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**RESEARCH ARTICLE**

# IMPORTANCE OF SOLUBILITY AND SOLUBILITY ENHANCEMENT TECHNIQUES

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## ABSTRACT

For a drug to elicit its pharmacological action it should be absorbed from the site of administration. The solubility and Dissolution of drug in GI fluid is the rate determining step in absorption of drug. More than 40% of drug developed by pharmaceutical industry are practically insoluble in water and therefore Enhancement of solubility of practically insoluble drug was the most challenging aspect of drug development. There are various technique available for increasing the solubility of the drug. The technique include physical and chemical modification of drug. This review aimed to compile the information on various solubility enhancement techniques and arrange them in a systematic manner to use as ready reference.

## INTRODUCTION

Solubility is define as the maximum amount of solute dissolve in the given amount of solvent or the concentration of solute in saturated solution at a certain temperature, pressure or presence of certain chemical (5).

**Table 1: Solubility criteria as per I.P., 1985, B.P. 2010**

| Descriptive Term | Solvent required for 1 part 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 30 to 1000 |
| Very slightly soluble | From 1000 to 10000 |
| Practically insoluble | Above 10,000 |

### Biopharmaceutical Classification System (BCS)

According to BCS, drug solubility are divided into four type:

Class 1: High soluble High permeable

Class 2: High soluble Low permeable

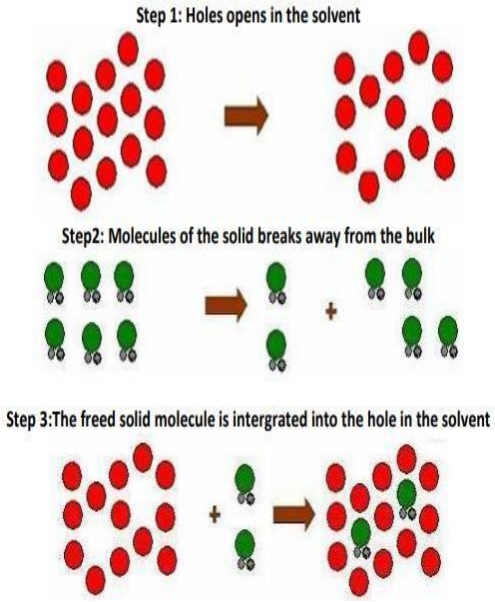
Class3: Low soluble High permeable

Class 4: Low soluble Low permeable (6).

### PROCESS OF SOLUBILISATION

The Solubilization involve breaking of inter ionic or intermolecular bond in the solute, separation of molecule of solvent provide space in the solvent for solute between solute and solvent.

Fig. 1: Process of Solubilization




### Factor Affecting the Solubility

A) Temperature

Solubility affected by temperature, increase in the temperature leads to increase in the solubility of the temperature while decreasing the temperature leads to decrease in the solubility.

B) Crystal characteristics

Many drugs exhibit polymorphism (different crystalline form of same substance), in the polymorphic form poses different lattice energies this difference reflect by the change in properties such as solubility and melting point.

The drug are present in amorphous form or the crystal form, the amorphous substance are more soluble than that of the crystal form

C) Molecular structure of solute

The solubility is depend on the nature of the solute molecule, the small change in the structure of solute (compound) change the solubility of the compound.

D) Polarity and Nature of solvent

Polarity of solvent and solute molecule affect the solubility of the compound the non-polar solute dissolve in the non-polar solvent while polar solvent dissolve in polar solvent

E) Particle size

The particle size of the compound affect the solubility, the smaller size particle are highly soluble due to presence of larger surface area, while larger size particle have low surface area so that the solubility of the compound will be less.

F) pH the pH affect the solubility of the compound, the solubility of unionized species is less than that of the ionized solute.

G) Dielectric Constant

The dielectric constant affect the solubility, the solubility is the function of the dielectric constant of polar and non-polar molecule.

**Importance of Solubility Enhancement**

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. Solubility is one of the important parameters to achieve preferred concentration of drug in systemic circulation for achieving required pharmacological response Hydrophobic drugs frequently require high doses and need high dosage regimens to influence therapeutic plasma concentrations after administration Low aqueous solubility is the main problem encountered with preparation and development of NCEs as well as for generic drugs For orally administered drugs solubility is the one of the important rate limiting parameters to reach their desired concentration in complete circulation for pharmacological response.

Water is the solvent of excellent for liquid pharmaceutical formulations Most of the drugs like weakly acidic or weakly basic having poor aqueous solubility Poorly water-soluble drugs having slow drug absorption leads to insufficient and gastrointestinal mucosal toxicity and variable bioavailability. (9)

Techniques for Solubility Enhancement:

Solubility Enhancement technique are categorized under physical modification and

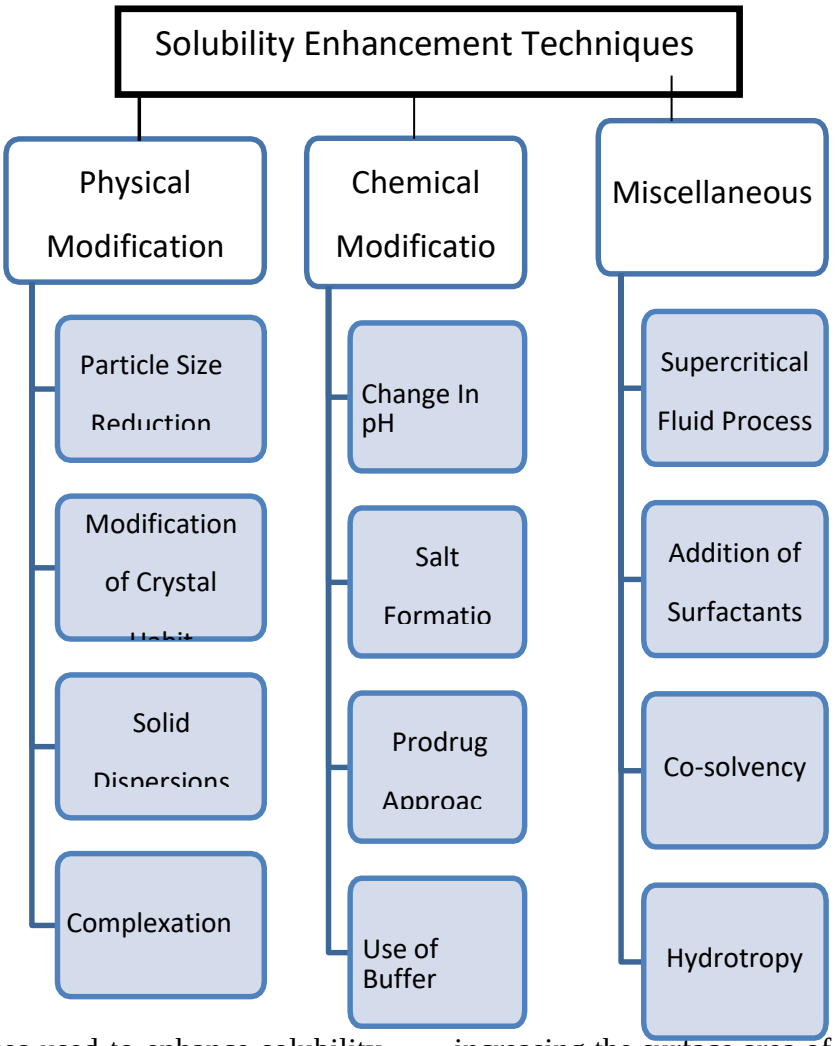



Fig. 2 Techniques used to enhance solubility of poorly soluble drugs

Chemical modification which are given bellow.

1) Physical Modification

The physical modifications of drug product such as reduction of particle size and modifying crystal habit are common approaches for increasing the solubility of drug.

1) Particle Size Reduction:

The reduction of the particle size will leads to increasing the surface area of the molecule so that the particle can be easily soluble in the solvent because there is larger solute solvent interaction. Particle size reduction is done by micro-ionization or Nano suspension. Micro-ionization (Limbachiya et al., 2011).

Micro-ionization increases dissolution rate of drug through increased surface area; it does not increase equilibrium solubility. Micro-ionization of drugs is done by milling

techniques using jet mill, rotor stator, colloidal mill etc. Micro-ionization not suitable for drugs having a high dose number because it does not change the saturation solubility of drug (12)

**Table 2 particle technologies for improvement of solubility of some drug**

| Particle Technologies | Method | Example Drugs |
|---|---|---|
| Mechanical Micronization | Jet milling Ball milling | Cilostazol , Ibuprofen Danazol, CarbamazepineDipyridamole, Indomethacin |
| Particle size reduction by novel engineering | Cryogenic spraying process | Danazol,carbamazepine,Glibenclamide |
| Complexation with cyclodextrins | Freeze drying, vacuum evaporation, kneading | Celecoib, Clotrimazole, Bifonazole |
| Polymeric micelles | Dialysis, freeze drying | Paclitaxel, Etoposide, Ecetaxel , Amphotericin-B |

2) Nano-suspension

Nano-suspension are submicron colloidal dispersions of pure particles of drug which are stabilized by surfactants. 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. Various particle technologies, from conventional size reduction methods to recent novel methods that can be used for formulating drugs with poor aqueous solubility as mentioned in Table 2.

**Other technique involves**

The spraying of drug solution in volatile organic solvent, rapid solvent evaporation result in precipitation of drug in presence of surfactant. Drying of Nano-suspension done by Lyophilization and spray drying.

**Homogenization**

The drug particle are reduce under high pressure and high velocity by applying the shear force. In these phenomenon drug particle get disperse, Homogenization depend on the pressure and nature of the drug.

There are three type of homogenizer are use in Pharmaceutical and biotechnology industry these are as follows

1: Conventional Homogenizer

2: Sonicator

3: High shear fluid homogenizer (13).

**Modification of Crystal Habit or Crystal Engineering**

The surface area of drug available for dissolution was depend on particle size and ability to wetted by liminal fluid. This particle size was critical to drug dissolution rate and depend on the condition of crystallization or an method of communication which done by impact milling or fluid energy milling the particle produce by communication technique are

highly charged, non-uniform and can produce agglomerates hence crystal engineering technique was developed for the control crystallization of drug to produce high purity well defined particle size distribution (16).

**Pharmaceutical Co-Crystals**

A Co-Crystal is defined as a crystalline compound that consist of two or more molecular species held together by non-covalent bond. Only three Co-crystalizing agents are considered as safe. Saccharin, Nicotinamide and Acetic Acid (16). Example: Carbamazepine saccharin co-crystal are superior to crystal forms of carbamazepine alone in terms of stability, dissolution, suspension stability and oral absorption profile.

**Solid Dispersions**

The Solid Dispersion (SD) Technology is the science of dispersing one or more active ingredients in an inert matrix. The solid dispersions was first described by sekiguchi and obi in 1961 in which they used concept of eutectic mixtures. It refers to a group of a solid products consisting of at least two components, a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous basically amorphous is having good solubility than crystalline substance because no energy is required to break up the crystal lattice of a drug during dissolution process. Drug solubility and wet ability may be increased by surrounding hydrophilic carriers (17).

**Types of Solid Dispersions**

Based on their molecular arrangement four different types of solid dispersions can be distinguished.

1. Eutectics
2. Amorphous precipitations in crystalline matrix
3. Solid solutions
4. Continuous solid solutions
5. Discontinuous solid solutions
6. Substitution solid solutions
7. Interstitial solid solutions
8. Glass suspensions and solutions

**Eutectic Mixtures**

The Eutectic mixture are form by the drug and polymer which is miscible in the molten state, but on cooling they crystallize into two distinct component with negligible miscibility.

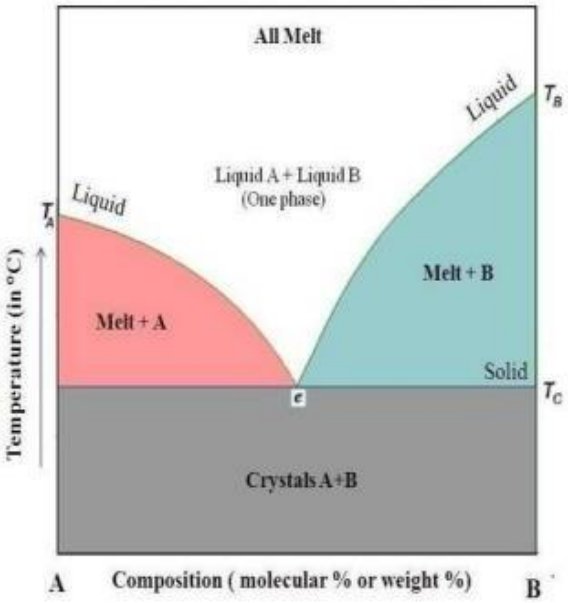



Fig.2. Eutectic Mixture

**Amorphous precipitation in crystalline matrix**

In these type amorphous solvent and solute molecule are dispersed irregularly. In earlier studies urea and sucrose are Use as a carrier but now a Days cellulose derivative and organic polymer (PVP, PEG) are used.

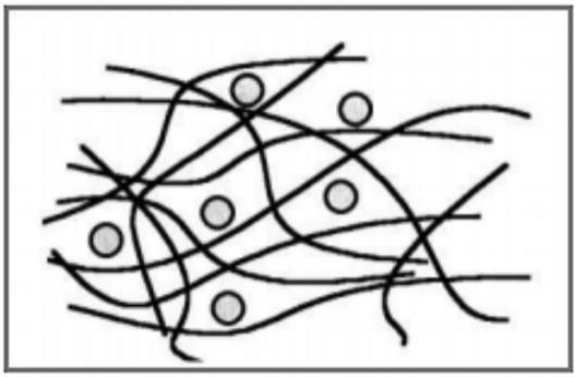


Fig.3. Amorphous precipitation in crystalline matrix

**Solid solutions**

In solid solution the two component are crystalized together in a homogenized one phase system. The particle size in the solid solution was reduced to a molecular size so that the solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture.

**Continuous solid solutions**

In the continuous solid solution the component are miscible in all proportion so that the bonding strength between two components is stronger than individual component.

**Discontinuous solid solutions**

In the discontinuous solid solution the stability of the component is limited in nature.

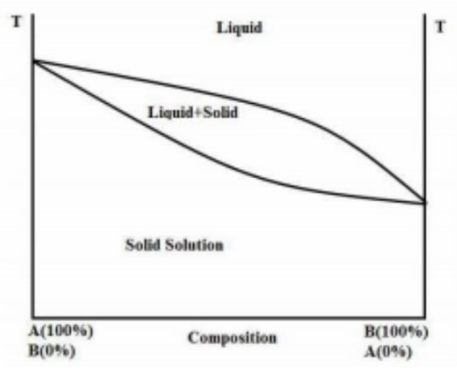



Fig.4. Continuous solid solutions phase diagram

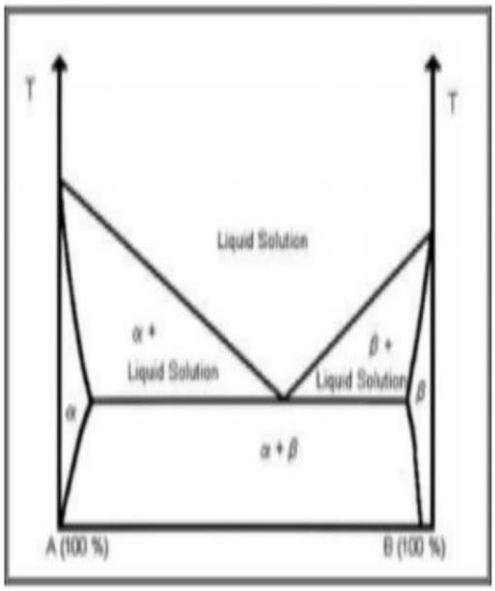



Fig.5. Discontinuous solid solutions phase diagram

**Substitution solid solutions**

In the substitution solid solution the solvent molecule are in the crystal lattice of the solid solvent molecule are substituted by solid molecule.

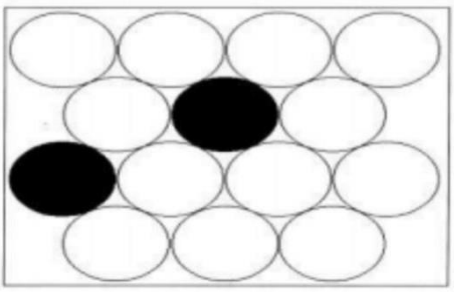


Fig.6. Substitution solid solutions

**Interstitial solid solutions**

In the interstitial solid solution the dissolved molecule are occupied the interstitial spaces between the solvent molecule.

4 Glass Solutions and Glass Suspensions

In these system solute dissolve in glassy solvent, the term glass can be used to described the pure chemical or mixture of the pure chemical in vitreous state [19]

**ADVANTAGES** (8)

The promising results of solid dispersion in solubility and dissolution rate enhancement of poorly soluble drugs can be attributed to various aspects: Uniform distribution of drug molecules in to carriers is achieved by solid dispersion method. It increases the wet ability of drug molecules which improve the solubility of drugs. Many carriers used in solid dispersion method like urea, colic acid, cellulose and bile salt create the surface activity.

Carriers of solid dispersion have high porosity which improves the solubility by faster release of drug.

**Carriers used in solid Dispersion**

The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidine (Povidone, PVP), Polyethylene glycols (PEG's), Plasdone-S630. Surfactants Tween-80, dosusate sodium, Myrj-52, Pluronic-F68 and sodium lauryl sulphate (SLS) (8).

**Complexation**

Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the non-polar molecule or the non-polar region of one molecule (Known as guest) into the cavity of another molecule or group of molecules (Known as Host) (19).

The most commonly used host molecules are cyclodextrin. The enzymatic degradation of starch by cyclodextrin glycol-syltransferase (CGT) produces cyclic oligomers, cyclodextrin (CD's). These are non-reducing crystalline water soluble and cyclic oligo-saccharide consisting of glucose monomers arranged in a donut shape having hydrophobic cavity and hydrophilic outer surface.

Three naturally occurring CD's are alfa cyclodextrin, Beta-cyclodextrin and gama-cyclodextrin (19). The surface of the cyclodextrin molecules makes them water soluble, nut the hydrophobic cavity provides a micro environment for appropriately sized non-polar molecules based on the structure

and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex (19).

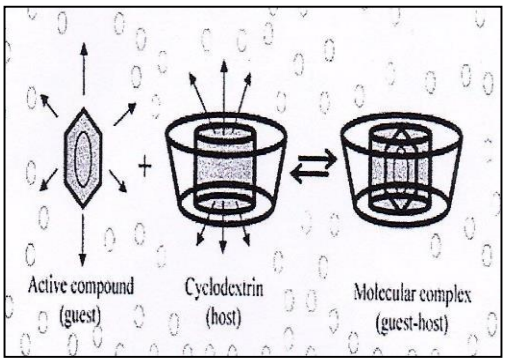



Fig. 7. Schematic representation of an inclusion complex formation (18).

(White dots represent water molecules. In an aqueous cyclodextrin solution, the hydrophobic compound would migrate to the hydrophobic cyclodextrin cavity)

Chemical Modifications:

Change in pH

The absorption of drug is largely dependent upon diffusion, which varies with pH of the individual regions within the gastro intestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization (17). Poorly water soluble drugs with the parts of the molecule that can be protonated (Base) or deprotonated (Acid) may potentially be dissolved in water by applying a pH change pH adjustment can in principle be used for both oral and parenteral Administration (17). Ionised form of drug is responsible for solubility in water. Since, most drugs are weak Electrolytes their degree of ionization depends upon the pH of the biological fluid. Relation between pH and degree of ionization.

For weak acidic drugs

Low pH Unionized » Insoluble/precipitate »

High pH Ionized » more soluble form »

For weak basic drugs:

Low pH Ionized » More soluble form »

High pH Unionized » Insoluble/precipitate »

Henderson-Hassel Bach equation is used to determine solubility of particular drug at given pH. Henderson-Hassel Bach Eq : (3).

% ionized = 100 1 + antilog (pH-pKa)

**Salt Formation**

Salts have improved solubility and dissolution characteristics in comparison to original drug. The minimum three unit difference between pKa value of the group and that of its counter ions required to form stable salt. Alkali metals salt of acidic drug like penicillin and strong acid salt of basic drug like atropine are more stable than parent Drug (18).

**Pro-Drug Approach**

Salt information is limited to molecules with ionisable groups, however pro drugs may be formed with any organic molecule having a chemically reactive functional group, Pro-drugs are synthetic derivatives (e.g. Esters

and amide) of the drug molecule that may have intrinsic pharmacological activity but usually must undergo some transformation In-vivo to liberate the active drug molecule. Through the formation of pro drug, a variety of side chains or functional groups may be added to improve the biological or pharmaceutical properties of compound (12). In 1980, Amidon suggested that the preparation of water soluble pro-drugs by the addition of specific amino acids are the substrates for enzymes located in intestinal brush border Using the lysine ester prodrug of estrone, a potential increase in absorption rate was found in vivo using perfused rat intestines (19).

**Miscellaneous: Supercritical Fluid Process**

The number of application and technologies involve in the super critical fluids extraction. 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 is safe, environment friendly and economical. The low operating conditions (Temperature and Pressure) make SCFs attractive for pharmaceutical research (19). Supercritical fluids (e.g. Carbon Dioxide) are fluids whose temperature and pressure are greater than its critical temperature and Critical Pressure, allowing it to assume the properties of both 0 liquids and a gas (5). Once the drug particles are solubilized within SCF, they may be re-crystallized at greatly reduced particle sizes. The flexibility and precision offered by SCFs Processes allows Micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. The flexibility and precision offered by SCF processes allows Micronization of drug particles within narrow ranges of particle size, often to sub-micron levels.

**Addition of surfactants**

Surfactants are the surface active agents commonly used to solubilize poorly water-soluble drugs by improving wetting and stabilization of formulations. Self-association of surfactant molecules in aqueous medium facilitates the formation of micelles. These micelles enhance the aqueous solubility of lipophilic poorly water soluble drugs via hydrophobic micelle core and interaction with head group with incorporation into the water micelle core and interaction with head group with incorporation into the water micelle interface (15).

**Co-solvency**

In this technique, water miscible organic solvent of low polarity is used to solubilize drug and the phenomenon is known as co-solvency (15). Co-solvents are mixtures of

water and one or more water miscible solvents used to create a solution with enhance solubility for poorly soluble compounds (17). Co-solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending (11) Choice of biocompatible solvents are limited such as to glycerin, propylene glycol, diethyl- sulfoxide, ethanol and N, N dimethyl formamide etc. (5)

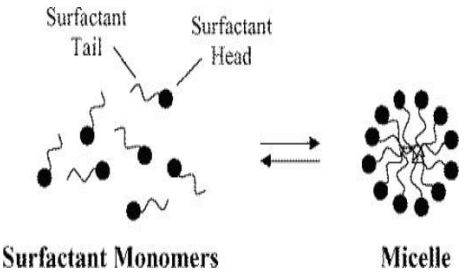



Fig. 8. Addition of surfactants

**Hydrotropy**

Hydrotropy is a Solubilization process whereby addition of a large amount of second solute results in a increase in the aqueous solubility of another solute (14) Concentrated aqueous hydrotropic solution 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. A wide variety of compounds have been reported to exhibit hydrotropic behavior. Specific example may include ethanol aromatic alcohols like resorcinol, pyrogallol, catechol, a- and b-naphtha's and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like Diacids, SDS (sodium dodecyl sulphate) and dodecyl atedoxidibenzene (5). Drug showing enhancement of solubility: Saquinavir in hydrotropic solutions showed 473- fold solubility enhancements with ascorbic acid, 462- fold with Nicotinamide, 49-fold with resorcinol and 52- fold with dimethyl urea (20).

**Advantages of hydrotropic Solubilization Technique (7):**

Hydrotropy is suggested to be superior to other Solubilization method, such as miscibility, micellar Solubilization, co solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.

It only requires missing the drug with the hydrotrope in water. It does not require chemical modification of hydro phobic drug, use of organic solvents, or preparation of emulsion system. Nanotechnology in pharmaceuticals Nanotechnology techniques have been emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water and decrease systemic side-effects.

Nanonization broadly refers to the study and use of materials and structures at the Nano scale level of approximately 100 nm or less. It is alternate to Micronization because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution. There are different techniques used for nanonization of drug including wet milling, homogenization, emulsification solvent evaporation technique, pear milling, and spray drying.

**Drug Nano crystal**

Drug Nano crystals are nanoscopic crystals of parent compounds with the dimension of They are composed of 100% drug without carriers and typically stabilized with surfactants or polymeric steric stabilizers. A dispersion of drug non-crystals in an outer liquid medium and stabilized by surface active agents is so-called Nano suspensions.

The dispersion medium can be water, aqueous, or non-aqueous media, e.g. liquid PEG and oils. The Nano suspensions can be used to formulate compounds that are insoluble in both water and oil and to reformulate existing drugs to remove toxicologically less favorable excipients (20)

**Nano morphs**

Nano morph technology converts drug substances with low water solubility from a coarse crystalline state into amorphous nanoparticles to enhance their dissolution. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately, the drug substance suspension is converted into a true molecular solution.

The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their Nano particulate state and prevents them from aggregation or growth. Water-redispersible dry powders can be obtained from the nanosized dispersion rather than by conventional methods (e.g., spray drying) (21)

## CONCLUSION

Solubility if drug is one of the important factors that governs the formulation development particularly for the rate and extent of drug to be absorbed. The Techniques discussed above are capable of improving the solubility of drug. These techniques along or in combination can be used to enhance the solubility of drug and thereby bioavailability. Proper selection of solubility enhancement method is the key to ensure the goals of good formulation.

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