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SOLUBILITY ENHANCEMENT TECHNIQUES: A REVIEW

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ABSTRACT

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Bioavailability is defined as the rate and extent/amount of absorption of unchanged drug from its dosage form. A drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor stability of dissolved drug at physiological pH, poor permeation through bio membrane and extensive pre-systemic metabolism. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development.

KEYWORDS: Solubility, Bioavailability, enhancement techniques.

INTRODUCTION[1-7]

Solubility is defined in quantitative as well as qualitative term. In quantitative term solubility is defined as the concentration of solute in a saturated solution at a certain temperature, and in qualitative term, it can be defined as spontaneous interaction of twoor more substances to form a homogeneous dispersion. Solubility is an intrinsic material propertythat can be altered only by chemical modification of the molecule.

The solubility of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and solvent. Solubility is the property of a solid, liquid, or gaseous chemical substances which is called as solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substances fundamentally depends on the solvent used as well as on temperature and pressure.

- **Need and Importance of solubility[8-15]:** Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membrane of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agent include; enhancing of solubility and dissolution rate of poorly water soluble drugs.

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. However, the major challenge with the design of oral dosage forms with their poor solubility and poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first- pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.

Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentration after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. More than 40% NSEs (new chemical entities) developed in pharmaceutical industry are

practically insoluble in water. These water insoluble drugs have slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is often important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist.

The improvement of drug solubility thereby its oral bioavailability remains one of the most challenging aspect of drug development process especially for oral drug delivery system. There are numerous approaches present and reported in literature to enhance the solubility of poorly water soluble drugs. The techniques are chosen on the basis of certain aspect such as properties of drug under consideration, nature of excipient to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous GI fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increase the bioavailability for BCS class II drugs.

Biopharmaceutical Classification System: The BCS categories drug molecule on the basic of their solubility and permeability. The BCS has gained much attention because of its potential to reduce the need for clinical studies. "If the ratio of the drug dose to the lowest drug saturation solubility in the pH range of 1-8 is greater than 250, then the drug is called as the poorly water soluble drug." BCS defines poorly water soluble drugs as the one which are not being soluble in ≤ 250 ml of aqueous media over pH range 1-7.

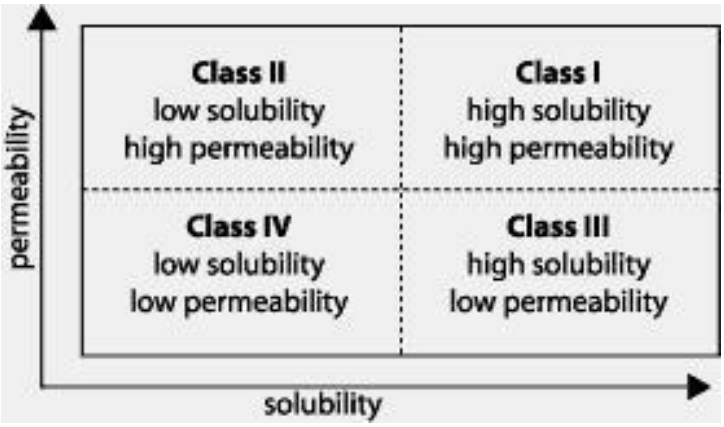


Fig. 1: Biopharmaceutical Classification System.

- **Descriptions of solubility**[16-18]

Table No. 1: Descriptions of Solubility.

Sr. No.	Descriptive term	Part of solvent required for part of solute
1	Very soluble	Less than 1
2	Freely soluble	1 to 10
3	Soluble	10 to 30
4	Sparingly soluble	30 to 100
5	Slightly soluble	100 to 1000
6	Very slightly soluble	1000 to 10000
7	Practically insoluble	More than 10000

 Mechanism Of Solubility:- The mechanism of solubility explain in 3 steps

1. Holes open in solvents.
2. Molecules of solid break away from the bulk.
3. The free solid molecules is integrated into the holes in solvent.

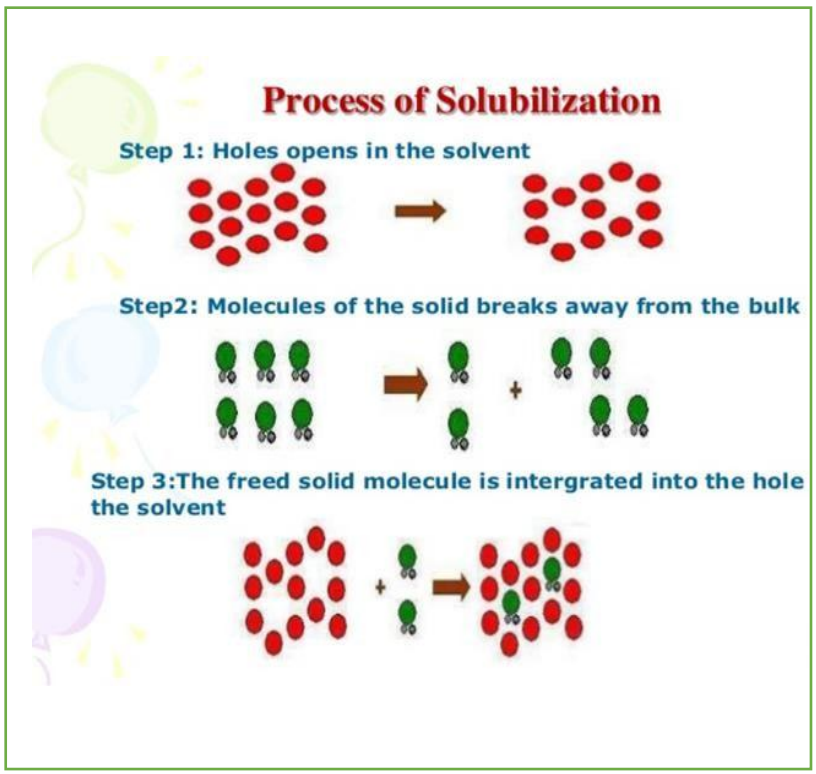


Fig. 2: Process Of Solubilization.

 Methods to measure the solubility[16-21]**:** To determine solubility of solids in liquids following two steps are used.

A. Preparation of saturated solution:

Solubility indicates the maximum amount of a substance that can be dissolved in a

solvent at a given temperature. Such a solution is called saturated. Solubility is measured rather in grams per 100 g of solvent (g/100g) or number of moles per 1 L of the solution.

B. Analysis of saturated solution:

Once the saturated solution is prepared its analysis is carried out to check the solubility. It depends upon the nature of the solute and accuracy of the method employed. Following methods are used for analysis.

a. Evaporation method
b. Volumetric method
c. Gravimetric method
d. Instrumental method.

Factors Affecting Solubility

✓ **Particle size-** The size of solid particle influences the solubility because as a particle become smaller, the surface area to volume ratio increases of the particle. The larger surface area allows a greater interaction with the solvent.

✓ **Polymorphism and amorphous:** Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility difference between different polymorphs is only 2-3 folds due to relatively small difference in free energy.

✓ **Hydrates/ solvates:** The stoichiometric type of adducts where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates. When the solvent in association with the drug is water, the solute is known as a hydrate. Generally the anhydrous form of drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal break-up in comparison to the anhydrous.

✓ **Temperature:** If the solution process absorbs energy then the temperature is increased as the solubility will be increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. For all gases, solubility decreases as the temperature of the solution increases.

✓ **Pressure:** For gaseous solutes, solubility is increases with the application of presser. For solids and liquid solutes, changes in pressure have nearly no effect on solubility.

✓ **Molecular size:** The larger the molecule or the higher its molecular weight the less soluble the substance.

- ✓ **Nature of solvent:** Solubility of a solute in a solvent purely depends on the nature of both solute and solvent. A polar solute dissolved in polar solvent. Solubility of a non- polar solvent is large. A polar solute has low solubility.

- **Methods To Over Come Poor Solubility**[22-40]

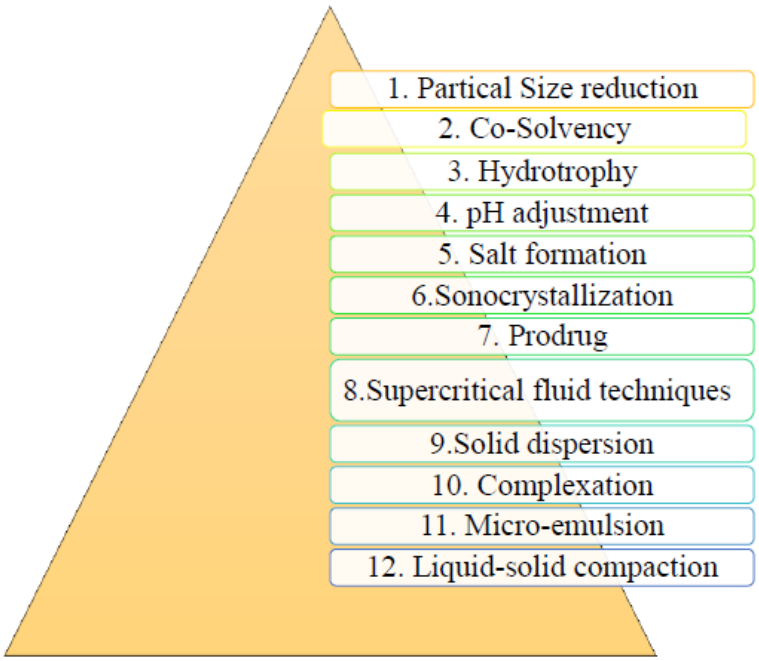


Fig.3: Methods To Over Come Poor Solubility.

1. Particle size reduction

The bioavailability intrinsically related to the drug particle size. By reduction in particle size, increased surface area improves the dissolution properties. It is done by milling techniques using jet mill, rotor stator colloid mills.

Particle size reduction can be achieved by;

i. **Micronization:** Micronization is a conventional technique that is used for reduction of particle size. This increases the dissolution rate of drugs by increased surface area but it does not increase equilibrium solubility. Decreasing the particle size of these drugs which cause increase in surface area, improves their rate of dissolution. Micronization of drugs is done by milling technique using jet mill, rotor stator colloidmills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

ii. **Nanonization:** The limitations of micronization can be overcome by another approach known as nanonization. Nanonization can result in improved drug solubility and

pharmacokinetics, and it might also decrease systemic side-effects. For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency to agglomerate, which leads to decrease in effective surface area for dissolution. There are different techniques used for nanonization of drug including wet milling, homogenization, emulsification, solvent evaporation technique, Pearl milling, spray drying etc.

iii. **Nano-suspension:** This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical Nano-suspension is biphasicsystems consisting of Nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in Nano-suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm.

2. **Co-solvency:** The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known asco-solvency and the solvent used in combination are known as co-solvent. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water.

3. **Hydro-trophy:** Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueoussolubility's of many poorly water-soluble drugs.

4. **pH adjustment:** Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.

5. **Salt formation:** Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salt of week acid dissolve more rapidly than that of

pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, patient compliance and commercilation.

6. **Sono-crystallization:** The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. It enhances solubility and dissolution of hydrophobic drugs and also used to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using liquid solvents and anti-solvent has also been employed successfully to reduce particle size.

7. **Pro-drug:** A pro-drug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound. Chemical modification of a drug via the attachment of pro-moiety generates the pro-drug. The properties of pro-drug enable it to cross the limiting barrier and is designed ideally to be cleaved efficiently by enzymatic or non-enzymatic processes. This is followed by the rapid elimination of released pro-moiety Pro-drug formation.

Classification of pro-drug

i. Carrier linked pro-drug
ii. Bipartite pro-drug
iii. Tripartite pro-drug
iv. Mutual pro-drugs

8. **Super critical fluid technology:** Those fluids are referred to as supercritical fluids which are having temperature and pressure greater than its critical temperature and critical pressure so as they are acquire properties of both gas and liquid. The best example of this is carbon dioxide. SCF are highly compressible at critical temperatures and allows alteration in density and mass transport characteristics which determines its solvent power due to moderate changes in pressure. As the drug gets solubilized within SCF they can be recrystallized with reduced particle size of drug.

9. **Solid dispersion**

9.1. Fusion method: Accurately weighed amounts of carrier(s) are placed in an aluminum

pan on a hot plate and liquefy, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of active drug is incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture is heated until a clear homogeneous melt is obtained. The pan is then removed from the hot plate and allowed to cool at room temperature.

9.2. Solvent evaporation method: Accurately weighed amounts of active drug and carrier(s) are dissolved in minimum quantities of chloroform in a round-bottom flask. The solvent is removed using a rotary evaporator. The obtained solid dispersion is transferred on to the aluminum pan and allowed to dry at room temperature.

9.3. Fusion solvent method: Accurately weighed amounts of carrier(s) are placed in an aluminum pan on a hot plate and liquefy, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of active drug is incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture is heated until a clear homogeneous melt is obtained. The pan is then removed from the hot plate and allowed to cool at room temperature.

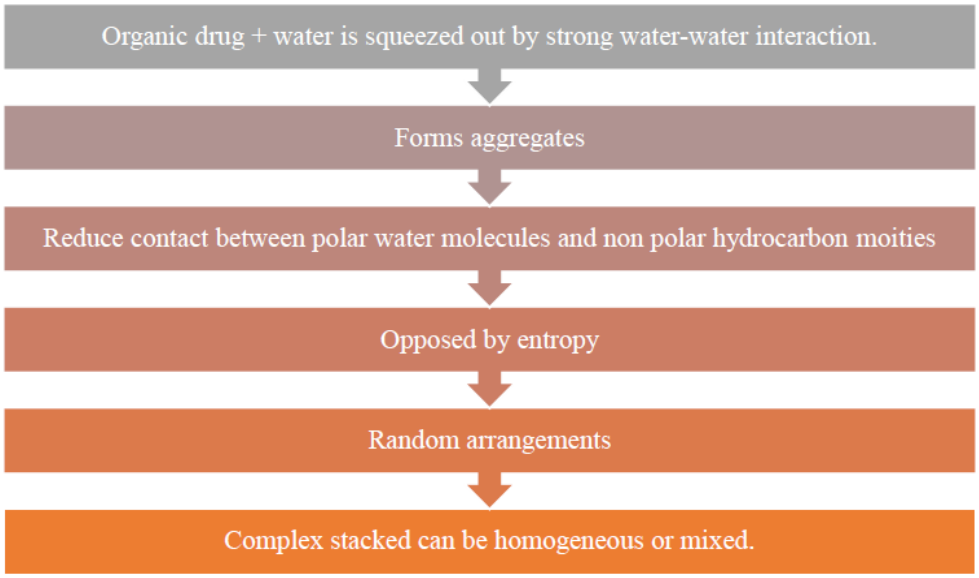
9.4. Hot melt extrusion: Hot-melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. High-shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. This technique offers the possibility of continuous production, which makes it suitable for large-scale production. the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

9.5. Lyophilization: Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophillization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

9.6. Spray Drying: Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation. Spray drying usually yields drugs in the amorphous state, but sometimes the drugmay be partially crystallized during processing.

10. Complexation

I. Self-association and stacking method



II. Solid inclusion

10.1. Physical mixture: Active drug with suitable polymer in different ratios mixed in a mortar for about one hour with constant trituration. The mixture is passed through sieve no. 80 and stored in desiccator over fused calcium chloride.

10.2. Kneading method: In this technique, cyclodextrin (CD) is added with water and converted to paste. Drug is then added and kneaded for specified time. The kneaded mixture is then dried and passed through sieve if required.

10.3. Co-precipitation method: The required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

10.4. Neutralization: Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β-CD is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is the filtered and dried.

10.5. Co-grinding: Drug and cyclodextrin are mixed and physical mixture is introduced in a

suitable mill like oscillatory mill and grinded for suitable time.

10.6. Spray drying: Drug is dissolved in suitable solvent and required stoichiometric amount of carrier material like β-CD 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.

10.7. Microwave irradiation method: Drug and cyclodextrin mixture is reacted in microwave oven to form inclusion. It is novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product.

11. Micro-emulsion: A micro-emulsion is a four-component system composed of external phase, internal phase, surfactant and co-surfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the co-surfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as micro- emulsion. The surfactant and the co-surfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the micro-emulsions.

12. Liquid-solid compaction: Liquid-solid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

CONCLUSION

From this article we conclude that , the solubility of the drug is the most important factor. This consider during the therapeutic efficacy of the drug , while dissolution of the drug is the rate determining step for the oral absorption of the poorly water soluble drugs and the solubility is also the basic requirement for the formulation and design of different dosages forms. There are many techniques used to enhanced the solubility. Because the solubility factor affects on drug bioavailability. Hence today solubility enhancement becomes a new challenge. Now it is possible with the help of various advanced techniques as mentioned above.

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