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Review Article

Modern Approaches for Enhancing Drug Solubility: An Overview of Technologies

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ABSTRACT

Solubility refers to the ability of a solute to dissolve in a solvent under specific conditions of pressure and temperature to form a uniform solution. However, many active pharmaceutical ingredients (APIs) are poorly water-soluble or hydrophobic, making solubility one of the most challenging factors in drug formulation development. Low aqueous solubility often leads to reduced bioavailability, limiting the drug's therapeutic potential and overall product performance. Therefore, enhancing solubility is essential to ensure optimal drug absorption and efficacy. Many promising drug candidates fail to progress in development due to poor solubility, despite having high pharmacological activity. To address this issue, various solubility enhancement strategies are employed. These include chemical modifications such as salt formation and co-crystallization; physical approaches like polymorph and habit modification; complexation techniques including physical mixtures and inclusion complexes; surfactant-based methods like self-emulsifying drug delivery systems (SEDDS); solid dispersion techniques; pH adjustment; and advanced technologies like liquisolid systems, supercritical fluid processing, and polymer-based modifications. This article aims to consolidate and apply multiple solubility enhancement techniques to improve the aqueous solubility and therapeutic performance of poorly water-soluble drugs.

INTRODUCTION

Solubility and dissolution enhancement remain crucial and actively explored areas in formulation science, despite being long-discussed topics with limited practical breakthroughs. These concepts are foundational to the design of any dosage form, playing a central role in both biopharmaceutical and pharmacokinetic performance of a drug. The therapeutic efficacy and production cost of solid dosage forms are significantly influenced by their physicochemical characteristics such as stability,

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particle size, flow properties, taste, moisture sensitivity, solubility, and excipient compatibility [1]. Solubility and permeability are critical factors that influence a drug's absorption and, ultimately, its therapeutic effectiveness. Solubility refers to the maximum amount of a solute that can dissolve in a given volume of solvent under constant temperature and pressure before reaching saturation. It can be defined in both qualitative and quantitative terms. Qualitatively, solubility describes the natural interaction between solute and solvent that leads to the formation of a uniform molecular dispersion. Quantitatively, it is expressed as the concentration of solute in a saturated solution at a specific temperature. In pharmaceutical sciences, various units are used to express solubility data, including molarity, normality, formality, mole fraction, percent solution, volume fraction, and molality. These parameters help in understanding and optimizing drug solubility during formulation development [2].

Expression for approximate solubility

As the majority of drugs are administered orally, more than 90% need to pass through the gastrointestinal tract (GIT). The aqueous solubility of a compound plays a crucial role in determining its pharmacokinetic behaviour, absorption efficiency, and overall bioavailability during oral administration [3, 4].

Table 1 Expression for Approximate Solubility

Descriptive Term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Sparingly insoluble	>10,000

BCS Classification of Drug

As per the Biopharmaceutic Classification System (BCS), drugs are categorized into four classes based on their aqueous solubility and intestinal permeability [5].

Table 2 BCS Classification

Class	Solubility	Permeability	Example
Class I	High Solubility	High Permeability	Metoprolol, Paracetamol
Class II	Low Solubility	High Permeability	Itraconazole, Ketoconazole
Class III	High Solubility	Low Permeability	Ranitidine, Atenolol
Class IV	Low Solubility	Low Permeability	Furosemide, Taxol

Factors Affecting Solubility

1. Drug particle size:

Particle size plays a crucial role in solubility. When particles become smaller, their surface area relative to volume increases. This greater surface area enhances the interaction between the particles and the surrounding solvent, leading to improved dissolution.

2. Nature of solvent as well as solute:

Both the solvent's and the solute's properties depend on concentration and temperature. At room temperature, two hundred gram of zinc chloride may dissolve one gram of lead (II) chloride in one hundred gram of water.

3. The size of molecules:

As the molecular sizes of particles change, so does their solubility. Because the solvent molecules find it more difficult to fully encase molecules, a material becomes less soluble as its molecular weight and size grow [6].

4. Temperature:

Solubility is influenced by temperature. When the dissolution process absorbs energy (endothermic), solubility tends to increase with rising temperature. Conversely, if the process releases energy (exothermic), solubility generally decreases as the temperature increases [7].

5. Pressure:

While a gaseous solute's solubility increases with increasing pressure and decreases with decreasing pressure, the solubility of a solid or liquid solute remains constant when pressure changes.

6. Polarity:

The solubility of a substance is influenced by the polarity of both the solute and the solvent. Typically, polar solutes tend to dissolve more readily in polar solvents, while non-polar solutes are more likely to dissolve in non-polar solvents. In essence, substances with similar polarity are generally more compatible and dissolve better in each other.

7. Polymorphs:

Polymorphism refers to the ability of a compound to exist in more than one crystalline form. A single substance can crystallize into various structural arrangements depending on the conditions during crystallization. These distinct forms, known as polymorphs, often exhibit different physical properties, such as melting points. Since solubility is closely linked to melting point, different polymorphs of the same substance may also display varying solubility profiles [8].

Techniques To Overcome Poor Solubility

The following are the techniques to overcome solubility [9]

Table 3 Solubility Enhancement Technique

Techniques	
Physical modifications	• Particle Size Reduction ❖ Conventional Method ❖ Micronization ❖ Nanoparticle or Nanosuspension ❖ High pressure homogenization ❖ Milling technique • Crystal Habit Modification ❖ Polymorphs ❖ Pseudopolymorphs • Complexation ❖ Physical Mixture ❖ Kneading Method ❖ Co-precipitation Method • Inclusion Complexation

	❖ Kneading Method ❖ Lyophilisation ❖ Microwave irradiation Method • Surfactant based Solubilisation ❖ Microemulsion • Solid Dispersion ❖ Physical Kneading ❖ Melting /Fusion ❖ Solvent Evaporation ❖ Spray Drying ❖ Hot melt Extrusion
Chemical modifications	• pH Adjustment • Salt formation. • Self-emulsifying systems • Polymeric micelles formation
Miscellaneous	• Supercritical fluid process

➢ **Physical Modification**

Physical modification-

A. Particle size reduction

A drug's solubility is often closely related to its particle size. Smaller particles naturally offer a higher surface area-to-volume ratio, allowing for greater interaction with the surrounding solvent. This enhanced surface contact leads to improved solubility. For poorly soluble drugs, reducing particle size plays a key role in boosting bioavailability. By increasing surface area through size reduction, a wider range of formulation and drug delivery strategies becomes available, ultimately enhancing the dissolution behaviour of the drug [10].

Merits of particle size reduction

- It is a reliable, cost-effective, and consistent method for enhancing solubility.
- For chemical substances, reducing particle size increases the surface area available for solvent interaction, thereby accelerating the dissolution rate.
- It also facilitates quicker solvent penetration [11].

Demerits of particle size

- It causes the breakdown of the active compound due to physical and mechanical stress.
- When small particles possess a high surface charge, they tend to aggregate more readily due to increased inter-particle attraction.
- Problems for thermo sensitive agents may present from thermal stress due to thermal stress.
- During formulation of solid dosage form with a high pay load and without encouraging grouping and sterile intravenous formulation is technically challenging [12].

a) Conventional method

Traditional particle size reduction methods rely on different mechanisms such as cutting, compression, impact, attrition, or a combination of impact and attrition to break down particles. This

technique, which uses mechanical force to separate the active ingredient, includes distribution and spray drying. An effective, affordable, and repeatable method of improving solubility is made possible by the reduction in particle size. However, the mechanical forces inherent in distribution, including grinding and milling, often cause the drug product to experience enough physical stress to cause degradation. When working with unstable active compounds or heat-sensitive materials, the risk of thermal stress during processes like spray drying and distribution must be carefully considered. Enhancing the solubility of poorly soluble drugs cannot be effectively achieved using conventional methods alone [13].

b) Micronization

This process requires substantial energy to break down large particles into smaller ones, typically around 5 μm in diameter. It results in a uniform and narrow particle size distribution, which is crucial for the consistent formulation of dosage forms. As particle size decreases during micronization, the surface area increases, leading to enhanced solubility. The flow properties of powders can vary depending on the micronization method used, including techniques like mechanical size reduction, spray drying, and supercritical fluid (SCF) technology [14].Micronization influences not only particle size but also distribution, shape, surface characteristics, and aggregation behavior. According to the Noyes–Whitney equation, delivering drugs in micronized form is a widely recognized strategy to improve the bioavailability of poorly water-soluble drugs. There is a clear relationship between smaller particle size and improved bioavailability. Milling methods, such as rotor-stator colloid mills and jet mills, are commonly employed to achieve this reduction. Currently, particle size reduction through micronization or nanosuspension is widely practiced, and the equipment used varies with the chosen method [15, 16].

Techniques for micronization

Several advanced techniques are employed to enhance solubility by reducing particle size and improving drug dispersion. These include micro-precipitation and micro-crystallization, jet milling or micronization using fluid energy mills, and spray freezing into liquid, which rapidly solidifies drug particles. Additionally, rotor-stator colloid mills are used for efficient particle breakdown, while controlled crystallization allows precise manipulation of crystal size and form. Supercritical fluid technology also plays a key role by enabling uniform particle formation under controlled conditions, making it a promising approach for solubility enhancement [17].

Merits of micronization

- Its micro-sized nature results in uniform particles, enhanced surface area, and improved separation based on particle size.

Demerits of micronization

- Amorphous regions are thermodynamically unstable and tend to recrystallize over time, especially when exposed to heat and humidity during storage.

- This process involves high energy input, leading to the disruption of the drug's crystal lattice and resulting in the formation of disordered or amorphous regions in the final product [18].

c) **Nanotechnology**

Nanotechnology was originally described as a transformative field aimed at manipulating atoms and molecules to build macroscale objects an idea now known as molecular nanotechnology. Today, the National Nanotechnology Initiative defines nanotechnology as the control of matter with dimensions between 1 and 100 nanometres. This definition emphasizes the role of quantum mechanical effects at this scale and broadens the scope from specific technological aims to encompass the unique properties materials exhibit below this threshold. This scale-based approach includes a variety of scientific fields such as molecular biology, organic chemistry, surface science, semiconductor physics, energy storage, engineering, micro fabrication, and molecular engineering. The future potential of nanotechnology is widely discussed, with predictions that it could lead to the creation of innovative materials and devices applicable in consumer goods, biomaterials, energy, nanomedicine, and nanoelectronics. However, like any emerging technology, nanotechnology raises concerns, particularly regarding nanomaterial toxicity and environmental impacts. While micronization enhances the oral bioavailability of poorly soluble drugs, it often falls short, as the micronized particles may still lack sufficient effective surface area for efficient dissolution [18-20].

Some preparation made by nanotechnology method

1. **Nanosuspension:**

This approach is applied to drugs that have poor solubility in both water and oil. Nanosuspensions, which are biphasic systems, consist of nanosized drug particles dispersed in an aqueous medium containing surfactants for stabilization. They are widely used in the pharmaceutical field for various routes of administration, including topical, oral, parenteral, and pulmonary. In nanosuspensions, solid particles typically below one micron are suspended, with an average size between 200 and 600 nm. These can be prepared using either top-down or bottom-up techniques [21]

Merits of Nanosuspension

- In this method, the reduction in particle size leads to an increase in surface area, which directly enhances solubility and bioavailability.
- They eliminate the use of organic solvents.
- Utilized to improve permeability.
- Nanosuspension formulation offers the benefit of accommodating a high amount of drug content.

Demerits of nanosuspension

- Facing some problems as crystals growth, instability due to summation, Ostwald ripening [22].

2. Micro emulsion

A microemulsion is a combination of hydrophilic solvent, hydrophilic surfactant, and oil that dissolves in a medication that is not very soluble in water. The selection criterion for HLB, non-toxicity, and surfactants. It is a translucent, isotropic, dynamically stable, and optically clear system. When the formulation comes into contact with water, it spontaneously forms a clear emulsion with uniformly small oil droplets that have low water solubility. This approach is commonly used to enhance the solubility of drugs that are poorly soluble in water and can also be adapted by incorporating proteins for oral or parenteral delivery. Among the types, oil-in-water (o/w) microemulsion and emulsions are

considered the most effective. By shrinking in size (less than 100 nm), they can also improve oral bioavailability. This will raise the rate of absorption since surfactants alter permeability, and dissolving compounds make them more soluble [23].

3. High-pressure homogenization

The high-pressure homogenization technique involves three main stages.

- The drug powder is dispersed in a stabilizing liquid to form a preliminary suspension
- The presuspension is often subjected to homogenization using a low- or high-pressure homogenizer, typically as a preliminary step in the preparation process.
- Final homogenization is typically carried out for 10 to 25 cycles under high pressure until the nanosuspensions reach the targeted particle size [24].

4. Milling Techniques

(a) Media milling

Media milling works by creating collisions between the drug particles and milling media, generating sufficient energy to break the particles down into nanoparticles. The process involves a grinding chamber containing the drug, a stabilizer, grinding beads, and a suitable liquid medium such as water or buffer. The beads rotate at high speed to form a nanoparticle suspension. A key drawback of this technique is the presence of residual materials in the final product [25].

(b) Dry grinding

Initially, nano suspensions were prepared using the wet grinding technique with a pearl ball mill. However, the current approach involves dry milling, where a poorly soluble drug is dispersed in a liquid medium and then subjected to dry grinding along with polymers and soluble copolymers to form nano suspensions [25].

B. Crystal habit modification

Solubility enhancement can be achieved through crystal modification, which involves altering a group of crystals and changing their properties, such as crystal habit. This process functions through two types of polymorphism.

a) Polymorph
b) Pseudo polymorph

An element or compound that exhibits polymorphism is one that crystallises in two or more crystalline forms. Despite having the same chemical makeup, the various drug types and their polymorphs exhibit distinct physiochemical characteristics, including density, solubility, melting point, stability, and texture. When a drug's crystalline and amorphous forms are compared, the amorphous form is better because of its higher energy association and consequently larger surface area. A few distinct solid medication forms are listed in sequence of dissolution as Stable polymorph > metastable polymorph > amorphous [26].

a. Polymorph

Depending on its intrinsic structure, a solid can be either crystalline or amorphous. A substance can have several crystalline forms; these forms are referred to as polymorphs, and the process by which they occur is called polymorphism. The amorphous form of a drug exhibits higher water solubility than its crystalline counterpart because more energy is required to dislodge molecules from the crystal lattice into a non-crystalline state. Polymorphs can exist in both stable and metastable

forms. Metastable polymorphs are often preferred in formulations due to their higher energy state, lower melting point, and enhanced aqueous solubility, which contribute to improved bioavailability [27].

b. Pseudo polymorph

The solvent in this polymorphic form can exist in different crystalline structures, known as pseudo-polymorphs, and the phenomenon is termed pseudo-polymorphism. This typically involves the use of a specific ratio. When solvent molecules are incorporated into the crystal lattice of a solid in a defined stoichiometric proportion, the resulting compounds are called solvates or trapped solvents. When water is the solvent involved, the compound is referred to as a hydrate, representing the combination of the drug and water molecules. When comparing solvate with hydrate, the solvate has a higher aqueous solubility since it requires less energy to shatter crystals than hydrate. Compared to non-solvates, organic solvates are more soluble in water. For instance, ampicillin and theophylline in their anhydrous forms are more soluble [28].

C. Complexation

Complexation involves the formation of a non-covalently bonded entity with a specific stoichiometry, resulting from the association between two or more molecules. In this process, two main types of complexes are typically formed.

(a) Stacking complex

The stacking complex refers to the interaction between the non-polar region of a drug and its complexing agent, which shields the non-polar part from water exposure. Regardless of whether the system is uniform or mixed, the final result is a clear solution [29].

(b) Inclusion complex

The process involves incorporating a non-polar molecule or region into the cavity of another molecular structure, often utilizing agents like cyclodextrins and their derivatives for complexation. Solid ternary complexes can be formed using various agents, such as amino acids (e.g., arginine, tryptophan, leucine, phenylalanine, methionine, isoleucine), carboxylic acids (e.g., citric acid, tartaric acid), and sugar alcohols like mannitol. These ternary agents assist in drug binding. Amino acids like L-lysine and arginine are commonly used to form ternary complexes with drugs, typically in molar ratios such as 1:1:2 or other suitable weight-based ratios. For optimal interaction, a basic ternary agent is used with acidic drugs, and vice versa, to create stable solid ternary complexes [30].

1. Physical mixture

The polymer, drug, or cyclodextrins (CDs) are finely ground using a mortar and pestle, then passed through an appropriate sieve to achieve the desired particle size in the final product.

2. Kneading method

This method involves preparing a paste by absorbing cyclodextrins (CDs) or a suitable polymer with a small amount of water or a hydro-alcoholic solution. The drug is then incorporated into the paste and kneaded for a specific duration. Following this, the resulting mixture is dried and passed through a sieve [31].

3. Co – precipitate method

This approach is applied on a big scale and has industrial applicability. Using regulated process parameters and magnetic agitation, this approach extracts the necessary amount of medication from the CD or appropriate polymer solution. The

complex is protected from light, precipitates out of the solution, is collected using vacuum filtration, and then dried at room temperature. This prevents the inclusion complex's textural water from being lost [32].

D. Inclusion complex

One of the most widely used strategies for enhancing the dissolution rate, aqueous solubility, and bioavailability of poorly water-soluble drugs is the formation of inclusion complexes. These complexes are formed when nonpolar molecules or specific nonpolar segments (referred to as guests) are enclosed within the cavity of another molecule or molecular assembly (the host). Successful inclusion requires a compatible structural fit between the guest and host. Among various solubility enhancement approaches, inclusion complexation has gained prominence due to its effectiveness. Cyclodextrins are the most commonly used host molecules for this purpose. Derived from starch through enzymatic action by cyclodextrin-glycosyltransferase (CGT), cyclodextrins (CDs) are cyclic oligosaccharides composed of glucose units arranged in a toroidal structure. These molecules are crystalline, water-soluble, and non-reducing, possessing a hydrophilic exterior and a hydrophobic central cavity. The three naturally occurring types of CDs are α-, β-, and γ-cyclodextrins. Their hydrophobic core creates a favourable environment for nonpolar molecules, while the hydrophilic exterior ensures solubility in aqueous media [33].

Various techniques are briefly outlined below.

a) Kneading Method

This method involves moistening cyclodextrins (CDs) with a small quantity of water or a hydro alcoholic solution to form a paste. The drug is then incorporated into this paste and kneaded thoroughly for a specific duration. Once kneading is complete, the mixture is dried and, if needed, sieved. On a lab scale, kneading can be performed using a mortar and pestle, while large-scale production may utilize extruders or other machinery. It is one of the simplest and most widely used techniques for preparing inclusion complexes and is highly cost-effective for manufacturing [34].

b) Lyophilisation /Freeze-Drying Technique

To obtain a porous, amorphous powder with strong drug–cyclodextrin (CD) interactions, lyophilisation or freeze-drying is considered a suitable method. This technique involves freezing the drug-CD solution and then drying it under reduced pressure to eliminate the solvent. It is particularly effective for converting thermo labile drugs into complex forms. However, it requires specialized equipment, is time-consuming, and often results in a powder with poor flow properties. Unlike solvent evaporation, this method enables molecular-level mixing of the drug and carrier within a common solvent system [36].

Advantages

- The interaction between the drug and an appropriate polymer to form a highly porous and amorphous powder is regarded as a valuable and effective technique.
- This method enables the successful formation of complexes even with thermo labile (heat-sensitive) substances.

Disadvantage

- Utilization of advanced or dedicated instruments.

- This process is time-intensive and results in a powder with poor flow properties.

c) Microwave Irradiation Method

The microwave irradiation technique involves the use of microwave energy to facilitate the interaction between the drug and a complexing agent. In this process, the drug and cyclodextrin (CD) are dissolved in a specific molar ratio using a combination of water and organic solvent within a round-bottom flask. This mixture is then subjected to microwave heating at 60°C for about one to two minutes. Once the reaction is complete, additional solvent mixture is added to remove excess CD and any uncomplexed drug. The resulting precipitate is filtered using Whatman filter paper and dried in a vacuum oven at 40°C. This method is especially advantageous for industrial applications due to its reduced reaction time and higher product yield [37].

E. Surfactant based solubilization

A surfactant contains a hydrocarbon chain attached to a polar group. It exhibits both polar and non-polar characteristics, making it amphiphilic in nature. It is possible for the polar group to be non-ionic, zwitterion, anionic, or cationic. Small polar molecules have the ability to gather in the micelles' hydrophobic core. This is most important for natural and industrial processes. By promoting the dissolving of lipophilic medicines in aqueous media, the addition of surfactant decreased surface tension and increased drug solubility. Stabilising drug suspension is its purpose. Micellization takes place when the concentration of surfactants surpasses their critical micelle concentration (CMC), typically between 0.05% and 0.10% for most surfactants. This phenomenon leads to the formation of micelles, which significantly enhance the solubility of poorly water-soluble drugs [38].

Microemulsion

Microemulsion are clear, transparent systems composed of two immiscible liquids, such as water and oil that are made miscible through the use of surfactants. Unlike regular emulsions, which are often opaque and require high energy for formation, microemulsions form spontaneously and are thermodynamically stable under certain conditions. However, they can still be sensitive to environmental changes like temperature or pH, which may affect their stability [39, 40, 41].

Advantages

This formulation approach offers easy manufacturing and scalability, making it highly suitable for industrial production without requiring complex equipment. Additionally, it is particularly beneficial for topical applications, such as creams, ointments, or gels, where localized delivery is desired. For instance, itraconazole-based emulgels and oleogels can be effectively applied to fungal-infected skin areas, providing targeted treatment with improved patient compliance. [42, 43, 44].

Disadvantages

A key limitation is that conventional dissolution testing methods may not accurately predict drug release, especially for formulations like lipid-based systems, self-emulsifying drug delivery systems (SEDDS), or solid lipid nanoparticles. These systems often require in vivo digestion processes (e.g., enzymatic or bile salt action in the gastrointestinal tract) before the drug becomes available for absorption. As a result, in vitro tests might underestimate or misrepresent the actual bioavailability of the drug, necessitating more specialized biorelevant dissolution or digestion models for accurate evaluation [45, 46,].

F. Drug dispersion in carrier

a) Solid dispersion:

Solid dispersion is a well-established technique aimed at enhancing the solubility and bioavailability of poorly water-soluble drugs. First proposed by Sekiguchi and Obi, this method involves dispersing a hydrophobic drug in a hydrophilic carrier matrix. In this system, two crystalline components are combined, leading to the formation of a new solid solution or mixed crystal when both components crystallize simultaneously. This arrangement promotes faster dissolution rates compared to simple eutectic mixtures due to better molecular dispersion. In some cases, the drug precipitates in an amorphous form within the carrier matrix—this is known as amorphous precipitation. Because the amorphous form is thermodynamically less stable and exists in a higher energy state than its crystalline counterpart, it dissolves more rapidly, contributing to improved drug absorption and bioavailability [47]. Hydrophilic carriers commonly used in solid dispersion formulations include polyethylene glycols (PEGs), polyvinylpyrrolidone (PVP), and plasdone-S630. These polymers enhance the wettability and dispersion of the hydrophobic drug. Additionally, surfactants such as Tween 80, sodium lauryl sulfate (SLS), Pluronic F68, Myrj-52, and docusate sodium are frequently employed to further enhance solubility by reducing interfacial tension and stabilizing the amorphous state. This approach has been successfully utilized to improve the solubility and therapeutic performance of several poorly soluble drugs, such as ritonavir, celecoxib, and halofantrine. Various preparation techniques for solid dispersions include hot-melt extrusion (HME), solvent evaporation, fusion method, spray drying, and kneading, each offering different advantages based on the drug's thermal and chemical stability. Overall, solid dispersion remains a practical and scalable strategy for overcoming solubility limitations in modern drug development. The following are techniques used to prepare solid dispersions of hydrophobic drugs in order to improve their aqueous solubility [48, 49, 50].

1. Solid solution:

When two crystalline solids are combined, they can form a new crystalline structure known as a mixed crystal. This occurs when both components crystallize together uniformly, resulting in a single-phase solid solution. In this mixed state, the molecules of each component are integrated within the same crystal lattice, leading to improved molecular dispersion. This structural modification often results in a notably enhanced dissolution rate compared to the dissolution of each individual component or conventional formulations like simple intestinal drug delivery systems. The improved dissolution is primarily due to the increased surface area, better wettability, and possible disruption of the crystal lattice, making it easier for the solvent to interact with and dissolve the solid components. This approach is especially useful in pharmaceutical applications to improve the solubility and bioavailability of poorly water-soluble drugs [51].

1. Kneading technique:

This technique involves first forming a wet paste by blending the drug carrier materials with water. The active drug compound is then uniformly mixed into this paste to ensure proper dispersion. The resulting mixture is subjected to compression or molding for a specific, controlled duration to allow adequate bonding and shape formation. After this processing step, the formed mass is dried thoroughly to remove any residual moisture. Finally, the dried material is passed through a sieve to obtain uniform-sized particles or granules, which enhances flow properties and ensures consistency in dosage [52].

2. Co-grinding method:

A blender is used to prepare the medicine and carrier combination (blending for a specific defined period and speed). Steel balls are then added to the prepared mixture after it has been moved to the vibration ball mill compartment. After pulverisation, the sample such as mannitol and chlordiazepoxide is removed and kept at room temperature [53].

3. Melting method:

This technique entails blending the drug and carrier using a mortar and pestle to ensure uniform distribution. The mixed components are then heated until they melt together, forming a homogenous molten mass. Once melted, the mixture is allowed to cool and solidify into a congealed mass. This solid mass is then crushed into fine particles and sieved to obtain a uniform powder [54]. This method helps enhance drug solubility by forming solid dispersions, where the drug is molecularly dispersed in the carrier matrix. For example, urea (a hydrophilic carrier) and albendazole (a poorly soluble antiparasitic drug) can be processed this way to form a solid dispersion, improving albendazole's dissolution rate and bioavailability. Similarly, polyethylene glycol (PEG) can be used as a carrier with drugs like ibuprofen or ketoconazole to enhance their aqueous solubility through this melt-fusion technique [55].

4. Fusion process:

In the fusion method, the drug is first dissolved or uniformly dispersed in a suitable carrier, which is then heated slightly above its melting point. Continuous stirring is applied during this process to ensure uniform distribution of the drug throughout the molten carrier matrix. Once a homogenous mixture is obtained, it is rapidly cooled often under controlled refrigeration conditions to solidify the matrix and maintain even drug distribution. This method may enhance solubility through multiple mechanisms, including the carrier's ability to improve drug wettability, its solubilizing capacity, formation of drug–carrier complexes, and reduction of interfacial tension due to hydrophobic interactions [56]. Additionally, the drug may crystallize into a metastable polymorphic form, which possesses altered thermodynamic properties that can lead to improved dissolution rates. However, a significant limitation of this technique is its unsuitability for thermosensitive drugs. Exposure to elevated temperatures during the melting process may degrade such compounds, potentially compromising their stability and therapeutic efficacy. In summary, the fusion method is a straightforward and effective technique for solubility enhancement, but it requires careful selection of drugs and carriers to avoid heat-induced degradation [57].

5. Solvent evaporation method:

In the solvent evaporation method, both the active pharmaceutical ingredient (API) and a suitable carrier are dissolved in an appropriate organic solvent—commonly ethanol, chloroform, or a mixture like dichloromethane and ethanol. This homogeneous solution is then subjected to evaporation, either by applying vacuum or elevated temperatures, to remove the solvent. As the solvent evaporates, the solution becomes supersaturated, prompting simultaneous precipitation of the drug and carrier, forming a solid co-precipitate. This co-precipitate is then carefully vacuum-dried to ensure complete removal of any residual solvent [58]. The absence of solvent residues is crucial for formulation safety and stability and is typically confirmed using advanced analytical techniques. Highly sensitive

thermal techniques such as Differential Thermal Analysis (DTA), Differential Scanning Calorimetry (DSC), and Thermogravimetric Analysis (TGA) are used to assess thermal behavior and solvent traces. Additionally, less sensitive but supportive techniques like spectroscopy (e.g., FTIR) or gravimetric analysis may also be employed [59, 60].

Advantages

- The degradation of drugs and carriers due to heat can be avoided.

Disadvantages

- Expensive
- It is challenging to completely eliminate the liquid solvent

6. Spray Drying:

In this technique, both the active pharmaceutical ingredient (API) and a suitable carrier are either dissolved or suspended in a volatile, pharmaceutically acceptable solvent. The resulting solution or suspension is then subjected to a drying process, typically by spraying it into a stream of hot air — a method commonly known as spray drying. As the droplets come into contact with the heated air, the solvent evaporates almost instantly due to the droplets' high surface area. This rapid evaporation leads to the formation of a solid dispersion, where the drug is molecularly dispersed within the carrier matrix [61]. A widely known example involves Itraconazole, a poorly water-soluble antifungal drug. To improve its solubility and dissolution rate, it can be spray-dried using hydroxypropyl methylcellulose (HPMC) or polyvinylpyrrolidone (PVP) as a carrier in a solvent like ethanol. The resulting solid dispersion enhances the drug's bioavailability by maintaining it in an amorphous, more soluble state. Another example is Nifedipine, a calcium channel blocker, spray-dried with PEG 4000 to increase its dissolution rate and oral absorption [62, 63].

7. Spray freeze drying (Lyophilisation):

Spray freeze drying (SFD) is an advanced technique designed to produce solid dispersions efficiently, especially for thermosensitive drugs, without requiring high temperatures. Unlike conventional methods like hot-melt extrusion or spray drying that involve significant heat, SFD operates at ambient temperatures, making it ideal for compounds that degrade or lose activity upon heating. In this process, a solution or suspension containing poorly soluble or insoluble active pharmaceutical ingredients (APIs) along with suitable excipients is atomized into fine droplets. These droplets are rapidly frozen by spraying them into a cryogenic medium such as liquid nitrogen [64, 65]. The rapid freezing helps maintain the molecular dispersion of the drug in an amorphous form, preventing crystallization. Subsequently, the frozen droplets are subjected to lyophilization (freeze-drying), where the ice is sublimated, leaving behind a porous, low-density dry powder with high surface area. This increased surface area and amorphous state significantly enhance the dissolution rate and bioavailability of poorly water-soluble drugs [66]. Advantages of Spray Freeze Drying: Low-temperature processing: Suitable for heat-sensitive drugs such as peptides, proteins, and certain antibiotics. Improved solubility and bioavailability: Due to formation of amorphous, high surface area particles. Enhanced stability and dispersibility in aqueous environments. Examples: Insulin – Spray freeze drying has been used to develop inhalable insulin powders, preserving the biological activity of the protein while improving absorption through the lungs [67, 68].

8. Hot-melt extrusion:

In hot-melt extrusion, the drug is incorporated after the excipients are heated beyond their melting point, allowing both to mix thoroughly. The formation of a molecular dispersion—where the drug is evenly distributed at the molecular level—depends on how saturated the mixture is and the rate at which it is cooled. A slower cooling rate or supersaturation can lead to crystallization, while rapid cooling often results in an amorphous system. For this method to be effective, both the drug and the carrier (vehicle) must have a relatively low melting point and be soluble in organic solvents. Once the molten mixture is formed, it is quickly cooled and solidified into the desired dosage form such as pellets, granules, films, or powders [69]. When components that are miscible (i.e., can mix homogeneously) are processed via hot-melt extrusion, an amorphous solid solution is typically formed. A good example is Itraconazole with HPMC-AS (Hydroxypropyl methylcellulose acetate succinate), where the drug is molecularly dispersed in the polymer matrix, resulting in significantly improved dissolution and bioavailability [70]. On the other hand, if the drug and excipient are immiscible, the drug remains as an amorphous dispersion embedded within a crystalline excipient matrix. For instance, Indomethacin with PEG 6000 often results in an amorphous drug distributed within a crystalline polyethylene glycol base. Originally popular in the polymer industry, hot-melt extrusion was later adapted for pharmaceutical applications. A typical HME setup includes a feeding port, where the raw drug and excipient blend is introduced. A heated barrel, equipped with rotating screws, which convey and thoroughly mix the components. And an exit die, which shapes the molten mass into the desired form [71]. As the mixture moves through the heated barrel, the intense mechanical shear and heat soften or melt the components, converting them into a semi-fluid state. This facilitates close and uniform mixing of the drug and carrier. The extruded material exits through a die, which can be customized to form tablets, thin films, granules, or micropellets, depending on the intended dosage form. The applications like Nifedipine and Soluplus® used to prepare amorphous solid dispersions with enhanced solubility and sustained release properties. The Carbamazepine and PVP VA64 were formulated via HME to overcome poor water solubility and provide immediate release. The Lopinavir and Kollidon® VA 64 to Enhance oral bioavailability in antiviral therapies. In conclusion, HME offers a solvent-free, scalable, and efficient way to enhance drug solubility and stability—especially beneficial for poorly water-soluble drugs in BCS Class II and IV [72, 73].

Advantages of Solid Dispersion:

- Promotes faster drug dissolution.
- Enhances the drug's absorption rate.
- Improves the solubility and bioavailability of poorly water-soluble drugs.
- Converts the drug from a crystalline to an amorphous form.
- Enables the formulation of fast-disintegrating oral tablets.
- Helps in masking the unpleasant taste of the drug.
- Prevents drug degradation or decomposition.[74]

Disadvantages of Solid Dispersion:

- Prone to stability issues.
- Sensitive to environmental factors like moisture and temperature, which can degrade the formulation.
- May develop crystallinity over time, leading to a reduced dissolution rate with aging [75].

➢ **Chemical Modification**

a) pH Adjustment:

Changing the pH of the water may aid in the dissolution of some drugs that aren't particularly water soluble since they contain basic or acidic parts of the molecule. It is theoretically possible to use pH adjustment for both parenteral and oral dosage. Blood acts as a powerful buffer, and due to its narrow pH range of 7.2 to 7.4, poorly soluble drugs may precipitate following intravenous administration [76]. The success of this approach primarily relies on the buffering capacity and the ability of the body to tolerate the chosen pH. A medication's solubility may alter as it passes through the intestines after being taken orally since the pH in the duodenum fluctuates from roughly 5 to 7.5, while in the stomach it is between 1 and 2. The best compounds are those that are stable and soluble at the desired pH and that can be ionised. [77].

ADVANTAGES:

- Easy to prepare and evaluate
- Requires only a minimal amount of compound for testing

DISADVANTAGES:

- There is a potential risk of precipitation during intravenous administration, which may cause embolism; oral administration may lead to inconsistent absorption.
- Both local and systemic tolerability and toxicity concerns may arise due to the use of non-physiological or extreme pH conditions.

b) Salt Formation:

When an acid and a base come into contact, the salt is mostly formed by a neutralisation reaction. The process of salt production is utilised to make ionised drugs more soluble. Salt is created when protons from acids are transferred to bases. If the difference between the acid and base's pKa (acid dissociation constant) is more than 3, then ionic bonding between salts can form and will remain stable. For instance, salt production may improve the compound's solubility if the drug's intrinsic solubility is between 1 and 10 mg/ml. It is uncommon to transfer compounds with inherent solubility greater than 10 mg/ml to their salt form unless their physical properties contradict the existing formulation. One of the main strategies to improve medication solubility is salt production. It is considered an inexpensive approach for enhancing drug solubility and is among the most efficient non-processing techniques [78].

c) Self-Emulsifying or Emulsifying Systems:

Self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) are innovative approaches designed to enhance the oral absorption of poorly water-soluble drugs. These systems utilize the concept of in situ emulsion formation—meaning that emulsification takes place directly within the gastrointestinal (GI) tract after oral administration. SEDDS are composed of a clear, isotropic mixture of components such as: Oils (e.g., medium-chain triglycerides), Surfactants (e.g., Tween 80, Cremophor RH40), Co-surfactants (e.g., Transcutol, PEG 400), and Hydrophilic co-solvents (e.g., ethanol or propylene glycol). Upon contact with the aqueous environment of the GI tract and gentle agitation from gut motility, these systems spontaneously form fine oil-in-water (o/w) emulsions or microemulsion [79]. The Lipophilic (fat-soluble) drugs often have low oral bioavailability because they do not dissolve well in the aqueous environment of the GI tract. By forming emulsions or microemulsion in situ, these delivery systems enhance drug solubility, improve

absorption by increasing the surface area for drug release, protect the drug from enzymatic degradation, and bypass some first-pass metabolism through lymphatic transport. The potent immunosuppressant Cyclosporine A with very low water solubility is marketed as Neoral®, a SEDDS formulation that significantly improves its oral bioavailability [80].

d) Polymeric Micellar Carriers

Drug solubility can be enhanced and precipitation in the gastrointestinal (GI) tract can be prevented by incorporating poorly water-soluble compounds into surface-active drug systems. In aqueous surfactant solutions, micellar systems form through a dynamic balance involving free monomeric surfactants, micelles (aggregated surfactants), and surfactants adsorbed at interfaces [81]. When the concentration of surfactants exceeds the critical micelle concentration (CMC), micelles spontaneously form. These micelles arise from amphiphilic copolymers containing both hydrophobic and hydrophilic segments. The hydrophobic portions gather in the core, while the hydrophilic tails form the micelle's outer shell, ensuring stability in aqueous environments. The hydrophobic core provides a reservoir for encapsulating lipophilic drugs, whereas the hydrophilic shell (corona) facilitates dispersion in water. This system significantly increases the solubility of lipophilic drugs such as itraconazole or paclitaxel. [82].

- **Miscellaneous**

a) Supercritical Fluids (SCF):

In recent years, the use of supercritical fluids (SCFs) has grown remarkably across various industries, including pharmaceuticals, food processing, and materials science. Among these fluids, carbon dioxide (CO_2) stands out as the most commonly used SCF due to its favourable critical parameters (critical temperature 31.1°C and critical pressure 73.8 bar). It has been employed for over a century as a solvent for extracting non-volatile compounds and offers several advantages: it is non-toxic, non-flammable, cost-effective, and environmentally friendly. SCFs exist in a unique state beyond their critical temperature and pressure, where they do not distinguish between liquid and gas phases. This single-phase nature allows them to exhibit hybrid properties such as the density of a liquid and the diffusivity of a gas which are highly beneficial in product development and processing. What makes SCFs particularly attractive is their tunable properties. By making small adjustments in temperature or pressure near the critical point, one can significantly alter properties like density, viscosity, diffusivity, polarity, and solvation capacity. This enables precise control over solubilization, precipitation, and extraction processes [83].

CONCLUSION

Poor aqueous solubility remains a major hurdle in the successful development of many promising drug candidates, often resulting in limited bioavailability and therapeutic inefficacy. Addressing this challenge is crucial to unlocking the full pharmacological potential of poorly water-soluble drugs. Over the years, numerous solubility enhancement strategies have been developed, ranging from conventional approaches like salt formation, co-crystallization, and solid dispersion to advanced technologies such as supercritical fluid processing, liquisolid systems, and high-pressure homogenization. Each technique offers unique advantages depending on the physicochemical properties of the drug and the intended dosage form. A tailored, case-specific approach often involving a combination of

methods—can significantly improve drug solubility, dissolution rate, and ultimately, patient outcomes. Continued research and innovation in this area will be essential to meet the growing demand for effective, bioavailable, and patient-friendly pharmaceutical formulations.

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