REVIEW ARTICLE

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A Path for Horizing Your Innovative Work

A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES

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Accepted Date: 03/02/2012 **Publish Date: 27/02/2012**

Abstract: 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 certain 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 microenvironment, Solvent Deposition, Precipitation pH adjustment , Nanonisation, Co-Solvency, Micellar Solubilisation, 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 amorphs,anhydrates,solvates and metastable polymorphs, micronization. Some Example Of Drug Which Solubility Improve by The Use Method Which Are Describe Above. This review article is describing the techniques of solubilizaton for the improvement of effective absorption and bioavailability.

Key Words: Solubility enhancement, Solubility, Hydrotrophy, Poorly water soluble.

INTRODUCTION

- **What Is Solubility[1]**

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 fraction.

EXPRESSION FOR APPROXIMATE SOLUBILITY[1]

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

1. Hydrotrophy [2]

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, nicotianamide, urea, caffeine, sorbitol, etc. is limited due to the following factors:

- Slight increase of saturation solubility with high concentration of excipients. (e.g. upto 50% nicotianamide with a triple increase in the saturation solubility)
- Isotonicity is not reached.
- Individual effects of the excipients.

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in 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”. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives.

The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.

Advantages of Hydrotropic Solubilization Technique:

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

2. It only requires mixing the drug with the hydrotrope in water.

3. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

4. The hydrotropes are known to self-assemble in solution

5. 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, and b-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.

2. Use of Salt Form[3, 4]

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 f the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like pencillins 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 solubilities than their corresponding inorganic salts. Acetic acid produced solubilities higher than those observed with nay of the inorganic acids.

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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[4].

3. Use of precipitation inhibitors[2]

A significant increase in free drug concentration above equilibrium solubility results in super saturation, which can lead to drug precipitation or crystallization. This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG etc.

4. Alteration of pH of the drug microenvironment[2]

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+]

Introduction

- 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 favoured 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

5. Solvent Deposition[3]

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.

6. Precipitation[3]

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.

In precipitation technique the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media.

Nanosuspension of Danazol Naproxen prepared by precipitation technique to improve their dissolution rate and oral bioavailability.

7. pH Adjustment[2]

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. Ionisable 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.

Solubilised 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.

The solubility of the poorly soluble drug is increase 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 used frequently in Survey as pre-clinically pH adjustment is a good technique to 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

- Advantages

✓ Simple to formulate and analyse.

✓ Simple to produce and fast track.

✓ Uses small quantities of compound, amenable to high throughput 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 solubilised 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 catalyse other degradation mechanisms.

8. Nanonisation[4]

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

Prepared megestrol acetate (MA) nanoparticles via a liquid precipitation technique. The as-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.

9. Co-Solvency[4]

The addition of a water-miscible or partiallay miscible organic solvent (i.e. cosolvent to water) is a common and effective way by which to increase solubility of a nonpolar drug . The technique is known as cosolvency (aka solvent ***blending***).

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 cosolvents. Co-solvents are mixtures of water and one or more water miscible solvents 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 may be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble compounds. The use of co-solvents is a highly effective technique to enhance the solubility of poorly soluble drugs.

The most frequently used low toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerine, and polyethylene glycol. Dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA) have been widely used as cosolvents because of their large solubilization capacity for poorly soluble drugs and their relatively low toxicity.

Multiple Cosolvents: It can provide a valuable method for solubilising a poorly water soluble drug when a dosage form necessitates limits on the amount and type of co solvent that can be used. Ex : A linear increase in the solubility of spironolactone was observe when the amount of PG or Glycerol is added to fixed PEG – 400 concentration

- Advantages

✓ Simple and rapid to formulate and produce.

✓ Simple and high degree of ↑se in solubility compared with other methods .

✓ No toxicity problems when compared with surfactants when given parentally

✓ Over complexing agents it doesn't require identification of a suitable substance that will form the complex .

✓ Prodrug formation and Salt formation require new drug entities as well as additional animal studies to confirm their efficacy and safety

- Disadvantages:

✓ As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.

✓ As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

✓ Toxic effects on renal , central , nervous , hepatic , and CVS system

as well as cell lysis and local tissue irritation .

✓ High tonicity leads to cell lysis or tissue necrosis.

10. Micellar Solubilisation[3]

Surfactants are compounds that have molecular structures with two distinct regions : A polar (hydrophilic) head group and a Nonpolar (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 lipophilic 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

- AMPHOLYTIC SURFACTANT (ZWITTERIONIC SURFACTANT): Molecule carries both negative and positive charge.

  E.g. N-dodecyl-N, N-dimethylbetaine

Non Traditional Surfactants

- NONIONIC SURFACTANT: 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 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.

Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs.

11. Super Critical Fluid Techniques[3]

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. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research (Markku Rantakyla et al., 2004). A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points.

Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, npentane, ethanol, ammonia, and water. Once the drug particles are solubilised within SCF, they may be recrystallised 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. Current SCF processes have demonstrated the ability to create nanosuspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specialising 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 compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallisation, Precipitation with Compressed Fluid Antisolvent, Impregnation or infusion of polymers with bioactive materials, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), supercritical antisolvents processes (SAS)

and aerosol supercritical extraction system (ASES).

12. Solid Dispersion[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.

Method for Preparation Of Solid dispersion:

- **Melt/Cool Method:**
  a. Melting Solvent Method
  b. Hot stage extrusion
- **Solvent Evaporation:**
  a. Hot Plate Drying
  b. Vacuum drying
  c. Slow evaporation at low temperature
  d. Rotary evaporation
  e. Spray drying
  f. Freeze drying
  g. Spin drying
  h. Fluid bed coating
- **Co-precipitation**
  a. Addition of an anti-solvent
- **Dropping method**

A solid dispersion of carbamazepine in polyethylene glycol 4000 (PEG-4000) increased the rate and extent of dissolution of carbamazepine. In this method, a precipitation vessel was loaded with solution of carbamazepine and PEG4000 in acetone, which was expanded with supercritical CO2 from the bottom of the vessel to obtain solvent-free particles.

A solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris-PEG®) is commercially available. Despite the promising aspects of dissolution enhancement and simplicity of concept, the solid dispersion technique has failed to gain popularity due to manufacturing, stability and scale-up issues.

Mechanism of Increased Dissolution Rate By Solid dispersion[4]

- ✓ Reduction in particle size.
- ✓ Solubilisation effect (use of carriers).
- ✓ Increased wettability and dispersibility by carriers
- ✓ Formation of metastable dispersion with reduced lattice energy for faster dissolution.
- ✓ Ex. Dissolution energy for furesamide is 17Kcal/mol while Dissolution energy.

Advantages

- Rapid dissolution rates that may be results in an increase in the rate and extent of the absorption of the drug.

- Reduction of presystematic metabolism may be due to the saturation of the enzyme responsible for biotransformation of the drug.

- Transformation of liquid form of the drug to a solid form.

- Protection of certain drugs by PEG against decomposition by saliva to allow buccal absorption.

Disadvantages

- Instability**.** Several systems have been shown changes in crystallinity and a decrease in dissolution rate with drug.

13. Complexation[3, 6]

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

Nonpolar 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 nonpolar 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 nonpolar molecule or the nonpolar region of a molecule (known as the **GUEST**) into the nonpolar 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 nonpolar 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 nonpolar moieties. The most commonly used host molecules are the cyclodextrins. These cyclic oligomers of glucose are relatively soluble in water and have cavities large enough to accept nonpolar 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 noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability.[51] 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) and the stability and photostability 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, 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. The solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents.

14. Micro Emulsions[3]

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

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 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 polyoxyethylene surfactants e.g. Brij or sugar esters like sorbitan monooleate (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.

Compared to macroemulsion pre-concentrates, microemulsion preconcentrates 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 microemulsion 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 applications and may not be advisable for long-term use due to the potential of causing diarrhoea.

- Advantages

✓ The pre-concentrates are relatively easy to manufacture.

✓ Well developed micro emulsion 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

✓ Formulation ns containing several compo nents become more challenging to validate.

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

15. Solid Solution

A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the 2 components crystallize together in a homogenous one phase system, solid solutions are also called as molecular dispersions or mixed crystals OR MELTS

Melts and co precipitates are solid dispersion that provides a means for reducing particle size to a molecular level. So solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersions. In all these cases, the solute is frequently a poorly water soluble drug acting as the **guest** and the solvent is a highly water-soluble compound or polymer acting as a **host or carrier**.

The use of dispersion method to obtain physically modified form of a drug which are much more rapidly soluble than pure compound

It is often called as mixed crystal because the two components crystallize together in a homogenous system.

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)
- Recrystallization inhibitors

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

I) Melting or Fusion method (Hot Melt Extrusion Technique)

II) Electrostatic Spinning Method

III) Fluidized Bed Coating System

IV) Supercritical Fluid Technique

V) Novel ultra-rapid freezing particle engineering process

16. Eutectic Mixture[4]

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

17. Selective Adsorption on Insoluble Carriers[4]

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 adsorbate, and hydration and swelling of the clay in the aqueous media.

Studied the use of three modified celluloses, carboxymethyl cellulose sodium, hydroxyethyl cellulose (HEC), and hydroxypropylmethyl cellulose (HPMC) as carriers in felodipine solid dispersion systems. 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 Â°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 a more linear release of the active ingredient than HEC.

18. Evaporative precipitation into aqueous solution[4]

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophiic 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.

19. Use Of Surfactant[4]

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

Studied 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 non-ionic 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.

20. Use of amorphs,anhydrates,solvates and metastable polymorphs[4]

Depending upon the internal structure of the solid drug, selection of proper form of drug 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

21. Micronization[4]

- ✓ Micronization is reduction of particle size up to micron level
- ✓ Any problem related with the bioavaibility of drug may be related with dissolution of drug and solubility of drug is affecting dissolution of drug.
- ✓ 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

$$\textbf{Log } S/S_O = 2\gamma\gamma/2.303RTr)$$

Where, S = the observed solubility, S_0= Inherent equilibrium solubility, γ= surface Energy of particle, R = Gas constant, T = Absolute Temperature, r = Radius of the particles.

Following methods can be use for achieving micronization

1. Jet milling
2. Solid solution & eutectic mixtures
3. Microprecipitation & microcrystalization
4. Controlled crystallization
5. Supercritical fluid technology
6. Spray freezing into liquid
7. Spray freeze dry (SFD)

DRUG	SOLUBILITY	SOLUBILITY ENHANCEMENT TECHNIQUES
Riboflavin[4]	Poorly Water Soluble	Hydrotrophy
Diazepam, Medazepam, Clonazepam[4]	Water Insoluble	Hydrotrophy
Saquinavir[4]	Aqueous Solubility	Hydrotrophy
Phenytoin[3]	Poorly Water Soluble	pH Adjustment:
Nimodipine Intravenous Injection[3]	Poorly Water Soluble	Co-Solvency
Digoxin Elixir Pediatric[3]	Poorly Water Soluble	Co-Solvency
Antidiabetic Drugs : glimepiride, glipizide,.[3]	Poorly Soluble	Micellar Solubilisation
Meloxicam[7]	Poorly Soluble	Solid Dispersion
Navirapine[8]	Poorly Water Soluble	Solid Dispersion
Valdecoxib[9]	Poorly Water Soluble	Co-Solvency
Nifedipine , Aceclofenac[10]	Poorly Aqueous Solubility	Solvent Deposition
Fenofibrate[11]	Poorly Water Soluble	Solid Dispersion
Glipizide[12]	Poorly Water Soluble	Solid Dispersion
Glimepiride[13]	Poorly Water Soluble	Solid Dispersion
Nifedipine[14]	Poorly Water Soluble	Nanonisation
Anti Cancer Agent[15]	Poorly Water Soluble	Complexation
Paclitaxel[16]	Poorly Water Soluble	Complexation
Lovastatin[17]	Poorly Water Soluble	Nanonisation
Aceclofenac[18]	Poorly Water Soluble	Solid Dispersion
Valsartan[20]	Poorly Water Soluble	Solid Dispersion

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 poorly 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

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