International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

**Review Article** **CODEN: IJPNL6**

# A review on bio-availability enhancement techniques of poorly soluble drug

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**ABSTRACT**

Solubility is the process of dissolution of solid in liquid phase to give a homogenous system and is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Dissolution rate of poorly water-soluble drugs is rate limiting step for its bioavailability so increase in bioavailability is the major challenging task in drug development. Because only 8% of new drug candidates have both high solubility and permeability. For BCS class II drugs, enhancement of Solubility and hence bioavailability is important parameter before formulation of dosage form. Hydrophobic drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include size reduction, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, hydrotropy etc. the main emphasis of review article is to describe the techniques of solubilisation for the attainment of effective absorption with improved bioavailability.

**Key words:** Solubility enhancement, Bioavailability, Hydro trophy, Hydrophobic, Dissolution.

## INTRODUCTION

Therapeutic effectiveness of a drug depends upon the dissolution, bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation and hence can be defined concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, and in another word can be describe as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Only 8% of new drug candidates have both high solubility and permeability. For BCS class II drugs, enhancement of Solubility and hence bioavailability is important parameter before formulation of dosage form. Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. [1-3] it was in August 2000, the U.S. FDA issued Guidance for Industry covering the Biopharmaceutical Classification System (BCS). The BCS is a scientific framework for classifying a drug substance on the basis of its equilibrium aqueous solubility and intestinal permeability[7.] In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor. Some new technologies have been recently developed to improve wettability and aqueous solubility of APIs.

Lipophilic molecules, especially those belonging to the biopharmaceutical classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect, and high interpatient variability. Today pharmaceutical company have been able to overcome the difficulties with very slightly soluble drug those with aqueous

solubility of less than 0.1mg/ml present some unique challenges. These drug are particularly good candidate for advance solubilisation technique develop companies specialising in drug delivery.

**HYDROTROPHY**[8, 9, 10, 11]-the phenomenon depends on the increase in saturation solubility of a substance in water by the addition of organic salts or also non-electrolytes, which must be physiologically compatible for pharmaceutical application. In another word it can be defined as solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agent's Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs. These hydrotropic substances are able to increase the number of hydrogen bridges in the water clusters. This makes the water more hydrophobic & thus it is a better solvent for non-polar drug. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism".

**Significance of hydrotropic solubilisation technique:**

1 Hydrotropy is suggested to be superior to other solubilisation method, such as micellar solubilisation, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
2 It only requires mixing the drug with the hydro trope in water.
3 It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system. The hydro tropes are known to self-assemble in solution.

**SALT FORMATION**[12, 13]

Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is the most common and effective method of increasing solubility and dissolution rate of acidic and basic drugs. Example of acidic or basic drug which is converted into salts has more solubility than that of respective drug like aspirin, theophylline, barbiturates etc. Salt formation is frequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation, which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure. Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between the pKa value of the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are water soluble than the parent drug.

**PARTICLE SIZE REDUCTION**[14, 15]

The bioavailability intrinsically related to drug particle size. By reducing particle size, increased surface area improves the dissolution hence bioavailability properties. Particle size reduction, it is done by milling techniques using jet mill, rotor stator colloid mills etc. Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Micronisation technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The solubility of drug is often intrinsically related to drug particle size as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent which cause increase in solubility. Nowadays Particle size reduction can be achieved by micronisation and nanosuspension. Nanosuspension is another technique which is sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. 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. Nanosuspensions are produced by homogenization and wet milling process.

**COSOLVANCY**[16, 17, 18, 19]

The solubility of a hydrophobic drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents. Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques

because it is simple to produce and evaluate. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Co-solvent formulations of poorly soluble drugs can be administered orally and parentrally.

Very high drug concentrations of poorly soluble compounds can be dissolved compared to other solubilisation approaches. However, the bioavailability may not be dramatically increased because the poorly soluble drug will typically uncontrollably crash out upon dilution into a crystalline or amorphous precipitate. In this case, dissolution of this precipitate is required for oral absorption. Co-solvents may be combined with other solubilisation techniques and pH adjustment to further increase solubility of poorly soluble compounds. The use of co-solvents is a highly effective technique to enhance the solubility of poorly soluble drugs. The most frequently used low toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerine, and polyethylene glycol. Dimethylsulfoxide and dimethylacetoamide (DMA) have been widely used as cosolvents because of their large solubilisation capacity for poorly soluble drugs and their relatively low toxicity.

**MEDIA MILLING (Nanocrystal or Nanosystems)** [20, 21]

The method is first developed and reported by Liversidge et.al. (1992).The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene resin. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of micro particulate drug to nanosized particles. A nanocrystal is a crystalline material with dimensions measured in nanometres; a nanoparticle with a structure that is mostly crystalline. The nanocrystallization is defined as a way of diminishing drug particles to the size range of 1-1000 nanometers. Nanocrystallization is thought to be a universal method that can be applied to any drug.

**Preparation Methods of Nanosuspensions Media milling –**

a) Using high-shear media mills.

b) The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days).

c) The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of micro particulate drug to nanosized particles.

ADVANTAGES-

1. Media milling is applicable to the drugs that are poorly soluble in both aqueous and organic media.
2. Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.

**SOLID DISPERSIONS**[22, 23, 24, 25]

As early as in 1961, the concept of solid dispersion to enhance absorption of poorly water-soluble drugs was developed. It involved formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. On the basis of these considerations, Chiou and Riegelman defined solid dispersion as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states.

Many times surfactants may also use in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used.

The solubility of celecoxib, halofantrine, ritonavir can be improved by solid dispersion using suitable hydrophilic carriers. There are various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility. The term ―solid dispersions‖ refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

**Methods of preparation of solid dispersion**

**Hot melt extrusion**[26]**:** Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. The hot-melt extrusion process is

highly dependent on the physicochemical properties of the compounds and their miscibility in the molten state. There is a potential that the API, the polymer or both may degrade if excessively high temperature is needed in the melt extrusion process, especially when the melting point of the API is high. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. This report details a novel method where the API was first converted to an amorphous form by solvent evaporation and then melt-extruded with a suitable polymer at a drug load of at least 20% w/w. By this means, melt extrusion could be performed much below the melting temperature of the drug substance It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipients. The process has been useful in the preparation of solid dispersions in a single step.

**Solvent evaporation[27]:** This method works best for water insoluble drugs. The solvent evaporation method provides good encapsulation efficiency and produces amorphous form of compound, which gave better solubility and dissolution than its crystalline form. Like required quantity of drug dissolved in suitable solvent (like Methanol for nitrezepam), then added to polymer by stirring & melted into water-bath (50-600C). This mixture was kept in water-bath until solvent gets evaporated. Afterward it was cooled to room temperature & pass through sieves as per requirement.

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents.

**Hot melt method (fusion method):**

a) Physical mixture of a drug and a water-soluble carrier was heated directly until it melted.
b) The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring.
c) The final solid mass was crushed, pulverized, and sieved, which can be compressed into tablets with the help of tableting agent.

**Dropping method-** The dropping method facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. A solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape.

**SUPERCRITICAL FLUID TECHNOLOGY [28, 29, 30]-**

Supercritical fluids are fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp). The SCF process can create nanoparticle of particles 5–2,000 nm in diameter12, 13. Solvent extraction-evaporation, solvent diffusion and organic phase separation are some conventional methods which require the use of organic solvents. These organic solvents are hazardous to the environment as well as to physiological systems.

It has been known for more than a century that supercritical fluids (SCFs) can dissolve non-volatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. Carbon dioxide is one of the most commonly used SCFs because of its low critical temperature (Tc = 31.1°C) and pressure (Pc = 73.8 bar). Apart from being nontoxic, non-flammable, and inexpensive, the low critical temperature of CO2 makes it attractive for processing heat-labile molecules. This technique consists of dissolving the drug and the inert carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. Various methods like rapid expansion of supercritical solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process are used to produce nanoparticles.

**COMPLEXATION[31, 32]**

Complexation is the association between two or more molecules to form a no bonded entity with a well-defined Stoichiometry. Complexation of drugs with cyclodextrins has been used to enhance aqueous

solubility and drug stability. SELF-ASSOCIATION AND STACKING COMPLEXATION- Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of the water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favoured by large planar nonpolar regions in the molecule. Stacked complexes can be homogenous or mixed. The former is known as self-association and the later as complexation. INCLUSION COMPLEX An inclusion complex is produced by the inclusion of a nonpolar molecule or the nonpolar region of a molecule (known as the GUEST) into the nonpolar cavity of another molecule or group of molecules (known as the HOST). When the guest molecule enters the host molecule the contact between water and the nonpolar regions of both is reduced. Thus, inclusion phenomena are the result of the same driving force that produces the micellization, Self-association, and stacking: namely the squeezing out from water of nonpolar moieties.

Cyclodextrins of pharmaceutical relevance contain 6, 7 or8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1, 4- configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non covalent inclusion complexes resulting in increased aqueous solubility and chemical stability Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-m-toluamide (DEET) and the stability and photo stability of sunscreens.

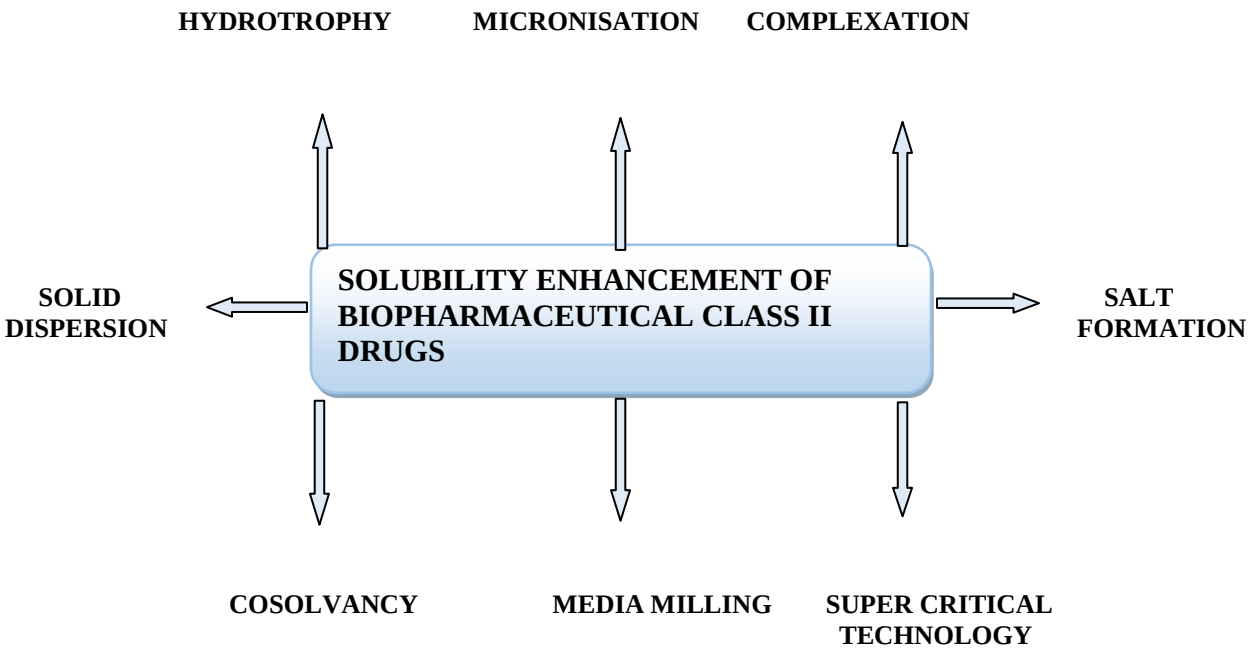
**CONCLUSION**

For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Proper selection of suitable method is the key for improvement of solubility, dissolution, bioavaibility and it helps to avoid the rejection of new chemical entities due to low solubility. Currently only 8% of new drug candidates have both high solubility and permeability.

**Table 1: Biopharmaceutical drug Classification system[4, 5, 6]**

| BCS CLASS | Solubility | PERMEABILITY |
|---|---|---|
| **I** | HIGH | HIGH |
| **II** | LOW | HIGH |
| **III** | HIGH | LOW |
| **IV** | LOW | LOW |

**FIG-1** VARIOUS TECHNIQUE FOR SOLUBILITY ENHANCEMENT OF HYDROPHOBIC DRUG

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