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SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT

Solubility refers to the process of a solid dissolving in a liquid phase to create a uniform system. This property is a critical factor in achieving the desired drug concentration in the systemic circulation for the manifestation of pharmacological responses. Drugs with poor water solubility often necessitate elevated doses to attain therapeutic plasma concentrations post oral administration. The primary challenge in formulating new chemical entities lies in overcoming low aqueous solubility. To facilitate absorption, it is imperative for a drug to exist in the form of an aqueous solution at the absorption site. Water stands out as the preferred solvent for liquid pharmaceutical formulations. Many drugs are weakly acidic or weakly basic with limited aqueous solubility, diverse techniques, such as micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, and hydrotropy, are employed to enhance the solubility of poorly water-soluble drugs. The objective of this review article is to elucidate the various solubilization techniques, aiming to achieve effective absorption and heightened bioavailability

Keywords: Solubility, Solubility enhancement, Co-solvent, pH, Emulsion

INTRODUCTION

Enhancing the solubilization and bioavailability of poorly water-soluble drugs can be achieved through a diverse range of approaches. Techniques such as

micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, and various other procedures are commonly employed for the solubilization of medications **[1]**. The Biopharmaceutics Classification System (BCS) serves as a scientific framework to categorize pharmaceuticals by considering their water solubility and intestinal permeability. When integrated with the in vitro dissolving properties of a drug product, the BCS takes into account three crucial elements: solubility, intestinal permeability, and dissolution rate **[2]**. Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure **[3]**. Pharmaceuticals characterized by limited solubility are classified within the Biopharmaceutics Classification System (BCS) as either class II or class IV drugs. Examples of class II drugs include phenytoin, danazol, and nifedipine, while class IV drugs encompass hydrochlorothiazide, furosemide, and taxol **[4]**.

TYPES OF SOLUBILIZATION TECHNIQUES

I. Physical Modification

A. Particle Size Reduction
B. Solubilization of Surfactant
C. Complexation
D. Drug Dispersion in Carrier

II. Chemical modification

A. Hydrotrophy
B. Co-Solvency
C. Nanotechnology
D. Salt Formation

III. pH Adjustment

IV. Polymeric Alteration

V. Liquisolid Technique

I]. PHYSICAL MODIFICATION

A]. PARTICLE SIZE REDUCTION:

The relationship between bioavailability and drug particle size is intrinsic. Reducing particle size enhances dissolution properties through increased surface area. Techniques such as milling using jet mills, rotor-stator colloid mills, etc., achieve particle size reduction. However, this approach is not suitable for drugs with a high dose number as it doesn't alter the saturation solubility of the drug. Bioavailability is inherently linked to drug particle size, with reduced size leading to improved dissolution properties due to increased surface area **[5]**.

Micronization stands as a conventional method utilized to reduce particle size in pharmaceutical applications. This technique enhances the dissolution rate of drugs by expanding their surface area, while leaving their equilibrium solubility unaffected **[6]**. Griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate underwent these procedures. In each case, micronization enhanced their gastrointestinal absorption, thereby elevating their bioavailability and clinical effectiveness. Specifically, micronized fenofibrate demonstrated a dissolution increase exceeding tenfold (from

1.3% to 20%) within 30 minutes in biorelevant media **[7, 8]**.

B]. SOLUBILIZATION OF SURFACTANT

Employing surfactants to enhance the dissolution properties of poorly soluble drugs is arguably one of the most fundamental and longstanding approaches. Surfactants act as agents that lower surface tension, thereby promoting the dissolution of hydrophobic drugs in aqueous environments. Solubilizing agents, such as superdisintegrants like crospovidone, crosscarmellose sodium, and sodium starch glycolate, play a crucial role in numerous formulations by enhancing the solubility and dissolution rate of poorly water-soluble drugs **[9]**. PEG 400 is employed specifically to enhance the solubility of hydrochlorothiazide. Additionally, Modified Gum Karaya (MGK), an innovative excipient, has been assessed as a carrier to improve the dissolution of the poorly soluble drug nimodipine **[10]**.

C]. COMPLEXATION

Complexation of drugs with cyclodextrins represents a widely utilized strategy aimed at enhancing aqueous solubility and stability of pharmaceutical compounds **[11]**. Cyclodextrins, including α, β, and γ-cyclodextrin, consist of 6, 7, or 8 dextrose molecules bound in a 1,4- configuration, forming rings of varying diameters. These rings possess a hydrophilic exterior and a lipophilic core, allowing appropriately sized organic molecules to form noncovalent inclusion complexes, thereby increasing aqueous solubility and chemical stability. Among cyclodextrins, derivatives such as hydroxypropyl-β-cyclodextrin (HP-β-CD) are commonly employed in pharmaceutical formulations due to their enhanced water solubility **[12, 13]**. Notably, cyclodextrin complexes have demonstrated efficacy in enhancing the stability, wettability, and dissolution of lipophilic compounds like N, N-diethyl-m-toluamide (DEET), as well as improving the stability and photostability of sunscreen. The permeation of cyclodextrins through the skin, however, presents complexities **[14]**. Loftsson and Masson highlighted that the impact on skin penetration may be influenced by cyclodextrin concentration, with higher concentrations generally associated with reduced flux and lower concentrations potentially leading to increased flux **[15]**. This phenomenon is attributed to the ability of cyclodextrins to complex with excess free drug, thereby altering flux proportional to the free drug concentration. Moreover, cyclodextrins are implicated in the extraction of stratum corneum lipids, potentially enhancing skin penetration **[16]**. However, it is noted that experiments utilizing rodent model membranes, which exhibit easier lipid extraction compared to human skin, may overestimate the penetration enhancement attributed to

cyclodextrin complexation **[17, 18]**.

D]. SOLID DISPERSIONS

Solid dispersion is a technique involving the dispersion of one or more active ingredients within an inert carrier or matrix while maintaining a solid state. In this method, poorly water-soluble drugs are dispersed within a highly soluble solid hydrophilic matrix, leading to improved drug dissolution **[19]**. This process can yield both molecular-level mixing, referred to as a solid solution, and non-molecular level mixing, such as the formation of eutectic products **[20]**. For example, the inclusion of PEG 4000 has been demonstrated to fasten dissolution rates. Despite its appealing characteristics and straightforward concept, solid dispersion encounters obstacles in achieving widespread adoption due to challenges associated with manufacturing, stability, and scalability **[21]**. It has been effectively utilized to enhance the solubility of various drugs, including Griseofulvin, Ketoprofen, Aceclofenac, Oxcarbazepine, Albendazole, and Bifonazole. Amorphous particles (also termed clusters) or crystalline particles are commonly observed in solid dispersions **[22]**. Water, methanol, ethanol, chloroform, DMSO, and acetic acid are among the frequently utilized solvents for formulating solid dispersions **[23]**.

II]. CHEMICAL MODIFICATION

A]. HYDROTROPHY

Hydrotropes are characterized by their possession of an anionic group alongside a hydrophobic aromatic ring or ring system. The mechanism underlying hydrotropy primarily revolves around complexation, wherein lipophilic drugs interact with hydrotropic agents like urea, nicotinamide, sodium alginate, sodium benzoate, and others. The hydrotropy technique operates with a solvent characteristic that remains unaffected by pH variations, demonstrating selectivity and eliminating the need for emulsification processes **[24]**. Hydrotropic agents offer a viable option for conducting titrimetric analysis of BCS class II drugs, such as ketoprofen, where sodium citrate serves as a prominent example of such an agent. Hydrotropy, sometimes referred to as a form of co-solvency, presents distinct advantages. This approach eliminates the need for altering the chemical structure of hydrophobic drugs, avoids reliance on organic solvents, and bypasses the necessity of preparing emulsion systems **[25]**.

B]. COSOLVENCY

Cosolvents involve the combination of water with one or more water-miscible solvents to create a solution that exhibits improved solubility for compounds with poor solubility **[26]**. Examples of solvents frequently included in cosolvent mixtures are PEG 300, propylene glycol, or ethanol. These formulations can be administered orally or parenterally. Cosolvents can be combined with other solubilization

techniques and pH adjustment to further enhance the solubility of poorly soluble compounds **[27]**. For parenteral use, low-toxicity cosolvents such as propylene glycol, ethanol, glycerin, and polyethylene glycol are commonly employed. Additionally, dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA) are used as cosolvents due to their notable solubilization capacity for poorly soluble drugs and relatively low toxicity **[28]**. Remarkable enhancements in solubility, up to 500-fold, have been achieved using 20% 2-pyrrolidone. Water-soluble organic solvents commonly employed include polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin. For instance, Pfizer's Procardia (nifedipine) formulation contains glycerin, peppermint oil, PEG 400, and sodium saccharin within soft gelatin capsules **[29]**. Conversely, water-insoluble solvents encompass long-chain triglycerides such as peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil, and hydrogenated soybean oil, as well as medium-chain triglycerides like Miglyol 812 **[30]**. Additionally, beeswax, d-α-tocopherol (vitamin E), and oleic acid are included in this category. A notable commercial example of this approach is Progesterone, a water-insoluble steroid solubilized in peanut oil **[31]**.

C]. NANOTECHNOLOGY

Nanocrystallization refers to a process aimed at reducing the size of drug particles to a range between 1 and 1000 nanometers. This technique employs two primary methods: 'bottom-up' and 'top-down' approaches. In the top-down methods, such as Milling and High-pressure homogenization, the reduction starts from a macroscopic level, typically from micron-sized powders. On the other hand, bottom-up methods like Precipitation and Cryo-vacuum involve the chemical composition of nanoscale materials from atomic and molecular components **[32]**. Pharmaceutical nanosuspensions represent biphasic systems comprising drug particles at the nano scale, stabilized by surfactants, suitable for various administration routes including oral, topical, parenteral, and pulmonary. Typically, the particle size distribution of solid particles in nanosuspensions is less than one micron, with an average particle size falling within the range of 200 to 600 nanometers. This approach finds application in enhancing the solubility of poorly soluble drugs, which exhibit insolubility in both water and oils **[33]**.

D]. SALT FORMATION

Salt formation has long been employed as a strategy to enhance the solubility of poorly soluble drug candidates, particularly those classified as weak acids or bases. This approach proves effective not only in parenteral and liquid formulations but also

in solid dosage forms **[34]**. A significant proportion of new chemical entities approved by the FDA between 1995 and 2006 were in salt forms, with hydrochloride being the predominant salt form for basic drugs. The selection of suitable salts depends on the aqueous solubility of the drug and its pH-solubility relationship, which determines the necessity and feasibility of salt formation and the choice of counter ions. Counter ions should ideally be FDA approved or supported by adequate toxicological data to ensure safety. Criteria for counter ion selection also include its ability to assist in salt formation and enhance dissolution properties. Phenytoin serves as a notable example, where its solubility is notably augmented through the inclusion of sodium hydroxide by salt formation. This adjustment facilitates the attainment of desired concentrations necessary for parenteral administration **[35]**.

III]. pH ADJUSTMENT

Poorly water-soluble drugs containing protonatable (basic) or deprotonatable (acidic) parts of the molecule may potentially be dissolved in water by inducing a pH change. This pH adjustment approach is applicable in both oral and parenteral administration. However, intravenous administration might lead to precipitation of the poorly soluble drug because blood serves as a strong buffer with a pH ranging between 7.2 and 7.4 **[36]**. The selection of a suitable pH for this approach necessitates considering the buffer capacity and tolerability. The stomach has a pH of around 1 to 2, while the duodenum ranges from pH 5 to 7.5 **[37]**. Therefore, oral administration can be influenced by the solubility of the drug as it passes through the intestines. Ionizable compounds that remain stable and soluble after pH adjustment are well-suited for this method, including acids, bases, or zwitterionic compounds **[38]**. Combining pH adjustment with co-solvents is a common practice to further enhance the solubility of poorly soluble drugs. In cases where precipitation upon dilution results in fine or amorphous particles, bioavailability can be increased due to an elevated concentration gradient and enhanced surface area for dissolution **[39]**. However, in situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, the increase in bioavailability may not be sufficient **[40]**. While pH adjustment is frequently employed in pre-clinical studies to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity, caution is needed as uncontrollable precipitation after contact with a less soluble pH may lead to misleading interpretations of results **[41, 42]**.

IV]. POLYMERIC ALTERATION

Polymorphs denote different crystalline

forms of a drug, each possessing distinct physicochemical attributes such as stability, melting point, vapor pressure, solubility, dissolution rate, morphology, density, and biological activities, including bioavailability **[43]**. Among these forms—stable, unstable, and metastable—metastable polymorphs are characterized by higher energy levels and increased surface area, consequently leading to enhanced solubility, bioavailability, and efficacy. In terms of bioavailability optimization, transitioning a drug from crystalline to metastable or amorphous forms is preferred **[44]**. However, it's crucial to acknowledge the potential risk of conversion from high-energy amorphous or metastable polymorphs to low-energy crystal forms with reduced solubility during manufacturing and storage. To ensure consistent bioavailability throughout the product's shelf-life under various real-world storage conditions, prioritizing the development of the most thermodynamically stable polymorph is advisable **[45]**.

V]. LIQUISOLID TECHNIQUE

The liquisolid technique represents an innovative approach in which a liquid is converted into a flowable, easily compressible, and seemingly dry powder through simple physical blending with carefully chosen carrier and coating materials. This method involves incorporating the liquid component, which could be a liquid drug, drug suspension, or drug solution in suitable non-volatile liquid carriers, into a porous carrier material. Upon saturation of the carrier with liquid, a liquid layer forms on the surface of the particles, promptly absorbed by the fine coating particles. As a result, a powder that appears dry, flows freely, and is compressible is produced **[46]**.

CONCLUSION

This article underscores the pivotal role of drug solubility in governing both drug formulation and therapeutic efficacy. It emerges as the most crucial factor in the entire formulation development process. The dissolution of a drug stands out as the rate-determining step for the oral absorption of poorly water-soluble drugs. Moreover, solubility serves as the fundamental prerequisite for the formulation and development of diverse dosage forms for various drugs. The techniques outlined earlier, either independently or in combination, offer viable approaches to enhance drug solubility. Numerous techniques exist to augment solubility, resulting in a significant increase in solubility levels. The solubility challenges encountered by many drugs directly impact their bioavailability, thereby necessitating interventions for solubility enhancement. Fortunately, advancements in various techniques, as discussed above, now make it

feasible to enhance the solubility of poorly soluble drugs.

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