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SOLUBILITY ENHANCEMENT TECHNIQUES: A MINI REVIEW

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ABSTRACT

Solubility behaviour of drugs remain the most challenging aspects in formulation development and thus solubility and dissolution properties of drug play an important role in the process of formulation development. Currently 40% of new chemical entities being discovered are poorly water soluble drugs. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement is necessary. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Enhancement of solubility, dissolution rate and bioavailability of drug is a very challenging task in drug development. Drug efficacy can be limited by poor aqueous solubility and some drugs show side effects due to their poor solubility. Aim of this review was to improve the solubility and bioavailability of poorly soluble drugs by using various solubility enhancement approaches like physical, chemical and other modification techniques and to reduce the percentage of poorly soluble drug entities to be eliminated from the development.
INTRODUCTION
Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown\(^1\). Almost more than 90% drugs are orally administered. Drug absorption sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium.\(^2\) When a drug is administered per-orally in solid dosage form such as tablet, capsules, or suspension it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. The bioavailability of many poorly water-soluble drugs is limited by their dissolution rates, which are in turn controlled by surface area that they present for dissolution. It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability. As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption \(^3\)

Table 1: SOLUBILITY DESCRIPTION TABLE \(^4\)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Parts of solvent required for one part of solute</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</td>
<td>100 – 1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000 – 10,000</td>
</tr>
<tr>
<td>Insoluble</td>
<td>&gt; 10,000</td>
</tr>
</tbody>
</table>

In this review attempt have been made on various novel techniques for solubility, dissolution and bioavailability enhancement of class II and IV drugs.

BCS CLASSIFICATION \(^5,6\)

**Class I: High permeability and solubility.**

**Formulation independent:** The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine.

Examples: Loxoprofen, Benzapril, Sumatriptan etc.

**Class II: High permeability but low solubility**

**Formulation dependent:** The bioavailability of class II compounds is limited by drug solubility/dissolution.

Examples: Aceclofenac, Valsartan, Nimesulide, Loratadine etc.
Class III: Low permeability but high solubility

Dependent on barrier properties: The bioavailability of class III compounds is limited by intestinal permeability.

Examples: Atropine, Gabapentine, Topiramate etc.

Class IV: Low permeability and low solubility

Formulation and barrier properties dependent: The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability.

Examples: Hydrochlorthiazide, Meloxicam, Furosemide etc.

METHODS FOR ENHANCEMENT OF BIOAVAILABILITY

Major approaches to overcome the bioavailability problems:

- **Pharmaceutics approach**
  Modification of formulation, manufacturing processes/physiochemical properties of drug

- **Pharmacokinetic approach**
  Pharmacokinetics of drug is altered by modifying its chemical structure.

- **Biological approach**
  In this, route of drug administration may be changed such as parenteral form instead of oral form. Rate dissolution and its solubility are very important factors in third approach. ⁷, ⁸

There are various techniques available to improve the solubility of hydrophobic drugs. Some traditional and novel approaches to improve the solubility are:

1. **pH ADJUSTMENT**

It is well documented that the influence of the changes in pH within the gastrointestinal tract upon the bioavailability of pharmaceuticals. By applying a pH change, poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water. While the importance of critical parameters like salt selection and pH adjustment has been stressed on pre-formulation, the use of pH altering excipients within drug delivery systems is also of significant utility. pH adjustment can in principle be used for both oral and parenteral administration. 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. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds.⁹⁻¹²
The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also usually 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 enhanced due to an increased concentration gradient and enhanced surface area for dissolution.

2. PARTICLE SIZE REDUCTION

By reducing particle size, the increased surface area may improve the dissolution properties of the drug to allow a wider range of formulation approaches and delivery technologies. The larger surface area allows a greater interaction with the solvent which cause increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. During comminution and spray drying is also a concern when processing thermo-sensitive or unstable active compounds, the thermal stress which may occur. Also, this traditional methods are often incapable of reducing the particle size of nearly insoluble drugs (<0.1mg/mL).

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size. Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Decreasing the particle size of these drugs which cause increase in surface area, improves their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. Nanosuspensions are produced by homogenization and wet milling process.

3. SOLID DISPERSION

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide
drug and a water-soluble carrier in the early 1960. 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. 17, 18

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 issues19, 20. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630, Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used. The solubility of celecoxib, halofantrine1, ritonavir can be improved by solid dispersion using suitable hydrophilic carriers. There are various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility.

- **Hot melt method (fusion method)**
  The physical mixture of a drug and a water soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved, which can be compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system 21.

- **Solvent Evaporation Method**
  The first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophillic R-carotene in the highly water soluble carrier polyvinylpyrrolidone. Many investigators studied solid dispersion of meloxicam15, naproxen and nimesulide using solvent evaporation technique.

- **Hot melt extrusion**
  Hot melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials.
4. CO-SOLVENCY

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. 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. 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. It is well-known that the addition of an organic co solvent to water can dramatically change the solubility of drugs. Most co solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, co solvents reduce waters ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non polar like the solute, cosolvents facilitate solubilization cosolvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Very high drug concentrations of poorly soluble compounds can be dissolved compared to other solubilization approaches.

5. HYDROTROPY

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. 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. 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 Solubilization Technique only requires mixing the drug with the hydrotrope in water. It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.
As the solvent character is independent of pH and has high selectivity. The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behavior. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, and naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.27

6. INCLUSION COMPLEXES/COMPLEXATION

Lipophillic drug-cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drug and excipients 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. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. Cyclodextrins consisting of 6, 7 and 8 D glucopyranosyl units connected to Q -1, 4 glycosidic linkages are known as Q, R, D, cyclodextrins, respectively [48]. Derivatives of R-cyclodextrin with increased water solubility (e.g. hydroxypropyl-R cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation. Cyclodextrins consist of glucose monomers arranged in a donut shape ring.28 The ring has a hydrophilic exterior and lipophillic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability29. The forces driving complexation were attributed to (i) the exclusion of high energy water from the cavity, (ii) the release of ring strain particularly in the case of Q -CD, (iii) Vander walls interactions, and (iv) hydrogen and hydrophobic bindings.30

There are various technologies adapted to prepare the inclusion complexes of poorly of poorly water soluble drugs with cyclodextrins.

- Kneading method

This method is based on impregnating the CDs with little amount of water or hydro alcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required31. Parik et al.32 have reported the dissolution enhancement of nimesulide using complexation method.
• **Lyophilization/Freeze drying technique**
  In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermo labile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique are considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent. 

• **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 °C 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 °C for 48 hrs.

• **Supercritical Antisolvent technique**
  Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost.

7. **MICELLAR SOLUBLIZATION**
The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. 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 polysorbates, polyoxyethylated
castor oil, polyoxyethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved. Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, gliptizide, repaglinide, pioglitazone, and rosiglitazone.

8. SUPERCRITICAL FLUID (SCF) PROCESS

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. 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. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power.

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). Once the drug particles are solubilised within the SCF (usually carbon dioxide), they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to submicron levels. 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, n-pentane, ethanol, ammonia, and water.

CONCLUSION

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 enhancement of poorly water soluble drugs constitute an innovative approach, which overcome the problems of solubility and dissolution rate limiting step and provide a quick onset of action. 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. 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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