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Review Article

## Particle Engineering Techniques: A Boon in Enhancing Dissolution Rate of Poorly Water Soluble Drugs

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### ABSTRACT

For any dosage forms enhancing dissolution is the first criteria i.e. it should give increased bioavailability in order to provide onset of action. In market many poorly soluble drugs are available which are having problem of low solubility. Low solubility of these poorly water soluble drugs are the main issue factor in preparing dosage forms of these drugs as with low solubility enhanced or effective dissolution to reach therapeutic effect is difficult. To overcome these problems there are main engineering techniques came in market which helps in enhancing the dissolution of these drugs. Some of the common use techniques are cryogenic, super critical fluid technology, evaporative precipitation into aqueous solution, nano- milling methods were developed based on the drug properties and required nanoparticles character. Making use of these techniques has increases the *in vitro* dissolution rates and *in vivo* bioavailability of many poorly water soluble drugs. This review highlights about the materialistic availability of particle engineering processes recently reported in the literature for enhancing the dissolution properties of poorly water soluble drugs.

**Keywords:** Solubility, Dissolution Rate, Poorly Soluble Drugs, Particle Engineering Techniques

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### Introduction:

Solubility is the quality of a solid, liquid, or gaseous chemical substance called solute to dissolve in a same substance of solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance basically depends on the solvent used at a particular temperature and pressure. The saturation concentration is measured as extent of solubility of a substance in a specific solvent where addition more solute will not increase its concentration in the solution. Solubility, permeability and dissolution are the three major factor that affects the bioavailability of drug<sup>1</sup>. Bioavailability of drug may be defined as the amount of drug that is absorbed from its site of administration and reaches in an unchanged form that is systemic circulation. These class II of drug which is poorly soluble drug majorly. BCS class of drug divided in to four categories-high solubility and high permeability, low solubility and high permeability, high solubility and low permeability, low solubility and low permeability. Increase in dissolution rate will increase the drug dissolution<sup>2</sup>. Increasing the surface area through particle size reduction of poorly soluble drugs results in poor bioavailability which Increases in dissolution rate. Poorly

soluble drug makes the problem in bioavailability, under this circumstances solid dispersion method is mostly used. Solid dispersion technique is outlined because the dispersion of 1 or a lot of active ingredient in associate degree inert carrier at solid state ready by melting, solvent, or melting solvent method. Solubility is the most important in pharmaceutical dosage form<sup>3</sup>.

Drug administered orally are more than 90% and having absorption, bioavailability and pharmacokinetic profile dependent on solubility parameter. Good dissolution and absorption indicates good solubility. Poorly soluble and dissolution are the main problems in pharmaceutical industry for designing a new dosage form. Many dissolution techniques are available for increasing solubility and permeability eg: coacervation, micronization, complexation solid dispersion and co-solvent<sup>4</sup>. Many manufacturing methods are available; fusion method, solvent evaporation method, hot melting extrusion, co-grinding method, supercritical method etc. The major problem for achieving good bioavailability is Aqueous solubility. To overcome this downside several ways has been investigate in drug development analysis<sup>5</sup>.

## Crystal Engineering

Crystal engineering is the exploitation of noncovalent interactions between molecular or ionic components for the rational design of solid-state structures that might show the interesting electrical, magnetic, and optical properties. It is also considered that it is becoming more evident that the directionality, specificity and predictability of intermolecular hydrogen bonds can be used in combining the supramolecular structures of few controlled dimensionality<sup>6</sup>. Crystal has numerous ways to increase dissolution through crystallization method by preparing co crystals, high energy amorphous forms, metastable polymorphs and ultrafine particle. The development of co crystals and molecular complexes are important subside for salt formation, unlike of neutral compound or those having weakly ionizable groups. The sequence of dissolution of different solid forms is stable polymorphism is less than metastable and meta stable is less than amorphous<sup>7</sup>.

### A. Supercritical Fluid Technology

#### 1. PGSS Process – Particles From Gas Saturated Solution:

SCF acts as a solute in the PGSS method. The SC-CO<sub>2</sub> is compressed and dissolved in a molten polymer after autoclave treatment, where the solution expands and becomes cooled by the Joule- Thomson effect microparticles are formed when operated at a relatively low pressure. This approach is advantageous over other SCF techniques since it uses low volumes of SCF. However, the application of this process is limited due to particle agglomeration and nozzle blockage<sup>8</sup>.

#### 2.RESS Process- Rapid Expansion of Supercritical Solution:

In a RESS process, SCF acts as a solute carrier, and this solution is expanded adiabatically leading to a quick drop in temperature and pressure and further generation of small-sized particles after spraying through a nozzle. In scheming this process, the solubility of the material plays a crucial role in particle formation and sort out since most of the pharmaceutical substances such as polymers, drugs, and high-molecular weight proteins are polar in nature<sup>9</sup>. In few instances, less amounts of organic solvents are added to improve the affinity of polar drug molecules. RESS is the simplest and an efficient method in the SCF technology, but it is limited in its application due its relatively high cost and poor solubility of polymers in non-polar SC-CO<sub>2</sub>. At industrial scales high amounts of SC-CO<sub>2</sub> are preferred to address this issue. To overcome certain limitations in further the evolution in the RESS process have been made. One of them is the RESS, method in an aqueous solution containing a surfactant or other reducing agents known as the rapid expansion of a supercritical solution into a liquid solvent (RESOLV) method, where the SCF is enlarge into a liquid medium<sup>10</sup>. This modified method stops the particle agglomeration in the expansion jet. The other modified methods in the rapid expansion of a supercritical solution with solid co-solvent (RESS-SC), which results in lesser-sized particles. During synthesis, the added co-solvent reinforce the solubility of the APIs to a greater extent by keeping away the superficial contact between particles, which increases the surface area of exposure to SCF and after some time, lyophilization can remove the co-solvent. Despite its evolution, RESS still has certain curb that are surpassed by the altered SCF behavior as anti-solvent in the reaction vessel<sup>11</sup>.

#### 3.SAS Process- Supercritical Anti-Solvent:

The supercritical anti-solvent process is proposed to process

the molecules with poor solubility in Supercritical fluid technology. This process predominantly utilizes an organic solvent such as acetone, dichloromethane, and dimethyl sulfoxide, to dissolve the materials, where Supercritical fluid technology behaves as a non-solvent to solute. During the process, the mixture expands to supersaturation and results in fast nucleation, demonstrating the high mass transfer ratio due to the low viscosity and high diffusivity of Supercritical fluid technology<sup>12</sup>. The outcome of this process utterly depends on the order of addition of solvent, Supercritical fluid technology, and other substrates. Additionally, factors such as temperature, pressure, chemical composition of solute i.e. drug, polymer, as well as organic solvent are required to be optimized. Supercritical anti solvent has gained better drug loading than the rapid expansion of supercritical solution process, enabling the formation of fine particles. Other Supercritical anti solvent processes comprise of GAS, which is based on the recrystallization of SCF insoluble solute and has a flexibility of choosing organic solvent to improve the solubility<sup>13</sup>. This process has less operational problems compared to the conventional Supercritical anti solvent method and is easy to scale-up in the manufacturing. Recent advancements in this method micronization techniques include, i.e., expanded liquid anti solvent and the supercritical-assisted injection in a liquid anti- solvent methods. however, deep analyses on these processes yet remain to be reported. Expanded liquid anti solvent is operated using SCF and an organic solvent at expanding liquidity conditions. The other modified SAS techniques include ASES, SCF-assisted extraction of emulsions (SFEE), SAS-EM, SEDS, and SpEDS<sup>14</sup>.

#### 4.SEDS Process- Solution Enhanced Dispersion By Supercritical Fluids:

SEDS is another important process of SAS technique operated at a lesser drying time and increased mass transfer rates, which decreases the ASES process curbs. In a distinctive SEDS process the scatter components are sprayed through a specially designed co-axial nozzle to control the particle morphology. Mass transfer of SCF into the sprayed droplet represents the particle formation by the rate of solvent transfer into SCF phase<sup>15</sup>. A high mass transfer allows an increased nucleation and results in smaller particle sizes with less agglomeration. In fact, the polymer processing using organic solvents is highly available with this process due to of its solubility problems. Moreover, the repeated SEDS operation has increases the period of time of chemical compound materials. Water-soluble compounds may be proscribed by mixing the organic solvent through a co-axial three-compartment nozzle<sup>16</sup>.

#### 5.Gas- Gas Antisolvent:

Intensive mixture of poorly water soluble medicine resolution and carbon dioxide gas in giant vessel causes speedy nucleation of drug to make micronized drug particles. A Cottrell precipitator is partly crammed with the drug resolution then gas is introduced at very cheap to attain a more robust mixture<sup>17</sup>. Drawback of this system is that particle size and size distribution square measure tough to regulate. In most cases, mother liquor cannot be completely removed and additional drying processes are required. In spite of these drawbacks, several drugs and explosives were successfully processed in this manner<sup>18</sup>.

### B. Cryogenic Techniques

Cryogenic techniques are developed to reinforce the dissolution rate of medication by making nanostructured amorphous drug particles with high degree of consistency at terribly low temperature conditions. Cryogenic inventions

were written by the kind of injection device capillary, rotary, pneumatic, and supersonic nozzle, location of nozzle (above or below the liquid level), and thus the composition of refrigerant liquid (hydrofluoroalkanes, N<sub>2</sub>, Ar, O<sub>2</sub>, and organic solvents). After refrigerant process, dry powder is obtained by varied drying processes like spray freeze drying, region freeze drying, vacuum freeze drying, and lyophilisation<sup>19</sup>.

### 1. Spray Freezing onto Cryogenic Fluids:

Briggs and Maxwell invented this method of spray freezing onto cryogenic fluids. In this method, the drug and therefore the carrier (maltose, inositol, lactose, mannitol or dextran) were dispersed in to water and pulverization top of the surface of a boiling ruffled halocarbon refrigerant. Sonication probe can be kept in the mixed refrigerant to reinforce the dispersion of the aqueous solution<sup>20</sup>.

### 2. Ultra-Rapid Freezing (URF):

Ultra-rapid phase transition could be a novel refrigerant technology that makes nanostructured drug particles with greatly increased expanse and desired surface morphology by victimization solid refrigerant substances. Application of medication resolution to the solid surface of refrigerant substrate results in instant phase transition and resulting drying up (for removal of solvent) forms micronized drug powder with improved solubility. Ultrafast phase transition hinders the section separation and therefore the crystallization of the pharmaceutical ingredients resulting in intimately mixed, amorphous drug-carrier solid dispersions, and solid solutions<sup>21</sup>.

### 3. Spray Freezing into Vapor over Liquid (SFV/L):

Freezing of drug solutions in refrigerant fluid vapours and resulting removal of frozen solvent produces fine drug particles with high wettability. During SFV/L the atomized droplets usually begin to freeze within the vapor section before they contact the refrigerant liquid. As the solvent freezes, the drug becomes concentrated within the liquescent regions of the atomized driblet, thus fine drug particles could nucleate and grow<sup>22</sup>.

### 4. Spray Freezing into Cryogenic Liquids (SFL):

The SFL particle engineering technology has been wont to turn out amorphous nanostructured aggregates of drug powder with high expanse and smart wettability. It incorporates direct liquid- liquid impingement between the automatized feed resolution and refrigerant liquid to produce intense atomization into microdroplets and consequently considerably quicker phase transition rates. The frozen particles square measure then preserved to get dry and free-flowing micronized powders<sup>23</sup>.

## C. Nanomilling

Nanomilling is a higher to lower level approach for converting large coarse particles into smaller, tiny particles. It is an inevitable in the application of mechanical energy to physically break down crystalline API structures. The main method used for nanomilling API is high energy media milling. This method is based on edge media—0.2-1 µm beads that are made from ceramics or highly cross linked polystyrene. The beads shear and collide with the API particles during the milling process, decreases their particle size<sup>24</sup>. During nanomilling, the API is suspended in an exceedingly resolution containing water and reduces the one of stabilizers to forestall reformation of particles over time. The nanomilling process provides an intermediate consisting of nanoparticles drap in to an aqueous vehicle. This is usually reflects as a nanoparticulate suspension. Nanosuspensions

are reproduced in to a good vary of dose forms, including oral liquids, capsules, tablets, films, injectables, aerosols, and more<sup>25</sup>.

## Conclusion

Dissolution of drug is that the rate determinative step for oral absorption of the poorly water soluble medicine and solubility is that the basic demand for the absorption of the drug from scum bag. The various techniques represented on top of alone or together is went to enhance the solubility of the medicine. Proper choice of solubility enhancing methodology is that the key to make sure the goals of a decent formulation like good oral bioavailability, reduce frequency of dosing and higher patient compliance combined with a coffee price of production. Selection of methodology for solubility enhancing depends upon drug characteristics like solubility, chemical nature, freezing point, absorption pathway, physical nature, pharmacokinetic behavior so forth.

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