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# Solubility Enhancement of Poorly Water Soluble Drugs: A Review

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## ABSTRACT

Many drugs which have low solubility and high permeability poorly soluble and insoluble drug profile creates problems in pharmaceutical industry.

The low dissolution rates and profile lower the bioavailability of drug when administered orally.

Various techniques which review for enhancement of solubility of poorly water soluble drug techniques like solid dispersion, complexation, co solvency, hydrotropy, for improvement of poorly water soluble drug.

The purpose of this review article is to describe the techniques of achievement of improved bioavailaibilty and absorption. Porosity and wettability improves and enhances the solubility and dissolution rate.

The primary aim of this review is to improve the solubility and Bioavailability of drugs because of their low solubility and dissolution rate and leading to improving the poorly water soluble drugs. The techniques which leads to enhancing the poorly soluble drugs and desired activity is obtained.

The solubility enhancement is most challenging aspect foe drug development pharmaceutically active ingredient with low solubility which creates problems in dru7g development and innovation.

***KEYWORDS:*** *Bioavalability, solubility, cosolvent, solubility enhancement, nanosuspension, dispersion, emulsion, pH*

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## INTRODUCTION

Biopharmaceutical Classification System (BCS) based on its solubility and permeability. Bioavailability of drug affected by three major factor like solubility, permeability and dissolution. Bioavailability of drug may be defined as the rate and extent of drug which is present in systemic circulation at particular period of time. Improvement in dissolution rate by increasing the surface area through particle size reduction of poorly soluble drugs results in poor bioavailability {1}.

Solubility is the property of a solid, liquid or gaseous chemical substance called solute to liquefy in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance is on a very basic level relies upon the dissolvable utilized as well as on temperature and pressure. How much solubility of a substance in a particular dissolvable is estimated as immersion focus where adding more solute doesn't rise its fixation in the arrangement {2}.

The Important Phenomenon and as a most of time discussed but a still or not a completely resolved issue, „"Solubility or dissolution enhancement technique remains a most challengeable field for the researchers in the formulation design and developmental process. Solubility and dissolution. These are the core concepts of any physical as well as chemical science including their biopharmaceutical and pharmacokinetic considerations in the treatment with any medicine {3}.

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution is a static property where as the drug dissolution rate is a dynamic

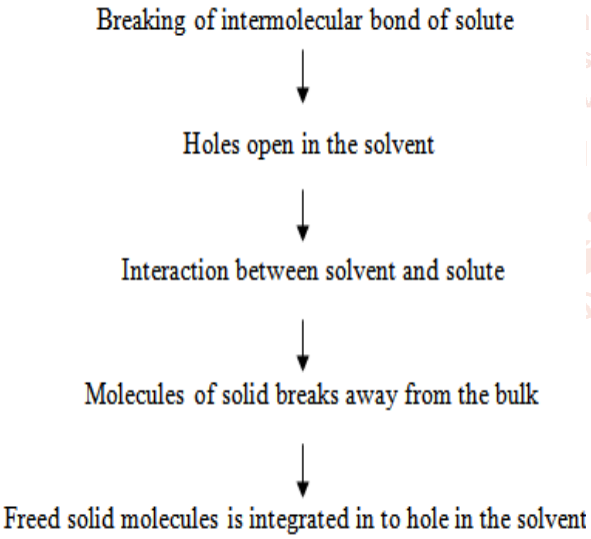
property that relates more closely to the bioavailability rate{4}.

Ineffectively solvent and disintegration profile makes issue in drug industry for improvement of measurements structure. Many solubilization techniques are available for increasing of solubility as well as permeability like micronization, coacervation, complexation solid dispersion and co-solvent. Solubility can be also enhanced by alteration in molecular level of physical form of drug {5}. The solubility of drugs in form by which the amount of drug dissolved in solvent is shown in various descriptive terms in Table-1

| Descriptive terms | Approximate volume of solvent in milliliters per gram of solute |
|---|---|
| Very soluble | Less than 1 |
| Freely Soluble | From 1 to 10 |
| Soluble | From 10 to 30 |
| Sparingly Soluble | From 30 to 100 |
| Slightly Soluble | From 100 to 1000 |
| Very Slightly Soluble | From 1000 to 10,000 |
| Insoluble | More than 10,000 |

**Table 1: Definitions of Solubility [4]**

**PROCESS OF SOLUBILISATION{6}**




**NEED OF SOLUBILTY ENHANCEMENT:**

According to recent estimates, nearly 40-50% of new chemical entities are rejected because of poor solubility i.e. biopharmaceutical properties. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response

Solubility enhancement is one of the fundamental boundaries which should be thought about in framework improvement of orally directed drug with horrible watery solvent. Solubility is the capability substantial effects with respect to the limit of a given substance, the solute, to disintegrate in a solvent. "The solubility is characterized as how much solute particles which disintegrate in a solubility or arrangements at a predefined temperature.{7}.

**Solubility enhancement techniques:**

The technology as 'solubility improve' can be misleading, since although the phenomenon of super-saturation is real, the techniques used do not increase the solubility of insoluble compounds. It is also important to be aware that water solubility also requires the specification of temperature and pH; many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be met at the site of absorption{8}.

The techniques that are used to overcome poor drug solubility are as followed,

**I. Physical Modifications**

A. Particle size reduction
1. Micronisation
2. Nanosuspension
3. Sonocrystallization
4. Supercritical fluid process

B. Modification of the crystal habit
A. Polymorphs
B. Pseudopolymorphs

C. Complexation
A. Use of Complexing agents

D. Solubilization by surfactants:
A. Microemulsions
B. Self microemulsifying drug delivery systems

E. Drug dispersion in carriers:
1. Solid dispersion method

**II. Chemical Modifications**

1. Salt Formation
2. Co-crystallisation
3. Co-solvent
4. Hydrotropy

**1. Micronization**

Reduction of particle size occur so as increase of surface area which increase the dissolution rate and bioavailability of drug. The particle size after micronization is 1-10 microns. This method involves spray drying and attrition method. Micronization increases the dissolution rate of drug through increasing surface area, it does not increase equilibrium solubility.

Decreasing the particle size of these drugs, which cause increase in surface area, progress their rate of dissolution. Micronization of drugs is done by milling techniques using rotor stator colloidal mill, rotor mills and so forth micronization is not suitable for drugs

having high dose number because it does not change the saturation solubility of drug. These procedures were applied to griseofulvin, spironolactonediosm, progesterone, in an fenofibrate{9}.

**2. Nanosuspension**

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactant. The advantages offered by Nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.{10}

**3. Sonocrystalization**

Application of ultrasound energy to adjust the nucleation of a crystallization procedure is called as sonocrystalization. The energy of ultrasound manners successive compression and expansion. After numerous cycles a bubble forms and grows then collapses. The collapse of the bubbles delivers energy to promote the nucleation process.[11]

**4. Supercritical fluid process**

Supercritical fluids (e.g. carbon dioxide) are fluids whose temperature and pressure are larger than its critical pressure and critical temperature allowing it to assume the properties of both gas and liquid. At near critical temperature supercritical fluids are extremely compressible, permitting moderate changes in pressure to greatly alter the density and mass transfer characteristics of a fluid that largely determine its solvent power. Once the drug are solubilized within SCF they may be recrystallization at significantly reduced particle size.[12]

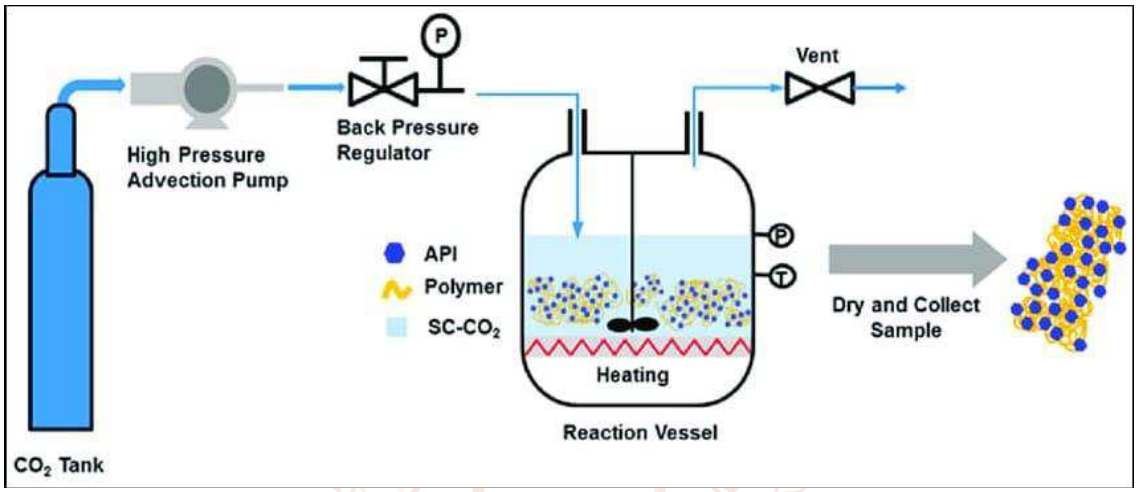



**Fig-1: Flow of Super critical fluid process**

**A. Modification of the crystal habit**

Polymorphism is the capability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including melting point texture, solubility, density, stability. Similarly amorphous form of drugs is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drugs is

**Amorphous > Metastable polymorphs > Stable polymorphs.[13]**

**B. Complexation:**

Cyclodextrins are a group of cyclic oligosaccharides obtained from enzyamatic degradation of starch.

The three major cyclodextrins are α,β, and ʎ-CD are composed of 6,7and 8 D-(+) glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups oriented outwords. Importantly cyclodextrins have a hydrophilic exterior and hydrophobic internal cavity. CD and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parentral delivery. When the aqueous solubility of the pure drug is low then there is a greater relative solubility enhancement which is obtained through cyclodextrin complexation{14}

There are certain forces which plays an imp role for the formation of complexation were attributed to-

1. The exclusion of high energy water from the cavity,
2. The release of ring strain particularly in the case of -CD,
3. Hydrogen and hydrophobic bindings
4. Van der Wal‟s interactions.{15}

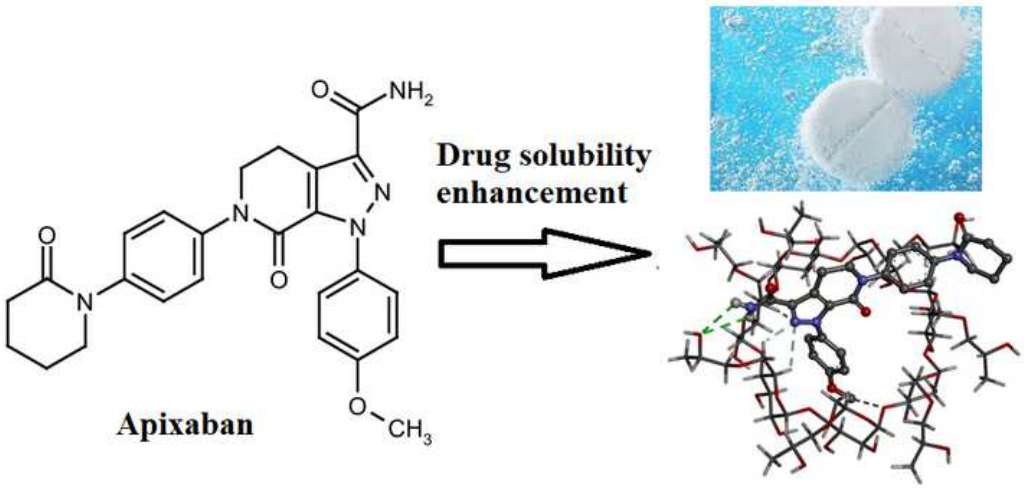



**Fig-2: Complexation solubility enhancement method**

**C. Solubilization by surfactants:**

Permeability and dissolution rate can be increased be surfactant. Absorption rate also be enhance due to increasing of particle size. Mechanism involves firstly wettability and then penetration of solvent in the particles of drug. Solubility of much poorly water soluble anti-microbial drugs can be increased by use of surfactant. Surfactant are three types; anionic, cationic and non-ionic. Anionic and cationic select over the non-ionic surfactant. It acts as good solubilizing agent {16}

**D. Drug dispersion in carriers:**

**[Solid Dispersion Method]**

The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles{17}**.**

Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemi8al (e.g. drug–polymer miscibility and stability) and pharmacokinetic (e.g. rate of absorption) constraints{**18}**.

**MECHANISM OF SOLID DISPERSION:**

The formulations of solid dispersions results into reduction in particle size, improved wettability and enhancement of the dispersibility of the drug, thereby markedly improving the dissolution rate. The suggested mechanism behind this tremendous increase in dissolution rate may include:{**19}**

- Partial transformation of crystalline drug to the amorphous state or altering the crystalline morphology

1. Formation of solid solution
2. Formation of complexes
3. Intimate mixing of the drug with hydrophilic excipients
4. Reduction of aggregation and agglomeration
5. Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer.

**Advantage of Solid Dispersion:**

1. Uniform distribution of drug molecules in to carriers is achieved by solid dispersions method.
2. It increases the wettability of drug molecules which improve the solubility of drugs.
3. Many carriers used in solid dispersion method like urea, colic acid, cellulose and bile salt are create the surface activity.
4. Carriers of solid dispersion have high porosity which improves the solubility by faster release of drug {20}.

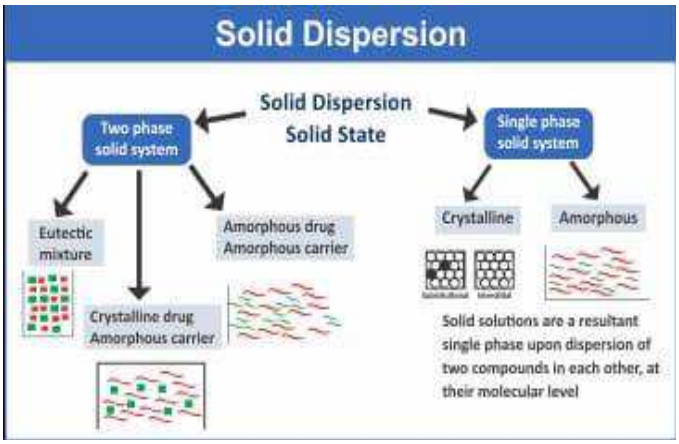



**Fig-3: Solid dispersion method**

**METHODS OF SOLID DISPERSION:**

Various methods have been developed for preparation of solid dispersions, these methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted.

**1. Solvent melting method**

Accurately weighed drug is dissolved in organic solvent. The solution is incorporated into the melt of mannitol and cooled suddenly and mass is kept in desiccator for complete drying.

The solidified mass is crushed, pulverized and passed through sieve. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose (less than 50 mg).{**21**}

**2. Spray-Drying Method**

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.{**22**}

**3. Hot Melt method**

Sekiguchi and Obi21 used a hot melt method to prepare solid dispersion. Sulphathiazole and urea were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process{23}.

An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important requisite is the thermostability of the drug and carrier.

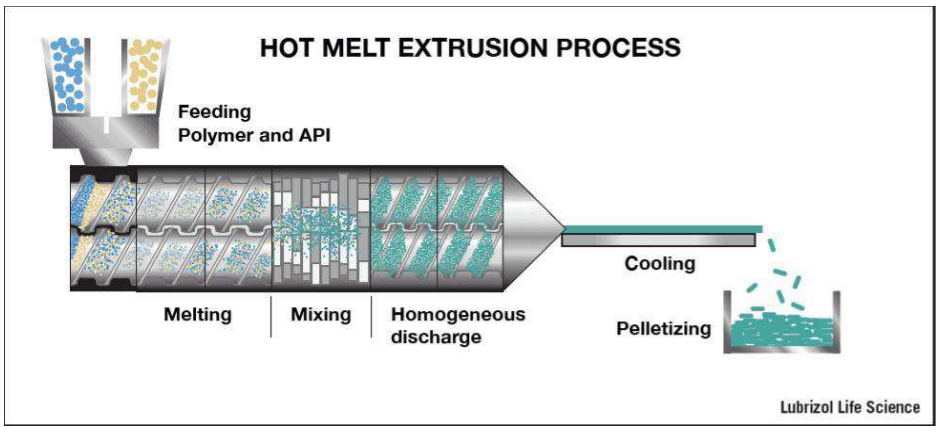



**Fig4:Hot melt extraction method**

**4. Solvent Evaporation Method:**

Evaporation method was taken by Mayersohn and GibaldiThey prepared solid solution of Griseofulvin and PVP in chloroform with enhanced dissolution up to 11 times.

Bates introduced the term co-precipitate to describe solid dispersion. An important prerequisite for manufacturing the solid dispersion using solvent method is solubility of drug and carrier in solvent.

Another issue is to remove solvent because of toxicity issue of organic solvent. To dry the solution vacuum drying is always used. Solution is dried by the application of vacuum and moderate heating. Another drying technique is spray drying.

Solution is dispersed in hot air as fine particles results in evaporation of solvent and solid dispersion is formed within seconds. An alternate to drying techniques is freeze drying {24}

**5. SUPERCRITICAL FLUIDS TECHNIQUES:**

Supercritical fluid (SCF) techniques were significantly applied for pursuing Chemical reactions, extraction, crystallization,precipitation,purification,and improvement of micro- and Nanoparticles.

To regulate solubility and Bioavailability of poorly soluble tablets thru SCF.SCF unearths a essential utility In the improvement of dry powder inhalers that as it should be supply particular Dose to the lungs.

Furthermore, SCF era may be explored for the improvement of sustain and controlled release type ofstructure. This era is an eco-friendly, inexperienced system that generates much less waste at some point of operation and produces satisfactory product at minimal cost.[25]

**A. Salt Formation**

Salt formation is the most common and effective technique of increasing solubility and dissolution rates of basic and acidic drugs. Basic or acidic drug transformed into salt having more solubility than corresponding drug. Ex. Theophylline, Aspirin, Barbiturates

**B. Co-crystallization**

Novel approach available for the improvement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes.

A co-crystals may be defined as crystalline material that comprise of two or more molecular (and electrically neutral) species held together by non-covalent forces. It can be prepared by grinding the machines together or evaporation of a heteromeric solution or by sublimation, growth from the melt and slurry preparation. It is progressively important as an alternative to salt formation, particularly for neutral compounds.

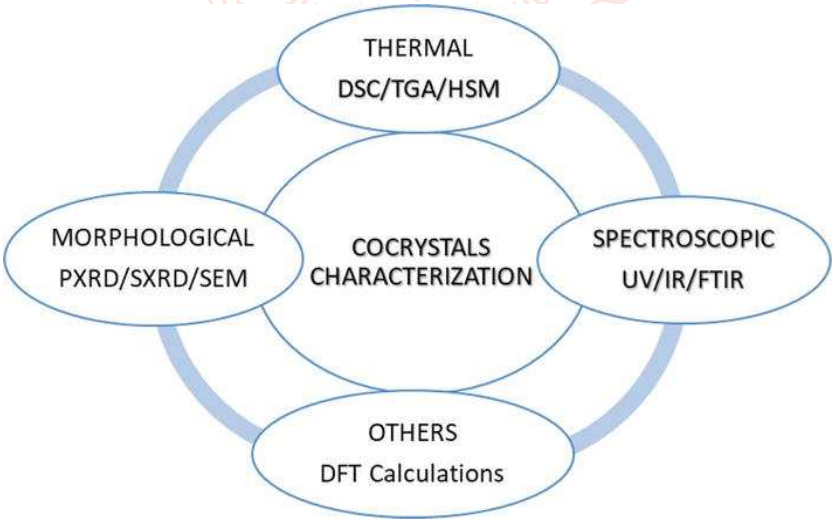



**Fig-5: Characterization of co-crystallization method**

**C. Co-solvent**

It is well-known that the adding of an organic co-solvent to water can intensely change the solubility of drugs. Weak electrolytes and nonionic molecules have poor water by the adding water miscible solvent in which the drug has good solubility the solubility of a poorly water soluble drug can be improved frequently known as co solvents also known as solvent blending. Co-solvent formulations of poorly soluble drugs can be administered parenterally and orally. It is also commonly mentioned as solvent blending.

Most co solvents have hydrogen bond donor and acceptor groups as well as small hydrocarbon areas. Their hydrophilic hydrogen bonding groups confirm water miscibility, while their hydrophobic hydrocarbon regions inhibit with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, co solvents reduce waters ability to squeeze out nonpolar, hydrophobic compounds, thus enhancing solubility.

### D. Hydrotropy

It designates to rise solubility in water due to presence of large amount of additives. It improves solubility by complexation relating weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) and solute. Ex. Sublimation of Theophylline with Sodium acetate and Sodium alginate.[26]

## CONCLUSION:

The drug solubility is important key factor for formulation development. The various techniques which describe the improvement or enhancing the poorly soluble drugs.

The solid dispersion method which is most useful for improving solubility and dissolution characteristics. The physical nature, chemical nature, pharmacokinetic behavior is determined to enhance solubility behaviour.

By this article we conclude that, for formulation of drug and its efficacy solubility is most important with solubility enhancement techniques are important by such parameter.

The solubility problems of drugs by bioavailability gets affected and hence solubility enhancement becomes necessary. Therefore by this article the solubility enhancement techniques are studied and used.

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