SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG BY USING VARIOUS SOLUBILITY ENHANCEMENT TECHNIQUES

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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. The bioavailability issue can be due to insufficient solubility or permeability. 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. This article explains the process of solubilization, Need for solubility enhancement, Factor affecting the solubilization and Methods of solubility enhancement.

KEYWORDS: Solubility enhancement techniques, Solubility, Permeability, Poorly water soluble drugs.

INTRODUCTION

Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development.[1] Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. As solubility and permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by solubility enhancement techniques.[2-5] 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 and 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”. 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.

The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction and mole fraction. Solubility enhancement is one of the important parameter which should be considered in formulation development of orally administered drug with poor aqueous solubility. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans depends upon the solubility of that compound in aqueous medium & they are recognized today as one of the major challenges in oral delivery of new drug substances.

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.

Table No: 1  USP & BP Solubility criteria.

<table>
<thead>
<tr>
<th>Descriptive term</th>
<th>Part of solvent required per part of solute between 15°C &amp; 25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1-10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10-30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>30-100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>100-1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000-10000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>&gt;10000</td>
</tr>
</tbody>
</table>

**PROCESS OF SOLUBILISATION**

Solubilisation process takes place as follows:

1. Breaking of intermolecular bonds in solute.
2. Separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.
It basically occurs in three steps:

- Holes open in a solvent
- Molecules of the solid breaks away from the bulk
- The free solid molecule is integrated into the hole in the solvent.

**NEED FOR SOLUBILITY ENHANCEMENT**

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

The drug in the dosage forms is released and dissolves in the surrounding gastrointestinal fluid to form a solution for easy absorption. This process is solubility limited. Once the drug is in the solution form it passes across the membrane of the cell lining the gastrointestinal tract. This process is permeability limited. Then afterwards the drug is absorbed into systemic circulation. In the sense, the oral bioavailability of drug is determined by the extent of drug solubility and permeability. Thus absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule.

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability.
For BCS class II & IV drugs rate limiting step is drug release from the dosage form and solubility in gastric fluid and not the absorption, so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs.

Table No: 2  BCS Classification.

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
<td>Propranolol, Metoprolol, Verapamil</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
<td>Nifedipine, Ketoconazole</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
<td>Acyclovir, Captopril</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
<td>Chlorothiazide, Tobramycin</td>
</tr>
</tbody>
</table>

FACTORS AFFECTING SOLUBILISATION[8-9]

**Particle size:** Particle size is inversely proportional to solubility. As particle size decreases, surface area increases thus increasing the solubility of the solute in the solvent. Particle size affect on solubility. As particle size decreases, the surface area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent. The effect of particle size on solubility can be described by,

\[ \log \frac{S_0}{S} = \frac{2 \gamma V}{2.303 g r} \]

Where,
- \( S \) = solubility of infinitely large particles
- \( S_0 \) = solubility of fine particles
- \( V \) = molar volume
- \( g \) = surface tension of the solid
- \( r \) = radius of the fine particle.

**Temperature:** Increase in temperature increases solubility. Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature.

**Pressure:** Solids and liquid solutes have no effect of pressure. But for gaseous solutes increase in pressure increases solubility and decrease in pressure decreases solubility.

**Nature of solute and solvent:** The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature. Example: at room temperature in
100gm of water only 1gm of PbCl2 can be dissolved while 200 grams of ZnCl2 can be dissolved.

**Molecular size:** Solubility of the substance is decreased with increase in molecular size and molecular weight. In case of organic molecules, due to increase in branching the solubility increases. Solubility affected by molecular size of particle. The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

**Polarity:** Polarity follows ‘like begets like’ phenomena. It is similar that polar solutes will dissolve in polar solvents only. Similarly, non-polar solutes will dissolve in non-polar solvents.

**Polymorphs:** Polymorphs can vary in melting point. Generally polymorphs are made as the changes in the structure results in the change in its solubility.

**METHODS OF SOLUBILITY ENHANCEMENT**

1. **Particle Size Reduction**
   - Conventional methods
     - Micronization
     - Nanonisation
   - **Cosolvency**
   - **pH adjustment**
   - **Hydrotropy**
   - **Solubilization by Surfactants**
   - **Supercritical fluid recrystallization (SCF)**
   - **Sonocrystallisation**
   - **Salt formation**
   - **Solid Dispersion**
     - Fusion method
     - Solvent method
     - Fusion-Solvent method
     - Dropping method
     - Spray drying Lyophilization
10. Inclusion Complexation

**Kneading method**

**Co-evaporation/solvent evaporation method**

**Microwave Irradiation Method**

**Lyophilization/Freeze-Drying Technique**

**Spray drying/ Atomization**

11. Liquisolid technique

12. High Pressure Homogenization

13. Self-Emulsifying Drug Delivery Systems

**PARTICLE SIZE REDUCTION**[^10-11]

The bioavailability or solubility of drug intrinsically connected to drug particle size. The particle size is inversely proportional to the surface area. As particle becomes smaller, the surface area increases which further improves the dissolution properties and vice-versa. The larger surface area allows greater interaction with the solvent which leads to an increase in solubility. Techniques of particle size reduction are as follows.[12-14]

**Conventional methods:** Particle size reduction is an economic, reproducible and efficient means of solubility improvement. Milling and grinding are the natural mechanical forces to comminution which impart significant amounts of physical stress upon the drug product leads to degradation. When processing of thermo sensitive or unstable active agents, the thermal stress is important during comminution and spray drying.

**Micronization:** Micronization is reduction of particle size upto 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. 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. Micronization increases the surface area by decreasing the particle size, thus increases the dissolution rate of drugs but it does not increase equilibrium solubility. It’s 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.
Nanonisation: It’s a process whereby the drug powder is converted to nanocrystals of size 200-600nm, e.g. amphotericin B. This technology is used for poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of nano sized drug particles which are stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration.

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

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

COSOLVENCY[15-18]

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent Cosolvents are mixtures of water and one or more water miscible solvents used to enhance the solubility for poorly soluble compounds. This is one of the most widely used techniques because it is simple to produce and evaluate. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. They can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Cosolvent system reduces the interfacial tension between the aqueous solution and hydrophobic solute, also called as solvent blending. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

The most frequently used low toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerin, and polyethylene glycol Dimethylsulfoxide (DMSO) and dimethylacetamide (DMA).

pH ADJUSTMENT[18-19]

pH is the negative logarithm to the base 10 of the hydronium ion concentration.

\[ \text{pH} = -\log[H_3O^+] \]
The pH adjustment may be the most simple, economic and effective way of increasing the aqueous solubility of the drug. 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. This process can be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may precipitate because blood is a strong buffer with pH between 7.2-7.4. 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. The ionized form of the drug is favored over unionized form because they are stable and soluble after pH adjustment. As per pH-partition hypothesis and Handerson-Hesselbatch equation, ionization of a compound is dependent on the ph of media and pKa of drug.

HYDROTROPY[20]

Hydrotropic effect, is the increase in saturation solubility of a substance in water by the addition of organic salts or also non-electrolytes, which 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. The hydrotropic substances increases the number of hydrogen bridges in the water clusters which 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:
1. Slight increase of saturation solubility with high concentration of excipients (eg. Upto 50% nicotinamide with a triple increase in the saturation solubility)
2. Isotonicity is not reached.
3. Individual effects of the excipients.

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 enhances the aqueous solubility of many poorly water-soluble drugs. Hydrotropes are amphiphilic molecules that cannot form well organized structures in water like micelles, but do increase the aqueous solubility of organic molecules. A
hydrotrope solubilises hydrophobic compound 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 are in use industrially. Hydrotropes are used in detergent formulations to allow more.

**SOLUBILIZATION BY SURFACTANTS**\(^{21-22}\)

Surfactants are the molecular structures with two distinct regions: A polar (hydrophilic) head group and a Non-polar (hydrophobic tail). Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. Surfactants reduces the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction and thus they increases the solubility of poorly soluble substances. The surfactants also stabilizes the drug suspensions. When the concentration of surfactants more than their critical micelle concentration (CMC) i.e. 0.05–0.10%, micelle formation occurs which entrap the drugs within the micelles known as micellization which enhances the the solubility of poorly soluble drugs.

**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.

**Non Traditional Surfactants**

Nonionic Surfactant: Poloxamers (Pluronics)

**SUPERCRITICAL FLUID RECRYSTALLIZATION (SCF)**\(^{23}\)

Supercritical fluids are the fluids having temperature and pressure greater than its critical temperature and critical pressure so as they shows properties of both gas and liquid. The best example of this is carbon dioxide because of its mild critical conditions (Tc = 31.1 C, Pc = 73.8 bars), non-toxicity, non-flammability, and low price. Supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide. Supercritical fluids greatly alter the density and mass transport characteristics because of moderate change in pressure, which determine its solvent power. 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. Supercritical fluids are environmentally safe.

Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia and water.

**SONO-CRYSTALLIZATION**

The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallisation. Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallization. Sonocrystallisation not only enhances the nucleation rate but also an effective means of size reduction by controlling size distribution of the active pharmaceutical ingredients. They also reduces the agglomeration. The formation of primary nuclei is a function of ultrasonic parameters such as frequency of oscillations, intensity of irradiation and physical properties of the liquid such as degree of super-saturation and operating parameters such as temperature.

**SALT FORMATION**

To enhance the solubility of poorly soluble drug candidates (weak acids and bases), salt formation has been a strategy for several decades. Salts have improved solubility and dissolution characteristics in comparison to the original drug. This is an effective method for parenteral and other liquid formulations, as well as in solid dosage forms. 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. 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. For the salt formation

- Drug should have ionisable groups that will assist salt formation.
- There should be minimum difference of 2-3 pKa units between the drug and the counterion.
- Counter ion should decrease crystal lattice forces.
● It should be FDA approved or should have enough toxicological data to support the selection of the counter ion.

SOLID DISPERSION\textsuperscript{[28-32]}

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 matrix can be either crystalline or amorphous. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the fusion, solvent, fusion-solvent, spray drying, dropping, lyophilization method.

The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate are used.

Fusion Process

In the fusion method of preparation, the carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix.

Solvent method

Accurately weighed amounts of active drug and carrier(s) are dissolved in minimum quantities of chloroform in a round-bottom flask. The solvent is removed using a rotary evaporator. The obtained solid dispersion is transferred on to the aluminum pan and allowed to dry at room temperature.

Fusion-Solvent Method

In the fusion methods a carrier(s) is/are melted and the drug(s) is / are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous. This method is particularly useful for drugs that have high melting points or that are thermolabile. The need for solvent removal is eliminated.

Dropping method

A solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles depends on the
viscosity of the melt and the size of the pipette. Because viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape.

**Spray Drying**

In this type of preparation, the carrier and the active ingredient are dissolved or suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly.

**Lyophilization (Spray Freeze Drying Method)**

This method is used to avoid the heating during the preparation of thermosensitive drugs. Spray freeze drying (SFD) has been successfully developed to prepare solid dispersions at ambient temperature. SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble APIs and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried. This process offers a variety of advantages compared to traditional technologies for solid dispersions, including amorphous structure and high surface area.

**INCLUSION COMPLEXATION**[^33-35]

As compared to other solubility enhancement techniques, 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 nonpolar molecule or the nonpolar region of one molecule i.e guest into the cavity of another molecule or group of molecules i.e host. Cyclodextrin is the most commonly used host molecule. The host must have large enough cavity to accommodate the guest and small enough to eliminate water, which helps to reduce the total contact between the water and the nonpolar regions of the host and the guest Solid inclusion complexes are prepared by various methods such as kneading method, co-precipitation, neutralization, co-grinding, spray drying method, and microwave irradiation method, lyophillization.

**Kneading**

The method involves the formation of paste of cyclodextrin with guest molecules by using small quantity of either water or ethanol to form kneaded mass. Kneaded mass can be dried at
45 °C and pulverized. In laboratory scale, kneading can be achieved by using a mortar and pestle. In large scale, kneading can be done by utilizing the extruders and other machines.

**Co-evaporation/Solvent evaporation method**

To the alcoholic solution of guest, aqueous solution of host is added and stirred for sometimes and evaporated at room temp until dried mass obtained, pulverized and sieved and fraction is collected.

**Microwave Irradiation Method**

This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in 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 short time of about one to two minutes at 60 ºc in the microwave oven. After the reaction completes, 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 vacuum oven at 40 ºc for 48 hrs.

**Lyophilization/Freeze-Drying Technique**

Lyophilization/freeze drying technique is used to get a porous, amorphous powder with high degree of interaction between drug and CD. 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 form by this method. The limitations of this technique are the use of specialized equipment, time consuming process, and yield poor flowing powdered product.

**Spray drying/Atomization**

In this method, host solution prepared generally in ethanol:water 50% v/v. To this guest is added and resulting mixture is stirred for 24 hr. at room temperature and solution is spray dried by observing following conditions-air flow rate, atomizing air pressure, inlet temperature, outlet temperature, flow rate of solution etc. Product obtained by passing through 63-160 micrometer granulometric sieve.
LIQUISOLID TECHNIQUE\textsuperscript{[36]}

Liquisolid formulation is a technique that utilizes hydrophobic drugs dissolved in non-volatile, nontoxic, hydrophilic solvents like polyethylene glycol, glycerine, propylene glycol, or polysorbate-80 (well known as Liquid Medications) mixed with carriers like microcrystalline cellulose, lactose, or polyvinyl pyrrolidone-K30 using coating materials like silica. The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained.

HIGH PRESSURE HOMOGENIZATION\textsuperscript{[37]}

High-pressure homogenization has been used to prepare 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 cavitations 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.

SELF-EMULSIFYING DRUG DELIVERY SYSTEMS\textsuperscript{[38]}

Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and cosolvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). This isotropic solutions of oil and surfactant which form oil-in-water microemulsions on mild agitation in the presence of water which improves dissolution and absorption of lipophilic drugs. Rate of emulsification, the emulsion size distribution and the charge of resulting droplets are the parameters for self-emulsifying performance. One of the advantages of SEDDS in relation to scale-up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The large quantity of surfactant in self-emulsifying formulations (30-60\%) irritates GIT.
CONCLUSION

Dissolution of 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.

Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs, therapeutic efficacy of the drug and for quantitative analysis. 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 frequency of dosing and better patient compliance combined with a low cost of production. The article concludes that solubility of poorly water soluble drugs is an important concept to reach into systemic circulation to show its pharmacological response.

REFERENCES


