MANTECH Publications

Journal of Pharmaceutical Analysis and Drug Research
Volume 3, Issue 1, January-April, 2021

Review on Solubility Enhancement Technique

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Abstract

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for achieving the required pharmacological response [12]. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities as well as generic development. This article is to focus on the Importance of Solubility, Techniques for Solubility Enhancement, Supercritical Fluid (SCF) Process, Cryogenic Techniques, Inclusion Complex Formation-Based Techniques, Hydrotrophy, Crystal Engineering, pH Adjustment, Co- Solvency etc.

***Keywords**: - Solubility Enhancement, Bioavailability, Dissolution, Inclusion complexes*

INTRODUCTION

Solubility is the property of a solid, liquid, or gaseous chemical substance called *solute* to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of the solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution [1].

The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas. The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water to poorly soluble, such as silver chloride in water. The term *insoluble* is often applied to poorly or very poorly soluble compounds [2].

Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions, equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable [3].

Solubility is not to be confused with the ability to dissolve or liquefy a substance since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in hydrochloric acid. Solubility does not also depend on particle size or other *kinetic* factors; given enough time, even large particles will eventually dissolve [4].

IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units [5].

Extensive use of solubility from a different perspective has led to solubility being expressed in various manners. It is commonly expressed as a concentration, either by mass (g of solute per kg of solvent, g per dL (100 mL) of solvent), molarity, molality, mole fraction, or other similar descriptions of concentration. The maximum equilibrium amount of solute that can dissolve per amount of solvent is the solubility of that solute in that solvent under the specified conditions [6].

The advantage of expressing solubility in this manner is its simplicity, while the disadvantage is that it can strongly depend on the presence of other species in the solvent (e.g., the common ion effect).

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

The solubility of that solute in that solvent under the specified conditions. [6]

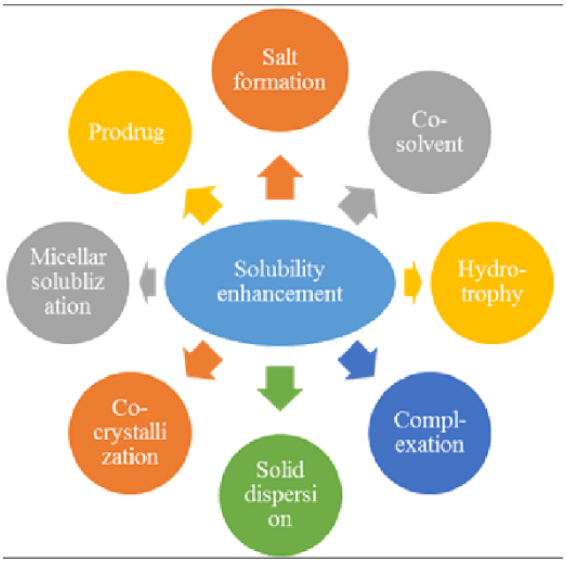

Figure1: Solubility enhancement technique.

The advantage of expressing solubility in thismanner is its simplicity, while the **disadvantage** is that it can strongly depend on the presence of other species in the solvent (e.g., the common ion effect).Saturated solutions of ionic compounds of relatively low solubility are sometimes described by solubility constants.It is a case of an equilibrium process. It describes the balance between dissolved ions from the salt and undissolved salt.Similar to other equilibrium constants, the temperature would affect the numerical value of the solubility constant. The value of this constant is generally independent of the presence of other species in the solvent.

The Flory-Huggins solution theory is a theoretical model describing the solubility of polymers. The Hansen Solubility Parameters and the Hildebrand solubility parameters are empirical methods for the prediction of solubility. It is also possible to predict solubility from other physical constants, such as the enthalpy of fusion.The partition coefficient (Log P) is a measure of differential solubility of a compound in a hydrophobic solvent (octanol) and a hydrophilic solvent (water). The logarithm of these two values enables compounds to be ranked in terms of hydrophilicity (or hydrophobicity).USP and BP classify the solubility regardless of the solvent used, just only in terms of quantification and have defined the criteria as given in Table 1 [7, 8].

The Biopharmaceutics Classification System (BCS) is a guide for predicting the

intestinal drug absorption provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability. Solubility is based on the highest-dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250mL or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water [9].The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important since 85% of the most sold drugs in the USA and Europe are orally administered.

All drugs have been divided into four classes: class I—high soluble and high permeable, class II—low soluble and high permeable, class III—low soluble and high permeable and class IV—low soluble and low permeable.

IMPORTANCE OF SOLUBILITY

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products [10].

However, the major challenge with the design of oral dosage forms lies in their poor bioavailability. The oral bioavailability depends on several factors, including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Solubility also plays a major role in other dosage forms like parenteral formulations as well [11]. Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for achieving required pharmacological response [12]. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities as well as generic development.

Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic, having poor aqueous solubility.More than 40% of NCEs (new chemical entities) developed in the pharmaceutical industry are practically insoluble in water. These poorly water-soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs, solubility is the most important rate-limiting parameter to achieve their desired concentration in systemic circulation for a pharmacological response. The problem of solubility is a major challenge for formulation scientists [13].

The improvement of drug solubility, thereby its oral bioavailability, remains one of the most challenging aspects of the drug development process, especially for the oral-drug delivery system. There are numerous approaches available and reported in the literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of the drug under consideration, nature of excipients to be selected, and nature of intended dosage form.

The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances, according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate-limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility, in turn, increases the bioavailability for BCS class II drugs [10, 13, 14].The negative effect of compounds with low solubility includes poor absorption and bioavailability, insufficient solubility for IV dosing, development challenges leading to increasing the development cost and time; the burden shifted to the patient (frequent high-dose administration) [11].

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

Solubility improvement techniques can be categorized into physical modification, chemical modifications of the drug substance, and other techniques.

Physical Modifications

Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and co-crystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

Chemical Modifications

Change of ph, use of buffer, derivatization, complexation, and salt formation.

Miscellaneous Methods

Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

PARTICLE SIZE REDUCTION

The solubility of the drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction, with the solvent which causes an increase in solubility.

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economicalmeans of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product, which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermosensitive or unstable active compounds.Using traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to the desired level.

Micronization is another conventional technique for particle size reduction. Micronization increases the dissolution rate of drugs through the increased surface area; it does not increase equilibrium solubility. Decreasing the particle size of these drugs, which causes an increase in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor-stator colloid mills, and so forth; micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [15].

These processes were applied to griseofulvin, progesterone, spironolactone

diosmin, and fenofibrate. For each drug, micronization improved their digestive absorption, and consequently, their bioavailability and clinical efficacy. Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes biorelevant media [16, 17].

SOLID DISPERSION

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s [18]. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), Plasdone-S630. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) also find a place in the formulation of solid dispersion.

The solubility of celecoxib, halofantrine, and ritonavir can be improved by solid dispersion using suitable hydrophilic carriers like celecoxib with povidone (PVP) and ritonavir with gelucire. Various techniques to prepare the solid dispersion of hydrophobic drugs with an aim to improve their aqueous solubility are listed here [19–21].

Figure 2: Solid dispersion technique

Hot-Melt Method (Fusion Method)

The main advantages of this direct melting method are its simplicity and economy.The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. In this method, the physical mixture of a drug and a water-soluble carrier is heated directly until the two melts. The melted mixture is then cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is then crushed, pulverized, and sieved, which can be compressed into tablets with the help of tableting agents.The melting point of a binary system is dependent upon its composition, that is, the selection of the carrier and the weight fraction of the drug in the system [22].An important requisite for the formation of solid dispersion by the hot-meltmethod is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermostability of both the drug and the carrier.

Solvent Evaporation Method

Tachibana and Nakamura 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 povidone. Many investigators studied solid dispersion of meloxicam, naproxen, and nimesulide using the solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for the improvement and stability of solid of poorly water-soluble drugs [15, 17].

The main advantage of the solvent evaporation method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, the disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing the organic solvent (a regulatory perspective), the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty in reproducing crystal forms [24].

Hot-Melt Extrusion

Hot-melt extrusion is essentially the same as the fusion method, except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, the miscibility of the drug and the matrix could be a problem. High-shear forces resulting in high local

temperature in the extruder is a problem for heat-sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder, the shape can be adapted to the next processing step without grinding [20].

NANOSUSPENSION

Nanosuspension technology has been developed as a promising candidate for the efficient delivery of hydrophobic drugs.This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system consisting of nano-sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600nm [25, 26].

Various methods utilized for the preparation of nanosuspensions include precipitation technique, media milling, high-pressure homogenization in water, high-pressure homogenization in non-aqueous media, and a combination of Precipitation and high-Pressure homogenization [27, 28].

Precipitation Technique

In the precipitation technique, thedrug is dissolved in a solvent, which is then added to antisolventto precipitate the crystals. The basic advantage ofprecipitation technique is the use of simple and low-cost equipments, but the challenge is the addition of the growingdrug crystals to avoid the formation of microparticles. The limitationof this precipitation technique is that the drug needs tobe soluble in at least one solvent, and this solvent needs to bemiscible with antisolvent. Moreover, precipitation techniqueis not applicable to drugs, which are simultaneously poorlysoluble in aqueous and nonaqueous media [29].Nanosuspension of Danazol and Naproxen has been prepared by precipitation technique to improve their dissolution rate andoral bioavailability. The size reduction of naproxen was alsoassociated with an apparent increase in the rate of absorptionby approximately 4-fold [30, 31].

Media Milling

The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug, and stabilizer is rotated at a

very high-shear rate under controlled temperatures for several days (at least 2–7 days). The milling medium is composed of glass, Zirconium oxide, or highly cross-linked polystyrene resin. High energy shear forces are generated as a result of the impaction of the milling media with the drug resulting in the breaking of the microparticulate drug to nanosized particles [28].

High Pressure Homogenization

High-pressure homogenization has been used to prepare the nanosuspension of many poorly water-soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high-pressure homogenizer.

The principle of this method is based on cavitation in the aqueous phase. The cavitation forces within the particles are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required [32]. Dissolution rate and bioavailability of poorly soluble drugs such as spironolactone, budesonide, and omeprazole have been improved by reducing their particle size by high-pressure homogenization [33–35].

Combined Precipitation and Homogenization

The precipitated drug nanoparticles have a tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (homogenisation). They are in completely amorphous, partially amorphous or completely crystalline forms, which create problems in long-term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized, which preserves the particle size obtained after the precipitation step.

SUPERCRITICAL FLUID (SCF) PROCESS

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp), allowing them to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density and

mass transport characteristics of the fluid that largely determine its solvent power.Once the drug particles are solubilised within the SCF (usually carbon dioxide), they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allow micronisation of drug particles within narrow ranges of particle size, often to submicron levels.

Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5–2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement.

Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with the compressed antisolvent process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvent processes (SAS), rapid expansion of supercritical solutions (RESS), gas anti-solvent recrystallization (GAS), and aerosol supercritical extraction system (ASES) [36, 37].

Cryogenic Techniques

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with a high degree of porosity at very low-temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), location of the nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N2, Ar,O2, and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze-drying, atmospheric freeze-drying, vacuum freeze drying, and lyophilisation [38–40].

Spray Freezing onto Cryogenic Fluids

Briggs and Maxwell invented the process of spray freezing onto cryogenic fluids.In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol, or dextran) were dissolved in water and atomized above the surface of a boiling, agitated fluorocarbon refrigerant. A sonication probe can be placed in the stirred refrigerant to enhance the dispersion of the aqueous solution [41].

Spray Freezing into Cryogenic Liquids (SFL)

The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability. It incorporates direct liquid-liquid impingement between the automatized feed solution and cryogenic liquid to provide intense atomization into microdroplets and consequently, significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders [42].

Spray Freezing into Vapor over Liquid (SFV/L)

Freezing of drug solutions in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability. During SFV/L, the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow [43].

Ultra-Rapid Freezing (URF)

Ultra-rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drug solution to the solid surface of the cryogenic substrate leads to instantaneous freezing, and subsequent lyophilization (for removal of solvent) forms micronized drug powder with improved solubility. Ultra-rapid freezing hinders the phase separation and the crystallization of the pharmaceutical ingredients leading to intimately mixed, amorphous drug-carrier solid dispersions and solid solutions [45].

INCLUSION COMPLEX FORMATION-BASED TECHNIQUES

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

The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-

glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins (CDs). These are non-reducing, crystalline, water-soluble, and cyclic oligosaccharides consisting of glucose monomers arranged in a donut-shaped ring having a hydrophobic cavity and hydrophilic outer surface as illustrated in CDs are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrin [46].The surface of the cyclodextrin molecules makes them water-soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules.

Various technologies adapted to prepare the inclusion complexes of poorly water-soluble drugs with cyclodextrins are briefly described below.

Kneading Method

This method is based on impregnating the CDs with a little amount of water or hydroalcoholic solutions to convert into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through a sieve if required. On a laboratory scale, kneading can be achieved by using a mortar and pestle. On a large scale, kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes, and it presents a very low cost of production [48].

Lyophilization/Freeze-Drying Technique

In order to get a porous, amorphous powder with a high degree of interaction between drug and CD, the lyophilization/freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex forms by this method.

The limitations of this technique are the use of specialized equipment, time-consuming process, and yield of the poor flowing powdered product. Lyophilization/freeze-drying technique is considered as an alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent [49].

Microwave Irradiation Method

This technique involves the microwave irradiation reaction between the drug and complexing agent using a microwave

oven. The drug and CD in a definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round-bottom flask. The mixture is reacted for a short time of about one to two minutes at 60°C in the microwave oven.

After the reaction completes, an adequate amount of solvent mixture is added to the above reaction mixture to remove the residual uncomplexed free drug and CD. The precipitate so obtained is separated using Whatman filter paper and dried in a vacuum oven at 40◦C. Microwave irradiation method is a novel method for industrial-scale preparation due to its major advantage of shorter reaction times and higher yield of the product [50].

MICELLAR SOLUBILIZATION

The use of surfactants to improve the dissolution performance of poorly soluble drug products is probably the basic, primary, and oldest method. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in an aqueous medium. They are also used to stabilise drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% formost surfactants),micelle formation occurs, which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs. Surfactant also improves the wetting of solids and increases the rate of disintegration of solid into finer particles [11].

Commonly used nonionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroyl-macroglycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved [51, 52].Examples of poorly soluble compounds that use Micellarsolubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone [53].

HYDROTROPHY

Hydrotrophy is a solubilisation process, whereby the addition of a large amount of the second solute, the hydrotropic agent, results in an increase in the aqueous solubility of the first solute.Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic acids.

Additives or salts that increase solubility in the given solvent are said to "salt in" the solute, and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts"; a phenomenon known as "hydrotropism." Hydrotrophy designates the increase in solubility in water due to the presence of a large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drugs [54, 55].

The hydrotropes are known to self-assemble in solution. The classification of hydrotropes on the basis of molecular structure is difficult since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate), and dodecylatedoxidibenzene. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism, and their effective hydrotrope action may be due to the availability of interactive pi (π) orbital [56]. Hydrotropes with the cationic hydrophilic group are rare, for example, salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, and so forth [57].

CRYSTAL ENGINEERING

The surface area of the drug available for dissolution is dependent on its particle size and ability to be wetted by luminal fluids. This particle size, which is critical to drug dissolution rate, is dependent on the conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. The comminution techniques can produce particles that are highly heterogeneous, charged, and cohesive, with the potential to cause problems in downstream processing and product performance. Hence, crystal engineering techniques are developed for the controlled crystallization

of drugs to produce high purity powders with a well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy [58].

By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangements; such crystals are called *polymorphs*.As a result, polymorphs for the same drug may differ in their physicochemical properties, such as solubility, dissolution rate, melting point, and stability. Most drugs exhibit structural polymorphism and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

A classic example of the importance of polymorphism on bioavailability is that of chloramphenicol palmitate suspensions. It was shown that the stable polymorph of chloramphenicol palmitate produced low serum levels, whereas the metastable polymorph yielded much higher serum levels when the same dose was administered [59].

In another study, it was found that tablets prepared from the form *A*polymorph of oxytetracycline dissolved significantly more slowly than the tablets with form *B* polymorph [60]. The tablets with form *A*polymorph exhibited about 55% dissolution at 30 min, while the tablets with form *B* polymorph exhibited almost complete (95%) dissolution at the same time.

The crystal engineering approach also involves the preparation of *hydrates and solvates* for enhancing the dissolution rate. During the crystallization process, it is possible to trap molecules of the solvent within the lattice. If the solvent used is water, the resultant crystal is a hydrate; if any other solvent is used, it is referred to as solvate. The dissolution rate and solubility of a drug can differ significantly for different solvates. For example, glibenclamide has been isolated as pentanol and toluene solvates, and these solvates exhibited higher solubility and dissolution rates than two non-solvated polymorphs [61].It is possible for the hydrates to have either a faster or slower dissolution rate than the anhydrous form. The most usual situation is for the

anhydrous form to have a faster dissolution rate than the hydrate. For example, the dissolution rate of theophylline anhydrate was faster than its hydrate form [62].

In certain cases, the hydrate form of the drug may show a rapid dissolution rate than its anhydrous form. Erythromycin dihydrate was found to exhibit significant differences in the dissolution rate when compared to monohydrate and anhydrate forms [63]. In general, it is undesirable to use solvates for drugs and pharmaceuticals as the presence of organic solvent residuesmaybe toxic. Also, all the organic solvents have specific limits for daily exposure to humans as a residual solvent in the formulated preparation. Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through in-depth knowledge of crystallization processes and the molecular properties of active pharmaceutical ingredients. The process involves dissolving the drug in a solvent and precipitating it in a controlled manner to produce *nanoparticles* through the addition of an antisolvent (usually water) [58].

*Pharmaceutical cocrystals*open a new avenue to address the problems of poorly soluble drugs. They contain two or more distinct molecules arranged to create a new crystal form whose properties are often superior to those of each of the separate entities. The pharmaceutical cocrystals are formed between a molecular or ionic drug and a cocrystal former that is solid under ambient conditions [64]. These are prepared by slow evaporation from a drug solution containing stoichiometric amounts of the components (cocrystal formers); however, sublimation, growth from the melt, or grinding of two or more solid cocrystal formers in a ball mill is also suitable methodologies [65].

Carbamazepine: saccharin cocrystal was shown to be superior to crystal forms of carbamazepine alone in terms of stability, dissolution, suspension stability, and oral absorption profile in dogs [66]. In another study by Childs et al.,fluoxetine HCl succinic acid cocrystal was found to exhibit an approximately twofold increase in aqueous solubility after only 5min [67]. It was observed that the itraconazole L-malic acid cocrystal exhibited a similar dissolution profile to that of the marketed formulation [68].

Traditional crystallization methods include sublimation, crystallization from solutions, evaporation, thermal treatment,

desolvation, or grinding/milling. These are being replaced with novel methods of crystal engineering such as*SCF technologies* [69, 70] to produce pharmaceutical solids with desired dissolution rate and stability. *Melt sonocrystallization* is yet another emerging technology that uses ultrasonic energy to produce porous fast-dissolving particles for hydrophobic drug molecules [71]. Based on these exciting reports, it appears that crystal engineering techniques need tobe exploited more for enhancing the dissolution rate of poorly soluble drugs. Other techniques that enhance the solubility of poorly water-soluble drugs include salt formation, change in dielectric constant of solvent, Chemical modification of the drug, use of hydrates or solvates, use of Soluble prodrug, application of ultrasonic waves, and spherical crystallization. See below **figure 3**.

pH ADJUSTMENT

Poorly water-soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can, in principle, be used for both oral andparenteral administration. Upon intravenous administration, the poorly soluble drug may be precipitate because blood is a strong buffer with pH between.

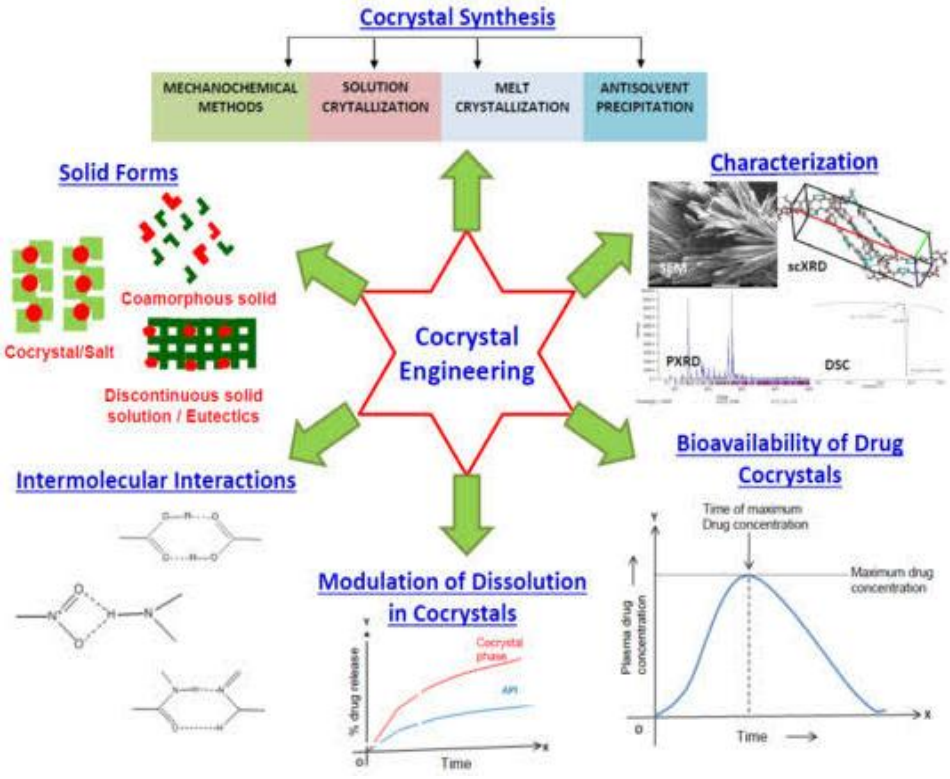

Figure 3: Cocrystal Engineering

To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are importantto consider. In the stomach, the pH is around 1 to 2, and in the duodenum, the pH is between 5-7.5, so upon oral administration, the degree of solubility is also likely to be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic, poorly soluble compounds.[72]

Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.[73]The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug. If the precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased. This approach is frequently used in surveys as pre-clinically pH adjustment is a good techniqueto assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading.

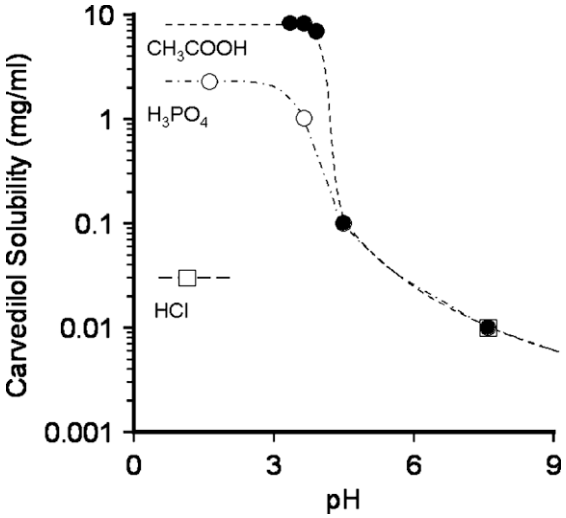

Figure 4: pH adjustment

Advantages

- Simple to formulate and analyse.
- Simple to produce and fast track.

- Uses small quantities of compound, amenable tohigh throughput evaluations.

Disadvantages

- The risk for precipitation upon dilution with aqueous media having a pH at which the compound is lesssoluble. Intravenously this may lead to emboli; orally, it may cause variability.
- Tolerability and toxicity (local and systemic) related with the use of a non-physiological pHand extreme pHs.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

Commercial products using pH adjustment

Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na+ per 5 ml ampoule) is an example of a pH-adjusted formulation containing co-solvents.

CO-SOLVENCY

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

Historically, this is one of the most widely used techniques because it is simple to produce and evaluate.Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. Parenteral formulations may require the addition of water or a dilution step with an aqueous media to lower the solvent concentration prior to administration. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Co-Solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Very high drug concentrations of poorly soluble compounds can be dissolved compared to other solubilization approaches.

However, the bioavailability may not be dramatically increased because the poorly soluble drug will typically uncontrollably crash out upon dilution into a crystalline or amorphous precipitate. In this case, dissolution of this precipitate is required for oral absorption. Co-solvents may be combined with other solubilization techniques and pH adjustment to further increase the solubility of poorly soluble componds. The use of co-solvents is a highly effective technique to enhance the solubility of poorly soluble drugs. The most frequently used low toxicity co-solvents for parenteral use are propylene glycol, ethanol, glycerin, and polyethylene glycol.[74] Dimethylsulfoxide (DMSO) and dimethylacetamide (DMA) have been widely used as co-solvents because of their large solubilization capacity for poorly soluble drugs and their relatively low toxicity.[75]

Advantages

- Simple and rapid to formulate and produce.

Disadvantages

- As with all excipients, the toxicity and tolerability related to the level of solvent administered have to be considered.
- Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size.
- Many of the insoluble compounds Phares works with are unsuited to co-solvents alone, particularly for intravenous administration. This is because the drugs are extremely insoluble in water and do not readily redissolve after precipitation from the co-solvent mixture. In these situations, there is a potential risk for embolism and local adverse effects at the injection site.
- As with all solubilized forms, the chemicalstability of the insoluble drug is worse than in acrystalline state.

Co-solvent products

Nimodipine Intravenous Injection(Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®,
GSK) are examples of co-solvent formulations.

MICROEMULSIONS

Microemulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with the incorporation of proteins for oral, parenteral, as well as percutaneous/ transdermal use.[78,79]

A microemulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent, which dissolves a poorly water-soluble drug. Upon contact with water, the formulations spontaneously disperse (or 'self emulsifies') to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug.

Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 20-200 nm.These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity. A self microemulsifying drug delivery system (SMEDDS) is an anhydrous system of microemulsions. It has also been referred to as microemulsion pre-concentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in an aqueous phase under gentle agitation.The agitation required for the self-emulsification comes from the stomach and intestinal motility.[80] The surfactant can be non-ionic like polyoxyethylene surfactants, e.g.,Brij or sugar esters like sorbitanmonooleate (Span 80), cationic, or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate, or zwitterionic such as phospholipids like lecithin (phosphatidylcholine) commercially available from soybean and eggs. Lecithin is very popular because it exhibits excellent biocompatibility. Combinations of ionic and non-ionic surfactants are also found to be effective.

The major disadvantage of microemulsions is their high concentration of surfactant/cosurfactant, making them unsuitable for IV administration. Dilution of microemulsions below the critical micelle concentration of the surfactants could cause precipitation of the drug; however, the fine particle size of the resulting precipitate would still enhance absorption.[81]

Compared to macroemulsion pre-concentrates, a microemulsion pre-concentrate remains optically clear after dilution and usually contains a higher amount of water-soluble surfactant and a higher content of a hydrophilic solvent.These formulations are only administered orally due to the nature of the excipients. Solubilization using

microemulsion pre-concentrates is suited to poorly soluble lipophilic compounds that have high solubility in the oil and surfactant mixtures. Most self-emulsifying systems are limited to administration in lipid-filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell.

Emulsion droplet size is a major factor influencing the bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain a high concentration of surfactants, they should be limited to oral applications and may not be advisable for long-term use due to the potential of causing diarrhea.[82]

Advantages

- The pre-concentrates are relatively easy tomanufacture.
- Well-developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food (i.e. the fasted state).

Disadvantages

- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended.
- Formulations containing several components become more challenging to validate.

Microemulsion products

Examples of poorly soluble compounds that use micro-emulsion pre-concentrates are the HIV protease inhibitor tipranavir (Aptivus® capsules, Boehringer IngelheimGmBH) and the category-defining immunosuppressant cyclosporine A, USP modified (Neoral® capsules, Novartis AG).

MICELLAR SOLUBLIZATION

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in an aqueous

medium.[83]They can also be used to stabilise drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05-0.10% for most surfactants), micelle formation occurs, entrapping the drugs within the micelles.This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroyl-macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved.[84]

Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs.Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone and rosiglitazone.[85]

COMPLEXATION

The complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contains 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability.

Derivatives of β-cyclodextrin with increased water solubility (e.g.,hydroxypropyl-β-cyclodextrin HP-β-CD) are most commonly used in pharmaceutical formulation. Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-m-toluamide (DEET) 57 and the stability and photostability of sunscreens.[86] Cyclodextrins are large molecules with molecular weights greater than 1000Da; therefore, it would be expected that they would not readily permeate the skin. Complexation with cyclodextrins has been variously reported to both increase60, 61 and decrease skin penetration.[87]

In a recent review of the available data, Loftsson and Masson concluded that the effect on skin penetration might be related to cyclodextrin concentration, with

reduced flux generally observed at relatively high cyclodextrin concentrations, whilst low cyclodextrin concentrations resulting in increased flux.[88]

As flux is proportional to the free drug concentration, where the cyclodextrin concentration is sufficient to complex only the drug, which is in excess of its solubility, an increase in flux might be expected. However, at higher cyclodextrin concentrations, the excess cyclodextrin would be expected to complex free drug and hence reduce flux.

Skin penetration enhancement has also been attributed to the extraction of stratum corneum lipids by cyclodextrins. Given that most experiments that have reported cyclodextrin mediated flux enhancement have used rodent model membranes in which lipid extraction is considerably easier than human skin, the penetration enhancement of cyclodextrin complexation may be an overestimate. Shaker and colleagues recently concluded that complexation with HP- β-CD had no effect on the flux of cortisone through hairless mouse skin by either of the proposed mechanisms.

Lipophilic drug- cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drug and excipient together, resulting in enhanced drug solubilization. Cyclodextrins (CD) are a group of structurally-related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface. Cyclodextrins consisting of 6, 7 and 8 D- glucopyranosyl units connected to α -1, 4 glycosidic linkages are known as α, β, γ, cyclodextrins, respectively. [89]

Hydrophilic may be toxic; hence, methyl, hydroxypropyl, sulfoalkylated and sulfated derivatives of natural cyclodextrins that cyclodextrins are nontoxic in normal doses while lipophilic ones possess improved aqueous solubility are preferred for pharmaceutical use. In the solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents. The permeability through the biological membrane is enhanced by the presence of cyclodextrins. Masson reported about the permeation enhancement property of poorly water-soluble drugs in the presence of the CDs. These act as permeation enhancers by carrying the drug through the aqueous barrier which exists before the lipophilic surface of biological membranes. This can

also be achieved through the double characteristics of the CDs, thus present a character much lipophilic as hydrophilic. CDs can also be used as nasal permeation enhancers acting by interaction with nasal epithelium by modifying tight junction & lipid and protein content of the membrane, which enhances the permeation of the membrane. [90]

CDs can also be utilized as permeation enhancers in pulmonary drug delivery systems. Rifampicin is a so-called concentration-dependent antibiotic; the rate and extent of bacterial kill are related to the attainment of high maximum concentration relative to the minimal inhibitory concentration. The rifampicin-CD inclusion compound can improve the lung transport of drug when nebulized with compatible pulmonary deposition and achieve a required concentration of drug in broncho-alveolar epithelium lining-fluid when administered as an aerosolized solution.[91]

The forces driving complexation were attributed to (i) the exclusion of high energy water from the cavity, (ii) the release of ring strain, particularly in the case of α -CD, (iii) Vander walls interactions, and (iv) hydrogen and hydrophobic bindings.[92]

Solublization by complexation is achieved through specific interaction rather than changes in the bulk solvent properties as in other solublizing systems such as co-solvents, emulsion and pH adjustments. The dissociation is very rapid, quantitative and therefore predictable. Another significant advantage of the complexationtechnique is that some commonly used complexing agents such as hydroxypropyl beta-cyclodextrin and sulfobutyl beta-cyclodextrin are less toxic compared to other solublizing agents such as surfactant and co-solvents. Since most complexes formed is 1:1 complexes of the AL type, the dilution of complexes will not result in a solution that is supersaturated with respect to the substrate. This can be important for very insoluble compounds that may precipitate upon injection when solublized by other systems such as co-solvents.

Despite all the attractive advantages of complexation, there are disadvantages. First of all, the compound has to be able to form complexes with the selected ligand. For compounds with very limited solubility to start with, solubility enhancement can be very limited. The second limitation is the complexes of Ap type, dilution of the system may still result in precipitation. This is also true for

solublization via a combined technique such as complexation with pH adjustment.

Lastly, the potential toxicity issue, regulatory and quality control issue related to the presence of ligand may add complication and cost to the development process.[93]

CONCLUSION

Dissolution of the drug is the rate-determining step for oral absorption of the poorly water-soluble drugs, and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce the frequency of dosing and better patient compliance combined with a low cost of production. Selection of a method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirements like tablet or capsule formulation, strength, immediate or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

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