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Techniques for solubility enhancement of poorly soluble drugs: an overview

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ABSTRACT

A success of formulation depends on how efficiently it makes the drug available at the site of action. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for drugs. This is true for parenterally, topically and orally administered solutions. Hence various techniques are used for the improvement of the solubility of poorly water soluble drugs include hydrotrophy, use of salt form, use of precipitation inhibitors, alteration of pH of the drug micro-environment, solvent deposition, precipitation pH adjustment, co-solvency, micellar solubilization, super critical fluid techniques, solid dispersion, complexation, micro-emulsion, solid solution, eutectic mixture, selective adsorption on insoluble carriers, evaporative precipitation into aqueous solution, use of surfactants, use of amorphous, anhydrates, solvates and nanonisation.

Keywords: Solubility, Solubility enhancement, Nanonisation, Poorly water solubleparameters.

INTRODUCTION

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fractionm. Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. Solubility is the characteristic physical property referring to the ability of a given substance, the solute, to dissolve in a solvent. Almost More than 90% drugs are orally administered. Drug absorption, sufficient & reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on Solubility of that compound in aqueous medium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs Employed by many pharmaceutical companies are poorly water soluble. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain of the 130 orally administered drugs on the WHO list 61 could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable). The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility. Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. Solvent is a component which forms major constituent of a solution & is capable to dissolve another substance to form a uniformly disperse mixture at

the molecular level. Solute is a substance that present in small quantity & dissolves in solvent. "The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature". In the other words, solubility can also define as the ability of one substance to form a solution with another substance [1].

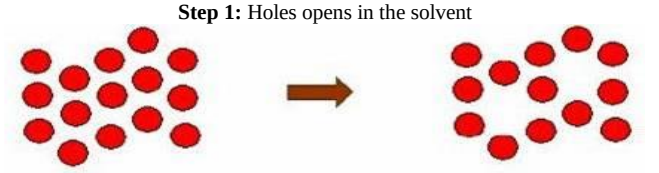
Table 1: Descriptive terms for solubility

Descriptive terms	Parts of solvent required to dissolve one part of solute
Very soluble	Less than 1
Freely soluble	More than 1 but less than 10
Soluble	More than 10 but less than 30
Sparingly soluble	More than 30 but less than 100
Slightly soluble	More than 100 but less than 1000
Very slightly soluble	More than 1000 but less than 10,000
Very very slightly soluble or practically Insoluble	More than 10,000

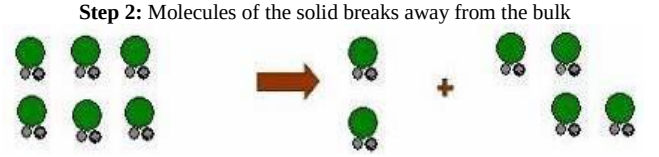
Solubilization

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

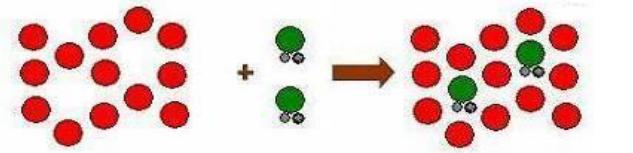
Step 1: Holes opens in the solvent



Step 2: Molecules of the solid breaks away from the bulk



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



Factors Affecting Solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium, particle size, temperature, pressure, nature of the solute and solvent, molecular size polarity, polymorphs, rate of solution.

Techniques for solubility enhancement hydro trophy

Hydrotropic effect, the meaning is taken as the increase in saturation solubility of a substance in water by the addition of organic salts or also non-electrolytes, which of course must be physiologically compatible for pharmaceutical application. The mode of action of the hydrotropic substances is thought to be due to either an associate formation, in low concentrations to a formation of molecular complexes or in higher concentrations to the water structure being influenced. These hydrotropic substances are able to increase the number of hydrogen bridges in the water clusters. This makes the water more hydrophobic & thus it is a better solvent for non-polar drug However, the use of hydrotropic substances such as sodium benzoate, nicotinamide, urea, caffeine, sorbitol, etc. is limited due to the following factors:

Slight increase of saturation solubility with high concentration of excipients. (E.g. up to 50% nicotinamide with a triple increase in the saturation solubility)

Isotonicity is not reached.

Individual effects of the excipients.

Hydrotropic solubilization is one of them. Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium aciculate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs. Hydrotropes are a class of amphiphilic molecules that cannot form well organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules. Often strong synergistic effects are observed when hydrotropes are added to aqueous surfactant or polymer solutions. A hydrotrope is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation. Hydrotropes do not have a critical concentration above which self-aggregation 'suddenly' starts to occur (as found for micelle- and vesicle-forming surfactants, which have a critical micelle concentration or CMC and a critical vesicle concentration, respectively Instead, some hydrotropes aggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many hydrotropes do not seem to self-aggregate at all, unless a solubilisate has been added.

Hydrotropes are in use industrially. Hydrotropes are used in detergent formulations to allow more [3].

Use of salt form

Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between the pKa value of the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are water soluble than the parent drug[3]. Salt formation is frequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation, which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure. The ideal characteristics of a salt are that it is chemically stable, not

hygroscopic, presents no processing problems, dissolves quickly from solid dosage forms (unless it is formed with the intent to delay dissolution and exhibits good bioavailability) Potentially Useful Salts: Salt formation is one of the simplest chemical reactions, involving either a proton transfer or a neutralization reaction between an acid and a base. Theoretically, every compound possessing acidic and/or basic properties can participate in salt formation.

Complex salt formation

Organic acid salt forms of basic drugs, such as amines, frequently have higher aqueous solubility than their corresponding inorganic salts. Acetic acid produced solubility higher than those observed with nay of the inorganic acids. Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of units between the pKa value of the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are water soluble than the parent drug[2]. Salt Formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin, Theophylline, Barbiturates.

Alteration of pH of the drug microenvironment

This can be achieved in two ways- in situ salt formation, and addition of buffers to the formulation e.g. buffered aspirin tablets. Definition of PH: PH is the negative logarithm to the base 10 of the hydronium ion concentration.

$pH = -\log [H3O+]$

For ionizable drugs, the aqueous solubility is strongly influenced by the pH of the solvent.

Thus, the pH adjustment may be the most simple, economic and effective Way of increasing the aq. solubility of the drug.

Solubilization by pH

For a drug to be formulated in a liquid dosage form is generally required to be dissolved in an aqueous media.

The ionized form of the drug is favored over unionized form to be solubilized in the aqueous solvent.

For weakly acidic drugs /salt,

Lower pH → unionized form → insoluble/ precipitation

Higher pH → ionized form → more solubility

For weakly basic drugs / salt,

Lower pH → ionized form → more solubility

Higher pH → unionized form → insoluble/precipitation [2].

Solvent deposition/ evaporation

In this method, the poorly aqueous soluble drug such as nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose by evaporation of solvent. The carrier is then dispersed in the solution by stirring and the solvent is removed by evaporation under temperature and pressure. The resultant mass is then dried, pulverized, and passed through a sieve. The Increase in the dissolution rate is ascribed to the reduced particle size of the drug deposited on the carrier and enhanced wet ability of the particles brought about by the carrier.

Precipitation

In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nano size particles. The product so prepared is also called as hydrosol. Nano-suspension of Danazol and Naproxen were prepared by precipitation technique to improve their dissolution rate and oral bioavailability. The solution with the drug is then injected into water, which act as bed solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nano-crystals. Nano-crystals can be removed from the solution by filtering then dried in air.

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 and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with Ph between 7.2–7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to 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 be influenced as the drug passes through the intestines.

Ionizable compounds that are stable and soluble after pH adjustment are best suited. As per pH-partition hypothesis and Handerson – Hessel batch equation, ionization of a compound is dependent on the pH of media and pKa of drug.

Advantages

Simple to formulate and analyze.

Simple to produce and fast track.

Uses small quantities of compound, amenable to high throughout evaluations.

Disadvantages

Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. 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 pH and 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.

Co-solvency

The addition of a water-miscible or partially miscible organic solvent (i.e. co-solvent to water) is a common and effective way by which to increase solubility of a non-polar drug. The technique is known as co-solvency. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol Solubility enhancement as high as 500-fold is achieved using 20% 2- pyrrolidone

Micellar solubilization

Surfactants are compounds that have molecular structures with two distinct regions: A polar (hydrophilic) head group and a Non-polar (hydrophobic tail). 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 lipophillic drugs in aqueous medium.

Traditional surfactants

Anionic Surfactant: Hydrophilic group carries a negative charge. E.g. SLS, Potassium laurate

Cationic Surfactant: Hydrophilic group carries a positive charge. E.g. Cetrimide, Benzalkonium Chloride (Zwitter-ion surfactant) Molecule carries both negative and positive charge. E.g. N-dodecyl-N, N-dimethylbetaine.

Nontraditional surfactants

Nonionic Surfactant: Poloxamers (Pluronics) Hydrophile carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene groups. E.g. Cetomacrogol (polyoxyethylated glycol monoethers), Spans and Tweens They can also be used to stabilize 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 poly-sorbates, poly-oxy-ethylated castor oil, poly- oxy-ethylated glycerides, lauryl macro-glycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize micro-emulsions and suspensions into which drugs are dissolved.

Super critical fluid techniques

The number of applications and Technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon-dioxide; the most widely used Supercritical fluid. It is safe, environmentally friendly, and economical. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels [4]. Novel nanoising and solubilization technology whose application has increased particle size reduction via supercritical fluid processes.

Solid dispersion

Solid dispersion, a concept firstly introduced by Sekiguchi & Obi. 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. However, the definition can now be broadened to include certain nanoparticles, microcapsules, microspheres and other dispersion of the drug in polymers prepared by using any one of the process [5]. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products.

Carriers for solid dispersions

Acids: – Citric Acid, Tartaric Acid, and Succinic Acid.

Sugars: – Sucrose, Dextrose, Sorbitol, Maltose, Galactose, and Xylitol.

Polymeric Materials: – Poly-vinyl-pyrollidone, PEG 4000 & 6000, Carboxy-mythyl cellulose, Hydroxy-propyl-cellulose, Guar gum, Xanthan gum, Sodium Alginate, Dextrin, Cyclodextrin.

Surfactants – Polyoxyethylene stearate, poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamine E TPGS NF.

Miscellaneous– Urea, Urethane, Hydroxyalkyl Xanthene, Penta-erythritol 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 amphiphilic in nature [6].

Mechanism of increased dissolution rate by solid dispersion

Reduction in particle size.

Solublization effect (use of carriers).

Increased wettability and dispersibility by carriers

Formation of metastable dispersion with reduced lattice energy for faster dissolution.

Dissolution energy for furesamide is 17Kcal/mol while Dissolution energy for 1:2 furesamide:PVP co-precipitate is 7.3Kcal/mol.

Advantages and disadvantages of solid dispersion advantages

Increase in dissolution rate & extent of absorption and reduction in pre-systemic metabolism. Transformation from liquid form of drug into solid form. Ex. Clofibrate & benzyl benzoate incorporated into PEG-6000 to give solid dispersion also avoidance of polymorphic changes so no bioavailability problems (as in case of

nabilone & PVP dispersions.

Disadvantages

Major problem is instability**.** There is change in crystallanity & decrease in dissolution rate with aging. Ex. Crystallization of ritonavir from supersaturated solution in solid dispersion System (main reason for withdrawal of ritonavir capsules [Norvir, Abbott] from market. Moisture and temperature increases deteriorating effect on solid dispersion than physical mixture.

Complexation

Complexation is the association between two or more molecules to form a no bonded entity with a well-defined stoichiometry. The two types of complexation that are useful for increasing the solubility of drugs in aqueous media are stacking and inclusion.

Self-association and stacking complexation

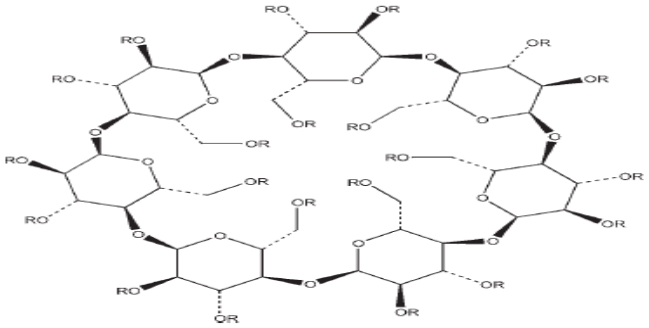
Non-polar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of the water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar non-polar regions in the molecule. Stacked complexes can be homogenous or mixed. The former is known as self-association and the later as complexation.

Inclusion complex

An inclusion complex is produced by the inclusion of a non-polar molecule or the non-polar region of a molecule (known as the Guest) into the non-polar cavity of another molecule or group of molecules (known as the Host).

When the guest molecule enters the host molecule the contact between water and the non-polar regions of both is reduced. Thus, inclusion phenomena are the result of the same driving force that produces the micellization, Self-association, and stacking: namely the squeezing out from water of non-polar moieties. The most commonly used host molecules are thecyclodextrins.

Figure 1: Structure of β-Cyclodextrin with 7 glucose units



Glucose molecules are relatively soluble in water and have cavities large enough to accept non-polar portions of common drug molecules. Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 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 non-covalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Derivatives of β-cyclodextrin with increased water solubility (e.g. hydroxyl-propyl-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) and the stability and photo stability of sunscreens. 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 increase and decrease skin penetration. 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, and cyclodextrins, respectively. Hydrophilic cyclodextrins are nontoxic in normal doses while lipophilic ones may be toxic; hence, methyl, hydroxypropyl, sulfoalkylated and sulfated derivatives of natural cyclodextrins that possess improved aqueous solubility are preferred for pharmaceutical use [7].

Micro-emulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous/ transdermal use. A micro-emulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poor 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. Micro-emulsions 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-micro-emulsifying drug delivery system (SMEDDS) is an anhydrous system of micro-emulsions. It has also been referred to as micro-emulsion pre-concentrate by some researchers. It is composed of oil, surfactant and co-surfactant and has the ability to form o/w micro-emulsion when dispersed in aqueous phase under gentle agitation. The agitation required for the self-emulsification comes from stomach and intestinal motility. The surfactant can be non-

ionic like poly-oxy-ethylene surfactants e.g. Brij or sugar esters like sorbitan-mono-oleate (Span 80), cationic, or anionic like alkyl-tri-methyl-ammonium bromide and sodium dodecyl-sulphate, or zwitter ionic 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 micro-emulsions is their high concentration of surfactant/co-surfactant, making them unsuitable for IV administration. Dilution of micro-emulsions 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. Compared to macro emulsion pre-concentrates, micro-emulsion pre-concentrates remain optically clear after dilution and usually contain 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 micro-emulsion pre-concentrates is suited to poorly soluble lipophilic compounds that have high solubility in the oil and surfactants 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 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 high concentration of surfactants, they should be limited to oral [8].

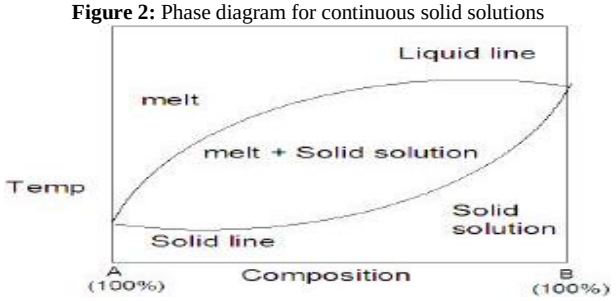
Solid solution

Two components crystallize together in homogenous one phase system. Particle size of drug in solid solution is reduced to its molecular size. Solid solutions shows faster dissolution rate than eutectic mixtures. More than 500 papers have been published on the subject and various materials are employed as drug carriers.

Classification of solid solutions, according to extent of miscibility of two components;

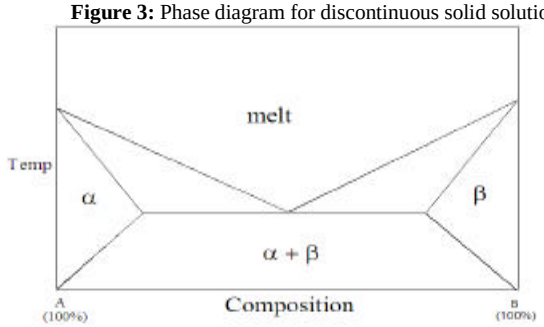
Continuous Solid Solution – Two solids miscible in solid state in all Preparation.

Figure 2: Phase diagram for continuous solid solutions



Discontinuous Solid Solutions – Exist at extremes of composition

Figure 3: Phase diagram for discontinuous solid solutions



According to criterion of molecular size of two components composition of the solid solution

Poorly water soluble drug

Carrier (polymer or polymer blends)

Solvent (to dissolve the phase if necessary, depends on the methodology used)

Additives (co solvents or glycerol)

Re-crystallization inhibitors

Substitutional solid solution

Here Substitution of solvent molecule by solute molecule in crystal lattice. Molecular size should not differ by 15% < Ex. Anthracene Acenapthacene, Ammonium-potassium thiocynate.

Interstitial solid solutions

In this solute (guest) molecule occupies interstitial space in solvent (host) lattice. Solute molecule diameter should be less than 0.59 times than that of solvent. Owing to their large molecular size polymers favors formation of interstitial solid solution. Ex. Solid solution of digoxin, prednisolone acetate in matrix of PEG 600.

Reasons of solubility enhancement in solid solution

Reduction of particle size.

The resulting enhanced surface area produces higher dissolution rate & bioavailability

Carrier material has solubilization effect on the drug.

Carrier material enhances wettability & dispersibility.

Formation of the metastable dispersions

Methods of Preparation

Melting or Fusion method (Hot Melt Extrusion Technique)

Electrostatic Spinning Method

Fluidized Bed Coating

Supercritical Fluid Technique

Novel ultra-rapid freezing particle engineering process.

Eutectic mixture

These systems are also prepared by fusion method. Eutectic melts differ from solid solutions in that the fused melt of solute –m solvent show complete miscibility but negligible solid-solid solubility, i.e., such systems are basically intimately blended physical mixture of two crystalline components.

Selective adsorption on insoluble carriers

A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water soluble

drugs such as griseofulvin, indomethacin And prednisone by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are- the weak physical bonding between the adsorb ate, and hydration and swelling of the clay in the aqueous media. This study was concerned with solid dispersions, which were prepared following the dissolution method using a common solvent. The drug-polymer interactions were studied using DSC and IR techniques, as well as HPLC purity after storage in strength conditions. Neither significant interactions nor degradation of the active ingredient was observed after storage at 40 °C for 3 months. In addition, felodipine release from the solid dispersion systems was studied and the factors influencing release, such as the drug-polymer ratio, interactions, and polymer properties were investigated. HPMC was observed to promote a more significant retard and amore linear release of the active ingredient than HEC [9].

Evaporative precipitation into aqueous solution

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. The solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution on the aqueous solution to optimize particle formation and stabilization.

Use of surfactant

Surfactants are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles. The study showed that solubility enhancement of antimicrobial drug enrofloxacin using a series of co-solvents and surfactants. Aqueous solubility of enrofloxacin could be increased up to 26 times. Co-solvents alone produced only small increase in solubility. However, the combined effect of co-solvents and buffer was synergistic and a large increase in solubility could be attained. Ionic surfactants were found to be much better solubilizing agents than nonionic surfactant. Amongst ionic surfactants, solubility was found to be very high in anionic surfactant, sodium dodecylsulphate as compared to the cationic surfactant, cetyltrimethylammonium bromide. Up to 3.8 mg/ml of enrofloxacin could be dissolved in sodium dodecylsulphate.

Use of amorphs, anhydrates, solvates and metastable polymorphs

Depending upon the internal structure of the solid drug, selection of proper form ofdrug with greater solubility is important. In general, amorphs are more soluble than metastable polymorhs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates. Studied the mechanism responsible for solubility enhancement of Nifedipine solid dispersion, prepared using Vitamin E TPGS or Solutol HS-15, PEG1000, and lipocol C-10 of varying drug/polymer ratios by a fusion method. The solubility enhancement was found to be in the order of vitamin E TPGS > solutol HS-15 > lipocol C-10 > PEG1000. Based on these results, it can be concluded that enhanced solubility using vitamin E TPGS and solutol HS-15 resulted from a partial conversion of crystalline drug to the amorphous form, increase in wettability of the drug by water soluble polymers, better separation of drug particles, micellar solubilization of drug by high concentrations of surfactant polymers, and interaction between polymer and drug at the molecular level.

Amorphous > Metastable polymorph > Stable polymorph> Micronization

Micronization is reduction of particle size up to micron level Any problem related with the bioavailability of drug may be related with dissolution of drug and solubility of drug is affecting dissolution of drug [11].

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In order to get better dissolution need to increase solubility and micronization is used as one of the solubilising tool to increase solubility By micronization we get uniform and narrow particle size distribution which is essential for developing uniform dosage form

As micronization occurs surface area increases with decreasing particle size and solubility increases and observed solubility increased with decreasing particle size in accordance this equation

$$\textbf{Log S/SO = 2(€/2.303RTr)}$$

Where, S = the observed solubility, S0= Inherent equilibrium solubility, €= surface Energy of particle, R = Gas constant, T = Absolute Temperature, r = Radius of the particles.

Following methods can be used for achieving Micronization

Solid solution & eutectic mixtures

Microprecipitation & microcrystalization

Controlled crystallization, Supercritical fluid technology

Spray freezing into liquid, Spray freeze dry (SFD)

Nanonisation

It's a process whereby the drug powder is converted to nanocrystals of size 200- 600nm, e.g. amphotericin B. The main production technologies currently in use to produce drug nanocrystals yield as a product a dispersion of drug nanocrystals in a liquid, typically water (called nanosuspension).

There are three basic technologies currently in use to prepare nanoparticles:

a. Pearl milling, **b**. Homogenisation in water (wet milling as in a colloid mill), **c.** Homogenization in non-aqueous media or in water with water- miscible liquids.

Jalali et.al. Prepared megestrol acetate (MA) nanoparticles via a liquid precipitation technique. The prepared MA particles had a mean size of 208 nm, and 90% of the particles were distributed in the range of 100−300 nm, whereas the raw MA had a mean particle size of about 3.02 μm, ranging widely from 0.2 μm to 30 μm. The freeze-dried MA nanoparticles exhibited improved wettability as demonstrated by the contact angle measurement result proving that particles were covered by a hydrophilic layer. In dissolution rate tests, the nanoparticles achieved 100% drug dissolution within 5 min, while the raw MA did not dissolve completely after 120 min, suggesting that the dissolution property of MA nanoparticles was significantly enhanced [10].

CONCLUSION

By this article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poor water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above. A drug administered in solution form is immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Although salt formation, particle 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. Solid dispersion is mainly used to mask the taste of the drug substances, and to prepare rapid disintegration oral tablets. Solid dispersion has also been used to produce sustained-release microspheres using tedious methods such as water-in-oil emulsions. Above review shows that, it is now possible that to increase the solubility of poorly soluble drugs with the help of solid dispersion technique effectively. Also this method is practically simple & less tedious than other methods.

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