WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 20, 1180-1206. Review Article ISSN 2277– 7105

A REVIEW ON FORMULATION STRATEGIES FOR ENHANCING BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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Article Received on
03 Oct. 2023,
Revised on 23 Oct. 2023,
Accepted on 13 Nov. 2023
DOI: 10. 20959/wjpr202320-30353

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1. ABSTRACT

The solubility of drugs is a critical factor for providing bioavailability and therapeutic efficacy. However, a significant number of pharmaceutical compounds exhibit poor solubility in aqueous media, which greatly impact the drug development. This review provides an in-depth knowledge of various strategies and techniques employed to enhance the solubility of poorly soluble drugs. The first section of the review discusses the Problems related to poor solubility, the need for solubility enhancement with a highlight on BCS classificationincluding examples and the factors that affect solubility. The second section focuses on formulation strategies with merits and demerits of each technique, the strategies include the use of solubilizing agents, complexation, and solid dispersion technologies. These methods are aimed at altering the drug's physical state or creating stable drug delivery systems that improve solubility and dissolution rates. The third section explores the application of nanotechnology in drug solubility enhancement. It mainly focuseson the preparation methods including Precipitation, Homogenisation, and milling techniques in detail. This section also shows some case studies and examples of drugs formulated as nanosuspension. The fourth sectiongives the principle, preparation, and drug's examples of Solid dispersion and Self-Emulsifying Drug Delivery System (SEDDS). The final section explains the role of Co-Crystallisation and Pro-Drugs on Solubility enhancement. By summarizing various strategies and approaches, it aims to facilitate the development of more effective and accessible medications for the benefit of patient healthcare.

KEYWORDS: Solubility enhancement, Bioavailability, Co-Solvents, Nanosuspensions,

Solid Dispersion, Homogenization, Co-Crystallization.

2. INTRODUCTION

Solubility is the process by which the substance dissolves in the liquid phase to form a homogeneous mixture. It is an important feature for the drug to achieve the desired pharmacological effect in the blood. The main problem encountered in this formulation is the poor water solubility of the new drug molecule. After oral administration, poorly water-soluble drugs must be injected to achieve maximum therapeutic plasma concentrations.[1,2]

As mentioned, approximately 60% of drugs in company pipelines are poorly water-soluble, being designated BCS class II compounds (low solubility and high permeability), Enhancing the way a drug dissolves in water will be the primary consideration for improving its bioavailability, as the solubility in an aqueous environment is the key limiting factor, according to Fahr and Liu in 2007. Aqueous solubility determination has proven extremely difficult for poorly water-soluble (PWS) drugs.[3,4]

Problems Related to Poor Solubility

1) **Reduced Oral Bioavailability:** To be absorbed effectively from the gastrointestinal tract, drugs must be in a soluble form. Poorly soluble drugs may exhibit slow and incomplete absorption rates, which can lead to lower and more variable drug levels in the bloodstream.[5,6]
2) **Poor Physical Stability:** Drugs with poor solubility are more susceptible to precipitating from solution. This precipitation can occur during formulation and storage, causing issues with drug stability.
3) **Increased Risk of Adverse Events:** Poorly soluble drugs are more prone to forming crystals within the body. In severe cases, the formation of crystals may lead to organ damage or failure, posing a considerable safety concern.[7-9]

Need For Solubility Enhancement

The solubility of the drug is important to ensure the right concentration of drug enters into the bloodstream, so the bioavailability of the drug causes the desired pharmacological response.[10]

A lower solubility means more of the drug is needed to cause the desired pharmacological response, which can mean an increase in negative side effects. [11-12]

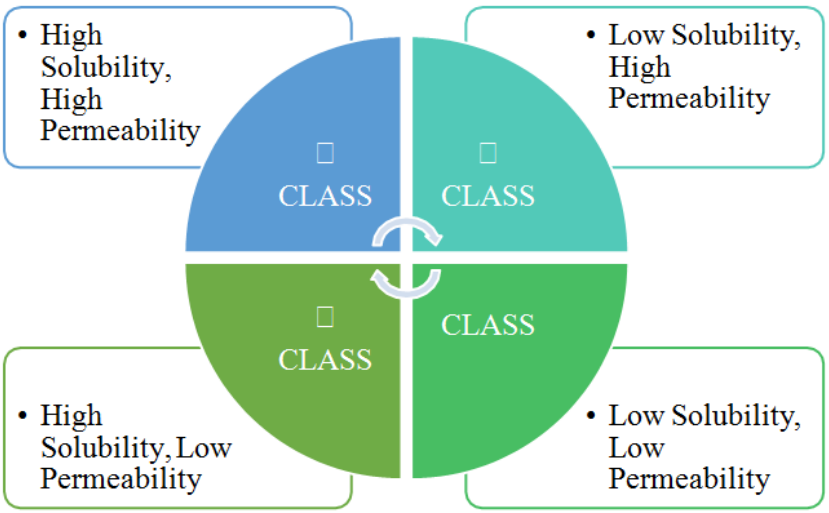

Figure 1: BCS Classification.

The Biopharmaceutical Classification System (BCS), introduced by Amidon and colleagues in 1995, provides a structured scientific framework for evaluating and categorizing drugs according to their characteristics related to aqueous solubility, intestinal permeability, and dissolution rate. As shown in Figure 1, BCS is a commonly used tool in drug development to determine the correlation of solubility and permeability with thebioavailability of drugs.[13] Here, Table 1 gives the example of drugs present in each BCS Class.

Table 1: BCS Classification Examples.

BCS class	Solubility	Permeability	Examples
Class I	High	High	Acetaminophen, Atenolol, Metoprolol, Paracetamol.
Class II	Low	High	Glibenclamide, Ibuprofen, Nifedipine, Propranolol.
Class III	High	Low	Cimetidine, Ranitidine, Warfarin.
Class IV	Low	Low	Bifonazole, Ciclosporin A, Danazol.

Factors Affecting Solubility

The following physicochemical properties of drugs can contribute to poor solubility:

1) **Molecular Size:** Drugs with larger molecular dimensions generally display reduced solubility in contrast to those with smaller molecular sizes. This is because larger molecules present a larger surfacearea, diminishing their ability to effectively engage with water molecules.[14-15]
2) **Chemical Polarity:** Polar drugs manifest superior solubility when compared to non-polar counterparts.
3) **Ionization:** Ionized drugs demonstrate heightened solubility in contrast to their non-

ionized counterparts.

4) **Crystalline Arrangement:** Crystalline drugs typically exhibit reduced solubility when juxtaposed with amorphous drugs. This dissimilarity emanates from the ordered and structured nature of crystalline drugs, which presents impediments to water molecules in penetrating and dissolving them.[16]
5) **Solution pH:** The solubility of drugs can be influenced by the pH of the solution. For instance, acidic drugs tend to dissolve more readily in acidic solutions, while basic drugs exhibit higher solubility in alkaline solutions.[17]
6) **Temperature:** Elevating the temperature of a solution generally leads to an increase in drug solubility.
7) **Pressure:** For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decreases the solubility.[18]
8) **Excipients:** The choice of specific excipients can form complexes with the drug, which may result in areduction of its solubility.[19-20]

3. STRATEGIES FOR OVERCOMING THE CHALLENGES OF POOR SOLUBILITY

Numerous approaches can be employed to address the challenges linked to poorly soluble compounds, as shown in Figure 2. These approaches encompass:[21-22]

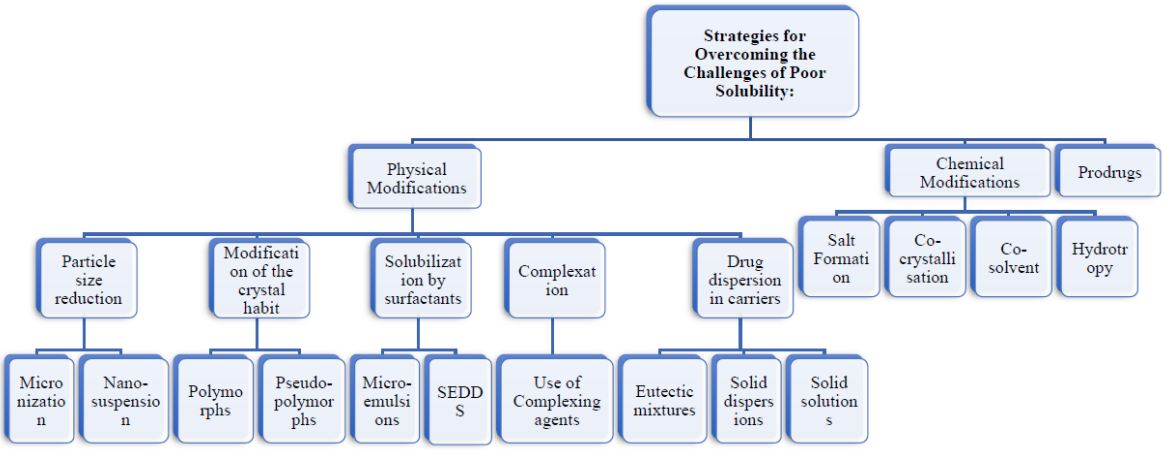

Figure 2: Strategies for Overcoming the Challenges of Poor Solubility.[23-26]

A. NANOSUSPENSIONS

Nanosuspensions consist of the poorly water-soluble drugs without any matrix material suspended in dispersion.[28] These can be used to enhance the solubility of drugs that are poorly soluble in water as well aslipid media.

Principle of Nanosuspension: A nanosuspension is a colloidal dispersion of solid drug particles in a liquid vehicle, where the particle size ranges from 10 to 1000 nanometers. Nanosuspensions are prepared by millingdrug particles to the nanosized range using various techniques, such as high-pressure homogenization, wet milling, and media milling.

Due to their small particle size, nanosuspensions have a higher surface area, which leads to increased solubilityand dissolution rate. Nanosuspensions can be used to deliver drugs with a narrow therapeutic index, which canhelp to reduce side effects.[70]

Components of Nanosuspension: The main components of a nanosuspension are:

a) **Drug particles:** The drug particles should be milled to the nanosized range using a suitable method.
b) **Liquid vehicle:** The liquid vehicle should be compatible with the drug and should be able to maintainthe drug particles in a suspended state.
c) **Stabilizers:** Stabilizers are used to prevent the drug particles from agglomerating and to maintain thestability of the nanosuspension.

Preparation of Nanosuspension: For the preparation of nanosuspensions, mostly two methods namely "Bottom-up technology" and "Top-down technology" are used.[31] The flowchart of preparation by both methods is given in Figure 3. Bottom-up technology refers to a method of creating nanoparticles by assembling them through processes such as precipitation, microemulsion, and melt emulsification. In contrast, top-down technology involves breaking down larger particles into nanoparticles, using techniques like high-pressure homogenization and various milling methods.

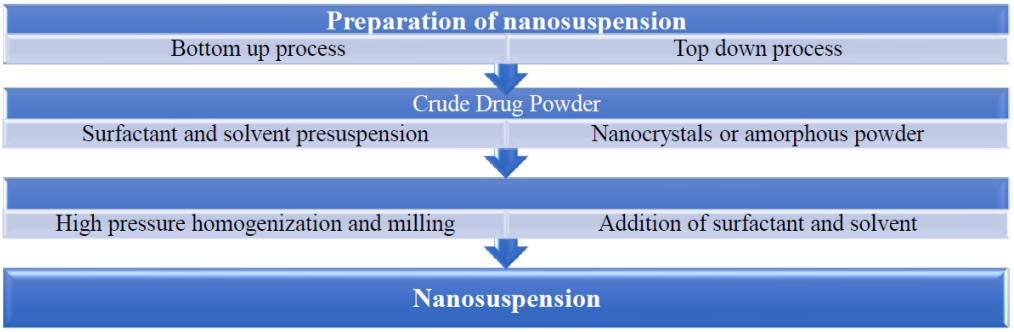

Figure 3: Preparation of Nanosuspension.

1) **Precipitation Method:** The precipitation method is a commonly employed technique for creating submicron particles of drugs with low solubility.[33–35] The Components and

process are shown in Figure 4. This approach involves dissolving a drug in a solvent and then combining this solution with another solvent in which the drug is not soluble, with the help of a surfactant. The quick introduction of the drug solution into the second solvent, typically water, results in a rapid increase in drug concentration, leading to the creation of extremely fine amorphous or crystalline drug particles. This method encompasses the processes of nucleus formation and crystal growth, with temperature playinga significant role in these phenomena. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size.[30]

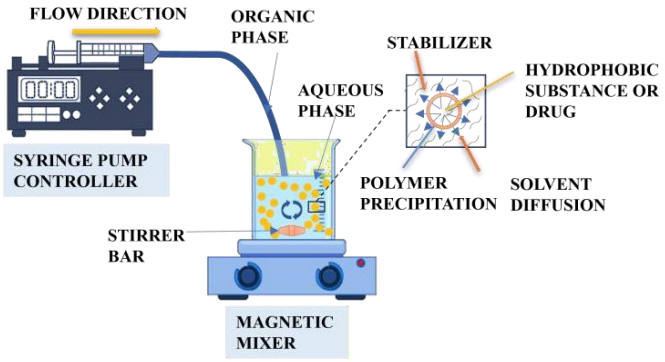

Figure 4: Precipitation Method.

2) HIGH-PRESSURE HOMOGENIZATION

The process of formation of Nanosuspension by Homogenisation isdescribed in Figure 5. This technique involves the following three steps: First, drug powders are dispersed in a stabilizer solution to form presuspension; Subsequently, the presuspension undergoes homogenization using a high-pressure homogenizer, initially at a lower pressure, which may involve preliminary milling. Finally, high-pressure homogenization is carried out for 10 to 25 cycles until thenanosuspensions reach the desired particle size.

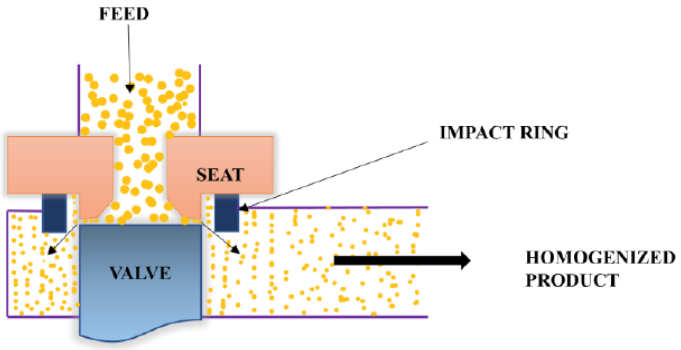

Figure 5: High Pressure Homogenizer.

2.1 Homogenization in Aqueous Media (Dissocubes): Dissocubes technology was developed by Muller in 1999. The instrument can be operated at pressure varying from 100 to 1500 bars (2 800 – 21 300 psi) and up to 2 000 bars with volume capacity of 40 ml (for laboratory scale). As per Bernoulli's Law, the volume of liquid flowing through a closed system per unit cross-sectional area remains constant. Various drugs like Amphotericin B, Ordinon, Thiomerasol, and Dexamethasone were prepared as nanosuspensions using this method.[27]

2.2 Homogenization in Nonaqueous Media (Nanopure): Nanopure is suspension homogenized in water-free medium. It is "deep-freeze" homogenization where the drug suspensions in nonaqueous medium are homogenized at 0°C or sometimes below the freezing point. Due to the extremely elevated boiling point and minimal vapor pressure of substances like water, oils, and fatty acids, the reduction in static pressure is insufficient to initiate cavitation in nanopure technology.[32] Other homogenization technologies and patents on the homogenization processes are shown in Table 2.[33]

3) MILLING TECHNIQUES

3.1 Media milling: Liversidge et al. had a patent on nanocrystal technology.[34] In this technique, drugs are subjected to media milling for nanoparticle production. The impact resulting from the collision between the milling media and the drugs provides the necessary energy for breaking down the microparticulate system into nanoparticles. Residues left behind in the finished product is a major problem of this method.[35]

3.2 Dry cogrinding: Since many years, nanosuspensions are prepared through wet grinding processes by using pearl ball mill. In modern times, it is possible to create nanosuspensions using dry milling techniques. Itoh et al. have described the colloidal particles formation of many poorly water-soluble drugs like nifedipine, griseofulvin, and glibenclamide with sodium dodecyl sulfate and polyvinylpyrrolidone as stabilizer. [36-38]

4) SUPERCRITICAL FLUID METHODS

Various methods like Rapid Expansion of Supercritical Solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process are used to produce nanoparticles. By using RESS method, Young et al. Nanoparticles of cyclosporine with a size ranging from 400 to 700 nm were produced. In the PCA method, the drug solution is sprayed into a highly pressurized CO2 chamber. In supercritical antisolvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the

drug solution becomes supersaturated.[39]

Applications of Nanosuspensions: Nanosuspensions have been successfully used to improve the oral bioavailability of a variety of poorly soluble drugs, including paclitaxel, ibuprofen, and griseofulvin. They have also been used to develop topical formulations for the treatment of skin conditions, such as psoriasis andeczema. Additionally, nanosuspensions are being investigated for the delivery of drugs to the brain and otherorgans. The Case studies on different category drugs are compiled in Table 2 below.

Table 2: Here are some case studies and examples of drugs formulated as nanosuspensions.

Drug	Category		Marketed brands	Side Effects	Treatment	Reference
Paclitaxel	Antineoplasti c agent	Treatment of breast, lung, ovarian, andother cancers	Taxol, Abraxane	Hair Loss, Bone Marrow Suppression,Nausea, Vomiting, Fatigue	Supportive care, such asblood transfusions and growthfactors	Ayoola O. Awosika, etal., 2021[52]
Ibuprofen	Nonsteroidal anti-inflammatory drug (NSAID)	Treatment of pain, inflammation, andfever	Advil, Motrin, Aleve	Stomach Upset, Heartburn, Bleeding,Ulcers	Antacids, H2 blockers,proton pumpinhibitors	Vincent Trung H. Ngo, etal., 2023.[54]
Griseofulvin	Antifungalagent	Treatment of fungal infections of the skin, hair, and nails	Grisactin, Fulvicin	Headache,Nausea, Vomiting, Diarrhea	Supportivecare	Jazmine M. Olson, et al., 2023[55]
Danazol	Androgenic steroid	Treatment of endometriosis, fibrocystic breastdisease, and other hormone-related conditions	Danocrine	Weight Gain, Acne, Hirsutism, Mood Changes	Hormonal therapy	Salman Ashfaq, etal., 2023[56]
Itraconaz ole	Antifungalagent	**Use**	Sporanox	Nausea, Vomiting,Diarrhea, Hair Loss	Supportivecare	Heidi Kurn, etal., 2023[57]
Simvastatin	Statin	Treatment of highholesterol and triglycerides toprevent heart disease and stroke	Zocor	Muscle Pain,Liver Damage, Rash	Discontinue statin andmonitor liver function tests	Om Talreja, etal., 2023[58]
Carbama zepine	Anticonvulsant and mood stabilizer	Treatment of epilepsy, bipolar disorder, andtrigeminal neuralgia	Tegretol, Carbatrol	Dizziness, Drowsiness, Blurred Vision, Nausea, Vomiting	Dose reduction or discontinuation of carbamazepine	Jasdave S. Maan, etal., 2023[59]
Cyclosporine	Immunosupp ressant	Prevention of organrejection after organtransplantation andtreatment of other autoimmune diseases such aspsoriasis and rheumatoid arthritis	Neoral, Sandimmune	Kidney Damage, High Blood Pressure, Liver Damage, Increased Risk ofInfection	Dose reduction or discontinuation of cyclosporine	Carolina Tapia, etal., 2023[53]

B. SOLID DISPERSIONS

Solid dispersions are a formulation method with the aim of increasing the solubility and effectiveness of drugsthat do not dissolve well. These dispersions can utilize either a polymer, a surfactant, or a combination of bothas the carrier material.[40]

Principle of Solid Dispersion: Solid dispersion is a method that ensures the uniform distribution of one or more active substances in a solid carrier. This is accomplished using different techniques like melting, solventuse, or a combination of both. The drug can take on various forms within the carrier material, such as molecular, amorphous, or crystalline, ensuring a consistent blend of the active ingredients.

Key Elements of Solid Dispersion: Solid dispersion primarily comprises two fundamental components

a) **Active Ingredient (Drug):** This is the substance that needs to be evenly distributed within the carriermaterial.

b) **Carrier:** The carrier serves as the non-reactive material responsible for dispersing the active ingredient. Carriers can fall into either the hydrophilic or hydrophobic category. Hydrophilic carriers are typically polymers like hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and polyethylene glycol (PEG). On the other hand, hydrophobic carriers include lipids such as stearic acidand glyceryl monostearate.

Preparation Method of Solid Dispersion

1) **Melting method:** The melting method, initially introduced by Sekiguchi and Obi, entails creating a physical mixture of a drug and a water-soluble carrier, then heating it until it transforms into a molten state. This molten mixture is rapidly solidified in a cold environment while being vigorously stirred. The resulting solid material is subsequently crushed, milled, and sieved. Moreover, rapidly cooling the molten mixture from a high temperature can often lead to a state of supersaturation for a solute or drug within the system.[36] In such circumstances, the solute molecules become immobilized in the solvent matrix due to the instant solidification process.[41]

2) **Solvent Evaporation method**: The Solvent Evaporation Method is described in Figure 6 below. This technique involves dissolving the drug and carrier, which are initially mixed together, in a shared solvent.The solvent is then evaporated until only a clear, solvent-free film remains. This film is then subjected to further drying until a constant weight is achieved. The main advantage of the solvent method is thermal decomposition of drugs or

carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.[42]

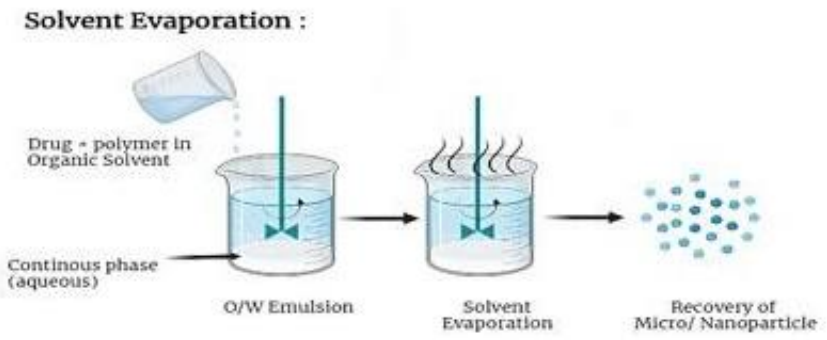

Figure 6: Solvent Evaporation Method.

3) **Melt Agglomeration Process**: This technique has been used to prepare Solid Dispersion wherein the binder acts as a carrier. In addition, Solid Dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer, as described in detail in Figure 7. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration.[43,44]

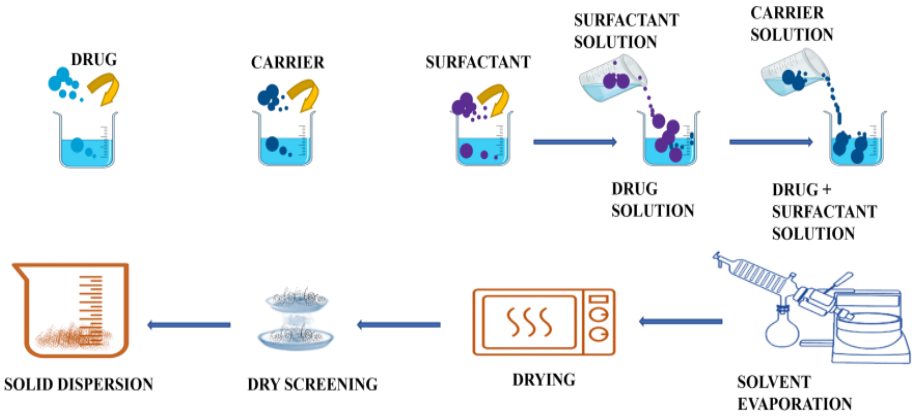

Figure 7: Preparation of Solid Dispersion.

Applications of Solid Dispersion

Solid dispersions are used to deliver a variety of poorly soluble drugs, including:

- Anti-cancer medications like paclitaxel and docetaxel.
- Antiretroviral medications like atazanavir and darunavir.

Few Examples of Drugs as Solid Dispersion are compiled in Table 3.

Table 3: Here are examples of drugs that have been successfully formulated as solid dispersions.

Drug	Category	Use	Marketed Brands	Side Effects	Treatment	Reference
Lopinavir And Ritonavir	Antiretroviral	HIV/AIDS	Kaletra	Diarrhea, Nausea, Abdominal Pain, Hyperlipidemia, Vomiting, Hyperglycemia	Antiretroviral Therapy, Supportive Care	Fule, R.R., et al., 2021[60]
Artemether	Antimalarial	Malaria	Coartem	Headache, Vomiting, Nausea, Diarrhea, Abdominal Pain, Dizziness	Antimalarial Therapy, Supportive Care	Fule, R.R., et al., 2021[60]
Praziquantel	Antischistosomal	Schistosomiasis	Biltricide	Drowsiness,Headache, Nausea, Vomiting, Diarrhea, Abdominal Pain	Antischistosom al Therapy, Supportive Care	Silva, C. M. et al.,2022[61]
Niclosamide	Antischistosomal	Cestode Infections	Niclosamide	Nausea, Diarrhea, Abdominal Pain, Headache, Vomiting, Dizziness	Supportive Care	Liu, J. etal., 2021[62]
Ibuprofen	Nonsteroidal Anti-Inflammatory Drug (NSAID)	Pain, Inflammation	Advil, Motrin	Nausea, Diarrhea, Abdominal Pain, Heartburn, Vomiting, Dizziness	Supportive Care	Kallakunta, V. R. etal., 2016[63]

C. SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)

Self-emulsifying drug delivery systems (SEDDS) consist of blends of oils, surfactants, and co-surfactants that, when mixed with water, create fine emulsions. These emulsions have tiny droplet sizes, promoting rapid dissolution and absorption of the drug.

Principles of SEDDS: SEDDS are based on the principle of spontaneous emulsification. These are isotropic mixtures of oils, surfactants, and co-surfactants that form fine emulsions when diluted with water. SEDDS work by forming microemulsions or nanoemulsions when diluted with water. When a SEDDS is diluted with water, the surfactant and co-surfactant molecules form a micelle around the oil droplets. The micelles prevent the oil droplets from coalescing and forming a larger emulsion. The small droplet size of the micelles also allows for rapid dissolution and absorption of the drug.[71]

Components of SEDDS: SEDDS are composed of three main components:

a) **Oil**: The oil phase of a SEDDS provides a solvent for the drug and helps to improve its solubility. The oil phase can be a vegetable oil, a mineral oil, or a synthetic oil.

b) **Surfactant**: The surfactant is responsible for forming the micelles that stabilize the emulsion. Common surfactants used in SEDDS include Labrasol, Cremophor EL, and Tween 80.

c) **Co-surfactant**: The co-surfactant helps to reduce the viscosity of the emulsion and improve its stability. Common co-surfactants used in SEDDS include propylene glycol and ethanol.

Application

- Improving the oral bioavailability of poorly soluble drugs.
- Enhancing the transdermal absorption of drugs.
- Formulating parenteral and ophthalmic drug delivery systems.
- Developing sustained-release drug delivery systems.

The examples of drugs with different categories, formulated as SEDDS are described in Table 4.

Table 4: Here are some examples showcasing the utilization of SEDDS in pharmaceutical formulations.

Drug	Category	Use	Marketed Brands	Side Effects	Treatment	Reference
Simvastatin	Statin	High cholesterol	Zocor	Muscle pain, vomiting, headache, nausea, diarrhea	Statin withdrawal, supportive care	Patel, R. B.et al., 2010[64]
Cyclosporine	Immunosuppressant	Organ transplant, autoimmune diseases	Neoral, Sandimmune	Hypertension, nephrotoxicity, hepatotoxicity	Blood pressure control, antihypertensive therapy, supportivecare	Gao, P. et al., 2013[65]
Paclitaxel	Antineoplastic	Cancer	Taxol	Myelosuppression, neuropathy, alopecia	Transfusion therapy, supportive care	Jain, N.et al., 2014[66]
Ritonavir	Antiretroviral	HIV/AIDS	Norvir	Diarrhea, vomiting, nausea, abdominal pain, hyperlipidemia, hyperglycemia	Antiretroviral therapy, supportive care	Shah, M.et al., 2013[67]
Fenofibrate	Fibric acid derivative	High cholesterol, high triglycerides	Tricor	Abdominal pain, nausea,diarrhea, vomiting, Headache	Supportivecare	Singh, B. et al., 2014[68]

D. CO-SOLVENTS

A co-solvent is a water-soluble organic solvent that is used in aqueous solution or in combination with other cosolvents to increase solubility by altering solution properties such as polarity, surface tension, and dielectric constant in poorly water-soluble drugs. The most common cosolvents used in injectable formulations are Polyethylene Glycol (PG) and ethanol. The pairing of these two solvents is commonly employed in injectable products to further adjust solubility characteristics. Other cosolvents that are present in marketed injectable products are polyethylene glycol 300, dimethylacetamide (DMA), and dimethylsulfoxide (DMSO).

Principle of Co-solvent: Co-solvency is a method employed to enhance the solubility of a poorly soluble drug in a solvent. It involves introducing a second solvent, known as a co-solvent, into the solution. Co-solvents operate by interfering with the interactions between water molecules and the drug molecules, making it moreconvenient for the drug to dissolve in water.[87] There are two primary ways in which co-solvents boost solubility:

a) "Like dissolves like": Co-solvents are typically more akin in terms of polarity to the

drug comparedto water.

b) **"Disruption of water structure":** Co-solvents can disturb the hydrogen bonding network among water molecules. This disruption weakens the interactions between water molecules, facilitating the dissolution of the drug in water.[69]

A co-solvent system is primarily composed of two key parts

a) **Co-solvent:** This is a solvent that can mix with water and is used to enhance the solubility of the drug.

b) **Vehicle:** The vehicle acts as the solvent for delivering the co-solvent system to the patient. While wateris often used as the vehicle, other solvents like saline or propylene glycol can also be used.[83]

Method of Preparation of Co-solvent Systems

Combining a cosolvent with a suitable vehicle is a straightforward method for creating a co-solvent system. However, selecting cosolvents and vehicles that are compatible with both each other and the drug is crucial. Additionally, the proportion of cosolvent and vehicle must be carefully considered since this will influence thedrug's solubility.[84]

Applications of Co-solvent Systems: Co-solvent systems can be used to improve the solubility of a drug ina number of ways.

- To formulate oral liquid preparations of poorly soluble drugs.
- To improve the solubility of drugs for injection.
- To improve the dissolution of drugs in solid dosage forms, such as tablets and capsules.[85]

Some Case studies of drugs as Co-Solvents are compiled in Table 5.

Table 5: Here are some case studies and examples of drugs formulated as Co-solvent.

Drug	Category	Use	Marketed brands	Side effects	Treatment	Reference
Paclitaxel	Antineoplastic	Cancer	Taxol	Myelosuppression, neuropathy, alopecia	Transfusion therapy, supportivecare	Gupta, R. et al., 2017[86]
Cyclosporine	Immunosuppressant	Organ transplant, autoimmune diseases	Neoral, Sandimmune	Hypertension, nephrotoxicity, hepatotoxicity	Blood pressure control, antihypertensive therapy, supportive care	Zhao, H. et al., 2017[87]
Simvastatin	Statin	High cholesterol	Zocor	Muscle pain, headache, nausea,	Statin withdrawal,	Mishra, R. et al.,

				vomiting,diarrhea	supportive care	2013[88]
Ritonavir	Antiretroviral	HIV/AIDS	Norvir	Diarrhea, nausea, vomiting, abdominal pain, hyperlipidemia, hyperglycemia	Antiretroviral therapy, supportive care	Zhang, M. et al., 2016[89]
Fenofibrate	Fibric acid derivative triglycerides	High cholesterol, high	Tricor	Abdominal pain, nausea,vomiting, diarrhea,headache	Supportivecare	Gupta, K. C. et al., 2013[90]

E. CO-CRYSTALLIZATION

A co-crystal is a structured, crystalline arrangement where specific stoichiometric quantities of noncovalent forces bind together two or more electrically neutral substances.[45] The co-crystallization of two active pharmaceutical ingredients, aspirin and acetaminophen, has been previously documented.[46] This process is akin to the production of salts, particularly when dealing with electrically neutral substances, and it can be achieved through methods such as evaporation, sublimation, melt growth, and slurry preparation.[48] Studies on the equilibrium solubility and dissolution of these co-crystals indicate that co-crystals involving ezetimibeand methylparaben could potentially serve as an effective strategy for enhancing solubility.[47]

Principle of Co-Crystallization: Co-crystallization is a pharmaceutical technique used to improve the physicochemical properties of active pharmaceutical ingredients (APIs) by combining them with a coformer to form a new multicomponent crystalline solid. The interactions between the API and coformer can modify the molecular packing of the API in the crystal lattice, which can lead to a variety of changes in physicochemical properties, including solubility, dissolution rate, stability, and hygroscopicity.[72]

Two essential components make up co-crystallization

a) **API (Active Pharmaceutical Ingredient):** The drug substance that undergoes modification during theco-crystallization process.

b) **Coformer:** A non-toxic, small molecule that is intentionally added to the API to form a co-crystal. Thecoformer plays a crucial role in altering the physicochemical properties of the API, enhancing its stability, solubility, and overall performance.

Preparation Methods of Co-Crystallization: The most common method is solution crystallization. In this method, the API and coformer are dissolved in a common solvent and the solution is then slowly evaporated to allow the co-crystals to form. Other methods for

preparing co-crystals include:

1) **Grinding:** The API and coformer are ground together in a mortar and pestle or in a ball mill. Thismethod is often used to prepare co-crystals of poorly soluble APIs.
2) **Microwave irradiation:** The API and coformer are mixed together and then irradiated withmicrowaves. This method can be used to prepare co-crystals quickly and efficiently.
3) **Spray drying:** The API and coformer are dissolved in a solution and then sprayed into a hot chamber.The solvent evaporates quickly, leaving behind the co-crystal powder.

Diagrammatic preparation method is described in Figure 8. Once the co-crystals have been formed, they needto be purified to remove any excess API, coformer, or solvent. This can be done by recrystallization, washing,or sublimation.[72]

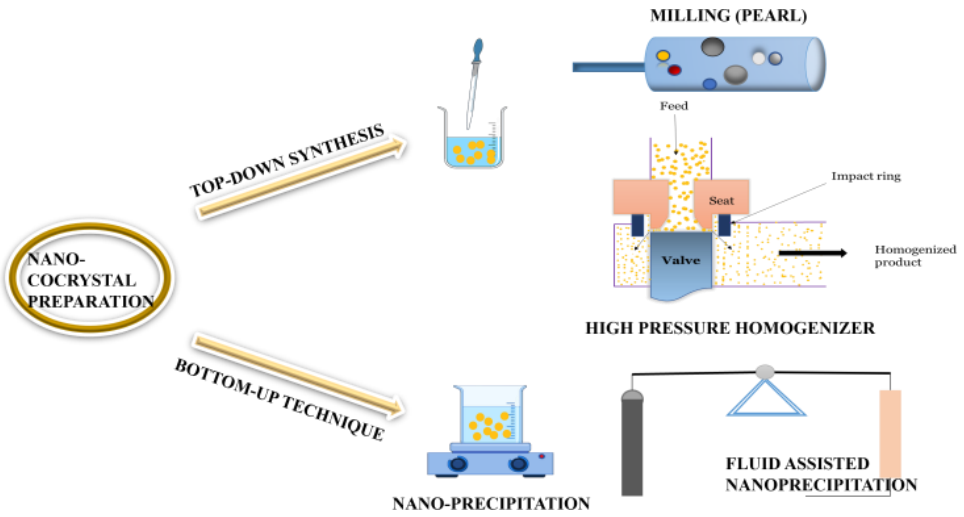

Figure 8: Preparation Methods of Co-Crystallization.

Applications of Co-crystallization: Co-crystallization emerges as a versatile tool to enhance the physicochemical attributes of APIs, encompassing a broad spectrum of benefits:

- **Solubility**: Co-crystallization stands out as a potent strategy to elevate the solubility of poorly solubledrugs, addressing their limited absorption and efficacy.
- **Dissolution rate**: Co-crystallization also contributes to a faster dissolution rate of drugs, allowing forquicker absorption and improved bioavailability.
- **Stability**: Co-crystallization plays a pivotal role in stabilizing both the physical and chemical properties of drugs, ensuring their longevity and effective pharmaceutical performance.

The Case studies of drugs formulated by Co-Crystallization is compiled in Table 6.

Table 6: Here are some case studies and examples of drugs formulated as Co-Crystallization.

Drug	Category	Use	Marketed Brands	Side Effects	Treatment	Reference
Carbamazepine	Anticonvulsant	Epilepsy	Tegretol	Drowsiness, Dizziness, Nausea, Vomiting, Diarrhea, Abdominal Pain	Anticonvulsant withdrawal, supportive care	Yu, X. etal., 2017[73]
Griseofulvin	Antifungal	Fungal infections	Grisactin	Headache, Nausea, Vomiting, Diarrhea,	Supportivecare	Kumar, S.et al., 2015[74]
				Abdominal Pain		
Nifedipine	Calcium channel blocker	Hypertension	Adalat	Headache, Flushing, Dizziness, Nausea, Vomiting, Diarrhea	Symptomatic treatment	Shete, A. R. et al., 2010[75]
Escitalopram	Antidepressant	Depression	Lexapro	Nausea, Vomiting, Diarrhea, Sexual Dysfunction	Symptomatic treatment	Kumar, A. et al., 2015[76]
Chloral hydrate	Hypnotic	Insomnia	Aquachlora L	Drowsiness, Dizziness, Nausea, Vomiting, Diarrhea, Abdominal Pain	Symptomatic treatment	Shete, A. R. et al., 2010[77]

F. PRODRUG

A prodrug is a chemically altered parent drug, initially inactive, with improved solubility in water, and capable of being transformed quickly into the active parent drug through biotransformation. In addition, such prodrugscan lead to pharmacokinetic profile optimization and decrease or remove the first-pass effect.[49] The two majorprodrug formulation groups to consider are: (i) Carrier-linked prodrugs, where the parent drug is chemically linked to a prodrug molecule, and (ii) bio precursor prodrugs. Carrier-linked prodrugs are further categorizedas bipartite prodrugs when the carrier is directly attached to the parent drug, or tripartite prodrugs when the carrier is connected to the parent drug through a spacer.[50,51]

Principle of Prodrug: A prodrug is a chemically modified drug that is biologically inactive until it is converted into its active form by a metabolic process. This conversion can be triggered by enzymes, pH, or other physiological factors. Prodrugs are designed to improve the delivery, absorption, metabolism, or excretion of a drug.[78] The Mechanism of Prodrugs is given in Figure 9.

Components of a Prodrug: A prodrug typically consists of two parts:

a) **A drug moiety:** which is the active portion of the prodrug and is responsible for its therapeutic effect.

b) **A carrier moiety:** which is responsible for the prodrug's physicochemical properties, such as solubility,stability, and permeability.

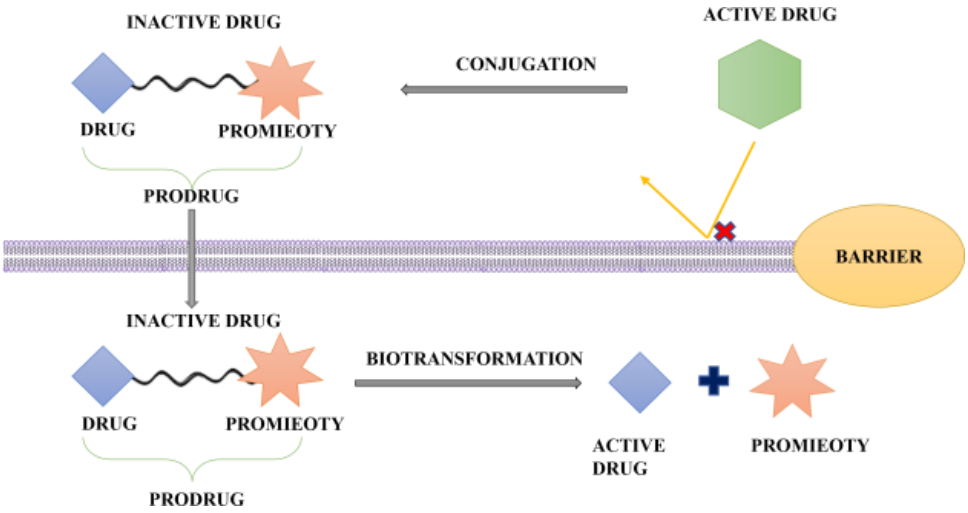

Figure 9: Mechanism of Prodrugs.

Method of Preparation of Prodrugs: Prodrugs can be prepared by a variety of chemical methods, depending on the drug and carrier moiety being used. Some common methods include:

1) **Esterification:** The drug moiety is covalently attached to an ester group. The ester bond is then cleavedby enzymes in the body to release the active drug.

2) **Conjugation with a hydrophilic carrier**: The drug moiety is covalently attached to a hydrophilic carrier, such as a sugar or a polypeptide. This increases the solubility of the prodrug and improves its absorption from the gastrointestinal tract.[79]

The Drugs with different Categories formulated as Prodrugs are compiled in Table 7.

Table 7: Here are some case studies and examples of drugs formulated as Prodrug.

Drug	Category	Use	Marketed brands	Side effects	Treatment	Reference
Valacyclovir	Antiviral	Herpes simplex virus, varicella-zoster virus infections	Valtrex	Headache, nausea, diarrhea, vomiting, abdominalpain	Supportivecare	Gilbert, L. R. et al., 2003[78]
Oseltamivir	Antiviral	Influenza	Tamiflu	Nausea, diarrhea, abdominalpain, vomiting, headache	Supportivecare	Gubareva, L. V. et al., 2004[79]
Capecitabine	Antineoplastic	Colorectal cancer, breastcancer	Xeloda	Nausea, diarrhea, vomiting, hand-footsyndrome	Antiemetics, supportive care	Saif, M.W. 2001[80]
Fosphenytoin	Anticonvulsant	Epilepsy	Cerebyx	Drowsiness, dizziness, nausea, diarrhea, vomiting abdominal Pain	Anticonvulsant withdrawal, supportive care	Johnson, T. R.2004[81]
Lansoprazole	Proton pump inhibitor	Gastroesophagea l reflux disease, peptic ulcers	Prevacid	Headache, nausea, diarrhea, vomiting, abdominal Pain	Antacids, H2 blockers	Laine, L. et al., 2001[82]

4. CONCLUSION

Poor solubility presents a significant challenge in drug development, limiting bioavailability and effectiveness. Various formulation strategies, such as particle size reduction, salt formation, solid dispersions, surfactants, and cosolvents, can enhance the solubility of poorly soluble drugs. The choice of formulation strategy depends on the drug's properties and desired therapeutic outcomes. Emerging technologies like nanotechnology, lipid-based formulations, supercritical fluid technology, and 3D printing offer innovative solutions to address solubility challenges. Formulation strategies are crucial for overcoming poor solubility. They enable the development of drug products that consistently and reliably deliver the required drug dose tothe target site.

Formulation strategies have the potential to revolutionize the pharmaceutical sector by facilitating the creation of new and improved treatments across various diseases. Enhanced solubility and bioavailability of poorly soluble drugs can lead to better patient outcomes and reduced healthcare costs. Examples of impacts include more convenient oral formulations, precise injectable options, and sustained-release formulations to enhance patient adherence. In summary, formulation strategies are pivotal in addressing poor solubility challenges and advancing drug development. As the field of drug delivery evolves, we anticipate the emergence of even more innovative strategies with profound impacts on the pharmaceutical

industry, improving drug development andpatient care.

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