INTRODUCTION:

More than 40% of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties (Prentis R.A. et al. 1988). These properties have a significant influence on the drug’s absorption, distribution, metabolism, excretion, and toxicity. Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties. Pharmaceutical companies have been primarily employing two strategies: rational drug design (RDD) and high throughput screening (HTS) for drug discovery. Lipophilicity literally means loving lipid (or fat). Drugs have this property of lipophilicity too little or too much is a bad thing. When this property expressed as Log P gets above about 5, the drug is getting too lipophilic (Lipinsky C.A. 2000).

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids (Leuner C. and Dressman J, 2000).

The poorly soluble drug having dissolution rate too slow therefore uptake cannot be completed within the time at absorption site. If it remains in GIT for longer period may lead to decomposition of drug. There are two parameters useful for identifying poorly soluble drugs. One is its aqueous solubility should be less than 100ug/ml and another is dose: solubility ratio. Dose: solubility ratio can be defined as volume of gastrointestinal fluids necessary to dissolve the administered dose.

Biopharmaceutical Classification System (BCS) classifies drug Products in to following categories:
Table No. 1: Biopharmaceutical Classification of drugs.

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>IVIVC</th>
<th>Rate of Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>High</td>
<td>High</td>
<td>Can be good</td>
<td>Gastric emptying</td>
</tr>
<tr>
<td>Class II</td>
<td>Low</td>
<td>High</td>
<td>Good</td>
<td>Dissolution</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
<td>Low</td>
<td>Poor</td>
<td>Permeability</td>
</tr>
<tr>
<td>Class IV</td>
<td>Low</td>
<td>Low</td>
<td>Poor</td>
<td>Dissolution &amp; Permeability</td>
</tr>
</tbody>
</table>

High solubility refers largest dose of drug should be soluble in 250 ml of water having pH range 1.0 to 7.5, while high permeability refers drug should pass 90 per cent of the administered dose through absorption membrane (Guidance for industry,2000;Micheal H. et al.2003;Yu L.X. et al 2002).

Recently, a quantitative BCS has highlighted the importance of transit flow, in addition to solubility and permeability, on the drug absorption process. The BCS defines three dimensionless numbers—dose number (Do), dissolution number (Dn), and absorption number (An)—to characterize drug substances. These numbers are a combination of physicochemical properties of the drug and physiological parameters. The Do attaches a physiological relevance to dose by considering the volume of fluid required to dissolve the total dose. Drugs with Do < 1 are classified as highly soluble, whereas those with Do > 1 are termed poorly soluble. In a recent attempt to categorize WHO essential drugs based on BCS, 27.7% of drugs were reported to be poorly soluble. The BCS has not only transformed the way scientists today approach drug delivery, but it has also revolutionized the development of new drug molecules.

The growing public interest in traditional medicine, particularly plants-based medicine, has led to extensive research on the potentials of natural origin substances. Hundreds of studies were conducted to investigate the effects of natural origin compounds on human health and prevention and treatment of chronic diseases. Among studied compounds, polyphenols appear as one of the
most promising groups. In plants, polyphenols are important for growth and protection against pathogens. Polyphones have recently received much attention in disease prevention and treatment due to their proven antioxidant capabilities. Polyphenols are derived from many components of the human food including peanuts, dark chocolate, green and black tea and turmeric. Among polyphenols, curcumin is currently one of the most studied substances. It is a hydrophobic, low molecular weight polyphenol widely used in form of the spice, turmeric.

TECHNIQUES OF SOLUBILITY ENHANCEMENT:


a) Micronization:

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronization is used to increased surface area for dissolution.

b) Solid dispersion:

It involves dispersion of one or more active ingredients in an inert carrier or matrix at solid state. Melting (fusion) method, solvent evaporation method or melting evaporation methods can be employed for the preparation of the solid dispersions. Dispersions obtained through the fusion process are called as melts and those obtained by the solvent evaporation method are referred as coprecipitates or coevaporates. The dissolution rate of the solid dispersion depends on the type of carriers used or the type of the matrix forming polymers used. Increase in the effective surface area of drug can be achieved with micronization. When such micronized drugs are encapsulated or tableted the powder tend to agglomerate resulting in decreased effective surface area for dissolution.

c) Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. 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.

d) Solid lipid nanoparticles

Nanoparticles are solid colloidal particles ranging in size from 10-1000 nm (0.01-1 µm) in which the active principle (drug or biologically active material) is dissolved, entrapped or on which the active principle is adsorbed or attached. For a decade, trials have been made to utilize solid lipid nanoparticles (SLNs) as alternative drug delivery systems to colloidal drug delivery systems such as lipid emulsions, liposomes and polymeric nanoparticles. Development of nanodispersed system provided substantial improvement in drug therapy, such as satisfying stability, increased selectivity, decreased toxicity, appropriate pharmacokinetic profile of an incorporated drug.

e) Nanostructured Lipid Carrier (NLC)

NLC, the new generation of lipid nanoparticles, overcome the limitations associated with the SLNs, namely, limited drug loading, risk of gelation and drug leakage during storage caused by lipid polymorphism. NLC consists of a mixture of especially very different lipid molecules, i.e., solid lipid(s) is blended with liquid lipid(s) (oils). This nanostructure improves drug loading and firmly incorporates the drug during storage. These NLCs can be produced by high-pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%.