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Review Article

Solubility and Solubilization Techniques - A Review

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ABSTRACT
Solubility is essential for the therapeutic effectiveness of the drug, independent of the route of administration. Poorly soluble drugs are often a challenging task for formulators in the industry. Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Solubilization may be affected by co-solvent water interaction, micellar solubilization, reduction in particle size, inclusion complexes, solid dispersion, and change in polymorph. Some new technologies are also available to increase the solubility like microemulsion, self emulsifying drug delivery system and supercritical fluid technology. This review focuses on the recent techniques of solubilization for the attainment of effective absorption and improved bioavailability.

Keywords: Solubilization, solubility, BCS classification, solubilization techniques.

INTRODUCTION

Solubility may be defined in quantitative terms: the concentrations of solute in saturated solution at a certain temperature and in qualitative terms: the spontaneous interaction between the two or more substance to form homogenous molecular dispersion

Solubilization may be defined as: The spontaneous passage of poorly water soluble solutes molecules into an aqueous solution of the surfactant.

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[5].

The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class III and IV drugs, compounds which feature poor solubility and high permeability, and poor solubility and poor permeability, respectively[6].

BCS Classification:

Table 1: BCS Classification[7]

Class	Solubility	Permeability	Absorption pattern	Rate limiting step in absorption	Examples
I	High	High	Well absorb	Gastric emptying	Diltiazam
II	Low	High	Variable	Dissolution	Nifedipine
III	High	Low	Variable	Permeability	Insulin
IV	Low	Low	Poorly absorb	Case by case	Taxol

Therapeutic drugs are often given systemically. Once given systemically, a drug will distribute throughout the body. By distributing in the body, the drug is essentially diluted out from its original concentration in the formulation/dosage form. Hence, the formulation is really a drug concentrate. For solid dosage forms, the dose to be delivered is not normally a physical problem. However, dose can become a significant formulation challenge for parenteral preparations, due to limitations in aqueous solubility and volume. Therefore, in order to obtain a solution formulation for drugs with poor solubility, it

is necessary to alter the formulation to facilitate solubilization[8].

The choice of solubilization method will depend upon how efficiently the drug can be solubilized, stability in the system, and upon the biocompatibility of the vehicle for a given delivery route. For solid dosage forms, it may be possible to alter the solid phase to enhance dissolution. For parenterals, the four most commonly used techniques for solubilization are: pH adjustment; cosolvent addition; micelle inclusion through surfactant addition and complexation.[8] 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[6]. In the other words the solubility can also define as the ability of one substance to form a solution with another substance[9]. 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[10].

Solubility Definition:

Table 2: Solubility definitions[5,10.11,12]:

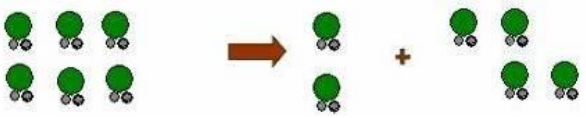
Definition	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Process of solubilisation[5, 11]

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. Polar solvent molecules can effectively separate the molecules of other polar substances. This happens when the positive end of a solvent molecule approaches the negative end of a solute molecule. A force of attraction then exists between the two molecules. The solute molecule is pulled into solution when the force overcomes the attractive force between the solute molecule and its neighboring solute molecule. Ethyl alcohol and water are examples of polar substance that readily dissolves in each other. The nonpolar molecules have no attraction for polar molecules and exert no force that can separate them. However, nonpolar substance such as fat will dissolve in nonpolar solvents. Polar solvents can generally dissolves solutes that are ionic. Then negative ion of the substance being dissolved is attracted to the positive end of neighboring solvent molecules. The positive ion of the solute is attracted to the negative end of the solvent molecule. The separation of ions by the action of a solvent is called dissociation.

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

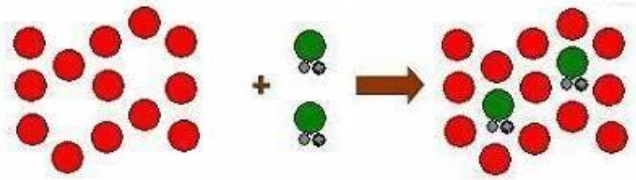


Fig. 1: Process of solubilization[5]

FACTORS AFFCTING ON SOLUBILITY[5, 10]

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.

Particle Size[5:]

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[7]. The effect of particle size on solubility can be described by

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

Where,

S_0- is the solubility of infinitely large particles

S- is the solubility of fine particles

V- is molar volume

γ-is the surface tension of the solid

r- is the radius of the fine particle

T- is the absolute temperature

R- is the gas constant

Temperature[5] :

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. 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. Organic compounds nearly always become soluble as the temperature is raised , in most solvents. The technique of recrystallisation, used for purification of solids, depends on this differences in solubility in hot and cold solvent. There are a few exceptions, such as certain cyclodextrins.

Pressure[5:]

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.

Nature of the solute and solvent[5] :

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 solute in a solvent is large. A polar solute has low solubility or insoluble in a non-polar 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.

Molecular size[5:]

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.

Polarity[5:]

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.

Polymorphs[5]:

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.

TECHNIQUES OF SOLUBILITY ENHANCEMENT[5]

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

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 Mod*ification*

a. pH control
b. salt formation

III. Miscellaneous methods

I. Physical Modifications:

A. Particle size reduction[5]:

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

1. Micronisation[5, 13]

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. Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. 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. This study was to investigate the effects of different micronization methods, including ball milling, jet milling and high-pressure micronization on the characteristics and various functional properties of carrot insoluble fibre-rich fraction (FRF). The results demonstrated that these treatments could effectively (p<0.05) pulverize the fibre particles to different micro-sizes. As particle size decreased, the bulk density of the insoluble FRF was significantly (p<0.05)

decreased and a redistribution of fibre components from insoluble to soluble fractions was observed. Furthermore, these treatments, especially the high-pressure micronization, could significantly (p<0.05) increase the physicochemical properties (e.g. water-holding capacity, swelling capacity, oil-holding capacity and cation-exchange capacity), glucose adsorption capacity, a amylase inhibitory activity and pancreatic lipase inhibitory activity of the insoluble FRF to different extents (from several to 29-fold). Our findings suggested that these micronization treatments would provide an opportunity to improve the functionality of carrot insoluble FRF in food applications.

2. Nanosuspension[5, 14, 15]

In recent years, there has been a considerable interest in the development of novel drug delivery systems using particulate delivery systems like nanoparticles. Nanoparticles represent a promising drug delivery system of controlled and targeted release. In this context, nanosuspensions will be effective in increasing the solubility, bioavailability of poorly soluble drugs. The review focuses on advantages, method of preparation, physical characteristics and evaluation of nanosuspensions.

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.[5] Disperse system of solid-in-liquid or solid-in-semisolid, the dispersed phase comprising pure active compound or an active compound mixture. The average diameter of the dispersed phase is between 10nm and 1,000nm. Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to uniform and narrow particle size range obtained, which eliminate the concentration gradient factor.

There are several possible interesting features of nanosuspensions[14]

- Increased saturation solubility and dissolution rate of drug;
- Increased adhesive nature, resulting in enhanced bioavailability;
- Increased amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility.
- Possibility of surface modification of nano-suspensions for site-specific delivery.
- Possibility of large-scale production, the prerequisite for the introduction of a delivery system to the market.

When introduced into water, aqueous media and/or organic solvents, the active compounds has an increased saturation solubility and an increased rate of dissolution compared with powders of the active compound prepared using an ultrasonic probe, a ball mill or a pearl mill, the solid particles having been comminuted, without prior conversion into a melt, by using cavitation or shearing and impact forces with introduction of a high amount of energy.[15]A large proportion of new chemical entities coming from drug discovery are water insoluble, and therefore poorly bioavailable, leading to hurdles in formulation development efforts. There are number of formulation approaches like micronisation, solubilization using cosolvents, precipitation techniques etc., to resolve the problems of low solubility and low bioavailability. The next development step is transformation of the micronized drug to drug nanoparticles and nanosuspensions. Nanoparticulate drug delivery system may offer plenty of advantages over conventional dosage forms which include improved efficacy, reduced toxicity, enhanced biodistribution and improved patient compliance.

Nanosuspension technology offers novel solution for these poorly soluble drugs. Nanosuspension consists of pure poorly water soluble drugs with or without any matrix material suspended in dispersion. They can be surfactant free; can also comprise surfactants or stabilizers or both. Nanosuspensions differ from nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid-lipid nanoparticles (SLN), which are lipidic carriers of drug.

Techniques for the production of nanosuspensions[5]

a) Homogenization[5]

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.

b) Wet milling[5]

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. Drying of nanosuspensions can be done by lyophilisation or spray drying.

OTHER TECHNIQUES FOR REDUCTION OF THE PARTICLE SIZE

1. Sonocrystallisation: [5, 16]

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients (API). Most applications use ultrasound in the range 20 kHz-5 MHz.

2. Supercritical fluid process: [5, 17, 18]

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense noncondensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). Through manipulation of the pressure of SCFs, the favorable characteristics of gases- high diffusivity, low viscosity and low surface tension may be imparted upon liquids to precisely control the solubilisation of a drug with a supercritical fluid. SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of fluid that largely determine its solvents power. Once the drug particles are solubilised within SCFs, they may be recrystalised at greatly reduced particle sizes. A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm in diameter. The most widely employed methods of SCF processing for micronized particles are rapid expansion of

supercritical solutions (RESS) and gas antisolvents recrystallisation (GAS), both of which are employed by the pharmaceutical industry using carbon dioxide (CO_2) as the SCF due to its favourable processing characteristics like its low critical temperature (Tc = 31.1-C) and pressure (Pc = 73.8 bar)[5].

Rapid expansion of supercriticle solutions (RESS):

RESS involves solubilising a drug or a drug-polymer mixture in SCF and subsequently spraying the SCF solution into a lower pressure environment via a conventional nozzle or capillary tube. The rapid expansion undergone by the solution reduces the density of the CO_2, correspondingly reducing its solvent power and supersaturating the lower pressure solution. This supersaturation results in the recrystallisation and precipitation of pure drug or drug-polymer particles of greatly reduced size, narrow size distribution and high purity. The solubility of nifedipine has been improved by RESS.[5]

Gas antisolvent recrystallisation (GAS):

It is well known phenomenon that a poor solvent of a particular solute can be added to the solution to precipitate the solute. This is called salting out and is widely used for crystallization purposes. However, disadvantages of this technique include poor control over the precipitated crystal morphology, size distribution and presence of residual solvents. Utilizing a similar principle, the solubility of pharmaceutical compounds in solvents can be decreased by using SCFs in gaseous form as antisolvents. It is supercritical. Possible to induce rapid crystallisation by introducing the antisolvent gas into a solution containing dissolved solute. One of the requirements for this approach is the carrier solvent and the SCF antisolvent must be at least partially miscible[17].GAS processing requires the drug or drug-polymer mixture be solubilised via conventional means into a solvent that is then sprayed into an SCF; the drug should be insoluble in the SCF, while the SCF should be miscible with the organic solvent. The SCF diffuses into the spray droplets, causing expansion of the solvent present and precipitation of the drug particles. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry.[5]

3. Spray drying: [5, 19]

Spray drying is a commonly used method of drying a liquid feed through a hot gas. Typically, this hot gas is air but sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying and nitrogen gas is used instead. The liquid feed varies depending on the material being dried and is not limited to food or pharmaceutical products and may be a solution, colloid or a suspension. This process of drying is a one step rapid process and eliminates additional processing. Spray drying involves the atomization of a liquid feedstock into a spray of droplets with hot air in a drying chamber. The srays are produced by either rotary (wheel) or nozzle atomizers. Evaporation of moisture from the droplets and formation of dry particles proceed under controlled temperature and airflow conditions. Powder is discharged continuously from the drying chamber. Operating conditions and drying design are selected according to the drying characteristics of the product and the powder specification. Every spray dryer consists of feed pump, atomizer, air heater, air disperser, drying chamber, and systems for exhaust air cleaning and powder recovery.

Fig. 2: Spray drying technology: nozzle atomizer in a spray dryer[19]

Fig. 3: Spray drying tehnology: rotary atomizer in a spray dryer[19]

Widely varying drying characteristics and quality requirements of the thousands of products spray dried determine the selection of the atomizer, the most suitable airflow pattern, and the drying chamber design. The formation of sprays having the required droplet size distribution is vital to any successful spray dryer operation so that powder specifications can be met. Atomization is a high technology area where Niro has played a central role in the development and use of nozzles and rotary atomizers in spray drying. Spray drying of the acid dispersed in acacia dispersed in acacia solutions resulted in as much as a 50% improvement in the solubility of poorly water soluble salicylic acid.

Air flow: [19]

The initial contact between spray droplets and drying air controls evaporation rates and product temperatures in the dryer. There are three modes of contact:

- Co-current
  Drying air and particles move through the drying chamber in the same direction. Product temperatures on discharge from the dryer are lower than the exhaust air temperature, and hence this is ideal mode for drying heat sensitive products. When operating with rotary atomizer, the air disperser creates a high degree of air rotation, giving uniform temperatures throughout the drying chamber. However, an alternative non-rotating airflow is often used in tower.
- Counter-current
  Drying air and particles move through the drying chamber in the opposite directions. This mode is suitable for products which require a degree of heat treatment during drying. The temperature of the powder leaving the dryer is usually higher than the exhaust air temperature.
- Mixed flow
  Particle movement through the drying chamber experiences both co-current and counter-current phases. This mode is suitable for heat stable products where coarse powder requirements necessitate the use of nozzle atomizers, spraying upwards into an incoming airflow, or for heat sensitive products where the atomizer sprays droplets downwards towards an integrated fluid bed and the air inlet and outlet are located at the top of the drying chamber.

B. MODIFICATION OF THE CRYSTAL HABIT[5, 20]

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[1]. Polymorphism is also relevant for intellectual property considerations because polymorphs with superior properties can be protected by patents, the aim of a polymorphism study is to search for, identify and characterize new polymorphic forms, hydrates and solvates of a substance and to understand the relationship between the different solid phases. To reliably search for polymorphs and pseudopolymorphs, a systemic approach and intelligent planning are essential. In order to be 100% sure that all forms of a certain compound are found Solvias' Micro-HTS polymorph screening is conceived as the basis for a complete polymorphism study. It allows for a wide variation of crystallization parameters within a short period of time and indicates suitable crystallization conditions for the preparation of new polymorphic or pseudopolymorphic forms. Less than 1g of drug substance is needed to carry out a high-throughput screening. Usually the screening is followed by a more thorough investigation covering some or all of the following points:

- Preparation of the new forms in larger quantities and through characterization by complementary techniques such as differential scanning calorimetry, X-ray powder diffraction, thermal gravimetry combined with Fourier-transform infrared spectroscopic analysis for detection of the new forms, e.g. by dynamic vapour sorption.
- Elucidation of the thermodynamic relationships between the forms and generation of a scheme showing these inter-relationships.
- Selection of a suitable form for production
- Optimization and scale-up of the crystallization procedure of the desired form
- Investigation of the physical and chemical stability in a given formulation and tha potential interactions with excipients.
- Method development and validation for tracing polymorphic impurities
- On-line spectroscopic monitoring of crystallization processes during production and
- Quality control of the final products[18].

C. DRUG DISPERSION IN CARRIERS[6, 21].

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961. 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.

A poorly water soluble compound has classically been defined as one dissolving in less than 1part per 10000 part of water. A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it take to be absorbed in the gastrointestinal tract. Thus a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug

products. Although salt formation, partical size reduction, etc. have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques the desired bioavailability enhancement may not always be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate prepare solid dispersion.

Chiou and Riegelman defined the term solid dispersion as

"A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures".

The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state, after few years Goldberg et.al. reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature

Surface active carriers uses in Pharmaceutical preparation:

Because of their unique functional properties, surface active carriers find a wide range of uses in pharmaceutical preparations. These include, depending on the type of product, improving the solubility or stability of the drug in the liquid preparation, stabilizing and modifying the texture of semisolid preparations, or altering the flow properties of the final tablet dosage form. In addition to their use as excipients to improve the physical and chemical characteristics of the formulation, surface active carriers may be included to improve the efficacy or the bioperformance of the product .The advantage of a surface-active carrier over a non-surface-active one in the dissolution of drug from a capsule formulation is shown schematically in Figure 4. The physical state of drug if a solid dispersion must, however, is carefully considered an evaluating the advantage of a surface-active vehicle. As mentioned earlier, the drug can be molecularly dispersed in the carrier to form a solid solution or it can be dispersed as particles. It can also be both partially dissolved and partially dispersed in the carrier. The potential for the formation of a continuous drug rich surface layer is possibly greater if the drug is molecularly dispersed, whereas the drug dispersed, as particulates may be more prone to dissociation from the water-soluble matrix. It is however, rare that the drug is dispersed just as particulates and is not at least partially dissolved in the vehicle. Therefore, a surface-active carrier is preferably in almost all cases for the solid dispersion of poorly water-soluble drugs.

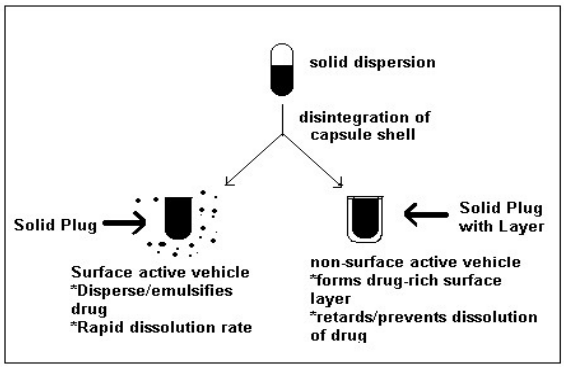


Fig. 4: A schematic representation of the comparative dissolution of a poorly water-soluble drug from surface-active versus non surface-active vehicle[21]

Block Copolymers as Pharmaceutical Surface active carriers

The toxicity of many pharmaceutical surface active carriers has led to the search of more acceptable solubilizers. Soluble surface-active block copolymers of polyoxyethylene and polyoxypropylene have been used widely in pharmaceuticals and significantly found favor for such critical applications as emulsifiers for intravenous lipids and as priming agents for heart lung apparatus. A range of commercial block copolymer surface active carriers are available under the Pluronic, Pluronic R, Tetronic, and pluradot trade names; their preparation and properties have been reviewed by schmolka. The corresponding nonproprietary names of the first three types are Poloxamer, Meroxapols and Poloxamine, respectively, there being no equivalent name for the plurodot compounds. Poloxamers are polyoxyethylene-polyoxypropylene-polyoxyethylene (ABA) block copolymers; The Meroxapols are polyoxypropylene-polyoxyethylene- polyoxypropylene (BAB) copolymers; The Poloxamine structure, $(AB)_2NCH_2CH_2N(BA)_2$, is in full form as below.

$$[H(C_2H_4O)_a(C_3H_6O)_b]_2NCH_2CH_2N[(C_3H_6O)_b(C_2H_4O)_aH]_2$$

The Poloxamers have been most widely studied to date, yet there has been considerable confusion in the literature over the exact nature of their colloidal behavior, in particular whether micelles are formed. Recently, surface tension measurement on a series of Poloxamers in aqueous solution and photon correlation spectroscopy has helped to resolve some of these problems, but as benefits their structure their behavior patterns tend to be complex. At low concentrations, approximating those at which more conventional nonionic detergents form micelles, the Poloxamers monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentration these monomolecular micelles associate to form aggregates of varying size, which have the ability to solubilize drugs and to increase the stability of solubilized agents.

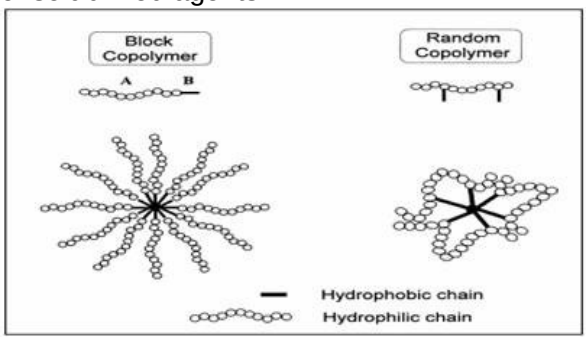


Fig. 5: Schematic representation of block and random copolymer micelles[21]

The solubilities of some parasubstituted acetanilide in aqueous Poloxamers solutions increase with increasing ethylene content of the polymer, although the more hydrophobic solutes do not show this trend. The results show that, e.g., 4-nitroacetanilide is less soluble in more hydrophilic Poloxamers, and this is the general trend shown by the halogenated derivatives. Pluronic F68 solubilizes some benzocaine, which above an apparent CMC of 0.23% w/v has a slope for the solubility curve K, of 0.019, i.e., $S = S_O + K(C_{surfactant} - CMC) = S_O + 0.019(C_{surfactant} - CMC)$. The order for solubilization of benzocaine is Triton WR1339 (a tert-octylphenol with ethylene oxide) > Brij 35 > Tetronic 908 > Pluronic F68. At 3% levels the half-life of

benzocaine is increased 4 times by Brij 35 and triton WR1399, but the limited solubility of benzocaine in Pluronic solutions results in only a marginal increase in half-life. Pluronic F68 lowers blood viscosity and has been advocated. Intravenous administration of Pluronic F38 is followed by rapid excretion in the urine; F68 appears in bile to the extent of 6% of the injected IV dose. Poloxamers 108 (Pluronic F38), although rapidly phagocytosed, is well tolerated even when administered intravenously in large doses.

Pluronic block copolymers are synthesized by sequential polymerization of propylene oxide and ethylene oxide. It consists of combined chain of oxyethylene with oxy propylene where oxyethylene impart hydrophillicity whereas oxypropylene impart lipophilicity. Each molecule is synthesized as long segment of the hydrophilic portion combined with long segment of hydrophobic portion referred to as block copolymer. A defining property of Pluronic is ability of individual block copolymer molecules termed as “unimers’’ to self assemble into micelles in aqueous solution. The “unimers” form a molecular dispersion in water at block copolymer concentrations below the critical micelle concentration. At concentration above CMC, the unimers molecule aggregate, forming micelles with propylene oxide bock in the inner core of micelles covered by the hydrophilic corona from ethylene oxide block. The water insoluble compounds are transpired into the propylene core of the micelles. Block copolymer micelles are aggregates that resemble many properties of micelles formed by low molecular weight surface active carriers. They are the consequence of a self-assembling tendency displayed by block copolymers when dissolved in a so-called selective solvent, which is a good solvent for one of the blocks, but a poor one for the other. Solvent selectivity and, hence, copolymer self-assembling, have been observed for a variety of block copolymers in water, polar and non-polar organic solvents and, more recently, in supercritical fluids. For this generality and for the possibility of tuning the aggregate properties by varying either the kind of monomer or the size and proportion of the constituting blocks, these aggregates are able to provide a much wider range of applications than that observed for normal surface active carriers, involving solubilization of drugs or pollutants, as nonreactors, in controlled drug delivery and as potential DNA carriers, among others.

Limitations of Surface active carrier based Solid Dispersions:

Solid dispersion in surface-active carriers may not be the answer to all bioavailability problems with poorly water-soluble drug. Some of the limitations of bioavailability enhancement by this method might be

1. Low solubility of drug in available carriers.
2. The desired dose of a drug cannot be solubilized and filled into the hard gelatin capsules if adequate solubility in a carrier cannot be obtained.
3. Dordunoo et al reported that the particle size of a drug in a solid dispersion remained unchanged if it is just mixed with the carrier instead of dissolving in it.
4. if the drug is dissolved by heating in excess of its solubility in a carrier under normal storage condition, it may subsequently crystallize out from the solid dispersion. Either situation would defect the purpose of bioavailability enhancement of poorly water-soluble drugs by solid dispersion.
5. Another possible limitation of the use of surface-active carrier reported by Aungst et al. is that the bioavailability of a drug may vary depending on the amount of carrier administered along with it.

This variation is because different amounts of a surface-active carrier may have different solubilization or dispersion effects on a drug in the gastrointestinal fluid. Serajuddin et al. reported a method whereby the rate and efficiency of

dispersion of drug in aqueous media from different formulations can be studied[21].

NEWER TECHNIQUES [21]

The two important breakthrough in formulation of solid dispersion are, the development of technologies to fill solid dispersions directly in to hard gelatin capsule and the ability of surface active & self-emulsifying agents carriers. The technique to fill solid dispersion directly into hard gelatin capsule as melts, which gets solidify at room temperature, was first described by Francol's & Jones in 1978. But the potential application of that technique was fully realized by Chatham. For ease of manufacturing the carriers must be amenable to liquid filling into hard gelatin capsules as melts. The melting temperature of carriers should be such that the solutions do not exceed ~70°C which is the maximum acceptable temperature for hard gelatin capsule shells. The water soluble carriers dissolves more rapidly than the drug, the drug rich layer has to form over the surface of dissolving plug, which prevent further dissolution of drug from solid dispersion because of this directly filled hard gelatin capsule is not a good method of preparation of solid dispersion unless the formation of drug rich layer on the surface of dissolving plug can be prevented.

The self-emulsifying agent will act as dispersing or self –emulsifying agent on drug through which the dissolution of drug can be increase by preventing the formation of any water insoluble surface layer, although the liberated drug remain undissolved in the dissolution medium. When its concentration exceeded its saturation solubility, it will disperse or emulsify into a finely divided state because of the surface activity of the dissolved vehicle the high surface area will be made available which will facilitate its dissolution in gastrointestinal fluid[21.] 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. Novel additional preparation techniques have included rapid precipitation by freeze drying and using supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. 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[5]. The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, celecoxib, halofantrine can be improved by solid dispersion using suitable hydrophilic carriers[5]. The eutectic combination of chloramphenicol/urea and sulphathiazole urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

1. Hot Melt method[5]

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[5]

Tachibana and Nakumara 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 or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 ^{0}C.

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. 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. Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions.

3. Hot-melt Extrusion[5]

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. 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. The process has been useful in the preparation of solid dispersions in a single step.

4. Melting –solvent method[6, 22]

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70^{0}C 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.

By Shah TJ et.al, the objective of their investigation was to improve the dissolution rate of Rofecoxib (RXB), a poorly water-soluble drug by solid dispersion technique using a water-soluble carrier, Poloxamer 188 (PXM). The melting method was used to prepare solid dispersions dissolution enhancement of RXB was obtained by preparing its solid dispersions in PXM using melting technique. The use of a factorial design approach helped in identifying the critical factors in the preparation and formulation of solid dispersion.

Table 3: Carriers for Solid Dispersions[6]

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

Successful developments of solid dispersion systems for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and as expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly.

D. Complexation[5]:

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. 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.

Table 4: List of Complexing Agents[5]

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

Staching complexation[5]

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

Higuchi and Kristiansen 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.

Inclusion complexation[5]

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[58]. 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. Complex formation of rofecoxib, celecoxib, clofibrate, melarsoprol,

taxol, cyclosporin A etc. with cyclodextrins improves the solubility of particular drugs.

Factors affecting complexation*[5]*:

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[23, 24]:

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. 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. Fenofibrate is a lipophilic compound and practically insoluble in water. Hence, dissolution study of fenofibrate dosage forms necessitates modifications in the dissolution medium to increase the solubility. Having no ionizable group, fenofibrate solubility was not influenced by changes in medium pH. However, the addition of surfactants is a reasonable approach, which if implemented correctly can approximate the GI fluid condition. Solubility was linearly increased from 244-fold (compared with water) at 0.025M SLS to 1139 fold at 0.1 MSLS[23]. Biosurfactants are amphiphilic compounds of microbial origin with considerable potential in commercial applications within various industries. They have advantages over their chemical counter parts in biodegradability and effectiveness at extreme temperature or pH and in having lower toxicity. Biosurfactants are beginning to acquire a status as potential performance effective molecules in various fields. At present biosurfactants are mainly used in studies on enhanced oil recovery and hydrocarbon bioremediation. The solubilization and emulsification of toxic chemicals by biosurfactants have also been reported. Biosurfactants also have potential applications in agriculture, cosmetics, pharmaceuticals, detergents, personal care products, food processing, textile manufacturing, laundry supplies, metal treatment and processing, pulp and paper processing and paint industries. Their uses and potential commercial application in these fields are reviewed[24].

***Microemulsion*[5]**

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. 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, and less inter- and intra-individual variability in drug pharmacokinetics.

II. CHEMICAL MODIFICATION[5, 25]

A large number of drugs are either weak acids or weak bases, therefore their solubility in water can influence by pH of the system. 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) 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. 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). Effect of pH-Sodium Laurly Sulfate Combination on solubilisation of PG-300095 (an Anti-HIV agent). Solubilisation of PG-300995 has been achieved using SLS at low pH. However, at a pH where both the solute and surfactant are ionized, desolubilisation can occur owing to the formation of an insoluble estolate salt. This salt can be solubilized by higher concentrations of SLS.

III. MISCELLANEOUS TECHNIQUES

1. Co-crystallisation[5, 21]:

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 crystal, 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. 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[5]:

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. 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.
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[5]:
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.
Example: Solubilisation of Theophylline with sodium acetate and sodium alginate

4. Solubilizing agents[5]:
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. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide.

5. Nanotechnology approaches[5]:
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. 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 and the next step taken was Nanonisation.

Nanocrystal[5]
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. 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[5]:
Nanoscale particles can be produced by wet-milling process. 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[5]:
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. 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[5]:

In the precipitation method a dilute solution is first produced by dissolving the substance in a solvent where its dissolution is good. 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[5]:

In the cryo-vacuum method the active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution. The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 ºC). 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 ºC. 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 ºC 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[5, 26]

The NanoMorph technology (figure 6) 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.

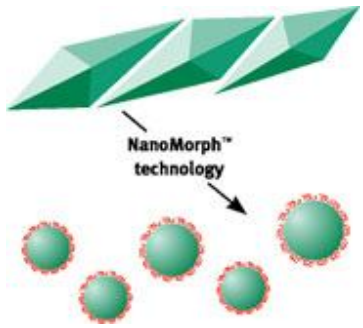


Fig. 6: Nanomorph Technology

6. Solution-Enhanced Dispersion[15]

The solution-enhanced dispersion by the supercritical fluids (SEDS) process was developed and patented by the University of Bradford. The use of a coaxial nozzle provides a means whereby the drug in the organic solvent solution mixes with the compressed fluid CO_2 (antisolvent) in the mixing chamber of the nozzle before dispersion and flows into a particle-formation vessel through a restricted orifice. This nozzle achieves solution breakup through the impact of the solution by a higher velocity fluid. The high velocity fluid creates high frictional surface forces, causing the solution to disintegrate into droplets. A wide range of materials have been prepared as carriers of microparticles and nanoparticles using the SEDS process. A key step in the formation of nanoparticles is to enhance the mass transfer rate between the droplets and the antisolvent before they coalesce to form bigger droplets. In another study, a significant decrease in the particle size is achieved using the ultrasonic nozzle based supercritical antisolvent process.

7. Spray Freezing into Liquid[15]

The technology of spray freezing into liquid (SFL) was developed and patented by the University of Texas at Austin in 2003 and commercialized by the Dow Chemical Company. This technique involves atomizing an aqueous-organic co-solvent solution, aqueous-organic emulsion, or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO_2, helium, propane, ethane) or the cryogenic liquids (i.e. nitrogen, argon, or hydrofluoroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. The use of acetonitrile as the solvent increased the drug loading and decreased the drying time for lyophilization. The dissolution rate was remarkably enhanced by the SFL powder containing amorphous nanostructured aggregates with high surface area and excellent wettability.

8. Evaporative Precipitation into Aqueous Solution[15]

The evaporative precipitation into aqueous solution (EPAS) process uses rapid phase separation to nucleate and grow nanoparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic point organic solvent. This solution is pumped through a tube, where it is heated under pressure to a temperature above the boiling point of the solvent and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and the aqueous solution to optimize particle formation and stabilization. In EPAS, the surfactant migrates to the drug-water interface during particle formation, and the hydrophilic segment is oriented toward the aqueous continuous phase. The hydrophilic stabilizer on the surface inhibits crystallization of the growing particles, facilitating dissolution rates.

9. Pearl Milling[15]

NanoCrystals involve filling an aqueous suspension of drug into a pearl mill containing glass or zirconium oxide pearls as milling media. The drug microparticles are ground to nanoparticles (less than 400nm) between the moving milling pearls over a period of several days. The milling efficiency is dependent on the properties of the drug, the medium, and the stabilizer. Rapamune, an immunosuppressant agent, is the first FDA-approved nanoparticle drug using NanoCrystals technology developed by Elan Drug Delivery. Emend is another product containing 80 or 125 mg aprepitant formulated by this technique. The limitation of the pearl milling process is the introduction of contamination to the product from the grinding material, batch-to-batch variations, and the risk of microbiological problems after milling in an aqueous environment for a few days.

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