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Solubility and Bioavailability Enhancing Strategies for Poorly Water-soluble Drugs: A Review

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Abstract: Drug solubility is a crucial characteristic that influences the bioavailability and dosing of medications. Low bioavailability is one of the main problems associated with poorly soluble medications. Over 40% of new chemical entities (NCEs) possess poor aqueous solubility and low oral bioavailability and absorption. Therefore, developing a suitable dosage form for these poorly soluble drug candidates has triggered growing interest among formulation scientists in developing new strategies for increasing water solubility without changing their molecular structure or biological activity. This review highlights various solubility enhancement techniques like particle size reduction, molecular complexation, solid dispersions, and solid-lipid nanoparticles. These are promising and emerging alternatives to facilitate the delivery of pharmaceutically active compounds for various medical applications to solve these problems. However, constructing an appropriate formulation strategy should be a crucial issue for developing poorly water-soluble pharmaceuticals to complete development operations within a constrained time frame.

Keywords: Solubility, Bioavailability, Nanotechnology, Complexation, Solid lipid nanoparticles, pH Modification.

1. Introduction

The process of discovering new drugs is indeed considered expensive and time-consuming. It involves several stages of research and development, stringent testing, and rigorous clinical trials to ensure safety and efficacy. The entire drug discovery process is time-consuming and expensive, with a high attrition rate due to various factors like safety concerns, lack of efficacy, or unforeseen side effects. Companies often spend significant resources on drugs that do not make it to market, contributing to the overall cost and time required to bring a new drug to patients. Few recent powerful therapeutic compounds with the best pharmacological characteristics made it to human Phase I clinical trials. Unfortunately, the historical average shows that clinical trials have an overall attrition rate of over 90% [1]. The majority of recently discovered chemical entities exhibit poor solubility, which ultimately results in poor bioavailability [2]. Unless their solubility and oral bioavailability are improved through formulation, a large proportion of promising clinical candidates won't reach the market or perform to their full potential. Drug solubility will always be a key consideration in formulation development. The number of weakly water-soluble compounds has increased significantly over the past few years with the development of synthetic methods for the synthesis of novel molecules in chemistry and improved screening techniques [1]. Drug development should be more challenging due to the poor oral bioavailability caused by poor water solubility. To improve the solubility, dissolution rate, and oral bioavailability of poorly water-soluble medicines, a variety of strategies have been devised listed in **Figure 1**. The construction of an appropriate formulation approach should be a crucial issue for the development of poorly water-soluble pharmaceuticals to complete development operations within a constrained time frame [3].

Solubility can be characterized qualitatively as the "spontaneous interaction of two or more substances to generate a homogenous molecular dispersion" and quantitatively as "the concentration of solute in a saturated solution at a specific temperature" [4]. Solubility or dissolving enhancement approaches continue to be a very active field for formulation researchers as they address a topic that is frequently discussed but has not yet been fully answered. The fundamental ideas of any physical or chemical science, including biopharmaceutical and pharmacokinetic aspects of treatment with any medication, are solubility and dissolution.

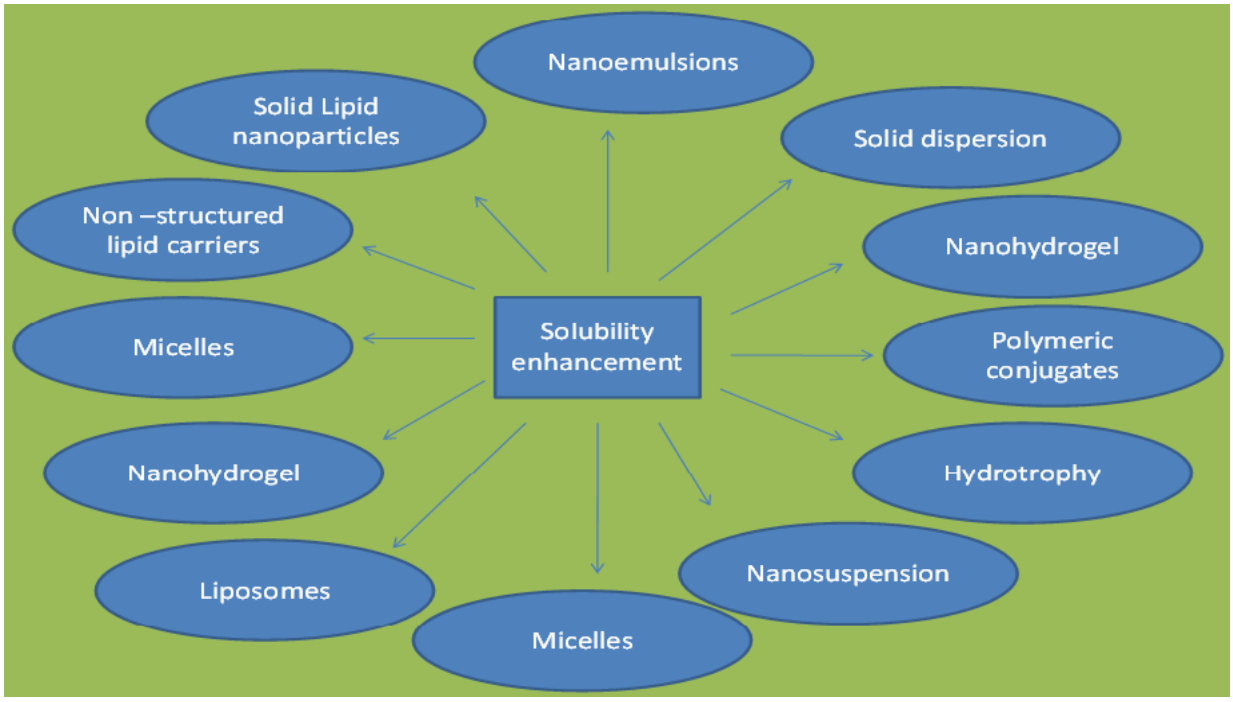

Figure 1: Variety of strategies to improve solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs.

However, as the synthetic technique expands and produces a large number of promising lead compounds for the majority of pharmacological categories, the molecules are likewise moving toward larger structures. As a result, non-optimal biopharmaceutical features cause ≥40% of novel molecules to enter the drug development pipeline [5]. The Pharmacokinetic properties of the drug can all be significantly influenced by these features, such as the pace and degree of absorption, distribution rate, and the dose to obtain the minimum effective concentration with fewer adverse effects. The methods for discovering new drugs have changed the nature of biopharmaceutical properties over time. The Biopharmaceutics Classification System (BCS) four categories for classifying drugs were made easier by the idea of permeability and solubility qualities (**Figure 2**). Insufficient bioavailability is frequently caused by poorly water-soluble medicines weak solubility & slow rate of dissolution in aqueous gastro-intestinal fluids. The bioavailability can be improved, particularly for class II drugs, by speeding up the drug's solubility and rate of dissolution in the fluids of the gastrointestinal tract [6-7].

Due to the sluggish rate of drug dissolution, two factors are helpful to recognize poorly soluble medications i.e., dose solubility ratio &aqueous solubility (should be ≤100ug/ml). The volume of gastrointestinal fluids required to dissolve the provided dose is known as the dose solubility ratio. Furthermore, quantitative BCS has emphasized the significant transit flow of the drug absorption process, in association with solubility & permeability [8]. Three figures {i.e., dose number (Do), dissolution number (Dn), and absorption number (An)} [9] combine the drug's physicochemical characteristics with physiological measures. By taking into account the amount of fluid necessary to dissolve the entire dose, the Do gives the dose a physiological context. Drugs are categorized as highly or poorly soluble depending on whether their Do value is greater than or less than 1. A recent attempt to classify WHO critical medications using BCS revealed that 27.7 percent of the medications were described as poorly soluble [10]. The BCS has revolutionized the creation of novel therapeutic compounds in addition to changing how scientists currently approach medication delivery. The dissolved solute concentration that is in equilibrium with the solid solute is considered to be a measure of a substance's solubility at a particular temperature.

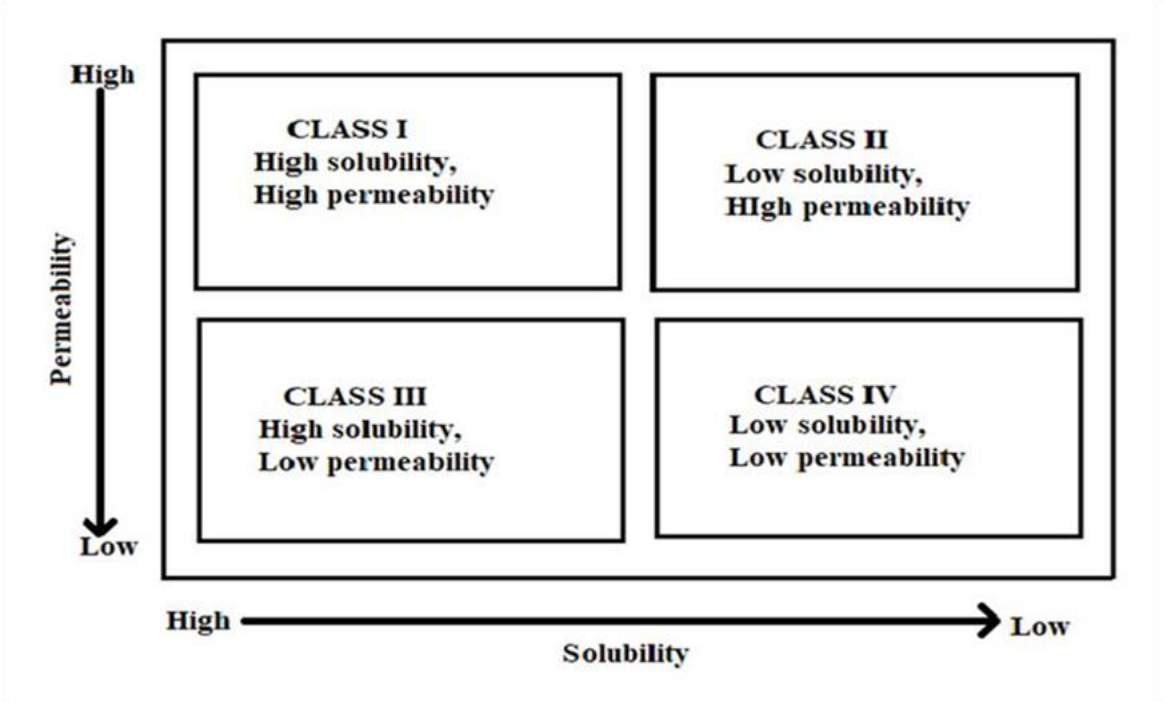

Figure 2: BCS Classification.

The characteristics of the molecule to form an H-bonding with the water along with the molecule's crystal lattice affect the overall solubility of a molecule. Equation 1 provides a good explanation for the effects of these elements [11].

$$S = f \times (\text{Cavitation energy} + \text{Crystal packing energy} + \text{Solvation energy}) \quad \ldots\ldots (1)$$

However, cavitation energy is needed to create a cavity within the solvent, crystal packing energy is needed to break the crystal lattice to interact solute molecules with solvent molecules, and salvation energy is the energy released following successful interactions between solute and solvent. Surfactants can be used to provide cavitation energy, and the amorphism or polymorphism of a solute can provide cavitation energy for crystal packing. The saturation solubility is therefore a crucial element in the rate at which a medication dissolves, together with surface area. It is based on the drug's physiochemical characteristics, like its crystalline shape, lipophilicity, and pKa.The dissolution procedure consists of two steps that follow one another [12].

1. Through an engineered reaction, solute molecules are released from the solid phase.

2. These molecules are then moved by convection or diffusion away from the interface and into the main body of the liquid phase.

In addition, the Noyes-Whitney equation {dm/dt = ka (Cs - C)} can be used to quantitatively explain how quickly a solid dissolves in a liquid.

The current challenges in drug development, specifically related to drug solubility and bioavailability, have prompted researchers to explore various solubility enhancement techniques. To address these challenges, we have meticulously examined several solubility enhancement strategies (like particle size reduction, molecular complexation, solid dispersions, solid-lipid nanoparticles, etc.), each with its unique approach to improving drug solubility and bioavailability. The comprehensive review of these solubility enhancement techniques sheds light on their respective strengths and limitations, helping researchers and pharmaceutical companies make informed decisions when selecting the most suitable approach for specific drugs. This review serves as a valuable guide for drug development and utilization, enabling more efficient and effective strategies to tackle solubility challenges. By employing these enhancement techniques, researchers can pave the way for the development of novel drugs with improved bioavailability, better therapeutic outcomes, and increased patient compliance.

2. Methods of Solubility Enhancement

The main difficulties in the formulation and distribution of pharmaceuticals are their poor solubility and dissolution. Numerous techniques have so far been adopted to enhance the solubility and dissolving characteristics of medicines [13]. Classical methods include pH adjustment, co-solvency, micelles, micro-emulsification, liposomes & emulsions [14], Salt formation, Particle Size Reduction, Solid solutions/dispersions, Lipid-Based Delivery Systems, Evaporative precipitation into aqueous solution (EPAS), Ultra-Rapid Freezing, Co-evaporate System / Co-precipitation, Solvent Deposition/Evaporation, Inclusion Complexes, Kneading Technique, Co-precipitation, Neutralization, Co-grinding, Spray-Drying Method, Liqui-solid Compacts Melt-Granulation, etc. [15]. However, the selection of the appropriate method is always a critical phase during the formulation development [16]. Various methodologies adopted for solubility enhancement (**Figure 3**) are explained below:

2.1 pH Adjustment

By manipulating the pH of the drug solution, solubility can be optimized, leading to improved drug dissolution and subsequent absorption in the body. The breakdown of steam-exploded cornstalks (SEC) and the generation of organic acids by an expanded microbial community were both accelerated by intermittent pH modification. After 84 hours of fermentation, the results revealed that increasing the pH increased the overall concentration of the two main water-soluble metabolites (propionate & acetate), with results of 1.86 g/l at pH 7.0, 2.04 g/l at pH 8.0, and 3.32 g/l at pH 9.0. The potential for the cellulose to be converted into other materials was thought to be improved by intermittent pH modification [17].

2.2 Complexation

Through methods like kneading or lyophilization/freeze drying, drug molecules can form complexes with carriers like cyclodextrins, which improve their solubility through inclusion in the carrier's hydrophobic core. One of the extensively researched techniques used for a more precise increase of the solubility and dissolution of weakly water-soluble medicines is the complexation of cyclodextrin (CD) with phospholipid (PL). The eligibility requirements (of pharmaceuticals) for the various procedures, the cost, the stability, and the efficacy of the complexes can all be taken into consideration when choosing a certain type of complexation. However, both methods can be used to create complex drugs with better biopharmaceutical properties yet as opposed to the PL complexation, the eligibility requirement for the CD complex is more geometric than chemical. The PL complexes, on the other hand, may also enhance the lipid solubility or permeability of BCS Class IV medicines, resulting in enhanced BA of permeability rate-limited medications as well. As a result, it can be concluded that enhancing the BA of BCS Class II and Class IV medications through CD and PL complexation of pharmaceuticals may be a very promising strategy [18]. In addition, numerous researches reveal that the cyclodextrins (CDs) complexation might be the potent approach to enhance the solubility, absorption and therefore bioavailability of the drug molecules [19].

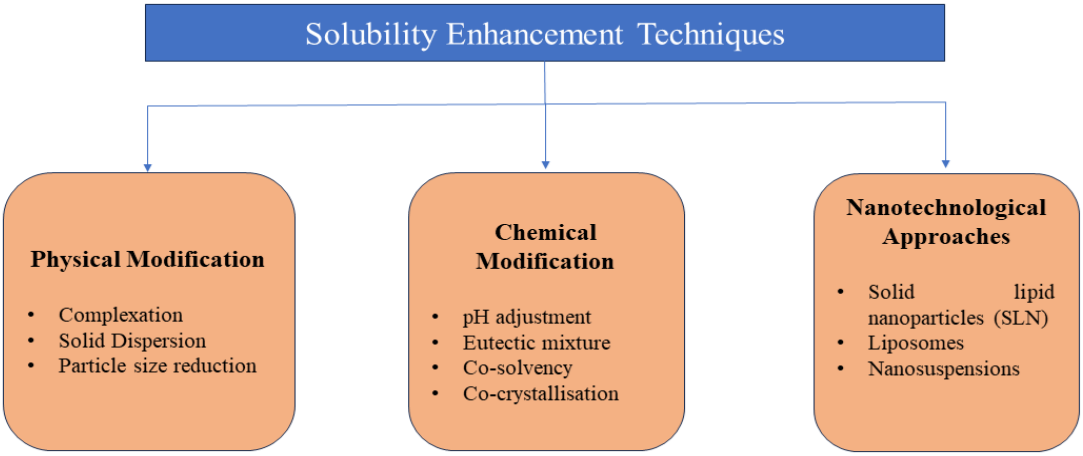

Figure 3: Solubility enhancement techniques.

Literature reveals that cilostazol inclusion complex with DM-β-CD (1:3) through complex formation technique showed significant fast-dissolving formulation with improved oral bioavailability. In addition, the phase solubility study demonstrates complex formation enhances the solubility of the drug, which was further enhanced through pH modification. Furthermore, the sharp endothermic peaks in the DSC & XRD study reveal a significant reduction in the micro-crystallinity of cilostazol [20]. Literature reveals that complexing domperidone (DMP) with large ring cyclodextrins (LR-CDs) could increase its water solubility. LR-CDs can entrap molecules to create inclusion complexes through relatively hydrophobic cavities. Compared to small CD-DMP complexes, the LR-CD-DMP complexes showed a 3-fold increase in DMP solubility [21]. In another study, cyclodextrins complex with riboflavin was examined for the enhancement of aqueous solubility and corneal permeability in eye drop formulations. This study has demonstrated that the α-cyclodextrin (100 mg/ml) & β-cyclodextrin (20-30 mg/ml) can be used to increase riboflavin's solubility and thereby boost its availability when employed in ocular medication formulations. This work demonstrated that cyclodextrins can remove lipids like cholesterol from ocular cell membranes, which might explain why the epithelium is disrupted and permeability is increased [22]. In another study, the solubility of nucleoside (adenine & guanosine) along with structurally related molecules (triamterene & acyclovir) was substantially enhanced by complex formation with water-soluble ligands (like amino acids, vitamins, & other non-toxic pharmaceutical excipients). A ligand pair consisting of ligands from the same class (either Class A or Class B) showed additive solubility enhancement concerning the water-insoluble base, nucleoside and other structurally related drugs. Using ligand pairs, it is possible to obtain much greater solubility enhancement [23].

Myricetin (a poorly soluble molecule) was converted from crystalline to amorphous form through complexation with HP-β-CD (1:1 stoichiometric ratio), as characterized by SEM, DSC& PXRD. According to the molecular inclusion processes discovered by 1HNMR & FT-IR, myricetin's B-ring and a portion of its C-ring were encased in the cavity of HP-β-CD via non-covalent bonds. In comparison to pure myricetin, the myricetin/HP-β-CD inclusion complex had significantly higher water solubility and dissolution rates. In addition, the antioxidant potential &oral bioavailability of myricetin in the inclusion complex were greatly enhanced in experimental animals [24]. In another study, the spray-drying process at 100°C for 20 minutes, chito-oligosaccharide (COS) was used to create a stable complex with hesperidin (HSD-COS). The aromatic rings of hesperidin were shown to interact with COS via hydrogen bonding, forming the HSD-COS complex. The author reported that HSD-COS had better water solubility and antioxidant activity than free hesperidin as a result of the study [25]. Theasinensis A, one of the natural components of tea, was found to be most active in increasing the solubility of hesperetin. The antioxidant activity of hesperetin was boosted by 4.2 and 3.9-fold, respectively, by ROE correlation signals between hesperetin-TPGS (tocopheryl polyethylene glycol 1000 succinate) micelles and hesperetin-PC (phosphatidylcholine) complexes respectively. It's significant to note that the in-vivo oral absorption on rats revealed that the micelles and complexes significantly raised the peak plasma concentration (Cmax) from 2.64g/ml - 20.67g/ml and 33.09 g/ml, respectively, and increased the area under the concentration-time curve of hesperetin after oral administration to 16.2 and 18.0-fold, respectively [26]. The examples of several drugs whose solubility is enhanced through complexation and pH adjustment methods are depicted in **Table 1**.

Table 1: Drugs with increased solubility.

S/n	Drug used	Technique used	Inference	Reference
1.	Cilostazol	Complexation/ pH adjustment	The result of the Phase solubility study showed that the solubility and stability of the selected complex were improved.	[20]
2.	Domperidone (DMP)	Inclusion complex	The large ring cyclodextrin-domperidone (LR-CD-DMP) complexes represented a 3-fold enhancement ofdomperidone solubility.	[21]
3.	Riboflavin	Complexation	The result of the study showed that enhancement of solubility can be achieved by using α-cyclodextrin (100 mg/ml) and β-cyclodextrin (20-30 mg/ml)	[22]

4.	Adenine, Guanosine, Acyclovir, or Triamterene	Complexation by using ligand	The apparent solubility of the substrates was dramatically improved by forming complexes with the ligands.	[23]
5.	Myricetin	Complexation	Significant improvement in the solubility along with the dissolution rate of myricetin was achieved through the myricetin-HP-β-CD inclusion complex.	[24]
6.	Hesperidin	Complexation by using spray drying	The author reported that HSD-COS had better water solubility than free hesperidin as a result of the study.	[25]
7.	Hesperidin	Complexation	The In-*Vivo* absorption study on rats showed an increase in the absorption of hesperidin.	[26]

2.3 Eutectic Mixture

Although known from ancient times, the eutectic mixture is still a little-explored technique for improving the poor aqueous solubility of medicines. But the number of articles has substantially increased, particularly recently. However, the surprisingly simple eutectic combinations offer significant benefits in addition to being potential systems for enhancing drug solubility. For example, both components of eutectic mixtures are available in crystalline form which overcomes the drawback of the amorphous state to recrystallize during manufacturing, dissolution or storage, particularly in high-humidity environments.

Another benefit of eutectic mixtures is that they can be produced by using simple, affordable, and easily scaleable technologies. Additionally, it permits the blending of therapeutically important active pharmaceutical ingredients in the creation of fixed-dose combined systems (drug-drug eutectic mixtures). Although the manufacture of solid dosage forms including eutectic mixtures is still understudied, it has caught the interest of numerous research groups due to the encouraging outcomes. It will undoubtedly be a field to develop in the upcoming years. Additionally, eutectic mixtures need to be scaled up significantly for commercial use [27]. The number of studies involving the creation of eutectic mixtures to enhance the oral bioavailability and solubility of poorly soluble pharmaceuticals, including drug-carrier and drug-drug mixtures, has significantly increased recently [28]. The example of various drugs whose solubility is enhanced through eutectic mixtures is depicted in **Table 2** and **Figure 4**.

Table 2 provides information that showcases a series of eutectic mixtures of pharmaceutical compounds, each designed to address the challenge of poor water solubility in drugs. These eutectic mixtures are prepared using specific techniques and ratios of components, aiming to enhance the solubility, dissolution rate, and overall bioavailability of these drugs. One notable example is the Glimepiride - L-arginine eutectic mixture, which was prepared using the neat grinding method and resulted in a significant improvement in the drug's solubility and dissolution rate in a phosphate buffer (pH 6.8) [29].

Similarly, the Diacerein - Fumaric Acid eutectic mixture, prepared through a liquid-assisted grinding method, demonstrated a substantial increase in kinetic solubility and in-vitro drug release compared to the raw diacerein [30]. Moreover, various eutectic mixtures, such as the Celecoxib - Saccharin or Adipic Acid combination and Nimesulide - Nicotinamide mixture, showed remarkable enhancements in solubility and dissolution rates when compared to the pure drugs [32-33]. The Lovastatin - Carboxylic Acids eutectic mixtures exhibited increased solubility for different combinations, emphasizing the versatility of this approach [34]. However, it's essential to note that the Febuxostat - Probenecid, Adipic Acid, or α-Ketoglutaric Acid eutectic mixtures displayed decreased solubility, highlighting that not all combinations yield the desired results [35]. Furthermore, eutectic mixtures like Irbesartan - Syringic Acid, Nicotinic Acid, and Ascorbic Acid showed remarkable enhancements in solubility, especially in acidic and aqueous conditions [36]. Glicazide - Succinic Acid eutectic mixtures, prepared using electrospray deposition and a liquid-assisted grinding technique, significantly improved the drug's dissolution rate, particularly at pH 1.2 [37].

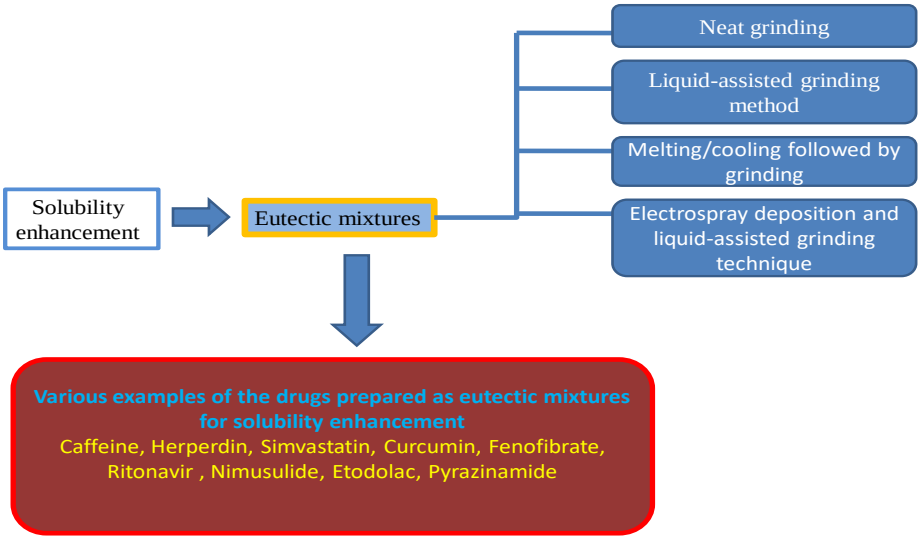

Figure 4: Example of various drugs whose solubility is enhanced through eutectic mixtures.

Felodipine - Nicotinamide or Malonic Acid eutectic mixtures exhibited increased solubility and dissolution rates in an acidic medium, making them potentially valuable for drug delivery [38]. Thus, these findings underscore the potential of eutectic mixtures as a promising strategy to overcome the challenges posed by poorly water-soluble drugs. By carefully selecting components and employing various preparation techniques, pharmaceutical researchers can enhance the solubility, dissolution rate, and ultimately, the therapeutic efficacy of these drugs. This approach holds significant promise for improving drug delivery and patient outcomes, particularly for medications with low water solubility, and is a valuable tool in modern pharmaceutical development.

Table 2: Example of eutectic mixtures for solubility enhancement.

S/n	Eutectic components		Method of preparation	Result	Reference
1.	Glimepiride	L-arginine	Neat grinding method	Significantly enhanced the solubility & dissolution rate of glimepiride in phosphate buffer (pH 6.8)	[29]
2.	Diacerein	Fumaric acid	Liquid-assisted grinding method	Significantly enhanced the kinetic solubility (3.15-folds) and *in-vitro* drug release of diacerein eutectic mixture (71.7%) as compared to raw diacerein (41.7%).	[30]
3.	Diacerein	2, 4-dihydroxy benzoic acid	Liquid-assisted grinding technique	Significant enhancement in solubility and dissolution rate of diacerein (*i.e.*, 2.5, 1.9 & 1.5-folds at a pH of 1.2, 4.5 & 6.8, respectively)	[31]
4.	Celecoxib	Saccharin or adipic acid	Liquid-assisted grinding technique	Showed remarkable enhancement of solubility & dissolution rate of celecoxib eutectic mixture in distilled water as compared to pure drug.	[32]

5.	Nimesulide	Nicotinamide	Solvent evaporation (spray drying) technique	Showed a significant increase in solubility of the eutectic mixture (14-times) in distilled water along with other media (*i.e.*, phosphate buffer (pH 8.4), 0.1N HCl & simulated gastric fluid) along with enhanced dissolution profile (4.7-4.9-folds) as compared to pure drug.	[33]
6.	Lovastatin	Carboxylic acids (like benzoic, salicylic & cinnamic acid)	Liquid-assisted grinding technique	Showed a significant increase in solubility (5-fold) in the lovastatin-salicylic acid combination and (4-fold) in the lovastatin-benzoic acid and lovastatin-cinnamic acid system.	[34]
7.	Febuxostat	Probenecid, adipic acid or α-ketoglutaric acid	Liquid-assisted grinding technique	Showed decreased solubility in all three eutectic mixtures as compared to that of the pure febuxostat.	[35]
8.	Irbesartan	Syringic acid, nicotinic acid and ascorbic acid	Liquid-assisted grinding technique	Showed remarkable enhancement in the solubility (5-9-fold) of irbesartan eutectic mixtures in 0.1N HCl (pH 1.2) and (4-7-fold) in water.	[36]
9.	Glicazide	Succinic acid	Electrospray deposition and liquid-assisted grinding technique	Showed significant enhancement in the dissolution rate of glicazide eutectic mixtures at pH 1.2 as compared to pure form.	[37]
10.	Felodipine	Nicotinamide or malonic acid	Liquid-assisted grinding technique	Eutectics displayed increased solubility & dissolution rate in 0.1N HCl (pH 1.2) for nicotinamide (120.24 µg/mL) & malonic acid (205.41 µg/mL) eutectics as compared to pure drug (25.05 µg/mL).	[38]
11.	Curcumin	Salicylic acid	Neat grinding technique	The eutectic mixture displayed a faster dissolution rate and solubility than raw curcumin.	[39]
12.	α-Eprosartan	p-Hydroxy benzoic acid	Liquid-assisted grinding technique	The eutectic mixture showed significant enhancement in the solubility and dissolution rate.	[40]

13.	Hesperitin	Adenine, theophylline, gallic acid or theobromine	Liquid-assisted grinding technique	The eutectics displayed improved dissolution profile with theophylline (3-fold), gallic acid (3.5-fold), theobromine (2.5-fold) and adenine (1.5-fold), respectively.	[41]
14.	Ibuprofen	Poloxamer	Melting/cooling followed by grinding technique	The eutectic mixtures showed significant enhancement in the dissolution rate in an acidic medium with a cumulative drug release of 58.27%.	[42]
15.	Nimesulide	PEG, urea or mannitol	Melting/cooling followed by grinding technique	The solubility of nimesulide in eutectic with PEG 4000 (at various concentrations) and urea showed linear enhancement of 2.3 and 1.6-fold respectively.	[43]
16.	Curcumin	Nicotinamide, ferulic acid, hydroquinone,	Neat grinding method	Showed a significant increase (3-11-fold) in the IDR values of eutectic mixtures as compared to pure curcumin.	[44]
17.	Ritonavir	Gelucire	Solvent evaporation and melting/cooling	Showed significantly enhanced dissolution rate in 0.1N HCl & bio-relevant medium as compared to pure drug.	[45]
18.	Fenofibrate, flurbiprofen	PEG	Melting/cooling followed by grinding	Showed significant enhancement in the dissolution rate of flurbiprofen & fenofibrate with different molecular weight PEGs.	[46]
19.	Flurbiprofen	Nicotinamide	Melting/cooling followed by grinding	Eutectic mixtures showed a significant dissolution rate of flurbiprofen in 0.1N HCl & distilled water as compared to pure drugs.	[47]
20.	Fenofibrate	PEG	Melting/cooling followed by grinding	Showed (a 10-fold) enhanced dissolution rate of fenofibrate in the eutectic mixture.	[48]
21.	Caffeine	Meloxicam, aceclofenac and flurbiprofen	Neat grinding	Showed significant enhancement in the dissolution rate of meloxicam, aceclofenac and flurbiprofen eutectic mixtures with 3.3, 1.4 & 1.7-fold respectively.	[49]
22.	Efavirenz	Tenofovir disoproxil fumarate	Neat grinding	Showed significant enhancement in the efavirenz dissolution and solubility rate in water and acidic conditions.	[50]

23.	Levetiracetam	Ibuprofen, naproxen, ketoprofen or flurbiprofen	Grinding (ball milled)	Showed significant improvement in the dissolution profile in phosphate buffer (pH 7.4).	[51]
24.	Posaconazole	Benznidazole	Melting/cooling	The eutectic mixture showed remarkable enhancement in dissolution rate of the eutectic mixture as compared to drugs alone.	[52]
25.	Hydrochlorothiazide	Atenolol	Neat grinding	Showed enhanced solubility (14-fold) of hydrochlorothiazide eutectic mixture in phosphate buffer (pH 7.4).	[53]
26.	Etodolac	Paracetamol or propranolol hydrochloride	Liquid-assisted grinding	Showed significant enhancement (6-9-fold) in the dissolution rate of the eutectic mixtures as compared to pure drugs.	[54]
27.	Pyrazinamide	Isoniazid	Neat grinding	Showed significant enhancement (2.5-fold) in the dissolution rate of pyrazinamide in eutectic mixtures.	[55]
28.	Simvastatin	Aspirin	Neat grinding	The eutectic mixture showed a significant increase in the dissolution rate (1.5 times) as compared to pure drugs.	[56]
29.	Fenofibrate	Acetylsalicylic acid	Neat grinding	Showed significant improvement (3-fold) in the dissolution rate in eutectic mixtures as compared to untreated drugs.	[57]

2.4 Solid Dispersion

Solid dispersion is an emerging technique used for the enhancement of drug solubility and dissolution rate. One of these methods that has been widely used in the sector is hot-melt extrusion (HME). It is a single-step, scalable technology for continuous production that has been effective in making pharmaceuticals that aren't very soluble more soluble. Due to a wider window between processing and carrier degradation, it presented no processing difficulties and had special properties that made it suitable for use in the HME process. The increased ability to maintain the amorphous state stable is thought to be the cause of better solubility enhancement. The study employed that the Kollicoat Smart seal is a potential carrier for the development of solid dispersion for solubility enhancement of BCS class II drugs such as itraconazole [58]. The presented **Table 3** provides a comprehensive overview of solid dispersion formulations, showcasing their pivotal role in tackling the inherent challenges associated with poorly water-soluble drugs. These formulations represent a significant advancement in pharmaceutical development, with a focus on enhancing drug solubility, dissolution rates, and overall bioavailability. Several key examples illustrate the versatility and effectiveness of solid dispersion techniques in achieving these goals. For instance, the Cannabidiol Solid Dispersion, prepared through hot melt extrusion with excipients such as mesoporous silica, cyclodextrins, and various polymers, successfully enhanced the dissolution rate and water solubility of cannabidiol, which is known for its low aqueous solubility. This is especially promising in the context of cannabinoid-based therapies [59].

Likewise, the Lovastatin Solid Dispersion, employing modified locust bean gum as an excipient and a modified solvent evaporation method, achieved optimal solubility enhancement when formulated in a specific ratio. This exemplifies the importance of carefully tailoring the formulation to maximize its efficacy [60]. Resveratrol Solid Dispersion, prepared through hot melt extrusion with Eudragit and PEG as excipients, exhibited a substantial 2.28-fold increase in solubility compared to the pure drug. Such improvements are critical for enhancing the therapeutic potential of resveratrol, a compound with various health benefits [61]. The Trans-resveratrol Solid Dispersion, utilizing Eudragit E/HCl and spray drying, demonstrated high supersaturation through micelle formation, further emphasizing the utility of solid dispersion techniques in enhancing solubility [62]. Quercetin Solid Dispersion, formulated with amorphous chitosan oligosaccharide, showcased a remarkable 1.64~2.25 times increase in oral bioavailability compared to the pure drug, emphasizing the potential of solid dispersions to enhance the delivery of flavonoids with therapeutic potential [63]. The Curcumin Solid Dispersion formulations, prepared using various techniques and excipients such as hydroxypropyl methylcellulose (HPMC), HPMCAS, lecithin, and isomalt, demonstrated enhanced solubility, dissolution rates, and bioavailability of curcumin, a compound with numerous health benefits [64-65]. Apigenin Solid Dispersion, developed using mesoporous silica and cellulose nanocrystals, significantly increased solubility and oral bioavailability, offering promise for enhancing the therapeutic utility of this natural flavonoid [67]. Thus, the diverse array of solid dispersion formulations presented underscores their versatility and effectiveness in overcoming the challenges posed by poorly water-soluble drugs. These advancements in pharmaceutical development hold the potential to greatly benefit patients and healthcare practitioners by improving drug delivery and therapeutic outcomes, ultimately contributing to better healthcare solutions. The example of various drugs whose solubility is enhanced through solid dispersion is depicted in **Table 3**.

Table 3: Example of some solid dispersion resulting in solubility enhancement.

S/n	Drug	Excipients	Method	Inference	Reference
1.	Cannabidiol	Mesoporous silica, cyclodextrins and polymers (K12PF, KVA64 and SOL)	Hot melt extrusion	The prepared solid dispersion showed remarkable enhancement in the dissolution rate and water solubility of cannabidiol.	[59]
2.	Lovastatin	Modified locust bean gum (MLBG)	Modified solvent evaporation method	The results established that the optimum increase in solubility of lovastatin was obtained in solid dispersion of LS/MLBG in a ratio of 1:5.	[60]
3.	Resveratrol	Eudragit and PEG	Hot melt extrusion method.	The saturation solubility study showed an increase in solubility (2.28 times) of solid dispersion resveratrol than pure drugs.	[61]
4.	Trans-resveratrol	Eudragit E/HCl	Spray drying method.	Solid dispersion of resveratrol and polymer (1:9) showed a high degree of supersaturation through Eudragit E/HCl micelles formation.	[62]
5.	Quercetin	Amorphous chitosan oligosaccharide	Amorphous solid dispersion	Showed a significant increase (1.64~2.25 times) in the oral bioavailability of quercetin solid dispersion as compared to pure drug.	[63]
6.	Curcumin	Hydroxypropyl methylcellulose	Solid dispersion	Showed increased water solubility along with encapsulation efficiency of curcumin.	[64]

7.	Curcumin	HPMCAS	Solid dispersion	Amorphous SD of curcumin remarkablyimproved the dissolution rate andenhanced the chemical stability of curcumin.	[65]
8.	Curcumin	Hydroxypropyl methylcellulose	Solid dispersion	Showed a significant increase in the oral bioavailability of curcumin.	[66]
9.	Apigenin	Mesoporous silica	Nanoparticles solid dispersion.	The SD exhibited a significant increase (25.11µg/ml) in the solubility and oral bioavailability (8.32 times) of apigenin.	[67]
10.	Hesperitin	--	Co-grinding and solvent evaporation.	SD of HSP co-crystals formulated through the solvent evaporation method exhibited increased solubility &synergistically reducedthe hepatic toxicity of CCl_4-induced oxidative stress in rats.	[68]
11.	Curcumin	Gelucire®50/13-aerosol	Solid dispersion	SD formulation of curcumin displayed a remarkable (3600-fold) enhancement in the solubility of curcumin.	[69]
12.	Curcumin	hydroxypropyl methyl cellulose, lecithin and isomalt	Hot melt extrusion technique	SD of curcumin exhibited (~13-fold) increased bioavailable of curcumin.	[70]
13.	Apigenin	CNP	Solid dispersion	CNP-based SD showed a significant increase in the solubility and oral bioavailability of Apigenin.	[71]
14.	Curcumin	Cellulose acetate	Sustain release solid dispersion	The solubility and dissolution rate of curcumin was improved remarkably in the sustained release SD formulation.	[72]
15.	Etoricoxib	Xanthan gum, guar gum, and gum acacia	Solvent evaporation	Showed significant enhancement in the solubility &dissolution rate of etoricoxib.	[73]
16.	Tadalafil	Glycyrrhizin	Spray drying.	Showed a significant increase (4.07 folds) in the dissolution rate of tadalafil.	[74]
17.	Ambrisentan	Daucus carota extract	Solid dispersion technique	SD showed significant enhancement in the improved absorption & bioavailability of ambrisentan.	[75]
18.	Ibuprofen	Guar gum, Hupugum and Xanthan gum	Surface Solid Dispersion	Pulsincap formulation with Ibuprofen: hupu gum (1:2 ratio) exhibited a significant increase in the solubility and drug release of ibuprofen.	[76]

Natural gums are useful in medicinal applications because they are affordable, nontoxic, readily available, chemically modifiable, and potentially biodegradable with a few exceptions. Polysaccharides are the focus of the majority of studies on natural polymers used in drug delivery systems. Natural gums can be altered to create products specifically designed for drug delivery systems, competing with the synthetic excipients that are currently on the market. While novel gums have been employed, some of them offer extraordinary properties, even if the usage of conventional gums has continued. There is a huge scope for study on newer plant-based gums and mucins, which may one day be used as a revolutionary natural polymer for the creation of various drug delivery systems in the pharmaceutical industry [77].

2.5 Nanotechnology

Nano-technology is an emerging approach for the development of novel drug delivery systems, especially for those potent drug candidates whose clinical development failed because of their poor aqueous solubility, inadequate bio-availability, low permeability as well as other poor biopharmaceutical characteristics [78-81]. The most common nanotechnology-based approaches used for the development of drug delivery systems include nano-emulsions, liposomes, dendrimers, solid lipid nanoparticles, polymeric micelles, carbon nanotubes, polymeric nanoparticles, etc., which provide targeted, controlled, and sustained drug delivery [82]. There are mainly two types of approaches which are used to prepare drug nanocrystals:

- The top-down approach, in which different types of milling or homogenization techniques are utilized to prepare nanosized particles by decreasing the particle size of bulk drugs in a liquid suspension [83].

- The bottom-up approach, where the nanosized particles are built molecule by molecule by precipitation [84].

Most commercial pharmaceutical products are produced by top-down methods, mostly by milling, because in these techniques the process repeatability is at a high level and changes in scaling are considerably easy to perform [85]. **Table 4** presents a comprehensive overview of innovative drug delivery systems that utilize polymers and nanotechnology to address the challenges associated with poorly water-soluble drugs. These advancements in pharmaceutical development hold significant promise in improving drug bioavailability and enhancing solubility, ultimately leading to more effective therapeutic outcomes.

Table 4: Example of nanotechnology for solubility enhancement.

S/n	Drug	Polymer	Nanotechnology	Inference	Reference
1.	Carvedilol	Carboxymethyl chitosan	Solid lipid nanoparticles	Showed significant improvement in the bioavailability of carvedilol along with protection from an acidic environment.	[86]
2.	Nitrendipine	---	Solid lipid nanoparticles	*In-vitro* and *in-vivo* drug release studies showed significant enhancement (3-4 times) in the bioavailability of nitrendipine.	[87]
3.	Nimodipine	---	Solid lipid nanoparticles	Showed a significant increase in oral bioavailability of nimodipine.	[88]
4.	Ramipril	Glyceryl monostearate, glyceryl monooleate with Tween 80,	Solid lipid nanoparticles	SLNs formulation of ramipril with glyceryl monooleate and Span 20 showed a significant increase in its bioavailability.	[89]

		poloxamer™ 188, and Span 20			
5.	Valsartan	---	Solid lipid nanoparticles	Enhanced lymphatic absorption with improved solubility and bioavailability of valsartan.	[90]
6.	Hesperidin	---	Solid lipid nanoparticles through supercritical anti-solvent technology	Showed significant improvement (4.5-fold) in the oral bioavailability of hesperidin	[91]
7.	Apigenin	Phospholipid 90H	liposomes	1.5-fold increased bioavailability as compared to a free drug suspension	[92]
8.	Carbamazepine	DMPG	liposomes	1.2-fold increased bioavailability as compared to Tegretol suspension	[93]
9.	Docetaxel	EPC:SA (1:0.2) with SDC and coating with Eudragit L100/S100 (4:1)	liposomes	3.1-fold increased bioavailability as compared to free drug solution in polysorbate 80/ethanol/saline (20:13:67)	[94]
10.	Fenofibrate	SPC: SDC (4:1)	liposomes	5.1-fold increased bioavailability as compared to micronized fenofibrate in capsule	[95]
11.	Lovastatin	SPC:CH (9:1)	liposomes	1.6-fold increased bioavailability as compared to a free drug suspension	[96]
12.	Silymarin	Phospholipid (82% PC)	liposomes	3.4-fold increased bioavailability as compared to powder drug	[97]
13.	Lopinavir	HSPC, CH (7:3)	liposomes	2.2-fold increased bioavailability as compared to a free drug suspension	[98]
14.	Zerumbone	--	Nanostructured lipid carriers	Increased water solubility	[99-102]
15.	Zerumbone		Nanosuspensions	Enhancement of solubility	[103]
16.	Zerumbone		Solid-lipid nanocarriers	Improve solubility and dissolution	[104]
17.	Cyclosporine A	ePC: Cremophor EL (10:0.5)	Solid: proliposomes	Ten-fold increased bioavailability as compared to a free drug suspension	[105]
18.	Cyclosporine A	SPC: SDC (3:1)	Liquid: liposome dispersion	1.5-fold increased bioavailability as compared to SandimmuneNeoral®®	[106]

19.	Paclitaxel	SPC:CH:SA (24.5:11.5:2 w/w)	Solid: freeze-dried liposomes	Four-fold increased bioavailability as compared to a free drug suspension	[107]

Solid Lipid Nanoparticles (SLNs) have emerged as a powerful tool for enhancing the bioavailability of drugs such as Carvedilol, Nitrendipine, Nimodipine, Hesperdin and Ramipril. These lipid-based carriers offer protection against harsh acidic environments and enable controlled release of drugs. Notably, the SLN formulation of Ramipril with glyceryl monooleate and Span 20 showcased substantial bioavailability enhancement, underscoring the potential of lipid-based carriers in drug delivery. Furthermore, Valsartan formulations incorporated into SLNs demonstrated improved solubility and absorption through the lymphatic system, highlighting their ability to tackle the challenges posed by poorly water-soluble drugs [86-91]. Liposomes, composed of phospholipids or lipid-like materials, have proven highly effective in enhancing the bioavailability of various drugs, including Apigenin, Carbamazepine, Docetaxel, Fenofibrate, Lovastatin, Silymarin, and Lopinavir. These liposomal formulations not only encapsulate the drug but also improve its solubility and stability. They enable controlled drug release and enhance drug absorption, leading to superior therapeutic outcomes. Liposome-based formulations have been particularly advantageous for drugs with poor solubility, illustrating their versatility and potential in pharmaceutical development [92- 98]. Nanosuspensions and Nanostructured Lipid Carriers have emerged as valuable strategies to enhance the solubility and dissolution rates of poorly water-soluble compounds like Zerumbone. These nanosystems offer increased water solubility, making them ideal for improving drug delivery. The ability to transform hydrophobic drugs into more readily soluble forms demonstrates the versatility and effectiveness of nanotechnology-based drug delivery systems [99-104]. Thus, the utilization of polymers and nanotechnology in drug formulations represents a significant advancement in pharmaceutical science. These innovative approaches offer solutions to the challenges posed by poorly water-soluble drugs, ultimately improving their bioavailability, solubility, and therapeutic efficacy. The choice of the most suitable carrier system depends on the specific drug and its properties, highlighting the importance of tailored drug delivery strategies in modern pharmaceutical development. These advancements hold the potential to benefit patients by ensuring better drug delivery and more effective treatments. The example of various drugs whose solubility is enhanced through nanotechnology is depicted in **Table 4** and **Figure 5**.

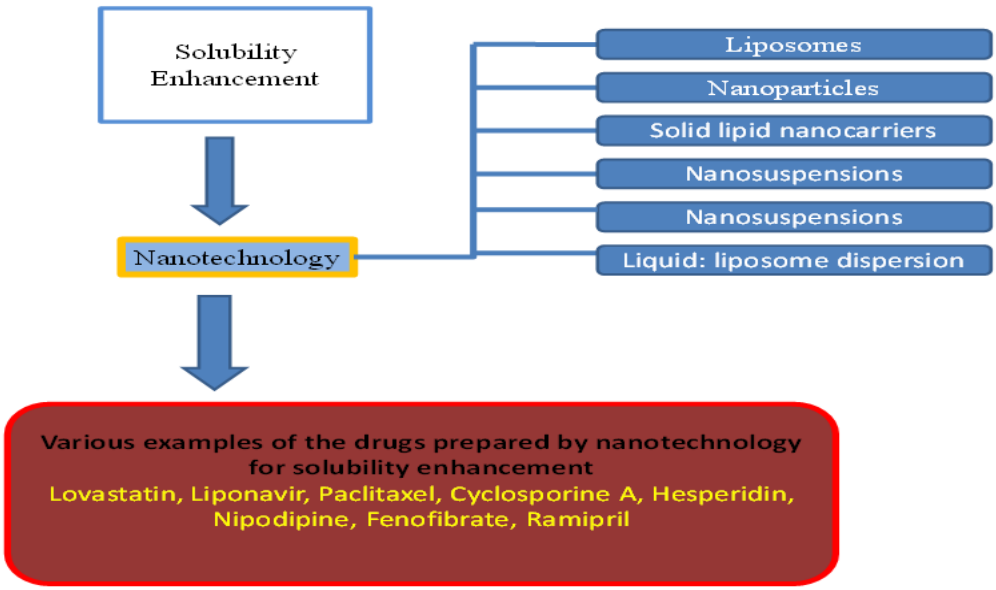

Figure 5: Various nanotechnological approaches to develop a drug with enhanced solubility.

3. Modified Approaches

Techniques such as micronization and nanosizing reduce drug particle size, increasing the surface area for dissolution, and subsequently improving solubility. According to a review of the literature, making an

amorphous solid dispersion (a modified coacervation method) with solubility-enhancing additives like sodium lauryl sulphate (SLS) and low viscosity polyethylene glycol (PEG 400) that enhanced amorphization and drug loading increases paracetamol's solubility. Additionally, the method resolves the majority of the issues that other methods face, such as issues with cost, safety, and the environment [108]. In another study, the solubility of paradoxically, Be2þ greatly increases in the physiological pH by the inclusion of serum proteins or Na2SO4.Even modest concentrations of sulfate ions, such as those contributed by pH adjustment with H2SO4, are sufficient to increase the apparent solubility [109].

4. Future Perspective on Solubility and Bioavailability Enhancing Approaches

Drug solubility enhancement techniques are indispensable in pharmaceutical development, addressing the formidable challenges posed by poorly water-soluble drugs. Solid Lipid Nanoparticles (SLNs) utilize biocompatible lipids to encapsulate drugs in nanometer-sized particles, effectively preventing drug crystallization, ensuring controlled release, and shielding drugs from harsh environments. Extensive studies demonstrate the remarkable potential of SLNs, with formulations such as Carvedilol and Nitrendipine exhibiting significantly improved bioavailability. Liposomes, lipid-based vesicles with aqueous cores, offer enhanced drug stability, controlled release, and improved absorption, particularly for hydrophobic drugs. Literature supports the utility of liposomal formulations, with Apigenin and Silymarin exemplifying notable bioavailability enhancements. Nanosuspensions and Nanostructured Lipid Carriers, through their ability to augment drug solubility and dissolution rates, represent a versatile approach to drug delivery, as evidenced by the increased solubility of Zerumbone. These techniques collectively represent substantial progress in pharmaceutical science, tailoring solutions for poorly water-soluble drugs and ultimately advancing patient care. The quest to enhance solubility and bioavailability for poorly water-soluble drugs shows significant promise, propelled by ongoing advancements in pharmaceutical research and technology. Overcoming the challenges associated with poor solubility remains a top priority in developing effective drug formulations. Nanoparticle-based drug delivery systems hold immense potential in improving drug solubility and bioavailability. Current research endeavors focus on refining nanoparticle characteristics, including surface modifications, targeting ligands, and sustained release mechanisms, to optimize drug delivery and therapeutic effectiveness. Simultaneously, the exploration of novel polymers and manufacturing techniques for amorphous solid dispersions is gaining momentum. These formulations have the capacity to stabilize amorphous drugs, thereby enhancing solubility and dissolution rates, ultimately improving drug performance. Additionally, researchers are actively investigating co-crystals and salt forms as viable strategies to enhance solubility. These crystal engineering approaches can lead to the creation of new drug forms with improved physicochemical properties. The implementation of continuous manufacturing processes has the potential to enhance drug product quality, control, and reproducibility, ultimately optimizing the solubility and bioavailability of poorly soluble drugs. The development of excipients specifically tailored for solubility enhancement is anticipated. Excipients that improve drug wettability, dissolution, and permeability will play a crucial role in formulating effective drug products. Furthermore, computational tools, such as molecular modeling and simulations, will continue to aid in predicting drug solubility and designing formulations with enhanced bioavailability, reducing the reliance on empirical experimentation. Moreover, advancements in personalized medicine may lead to patient-specific formulations that account for individual variations in drug absorption and metabolism, thereby improving therapeutic outcomes. Innovative combination therapies, where poorly soluble drugs are co-administered with solubility-enhancing agents or other compatible drugs, could open up new avenues for drug development and treatment. In summary, the future of solubility and bioavailability enhancement for poorly water-soluble drugs lies in interdisciplinary collaborations, advanced technologies, and a deeper understanding of drug physicochemical properties. Continued exploration of these approaches will lead to more efficient drug development, improved patient compliance, and better therapeutic outcomes for challenging medical conditions.

5. Conclusion

Solubility stands as an undeniable paramount parameter in the realm of drug formulation development. It exerts a direct influence on a drug's efficacy, bioavailability, and safety. Consequently, pharmaceutical companies are ardently dedicated to surmounting solubility challenges via diverse methodologies. These methodologies not only pave the way for the introduction of previously unapproved drug molecules but also enhance patient acceptance through innovative drug compounds. Traditionally, solubility enhancement techniques have encompassed a range of approaches, including pH adjustment, surfactant addition, self-emulsifying drug

delivery systems, particle size reduction, and complexation methods such as kneading and lyophilization/freeze drying. These techniques have been stalwarts in addressing solubility issues. However, in recent times, nanotechnology has emerged as a promising avenue for bolstering drug solubility. Nanoparticles, characterized by their high specific surface areas, offer a potent means to formulate drug compounds that substantially elevate their solubility. The prudent selection of a solubility enhancement method plays a pivotal role in achieving the goals of a successful formulation. These objectives encompass optimizing oral bioavailability, reducing dosing frequency, ensuring better patient compliance, and maintaining cost-effective production. Effective solubility enhancement bestows upon pharmaceutical companies the power to introduce previously formidable drug molecules to the market. This, in turn, leads to more effective treatments and novel therapeutic options for patients. In conclusion, the diverse array of approaches to address solubility issues not only benefits drug development and pharmaceutical research but also profoundly impacts patient care and treatment outcomes. The ongoing exploration of solubility enhancement techniques promises to advance drug formulation technology and contribute to improved healthcare on a global scale. The analysis underscores that addressing solubility challenges not only benefits drug development and pharmaceutical research but also significantly influences patient care and treatment outcomes, resulting in more effective therapies and innovative treatment options. In conclusion, the artilce offers a comprehensive overview of diverse techniques and strategies for improving drug solubility and bioavailability. It emphasizes the crucial role of these advancements in pharmaceutical development and patient care, highlighting the ongoing research efforts and interdisciplinary collaborations that are propelling progress in this field.

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Conflict of interest

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