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Review Article

AN OVERVIEW ON VARIOUS APPROACHES USED FOR SOLUBILIZATION OF POORLY SOLUBLE DRUGS

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ABSTRACT

The aim of this review is to improve the solubilization of poorly soluble drugs by using various approaches. The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. In the other words the solubility can also define as the ability of one substance to form a solution with another substance Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown and dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules Currently only 8% of new drug candidates have both high solubility and permeability. The mechanism of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system. Various techniques available to improve the solubility of poorly soluble drugs by physical and chemical modifications.

Key words: Solubility, dissolution, therapeutic effectiveness, solubilization techniques.

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1.0 INTRODUCTION

Therapeutic effectiveness of a drug depends upon the 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 for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability [1].

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature [2]. In the other words the solubility can also define as the ability of one substance to form a solution with another substance [Adam]. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution, or hydration if the solvent is water [4].

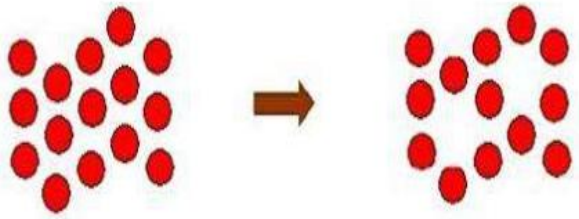
SOLUBILITY DEFINITIONS[5] :

Definition	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

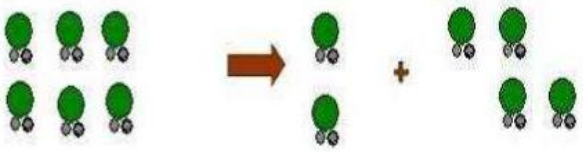
2.0 PROCESS OF SOLUBILISATION[3] :

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

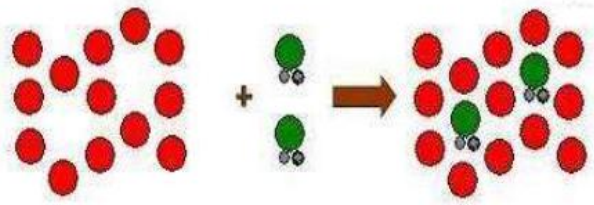
Step 1: Holes opens in the solvent



Step2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is intergrated into the hole in the solvent



2.1 FACTORS AFFECTING SOLUBILITY:

The solubility depends on the physical form of the solid, the nature and composition of solvent

medium as well as temperature and pressure of system [6].

2.1.1 Particle Size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by[3].

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

Sis the solubility of infinitely large particles

Sis the solubility of fine particles

V is molar volume

g is the surface tension of the solid

r is the radius of the fine particle

2.1.2 Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature [7]. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

2.1.3 Pressure

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

2.1.4 Nature of the solute and solvent

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their natures.

2.1.5 Molecular size

Molecular size will affect the solubility. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent [7].

2.1.6 Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar

solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules[7].

2.1.7 Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only

2-3 folds due to relatively small differences in free energy [8].

2.2 TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are [9]:

I. Physical Modifications

A. Particle size reduction
a. Micronization
b. Nanosuspension
B. Modification of the crystal habit
a. Polymorphs
b. Pseudopolymorphs
C. Drug dispersion in carriers
a. Eutectic mixtures
b. Solid dispersions
c. Solid solutions
D. Complexation
a. Use of complexing agents
E. Solubilization by surfactants:
a. Microemulsions
b. Self microemulsifying drug delivery systems

II. Chemical Modifications

I. Physical Modifications:

A. Particle size reduction:

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

a. Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution [10].

Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility [11]. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

b. Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants [12]. 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 fact

Techniques for the production of nanosuspensions[13] :

a) Homogenization:

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles.

Three types of homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors [13].

b) Wet milling:

Active drug in the presence of surfactant is defragmented by milling.

Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants.

The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form,

which may not be therapeutically active one[14]. Drying of nanosuspensions can be done by lyophilisation or spray drying.

B. Modification of the crystal habit:

Polymorphism is the ability of an element or compound to crystallize in more then one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area.

Generally, the anhydrous form of a 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 breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates.

Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is

Amorphous >Metastable polymorph >Stable polymorph

Melting followed by a rapid cooling or recrystallization from different solvents can be produce metastable forms of a drug.

C. Drug dispersion in carriers:

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961[16]. 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[17]. Novel additional preparation techniques have included rapid precipitation by freeze drying[18] and using supercritical fluids[19] and spray drying [20], often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion [21]. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone[22], [23], polyethylene glycols[Doshi DH,] Plasdone-S630 [24]. Many times surfactants may also used in the

formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used [25].

The solubility of etoposide [26], glyburide [27], itraconazole [28], ampelopsin [29], valdecoxib[30], celecoxib[31], halofantrine [32] can be improved by solid dispersion using suitable hydrophilic carriers.

The eutectic combination of chloramphenicol/urea[33] and sulphathiazole/ urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

1. Hot Melt method

Sekiguchi and Obi 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. 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.

2. Solvent Evaporation Method

Tachibana and Nakumara[34] were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying[36] or by freeze-drying [37] . Temperatures used for solvent evaporation generally lie in the range 23-65 C [38, 39] .

The solid dispersion of the 5-lipoxygenase/cyclooxygenase inhibitor ER-34122 shown improved in vitro dissolution rate compared to the crystalline drug substance which was prepared by solvent evaporation [40] . These techniques have problems such as negative effects of the solvents on the environment and high cost of production due to extra facility for removal of solvents [41] . Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions[42] .

3. Hot-melt Extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971 [43].

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 excipient[44] . The process has been useful in the preparation of solid dispersions in a single step.

4. Melting –solvent method

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

Carriers for Solid Dispersions

S. No.	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, Cyclodextrins, Galactomannan
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamine E TPGS NF
5	Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthines

D. Complexation:

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as london forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and a partial list can be found in below table.

List of Complexing Agents

S.No.	Types	Examples
1	Inorganic	I_B^-
2	Coordination	Hexamine cobalt(III) chloride
3	Chelates	EDTA, EGTA
4	Metal-Olefin	Ferrocene
5	Inclusion	Cyclodextrins, Choleic acid
6	Molecular Complexes	Polymers

a. Staching complexation

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation. Some compounds that are known to form staching complexes are as follows:

Nicotinamide [45], Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene etc.

Higuchi and Kristiansen [46] proposed a model according to which the compounds capable of undergoing stacking can be classified into two classes (classes A and B) based on their structure. The compounds in class A have higher affinity for compounds in class B than for those in class A and vice versa[47].

b. Inclusion complexation

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced.

The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility[48]. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule.

Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules.

The kinetics of cyclodextrin inclusion complexation has been usually analyzed in terms of a one-step reaction or a consecutive two-step reaction involving intracomplex structural transformation as a second step. Cyclodextrins is to enhance aqueous solubility of drugs through inclusion complexation. It was found that cyclodextrins increased the paclitaxel solubility by 950 fold [49]. Complex formation of rofecoxib[50], celecoxib[51], clofibrate [52], melarsoprol [53], taxol [54], cyclosporin [55] etc. with cyclodextrins improves the solubility of particular drugs.

c. Factors affecting complexation [56]:

1. Steric effects
2. Electronic effects

a. Effect of proximity of charge to CD cavity

b. Effect of charge density

c. Effect of charge state of CD and drug

3. Temperature, additives and cosolvent effects

E. Solubilization by surfactants:

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic [57]. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent.

Microemulsion

The term microemulsion was first used by Jack H. Shulman in 1959. A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions [58]. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages of microemulsion over coarse emulsion include its ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability [59, 60], and less inter- and intra-individual variability in drug pharmacokinetics.

II. Chemical Modifications:-

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant (a ratio of the capacitance of one material to a reference standard)[61] of the solvent by the use of co-solvents rather than the pH of the solvent.

The use of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs [62]. An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates).

Other techniques:

1. Co-crystallisation:

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystals, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex. A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces.

Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystallisation between two active pharmaceutical ingredients has also been reported. This may require the use of subtherapeutic amounts of drug substances such as aspirin or acetaminophen. At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals [63]. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation. The

formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups.

2. Cosolvency:

The solubilisation of drugs in co-solvents is another technique for improving the solubility of poorly soluble drug. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs [64].

Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending [65].

Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, cosolvents reduce waters ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization. Solubility enhancement as high as 500-fold is achieved using 20% 2-pyrrolidone.

3. Hydrotrophy:

Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute [66].

Example: Solubilisation of Theophylline with sodium acetate and sodium alginate

4. Solubilizing agents:

The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine[67]. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide.

5. Nanotechnology approaches:

Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale

level of approximately 100 nanometers (nm) or less [68]. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution [69] and the next step taken was Nanonisation[69].

Nanocrystal

A nanocrystal is a crystalline material with dimensions measured in nanometers; 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.

There are two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development [70]. The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo-vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

a) Milling:

Nanoscale particles can be produced by wet-milling process [71]. In ball mills, particle size reduction is achieved by using both impact and attrition forces. The most common models are a tumbling ball mill and a stirred media mill. One problem of this method is the degradation of mill surfaces and subsequent suspension contamination.

b) High pressure homogenization:

In high pressure homogenization, an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Homogenisation can be performed in water (DissoCubes) or alternatively in non-aqueous media or water-reduced media (Nanopure). The particles are disintegrated by cavitation and shear forces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves which make the crystals collide, leading to particle disintegration. A heat exchanger should be used when operating on temperature sensitive materials because high pressure homogenization causes increase in the sample temperature [Hecq J]. The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles.

c) Precipitation:

In the precipitation method a dilute solution is first produced by dissolving the substance in a solvent where its dissolution is good [73]. The

solution with the drug is then injected into water, which acts as a bad solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nanocrystals. Nanocrystals can be removed from the solution by filtering and then dried in air.

d) Cryo-vacuum method:

In the cryo-vacuum method the active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution [74]. The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 °C). Rapid cooling causes a very fast rise in the degree of saturation based on the decrease of solubility and development of ice crystals when the temperature drops below 0 °C. This leads to a fast nucleation of the dissolved substance at the edges of the ice crystals. The solvent must be completely frozen before the vessel is removed from the liquid nitrogen. Next the solvent is removed by sublimation in a lyophilization chamber where the temperature is kept at constant -22 °C and the pressure is lowered to 10^{-2} mbar. Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of the particles produced, so they will remain crystalline. The method yields very pure nanocrystals since there is no need to use surfactants or harmful reagents.

NanoMorph

The NanoMorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles. 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 nanoparticulate state and prevents them from aggregation or growth. Water redispersable dry powders can be obtained from the nanosized dispersion by conventional methods, e.g. spray-drying.

Using this technology the coarse crystalline drug substances are transformed into a nanodispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles[75] .

Nanotechnology approaches to improve the solubility of hydrophobic drugs [75]

Company	Nanoparticulate Technologies	Description
Elan	NanoCrystal	NanoCrystal drug particles (<1,000 nm) produced by wet-milling and stabilised against agglomeration through surface adsorption of stabilisers; applied to NMEs egaprepitant/reformulation of existing drugs eg. sirolimus
Eurand	Biorise	Nanocrystals/amorphous drug produced by physical breakdown of the crystal lattice and stabilised with biocompatible carriers (swellable microparticles or cyclodextrins)
SkyePharma	IDD	Insoluble Drug Delivery: micro-nm particulate/droplet water-insoluble drug core stabilised by phospholipids; formulations are produced by high shear, cavitation or impaction
BioSante	CAP	Calcium Phosphate-based nanoparticles: for improved oral bioavailability of hormones/proteins such as insulin; also as vaccine adjuvant
American Bioscience	NAB	Nanoparticle Albumin-Bound technology: injectable suspension of biocompatible protein with drug improves solubility/removes need for toxic solvents; eg paclitaxel-albumin nanoparticles
		Nanoparticle Albumin-Bound technology: injectable suspension of biocompatible protein with drug improves solubility/removes need for toxic solvents; eg paclitaxel-albumin nanoparticles
Baxter	Nanoedge	Nanoedge technology: drug particle size reduction to nanorange by platforms including direct homogenisation, microprecipitation, lipid emulsions and other dispersed-phase technology
Company	**Nanostructuring Technologies**	**Description**
pSivida	BioSilicon	Drug particles are structured within the nano-width pores of biocompatible BioSilicon microparticles, membranes or fibres; gives controlled release/improves solubility of hydrophobic drugs
iMEDD	NanoGate	Silicon membrane with nano-width pores (10-100 nm) used as part of an implantable system for drug delivery and biofiltration
PharmaSol	NLC8	Nanostructured Lipid Carriers: nanostructured lipid particle dispersions with solid contents produced by high-pressure homogenisation; lipid-drug conjugate nanoparticles provide high-loading capacity for hydrophilic drugs for oral delivery

Conclusion:

A drug administered in solution form immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

REFERENCES:

1. Improving solubility & permeability in drug candidates. Conference: 23rd & 24th June 2005,Pre-conference workshop: 22nd June 2005, Thistle Marble Arch, London, UK
2. Solubility.http://www.sciencebyjones.com/Teaching%20Menu.htm
3. Adam M. Persky and Jeffrey A. Hughes, Solutions and Solubility. http://www.cop.ufl.edu/safezone/prokai/pha5100/pha5110.htm
4. Solubility, From Wikipedia, the free encyclopedia. Retrieved from http://en.wikipedia.org/wiki/Solubility
5. Indian Pharmacopoeia, Ministry of Health and family welfare, Government of India, Published by the controller of publications, Delhi, 1996, 1, 7.
6. James K., "Solubility and related properties", vol. 28, Marcel Dekker Inc., Newyork, 986, 127 –146, 355 – 395.
7. Solubility of Solutes and Aqueous Solutions. http://www.chem.lsu.edu/lucid/tutorials/tutorials.html
8. D.Singhal, W. Curatolo, Drug polymorphism and dosage form design: a practical perspective, Adv. Drug. Deliv. Rev., 2004, 56, 335-347.
9. Pinnamaneni S., Das N.G., Das S.K., Formulation approaches for orally administered poorly soluble drugs. Pharmazie, 2002, 57, 291 – 300.
10. J.C. Chaumeil, Micronisation: a method of improving the bioavailability of poorly solubledrugs, Methods and Findings in Experimental and Clinical Pharmacology, 1998, 20,211-215.
11. N. Blagden, M. de Matas, P.T. Gavan, P. York, Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Advanced Drug Delivery Reviews (2007) 10 May.
12. Nanosuspension drug delivery Technology and application - Nanotech - Express Pharma Pulse.htm,http://www.expresspharmapulse.com

13. Medical Design Technology online at www.mdtmag.com or Microfluidics at http://www.microfluidicscorp.com
14. Aulton M.E., Pharmaceutics, The science of dosage form design, 2nd edition, Churchill Livingstone, London, 2002, 113 – 138, 234 – 252.
15. Michael Hite, Lead Research Associate, Stephen Turner, Oral Delivery of Poorly Soluble Drugs 400, Pharmaceutical Manufacturing and Packing Sourcer Summer '03 issue. Samedan Ltd. 2003.
16. K. Sekiguchi, N. Obi, Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man, Chem. Pharm. Bull., 1961, 9, 866-872.
17. W.L. Chiou, S. Riegelman, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 1971, 60, 1281-1302.
18. L.H. Emara,R.M. Badr, A.A. Elbary, Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers, Drug. Dev."Ind.Pharm., 2002, 28, 795-807.
19. A.M. Juppo, C. Boissier, C. Khoo, Evaluation of solid dispersion particles prepared by SEDS, Int. J. Pharm., 2003, 250, 385-401.
20. T. Kai, Y. Akiyama, S. Nomura, M. Sato, Oral absorption improvement of poorly soluble drug using solid dispersion technique,Chem. Pharm. Bull., 1996, 44,568-571.
21. A. Forster, J. Hempenstall, T. Rades, Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers, J. Pharm. Pharmacol., 2001, 53, 303-315.
22. Ambike AA, Mahadik KR, Paradkar A. Stabi lity study of amorphous valdecoxib. Int J Pharm. 2004, 282, 151-162.
23. Paradkar A, Ambike AA, Jadhav BK, Mahadi k KR. Characterization of curcumin— PVP solid dispersion obtained by spray drying. Int J Pharm, 2004, 271, 281-286.
24. Doshi DH, Ravis WR, Betageri GV. Carbam azepine and polyethylene glycol solid dispersion preparation, invitro dissolution, and characterization. Drug Dev Ind Pharm., 1967, 23, 1167-1176.
25. Alazar N. Ghebremeskel , Chandra Vemavarapu, Mayur Lodaya, Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer–surfactant combinations using solubility parameters and testing the processability, International Journal of Pharmaceutics, 2007, 328, 119–129.
26. Jaymin C. Shah, Jivn R. Chen, Diana Chow, Preformulation study of etoposide: II. Increased solubility and dissolution rate by solid-solid dispersions, International Journal of Pharmaceutics, 1995, 113, 103-111.
27. G.V. Betageri, K.R. Makarla, Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques,

International Journal of Pharmaceutics, 1995, 126, 155-160.

28. Jae-Young Jung, Sun Dong Yoo, Sang-Heon Lee, Kye-Hyun Kim, Doo-Sun Yoon, Kyu-Hyun Lee, Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique, International Journal of Pharmaceutics, 1999, 187, 209–218.
29. Li-Ping Ruan, Bo-Yang Yu , Guang-Miao Fu, Dan-ni Zh, Improving the solubility of ampelopsin by solid dispersions and inclusion complexes, Journal of Pharmaceutical and Biomedical Analysis, 2005, 38, 457–464.
30. Aftab Modi and Pralhad Tayade, Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique, AAPS PharmSciTech 2006; 7 (3) Article 68.
31. Piyush Gupta, Vasu Kumar Kakumanu and Arvind K. Bansal, Stability and Solubility of Celecoxib-PVP Amorphous Dispersions: A Molecular Perspective, Pharmaceutical Research, 2004, 21, 1762-1769.
32. Ahmad M. Abdul-Fattah, Hridaya N. Bhargava, Preparation and in vitro evaluation of solid dispersions of Halofantrine, International Journal of Pharmaceutics, 2002, 235, 17–33.
33. K. Sekiguchi, N. Obi, Y. Ueda, Studies on absorption of eutectic mixtures. II. Absorption of fused conglomerates of chloramphenicol and urea in rabbits, Chem. Pharm. Bull., 1964, 12, 134-144.
34. Christian Leuner, Jennifer Dressman, Improving drug solubility for oral delivery using solid dispersions, European Journal of Pharmaceutics and Biopharmaceutics, 2000, 50, 47-60.
35. T. Tachibana, A. Nakamura, A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of beta-carotene by polyvinylpyrrolidone, Kolloid-Z. Polym., 1965, 203, 130-133.
36. W.Y. Lo, S.L. Law, Dissolution behavior of griseofulvin solid dispersions using polyethylene glycol, talc, and their combination as dispersion carriers, Drug Dev. Ind. Pharm., 1996, 22, 231-236.
37. G.V. Betageri, K.R. Makarla, Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques, Int. J. Pharm., 1995, 126, 155-160.
38. A.S. Kearney, D.L. Gabriel, S.C. Mehta, G.W. Radebaugh, Effect of polyvinylpyrrolidone on the crystallinity and dissolution rate of solid dispersions of the antiin ammatory Ci-987, Int. J. Pharm., 1994, 104, 169-174.
39. H. El-Zein, L. Riad, A.A. Elbary, Enhancement of Carbamazepine dissolution - in vitro and in vivo evaluation, Int. J. Pharm., 1998, 168, 209-220.
40. I. Kushida, M. Ichikawa, N. Asakawa, Improvement of dissolution and oral absorption of ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor with anti-inflammatory activity by

preparing solid dispersion, J. Pharm. Sci., 2002, 9, 258-266.

41. Serajuddin, A.T.M., 1999. Solid dispersion of poorly watersoluble drugs: early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci., 88, 1058-1066.
42. Vadnere M. K., Coprecipitates and melts in "Encyclopedia of pharmaceutical technology", 2nd edition, Marcel Dekker Inc., Newyork, 2002,1, 641 -648.
43. el-Egakey MA, Soliva M, Speise P. Hot extruded dosage forms. Pharm Acta Helv., 1971, 46, 31-52.
44. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm., 2002, 54,107-117.
45. RiteshSanghvi, Daniel Evans, Samuel H. Yalkowsky, Stacking complexation by nicotinamide: A useful way of enhancing drug solubility, International Journal of Pharmaceutics, 2007, 336, 35–41.
46. Higuchi, T., Kristiansen, H., Binding specificities between small organic solutes in aqueous solutions: classification of some solutes into two groups according to binding tendencies. J. Pharm. Sci., 1970, 59, 1601–1608.
47. R.A. Rajewski, V.J. Stella, Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery, J. Pharm. Sci., 1996, 85, 1142-1169.
48. Kaneto Uekama, Fumitoshi Hirayama, and Tetsumi Irie, Cyclodextrin Drug Carrier Systems, Chem. Rev.,1998, 98, 2045 -2076.
49. Anil K. Singla , Alka Garg, Deepika Aggarwal, Paclitaxel and its formulations, International Journal of Pharmaceutics, 2002, 235, 179–192.
50. Rawat S.,Jain S. K , Rofecoxib-β-cyclodextrin inclusion complex for solubility enhancement, Pharmazie, 2003,58, 639-641.
51. Swati Rawat, Sanjay K. Jain, Solubility enhancement of celecoxib using β-cyclodextrin inclusion complexes, European Journal of Pharmaceutics and Biopharmaceutics, 2004, 57, 263–267.
52. S. Anguiano-Igea, F.J. Otero-Espinar, J.L. Vila-Jato, J. Blanco-M6ndez, Improvement of clofibrate dissolution by complexation with cyclodextrin, International Journal of Pharmaceutics,1996, 135, 161-166.
53. St´ephaneGibaud , Siham Ben Zirar , Pierre Mutzenhardt, Melarsoprol–cyclodextrins inclusion complexes, International Journal of Pharmaceutics, 2005, 306, 107–121.
54. Stephen K. Dordunoo, Helen M. Burt, Solubility and stability of taxol: effects of buffers and Cyclodextrins, International Journal of Pharmaceutics, 1996, 133,191-201.
55. Ran Y,Zhao L, Xu Q, Yalkowsky SH. Solubilization of Cyclosporin A. AAPS PharmSciTech. 2001; 2(1): article 2.
56. Mosher G., Thompson D.O., Complexation and cyclodextrins, in "Encyclopedia of pharmaceutical technology", 2nd edition, Marcel Dekker Inc., Newyork, 2002, 1,531 – 558.

57. Swarbrick J., Boylan J.C., Encyclopedia Of Pharmaceutical Technology; 2nd edn,2002, 3, 2458-2479.
58. Lawrence M.J., Rees G.D., Microemulsions based media as novel drug delivery systems, Adv. Drug. Del. Rev., 2000, 45, 89 – 121.
59. Tenjarla SN: Microemulsions: An overview and pharmaceutical applications. Critical Reviews TM in Therapeutic Drug Carrier Systems, 1999, 16, 461-521.
60. Lieberman HA, Rieger MM, Banker GS: Pharmaceutical Dosage Forms: Disperse Systems, 2nd edn,. New York, Marcel Decker, 1996, 1, 211–281, 315–370.
61. Solutions and Solubility. Adam M. Persky and Jeffrey A. Hughes, University of Florida, College of Pharmacy, Gainesville, FL 32610, USA.
62. Abu T.M. Serajuddin, Salt formation to improve drug solubility, Advanced Drug Delivery Reviews (2007).
63. A.V. Trask, W.D.S. Motherwell, W. Jones, Solvent-drop grinding: green polymorph control of co-crystallisation Chem. Comm., 2004, 890-891.
64. Yalkowsky,S.H., Roseman, T.J. 1981. Solubilization of drugs by cosolvents. In: Yalkowsky, S.H. (Ed.), Techniques of Soluhilization of Drugs. Dekker, New York.
65. Jeffrey W. Millard, F.A. Alvarez-Nu´n˜ez , S.H. Yalkowsky, Solubilization by cosolvents Establishing useful constants for the log /linear model, International Journal of Pharmaceutics, 2002, 245, 153-166.
66. Lachman L., Liberman H.A., Kanig J.L.,The Theory and Practice of Industrial Pharmacy, Verghese Publishing, Indian edition, 3rd edn.,1987, 462-466.
67. G.V. Murali Mohan Babu, Ch. D.S. Prasad, K.V. Ramana Murthy, Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water-soluble drug nimodipine, International Journal of Pharmaceutics, 2002, 234, 1–17.
68. Lynn L Bergeson and Michael F Cole, NanoBioConvergence – Emerging Diagnostic and Therapeutic Applications, www.touchbriefings.com, bioprocessing & biopartnering 2006, 1-4.
69. Valizadeh H, Nokhodchi A, Qarakhani N, et al. Physicochemical characterization of solid dispersions of indomethacin PEG 6000, Myrj 52, lactose, sorbitol, dextrin and Eudragit E100. Drug Dev Ind Pharm. 2004, 30, 303-317.
70. Keck CM, Müller RH, Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm., 2006, 62, 3-16.
71. Mazzola L, Commercializing nanotechnology. Nat Biotechnol, 2003, 10, 1137-1143.
72. Kondo N, Iwao T, Masuda H, Yamanouchi K, Ishihara Y, Yamada N, Haga T, Ogawa Y, Yokoyama K: Improved oral absorption of a poorly water-soluble drug, HO-221, by wet-

bead milling producing particles in submicron region. Chem Pharm Bull, 1993, 41, 737-740.

73. Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K: Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm, 2005, 299, 167-177.
74. Chung H-R, Kwon E, Oikawa H, Kasai H, Nakanishi H: Effect of solvent on organic nanocrystal growth using the reprecipitation method. J Cryst Growth, 2006, 2, 459-463.
75. Salvadori B, Capitani GC, Mellini M, Dei L, A novel method to prepare inorganic water-soluble nanocrystals. J Colloid Interface Sci, 2006, 1, 487-490.
76. NanoMorph technology for Amorphous Nanoparticles, www.soliqs.com
77. Dr Roghieh Saffie-Siebert, Dr Jill Ogden and Dr Mark Parry-Billings, Nanotechnology approaches to solving the problems of poorly water-soluble drugs, Drug Discovery World Summer 2005, 71-76.