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Review Article

TECHNIQUES FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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Abstract
Poor aqueous solubility is a major challenge in pharmaceutical drug development, as it significantly affects dissolution rate, absorption, and oral bioavailability. A large proportion of newly discovered drug candidates fall under BCS Class II and IV, where solubility becomes the primary limiting factor for therapeutic effectiveness. Therefore, improving solubility is essential to ensure adequate drug concentration in systemic circulation and to achieve optimal pharmacological response. This review discusses the fundamental concepts of drug solubility and highlights various solubility enhancement techniques, including physical modifications such as particle size reduction, crystal engineering, and solid dispersion; chemical approaches like salt formation, prodrug development, and pH adjustment; and advanced methods such as surfactant-based systems, lipid-based drug delivery, nanocrystals, and hot-melt extrusion. The appropriate selection and application of these strategies can significantly enhance dissolution rate, bioavailability, and overall therapeutic performance.

Keywords: Solubility enhancement; Poorly soluble drugs; Bioavailability; Dissolution rate; Pharmaceutical formulation.

INTRODUCTION

Poor aqueous solubility remains a major challenge in pharmaceutical formulation development. A substantial proportion of newly discovered drug candidates obtained through combinatorial chemistry and high-throughput screening exhibit low water solubility, thereby limiting their suitability for conventional dosage forms and reducing their therapeutic potential [2]. It has been reported that approximately 40% of marketed drugs and nearly 90% of drug candidates are poorly water-soluble [3]. Because inadequate solubility leads to slow dissolution, limited absorption, and low oral bioavailability, improvement of solubility and dissolution rate has become a critical objective in modern drug development [2].

Oral administration is the most convenient and widely preferred route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, and flexibility in dosage form design [1]. However, the oral bioavailability of many drugs is frequently compromised by poor aqueous solubility and limited intestinal permeability [1]. Among these factors, solubility is considered a primary rate-limiting step in achieving the required drug concentration in systemic circulation and eliciting an optimal pharmacological response. Consequently, poor oral bioavailability represents a significant challenge in dosage form design and underscores the importance of solubility enhancement strategies in pharmaceutical formulation [1].

The bioavailability of a drug is influenced by multiple factors, including aqueous solubility, dissolution rate, intestinal permeability, susceptibility to efflux mechanisms, and first-pass metabolism [1]. Solubility is defined as the maximum amount of a solute that can dissolve in a given quantity of solvent at a specified temperature and pressure to form a homogeneous solution. It may be expressed using various concentration units such as percentage, molarity, molality, mole fraction, and volume fraction. For efficient absorption following oral administration, a drug must be present in a dissolved state at the site of absorption; failure to do so may result in suboptimal therapeutic response [1].

The Biopharmaceutics Classification System (BCS) provides a scientific framework for categorizing drugs based on their aqueous solubility and intestinal permeability and serves as a predictive tool for dissolution behavior and in vivo bioavailability [1]. Drugs classified under BCS Classes II and IV, characterized by low solubility, often require the application of specialized solubility enhancement techniques to achieve satisfactory therapeutic performance.[2]

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2. FUNDAMENTALS OF DRUG SOLUBILITY

2.1 Definition of Solubility and Dissolution

Solubility

Solubility is defined as the maximum amount of a solute (such as a drug) that can dissolve in a given quantity of solvent at a specified temperature and pressure to form a homogeneous solution. It is a thermodynamic property that reflects the equilibrium between dissolved and undissolved solute. Solubility may be expressed in various units such as molarity, molality, mole fraction, percentage, or parts per million.

In pharmaceutical sciences, solubility is a critical parameter because a drug must be dissolved in biological fluids before it can be absorbed into systemic circulation and produce a therapeutic effect.[3]

Dissolution

Dissolution is the process by which a solid substance enters into solution and becomes molecularly dispersed in a solvent. Unlike solubility, which is an equilibrium property, dissolution is a kinetic process that describes the rate at which a drug dissolves in a given medium. The dissolution rate depends on several factors, including particle size, surface area, temperature, agitation (stirring rate), nature of the solvent, and physicochemical properties of the drug. In pharmaceutical dosage forms, dissolution plays a vital role in determining the onset, intensity, and duration of drug action, particularly for orally administered drugs.[1.4]

2.2 Physicochemical Factors Affecting Solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system.

Particle size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent.[4]

Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process difference in the solubilities of these two substances is the result of differences in their nature. [4]

Molecular size

The larger the molecule or the higher its molecular weight the less soluble the releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases. Pressure For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility. [5]

Nature of the solute and solvent

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent . [5]

Polarity

Generally non-polar solute molecules will dissolve in non polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. [5]

Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism .Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques. [6]

Polymer type:

The selection of the polymer used in extended-release systems can influence both the mechanism of release and the rate at which dissolution occurs. [6]

Device type: the characteristics of the dosage form, like the shape and composition of tablets or pellets, can impact their adhesion properties and the manner in which they release their contents. [6]

Dissolution media:

The solubility and hydration duration of the polymer matrix, and consequently the release rate, can be impacted by the choice of solvent or dissolution medium utilized in the dissolution process[7].

Excipients:

In co-crystallization, the inclusion of excipients such as co-formers can boost both solubility and the rate of dissolution. [7]

Polymer coating systems:

The release profiles of sustained-release drug pellets can be influenced by the solubility of the drug within the polymer solution and the amount of coating applied. [7]

2.3 Biopharmaceutics Classification System (BCS)

CLASS	SOLUBILITY	PERMEABILITY	EXAMPLES
Class – I	High	High	Metoprolol, Propranolol
Class – II	Low	High	Nifedipine, Naproxen
Class – III	High	Low	Cimetidine, Metformin
Class – IV	Low	Low	Taxol, Clorthiazole

Table.No.01: Biopharmaceutical classification system with examples [8]

3. NEED FOR SOLUBILITY ENHANCEMENT

• Rate and oral bioavailability

Achieve better Solubility enhancement is essential in pharmaceutical formulation because many drug candidates exhibit poor aqueous solubility, which limits their dissolution, absorption, and overall bioavailability. Since a drug must dissolve in gastrointestinal fluids before absorption, low solubility becomes a major barrier to achieving optimal therapeutic effect.

Enhancing solubility helps to:

Improve dissolution and faster therapeutic response

- Reduce required dose and side effects
- Minimize variability in drug absorption
- Enable successful formulation of BCS Class II and IV drugs
- Support development of advanced and effective dosage forms

Therefore, solubility enhancement plays a crucial role in improving drug performance, patient compliance, and overall treatment success. [9]

4. CLASSIFICATION OF SOLUBILITY ENHANCEMENT TECHNIQUES

4.1 Physical Modification Techniques

• Particle Size Reduction

It is commonly utilized to improve the solubility of pharmaceuticals and enhance their bioavailability. Various techniques are employed for this purpose, including milling, liquid anti-solvent crystallization, spray drying, high-pressure homogenization, spray freeze-drying, micronization, pulsed laser ablation, and combined methods22. Studies have shown that high-pressure homogenization followed by bead milling, consistently achieve superior decreases in particle size when compared to alternative techniques23. Furthermore, strategies such as solid dispersion, nanonization, pH adjustment, co solvency, complexation, hydrotropy, and the use of vitamin E TPGS-based microemulsions are Utilized to improve the solubility of drugs that have low water solubility[10]

• Crystal Engineering

The extent to which a drug can disintegrate is determined by the surface area it occupies and its ability to be moistened by luminal liquids, which is influenced by the size of its molecules. The size of this molecule, which is crucial for the speed at which medicine breaks down, relies on either its crystallisation states or the methods used to break it down, such as agitation processing and liquid energy processing. Comminution processes possess the capacity to generate particles that are extremely heterogeneous, charged, and persistent. These particles have the ability to interfere with item execution and downstream management. To achieve the production of very pure powders with clear distribution of molecule size, crystal orientation, crystal structure (crystalline or amorphous), surface characteristics, and surface energy, techniques for crystal engineering have been developed. By modifying the crystallisation circumstances, such as employing various solvents, altering the mixing process, or introducing additional components, it is feasible to create gems with diverse pressing techniques in drug organisation. These precious stones are commonly referred to as polymorphs.

Quinine (QUN), a drug used to treat malaria, has low water solubility. QUN's adoption of a specific conformation in complexes implies that the structure class has a greater statistical probability43. Vanillin (VAN) is extensively utilised in the fields of food, medicine, and optoelectronics. However, its limited solubility hampers its bioavailability and increases its application costs. Three active pharmaceutical ingredient (API) namely nicotinaimde (NIC) sisonicotinamide (INM), and isoniazide (INH), were employed to generate cocrystals with VAN. The present work establishes a foundation for developing cocrystals of natural goods and drugs, which will enhance the solubility and dissolution rate of natural products. [7,10]

• Solid Dispersions

Solid dispersion method is the most essential for improve the solubility of poorly water soluble drugs and also improving bioavailability by the physical modification. They are classify into six types; eutectic mixture, solid solution, glass suspension, amorphous precipitates, complex and combination. solid dispersion increase the solubility and dissolution rate by reduce the porosity. Solid dispersion prepared by the solvent evaporation, co grinding, hot melt extrusion and supercritical method and etc. Select the polymer is the essential step in creating solid dispersion. Select the polymer based on various consideration, The glass transition temperature, hydroscopic, solubilization, and the solid capacity of solutions. [3,5]

4.2 Chemical Modification Techniques

• Salt Formation

Improving solubility is a crucial aspect, and various methodologies have been explored for this purpose. These include strategies such as reducing particle size, forming salts, creating solid dispersions, generating complexes, utilizing cosolvent techniques, employing surfactants, undergoing physical and chemical modifications, and adjusting ph through buffering agents. Among these approaches, salt formation stands out as a promising avenue for enhancing both solubility and dissolution rates of active pharmaceutical ingredients. Additionally, hot melt extrusion (HME) emerges as a scalable and industrially viable technique, which has demonstrated effectiveness in improving the solubility. [5]

• Prodrug Approach

Prodrug Approach (As per the given PDF – Short Explanation)

The prodrug approach is a chemical modification technique used to enhance the solubility of poorly water-soluble drugs. In this method, the active drug is chemically modified into a more water-soluble derivative (prodrug), which improves its dissolution and absorption.

After administration, the prodrug is converted back into the active parent drug in the body through enzymatic or chemical processes.

Advantages:

- Improves aqueous solubility
- Enhances dissolution rate
- Increases bioavailability
- Helps overcome poor absorption issues

• pH Adjustment and Buffering

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4.3 Solvent and Surfactant-Based Techniques

• Co-solvency

The solubility of chemicals that are not easily soluble in water can be increased by using a cosolvent, which is a water-miscible substance that can dissolve the material53. The co-solvent consists of water and at least one chemical. An aqueous solvent employed to induce a reaction that enhances the solubility of the inert solvent. This programme might be regarded as the most often utilised software due to its simplicity in distribution and assessment. Some solvents that can be used for mixing include PEG 300, propylene glycol, and ethanol. Co-dissolution refers to the ability to give drugs that have low solubility through both oral and parenteral routes. To minimise the concentration of dissociation in front of the tissue, injection schemes may necessitate the inclusion of water or the dilution with aqueous medium. Co-solvents have the ability to significantly enhance the solubility of a combined solvent in water, increasing it by thousands of times compared to the solubility of a single solvent. Cosolvents can enhance the solubility of insoluble solvents by combining them with other solubilization procedures and adjusting the pH. Utilising cosolvents is a very efficient approach to enhance the solubility of drugs that have low solubility.

To enhance the water solubility of etoricoxib, three distinct cosolvents, such as PEG 400, PG, and glycerol, were employed. This investigation also yielded data on the solubility of etoricoxib in different pharmaceutical solvents, which will facilitate the development and manufacturing of liquid products containing etoricoxib. [11]

Surfactants and Wetting Agents

Permeability and dissolution rate can be enlarged be surfactant. Absorption rate also be enlarge due to increasing of particle size. Mechanism include firstly permeability and then penetration of solvent in the particles of drug. Solubility of much poorly water soluble anti microbial drugs can be increasing use of surfactant.

Three types of surfactant;cationic,anionic and non ionic. Anionic and cationic select over the non ionic surfactant. It act as good solubility agent. [11,12]

• Micellar Solubilization

Employing supplementary surfactants to produce a product devoid of solvents would be a crucial, indispensable, and effective approach. Surfactants decrease the surface area and facilitate the segregation of lipophilic compounds in liquids. Additionally, they are employed for the purpose of stabilising suspensions. Micelle production takes place when the concentration of the surfactant exceeds the critical micelle concentration (CMC), typically ranging from 0.05% to 0.10% for most surfactants. This concentration threshold allows the surfactant to capture and enclose the within the micelles. This process is known as micellization and often enhances the solubility of soluble medicines in an inefficient manner. Surfactants enhance the ability of wastes to be wetted and accelerate the pace at which goods break down65.Non-ionic surfactants that are often employed include polysorbates, poly-oxyethylene castor oil, poly-oxyethylene glycerides, lauryl macroglycerides, and monounsaturated and saturated fatty esters of lower molecular weight polyethylene glycol. Surfactants are frequently employed to solubilize microemulsions and eliminate contaminants.

Limited aqueous solubility frequently poses a significant challenge in the process of clinical advancement. Micellar solubilization is a commonly employed technique for enhancing the solubility of poorly regulated pharmaceuticals. The study focuses on the synthesis of seven antidiabetic s, namely gliclazide, glibenclamide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone. These pharmaceuticals are developed employing cationic, anionic, and non-ionic surfactants,

as well as solubility combinations. The synergistic action of surfactants and buffers in ionic nonionic mixed surfactant systems enhance solubilization and can serve as very effective solubilization devices. [12]

4.4 Complexation Techniques

• Inclusion Complexes

Inclusion complexes are formed when a host molecule (commonly cyclodextrins) encapsulates a poorly soluble drug molecule inside its cavity.

- Improve aqueous solubility
- Enhance dissolution rate
- Increase stability
- Protect drug from degradation

This technique is especially useful for BCS Class II and IV drugs where solubility limits bioavailability. [13,20]

• Polymer–Drug Complexes

Polymer–drug complexes are formed through interactions such as hydrogen bonding or ionic interactions between drug molecules and polymers (e.g., PVP, PEG).

- Improve wettability
- Reduce drug crystallinity
- Enhance dissolution rate
- Increase bioavailability
- Improve physical stability

They are commonly used in solid dispersion systems. [13]

4.5 Lipid-Based Drug Delivery Systems

• SEDDS and SMEDDS

Self-Emulsifying Drug Delivery Systems (SEDDS) and Self-Microemulsifying Drug Delivery Systems (SMEDDS) are mixtures of oils, surfactants, and co-surfactants.

- Form fine emulsions in gastrointestinal fluids
- Improve solubilization of lipophilic drugs
- Enhance absorption and bioavailability
- SMEDDS produce smaller droplet sizes than SEDDS

These systems improve oral delivery of poorly soluble drugs.

• Liposomes and Nanoemulsions

Liposomes are vesicles composed of phospholipid bilayers that encapsulate drugs.

- Improve solubility of hydrophilic and lipophilic drugs
- Provide controlled release
- Reduce toxicity

Nanoemulsions are fine oil-water dispersions with nanosized droplets.

- Increase surface area
- Enhance dissolution rate
- Improve drug absorption

Solid Lipid Nanoparticles (SLN)

Solid Lipid Nanoparticles are submicron particles made from solid lipids stabilized by surfactants.

- Improve drug stability
- Provide controlled drug release
- Enhance bioavailability
- Suitable for poorly water-soluble drugs [14,15,16]

4.6 Novel and Advanced Approaches

• Nanocrystals and Nano suspensions

Nanocrystals are pure drug particles reduced to nanosize.

- Increase surface area
- Improve saturation solubility
- Enhance dissolution rate
- Improve bioavailability

They are prepared by high-pressure homogenization, milling, and other size reduction techniques. [16]

• Supercritical Fluid Technology

This method uses supercritical fluids (commonly CO_2) to produce fine drug particles.

- Produces uniform particle size
- Improves dissolution
- Avoids residual solvents
- Useful in crystal engineering

It is an advanced alternative to conventional crystallization. [17,19]

• Hot-Melt Extrusion (HME)

Hot-Melt Extrusion is a solvent-free process where drug and polymer are melted and mixed under heat and pressure.

- Produces amorphous solid dispersions
- Enhances solubility and dissolution
- Industrially scalable
- Improves bioavailability [18]

5. FUTURE PERSPECTIVES

The continuous emergence of poorly water-soluble drug candidates, particularly from modern drug discovery platforms, necessitates innovative and integrated solubility enhancement strategies. Future research in this field is expected to move beyond conventional particle size reduction and salt formation toward multidisciplinary, technology-driven, and patient-centered solutions. The following perspectives outline promising directions for future development:

6. CONCLUSION

Poor aqueous solubility remains one of the most significant challenges in modern pharmaceutical development, particularly with the increasing number of newly discovered drug candidates classified under BCS Class II and IV. Since solubility and dissolution rate directly influence oral absorption and bioavailability, the successful formulation of poorly water-soluble drugs requires the application of appropriate solubility enhancement strategies.

Each technique mentioned offers distinct advantages and limitations, and no single approach is universally applicable. The selection of an appropriate method depends on the drug's physicochemical properties, therapeutic dose, stability profile, route of administration, scalability, and regulatory considerations. Recent advancements in nanotechnology, lipid-based systems, and polymer science have significantly expanded the formulation toolbox, enabling improved dissolution behavior, enhanced permeability, and better therapeutic outcomes.

In conclusion, solubility enhancement remains a critical and evolving area in pharmaceutical research. Continued innovation, integration of novel technologies, and a deeper understanding of drug–excipient interactions will be essential to address the challenges posed by poorly soluble drugs and to ensure the development of safe, effective, and patient-compliant dosage forms in the future.

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