



## A REVIEW ON VARIOUS METHODS TO ENHANCE THE SOLUBILITY AND BIOAVAILABILITY OF DRUGS

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### ABSTRACT

Solubility is one of the important parameters to achieve the required concentration of drug in systemic circulation for getting the pharmacological actions. The poor solubility and low dissolution rate of poorly soluble drugs causes insufficient bioavailability in gastrointestinal fluids. Many pharmaceutical techniques have been developed to increase the solubility of drugs thereby enhancing their bioavailability. Each technique has own advantages and disadvantages. Knowledge of factors influencing solubility and dissolution of drugs helps in developing new methods to enhance bioavailability of drugs.

**KEYWORDS:** solubility, dissolution, bioavailability, factors, techniques.

### INTRODUCTION

Solubility is defined as the amount of solute that dissolves in a solvent at certain temperature. Solubility is one of the important parameters to achieve the required concentration of drug in systemic circulation for getting the pharmacological actions.<sup>[1]</sup> Non polar drugs are not soluble in water and thus they are not absorbed by tissues. Low solubility drugs are used to make drug caps. For example, some vitamins are not very soluble, if you consume a large quantity. Because of their low solubility, they may stay inside your body for long time, and may cause negative effects. Due to their low solubility they are used to make drug caps in which the drug can be placed.

More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are not soluble in water. These poorly water soluble drugs having slow drug absorption leads to low bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important parameter to achieve their bioavailability and to get required pharmacological response.<sup>[2]</sup>

The poor solubility and low dissolution rate of poorly soluble drugs causes insufficient bioavailability in gastrointestinal fluids. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be improved by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.

For BCS class II drugs, the rate limiting step is not the absorption but the drug release from the dosage form and solubility in the gastric fluid. So by increasing the solubility we can increase the bioavailability for BCS class II drugs.<sup>[3]</sup>

### Factors Influencing Solubility Of Drugs

The factors that influence the solubility of drugs are listed as internal and external factors.

#### A. Internal factors

Internal factors are governed by the molecular structure. If the drug molecule has more intermolecular interactions with the solvent, then it increases the solubility. For example, if an organic drug molecule has more hydrogen bond donating/ accepting groups like -OH, -NH<sub>2</sub>, -COO- and so on, then it can form more hydrogen bonds with solvent (water). Hence it is more soluble in water.

#### B. External Factors

External factors includes the following

- 1. Temperature** – drugs are generally more soluble at high temperatures.<sup>[4]</sup>
- 2. PH** - Acidic and basic drugs have equal solubility in water medium. For acid drugs, the equilibrium is  $HA(s) \rightleftharpoons H^+(aq) + A^-(aq)$ ; as pH decrease (more H<sup>+</sup>), the equilibrium shifts to left and drug is less soluble, and vice versa.

For base drugs, the equilibrium is  $BH^+(aq) \rightleftharpoons B(s) +$

H+(aq) ; as pH decrease (more H+), the equilibrium shifts to left and drug is more soluble, and vice versa.<sup>[5]</sup>

3. **Contact area with solvent** - Drug particles having greater contact surface area with solvent have higher solubility rate. For example, powdered drug is more soluble than the coarse drug because powdered drug particles have greater contact surface area with solvent molecules.
4. **Dosage form** - Gaseous drug is more soluble than liquid drug, whereas liquid drug is more soluble than solid one. Gas molecules can more readily disperse in solvent medium than liquid molecules, and liquid molecules disperse more readily than solid molecules.
5. **Polarity**- Polarity of the solvent, polarity of the solute also affects the solubility of the drug molecules.<sup>[6]</sup>
6. **Salvation**- salvation /hydration, hydrogen bond interactions between solvent and solute, bonding in the crystal and bonding to solvent molecules also affects the solubility. High melting point organic compounds are usually less soluble than low melting point compounds. Liquid - liquid solubility can be affected strongly by the ratio of the ingredients that are used.

#### Methods To Increase Solubility Of Drugs

The techniques that are used to improve the solubility can be categorized as follows: physical modification, chemical modifications of the drug substance, and other techniques.

##### A. Physical Modifications

These methods include Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and crystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

##### B. Chemical Modifications

These methods include Change of pH, use of buffer, complexation, and salt formation.

##### C. Miscellaneous Methods

Miscellaneous Methods include Supercritical fluid process; use of surfactants, solubilizers, cosolvency, hydrotrophy, and by using novel excipients.<sup>[7]</sup>

Let's see all these methods in detail.

#### Particle size reduction

Solubility of the drug depends mainly upon the particle size of the drug, as the particle size decreases the surface area of the powder particles increases thereby it increases the solubility of the drug and in turn it increases the absorption of the drug particles.<sup>[8]</sup> The size reduction methods help in increase of surface area of particles by decreasing the particle size, resulting in the increase in drug solubility. Size reduction involves well established milling procedures, which are typical part in formulation of drug and its preparation. It can be accomplished by micronization and nanosuspension methods.<sup>[9]</sup>

#### Micronisation

Micronization is the process of reducing the size of solid particles. Traditional techniques for micronization include mechanical methods such as milling and grinding. Modern techniques make use of the properties of supercritical fluids and manipulate the principles of solubility. Micronisation increases the solubility by decreasing the particle size of the drug. Decrease in the particle size of the drug increases the surface area and it will increase the dissolution rate of the drug. Micronization of drugs is done by milling techniques by using jet mill, rotor stator colloid mills and so on. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. This process is employed to the drugs like griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate. For each drug, micronization improves their digestive absorption, and consequently their bioavailability and clinical efficacy.

Example: Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes.<sup>[10]</sup>

Progesterone can be micronized by making very tiny crystals<sup>[11]</sup> micronized progesterone can be supplied as sublingual tablets, oil caps, or transdermal creams.<sup>[12]</sup> Creatine is the other drug that is micronized and used.<sup>[13]</sup>

#### Nano suspension

Nano suspensions are colloidal dispersed particles. These are solid-liquid systems having particle size less than one micrometer. Nano suspensions decrease the particle size thereby increasing solubility of the particles.

Nano suspensions are of great importance in case of substances that are sparingly soluble in water. Biopharmaceutical properties of drugs like absorption and bioavailability are enhanced by formulating them as nanosuspensions. Some marketed nanosuspensions are Rapamune (sirolimus) and Prograf (tacrolimus).<sup>[14]</sup> Nanosuspension can be achieved by precipitation. It is simple and economical method in which the drug substance is dissolved in a solvent and the resulting solution is then added to non-solvent for precipitating the crystals.<sup>[15]</sup> Ball milling or bead milling process can also be employed for producing nano particles. Use of piston-gap homogenizer is an improved technique in the production of nanoparticles. In this technique, the microfine suspension is forced through a gap (5-50  $\mu\text{m}$ ) under high pressure (1500-4000 bar) that results in the formation of desired size product.<sup>[16]</sup>

#### Micellar solubilisation

Micellar solubilization is very useful in improving the solubility of hydrophobic drugs in aqueous environment. Micellar solubilization is defined as "the process of incorporating the solubilize (the component that undergoes solubilization) into or onto the micelles". For solubilization to take place system should contain a solvent, an association colloid and at least one other

solubilize.<sup>[17]</sup>

The surfactants are used to improve the dissolution of poorly soluble drug products. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles and increases their solubility. This is known as micellization and generally improves the solubility of poorly soluble drugs.

Commonly used nonionic surfactants are polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroylmacroglycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions to dissolve the poorly soluble drugs.<sup>[18,19]</sup>

The poorly soluble compounds that use Micellar solubilization process are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone.<sup>[20]</sup>

#### **Hot-melt method [Fusion method]**

In this method the physical mixture of a drug and a water-soluble vehicle are heated directly until they melt. The melted mixture is then cooled and solidified rapidly in an ice bath with vigorous continuous stirring. The final solid mass is then crushed, pulverized, and sieved, and finally compressed into tablets with the help of tableting agent.

The melting point of a binary system is dependent upon its composition, that is, the selection of the carrier and the weight fraction of the drug in the system.<sup>[21]</sup>

An important necessity for the formation of solid dispersion by using hot-melt method is the miscibility of the drug and the carrier in the molten form. Another important requirement is the thermostability of both the drug and the carrier. The main advantages of this direct melting method is its simplicity and economy.

#### **Solvent evaporation method**

In the solvent evaporation method, the drug is dissolved, dispersed or emulsified into an organic polymer solution, which is then emulsified into an external aqueous or oil phase. The microspheres are formed after solvent diffusion/evaporation and polymer precipitation.

Solvent evaporation involves emulsification of polymer in aqueous phase and then dispersion in a volatile solvent like dichloromethane, chloroform, and ethyl acetate. Then the solvent is evaporated by using high temperature, vacuum, or by continuous stirring. Size of the particles can be controlled by adjusting parameters like evaporation, temperature, controlling the rate of

evaporation, and by manipulating stirring rate.

This method is being practiced for the development of nanoparticles which uses respective polymers such as PLA, PLGA, PCL, polyhydroxybutyrate, etc. loaded with various drugs like tetanus toxoid, testosterone, loperamide, cyclosporin A, and indomethacin. This method can also be used this to prepare PLGA nanoparticles for various drug loading. This method is used to develop PEG-coated, PEG-PLA copolymer nanospheres to load modelprotein, HAS.<sup>[22]</sup>

#### **Precipitation technique**

This is a process in which the condensation of a solid occurs from a solution during a chemical reaction. In this technique the drug is dissolved in a solvent, which is then added to anti solvent to precipitate the crystals.

The main advantage of this technique is simple and economical. The drawback of this technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with antisolvent. Precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media.<sup>[23]</sup> Nanosuspension of Danazol and Naproxen has been prepared by precipitation technique to improve their dissolution rate and oral bioavailability. The size reduction of naproxen was also associated with an apparent increase in the rate of absorption by approximately 4-fold.<sup>[24]</sup>

#### **Solid dispersion**

This method is very effective for increasing the dissolution rate of poorly soluble drugs, hence it improves their bioavailability. When solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting product with improved surface area produces higher dissolution rate and bioavailability in case of poor water soluble drugs. In addition, the solid dispersion of drug dissolves immediately to saturate the gastrointestinal fluids, and excess drug precipitates as fine colloidal particles or oily globules of submicron size.<sup>[25]</sup> The use of solid dispersions has been studied extensively. The commercial use of solid dispersions has been very limited, primarily due to the manufacturing difficulties and stability problems. A significant problem with the systems is the difficulties in the formulation development and subsequent scaling-up. Thermosensitive drugs and carriers may be destabilized during the melting or solvent-facilitated melting process since high melting temperatures are usually applied. The soft and tacky properties of solid dispersion powders result in poor flow ability, mixing property and compressibility, which may complicate the operations and render poor reproducibility of physicochemical properties of final products. However, problems associated with the miscibility and thermostability of molten drugs and carriers limit the application of this technique. Moisture & Temperature increases deteriorating effect on solid

Dispersion than physical mixtures.<sup>[26]</sup>

### Media milling

Milling involves the application of mechanical energy, the physical break down of coarse particles to finer ones. Fine drug particulates are especially desired in formulations that are designed for parenteral, respiratory and transdermal use. The mechanisms by which milling enhances drug dissolution and solubility include alterations in the size, specific surface area and shape of the drug particles as well as milling-induced amorphization and/or structural disordering of the drug crystal. Technology advancements in milling are the production of drug micro- and nano-particles on a commercial scale.<sup>[27]</sup>

The nanosuspensions are prepared by using high shear media mills. The milling chamber charged with milling media, water, drug, and the stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2 to 7 days). The milling medium is composed of glass, Zirconium oxide, or highly cross linked polystyrene resin. High energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particle.<sup>[28]</sup>

### Super critical fluid [SCF] process

A supercritical fluid (SCF) is a material that can be either liquid or gas, used in a state above the critical temperature and critical pressure where gases and liquids can co-exist. It can effuse through solids like a gas, and dissolve materials like a liquid.

The formation of small particles of a substance with a narrow size distribution is an important process in the pharmaceutical and other industries. Supercritical fluids can achieve this by rapidly exceeding the saturation point of a solute by dilution, depressurization or by both.

This process occurs faster in supercritical fluids than in liquids, promoting nucleation or spinodal decomposition over crystal growth and yielding very small and regularly sized particles. Recent supercritical fluids have shown the capability to reduce particles up to a range of 5-2000 nm.<sup>[29]</sup>

Pharmaceutical co-crystals are the novel crystalline forms of Active Pharmaceutical Ingredients which are formed by using Supercritical fluids. Supercritical fluid technology offers a new platform that allows a single-step generation of particles that are difficult or even impossible to obtain by traditional techniques. The generation of pure and dried new co-crystals (crystalline molecular complexes comprising the API and one or more conformers in the crystal lattice) can be achieved due to unique properties of SCFs by using different supercritical fluid properties.<sup>[30]</sup>

## CONCLUSION

For poor water soluble drugs, dissolution is the rate determining step for oral absorption.

Absorption of drugs is mainly dependent on solubility of drugs which is further influenced by drug dissolution. The methods described can be used alone or in combination to improve the solubility of drugs. A good formulation with good oral bioavailability can be achieved by proper selection of solubility enhancing method. The selected method should also be cost-effective.

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