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Improving Bioavailability and Solubility of Poorly Soluble Drugs- A systematic review

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ABSTRACT

Poor solubility is one of the primary reasons for the failure of new drug formulations to reach the market. In fact, a large proportion of new chemical entities (NCEs) exhibit poor water solubility, which limits their absorption and bioavailability. Bioavailability is the fraction of the administered dose of a drug that reaches the systemic circulation and is available at its site of action. Poor bioavailability can result from a variety of factors, including poor solubility, extensive first-pass metabolism, instability of the molecule in circulation and the properties of the drug molecule itself. Enhancing the solubility of poorly soluble drugs is, therefore, a major focus of pharmaceutical research, as it directly impacts their bioavailability and therapeutic efficacy. In this review we summarize the strategies and techniques used to improve the bioavailability and solubility of poorly soluble drug molecules and formulations. These include both physical and chemical modifications to drug formulations, as well as new technologies such as nanotechnology. By improving solubility, it is possible to enhance the drug's absorption, thereby increasing bioavailability. Various methods such as salt formation, the use of surfactants, lipid-based drug delivery systems, solid dispersion techniques, and nanocrystal formulations are discussed. Finally, the challenges associated with each strategy, as well as future directions in this field, are considered.

1. INTRODUCTION

Drug bioavailability and solubility are critical factors influencing the therapeutic effectiveness of pharmaceuticals. A significant number of drugs face challenges in solubility, and this is particularly true for many newly developed drugs. More than 40% of new chemical entities (NCEs) in the pharmaceutical industry exhibit poor solubility, leading to issues with bioavailability (Savjani KT et al., 2012). Poorly soluble drugs often show low and variable absorption when administered orally, which can affect their clinical effectiveness. Therefore, increasing the solubility of these compounds is a major challenge in drug development.

Bioavailability is defined as the rate and extent to which the active pharmaceutical ingredient (API) or drug reaches the systemic circulation and its target site (Chow SC et al.2014). Solubility, on the other hand, refers to the ability of a drug to dissolve in a given solvent. For most orally administered drugs, solubility is the rate-limiting step for absorption. Thus, methods to improve solubility directly influence the bioavailability of the drug. When two formulations of the same drug or two drug products are claimed bioequivalent, it is assumed that they will provide the same therapeutic effect or that they are therapeutically equivalent. Although, most people interpret that they can be used interchangeably but the challenge remains in their dosage or pharmaceutical alternatives (i.e., different dosage forms) and if their rates and extents of absorption do not show a significant difference. Hence absoption also plays critical role in determining Bioequivalence

The aim of this review is to summarize different strategies that have been developed to improve the solubility and bioavailability of poorly soluble drugs. These strategies include changes in the chemical structure of the drug molecule, use of excipients, and the application of novel technologies. The review also discusses the future challenges and necessary improvement in technologies and processes for Drug Bioavailability and solubility.

2. FACTORS AFFECTING SOLUBILITY AND BIOAVAILABILITY

Several factors can affect the solubility and bioavailability of drugs:

1.1. Physicochemical Properties of the Drug:

The intrinsic solubility of a drug is governed by its chemical structure, which affects its ability to dissolve in a solvent. Factors such as molecular weight, crystal form, and polarity influence solubility (Shahrin N, 2013). Solutes (and solvents) can be broadly classified as polar (hydrophilic) and non-polar (lipophilic). The polarity can be represented through the dielectric constant or the dipole moment of a molecule. A dipole moment can be defined as a nonuniform distribution of negative and positive charges amongst the various atoms of the molecule, which by virtue of its nonuniform distribution can present an overall charge surplus to the moiety. Molecules with a permanent dipole moment are said to be polar. The polarity of a molecule is thus related to its atomic composition, its geometry, and its size. Generally polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in nonpolar solvents. Dipole-dipole interactions (e.g. hydrogen bonding as water is the encountered solvent *in vivo*) are responsible for the dissolution of many pharmaceutical drugs; the solubility of the low molecular weight organic acids, alcohols, amides, amines, esters, ketones and sugars in polar solvents is a result of dipole-dipole interactions. Although, it has to be noted that strong inter and/or intramolecular bonds may possibly be a cause of poor water solubility (Delaney, J.S. et al., 2005). Lipophilic drugs tend to have low solubility in water, which can limit their absorption in the gastrointestinal tract (GIT).

1.2. Gastrointestinal Tract (GIT) Environment:

The solubility of a drug in the gastrointestinal environment can be affected by factors such as pH, the presence of food, and gastrointestinal motility. These factors can impact the rate at which a drug dissolves and is absorbed. *in vivo* GIT pH profile is of high relevance when considering weak acids and weak bases as their solubility and thus their dissolution will be either greater in the intestinal fluids than in the stomach or greater in the stomach than in intestinal fluids, respectively. The fasted and fed state conditions also need to be taken into account as they are both characterized by different stomachal pH, implying a resulting different behavior of these kind of compounds. Furthermore, for poorly water-soluble weak bases, if rapid and complete dissolution occurs in the stomach, the possibility of reprecipitation following stomach exiting shall be considered (Hecq, J. et al. 2006).

1.3. Particle Size:

The size of the drug particles significantly affects the dissolution rate. Smaller particles have a larger surface area, which increases their solubility and absorption rate. Concerning molecular size, generally, the larger the molecule (i.e. the higher its molecular weight) the less soluble the substance will be. For example, within alkanes, molecular size is the primary determinant of their solubility in water, and increasing molecular size results in a decrease in water solubility mainly due to the increased free energy penalty for cavity formation in water. The increase in the saturation solubility with respect to diminution of particle size is explained by the Ostwald-Freundlich equation:

$$C_s = C_\infty \, e^{\frac{2\gamma M}{RT\phi r}}$$

Cs: Solubility (mg/ml)
C∞: Solubility of infinite radius particles
γ: Interfacial tension between drug particles and the solubilizing fluids
M: Molecular weight
R: Ideal gas constant
T: Absolute temperature
□: Density of the solid

r: Radius of the particles

The Ostwald-Freundlich equation is the equation used to explain crystal growth in a dispersed system. Any particle system dispersed in a medium and having a certain degree of solubility in it is thermodynamically unstable due to its large interface area. One way of decreasing the high interfacial energy associated with this large interfacial area is through particle growth, and the mechanism most likely to achieve this reduction is called the Ostwald ripening (Leite ER. et al. 2003). This Ostwald ripening is due to the solubility difference between smaller and larger particles, i.e. enhanced solubility for smaller particles.

First-Pass Metabolism:

Some drugs undergo significant metabolism in the liver before reaching systemic circulation, reducing their bioavailability. This is often a major issue for drugs that are poorly absorbed in the GIT. The transfer of orally administered, highly lipid-soluble drugs to the lymphatic system is mediated by their association with chylomicrons, large intestinal lipoproteins that are assembled in the enterocytes in the presence of long-chain triglycerides or long-chain fatty acids (*Franco V et al. 2020*). UDP-glucuronosyltransferases (UGTs) is a significant metabolic pathway that facilitates efficient elimination of numerous endobiotics and xenobiotics, including phenolics. Moreover, extensive glucuronidation can be a barrier to oral bioavailability as the first-pass glucuronidation (or premature clearance by UGTs) of orally administered agents usually results in the poor oral bioavailability and lack of efficacy (Wu B et al. 2011). Holistically, the phenomenon of First pass metabolism critically effect the bioavailability and absorption of any molecule and their presence in circulation

Strategies for Improving Solubility and Bioavailability

Several strategies have been developed to improve the solubility and bioavailability of poorly soluble drugs. These methods can be classified into two broad categories: physical approaches and chemical approaches.

3.1. Physical Approaches

3.1.1 Particle Size Reduction (Micronization and Nanosizing)

Particle size reduction is one of the most common approaches to improving the solubility of poorly soluble drugs. Reducing the particle size increases the surface area, thereby enhancing the dissolution rate of the drug. Micronization (reducing the particle size to the micrometer range) and nanosizing (reducing the particle size to the nanometer range) are both effective strategies.**Micronization**: By reducing particle size to the micron range, the surface area of the drug is increased, which promotes faster dissolution. Micronized drugs dissolve more readily in aqueous environments, which can increase their bioavailability. The common technique for the preparation of micron-size drugs is the mechanical comminution (e.g., by crushing, grinding, and milling) of previously formed larger particles. In spite of the widespread use of this technique, the milling process does not represent the ideal way for the production of small particles because drug substance properties and surface properties are altered in a mainly uncontrolled manner (Rasenack N &Muller BW, 2004) **Nanocrystals**: Nanocrystals are even smaller than micronized particles and have enhanced solubility due to their extremely high surface area to volume ratio. The nanocrystals are typically stabilized with surfactants to prevent aggregation. This technology has shown promise in improving the bioavailability of poorly soluble drugs such as indomethacin and cyclosporine. There are various approaches for nanosizing drugs and these are classified as top-down, bottom-up and combination approaches. Top-down techniques involve particle size reduction using high energy approaches such as media milling and high pressure homogenization. Currently, there are six FDA approved nanocrystal drugs in the market which have been prepared by top-down techniques (Al Kassas R et al. 2017). All these processes are conducted in a liquid medium and thus they form nanosuspensions which are later processed into capsules or tablets or marketed as suspensions (Kesisoglou F et al. 2007).Nanosuspensions refer to colloidal dispersions of sub-micron drug particles which are stabilized by addition of a suitable polymer or surfactant, and are of a particle size below 1000 nm (Loh ZH et al. 2015). The dispersion medium can be aqueous e.g. water, or non-aqueous e.g. liquid polyethylene glycol and oils. Bottom-up techniques are essentially a precipitation technique as the nanosized drug particles are obtained after precipitation from a supersaturated drug solution (Butler JM & Dressman JB, 2010). Bottom-up techniques offer many advantages such as being low energy processes and less expensive in comparison with other nanosizing methods, and produce particles with narrow size distribution. However, very few products prepared by bottom-up techniques have made it to market . Bottom-up techniques have recently been used in combination with top-down techniques to obtain even smaller particles. Although these techniques have been in use for at least a decade, very few nanocrystals with a particle size of 100 nm have been obtained. Various attempts have been made to develop particles of < 100 nm as it has been reported that drug nanocrystals of < 100 nm have novel physical properties and show improvement in permeation through various biological barriers (Butler JM & Dressman JB, 2010). Drug nanocrystals have improved the bioavailability of poorly-soluble drugs that are administered through a variety of routes including oral, dermal, ocular, buccal and pulmonary.

3.1.2 Solid Dispersions

Solid dispersion involves the dispersion of the drug in an inert carrier matrix, usually in the form of an amorphous solid. The

amorphous form of the drug has higher solubility than the crystalline form, making solid dispersions effective in enhancing solubility. The drug is either dispersed in a polymer matrix or in a mixture of a carrier substance. Common carriers include polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and sorbitol.

There are various method of preparation of solid dispersion systems available and their utilization is based on the drug type and properties (Argade PS et al. 2013). These methods are:

A) Melting Method: The melting or fusion method is the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

B) Solvent Method: In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. 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.

C) Melting solvent method (melt evaporation): It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol.

D) Melt Extrusion Method: The drug/carrier mix is typically processed with a twin screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermos labile to be processed.

E) Lyophilization: Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

F) Melt Agglomeration Process: This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, solid dispersion 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. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates.

Apart from the above-mentioned processes, modern methods e.g. Electro Spinning, Super Critical Fluid Technology or High-Pressure Homogenization are used for the same purposes.

3.1.3 Lipid-Based Formulations

Lipid-based formulations utilize the properties of lipids to improve the solubility of poorly water-soluble drugs. Lipids, such as oils, phospholipids, and surfactants, can solubilize drugs and enhance absorption through the lymphatic system, bypassing first-pass metabolism in the liver.

Self-Emulsifying Drug Delivery Systems (SEDDS): SEDDS are formulations that consist of a mixture of oils, surfactants, and co-surfactants. Upon contact with water, they form microemulsions or nanoemulsions, which enhance drug solubility and absorption. SEDDS and isotropic mixtures, are composed of oils, surfactants, and occasionally cosolvents. The ability of these formulations and methods to produce microemulsions or fine oil-in-water (o/w) emulsions after moderate stirring and dilution by water phase along the GI tract might be a promising technique for lipophilic agents with dissolution rate-limited absorption (Salawi A, 2022). By integrating suitable polymer into the formulation, SEDDS may be studied for the creation of a formulation with sustained drug release. This technology's improvement might lead to a new application in the field of medicine delivery.

Phospholipid Complexes: Complexation of poorly soluble drugs with phospholipids can enhance solubility. Phospholipids can form micelles or liposomes that encapsulate the drug, allowing it to be more readily absorbed in the gastrointestinal tract. phospholipids possess a very low toxicity profile and can be used for any route of administration. They can be technologically used as an emulsifier, wetting agent, solubilizer, and agent in the formation of liposomes and mixed micelles, to name a few

(Drescher S & van Hoogevest PV, 2020).

From a pharmaceutical perspective, they are used as key excipients for parenteral administration for solubilizing formulations such as liposomes, mixed micelles, and oil-in-water (o/w) emulsions; in liposomes for drug targeting and slow release; and for topical administration to the lung and the skin for slow release and enhanced skin interaction, respectively. After oral administration, phospholipids are used to suppress gastrointestinal (GI) side effects of, for example, non-steroidal anti-inflammatory drugs (NSAIDs) and explored as solubilizers to enhance the oral absorption of poorly water-soluble compounds. Nevertheless, phospholipids are still not widely applied as excipients for the development and manufacture of pharmaceuticals, although they represent, as natural compounds, for instance, very effective alternatives to synthetic (non-natural) emulsifiers such as polysorbates, polyoxyethylene castor oil derivatives, and sucrose esters

3.2. Chemical Approaches

3.2.1 Salt Formation

One of the most widely used methods for improving the solubility of drugs is salt formation. A salt is formed by reacting the drug with a counter-ion, which can modify the solubility characteristics of the compound. Salt forms of drugs are often more soluble in water than their neutral forms. Salts are formed when a compound is ionized in solution and forms a strong ionic interaction with an oppositely charged counterion, leading to crystallization of the salt form. In the aqueous or organic phase, the drug and counterion are ionized according to the dielectric constant of the liquid medium. The charged groups in the drug's structure and the counterion are attracted by an intermolecular coulombic force. During favorable conditions, this force crystallizes the salt form. All acidic and basic compounds can participate in salt formation (Bhattacharya SN et al. 2006). However, the success and stability of salt formation depends upon the relative strength of the acid or base or the acidity or basicity constants of the species involved (Bighley LD et al. 1996).

The salt form is separated into individual entities (ionized and counter ion) in dissolution medium, and its solubility depends upon the solvation energy in the solvent. The solvent must overcome the crystal lattice energy of the solid salt and create space for the solute. Thus, the solubility of a salt depends on its polarity, lipophilicity, ionization potential, and size. A salt's solubility also depends on the properties of solvent and solid such as the crystal packing and presence of solvates(Florence AT and Attwood D 1996).

Basic Drugs: For basic drugs, salts can be formed with acids such as hydrochloric acid, sulfuric acid, or citric acid.

Acidic Drugs: For acidic drugs, salts can be formed with basic counter-ions like sodium, potassium, or calcium.

3.2.2 Co-Crystals

Co-crystals are another strategy to improve solubility. A co-crystal consists of a drug and a co-former (usually another molecule) that is capable of forming a stable solid phase. Unlike salts, co-crystals do not involve proton transfer, but rather, they rely on non-covalent interactions such as hydrogen bonding. Co-crystals can improve the solubility of a drug while maintaining its chemical integrity. A few cocrystals are now on the market or in clinical trial phases, e.g., sacubitril-disodium valsartan-water (Entresto™), escitalopram oxalate-oxalic acid (Lexapro®), ertuglifozin-L-pyroglutamic acid and tramadol-celecoxib. The FDA defines pharmaceutical cocrystals as “crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and cocrystal formers (‘coformers’), in the same crystal lattice” (FDA Regulation 2018). Co crystallisation is an attractive strategy to modify and improve the physicochemical properties of an API without making covalent changes to the drug molecule itself. Very often cocrystals are designed to tackle the poor dissolution behavior and low bioavailability of Biopharmaceutics Classification System (BCS) class II and IV drugs that make up 70% of the drug candidates in the development pipeline (Williams HD et al. 2013). However, chemical stability, hygroscopicity, mechanical, and flow properties have also been improved through cocrystal formation (Erxlaben A, 2020). Furthermore, co crystallisation can be used as a purification and enantiomeric separation method.

3.2.3 Complexation with Cyclodextrins

Cyclodextrins are cyclic oligosaccharides that can form inclusion complexes with poorly soluble drugs. These complexes help to increase the solubility of drugs by encapsulating them within the hydrophobic cavity of the cyclodextrin. This approach is particularly effective for lipophilic drugs and has been used for a variety of drug molecules such as itraconazole and dexamethasone.

Conclusions and Future Directions

While there are a variety of approaches to improve drug solubility and bioavailability, each comes with its challenges. For example, particle size reduction and solid dispersions can lead to formulation instability, while lipid-based systems may have issues with drug content uniformity. Moreover, scaling up these techniques from the laboratory to commercial production can be difficult and costly. The future directions in improving the bioavailability and solubility of drugs focus on several cutting-edge strategies that are poised to address the limitations of current drug formulations and delivery systems. These strategies are designed to overcome issues such as poor water solubility, low bioavailability, and the inability of certain drugs

to reach therapeutic levels in the body.

The bioavailability of drugs can vary depending on different factors, such as the timing of intake, food consumption, and the duration of drug use. Keeping these factors under control can be difficult, as they can impact the results of bioavailability studies and their interpretation. Advancements in bioavailability research have led to the development of new trends and technologies that seek to enhance the effectiveness and safety of drug therapy. These innovations aim to better understand bioavailability and improve its control. Thanks to modern technologies, it is possible to move toward personalized therapy, which targets specific patients and considers individual factors affecting drug bioavailability. Recent advances in nanotechnology and drug delivery technologies are revolutionizing the field of medicine by improving the bioavailability of drugs. By delivering drugs directly to the targeted tissues, drug nanoparticles can easily cross biological barriers and reach the appropriate site in the body.

Various ligands, antibodies, aptamers, peptides, or proteins can be used to achieve targeted actions to alter the surface of nanoparticles. Examples of ligands include adenosine, folic acid, and glucose. Adenosine targets nanoparticles to tumor co-cells via the A1 receptor. Folate receptors, overexpressed in some cancers, allow for the selective uptake of nanoparticles. Biofilms and mucus layers can affect the degradation of nanoparticles by trapping them in different pore sizes or through non-specific interactions, which can lead to their removal from the epithelial surface. Given the vital role of the microenvironment for nanoparticles, there is a need to design new types of nanoparticles or to modify them to take advantage of this variability. Exogenous triggers, such as near-infrared light, radio waves, or magnetic fields, allow for the controlled delivery of nanoparticles from the outside. Even surrounding nanoparticles with the membranes of immune cells, such as macrophages or leukocytes, improves their effectiveness in targeted cancer cells. Nanoparticles surrounded by cell membranes show significantly enhanced drug activity compared to free drugs.

Studying drug bioavailability enables the personalization of therapy, considering individual factors affecting bioavailability. Drug doses and dosing regimens can be tailored to individual patients by identifying genetic variants, drug interactions, and other factors. Bioavailability is essential in the development of new drugs and formulations. More effective and efficient active ingredients can be designed by understanding the factors that affect bioavailability, such as solubility, chemical stability, and pharmaceutical forms. This leads to innovative drugs with higher bioavailability and a better therapeutic profile. For rare and hard-to-treat conditions, the availability of effective drugs may be limited. Consequently, bioavailability research allows for the identification of new drug delivery approaches, such as nanotechnology or genetically targeted therapies. This opens up new therapeutic perspectives for patients with rare diseases. By fine-tuning doses and the frequency of administration, over-medication or toxic effects can be avoided, thereby minimizing the risk of adverse effects. Understanding bioavailability improves drug use and health care by optimizing prescription design, treating rare disorders, and discovering new formulations

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