 gram per 100 grams of water, but zinc chloride may dissolve up to 200 grams. The significant disparity in the solubilities of these two compounds arises from variations in their inherent characteristics [15].

1.5. Techniques for Solubility Enhancement

Significant challenges faced by several pharmaceutical firms include low water solubility and limited bioavailability [16]. Pharmaceutical compounds that possess high solubility have favorable absorption when taken orally, leading to enhanced bioavailability. The most critical stage in the development of drugs, especially for oral medications, is the improvement of drug solubility [16].

In the process of developing new medications, it may be very difficult to increase a drug's solubility and, therefore, its oral bioavailability, especially for oral drug delivery systems. There are several methods documented in literature to improve the solubility of drugs that have low water solubility. The selection of procedures is based on specific factors like the characteristics of the medicine being considered, the qualities of the selection of excipients, and the type of the planned dosage form. Orally given medications achieve full absorption only when they have sufficient solubility in the stomach and exhibit excellent bioavailability [17]. The drug's solubility is a crucial factor to be taken into account during the production of pharmaceutical goods. The low solubility of medicines in water reduces their bioavailability [18]. Numerous techniques have been used to address the solubility problem, but the expensive and sophisticated equipment has not been able to raise the proper bioavailability of drugs with poor solubility. [19].

The approaches for improving solubility may be classified into physical modification, chemical modification of the medicinal ingredient, and additional ways shown in figure 1.

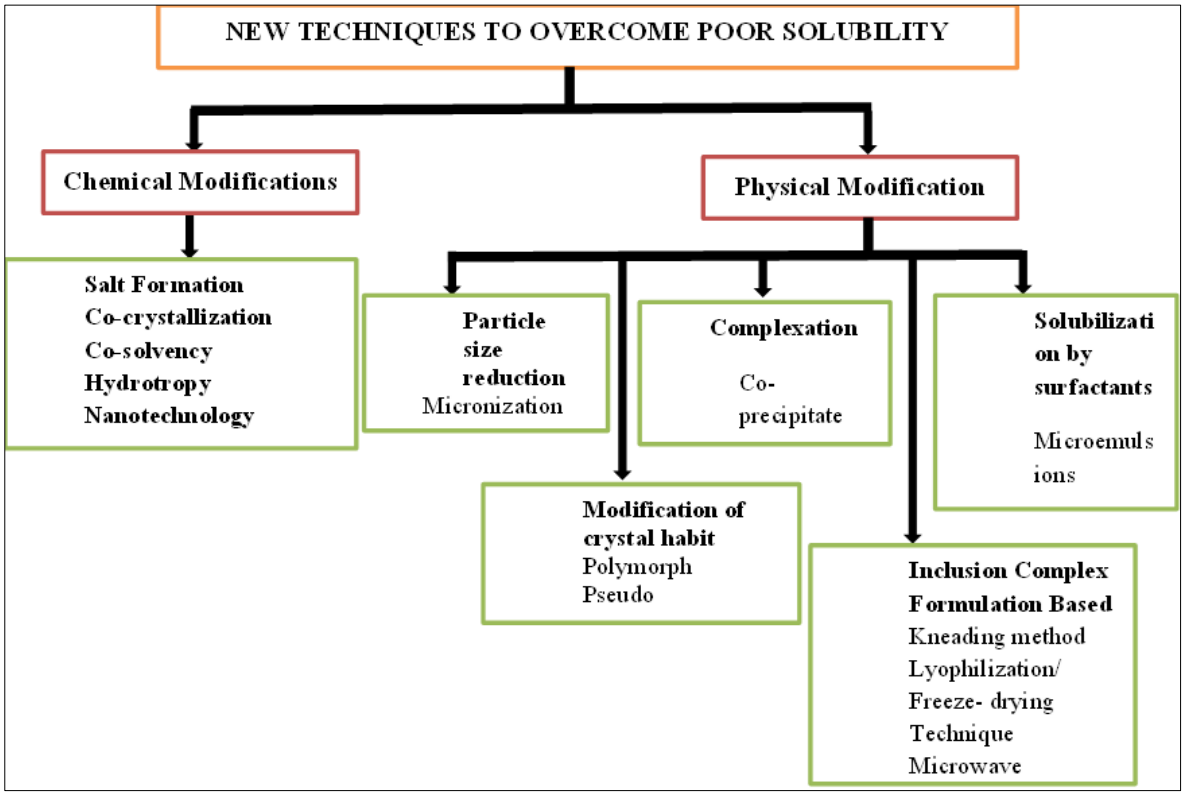

Figure 1 Techniques for solubility enhancement

2. Chemical modification

The solubility of a substance may be enhanced by introducing polar functional groups such as carboxylic acids, ketones, and amines. By strengthening hydrogen bonds and enhancing the contact with water, this is accomplished. The chemical alteration of is at the forefront of advancements in biological imaging and biopharmaceutics. There are different methods for chemical modifications which include Salt Formation, Co-crystallization, Co-solvency, Hydrotropy, Use of novel solubilizer and Nanotechnology [20].

2.1. Salt formation

The process of salt production is widely recognized as the greatest prevalent and efficient approach to enhance the solubility and dissolution rates of both acidic and basic pharmaceutical compounds. Multiple variables, including S0 (intrinsic solubility), pH, pKa, Ksp (solubility product), and pH max (pH of maximum solubility), contribute to the overall outcome [14]. Oftentimes, an active pharmaceutical ingredient (API) cannot be developed in its original state owing to different instability problems. Consequently, they undergo a transformation into solid structures such as salts, co-crystals, solvates, hydrates, and polymorphs. Each of these properties has a distinct impact on the stability, bioavailability, purity, and manufacturability of the medication, enhancing its overall performance qualities. The method of forming salts of weak acids and bases has been used for many years to enhance the solubility of poorly soluble medication candidates. Salts are produced by the process of ionization of a chemical in a solution. This method works effectively for both solid dosage forms and parenteral and other liquid formulations. An acidic or basic medicine is transformed into a salt form that exhibits higher solubility compared to the original drug. An example of this strategy that is available is Progesterone, which is a steroid that is not Water soluble, however it may also dissolve in peanut oil. Other examples which include Aspirin, Theophylline, and Barbiturates [21].

2.2. Co-crystallization

A multicomponent crystal that develops between two solid substances under ambient conditions is known as a co-crystal, with at least one component being an acceptable ion or molecule. Co-crystals are composed of an API and an equivalent quantity of a co-crystal former that is accepted for use in pharmaceuticals. They are supramolecular complexes that are nonionic in nature. They are used in pharmaceutical research to tackle challenges related to physical properties, such as solubility, stability, and bioavailability. Importantly, they do this without altering the chemical makeup of the API.

Co-crystallization mitigates the numerous physical, chemical, or physiological limitations of an API. Co-crystallization modifies the molecular interactions and composition of medicinal materials, making it a superior method for optimizing therapeutic characteristics. Co-crystals provide an alternative route for co-crystallization of any API, irrespective of its acidic, basic, or ionizable characteristics [22].

2.2.1. Different techniques for co crystallization

Solvent Evaporation

The pharmaceutical industry makes extensive use of the solvent evaporation technology for microencapsulation [23]. Micro and nanospheres may be created via a range of methods, including phase or wet inversion, polymerization, solvent evaporation, solvent removal, hot-melt encapsulation, coacervation, spray drying, and spray congealing. Solvent evaporation is one of the most popular, well-researched, simple, and patent-applicable techniques among all of them [24]. This technique entails dissolving the coformers in an appropriate solvent and then evaporating the solvent. During the process of evaporation, an excess of solute is produced, which causes the formation and development of cocrystals. This experimental screening approach is commonly used for assessing the potential development of cocrystals. It is favoured for its straightforwardness and effectiveness in identifying the optimal circumstances for cocrystal formation. Multiple writers have effectively used this method to identify cocrystals. In the cocrystal screening procedure using solvent evaporation, the coformers' solution may be rapidly evaporated using a rotary evaporator or allowed to evaporate naturally in a controlled setting, such as an incubator or a fumehood, until crystals become visible [25].

Various Methods of Solvent Evaporation

- Single emulsion method
    - This technique of drug entrapment is fairly efficient due to the inherent problem of medications that are water soluble and somewhat water soluble being encapsulated quite poorly. The inventory of nanoparticles produced using the solvent evaporation procedure using the single emulsion method.

- Multiple emulsion method
    - This technique is often used to produce microspheres containing water-soluble medicines, proteins, peptides, and vaccines, which are typically in the form of double or multiple emulsions.

Slurry Co Crystallization

Slurry cocrystallization is a method that may be used as an alternative to produce cocrystals when the coformers have different solubilities. The method starts by suspending one or both of the coformer crystals in a tiny quantity of solvent, thereby causing a slurry to develop. During the nucleation and growth of the stable cocrystal, the individual crystals of the single component disintegrate, similar to the process of solution-mediated polymorphic transformation. This approach is suitable for cocrystal formation only if the desired cocrystal is the most thermodynamically steady shape compared to other crystal forms. Therefore, the method may also be used to evaluate the most enduring configuration of the crystal [25].

Solvent drop grinding

The method demonstrates the activation of targeted polymorph transformations via the utilization of two individual systems. In this process, a certain crystal structure undergoes conversion upon exposure to solid-state grinding when a small amount of a specified solvent is present [26]. The utilization of the solvent drop grinding technique offers various notable benefits, including the addition of only a small amount of solvent (an environmentally friendly approach), the avoidance of excessive solvent evaporation, a significantly shorter duration for the formation of co-crystal phases, the use of compatible components in an equimolar ratio for the co-crystal, enhanced co-crystal formation, and the potential to obtain pure co-crystals [27].

Sonocrystallization Method

Sonocrystallization accelerates the formation of nuclei, resulting in the production of smaller crystals with a narrower range of sizes compared to crystallizations that occur without any agitation. The precise process via which ultrasound triggers nucleation is still not fully understood, despite the existence of papers suggesting the possible involvement of shockwaves and the promotion of heterogeneous nucleation. Furthermore, the disintegration of molecular crystals under the influence of ultrasonic waves is a developing phenomenon in the fields of sonocrystallization and nucleation. Decoupling studies were conducted to verify that the primary cause of crystal breaking is the interaction between shockwaves and crystals [28].

2.3. Co-solvency/ Solvent Blending

Cosolvency, a safe and non-toxic organic solvent blended with water, is the most common way to increase the solubility of prescription medications in water. The pharmaceutical business often utilizes ethanol, propylene glycol, glycerine, glycofural, and polyethylene glycols as cosolvents. The co-solvency of solvent mixes that are not water-based is also significant from a pharmaceutical perspective. In pharmaceutical applications, it is important to consider that the inclusion of a cosolvent in an aqueous solution might impact the chemical stability of the medication, the acid dissociation constants of the solute, as well as the viscosity and surface tension of the solution. The cosolvency models may be categorized as theoretical, semi-empirical, and empirical models. The theoretical models provide fundamental insights into the solution, while the empirical models are well-suited for studying solubility correlations. The Yalkowsky log-linear model is a basic cosolvency model that estimates the solubility of a drug in water-cosolvent mixtures based on the drug's solubility in water. On the other hand, the Jouyban-Acree model predicts solubility with an acceptable level of error, but requires an additional data point (the solubility in pure cosolvent) as input in the prediction process [29].

To enhance the solubility of a pharmaceutical that is not easily soluble in water, one may add a water-miscible solvent in which the drug has high solubility. This is performed by reducing the tension between the aqueous solution and the hydrophobic medication. The pharmaceutical formulation maintains a steady liquid condition. The co-solvent approach is appropriate for poorly soluble compounds that are lipophilic or highly crystalline and have a high solubility in the mixture of solvents. The main use of this substance is in injectable drug formulations because of the low toxicity of some co-solvents and their excellent ability to dissolve nonpolar medications. The often-used cosolvents are glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol [21].

2.4. Hydrotropy

Despite being a well applied scientific method, hydrotropy aids in everyone's solubilization. From the idea's origin in 1916 until its first application in 1982 for improving drug solubility in the direction of improved pharmaceutical

analysis, the idea was not used to drug analysis for 66 long years [30]. Substances or compounds that enhance the ability of a solute to dissolve in a certain solvent are referred to as "salting in" agents, whereas those salts that reduce the solute's solubility are referred to as "salting out" agents. The presence of hydrotropic salts, which are soluble in water and have large anions or cations, causes the phenomena of "salting in" of non-electrolytes. This process is referred to as "hydrotropism". Hydrotropic solutions lack colloidal characteristics and are characterized by a feeble contact between the hydrotropic agent and solute. Hydrotropy refers to the enhancement of solubility in water caused by the presence of a significant quantity of additives. The enhancement of solubility is mostly attributed to complexation, which involves a weak contact between hydrotropic agents such as sodium benzoate, sodium acetate, sodium alginate, urea, and the medications with low solubility. Hydrotropy is a unique and unparalleled method of increasing the solubility of poorly soluble substances using specific chemical components called hydrotropes [31].

The hydrotropic agents' synergistic effect produced a spectacular increase in solubility. Because of this unique quality, mixed hydrotropes outperform simple hydrotropy and produce higher percent yields of components in extraction processes and separation methods such as chromatography. Numerous scholars came to the conclusion that since hydrotropes are composed of two parts—one polar and the other nonpolar—they are amphiphilic in nature [32].

2.5. Nanotechnology

Nanotechnology has defined a new perspective by altering the characteristics of nanoparticles and using them in the production of nano formulations, nutritional supplements, and the food business. Nanomaterials possess unique characteristics due to their tiny dimensions and large surface-to-volume ratio, making them very suitable for applications in the nutraceuticals and food industry [33].

Nanotechnology is a field that encompasses the examination and use of materials and structures at a very small size, often less than 100 nanometers (nm). For several novel chemical compounds with very poor solubility, the improvement of oral bioavailability by micronization alone is inadequate due to the micronized product's limited surface area for dissolving. Consequently, the subsequent approach used was nanonization [21].

Nanotechnology methods have been widely used to increase the solubility, oral bioavailability, stability, and controlled release of resveratrol. The anticancer activity of resveratrol nanoparticles has been significantly increased, both in laboratory settings (in vitro) and in living organisms (in vivo). This suggests that using resveratrol nanoparticles might be a promising approach in combating different types of malignancies [34].

2.5.1. Advantages of nanotechnology

The technique results in the formation of nano or micro-scale spherical particles with smooth surfaces, a restricted range of particle sizes, and a large specific surface area. Consequently, it increases the rate at which it dissolves and its solubility.

2.5.2. Drawback of nanotechnology

The issue of agglomeration is fundamental and poses significant challenges to solve.

3. Physical Modifications

3.1. Particle size reduction

The solubility of a medicine is often inherently linked to the size of its particles. As the size of particles decreases, the ratio of surface area to volume rises. A greater surface area facilitates enhanced contact with the solvent, resulting in an elevation in solubility [35]. The process of drug micronization has traditionally been regarded as the most efficient approach to achieve these improvements. Nevertheless, the decrease in size of some innovative chemical compounds within this range does not significantly affect their already very low solubility. Reducing the size to the nanometric scale is crucial [36]. The conversion rates reached a maximum of around 50% by physical size reduction, whereas chemical modification produced conversions above 70% independent of the size of the biomass particles. Research on thermochemical pretreatments, considering particle size as a variable, has shown a diverse range of maximum sizes [37]. The efficacy of particle size reduction techniques relies on crucial elements such as the used technology, equipment, and physicochemical qualities of the medicine. Wet bead milling and high-pressure homogenization are two frequently used techniques for lowering the particle size of poorly soluble medications, leading to efficient formulation and commercialization. Nevertheless, these methods have constraints in their ability to reduce particle size effectively, including time-consuming manufacturing processes and the need of using a micronized medication as the initial

substance. These technologies were devised to enhance the efficiency of established approaches in reducing particle size [38]. The digestive absorption of poorly soluble medicines is contingent upon their dissolving rate. Reducing the particle size of these medications enhances their dissolving rate. Fine grinding mills, such as jar mills or fluid energy mills, are used for the purpose of micronizing particles. These techniques were used on griseofulvin, progesterone, spironolactone, and diosmin. Micronization enhanced the gastrointestinal absorption of each medicine, hence increasing their bioavailability and therapeutic effectiveness [39].

3.1.1. Micronization

The use of medication powders comprising micronized drug particles has been on the rise in various pharmaceutical dosage forms as a means to address challenges related to dissolution and bioavailability. The majority of recently created medications have low water solubility, which restricts their capacity to dissolve quickly and be absorbed by the body. Micronizing the medication particles might increase the solubility rate. The particular micronization process used affects the features of the micronized medicinal material, such as particle size, size distribution, shape, surface properties, agglomeration behavior, and powder flow [40].

3.1.2. Nanosuspension

The nanosuspension drug delivery system (DDS) was first created in 1994 and has since garnered increasing interest as a viable alternative for poorly soluble medicines [41]. Nanosuspensions consists of pure drug particles in submicron colloidal dispersions, stabilized by a minimal number of excipients. These nanosuspensions have the potential to significantly improve the saturation solubility, dissolution rate, and adherence of drug particles to cell membranes. Nanosuspensions are ideal for medications that need high dosage or have restricted administration volume [42]. The inherent features of nanosuspension, including its ease of modification, process flexibility, targeting capabilities, and changed pharmacokinetic profile leading to safety and effectiveness, have made it an effective and promising approach for delivering insoluble medicines [43]. The objectives of developing nanosuspensions of nanoscale materials are expanding owing to their immense potential as a versatile drug delivery technology with a broad spectrum of applications. Nanosuspension is an exceptional method for enhancing the bioavailability of medicines that have low solubility. Nanosuspension drug delivery has a broad spectrum of applications, including oral, injectable, transdermal, inhalation, peroral, ocular, pulmonary, and topical administration. It achieves these applications by enhancing bioavailability, reducing dosage requirements, minimizing gastric irritation, decreasing variability between subjects, and improving adhesion to the intestinal membrane. Nanosuspensions are used to regulate the size, surface characteristics, and release of pharmacologically active substances, with the aim of achieving targeted medication action at the most effective rate, modifying the dosing schedule and increasing the bioavailability of medications with poor solubility [44].

3.2. Modification of Crystal Habit

Varying solvents and processing conditions may modify the crystal morphology and also induce changes in the polymorphic form. Moreover, changes in behavior might occur due to the formation of crystals over time. Therefore, it is necessary to comprehend the aspects that affect crystal habit and to thoroughly assess its impact on the effectiveness of dose forms [45]. The alteration of the habit was ascribed to the selective adsorption of PSA onto the most rapidly developing crystal face of the needle-like crystal structure, hence impeding its development. The griseofulvin and PSA particles were characterized using scanning electron microscopy (SEM), which provided findings in line with a method of selective growth inhibition [46]. Various polymorphic forms may impact the efficacy of the medication. Furthermore, isomorphic crystals exhibit distinct chemical and physical characteristics as a result of alterations in their crystal habit. Nevertheless, it remains uncertain if the crystal habit leads to distinct pharmacological effects. This research aimed to examine if the pharmacological efficacy of ibuprofen may be influenced by the diversity of its crystal morphology [47].

3.2.1. Polymorph

Polymorphism is a frequent occurrence in pharmaceuticals, where it may negatively impact their quality by altering their physical and chemical characteristics, including solubility, and thus decreasing their bioavailability. Polymorphism is the phenomenon where a substance may exist in several crystal structures. Polymorphs are substances that have the same chemical makeup but vary in the arrangement of their molecules in the crystalline form [48].

3.2.2. Pseudopolymorphs

The substance exhibits several polymorphs, each characterized by distinct solid crystalline phases and internal crystal lattices. In the field of pharmaceuticals, the presence of polymorphism and pseudo polymorphism may have an impact on the drug's bioavailability and its effectiveness in clinical applications [49].

3.3. Complexation

The shape of protein aggregates has a vital function in the electrostatic complexation of protein and polysaccharide, as well as in determining the functional qualities of the resulting complexes. These interactions are of great significance in the advancement of novel dietary components [50]. In order for medications to be effective when taken orally or applied topically to the eye, they need to have a certain level of solubility in water. Additionally, pharmaceuticals need to be soluble in order to be produced as aqueous solutions for methods such as parenteral delivery. Various techniques may be used to improve the solubility of pharmaceuticals that have low solubility in water, one of which involves the utilisation of solubilizing complexing agents. There are a multitude of complexes, with varying degrees of water solubility [51].

3.3.1. Co-precipitate method

The method of directly co-precipitating amorphous solid dispersions (ASDs) during the last phase of chemical processing is known as co-processing. [52]. The use of co-precipitation represented an innovative approach to enhance the functional characteristics of proteins in their pure form [53]. In order to accomplish targeted medication administration, titanium with nanotubular structures was anodized and then loaded with penicillin-based antibiotics. This was done utilising a co-precipitation approach, where the drug molecules were combined with simulated bodily fluid to collectively precipitate with calcium phosphate crystals [54]. The technique also relies on the co-precipitation of the active component with glycinin, a biodegradable protein matrix derived from edible soybean protein, facilitated by the presence of carbon dioxide. Glycinin readily precipitates under isoelectric circumstances and acts as the framework in which the active component is captured during the precipitation process. The lipase enzyme derived from *Candida rugosa* was effectively co-precipitated with the protein pellet as a means of demonstrating the underlying concept [55]. A prior study used a co-precipitation approach with samarium hydroxide to determine the co-precipitation behaviour of several elements. The results indicated that this behaviour was influenced by the elements' propensity to produce hydroxide precipitates and/or ammine complex ions [56]. Nevertheless, the comprehensive elucidation of the immobilisation of signal molecules using calcium phosphate coatings and their biological use is lacking. This study provides a comprehensive summary and analysis of the current coprecipitation techniques and tactics used in biological applications [57].

3.4. Inclusion Complex Formulation Based

3.4.1. Kneading method

Kneading rapidly combines high-performance materials (HPs) with a solution of polyethyleneimine (PEI) polymer, resulting in the generation of a "dough" that aids in the creation of stable suspensions in water-based solutions [58]. The ultimate dimensions may be adjusted based on the quantity and features of the salt-kneading substance. The presence of this technique enables pharmaceutical researchers to use a size-reduction procedure that produces minuscule, spherical, and easily flowing particles of the poorly soluble API, while also minimizing the occurrence of undesirable needle-like shapes [59]. In order to optimize the kneading process, the quantity of solvent and mixing time was used as independent variables, and the super disintegrants were utilized to create the appropriate formulation [60]. Pharmaceutical powders were kneaded when wet using different blade components and operation circumstances. The compressive characteristics of a wet kneaded mass were examined, and the distribution of a hindering liquid (water) throughout the mass was explored by analyzing a tracer aqueous pigment [61]. Out of the many ways of production, the SiO2-MgO catalysts produced by wet-kneading generally exhibit superior performance due to the formation of magnesium silicates on the catalyst's surface during the wet-kneading process. While the thermal treatment is crucial as the last stage in catalyst synthesis, the impact of the calcination temperature of the wet-kneaded SiO2-MgO on the Lebedev process remains unclear [62]. The kneading process is affected by several factors, including the duration of kneading, the temperature of the dough, the speed of kneading, the aeration of the dough, the temperature of the water, and the overall water content. Properly managing the kneading process and using enhancement tactics may greatly improve the rheology of dough and the subsequent features of bread [63].

3.4.2. Lyophilization/ Freeze- drying Technique

Freeze-drying is an intricate procedure, despite its few steps. This is due to the fact that the processes of freezing, sublimation, desorption, and reconstitution all affect the quality of the finished product and might expose it to different pressures at each level. [64]. Freeze-drying, also known as lyophilization, eliminates water from a frozen material by the processes of sublimation and desorption. The process may be conceptualized as a three-step sequence including of freezing, primary drying, and secondary drying [65]. Cryopreservation has emerged as a crucial method for safeguarding biological products [66]. Various forms of polymeric and lipid nanoparticles were created and analyzed.

Subsequently, the samples underwent spray freeze drying by being sprayed into a stream of cold air containing varying cryoprotectants. The resulting frozen spherules were then collected for further freeze drying [67].

3.4.3. Microwave irradiation method

Utilizing microwave irradiation in the peptide synthesis in solid phase enhances product purity and decreases reaction time [68]. Utilizing process intensification techniques like ultrasound and microwave irradiation may improve reaction efficiency by increasing product recovery, reducing the generation of by-products, and decreasing energy usage [69]. The use of microwave irradiation, which has distinct heating processes, may stimulate drug-polymer interaction and alter the dissolving characteristics. Microwaves provide several advantages, including enhancing product quality, boosting energy efficiency, and lowering processing times. Microwave technology offers a novel approach to heat and dry substances in the realm of pharmaceuticals [70]. An investigation was conducted on the development of silver nanostructures, both spherical and dendritic, using microwave irradiation. The focus was on the relationship between the irradiation period and the speed and environmental impact of the formation process [71]. The optimization of solvent selection, solvent volume, microwave power, irradiation period, and sample mass were carried out using the simplex technique [72].

3.5. Solubilization by surfactants

Surfactants have the capacity to decrease surface tension at low levels, leading to emulsification, foaming, wetting, and solubilization [73]. Surfactants that create micelles in water-based solutions are very effective in dissolving phospholipids by transforming them into mixed micelles [74]. The assessment of solubilization capability included the evaluation of many parameters, such as the number of aggregation (Nagg), binding constant (K1), micelle-water partition coefficient (Kmc), molar solubilization ratio (MSR), critical micellar concentration (CMC), and Stern-Volmer constant (Ksv) [75]. The notion of micellar solubilization plays a crucial role in the transportation of medications that have low solubility in water. Comprehensive solubility studies are necessary to make a sensible decision about the appropriate kind and quantity of surfactant to be included in a formulation [76]. Surfactants have a tendency to distribute themselves between vesicles and the surrounding fluid. It has been shown that only surfactants with appropriate hydrophobic properties have the capability to dissolve vesicles by creating tiny mixed micelles. Surfactants without sufficient hydrophobicity tend to remain in the bulk solution, with only a limited number of them being able to enter the vesicle [77]. An investigation was conducted on the solubilization of three primary constituents, namely palmitic, oleic, and linoleic acids, in palm oil using ethoxylated surfactants [78].

3.5.1. Microemulsions

The total miscibility of water and oil may be achieved by introducing an adequate quantity of an amphiphilic substance, such as soap or detergent. The term "microemulsions" is used to refer to stable homogenous solutions due to its historical significance [79]. A microemulsion is a thermodynamically stable system composed of water, oil, surfactants, and cosurfactant. In order to facilitate the production of microemulsions, it is frequently necessary to include a cosurfactant, since it helps to reduce the interfacial tension at the contact. The tiny droplet diameter of microemulsions is responsible for their transparency. The droplet size in stable microemulsions typically falls between 10 and 140 nanometers. Microemulsions are visually shown as regions of stability in triangular phase diagrams, with each corner of the triangle representing a specific component. Microemulsions are, in fact, quaternary (pseudoternary) systems [80]. Jack H Schulman discovered microemulsions, significant advancements have been achieved in using microemulsion systems in many scientific and industrial processes. Microemulsions are homogeneous systems composed of water, oil, and an amphiphile, and they exhibit optical isotropy. These systems provide advantages because of their thermodynamic stability, optical transparency, simplicity of synthesis, and increased rates of diffusion and absorption [81].

3.5.2. Self microemulsifying drug delivery system

The use of self-microemulsifying drug delivery system (SMEDDS) has become an important approach for formulating poorly water-soluble drugs in order to improve their bioavailability. Nevertheless, SMEDDS formulations have certain drawbacks, such as drug precipitation inside the body, difficulties in managing the formulation, restricted absorption by the lymphatic system, absence of reliable in vitro testing for prediction, and oxidation of unsaturated fatty acids [82]. A supersaturable self-microemulsifying drug delivery system (SuSMEDDS) was created to improve the solubility and absorption of telmisartan (TMS), an anti-hypertensive medication that is not easily soluble in water [83]. A self-emulsifying drug delivery system (SEDDS) is a homogeneous blend of lipid, surfactant, and co-surfactant that, when exposed to a gentle stirring in an aqueous solution, generates a fine emulsion. SEDDS is regarded as a promising platform for orally administering hydrophobic drugs to address the issues of their low and inconsistent bioavailability [84]. SMEDDS, which is a lipid-based nano-formulation of type IV, has garnered attention in the pharmaceutical research

sector because of its ability to customize the physicochemical characteristics of pharmaceutical compounds [85]. An in vivo evaluation was conducted to assess the impact of a SMEDDS on the pharmacokinetics of acyclovir. Acyclovir is an antiviral drug with low bioavailability (BA) and a short half-life ($t_{1/2}$). The evaluation focused on the optimized drug loading capacity, stability, dispersibility in aqueous media, and in vitro drug release profile of the SMEDDS [86]. The SMEDDS also addresses the constraints associated with hydrophobic substances, hence improving their bioavailability. Hence the solubility of a hydrophobic drug in lipid excipients, such as oil, surfactant, and co-surfactant, has a significant impact on the drug loading and the stability [87]. The use of SMEDDS was employed to augment the oral bioavailability and lymphatic absorption and conveyance of Hup-A. The researchers used a single-pass intestinal perfusion (SPIP) method and a chylomicron flow-blocking strategy to investigate the absorption of the substance in the intestines, its distribution in the mesenteric lymph nodes, and its uptake by the intestinal lymphatic system [88].

4. Conclusion

In this comprehensive review, we have explored a diverse array of solubility enhancement techniques that play a pivotal role in addressing the difficulties posed by poorly soluble medications. From conventional methods such as particle size reduction and solid dispersion to cutting-edge nanotechnological approaches like nanosuspensions and lipid-based nanocarriers, the arsenal of strategies available to pharmaceutical researchers is extensive. Moreover, the integration of computational methods for predicting and optimizing solubility enhancement techniques emerges as a crucial aspect of modern drug development. The synergy between experimental and computational approaches holds promise for more efficient and informed decision-making in the formulation of pharmaceuticals. As we continue to explore emerging techniques like co-crystallization, ionic liquids, and supercritical fluid technology, it is clear that solubility enhancement remains a dynamic and evolving field. Future advancements will likely be shaped by interdisciplinary collaborations, technological innovations, and a deeper understanding of the complex interactions governing drug solubility.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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