2. REVIEW OF LITERATURE

Today, 35-40% of all new chemical entities suffer from poor aqueous solubility; hence the enhancement of the solubility of poorly water-soluble drug is one of the most challenging aspects of modern drug development.

Among the various parameters those hinder the development of pharmaceutical products and restrict the bioavailability of oral products solubility is the most important to be deemed for formulation scientist. (Vertzoni M et al 2007)

Preformulation studies are the preliminary studies carried out to characterize the drug substance in pharmaceutical industry in order to obtain the necessary information for the consequent formulation of a physicochemically recognized and biopharmaceutically appropriate drug dosage form. Solubility of New Chemical Entity (NCE) in water is the first and most important step in initial preformulation stages during product development programme. Also the rate-limiting step of the absorption of drugs from the gastrointestinal (GI) tract is frequently the dissolution of a solid dosage form. One can only get idea about the release of any drug substance from any dosage form if one is known of its solubility in water as well as in various biological fluids. (Arunachalam A. and Karthikeyan M. 2010) Drug discovery strategies based on the technology of combinatorial chemistry information, high throughput screening, genomics, robotic technology and miniaturization have increased the drug libraries of many pharmaceutical companies to millions. However, during drug discovery processes attempts those are being made to enhance pharmacological activities of NCE, some very basic physicochemical properties like solubility always suffers a lot. (Ford J.L.1986) Drug molecules with restricted aqueous solubility are becoming more and more common in the research and development portfolios of discovery focused pharmaceutical companies. Since compound shaped as a result of above mentioned technologies are very good in permeability properties in various tissues but may potentially show the way to slow dissolution in biological fluids, insufficient and
Inconsistent systemic exposure and consequent sub-optimal efficacy in patients, particularly when delivered via the oral route. By many estimates up to 40% of new chemical entities discovered by pharmaceutical industry today are poorly soluble lipophilic compounds. Not only the NCE but also many of existing drugs in different formulations suffer from poor solubility issues and hence limited bioavailability issues. Since the percentage of NCE having the bioavailability and related problems is significant and can’t be neglected on the basis of economic as well as therapeutic point of view, the ability to deliver poorly soluble drugs will grow in significance in coming years as NCEs are relied upon for a larger share of returns within pharmaceutical market by innovator companies. Similarly generic drug companies will need to employ economically efficient methods of delivery as more low solubility drugs go off patent in order to maintain a competitive edge. Although pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs, those with aqueous solubility of less than 0.1 mg/ml present some unique challenges and require special attention.

2.1 SOLUBILITY

2.1.1 Basic Consideration

The solubility of a substance is defined as an extent to which it dissolves in the given solvent at particular sets of temperature and pressure. (Dannenfelser R. et al 2004)

Solubility in different solvents is an intrinsic material characteristic for a defined molecule. Another definition of solubility of a given solute is the maximum concentration to which it can be dissolved in a particular solvent to yield a homogeneous monophasic system. When a solute dissolves, forces of attraction between the solute and the solvent must overcome intermolecular forces of attraction of the substances. (Shah T.J. Amin and A.F.Parikh J.R. 2007) It represents breaking of solute-solute forces and solvent-solvent forces to achieve solute-solvent interaction. The solubility of a solute in a given solvent is determined at a fixed temperature (normally a little higher than room temperature). (Shah T.J. Amin and A.F.Parikh J.R. 2007)
2.1.2 **Intrinsic Solubility** is defined as the maximum concentration to which a solution can be prepared with a specific solute and solvent. Solubility depends on the solute & solvent as well as temperature, pressure and pH also in simple words intrinsic solubility of any compound is the solubility of that compound in its native form that is pure form. (Mooter G. V. D et al 1998)

2.1.3 **Kinetic solubility** is the solubility at the time when an induced precipitate first appears in a solution. (Sethia S.et al 2003)

2.1.4 **Equilibrium solubility** is the concentration of compound in a saturated solution when excess solid is present, and solution and solid are at equilibrium. The equilibrium solubility of the free acid or base form of an ionisable compound at a pH where it is fully un-ionized is called the equilibrium solubility. (Thayer A.M. 2010) 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. Currently only 8% of new drug candidates have both high solubility and permeability. (Thistle Marble Arch, London, UK 2005) 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. (Adam M., Persky, Jeffrey A 2000) In the other words the solubility can also define as the ability of one substance to form a solution with another substance. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water. (Indian Pharmacopoeia 1996)
Table 2.1 Solubility Classification

<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 soluble</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>

Noyes-Whitney equation (2.1) illustrates how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability

\[
dC/dt \times h = AD. (Cs - C) \text{ } \text{ } \text{ } \text{ } \text{ (eq.2.1)}
\]

Where, \( dC/dt \) is the rate of dissolution,

A is the surface area available for dissolution,

D is the diffusion coefficient of the compound,

Cs is the solubility of the compound in the dissolution medium,

C is the concentration of drug in the medium at time t,

h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

2.1.5 Process of solubilization

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the 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.
2.1.6 Factors affecting solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system. (James K. 1986)
2.1.6.1 Particle Size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by

\[
\log \frac{S}{S_0} = \frac{2}{2.303} \left( \frac{r V}{R T} g \right)
\]

--------- (eq.2.2)

Where,

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

2.1.6.1 Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

2.1.6.3 Pressure

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.
2.1.6.4 Nature of the solute and solvent
While only 1gm of lead (II) chloride can be dissolved in 100 gms of water at room temperature, 200 gms of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their natures.

2.1.6.5 Molecular size
Molecular size will affect the solubility. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent. (Singhal D 2004)

2.1.6.6 Polarity
Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.

2.1.6.7 Polymorphs
A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is
polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy. (Draft Guidance for Industry 1999)

2.1.7 Factors affecting rate of solution

The rate of solution is a measure of how fast substances dissolve in solvents.

2.1.7.1 Size of the particles

When the total surface area of the solute particles is increased, the solute dissolves more rapidly because the action takes place only at the surface of each particle. Breaking a solute into smaller pieces increases its surface area and hence its rate of solution.

2.1.7.2 Temperature

For liquids and solid solutes, increasing the temperature not only increases the amount of solute that will dissolve but also increases the rate at which the solute will dissolve. For the gases, reverse is true.

2.1.7.3 Amount of solute already dissolved

When there is little solute already in solution, dissolution takes place relatively rapidly. As the solution approaches the point where no solute can be dissolved, dissolution takes place more slowly.

2.1.7.4 Stirring

With liquid and solid solutes, stirring brings fresh portions of the solvent in contact with the solute, thereby increasing the rate of solution. (Lennernas H. and Crison J. R. A.1996)
2.2 BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS) AND SOLUBILITY

Above and beyond the aqueous solubility of a drug substance, its permeability is a second critical aspect for oral bioavailability. The Biopharmaceutical Classification System (BCS) was introduced in the mid-1990s to classify the drug substances with respect to their aqueous solubility and membrane permeability. (Guidance for Industry 1995) As per BCS any drug substance is classified into four categories on the basis of their solubility and permeability properties.

Class-I- Drugs having high solubility and high permeability
Class-II- Drug having low solubility and high permeability
Class-III- Drugs having high solubility and low permeability
Class-IV- Drugs having poor solubility and poor permeability

Now a days BCS is widely relevant to dosage form development since it relates in vitro drug release of the drug with that of the in vivo bioavailability on the assumption that drug solubility and drug permeability are the fundamental parameter that will govern the absorption of the drug. Based on the above mentioned classes of drug substance, suggestions are made to set the standards for in vitro drug dissolution and its correlation with that of in vivo process. In other words it is a very important tool for in vitro in vivo correlations that will take in to account the physicochemical properties of a compound like solubility and permeability. (Guidance for Industry 1995)

The classification of drugs in various classes is mainly on the basis of two important indexes called Dissolution Index (DI) and Permeability Index (PI) (Devane J. 1998)

Table 2.2 Drug Classification according to dissolution and permeability index

<table>
<thead>
<tr>
<th>Class of drug as per BCS</th>
<th>Dissolution Index</th>
<th>Permeability Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class-I</td>
<td>Greater than 3</td>
<td>Greater than 3</td>
</tr>
<tr>
<td>Class-II</td>
<td>Less than 3</td>
<td>Greater than 3</td>
</tr>
<tr>
<td>Class-III</td>
<td>Greater than 3</td>
<td>Less than 3</td>
</tr>
<tr>
<td>Class-IV</td>
<td>Less than 3</td>
<td>Less than 3</td>
</tr>
</tbody>
</table>
Figure 2.2. BCS Classification System.

Upon knowing solubility and permeability characteristics of any compound, it is more easier task for any formulation scientist to decide which drug delivery system is to be focused and to be developed. As class-I drugs are highly soluble and highly permeable it is difficult to achieve desire release profile with them to achieve desire pharmacokinetic and pharmacodynamic characteristic of dosage form. Formulation approaches include both control of release rate and certain physicochemical properties of drugs like pH-solubility profile of drug. The systems those are developed for class II drugs are based on micronization, lyophilization, and addition of surfactants, formulation as emulsions and microemulsions systems, and use of complexing agents like cyclodextrins. Here drugs having problem associated with that of poor solubility comes and this class is ideal for drug selection for solubility enhancement. Class III drugs require the technologies that address to fundamental limitations of absolute or regional permeability. Peptides and proteins constitute the part of class III and the technologies handling such materials are on rise now days. Class IV drugs present a major challenge for development of drug delivery system and the route of choice for administering such drugs is parenteral with the formulation containing solubility enhancers. In other words more attention has to be given on formulation development side while considering class-II drugs and early attention at chemical level has to be given during lead optimization of class-III and IV
drugs for solving bioavailability problems. Thus BCS system seems to be very useful in getting idea about how to improve bioavailability of drug substances that is by formulation approach or by material engineering that is by chemical modification of drug substance. (Kim J.S. et al. 2006; Cao X. et al, 2006)

2.2.1 Methods of determination of solubility
There are several methods available for the determination of solubility of a drug. Some of these are:

- Equilibrium method
- Intrinsic dissolution method
- Non equilibrium method
- Partition coefficient measurement
- Calculation Based on Melting Point and Octanol–Water Partition Coefficient

2.2.1.1 Equilibrium method
This method is the most common method of determining the solubility of any compound at laboratory scale. According to this method an excess of the compound is dissolved in particular medium filled in vials and allow to shake for specified period of time at specified sets of temperature condition, until equilibrium is achieved, after specified time intervals the solubilized compound is taken from the supernant and quantity dissolved is determined by validated analytical procedure such as thermal analysis, HPLC or spectrophometric methods. In this method multiple sets of vials are to be placed and when two sets of vials give same result at particular time it can be said equilibrium has been achieved.

This method is most suitable for estimating Equilibrium solubility. Advantages of the methods include simplicity and easiness. This method suffers from several disadvantages which include lack of sensitive analytical procedures during early stages of drug discovery as well as measurement of solubility by this method includes a time period of 24 or 48 hrs or sometime it will take one week also. Also the method includes the addition of excess amount of drug which will not be tolerated by pharmaceutical companies during early stages of drug development where very few milligram of drug is available for use. (Lennernas H et al. 1997)
2.2.1.2 Non Equilibrium method/Shake Flask Method
The method includes solubilization of 10 ug/ml of compound in few ml of DMSO and pouring around 1 ug/ml of solution of compound in chloride free buffer solution of pH 7.4 until the compound precipitates out from the solution. Hence the method does not require equilibrium to be attained between solute and solvent. The precipitation can be characterized by rapid change in absorbance of solution (Artursson P and Karlson J, 1991).

2.2.1.3 Intrinsic Dissolution Rate Method
The dissolution rate is directly proportional to the equilibrium solubility if the appropriate experimental conditions such as the ones used for intrinsic dissolution rate measurements are selected. The rotating-disk method is the most useful and most widely used technique for measuring intrinsic dissolution rates. Intrinsic dissolution means the dissolution of drug without its formulation in any suitable dosage form which is nearly equivalent to that of solubility of drug in pure form, so measuring intrinsic dissolution rate by selecting appropriate experimental condition will give equilibrium solubility of the drug. (Higuchi Tand Kristiansen H 1970)

The intrinsic dissolution rate method is most useful where the equilibrium method cannot be used. For example, when one wishes to examine the influence of crystal habit, solvates and hydrates, polymorphism, and crystal defects on apparent solubility, the intrinsic dissolution rate method will usually avoid the crystal transitions likely to occur in equilibrium methods. (Rong et al 2004)

2.2.1.4 Determination of partition coefficient
When compound is highly lipophilic and it is practically impossible to dissolve it any suitable solvent, measurement of partition co-efficient is a suitable method for predicting solubility. Once the solubility of these compounds in some typical organic solvent has been measured, solubility in aqueous solvent can be measured by measuring partition co-efficient of the compound in the mixture of aqueous phase and organic phase.
The method has another application for the drugs and prodrugs having instability in aqueous medium. The advantage of this method includes simplicity and rapid determination of partition coefficient of compound simply by vigorous shaking for few minutes followed by separation of two phases by gravity. (Venkatesh S. et al 2003; Sharma DK and Joshi S. B. 2007)

2.2.1.5 Calculation based on melting point and Octanol-Water Partition coefficient

Imperial formula is available based on the Octanol water partition coefficient and melting point to measure the solubility of any compound by considering the transfer of a solute from the solid state to Octanol followed by its transfer to the aqueous phase.

\[
\log S_{aq} = -\log \frac{P_o}{w} - 0.01MP + 1.05 \quad \text{eq.2.3}
\]

Where \( S_{aq} \) is the aqueous solubility of the drug, \( \frac{P_o}{w} \) is the Octanol/water partition coefficient, and MP is the melting point.

As it is an imperial formula it does not work for all type of compounds but it is suitable for few compounds. (Yalkowst Sy H. and Valvani C.1980)

2.3 TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are. (Pinnamaneni S et al 2002)

2.3.1 Physical modifications

- Particle size reduction
  - Micronization
  - Nanosuspension
  - Sonocrystalisation
- Modification of the crystal habit
  - Polymorphs
  - Pseudopolymorphs
- Complexation
  - Use of complexing agents
Solubilization by surfactants:
- Microemulsions
- Self microemulsifying drug delivery systems

Drug dispersion in carriers
- Eutectic mixtures
- Solid dispersions
- Solid solutions

2) Chemical Modifications

3) Other Methods
- Cocrystalisation
- Cosolvency
- Hydrotropy
- Solvent deposition
- Selective adsorption on insoluble carrier
- Functional polymer technology
- Nanotechnology approaches

2.3.1 Physical Modifications

2.3.1.1 Particle size reduction: Particle size reduction can be achieved by micronization and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

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.(Chaumeil J. C. et al 1998) Micronization increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility.(Blagden N et al 2007)

b. Nanosuspension: Nanosuspension 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. Techniques for the production of nanosuspension include Homogenization and wet milling Active drug in the presence of surfactant is defragmented by milling. Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants. (Aulton M E et al 2002)

c. Sonocrystallisation: The novel approach for particle size reduction on the basis of crystallization by using ultrasound is sonocrystallization. Sonocrystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. It’s not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. (Sharma D. K and Joshi S. B. 2007)

2.3.1.2 Modification of the crystal habit:
Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area.

Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different
solid forms of drug is Amorphous > Metastable polymorph > Stable polymorph (Banga S et al 2004)

2.3.1.3 Complexation: Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. (Sanghvi R. et al 2007)

a. Staching complexation: Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of 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. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation. (Rajewski R A and Stella V J 1996)

b. Inclusion complexation: 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) (Park J Woo et al 2005) The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced. Three naturally occurring CDs are α-Cyclodextrins, β-Cyclodextrins, and γ-Cyclodextrins. The complexation with cyclodextrins is used for enhancement of solubility (Uekama K et al 1998)

![Figure 2.3-D sketch of β-CD derivatives.](image)
2.3.1.4 Solubilization by surfactants

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. (Swarbrick J and Boylan J C 2002)

a. Microemulsions:

A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions. (Lawrence M J et al 2000)

2.3.1.5 Drug dispersion in carriers:

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognized in 1961. The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying and using supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, plasdone -S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, docusate sodium, Myrij-52, Pluronic-F68 poloxamer and sodium lauryl Sulphate used. (Sekiguchi K and Obi N 1961)
2.3.2 Chemical Modifications
For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant. (Agharkar S et al 1976)

of the solvent by the use of co-solvents rather than the pH of the solvent. The use of salt forms is a well known technique to enhanced dissolution profiles. (Serajuddin A T M et al 2007) Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water. The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed.

2.3.3 Other Methods
a. Co-crystallization: The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystal, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate. (Aakeroy C B et al 1997) A co-crystal may be defined as a crystalline material that consists of two or more molecular species held together by non-covalent forces. (Almarsson O and Zaworotko M J 2004) Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognized as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications.
Co-crystallization between two active pharmaceutical ingredients has also been reported. This may require the use of sub therapeutic amounts of drug substances such as aspirin or acetaminophen. (Trask A Vet al 2004). At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals. (Amin K et al 2004)

b. Cosolvency: The solubilization of drugs in co-solvents is a technique for improving the solubility of poorly soluble drug. (Yalkowsky S H and Roseman T J 1981) It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. (Jeffrey W Millard and Alvarez-Nunez F A 2000) Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending. (Jain P and Yalkowsky S H 2007) Most cosolvents 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, cosolvents 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. (Solubility enhancement as high as 500-fold is achieved using 20 % 2-pyrrolidone. (Vervaet Cand Remon J P 1997; Lachman L et al 1987)

c. Hydrotrophy: Hydrotropic solubilization is one of them. Hydrotropy is a solubilization phenomenon whereby addition of large amounts of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium aciculate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs. Hydrotropes are a class of amphiphilic molecules that cannot form well organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules. Often strong synergistic effects are observed when hydrotropes are added to aqueous surfactant or polymer solutions. A hydrotrope is a compound that
solubilizes hydrophobic compounds in aqueous solutions. Typically, hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self aggregation. (Valizadeh H et al 2004)

d. Solvent Deposition: 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.

e. Selective Adsorption on insoluble Carriers: A highly active adsorbent such as the inorganic clays like bentonite can enhance the dissolution rate of poorly water-soluble drugs such as grisiofulvin, 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 the adsorbent, and hydration and swelling of the clay in the aqueous media.

F. Functional polymer technology: Functional polymer enhances the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex, known as, “Resinate”, can be formulated as a suspension, dry powder or tablet. The resins are insoluble and not absorbed into the body and the drug is released from the resinate on exposure to the physiological fluids. In other word, the dissolution rate of poorly soluble, ionizable drug like cationic, anionic and amphoteric actives can be enhanced by this technology. This can also be heat applicable to heat sensitive materials and oils.

g. Nanotechnology approaches: Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. (Keck C M and Muller R. H 2006) For many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased
effective surface area for dissolution (Radtke M. et al. 2001) and the next step taken was Nanonisation. (Mazzola L. 2003)

2.4 SOLID DISPERSION

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. (Riegelman S. and Chiou WL 1969)

2.4.1 First generation solid dispersions: The first description of solid dispersions was given from Sekiguchi and Obi in 1961 showed that formulation of eutectic mixtures improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Later, Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones. (Pouton, C.W. 2006)

![Figure 2.4 The classification of solid dispersions.](image-url)
2.4.2 Second generation solid dispersions

It was noticed in the late sixties (Simonelli et al. 1969; Chiou and Riegelman, 1969), that solid dispersion with drug in the crystalline state is not as effective as amorphous because they are thermodynamically stable. Therefore second generations of solid dispersions were introduced having amorphous carriers instead of crystalline. Formerly, the drugs were molecularly dispersed in amorphous carriers which are usually polymers in random pattern. (Khan MSA. 2010)

2.4.3 Third generation solid dispersions

Third generation of solid dispersions appeared as the dissolution profile could be increased by using carriers having surface activity and self-emulsifying characteristics these contain surfactant carriers or a mixture of amorphous polymers and a surfactant as carrier. The third generation solid dispersions stabilize the solid dispersions, increase the bioavailability of the poorly soluble drugs and reduce recrystallization of drug. (Ghaste R et al 2009) Surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility (Aggarwal S et al 2010)

2.4.4 Advantages (Kalia A.and Poddar M. 2011; Kumar S. Malviya R.2011

- Solid dispersion are used for the improvement of the bioavailability of poorly water soluble drugs.
- Enhance the dissolution of drug.
- Reduce presystamic metabolism this may be due to carrier inhibit the enzyme responsible for biotransformation of drug
- Through use of the solid dispersion ,the liquid form of drug can be transformed to the solid form
- Solid dispersions are in the solid state hence preferred by patients as compare to the solubilization products are in the liquid state.
- Solid dispersion better than other particle size reducing techniques to enhance the solubility ,because the other size reduction techniques reduces the size to a limit approximately 2-5 µm which does not cause enough enhancement in drug solubility or drug release in small intestine and to improve the bioavaibility
• The problem of solid powder such as less size of particle shows poor mechanical properties (include high adhesion and poor flow properties) can be overcome by use of solid dispersion
• The equipment involved in the preparation are available at small and large scale
• There are various carriers which can acts as ‘Solid’ solvent
• The extended release solid dispersion can also be prepared

2.4.5 Disadvantages

• Aging may decrease dissolution rate and there may be changes in crystallinity
• Due to tackiness in some solid dispersion leads to handling problems
• Solid dispersion may be deteriorated in presence of moisture and excessive temperature. The presence of moisture influences crystallinity of the drugs. Some polymers used in the SD are hygroscopic in nature and may absorb moisture, that may result in crystal growth or amorphous form may convert in to crystalline states.

2.4.6 Physicochemical classification of solid dispersions

Solid dispersion can be classified as follows:
  a) Simple eutectic mixture
  b) Solid solution
  c) Glass solution
  d) Complex formation
  e) Amorphous precipitation in a crystalline carrier
2.4.6.1 Simple eutectic mixture

A simple eutectic mixture can be described as an intimately blended physical mixture of two crystalline components, which are completely miscible in the liquid state, but not in the solid state (Figure 2.5).

![Phase diagram for eutectic system](image)

Figure 2.5 Phase diagram for eutectic system

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously. However, when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a eutectic mixture, composed of a poorly soluble drug and a highly soluble carrier, is exposed to water or gastrointestinal fluids, the soluble carriers dissolve rapidly leaving very fine crystalline state that will rapidly go into solution. (Goldberg AH et al 1966) Due to increased surface area of the insoluble compound, an enhanced dissolution rate and hence an increased oral absorption is obtained as can be derived from the Noyes-Whitney equation.

Differential thermal analysis (DTA) of binary mixtures normally exhibits two endotherms, but a binary mixture of eutectic composition usually exhibits a single endotherm. In the case of a simple eutectic system, the thaw points of binary mixtures of varying compositions are equal to the eutectic temperature of the system. (Sekigushi K and Obi N. 1961)
2.4.6.2 Solid solutions

Solid solution consists of a solid solute dissolved in a solid solvent. The particle size in solid solution is reduced to molecular level. It was reported that a solid solution of a poorly soluble drug in a fast dissolving carrier achieves a faster dissolution rate than a eutectic mixture because the drug particle size is reduced to its absolute minimum as it is molecularly dispersed in the carrier in a solid solution. (Levy G. 1963; Kanig JL 1964) As the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. (Gibaldi M and Kanig JL. 1965) In the case of felodipine-PVP solid dispersions, hydrogen bond interaction between felodipine and PVP has shown to enhance drug dissolution. (Karavas E et al 2006) Solid solutions have also improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility. (Yoshioka M et al 1995) Solid solutions can be classified by their miscibility characteristics (continuous or discontinuous) or by the way in which the solute/solvent molecules are distributed in the lattice (interstitial, substitutional or amorphous).

a. Continuous solid solutions

In a continuous solid solution the components are totally miscible with one another in all proportions in both the liquid and solid state. The lattice energy of the continuous solid solution at all compositions is higher than that of the respective pure components in the solid state, because the heteromolecular bonding strength is higher than the homomolecular one in order to form a continuous solid solution. Figure 2.6 shows the hypothetical phase diagram of a continuous solid solution.

![Figure 2.6 Hypothetical phase diagram of a continuous solid solution](image-url)
b. Discontinuous solid solution

In discontinuous solid solutions, the miscibility or solubility of one component in the other is limited. Figure 2.7 shows a typical phase diagram of a discontinuous solid solution. α and β shows the regions of true solid solutions. The region labelled α is a solid solution of B in A that is component A would be regarded as the solvent and B as the solute. Similarly the region labelled β is a solid solution of A in B. Below a certain temperature, the mutual solubilities of the two components start to decrease. (Ford JL. 1986)

![Figure 2.7 hypothetical phase diagram of a discontinuous solid solution](image)

**Figure 2.7 hypothetical phase diagram of a discontinuous solid solution**

c. Substitutional solid solution

In substitutional solid solutions the solid molecules replace the solvent molecule in the crystal lattice of the solid solvent. An extensive solid solution can only be formed when the effective diameter of the solute differs by less than 15% from that of the solvent and when the packing patterns of solvent and solute are comparable. (Sopade P.A et al 2007)

A substitutional solid solution is shown in Figure 2.8.

![Figure 2.8: Substitutional solid solution](image)
d. Interstitial solid solution

In interstitial solid solutions the dissolved molecules occupy the interstitial spaces between the solvent molecules in the solvent crystal lattice. In order to fit into the interstices, the size of the solute molecules is critical. The diameter of solute molecules should be less than 59% of the diameter of the solvent molecules (Reed-Hill RE 1964) Furthermore, the volume of the solute molecules should be less than 20% of that of the solvent. Figure 2.9 shows the arrangement of molecules in an interstitial solid solution.

![Figure 2.9: Interstitial solid solution](image)
e. Amorphous solid solutions

The solute molecules are dispersed molecularly but irregularly within the amorphous solvent. (Chiou WL and Riegelman S. 1969) Were prepared solid dispersion using grisiofulvin in citric acid and showed that they form amorphous solid solution to increase drug dissolution properties. Various carriers that were used included urea, sucrose, dextrose, galactose, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG).

Polymer carriers are particularly to form amorphous solid solutions as the polymer itself is present in the form of an amorphous polymer chain network. In addition, the solute molecules may save to plasticize the polymer, leading to a reduction in its glass transition temperature. An amorphous solid solution is depicted in Figure 2.10

![Figure 2.10: Amorphous solid solution](image)

2.4.6.3 Glass solutions

A glass solution, also known as an amorphous solution, is a homogeneous system in which a glassy or a vitreous form of the carrier solubilizes drug molecules. The glassy or vitreous state is characterized by transparency and brittleness below the glass transition temperature \( T_g \). The temperature at which a glassy polymer becomes rubbery on heating and a rubbery polymer reverts to a glassy one on cooling is called the glass transition temperature, \( T_g \). The glass transition is not a sharp transition but a gradual transition and is the mid value of the temperature region of transition between brittle and soft. Well below the \( T_g \), the glass solutions are hard, stiff glassy materials; at the temperature well
above $T_g$, the materials are rubbery. They are formed by either (rapid) cooling of the melt or (rapid) evaporation of a solution. Upon cooling or evaporation, the drug is vitrified into its glassy state in the amorphous carrier. Specific volume, specific heat, viscosity, refractive index, compressibility, thermal conductivity and other physico-chemical properties of the glass show changes when cooled or heated through the glass transition temperature. Figure 2.11 shows the relationship between temperature (T) and volume (V) or enthalpy (H) for the liquid, glassy and crystalline state of a material.

![Figure 2.11: Schematic picture of the variation of enthalpy (or volume) with temperature](image)

As the melted crystalline component is cooled, it may solidify below the melting point ($T_m$) into a crystalline state, or form a glass. Consider a molecular liquid that is slowly cooled. There is a discontinuity in both H and V at the melting temperature ($T_m$) representing the first order phase transition to the solid state. The average kinetic energy of molecules no longer exceeds the binding energy between neighboring molecules and growth of organized solid crystals begins. Formation of an order system takes a certain amount of time. (Zhang MQ et al 1999) Upon rapid cooling the melt the values of H and V may follow the equilibrium line for the liquid beyond the melting temperature ($T_m$) into a “super cooled liquid” region. On cooling further a change in slope is usually seen at a temperature $T_g$. At $T_g$ the properties of the glassy material deviate from those of the equilibrium super cooled liquid to give nonequilibrium state having higher H and V than the super cooled liquid. As a result of higher internal energy the amorphous state should
have enhanced thermodynamic properties relative to the crystalline state (e.g., solubility, vapor pressure) and greater molecular motion. Below $T_g$ the material is kinetically frozen into a thermodynamically unstable glassy state with respect to both the equilibrium liquid and the crystalline phase. The high internal energy and specific volume of the amorphous state relative to the crystalline state lead to enhance dissolution and bioavailability (Huttenrauch R. 1978) The main advantage of glass solutions over solid solutions is that they do not possess a strong lattice as true solid solutions and hence they do not present this barrier to rapid dissolution. An important disadvantage of glass solutions is that the glassy state is Metastable compared to the crystalline state, and depending on its physicochemical properties and storage conditions a glass can convert into a crystalline solid (Yoshioka M et al 1994) Crystallization from the amorphous state over practical time scales can be prevented by keeping the operating temperature below $T_g$ (Gutzow I. and Petroff B. 2004) by reducing the water content or by raising the $T_g$ of the system using additives with high $T_g$ value.(Okamoto N and Oguni M. 1996)

### 2.4.6.4 Complex formation

These are dispersions in which a drug forms a complex with an inert water soluble carrier in the solid state. The availability of the drug depends on the solubility and stability constant of the complex and the absorption rate of the drug. The dissolution rate of the drug and oral absorption are believed to be enhanced by formation of a water soluble complex with a high dissociation constant. (Brewster ME, Loftsson T.2002)

Cyclodextrins are frequently used complex carriers. Cyclodextrins are cyclic ($\alpha$-1,4) linked oligosaccharides of $\alpha$-D-glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. The parent or natural cyclodextrins consist of 6,7 or 8 glucopyranose units and are referred to as alpha($\alpha$-), beta($\beta$-) and gamma ($\gamma$-) cyclodextrins respectively. Cyclodextrin forming a cavity of which the interior is rather hydrophobic, whereas the exterior is highly hydrophilic. (Veiga MD et al 1998)The resulting complex hides most of the hydrophobic functionality in the interior cavity of the cyclodextrins while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is that a water soluble cyclodextrin-drug complex is formed. Solubility of the various poorly water soluble drugs can be increased by this system. (Duchene D et al 1990)
2.4.6.5 Amorphous precipitation in a crystalline carrier

Instead of simultaneous crystallization of the drug and the carrier (eutectic system), the drug may also precipitate in an amorphous form in the crystalline carrier. The high energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug. (Sato T et al 1981)

2.5 MELT SONOCRYSTALIZATION

Particle engineering approaches, which can potentially be applied to a wide range of crystalline drugs, can offers alternatives for improvement of the solubility, dissolution rate, permeability and subsequent bioavailability of poorly soluble drugs (Lacocca R.G. and Burcham C.L. 2010)

Ultrasound irradiation is commonly known to induced acoustic streaming, microstreaming and highly localized changes in temperature and pressure within a fluid, this effect offering considerable benefits to crystallization processes on the use of a sonotrode. Ultrasound energy has been used to induced nucleation at super saturation during the crystallization processes, or as terminal treatment to achieve deagglomeration and desired crystal habit. (Maheshwary M et al 2005)

These effects lend considerable advantages to the crystallization process, such as the rapid induction of primary nucleation, a reduction of crystal size, inhibition of agglomeration and manipulation of crystal size distribution. Recrystallization of poorly soluble materials through the use of liquid solvents and antisolvents has also been employed successfully to reduced particle size. (Kordylla A. and Koch S. 2008; Asua J A 2002)

Novel approaches for particle size reduction on the basis of crystallization from the melt and solution by the application of ultrasound is sonocrystallization. (Ambrus R. and Amizadi N.N. 2010) Sonocrystallization utilizes ultrasound power characterized by the frequency range 20-100 kHz to induced crystallization. Most application makes use of ultra sound in the range 20 kHz-5MHz. Sandilya D.K et al 2010)
Figure 2.12 Protocol of Samples preparation

- Poorly Soluble Model Drug
  - Solvent Additives
- Sonocrystallization From Solution
  - Drying
  - Particles with optimized size and morphology
  - Improved bioavailability and processibility
- Sonocrystallization From Melt
  - Drying