

# Solubility Enhancement Techniques of Poorly Water Soluble Drug

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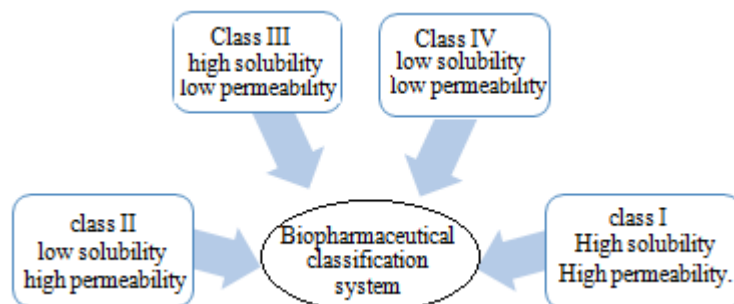
**Abstract:** *The poorly aqueous solubility of BCS class II drug represent a major challenge for oral dosage form development. Poorly aqueous solubility for new chemical entities present various challenges in development of effective drug delivery system for various delivery routes. Chemical Entities has dramatically increasing solubility and permeability. Solubilization technology having to increasing dissolution and dissolved drug in level on to achieve the extent or oral absorption. Term solid dispersion refer to group of solid product consisting least two different component generally hydrophilic drug and hydrophobic drug. Solid dispersion in water soluble carrier engrossed in the increase dissolution rate and bioavailability in hydrophobic drug. For enhancement of solubility dissolution rate poorly water soluble drug, according to (chiou and Rielman 1971) pharmaceutical solid dispersion is the dispersion of one or more active ingredient inert carrier matrix are solid state. Solubility behavior of drug remain one of the exigent aspect in formulation development. Solid dispersion as dosages form has been established superior option for the drug having poorly aqueous solubility. A solubility dispersion generally composed of two component the drug and polymer matrix. An numerous method are existing to prepare the solid dispersion or solubility such as melting method, solvent Evaporation method, fusion method, kneading method, spray drying, co-grinding method, lyophilization method, hot melt extrusion method, melt agglomeration method, supercritical fluid method, etc.*

**Keyword:** poorly water soluble, solubility enhancement, dissolution, spray drying versus freeze drying

## 1. Introduction

The poor aqueous solubility and dissolution rate of API is one of the biggest challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high through put and combinatorial screening tools during the drug discovery and selection phase. According to the pharmaceutical classification system. A drug compound is poorly soluble if the highest dose strength is not soluble in aqueous media over the PH ranges at 37c. these compounds mostly belong to class II drug, which are poorly water soluble and highly permeable according to the PH of the gastrointestinal fluid and trend to present dissolution- limited adsorption. Despite their high permeability, these drug often have low oral bioavailability because of their slow and limited release of drug in gastrointestinal fluid. There force, one of the major challenges of the pharmaceutical industry is to apply soluble drug develop such problematic compounds into orally bio available and therapeutic effective drugs. Various approaches to overcome the poorly aqueous solubility of drug candidates have been investigated in drug research and development such as salt formulation. Pro-drug formation, particle size reduction, Complexation, micro-emulsion, Nano-emulsion, Nano-suspension, solid liquid Nana-particle and solid dispersion which is considered one of the most successful strategies to improve the dissolution profile of poorly soluble drug. The term solid dispersion has been defined as a dispersion of one or more API in an inert carrier or matrix at the solid state prepared by solvent, melting or solvent melting method. The API in solid dispersion can be dispersed in separate molecules, amorphous particle or

crystalline particle while the carrier can be in crystalline or amorphous state. Numerous studies on solid dispersion have been published and have showed many advantages properties of solid dispersion in improving the solubility and dissolution rate of poorly water soluble drug. These advantages include reducing particle size possibly to molecular level, enhance wetting and porosity as well as changing drug crystalline state, preferably into amorphous state. Despite such high active research interests, the number of marketed products arising from solid dispersion approaches is disappointingly low. This low number is mainly due to scale-up problems and physicochemical instability in the manufacturing process or during storage leading to phase separation and crystallization. Only a few commercial products have been marketed during the past half-century. Therefore in-depth knowledge that has been acquired on various aspects of solid dispersions such as carrier properties, preparation methods, physicochemical characterization techniques as well as the pharmaceutical mechanism of matrix formation and drug release are very important to ensure the preparation of a productive and marketable solid dispersion. The aim of this review is to provide new knowledge from recent advances on solid dispersion areas to overcome some problems and issues that limit the marketability of solid dispersion products. As a continued work of previous reviews in this field, this article newly suggests the four classifications of solid dispersions according to the development by generation-to-generation that has been investigated so far. Finally, the future perspectives and strategies of solid dispersions are also discussed.



## 2. Material and Method

### Particle size reduction

Particle size reduction can be achieved by,

- Microonization
- Nano suspension
- Sonocrystalisation

### Microonization

Micronization increases the dissolution rate of the drug through increased surface area. Micronization of drug is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drug having a high dose number because it does not change the saturation solubility of the drug. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of attrition methods. The process is called Micro-milling.

### Nano-suspension

Nano-suspensions are sub-micro colloidal dispersion of pure particle of the drug, which are stability by surfactants. Nano-suspension technology is used for efficient delivery of hydrophobic drug. The particle size distribution of the solid particle in Nano suspension is usually less than one micron with an average particle ranging between 200 and 600nm.

### Sonocrystalisation

Particle size reduction on the basis of the crystallization by using ultrasound is Sonocrystalisation. Sonocrystalisation utilizes ultrasound power for inducing crystallization. It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredient. Most application use ultrasound in the range 20 KHz-5MHz.

### Kneading Techniques

Active drug with suitable polymer in different ratio added to the motor and triturated with small quantity of ethanol to prepare the slurry. Slowly the drug is incorporated into the slurry with constant trituration the prepared slurry is then air dried 250 ° c for 24hrs.

### Hydrotropy

Hydrotropy is a Solubilization phenomenon where by benzoate, sodium salicylate urea, and nicotinamide, sodium citrate, and sodium acetate having been observed to enhance the aqueous solubilizes of the many poorly water soluble drug.

### pH Adjustment

To access the solubility of this approach the buffer capacity and tolerability for selected pH are imported to consider. Solubilized excipient that increases environmental pH within the dosage form to range higher than Pka weakly acidic drug increase the solubility of that drug. These excipient that act as alkaline agent may increase the solubility of weakly basic drug.

### Complexation:

Complexation of drug with cyclodextrin has been used to enhance aqueous solubility and drug stability cyclodextrin of the pharmaceutical relevance contain 6, 7, 8, molecules bound in a 1, 4 configuration to form rings of various diameter. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecule can form no covalent inclusion complexes resulting increase aqueous solubility and chemical stability. Complexation retain in the relatively weak forces such hydrogen bonding and hydrophobic interaction.

### Inclusion Complexation formulation based on the techniques:

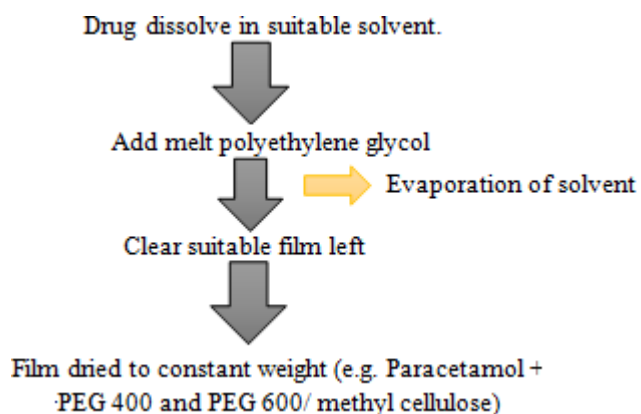
Inclusion Complexation are formed by insertions of the nonpolar molecular (or) the nonpolar region of one molecule into the cavity on the another molecular (or) group of molecule.

### Hot melt Method

Drug +vehicle (M.P.low, organic solvent in soluble)  
 + (heating)  
 Melting  
 +  
 Freezing quickly  
 +  
 Dosage forms (Suitable to drug and vehicles with promising heat stability)

A molecular dispersion can be achieved or not, depends on the degree of super saturation and rate of cooling used in the process. (**Important:** Miscibility of the drug & carrier in the molten form, thermo stability of the drug & carrier.)

**Melt solvent Method**



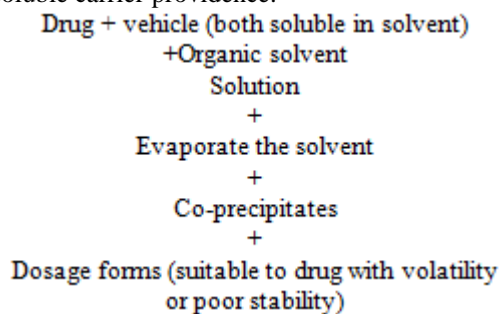
**(Important:** the solvent evaporation can be done by spray drying or freeze drying, temperature used for solvent evaporation generally lie in the range 23-65°C, Tachibana and Nakamura were the first to dissolve both the drug and the carrier in a common solvent and

**Hot melt Extrusion Technology:**

Hot melt extrusion is essentially same as the fusion method except that intense mixing of component is induced by extruder. However compared to the traditional fusion method. This technique offers the possibility of continuous production which makes it suitable for large scale production. Furthermore the products is easier to handle at the outlet of the extruder the shape can be adapted to the next processing step without grinding. Hot melt extrusion of miscible component results in amorphous solid solution formation, where extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersion in a single step.

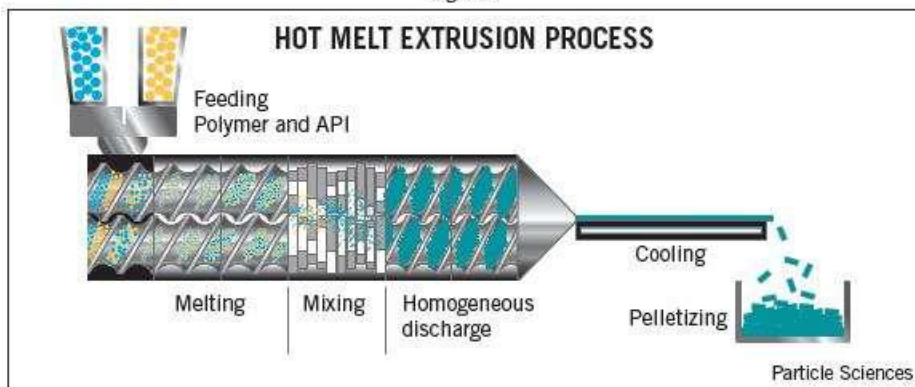
**Solvent Evaporation Method**

In this Method of solvent Evaporation, the drug and carrier are dissolved in common solvent and then the solvent is evaporated under vacuum to produce a solid. Example, solid solution of the highly lipophilic β-carotene in the highly water soluble carrier providence.



**(Important;** thermo-sensitive drugs and carrier would not be used in this technique as they will be subjected to degradation.)

Figure 1

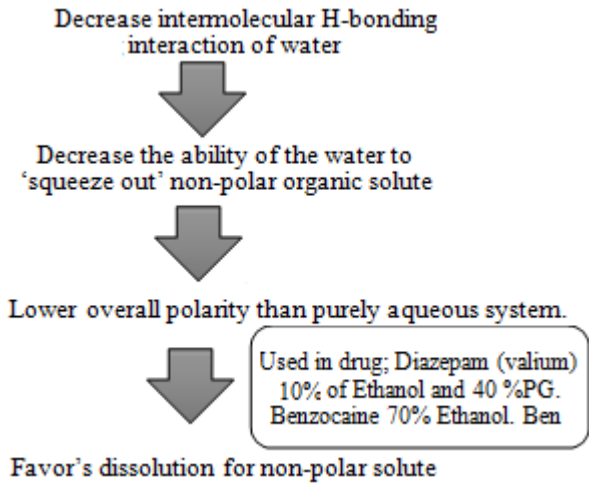


**Figure 1:** Diagrammatic representation of Hot melt Extrusion technique

**Co-solvency:**

The solubility of poorly water soluble drug can be increase frequently by addition water miscible solvent in which the drug has good solubility and such as technique. Co-solvent are mixture of water and one or more water miscible solvent used to create solution with enhanced solubility or poorly soluble compound. Co-solvent can increasing the solubility for the poorly soluble compound several thousand compared to aqueous solubility of the drug alone. Very high concentration of poorly water soluble compound dissolved compared to Solubilization approaches.

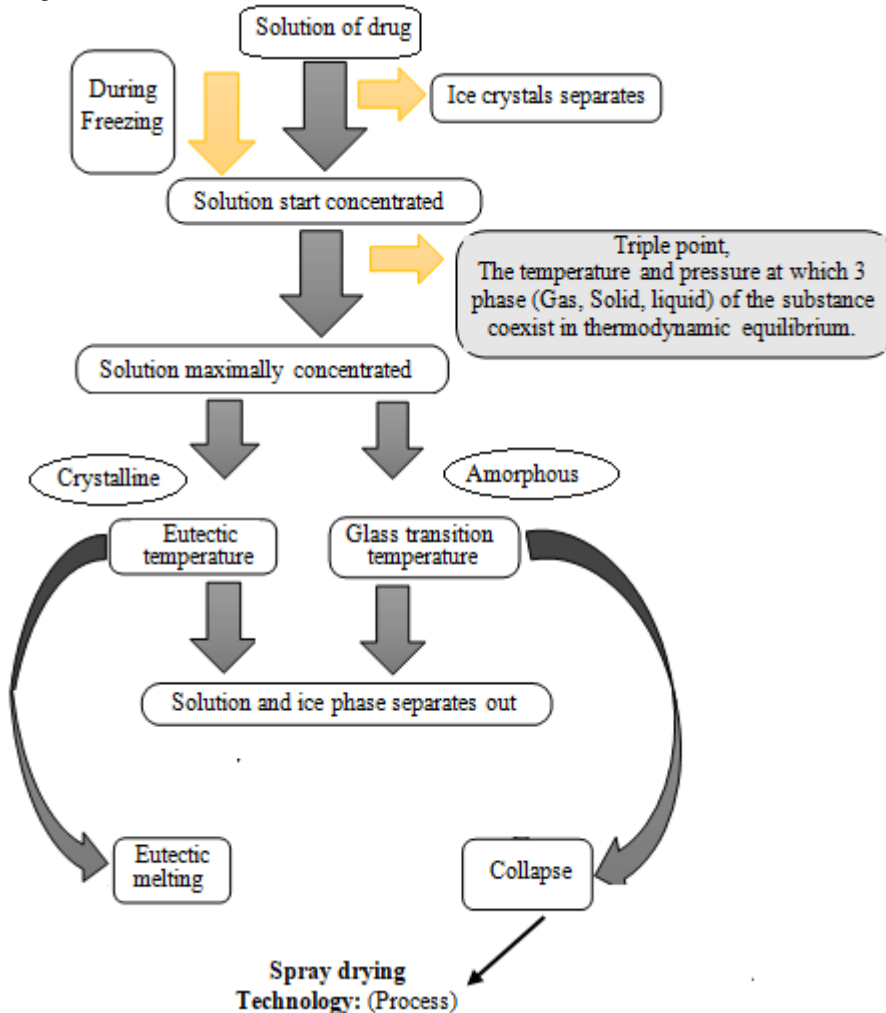
**Mechanism of Action**



common solvent frozen and sublimed to obtain a lyophilized molecular dispersion. This technique was proposed as an alternative method to solvent evaporation. It's applicable for the thermo bile or otherwise product unstable in aqueous solution for prolonged storage periods, but that are stable in the dry state.

**Lyphilization**

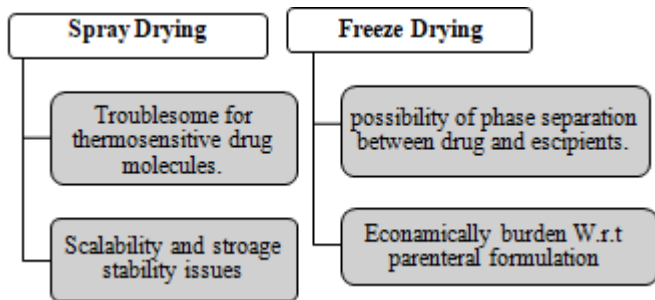
Lyphilization has been thought of a molecular mixing technique where the drug and carrier are so dissolved in a



**Figure 2: Lyphilization Process**



**Spray drying Technology: (Process)**



**Concentration**

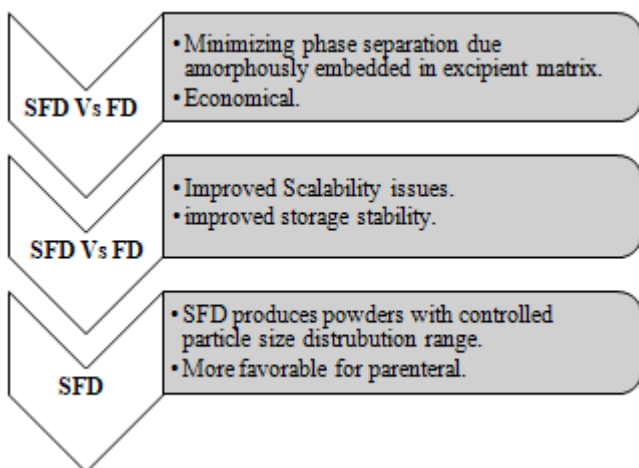
To increase the solid content. Reducing the amount of liquid that must be evaporation in the spray dryer.

**Atomization**

To create the optimum condition for evaporation. To lead to dried product having the desired characteristics.

**Droplet Air contact**

The element of the spray dryer in the spray dryer chamber where atomized liquid brought into contact with hot gas, resulting in the evaporation 95% +water. The way in which the spray makes contact with the air in the dryer influence in the behavior of the droplet during the dryer phase and has a direct bearing on the properties of dried product.



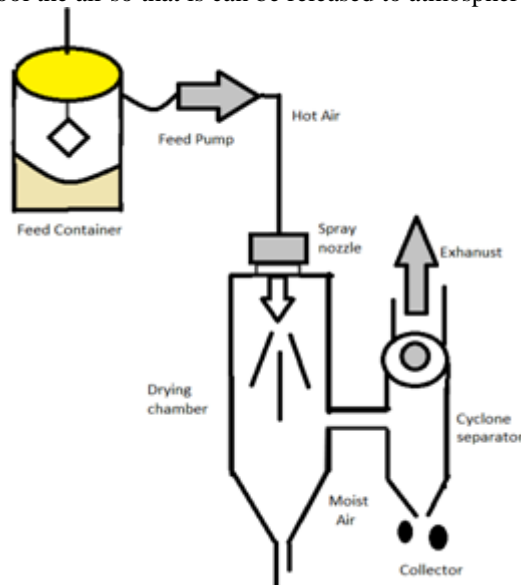
**Droplet drying**

First Stage	Second Stage
<ul style="list-style-type: none"> <li>• <b>There</b> is sufficient moisture in the drop to replace the liquid evaporated at the surface.</li> <li>• Evaporation takes place at a relatively constant rate.</li> </ul>	<ul style="list-style-type: none"> <li>• Begins when is no longer enough moisture to maintain saturated condition at the droplet surface.</li> <li>• It cause a dried shell to form at the surface.</li> <li>• Evaporation then depends on the diffusion of moisture through the shell, which is the increasing in thickness.</li> </ul>

**Separation**

Primary separation is accomplished by the particles simply falling to the bottom of the chamber & small fraction of the particle remain entrained with the air and must be recovered in separation equipment. Cyclones, bag, filters, and electrostatic precipitators may be used for the final

separation stage & wet scrubber are then often used to purify and cool the air so that is can be released to atmosphere.



**Figure 3:** Typical layout of a spray dryer process and its components.

**Solubility Enhancement mechanisms of spray drying technology**

The solubility enhancement mechanisms of spray drying technology are highly dependent upon the physiochemical characteristics of API and final formulation. In the GIT lumen, aqueous phase diffuse into the inner core of spray dried particles and the polymer hydration occurs. If the drug is highly soluble, the particle wear away at the edges and the API diffuses at the boundary layer, comparable to a classic dissolution from a crystal. However, if the drug is highly lipophilic, amorphous polymeric domains of drug rich particles are separated leading to disintegration and the formation of highly activated drug nanostructures in polymeric domains. The key molecular mechanism for absorption is freely solvated drug partitioned into bile salt micelles, which are in rapid equilibrium with the unbound molecules. Due to Nano particulate size, these molecules rapidly travel across the mucus boundary layer and provide high free-drug concentrations at the epithelium, driving absorption. These polymeric spray dried particles are high-energy, high surface area repositories which maintain super saturation and provide enhanced absorption of the lipophilic drugs.

**Formulation approaches in spray drying technology**

Amorphous solid dispersions are the dispersions of drug molecules in an inert carrier matrix in which the lipophilic active pharmaceutical ingredient exists in crystalline or amorphous or solubilized state. The rationale behind solubility enhancement with this technique is that the drug remains in amorphous phase which is in the higher energy state to get solubilized as compared to crystalline phase. Solid dispersions acquired major limitation such as crystallization of the amorphous state after storage at various storage conditions due to incompatibilities attributed to polymer-drug miscibility. This limitation can be overcome by spray drying the solid dispersion formulation which induces crystalline to amorphous transition due to high

thermodynamic stability, better porosity and surface area providing improved solubility and bioavailability

### Solid-self Micro-emulsifying drug delivery system (SMEDDS)

Self-micro-emulsifying drug delivery systems (SMEDDS), the micro-emulsion pre-concentrates, are anhydrous isotropic mixtures, when introduced into aqueous phase under conditions of gentle agitation, spontaneously form o/w micro-emulsions. Liquid SMEDDS have a tendency to leach lipid excipients out of the dosage forms upon storage causing softness or brittleness of the capsule shell due to incompatibility issues or precipitation of the drug in gastrointestinal lumen. To address these problems in this regard, endeavors have been made to convert liquid SMEDDS into solid SMEDDS that are gaining more popularity due to their high stability, low production cost and better patient compliance. Spray dried solid SMEDDS produces small particle size in the micro/Nano range and provide a larger surface area for absorption and dissolution. Governs various scientific reports on solid dispersions and solid SMEDDS by spray drying for solubility enhancement purposes.

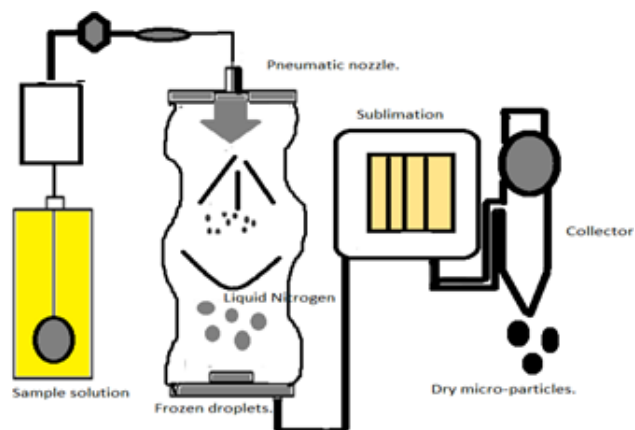


Figure 4: Illustration of spray drying technology. (SFD)

## 3. Particle Size Reduction Techniques

### Anti-solvent precipitation

In this technique, lipophilic API is solubilized in a suitable organic solvent, usually non-polar for complete miscibility. The resultant solution is continuously added into the anti-solvent having polar nature like water and subjected to four critical steps like super saturation, nucleation, solute diffusion and particle growth formation to get the particle size to Nano scale range. Nano precipitation technology offers certain advantages in terms of ease of operation, fast and cost effective, but the higher reaction rate limits the use of organic solvent that have high flammability leading to non-uniformity in the system. To overcome this, micro mixing is the new tool in Nano precipitation technology that limits the use of organic solvents and high reaction rates. This technology produces wide distribution of particle size ranges with different growth rates that affects the physiochemical properties of Nano sized API produced.

### Ultrasonic precipitation

Sono precipitation utilizes ultrasonic waves for preparing Nano-composites or engineered nanoparticles of drug with

poor aqueous solubility. Sono precipitation usually gives high percentage yield, controlled particle size distribution, solid state characteristics and dissolution improvement. The final morphology of the Nano sized API produced primarily depends upon various process variables such as instrument operating conditions like frequency and intensity of ultrasonic waves, horn tip size, immersion depth, flow rate and optimal process temperature conditions. Sono precipitation produces Nano sized API with a greater surface area, narrow particle size distribution and good solid state characteristics.

### High pressure homogenization (HPH)

High pressure homogenization (HPH), a mechanical micro-negation technology, is a widely used technique for enhancing the dissolution rate and bioavailability of poorly water soluble drugs (PWS) by effectively achieving the Nano particulate range. The production of extremely high energy mechanically activates the drug particles leading to partial or complete conversion of crystalline to Amorphization of the drug. In this process, the coarse particles to be comminuted are first dispersed in a suitable solvent and then forced under high pressure (10–7 Motor/1000–5000 bars) and high velocity (500 m/s) through an aperture valve of Nano sized range, the coarse particles experiences; turbulent flow conditions, sudden pressure drop and cavitation phenomena. In advantageous aspects of oral dosage forms, high pressure homogenization is robust technique and minimizes the chances of crystal growth and improves the stability of the engineered dispersed particles during storage. In conclusion, HPH technique is widely employed for maintaining the saturation solubility and improving the dissolution rate of poorly soluble drugs.

### Solubilization by surfactants

Surfactants are molecule with distinct polar and nonpolar regions. Most surfactants consists to a polar group the polar group can be anionic, cationic, nonionic. The presence of the surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent. Micro emulsion is a four component system composed of external phase, internal phase, surfactant and co surfactants. The addition of surfactant which is predominately soluble in the internal phase unlike the co-surfactant, result in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It termed as micro emulsion because of the internal phase is  $\leq 0.1$  micron droplet diameter. The surfactants and the co-surfactant alternate each other and form a mixed film at the interface which contribute to the stability of the micro-emulsion. Nonionic surfactants such as Tweens (polysorbates) and labrafil (polyoxyethylated oleic glycerides) with high hydrophile-lipophile balances are often used to ensure immediate formation of oil in water droplet production.

### Fluid bed coating drying:

A continuous fluid bed system is machine in which a continuous flow of 'wet' powder granules or flakes material is conveyed over perforated bed, hot drying air is blow through the hole of perforated plate. The wet solid are lifted from the bottom and cause the solid to behave as a fluid. The air velocity is adjusted to keep moving layer of material fluidized. Conveying of the product is achieved by means of

a low frequency, high amplitude shaker mechanism, the shaking motion plug flow of the tama fluid bed allows first in, first out drying of the product and well mixed fluidization, which covers the entire spectrum and is able accurately control the spread of residence time.

### Electrospinning

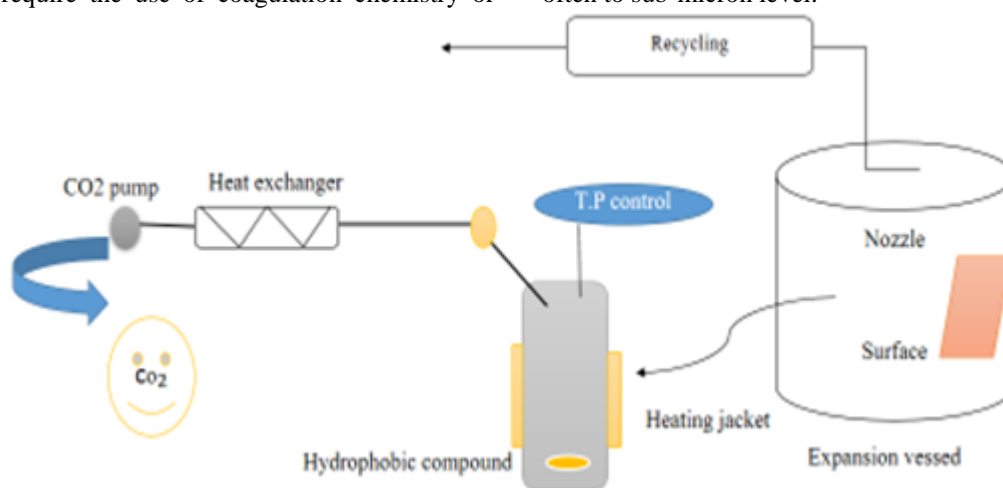
Ultrathin polymer Nano fibers with diameter down to a few nanometer are accessible via the Electrospinning process. It involves the application of the strong electric field to a pendent drop of a polymer solution or polymer melt. A jet is ejected and move toward the counter electrode if the electrostatic force. Overcome the surface and viscous force. A broad range of polymer including polyimides, polylactides, cellulose derivatives water soluble polymer such as polyethylenoxide, polymer blends or polymers containing solid nanoparticle or functional small molecules can be electrospun. Electrospinning use an electrical charge to draw very fine fibers from a liquid. Electrospinning shares characteristics of both electro spraying and conventional solution dry spinning of fibers. The process is noninvasive and does not require the use of coagulation chemistry or

high temperature to produce solid threads from solution. This makes the process particularly suited to the production of the fibers using large and complex molecules. Electrospinning from the molten precursors is also practiced this method ensure that no solvent can be carried over into the final product.

### Supercritical fluid process

A supercritical fluids are dense non-condensable fluid whose temperature and pressure are greater than its critical temperature and critical pressure allowing it to assume the properties of the both a liquid and a gas. Through manipulation of the pressure of SCF the favorable characteristics of gas high diffusivity low viscosity and low surface tension may be imparted upon the liquid to precisely control the Solubilization of the drug with a supercritical fluids. Once the drug particle are solubilized within SCFs they may be recrystallized at greatly

Reduced particle sizes, a SCFs process allow Micronization of the drug particle within narrow range of particle size, often to sub-micron level.



## 4. Conclusion

Dissolution of the drug is the determining step for oral absorption of the poorly water soluble drug and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Proper selection of solubility enhancement method is the key to ensure the goals oral bioavailability, reduce the frequency of dosing and better patient compliance combined with a low cost of production. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirement like maximum daily dose of any excipients and drug, approved excipients analytical accuracy.

## References

[1] Ansel H C, Allen L V and Popovich CG. Eds. In; Pharmaceutical dosage forms and drug delivery systems,

7th Edn, Lippincott Williams and Wilkins, 2000, 60-61,66.

- [2] Ohara T, Kitamura S, Kitagawa T and Terada K. Dissolution mechanism of poorly water-soluble Drug from extended solid dispersion system with ethyl cellulose and hydroxypropyl methylcellulose. *Int. J. Pharm.* 302, 2005, 95-102.
- [3] Mooter G V den, Weuts I, Rider T D and Blaton N. Evaluation of Inutec SPI as a new carrier in the formulation of solid dispersion for poorly water drugs. *Int. J. Pharm.* 316, 2006, 1-6.
- [4] Hecq J, Deleers M, Fanara D, Vranckx H and Amighi K. Preparation and characterization of Nanaocrystals for solubility and dissolution rate enhancement of nifedipine. *Int. J. Pharm.* 299, 2005, 167-177.
- [5] Kapsi S G and Ayres J W. Processing factors in development of solid solution formulation of Itraconazole for enhancement of drug dissolution and bioavailability. *Int. J. Pharm.* 299, 2001
- [6] Orienti I, Bigucci F, Luppi B, Cerchiara T, Zuccari G, Giunchedi P and Zecchi V. Polyvinylalcohol substituted with triethyleneglycolmonoethylether as a new material for preparation of solid dispersions of hydrophobic drugs. *Int. J. Pharm.* 54, 2002, 229-233.

- [7] Patro S, Himasankar K, Choudhury A A and Rao M E B. Effect of some hydrophilic polymers on dissolution rate of roxithromycin. *Indian J. Pharm. Sci.* 67(3), 2005, 334-341.
- [8] Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci.* 1971, **60**: 1281Y1302.
- [9] Krishnaiah YSR. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. *J Bioequiv Bioavailable* 2010; 2:28e36.
- [10] Kawabata Y, Wada K, Nakatani M, et al. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. *Int J Pharm* 2011; 420:1e10.
- [11] Kumar S, Bhargava D, Thakkar A, et al. Drug carrier systems for solubility enhancement of BCS class II drugs: a critical review. *Crist Rev Ther Drug Carrier Syst* 2013; 30:217e256.
- [12] Rogers TL, Nelsen AC, Sarkari M, et al. Enhanced aqueous dissolution of a poorly water soluble drug by novel particle engineering technology: Spray-freezing into liquid with atmospheric freeze-drying. *Pharm Res* 2003; 20:485e493.
- [13] Prabha S, Ortega M, Ma c. novel lipid based formulation enhancement the in vitro dissolution and permeability characteristics of a poorly water soluble drug, *Int J pharm.* 2005:301:209-216.
- [14] Karatas A, Yuksel N, Baykara T, Improved solubility and dissolution rate of piroxicam using gelucire 44/14 and labrasol. *Farmaco.* 2005:60:777-782.
- [15] Dixit M, kini AG, Kulkarni PK, preparation and characterization of microparticle of piroxicam by spray drying and spray chilling method. *Res pharma Sci.* 2010:5:89-97.
- [16] Patel DM, Shah RR, Jogani PD. Studies to enhance dissolution of celecoxib. *Rasayan J chem.* 2010:3:314-320.
- [17] Fernandez N, Inna M, Muhammad JH, james FB, muhammed DH, Enhanced dissolution and oral bioavailability formulation. Modulating effect of phospholipids pharmaceuticals. 2010; 2:339-350.
- [18] Teagarden DL, Baker DS, practical aspects of lyophilization using Nano-aqueous co-solvent systems. *Eur J pharma Sci.* 2002; 15:115-133.
- [19] Mahmoud El-Badry, Gihan Fetih, Mohamed Fathy, Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG4000. *Saudi Pharmaceutical Journal* (2009) 17, 217-225.
- [20] Mohan Babu G V M, Prasad D S, and Ramana Murthy K V, Evaluation of modified as carrier for the dissolution enhancement of poorly water-soluble drug Nimodipine. *Int. J, p harm.* 234 2002.
- [21] Hayes, Davis, Morella and Angelo Mario. Pharmaceutical compositions for poorly water-soluble drugs. United States Patent. No. 6881745, 2005.
- [22] Butler and Matthew J. Method of producing a solid dispersion of a poorly water-soluble drug. United State Patent No. 5985326, 1999.
- [23] Betageri G V and Makarla K R. Enhancement of dissolution of Glyburide by solid dispersion and Lyophilization techniques. *Int. J. Pharm.* 126, 1995, 155-160.
- [24] Joshi H N, Tejwani R W, Davidovich M, Sahasrabudhe V P, Jemal M, Bathala M S, Varia S A and Serajuddin A T M. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol polysorbates 80 mixture. *Int. J. Pharm.* 269, 2004.
- [25] Sheen P C, Khetarpal V K, Cariole C.M and Rowling's C E. Formulation studies of a poorly water-soluble drug in solid dispersions to improve bioavailability.
- [26] Dohrn R, Betakes E, Behrend O, Voutsas E and Tassios D. Melting point depression by using supercritical CO<sub>2</sub> for a novel melt dispersion Micronization process. *J of Molecular Liquids* 131- 132, 2007, 53-59.
- [27] Mooter G V den, Weuts I, Rider T D and Blaton N. Evaluation of Inutec SPI as a new carrier in the formulation of solid dispersion for poorly water soluble drugs. *Int. J. Pharm.* 316, 2006, 1-6.