Chapter 1

Introduction
INTRODUCTION

Over the last 25 years, Pharmacokinetics has emerged as an integral part of development of drug, especially when identifying the biological properties of drug. By Pharmacokinetics, one means, the application of kinetics to drugs and poisons. Thus the term implies the time course and fate of drugs in the body. This general definition broadly includes Absorption, Distribution, Metabolism and Excretion. The very important property of any non-intravenous dosage form is the ability to deliver the active ingredient to the blood stream to cause pharmacologic response. This property of a dosage form has historically been identified as bioavailability. Bioavailability captures two essential features namely rate and extent of absorption. In principle these two properties of non-intravenous dosage forms are important in identifying the response to a drug dose.

As bioavailability is concerned with the rate and extent of drug absorption, the drug with poor bioavailability is the one with

1. Poor aqueous solubility and/or slow dissolution rate in the biological fluid
2. Poor stability of the drug at physiologic pH
3. Inadequate partition coefficient and thus poor permeation through the bio membrane
4. Extensive presystemic metabolism

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacologic response. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption. The challenge for poorly water soluble drugs is to enhance the rate of dissolution. This in turn subsequently improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced.

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order
for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract. Thus, one of the major challenges in drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity.3,4

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. It is important to improve the solubility and/or dissolution rate of 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.5 Actually, only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action (vascular system for instance). Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.6

Table 1: Solubility description table

<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>
1.1 BIOAVAILABILITY AND SOLUBILITY

Solubility is one of the very important parameters to achieve desired concentration of drug in blood for pharmacologic response to be shown. Poorly water soluble drugs involve many difficulties in the development of pharmacological dosage forms for oral delivery systems because of their low bioavailability.

The process of solubilization involves the breaking of intermolecular or inter-ionic 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 molecules or ions. Solubilization process occurs in three steps.

![Figure 1: Process of Solubilization](image)

1.2 BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

Based on aqueous solubility and intestinal permeability drug substances can be classified and the scientific framework for this classification is known as Biopharmaceutics Classification System (BCS). It allows for the prediction of
in-vivo pharmacokinetics of oral immediate release drug products by classifying drug compounds into four classes based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form.\textsuperscript{7}

Table 2: BCS classification

<table>
<thead>
<tr>
<th>CLASS</th>
<th>SOLUBILITY</th>
<th>PERMEABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Class II</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Class III</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Class IV</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

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: Piroxicam, 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.
1.3 BIOAVAILABILITY AND ORAL DOSAGE FORMS

The nature of the dosage form itself may have an effect on drug absorption characteristics. The decreasing bioavailability is related to the number of steps involved in the absorption process following administration. The greater the number of steps a product must undergo before the final absorption step, the slower is the availability and the greater is the potential for bioavailability differences to occur.

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these orally administered drugs was its low solubility in biological fluids, which results into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Therefore, Pharmaceutical researchers focuses on two areas for improving the oral bioavailability of drugs include:

1. Enhancing solubility and dissolution rate of poorly water-soluble drugs and
2. Enhancing permeability of poorly permeable drugs.

Dissolution rate of drug plays a vital role in absorption of the drug from the dosage form and hence its bioavailability. When a drug is administered orally in
solid dosage form (such as tablets or capsules), it is designed to undergo series of predetermined stages. The first step towards the absorption process is the disintegration of the dosage form. The second and in fact the slowest or rate-limiting step is found to be dissolution of drug in the fluid at the absorption site. When dissolution is the controlling step in the overall process, absorption is said to be dissolution rate limited. Since the rate-limiting step in the absorption process is dissolution of drug, therefore, any factor influencing the rate of dissolution must also influence the rate of absorption. According to dissolution theory, two important parameters determining the dissolution rate of a solid in a given solvent are:

1. The solubility of the drug in the dissolution medium and
2. The surface area of the drug exposed to the dissolution medium.⁹

Before the therapeutic effect of an orally administered drug can be realized, the drug must be absorbed. The systemic absorption of an orally administered drug in a solid dosage form is comprised of three distinct steps.

- Disintegration of the drug product
- Distribution of the drug in fluids at the absorption site
- Transfer of drug molecules across the membrane lining of the GI tract, into the systemic circulation.

### 1.4 PHARMACEUTICAL APPROACHES TO ENHANCE DISSOLUTION OF DRUGS

The rate limiting step for oral solid dosage forms is drug release and membrane permeability, particularly for drugs with low gastrointestinal solubility. The low bioavailability of high permeable drug has low water solubility and by improving the drug release profile of these drugs, enhancement of their bioavailability is possible. For the enhancement of solubility, different techniques are used, that are: ⁶, ¹⁰
a. Micronization

The oral bioavailability of drugs presented in a solid dosage form depends mainly on size, size distribution and morphology of particles. This is due to enhanced surface area of drug particles available for dissolution. Hence, a variety of micronization technologies such as spray-drying, freeze-drying, crystallization and milling processes were developed to decrease the particle size. Micronization reduces the size of particles. It increases the surface area and also increases the intrinsic solubility and dissolution rate of the drug.

b. Reduction in hydrophobicity (by coating and granulation with hydrophilic materials or surfactants etc.)

- Reduction in hydrophobicity by coating and granulation with hydrophilic materials such as PEG, PVP, Dextrose etc. which is coated on the surface of the hydrophobic drug particles and render them hydrophilic.

- Reduction in hydrophobicity by the use of surfactants as a wetting agent that will decreases the interfacial tension and displaces the adsorbed air with solvent.

The reduction in hydrophobicity will helps to convert the absolute surface area (the total area of solid surface of any particle) to their effective surface area (the area of solid surface exposed to the dissolution medium).

c. Formulation of solvates and hydrates/Pseudo polymorphism.

The crystalline form of a drug can either a polymorph or a molecular adduct or both. The solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates, and the trapped solvents as solvent of crystallization. The solvates can exist in different crystalline forms called as pseudo polymorphs and the phenomenon is called pseudo polymorphism. When the solvent in association with the drug is water, the solvate is known as a hydrate. The hydrates interact with water and therefore they dissolve at a faster rate and
shows better bioavailability. The organic solvates have greater aqueous solubility than the non-solvates.

d. **Polymorphism and change in crystal form**

A solid can exist either in a crystalline or amorphous form depending upon the internal structure. When a substance exists in more than one crystalline form, the different forms are named as polymorphs and the phenomenon is known as Polymorphism.

**Polymorphs are of two types**

1. Enantiotropic polymorph
2. Monotropic polymorph

Polymorphs can further be stable or metastable polymorphs. Polymorphs differ from each other with respect to their physical properties such as solubility, melting point, density, hardness and compression characteristics. This technique includes conversion of stable polymorph into metastable polymorph. As the latter shows more solubility than the stable polymorphs, enhancement of bioavailability can be achieved.

e. **Salt formation**

Salt formation will improve the solubility and dissolution characteristics of the original drug. Alkali metal salt of acidic drugs like penicillins and strong acid salts of basic drug like atropine are more water soluble than the parent drug. Factors that influence the salt selection are physical and chemical properties of the salt, safety of counter ion, therapeutic indications and route of administration.

f. **Adsorption**

A highly active adsorbent such as the clays like bentonite can enhance the dissolution rate of poorly water soluble drugs (eg: griseofulvin, indomethacin, and prednisone). Two reasons for the rapid release of drugs from the surface of the adsorbents are
1. The weak physical bonding between the adsorbate and adsorbent.

2. The hydration and swelling of the adsorbent in the aqueous media.

g. **Complexation**

Sparingly soluble drugs have been shown to display improved dissolution by the formation of a complex with water soluble complexation agents. The most widely used complexation agents are cyclodextrins. Cyclodextrin complexes are formed by the binding of the hydrophobic core of the agent with the hydrophobic region of the drug. The characteristic feature of these complexes is that, they are reversible; hence facilitating the absorption by releasing the drug from the complex during dissolution as it is soluble in the fluids of the gastro-intestinal tract. Explained that, the solubility of the sparingly soluble drugs can be improved by the application of cyclodextrin complexes. Aqueous solution of cyclodextrins was used to increase the solubility of a variety of steroids. Complex formation has been used to alter the physico chemical and biopharmaceutical properties of a drug. A complexed drug may have altered stability, solubility, molecular size, partition coefficient and diffusion coefficient. The complexes are pharmacologically inert and must dissociate either at the absorption site or following absorption into the systemic circulation.

h. **Adjustment of P**\textsubscript{H}**\textsuperscript{H}**

Adjustment of environmental P\textsubscript{H} is the simplest and commonly used method to increase water solubility of the ionisable compounds which modify the ionization behavior of the particular compound. As per P\textsubscript{H}-partition hypothesis, the ionization of a compound is dependent upon the P\textsubscript{H} of media and pKa of drug which in turn influences the solubility. The addition of buffers to the formulation alters P\textsubscript{H} of the drug microenvironment and then affects the drug solubility Eg. Buffered Aspirin tablets.

i. **Hot-melt extrusion**

In this process the drug or carrier physical mixture is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets,
sheets, sticks and powder. The intermediates can then be further processed into conventional tablets. Eg: The Troglitazone formulation in PVP was actually manufactured by melt extrusion method and Isoptin SR-E 240 is a sustained release extrudate tablet of Verapamil made using the hot-melt extrusion process. This method is essentially a combination of melting and mechanical preparation methods.

j. Micellar solubilization

The surfactants 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, polyoxy ethylated castor oil, polyoxy ethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycol. The surfactants improve the dissolution performance of poorly soluble drug products by lowering the surface tension and improve the dissolution of lipophilic drugs in aqueous medium.

k. Self-emulsifying systems

The emulsifying systems perform the function of dispersing the liquid vehicle on dilution in GI fluid. Hence the drug is present in fine droplets of oil or surfactant mixture which spread readily in the GIT. Self-emulsifying or micro emulsifying systems are formed using an oily vehicle (or a mixture of hydrophillic phase and a lipophilic phase), a surfactant with a high HLB and if required, a co-surfactant. Unlike emulsions, the resultant liquid is almost clear. These pre-concentrates form spontaneously an emulsion in aqueous media.

l. Co-crystallisation

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, also referred as molecular complexes. A co-crystal may be defined as a crystalline material that consists of two or more
molecular (electrically neutral) species held together by non-covalent forces. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionisable groups.

m. Solid dispersion

Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state is a well-known approach for improvement of the dissolution rate and bioavailability of drugs that are poorly water soluble. The carriers used have to be physiologically inert compounds that are readily water-soluble or water insoluble for fast or controlled dissolution respectively. To achieve faster dissolution rate, poorly water-soluble drug is dispersed at molecular level in a rapidly water-soluble inert carrier to form a solid dispersion. Successful dispersion of the drug in the carrier, at molecular level, leads to formation of homogeneous phase of the solid dispersion. When such a product comes in contact with gastric fluid, then the water-soluble carrier rapidly dissolves leading to immediate release of the drug at the desired molecular level to cause dissolution with consequent improvement of bioavailability.

1.5 SOLID DISPERSION

Much of the researches regarding on solid dispersion technologies involves drugs that are poorly water soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. There too, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drugs. The term solid dispersion refers to a group of solid products containing two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in
crystalline particles. Based on the molecular arrangement; six different types of solid dispersions can be distinguished. They are:

**Table 3: Types of solid dispersion**

<table>
<thead>
<tr>
<th>Type of solid dispersion</th>
<th>Matrix</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eutectics</td>
<td>Crystalline</td>
<td>Crystalline</td>
</tr>
<tr>
<td>Amorphous precipitation in crystalline matrix</td>
<td>Crystalline</td>
<td>Amorphous</td>
</tr>
<tr>
<td>Solid solutions</td>
<td>Crystalline</td>
<td>Molecular</td>
</tr>
<tr>
<td>Glass suspension</td>
<td>Amorphous</td>
<td>Crystalline</td>
</tr>
<tr>
<td>Glass suspension</td>
<td>Amorphous</td>
<td>Amorphous</td>
</tr>
<tr>
<td>Glass solution</td>
<td>Amorphous</td>
<td>Molecular</td>
</tr>
</tbody>
</table>

Schematic representation of three modes of incorporation of the drug in a solid dispersion is shown below.

**Figure 3: Representation of solid dispersion**

**1.5.1 Advantages of solid dispersion**

- Particles with reduced size: Molecular dispersions represent the last state on particle size reduction and after carrier dissolution, the drug is molecularly dispersed in dissolution medium. Solid dispersion apply this principle to drug release by creating a mixture of poorly water soluble drug
and highly soluble carriers. A high surface area is formed resulting in an increased dissolution rate and improved bioavailability.

- **Particles with improved bioavailability:** The drug solubility enhancement is strongly related to the drug wettability improvement verified in solid dispersions. Carriers with or without surface activity improved wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co solvent effect.

- **Particles with higher porosity:** Particles in solid dispersion have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties of the instance; the solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore result in a higher dissolution rate. The increase in porosity of solid dispersion particles fastens the drug release profile.

- **Drugs in amorphous state:** The enhancement of drug release can usually be achieved using the drug in its amorphous form, because no energy is needed to break up the crystal lattice during the dissolution process. In solid dispersions drugs are presented as supersaturated solutions after system dissolution and it is assumed that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the stable crystal form.

Surface solid dispersion is a technique which provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of the drug on an inert carrier causes a reduction in the particle size of the product thus provides a faster dissolution rate. Various hydrophilic excipients with high surface area can be utilized for deposition of the drug on their surfaces. Surface modifications and solid dispersion formulations using hydrophilic excipients can significantly alter the dissolution behavior of hydrophobic drug materials\(^{12}\).
1.5.2 Solid dispersions can be prepared by using following methods: 12,13

- **The Fusion (Melt) Method:** Accurately weighed amounts of carrier(s) are placed in an aluminum pan on a hot plate and melted, with constant stirring at a temperature of about 60°C. An accurately weighed amount of active drug is incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture is heated until a clear homogeneous melt is obtained. The pan is then removed from the hot plate and allowed to cool at room temperature.

- **The Solvent Evaporation Method:** Accurately weighed amounts of active drug and carrier(s) are dissolved in minimum quantities of solvent in a vessel. The solvent is removed using a rotary evaporator or water bath. The resultant solid dispersion is transferred to an aluminum pan and allowed to dry in a hot air oven.

- **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 can be influenced by factors such as the viscosity of the melt and the size of the pipette. As 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.

1.6 SOLVENT DEPOSITION

In this method, the rate of dissolution is increased by depositing drug in minuscule form on the surface of an adsorbent. Minuscule form implies the molecularly micronized form of drug, when it is extensively dispersed on the extensive surface of the microparticulate adsorbents. During dissolution the minuscule drug system releases only free, absorbable drug into solution. Hydrogen bonding and Van der Waal’s forces are accounted for desorption of the drug from the adsorbent surface. The minuscule drug delivery system can be regarded as drug in a micro particulate form molecularly dispersed on the very extensive surface of carrier. The decrease in particle size and the resulting increase
in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which greatly enhances the rate of solution of the drug. The solvent deposition system is usually prepared by simple evaporation of the solvent used for distribution of the drug on the matrix\textsuperscript{14}.

Provide a solution comprising a non-polar solvent or a mixture of non-polar solvents and an active pharmaceutical ingredient being practically insoluble in water and optionally one or more water soluble agents. Combine the solution with a solid support carrier in the form of particles or porous particulate material, and then removing the solvent to form an API/carrier adsorbate or solvent deposition system. Schematic diagram of method of preparation of solvent deposition system is given in the figure 4.

![Figure 4: Preparation of solvent deposition](image)

**Advantages of solvent deposition**

- This method is readily adaptable for thermo labile drugs and carriers.
- Many polymers with high melting temperatures that cannot be utilized in melt solid dispersion processes could be carriers for solvent deposited drug formulations.
- Tackiness and stickiness associated with melt or fusion method can be avoided.
1.7 COMPLEXATION

Inclusion complex formation technique has been most frequently employed to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs. Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Among all the 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. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1, 4- configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Derivatives of the β-cyclodextrin with the increased water solubility are employed. e.g. Hydroxypropyl-β-cyclodextrin (HP-β-CD) is most commonly used in pharmaceutical formulations.\textsuperscript{15,16}

![Figure 5: Types of Cyclodextrins\textsuperscript{15,16}]

\textbf{α-cyclodextrin} \hspace{1cm} \textbf{β-cyclodextrin} \hspace{1cm} \textbf{γ-cyclodextrin}
A strategy often used to improve complexation between drugs and cyclodextrins is the addition of small amounts of water-soluble polymers to the system, which causes an increase in solubilisation efficiency. Ternary cyclodextrin complexes, including hydrophilic polymers, were found to be more stable. The complexation efficiency and solubilizing effect of cyclodextrins in aqueous solution can be increased by addition of water soluble polymers. When a water-soluble polymer, a CD and a drug are mixed together in a solution to obtain the so-called ternary complexes, it is possible to increase drug solubilisation, when compared to the polymer and cyclodextrin separately, which is a result of the synergistic effect between these components. The interaction of water-soluble polymers with drug molecules may occur by means of ion-ion, ion-dipole and dipole-dipole electrostatic bonds, Van der Waals force, or a 3-center, 2-electron bonds. Similarly, the interaction between polymers and cyclodextrin and drug:cyclodextrin complexes begins to occur on the external surface of the cyclodextrin molecule. Cyclodextrins, polymers and drug:cyclodextrin complexes form aggregates capable of solubilizing drugs and other hydrophobic molecules. Obtaining complexes with Cyclodextrins, drugs and water-soluble polymers has gained greater acceptance due to the relatively low cost of polymers. The amount of polymer must be such that the solubilising effect is maximized, but not sufficient to cause a significant increase in viscosity.\textsuperscript{15, 16}

\textbf{Figure 6: Formation of inclusion complexes}\textsuperscript{17, 18}
A: drug molecule; B: cyclodextrin (CD cavity); C: drug-CD complex
1.7.1 Solid inclusion complexes can be prepared by using following methods: 11

- **Kneading Technique:** In this technique, cyclodextrin is impregnated with water and converted to paste. Drug is then added and kneaded for specified time. The kneaded mixture is then dried and passed through sieve if required.

- **Co Precipitation:** Required amount of drug is added to the solution of cyclodextrin. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

- **Neutralization:** Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation, is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.

- **Co-Grinding:** Drug and cyclodextrin are mixed and the physical mixture is introduced in a suitable mill like oscillatory mill and grinded for a suitable time.

- **Spray-Drying Method:** Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.

- **Microwave Irradiation Method:** Drug and cyclodextrin mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product.
1.8 EXPERIMENTAL DESIGNS

Design of Experiments (DOE) is a systematic approach to investigate a system or process. A series of structured tests are designed in which planned changes are made to the input variables of a processor system. The effects of these changes on a predefined output are then assessed. DOE is important as a formal way of maximizing information gained while minimizing resources required. It has more to offer than “one change at a time” experimental methods, because it allows judgment on the significance to the output of input variables acting alone, as well input variables acting in combination with one another. Experimental design affects the systematic and effective evaluation of differences among formulations. A design in which every setting of every factor appears with every setting of every other factor is a full factorial design.

1.8.1 Factorial design

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations are developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. Factorial designs can be defined as any statistical designs that are structured to use factors (i.e., explanatory variables) to organize meaningful groups of treatment conditions. These designs are very powerful statistical tools because they allow a researcher to simultaneously test the effects of multiple factor-level combinations on a response of interest. In factorial designs, each explanatory variable is called a factor and specific conditions within each factor are called levels.

Factorial designs are the most frequently used response surface design. These are generally based upon first degree mathematical models. Full factorial design involves studying the effect of all the factors (n) at all the levels(x),
including the interaction amongst them, with the total number of experiments as $x^n$. The smallest factorial design involves study of two factors at two levels. Factorial design are said to be symmetric, if each factor has same number of levels, and asymmetric, if the number of levels different for each factor.

The mathematical model associated with the design consist of the main effects of each variable plus all the possible interaction effects i.e. interaction between the two variables, and in fact, between as many factors as are there in the model. The mathematical model generally postulated for factorial design is given below

$$Y = b_0 + b_1A_1 + b_2B_2 + b_{11}A_1B_1 + b_{22}B_2B_2 + b_{12}A_1B_2$$

Where $Y$ is the dependent variable, $b_0$ is the arithmetic mean response of the nine runs and $b_1$ is the estimated coefficient for the factor $A$. The main effects ($A_1$ and $B_2$) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($A_1B_1$) show how the response changes when two factors are simultaneously changed.

A $3^2$ randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations $^{19,20}$.

1.9 TABLET COMPRESSION

Compression is the process of applying pressure to a material. In pharmaceutical tableting, an appropriate volume of granules in a die cavity is compressed between upper and lower punches to consolidate the material into a single solid matrix, which is subsequently ejected from the die cavity as an intact tablet.

1.9.1 Direct compression

Until the late 1950s, the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powdered constituents prior to tableting. The primary purpose of the granulation step is to produce a free-flowing and compressible mixture of active ingredients and excipients. The
availability of new excipients or new forms of old excipients, particularly fillers and binders, and the invention of new (or the modification of old) tablet machinery allowed the production of tablets by the much simpler procedure of direct compression. The term direct compression was long used to identify the compression of a single crystalline compound (usually inorganic salts with cubic crystal structures such as sodium chloride, sodium bromide or potassium bromide) into a compact without the addition of other substances. Few chemicals possess the flow, cohesion, and lubricating properties under pressure to make such compacts possible 21.

1.9.2 Advantages of direct compression

- **Economy**
  
  Savings can occur in a number of areas including reduced processing time and thus reduced labor costs, fewer manufacturing steps and pieces of equipment, less process validation and a lower consumption of power.

- **Tablet quality**
  
  In the case of wet granulation, there is an inherent need for moisture and heat. Also, when tablets are produced by slugging or roll compaction, high compaction pressures are involved. These can be avoided by direct compression. In addition to the primary problem of stability of active ingredient, the variability encountered in the processing of a granulation can lead to innumerable tableting problems.

- **Optimization of tablet disintegration**
  
  Each primary drug particle is liberated from the tablet mass and is available for dissolution.

- **Fewer chemical stability problems**
  
  The primary cause of instability in tablets is moisture. While some direct compression excipients do contain apparently high levels of moisture, this moisture in most cases is tightly bound either as water of hydration or by hydrogen bonding.
Also, changes in dissolution profiles are less likely to occur in tablets made by direct compression than in those made from granulations\textsuperscript{21}.

Solubility is the major criteria to achieve the desired concentration of the drug in systemic circulation. About 80\% of the drugs are poorly soluble in nature. So in order to overcome that problem, several techniques have been developed to enhance the solubility of those drugs. The significant enhancement in aqueous solubility and dissolution of various drugs achieved by different solubility enhancement techniques opens up the possibility of development of systems with newer water-insoluble and inert excipients. Carvedilol used in the treatment of hypertension and congestive heart failure is having low solubility and high permeability. By the different solubility enhancement techniques the solubility of carvedilol in the biological fluid can be enhanced which in turn increase the dissolution rate & bioavailability of the drug. Thus the kinetic studies and formulation aspects jointly leads to a patient friendly efficient formulation meeting all its therapeutic needs with minimum discomfort to this present day lifestyle.