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A REVIEW ON NOVEL TECHNIQUES TO ENHANCE SOLUBILITY OF POORLY AQUEOUS SOLUBLE DRUGS

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ABSTRACT

Solubility, the phenomenon of dissolution of solute in a solvent in a specified condition to give a homogenous system, is the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Due to their low solubility and dissolution rate, the main goal of this review was to increase the solubility of BCS Class II medicines. Thus, the hardest part of developing new drugs was making essentially insoluble drugs more soluble. Low solubility pharmaceutically active compounds indicate a higher chance of medication development and innovation failure. Their solubility has a huge impact on pharmacokinetics, pharmacodynamics, and a few other characteristics like drug absorption, drug distribution, protein binding, etc. Oral dosage forms account for over half of all pharmaceutical dosage forms, and the drug molecule needs to be soluble in water. Solubility and bioavailability are key components in ensuring the drug molecule has good therapeutic action at the target site. Therefore, as chemical science advances, pharmaceutical technologies must be developed to increase patient adherence to medicine. In order to obtain effective absorption and improved bioavailability, this article aims to describe various solubility enhancement techniques. These techniques include both traditional and novel approaches, such as pH adjustment, micronization, homogenization, salt formation, lyophilization, hot melt extrusion, solvent evaporation, sonocrystallization, prodrug approach, co-solvent approach, spherical agglomeration, combination with other drugs, dissolution testing, etc. The objective of this paper is to provide an overview of solubilization strategies that can be used to increase bioavailability and achieve efficient absorption.

KEYWORDS: Bioavailability, Solubility, BCS classification, lyophilisation and sonocrystallization.

INTRODUCTION

Solubility is the phenomenon of dissolving a solute in a solvent, which is essential to produce a homogenous system. In quantitative terms, solubility may be defined as the required strength of the solute dissolved in a solution at a given pH, temperature, and pressure. Solubility is standardly determined using two approaches: thermodynamic solubility and kinetic solubility. In contrast, the term "solubility" refers to the highest concentration of a solute that may dissolve in a solvent at a specific temperature drugs administered via the oral route in a solid dosage form are first disintegrated into smaller parts or even primary particles, from which the drug molecules are freer to dissolve in the gastrointestinal tract (GIT) fluids than from an intact tablet; the molecular dissolution of the drug is then followed by its penetration through the intestinal barrier. Given that all bodily fluids are water-based solutions, aqueous solubility is an essential criterion to achieve the appropriate concentrations of the drug molecules in the systemic circulation to elicit the required therapeutic efficacy.[1] If a drug molecule has very low solubility, it cannot be dissolved in the GIT fluids, which hinders its permeability and, thus, bioavailability because it is directly related to the drug solubility. Low bioavailability observed with poorly soluble drugs make the final formulation expensive because high doses are needed to obtain therapeutic benefits and, sometimes, they might cause toxicity.[2]

Depending on the solubility and permeability in the GIT, drug substances are categorized in four BCS classes.

Because of low solubility, despite high permeability, BCS class II drugs are associated with a slower dissolution rate in the GI tract, leading to low bioavailability. Owing to low aqueous solubility, a small concentration gradient between the intestine and the bloodstream results in restricted transport across biological membranes and, consequently, poor absorption is often reported. In contrast, in addition to low aqueous solubility, BCS-class IV drugs also have low permeability, which reduces their ability to be absorbed. However, BCS class IV drugs sometimes make poor drug development candidates due to limited membrane permeability since solubility and dissolution augmentation may not be sufficient to increase their bioavailability. It has been reported that only eight percent of novel drug candidates currently exhibit excellent permeability and solubility. Water- insoluble or poorly water-soluble medications account for more than 1/3 of the pharmaceuticals classified in the US Pharmacopeia Recently, it was claimed that around half of all drug molecules failed during the development stage due to poor aqueous solubility. Lead compounds with poor solubility characteristics resulted in inefficient absorption from the administration site, resulting in a higher rate of therapeutic loss due to poor pharmacokinetics.[3]

Factors Affecting Solubility[4,5]

Particle size

Particle size affects solubility. As particle size decreases, the surface area to volume ratio increases. As the surface area of the particle increases, it causes greater interaction with the solvent.

Temperature

Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature.

Molecular size

The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules to solvate the substance. Nature of solute and solvent: The nature of solute and solvent depends on the concentration of solute in a specific quantity of solvent at a specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved.

Pressure: For gaseous solutes, an increase in pressure increases solubility, and a decrease in a pressure decrease the solubility. For solids and liquid solutes, changes in pressure do not affect solubility.

Polarity: Polarity of both solute and solvent molecules affects the solubility. Generally, polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solvents.

Polymorphs: The ability of a substance to crystallize in more than one crystalline form is polymorphism. Polymorph is an agent having the ability to crystallize in more than one.

Traditional Techniques For Solubility Enhancement[6,7]

- Micro emulsion
- PH adjustment
- By using surfactants
- Co-solvent approach
- Complexation
- Solid dispersion
- Floating granules
- Micronisation
- Super disintegrants
- Salt formation

pH Adjustment

Poorly water-soluble drugs with parts of the molecule that can be base or acid may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration, the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach, the pH is around 1 to 2 and in the duodenum, the pH is between 5- 7.5, so upon oral administration, the degree of solubility is also likely to be influenced as the drug passes through the intestines.

Salt Formation

Acidic and basic drugs have low solubility in water as compared to their salts. For the development of parenteral administration, the most favored strategy is solubility enhancement by salt formation.

Solid dispersion

Certainly, solid dispersion stands among the most broadly applied strategies for solubility and dissolution rate enhancement of hydrophobic drugs (Mogal et al. 2012). Riegelman 1971). In line with the Noyes-Whitney equation, enhancement of dissolution rates can be expected in these systems since solid dispersion techniques improve drug dispersibility, thus increasing the surface area available for the drug to dissolve. Furthermore, this approach can result in a high-energy state of the drug that largely improves the drug dissolution, such as amorphous, colloidal crystal, or molecular states (Zhang et al. 2018).

Novel Methods for Solubility Enhancement

- Spherical agglomeration
- Sono crystallization

- By using prodrug
- Combination with other drugs
- Lipid-based formulations

Spherical Agglomeration[11]

It is a process in which combined unit process of crystallization, Agglomeration and Spheronization. The resultant crystals can be designated as spherical agglomerates. Due to the their spherical shape, the particle characterization properties such as flow ability as well as compressibility of the obtained crystals are more, which makes it more viable for direct tableting or coating without any further made by simply fusing with Gelucire 44/14 which showed a 3 hrs. Residence time with 100% drug release. Spherical agglomeration is a particle engineering technique used in pharmaceuticals and other industries to create spherical granules or pellets from fine powders. It involves the controlled aggregation of small particles into larger, more uniform spheres through the use of a binding liquid or a bridging liquid. The process typically consists of three main steps: nucleation, growth, and consolidation. In nucleation, the fine particles are suspended in a liquid medium and allowed to form small nuclei.

Sono Crystallization[12,13]

It is the process in which the application of ultrasound energy to modify the nucleation of crystallization. The energy of ultrasound leads to compression as well as expansion. After completion of some cycles it forms a bubbles and grows then it collapse. This collapse of formed bubbles gives the energy to enhance the nucleation process which leads to a highly repeatable as well as predictable crystallization process. Significance of applying Ultrasound to crystallization is as follows

- It narrows the metastable zone width
- Narrows the distribution of particle size
- Minimizes the level of cooling process for achieving the crystallization
- The process is highly repeatable as well as predictable.
- Controls the polymorphs.

Sono-crystallization, also known as ultrasound-assisted crystallization or sono crystallization, is a process that utilizes high-frequency ultrasound waves to promote and control the crystallization of materials from a solution or a melt. The application of ultrasound waves induces cavitation, which creates microscopic bubbles in the solution or melt. These bubbles collapse rapidly, generating localized high temperatures and pressures. In pharmaceuticals, it can be used to improve the purity, size distribution, and dissolution properties of drug crystals, which can lead to better drug formulations with improved bioavailability. Overall, sono-crystallization is a promising technique for controlling the crystallization process and obtaining desirable crystal properties for a wide range of applications.

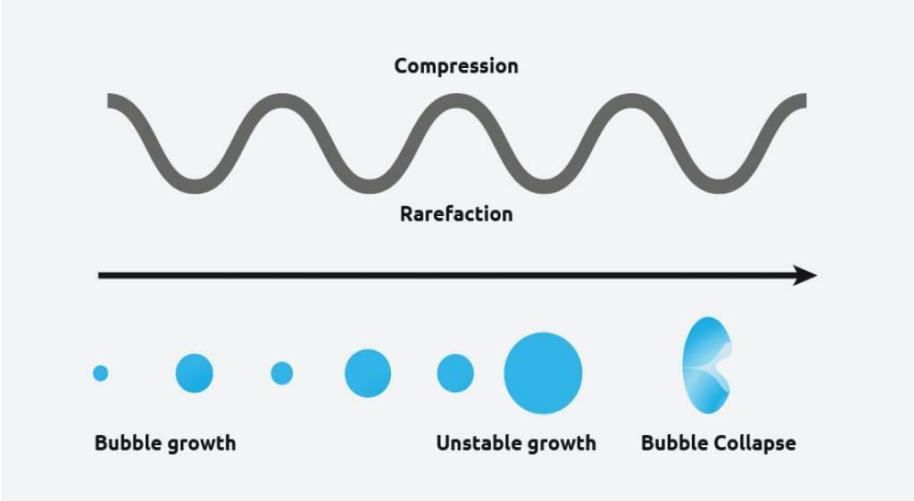

Fig. 1: Sono crystallization process.

By Using Prodrug[14,15]

A prodrug is a drug molecule which is a covalently bound to a pharmacologically inactive moiety also known as promoiety with the aim to overcome on the various physicochemical and biopharmaceutical limitations of the parent drug so because of that the therapeutic effect of the drug would be realized. For getting a accurate pharmacological result or effect a prodrug have must undergo a chemical or biochemical transformation to the parent drug within the body at a reasonable rate and extent. It is a key objective when applying into a class II or IV poorly soluble drug with respect to solubility enhancement. Prodrug is a biologically inactive compound that, when administered, undergoes a chemical transformation within the body to release the active drug. This approach is used to improve the absorption, distribution, metabolism, or elimination of a drug.

Using a prodrug can have several potential benefits
Improved Bioavailability

Some drugs may have low bioavailability, meaning they

are not effectively absorbed by the body. Converting them into a prodrug form can enhance their absorption.

Reduced Side Effects
Prodrugs can be designed to target specific tissues or cells, reducing the exposure of non-targeted tissues and potentially minimizing side effects.

Improved Stability
Some drugs are unstable or rapidly metabolized in the body. Converting them into a prodrug can increase their stability and extend their duration of action.

Controlled Release
Prodrugs can be designed to release the active drug over a longer period, leading to a sustained therapeutic effect.

Masking Bitter Taste or Odour
Prodrugs can be used to mask the unpleasant taste or odor of a drug, improving patient compliance, especially for pediatric or geriatric patients.

Avoidance of First-Pass Metabolism
Prodrugs can bypass first-pass metabolism in the liver, which can be significant for drugs that are extensively metabolized before reaching systemic circulation.

Lipid-Based Formulations
The formulation of drugs in a lipid carrier system composed glycerides, surfactants and co-solvents has attracted significant attention due to the markedly increased drug oral bioavailability (Porter et al., 2007). Apart from the solubility enhancement effect, the mechanism of improved bioavailability of lipid-based formulations (LBF) is attributed also to increased intestinal absorption via supersaturation (Gao and Morozowich, 2006) and reduced first pass effect via lymphatic transport (Trevaskis et al., 2008). LBF are primarily applied for BCS Class II and Class IV drugsubstances, which are characterized by solubility-limited absorption. The lipid formulation classification system (LFCS) separates LBF in 4 main types, depending on LBF composition, see Table 1 (Pouton, 2006). Each type is characterized by a set of advantages and drawbacks. For example, the glyceride-rich types 1 and 2 usually have poor drug solvent capacity but are unlikely to lose that solvency upon dispersion in the intestinal fluids, whereas the solvent- and surfactant-rich LBF types III and IV can dissolve higher drug concentrations but suffer from significant phase changes and potential drug precipitation upon dispersion. One aspect of LBF is that a significant fraction of the surfactants used may be digestible, which should be considered during formulation development (Vithani et al., 2017). The different formulation strategies and the materials used are described in detail in several dedicated reviews (Hauss, 2007; Pouton and Porter, 2008). However, as the oral absorption depends on the intestinal concentration of dissolved drug, another LBF classification related to formulation performance has been proposed (Williams et al., 2014b). The latter groups LBF into four grades (A, B, C and D) where grade A provides the most robust solubility enhancement after dispersion and digestion, whereas drug precipitation is expected with increasing.

CONCLUSION

The study suggests that innovative methods for improving the solubility of medications that are poorly soluble in water present interesting directions for future developments in medicine. By using strategies including prod rug design, lipid-based formulations, Sono-crystallization, and spherical agglomeration, researchers have made great strides towards resolving solubility issues. These methods not only increase the bioavailability and absorption of drugs, but they also pave the way for more successful therapeutic treatments.

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