Chapter 1
Introduction
## Chapter 1

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1.1 SPARINGLY SOLUBLE DRUG

The dissolution of a drug from a dosage form is dependent on various factors like physicochemical properties of the drug, dissolution conditions, manufacturing and formulation factors etc. Solubility of drug in dissolution medium/physiological environment is one of the key physicochemical parameters for dissolution [1]. Dissolution of a drug from a dosage form occurs in following steps: [2-3].

i. Liberation of the solute or drug from the formulation matrix (disintegration)

ii. It is followed by dissolution of the drug (solubilization of drug particles)

The properties like disintegration or erosion in case of solid dosage forms and dispersion of lipids or partitioning of the drug from the lipid phase are important in the first step of dissolution. If this step is rate limiting then the rate of dissolution is considered to be disintegration controlled.

While physicochemical properties of the drug such as its chemical form (e.g. salt, free acid, free base) and physical form (e.g. amorphous or polymorph and particle size) play a key role in the second step of dissolution. It this step is rate limiting then the rate of dissolution is considered to be intrinsic dissolution controlled. As per the modified Noyes-Whitney equation [4]:

\[
\frac{Dc}{dt} = \frac{A \times D \times (Cs - C)}{h}
\]

Where, \( \frac{Dc}{dt} \) = rate of dissolution

A = Surface area available for dissolution

D = Diffusion coefficient of the substance

Cs = Solubility of substance in dissolution medium

C= concentration of drug in medium at time ‘t’

h = thickness of diffusion boundary layer adjacent to the surface of the dissolving compound.
Solubility of the drug can be classified as follows [5, 6]:

<table>
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<tr>
<th>Descriptive Term</th>
<th>Approximate volume of solvent in ml per gm of solute</th>
</tr>
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<tbody>
<tr>
<td>Very soluble</td>
<td>Less than 1</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>1 to 10</td>
</tr>
<tr>
<td>Soluble</td>
<td>10 to 30</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>30 to 100</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>100 to 1000</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>1000 to 10000</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>More than 10,000</td>
</tr>
</tbody>
</table>

**Note:** (i) All above values are at temperature between 15°C-25°C  
(ii) The term ‘partly soluble’ is used to describe a mixture of which only some of the components dissolve.

Thus, a poorly water soluble compound has classically been defined as one dissolving in less than 1 part per 10000 part of water. A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluids than it takes to be absorbed in the gastrointestinal tract [7]. This drug can be defined on the basis of administered dose and aqueous solubility. Thus, a greater understanding of dissolution and absorption behaviours of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.
1.2 BCS CLASSIFICATION

Aqueous solubility and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. The fundamental basis for the BCS classification was given by Dr. Gordon Amidon. The Biopharmaceutics Classification System is guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration [8]. It has been useful guides for recognizing dissolution tests that can help in the design and evaluation of oral dosage forms and for defining tests that are most suitable for ensuring in vivo bioequivalence [9].

This system classifies drugs based on estimates of the contribution of solubility, permeability and dissolution to oral drug absorption from immediate release dosage forms. The solubility classification is based on a United States Pharmacopoeia (USP) apertures. The intestinal permeability classification is based on a comparison to the intravenous injection [10-12].

The key definitions on which BCS depend are:

- Low-solubility: Compounds whose highest dose is not soluble in 250 ml or less of aqueous media from pH 1.2 to 7.5 at 37°C.
- High permeability: Human absorption of 90% or more of the administered dose.
- Rapidly dissolving: Rapidly dissolving immediate release drug product is defined as one for which no less than 85% of the label claim is dissolved within 30 min by dissolution testing in Apparatus I and Apparatus II in a volume of ≤ 900 ml buffer solutions.

According to the Biopharmaceutics Classification System (BCS), drug substances are classified as follows [13, 14]:

- **Class I - High Permeability, High Solubility**
  - These compounds are well absorbed and their absorption rate is usually higher than excretion.
  - Here, rate limiting step for drug absorption is gastric emptying. Absorption of drug from drug product undergoing 5% dissolution in 15 min under
mild dissolution test conditions in 0.1 N HCl is not limited by dissolution. If the dissolution is lower than gastric emptying then a dissolution profile with multiple time point in multimedia is recommended.

- **Class II - High Permeability, Low Solubility**
  The bioavailability of those products is limited by their solvation rate. A correlation between the in vivo bioavailability and the in vitro solvation can be found. Here, drug dissolution may be the rate limiting step for drug absorption and an In vitro-in vivo correlation (IVIVC) is recommended.

- **Class III - Low Permeability, High Solubility**
  The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied. Here, permeability is the rate limiting step and a limited IVIVC may be dependent on relative rates of dissolution and intestinal transit.

- **Class IV - Low Permeability, Low Solubility**
  These compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected. This shows significant problems in drug delivery.

**BCS classification of Essential WHO immediate release dosage forms:**

BCS classification of 123 oral WHO drugs were provisionally classified into the BCS classes based on dose number and log P or dose number and Clog P value. However, classification based on dose number and log D was not used because of limited availability of pKa values from reference sources. The percentages of the drugs in immediate release dosage forms that were classified as BCS Class 1, Class 2, Class 3 and class 4 either using log P and Clog P values or dose number and log P values and dose number and Clog P values.
Chapter 1

1.3 DISSOLUTION ENHANCEMENT TECHNIQUES

The development of new drug candidates is increasing day by day due to the application of combinatorial chemistry and high-throughout screening. The majority of these drugs exhibit poor solubility and thereby poor bioavailability [15]. It is well experienced that if the substance has an aqueous solubility below 1 mg/ml over the pH range of 1-7, a potential absorption problem may occur. A review of new monograph in the European Pharmacopoeia shows that more than 40% of the drug substances have the aqueous solubility below 1 mg/ml and that 32% have an aqueous solubility below 0.1 mg/ml [16]. The poorly soluble drug exhibits following dissolution related problems. Firstly, the extent of release is too low so that 100% of the drug does not dissolve. Secondly, rate of release is too slow for fast dissolution to occur [17]. The drug release is the rate limiting step for oral drug absorption of these substances. Thus, development of dosage form from these drugs remains a great challenge for the formulation scientist. Also proper understanding of dissolution and absorption behavior of drugs is required to successfully formulate them into bioavailability drug products. A wide range of principles and methods are available for the purpose of enhancing dissolution rate of low solubility substances. Researchers have tried various techniques to enhance the dissolution of poorly soluble drugs [18-22]. These are summarized in Table 1.2.

<table>
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<td>Precipitation Technologies</td>
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<td>Nanosizing technologies</td>
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<td>Spray Drying</td>
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<td>Hydrates or solvate formation</td>
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<td>Electrostatic Spinning</td>
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1.3.1 Solid Dispersion:

Chiou and Riegelman [23] defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”

The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Dispersion obtained through the fusion process often called “melts” and those obtained by solvent method is called as coprecipitates and co evaporators. Coprecipitates and melts are solid dispersion that provides a means of reducing particle size to molecular level so improved bioavailability of poorly water soluble drugs can be achieved. Sekiguchi and Obi [24] suggested that the drug was present in a eutectic mixture in a microcrystalline state.

Goldberg et al [25] reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution

**Melting or Fusion Method:**

A physical mixture of active agent and water-soluble carrier is heated until it is melted. The melt is solidified rapidly on an ice bath under rigorous stirring, pulverized and then sieved. Rapid congealing is desirable because it results in super saturation of drug as a result or entrapment of solute molecule in solvent matrix by instantaneous solidification. This solidification may be achieved on stainless steel plates attached to a cooling system to favor rapid heat loss.

**Advantages:**
- Simple
- Economic as no solvent or specialized equipment is required.

**Disadvantages:**
- Tacky and intractable nature of resultant solidified mass
• Irregular crystallization owing to the presence of miscibility gap on the phase diagram for given drug carrier system if the drug or the carrier is unstable at the fusion temperature.

• Only useful for carriers having lower melting point

e.g. Steroids-PEG, griseofulvin-pentaerythritol etc.

**Solvent Method:**

Drug and the carrier are dissolved in the common solvent and the solvent is removed by evaporation. Evaporation can be done at room temperature or higher temperature or by use of vacuum.

**Advantages:**

• No thermal decomposition of the drug and carriers as in case of fusion method

• Drug and carrier can be completely solubilized by selecting suitable solvent.

**Disadvantages:**

• Large amount of solvent is required so costly method

• Difficulty in complete removal of solvent so chances of adverse effects of residual solvent.

e.g. Griseofulvin in PVP, sulphathiazole-PVP, reserpine deoxy cholic acid prepared by this method.

**Classification of Solid Dispersion:**

a. Simple eutectic mixture

b. Solid solution

c. Glass solution

d. Glass suspension

e. Amorphous precipitation in crystalline carrier compound or complex formation.

f. Combination of previous five types
a. *Simple Eutectic Mixture:*

It is prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility but negligible solid solubility. System is an intimately blended mixture of its two crystalline components e.g. the dispersion of Griesofulvin and tolbutamide in Polyethylene glycol (PEG) 2000.

b. *Solid Solution:*

Two components are crystallized together in a homogenous one-phase system. The practical size of the drug in the solid solution is reduced to its molecular size. It has faster dissolution rate than the corresponding eutectic mixture. Solid solution is classified by two methods, continuous and discontinuous. In continues solution two components are miscible or soluble at solid state at all proportion. Solid solution above the temperature of solubility gap is thermodynamically stable. The solubility gap observed due to limited solid state solubility at lower temperature (Figure 1.1). While in discontinuous solid solution system, there is a limited solubility of solute in solid solvent (Figure 1.2). The α and β are the regions of solid solution formation in the diagram [23].

![Figure 1.1: Phase diagram of continuous solid solution of a binary system A and B](image-url)
Depending on the criteria of molecular size of the two components the solid solutions are classified as substitution type or interstitial type.

1. **Substitution Type:**
   The solute molecule substitutes for the solvent molecule in crystal lattice. Molecular size does not differ more than 15%. Example: parachlorobromo benzene-di-bromo benzene and anthracene-acenaphene.

2. **Interstitial method:**
   When the solute molecules occupies interstitial space in the solvent lattice. Solute molecule diameter is less than solvent molecule so solute molecule volume is < 20% of solvent molecule. Examples: Digitoxin, Methyl testosterone, Prednisolone acetate in matrix of PEG 6000.

c. **Glass Solution and Suspension**
   A Glass solution is a homogeneous glass system in which a solute is dissolved in the glassy system. Glass suspensions are referred to as a mixture in which precipitated particles are suspended in a glassy solvent. Glassy state is characterized by transparency and brittleness below the glass transition temp. The lattice energy represents a barrier to a rapid dissolution, which is much lower in glass solution then
in solid solution. Typical examples of carriers that form glass solution and suspension include citric acid, sugar like dextrose/sucrose/galactose, PVP, urea, PEG.

d. Amorphous precipitation in a Crystal Carrier

Instead of crystallizing drug and carrier simultaneously by melt or coprecipitates method, here the drug is precipitating out in an amorphous form in the crystalline carrier. As the amorphous form is the highest energy form of a pure drug, it enhances dissolution of drug. e.g. Sulphathiazole precipitated in amorphous form in crystalline urea.

e. Compound or Complex Formation

Drug form molecular compound/complex with carrier. If this complex is weaker then it increases solubility of drug. E.g. Griseofulvin-PEG

Method of analysis

1. X-ray diffraction studies
2. Thermodynamic Methods
3. Dissolution rate
4. Microscopic Examination
4. Spectroscopic studies
5. Dissolution rate

Mechanism of Increased Dissolution Rate [26]:

- Reduction of particle size in case of glass, solid solution and amorphous dispersion, so increase in effective surface area and solubilization.
- Decrease in the crystallinity of drug or conversion of drug from crystalline to amorphous form.
- The carrier material as it dissolves may have a solubilization effect on drug.
- The carrier material may have enhancing effect on wettability and dispersion of drug in dissolution media. This should retard slow dissolution which generally occurs due to agglomeration and aggregation of particles.
- Formation of metasable crystals that has greater solubility and result in faster dissolution rate.


**Carrier Selection:**

A carrier should meet following criteria as it influences dissolution characteristics of dispersed drug:

- It is freely water soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert
- Heat stable with low melting point
- Soluble in a variety of solvent
- Able to increase the aqueous solubility of the drug and chemically compatible with drug and not it should not form a strong bonded complex with drug. The most widely used carriers are listed in Table 1.3.

<table>
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<tr>
<th>Material</th>
<th>Examples</th>
</tr>
</thead>
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<tr>
<td>Sugars</td>
<td>Sucrose, dextrose, mannitol, sorbitol, maltose, xylitol, galactose</td>
</tr>
<tr>
<td>Acids</td>
<td>Citric acid, succinic acid</td>
</tr>
<tr>
<td>Polymers</td>
<td>Poly vinyl pyrrolidone, polyethylene glycols, L-hydroxyl propyl methyl cellulose, methyl cellulose, pectin</td>
</tr>
<tr>
<td>Insoluble polymers</td>
<td>Eudragit L-100, Eudragit S-100, Eudragit RL and Eudragit RS, HPMC phthalate</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Poloxamer 188, gelucire 44/14, Tweens, spans,</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Urea, Urethane</td>
</tr>
</tbody>
</table>

**Difficulties with conventional solid dispersion:**

In spite of tremendous research activity in the area of solid dispersion very less solid dispersion formulation are available in the market. The limited commercial utilization may be due to

- Instability of solid dispersion on ageing
- Reproducibility of physicochemical properties
- Difficulties in development of the dosage form i.e tableting etc.
- High content of carrier which make dosage form bulky and impracticable to scale up
- Manufacturing problems like multi step processing i.e. use of organic solvent, solvent removal etc.
- Laborious technique as it requires strong pulverizing of the product.(i.e. melts or coprecipitates)
Newer approaches to solid dispersion technique [19, 20, 27]:

This difficulties could be overcome due to novel formulating methods which are not only practically feasible but also it retain both the physicochemical and bioavailability enhancing properties of solid dispersions. The two important breakthrough in formulation of solid dispersion are, the development of technologies to fill solid dispersions directly in to hard gelatin capsule and the availability of meltable surface active & self-emulsifying agents carriers like e.g. PEG’s & Gelucire ® 44/14.

1. Direct capsule filing method:

Low melting point semisolid carriers are suitable for this method. Walker and coworker demonstrated the feasibility of liquid filling of gelatin capsules with the liquid melt which solidify at room temperature. This was done for triamterene-PEG 1500 system using a Zanasi LZ 64 capsule filling machine[28, 29].

Advantages:

- No powdering is required as in conventional solid dispersion Thus, it avoids grinding induced changes in the crystallinity.
- Dosage form can be developed and prepared using small amounts of drugs.

2. Use of surface active and self emulsifying carriers:

These carriers are of widely used today for poorly soluble drug. In this method, carriers are generally melted and drug is dissolved in it. These substances are adsorbed on to the surfaces or interfaces of a system. This alters the surface or interfacial free energy and the surface and the interfacial tension at low concentration. Surface-active agents are amphiphilic in nature. Thus, they possesses both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. They are used to improve the solubility and stability of the drug in the liquid dosage forms, stabilizing and modifying the texture of semisolid preparations or altering the flow properties of the final tablet as well as to improve the efficacy or the bioperformance of the product. Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) are important surface
active carriers. PEG-polysorbate 80 mixture is also used by the researchers to enhance the dissolution of poorly soluble drug.

**Advantages:**

- Simplicity of manufacturing
- Scale up is feasible

**Disadvantages:**

- Low solubility of drug in available carriers. The crystallization of Ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule from the market by Norvir, Abott co.

- Another possible limitation of the use of surface-active carrier reported by August et al. [30] is variability in the bioavailability of a drug because different amounts of a surface-active carrier may have different solubilization or dispersion effects on a drug in the gastrointestinal fluid.

- Toxicity of surface active carrier.

**Block Copolymers as Pharmaceutical Surface active carriers:**

Toxicity of surface active carriers given a search of newer carriers which are pharmaceutically acceptable. Block copolymer surface active carriers are available for this purpose. These include Pluronic, Pluronic R, Tetronic, and etc. The corresponding nonproprietary names of the first three types are Poloxamer, Meroxapols and Poloxamine, respectively, there being no equivalent name for the Pluradot compounds.

**Other methods:**

Supercritical fluid technology, Hot melt granulation, Surface solid dispersion, melt extrusion, Electrostatic spinning method and fluidized coating system etc. can be used for formulating solid dispersion on large scale.
1.3.2 Inclusion Complexation [31-34]:

An inclusion complex is a unique form of inclusion chemical complex in which one molecule is enclosed within another molecule or structure of molecules. The combination is characterized by absence of ordinary chemical bonds, the essential criteria is that enclosed molecular or guest be of a suitable size and shape to fit into a cavity within a solid structure formed by a host molecule.

The stereochemistry, possibly of both host and guest molecules determine whether the inclusion complex can occur. The resulting close fit of the two components produce a combination of significant strength due to total dispersion force between interacting components. This type of spatial complex does not occur by means of ionic, covalent or co-ordinate covalent bond but is dependent upon dispersion forces and possibly highly oriented dipoles for stability and differ greatly from chemical complexation. Mylius [35] in Hydroquinone and several volatile compounds first observed inclusion complexes. He proposed that two chemical components were interacting without chemical bonding and suggested one molecule was enclosed into another. X-ray studies confirmed those studies showing formation of Cage-like structure. Schlenk [36] first used the general title for this class of complexes. Other terms used to describe these compounds are ‘occlusion compounds’ ‘adducts’ and clatharates’.

Classification of inclusion compounds:

1) Polymolecular inclusion compounds
2) Compounds forming channel like void spaces
   - Urea and Thiourea and Choleic acid
3) Compounds forming cage like void spaces.
   - Hydroquinone, Water, Phenol, Dianin’s compound and Cycloveratril
4) Monomolecular inclusion compounds
   - Cyclodextrin
5) Products of Blue-iodine reaction
6) Macromolecular Inclusion compounds.

Monomolecular inclusion Compounds:

Monomolecular inclusion compounds represent the complexation of a single host molecule and single guest molecule. The host molecule is characterized by the presence
of a cavity or hole into which the guest molecule is inserted. Cyclodextrins are most thoroughly investigated monomolecular inclusion compounds.

**Cyclodextrin [37-38]:**

Cyclodextrins was first isolated from cellulose by Villers in 1891 soon after Schrödinger identify the three naturally occurring cyclodextrin alpha beta and gamma. Tringsheia demonstrated that these “Schrödinger” sugars could be used to form stable complexes with other chemicals.

From the mid 1970s much data was collected on physical and chemical properties of the natural cyclodextrins in an effort to elucidate how and why they were able to increase the solubility of compounds, which were otherwise insoluble.

**Chemistry of Cyclodextrins:**

The Cyclodextrins or so called Schrödinger sugars cycloamylases or cyclolucans. They are cyclic olio saccharides in which the glucose units are like by alpha (1-4) glyceridic bonds. The cyclodextrins are the most common ones.

- Alpha cyclodextrin containing 6 glucose units arrange in a ring.
- Beta cyclodextrin containing 7 glucose units arranged in a ring.
- Gamma cyclodextrin containing 8 glucose units arranged in a ring.

The cavity size of α-CD is insufficient for many drugs and γ-CD is expensive. Thus, β–CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size suitable for the widest range of drugs. But the low aqueous solubility and nephrotoxicity limited the use of β–CD especially in parenteral drug delivery. Chemically modified CD derivatives have been prepared with a view to extend the physicochemical properties and inclusion capacity of parent CDs. Several amorphous, noncrystallizable CD derivatives with enhanced aqueous solubility, physical and microbiological stability, and reduced parenteral toxicity have been developed by chemical modification of parent CDs. A chemical structure of β–CD is shown in Figure 1.3. The characteristics of cyclodextrin are shown in Table 1.4.
Table 1.4: Characteristics of α, β, and γ Cyclodextrins [38, 39]

<table>
<thead>
<tr>
<th>Type of CD</th>
<th>Cavity Diameter in Å°</th>
<th>Molecular Weight</th>
<th>Solubility (gm/100ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>4.7-5.3</td>
<td>972</td>
<td>14.5</td>
</tr>
<tr>
<td>β</td>
<td>6.0-6.5</td>
<td>1135</td>
<td>1.85</td>
</tr>
<tr>
<td>γ</td>
<td>7.5-8.3</td>
<td>1297</td>
<td>23.2</td>
</tr>
<tr>
<td>Δ</td>
<td>10.3-11.2</td>
<td>1459</td>
<td>8.19</td>
</tr>
</tbody>
</table>

Mechanism of Action of Cyclodextrin:

Due to arrangement of hydroxyl groups in the Cyclodextrin molecule the internal surface cavity is hydrophobic while the outside of the torus is hydrophilic. This arrangement permits the cyclodextrin to accumulate a guest molecule within the cavity so forming an inclusion complex. The detailed process of formation of inclusion compounds with cyclodextrin is as follows:

- Approach of the guest or substrate molecules to cyclodextrin molecules.
- Loss of water structure within the cyclodextrin cavity with removal of some water molecules.
- Breakdown of water structure around the portion of the substrate of that will be included and transport of some water molecules in the solid state.
- Interaction of the constituent groups of the substrate with groups on the rim or inside the cyclodextrin rim.
- Possible formation of the bonds between the cyclodextrin and substrate.
• Reestablishment of the water structure around the exposed parts of the substrate after inclusion of complex.
• The inclusion compounds form with polar molecules is only slightly soluble in water where as those form with polar molecules are moderately soluble.

Complexation of Cyclodextrin:

As a consequence of the uniform stereochemistry of the C1 carbons of glucopyranose units of cyclodextrin, or secondary hydroxyl groups located on the "Cylinder" like cyclodextrin molecule, while primary hydroxyl groups are located on the other edge. Hydrogen and glycosidic oxygen atoms from the lining of cylinder cavity. Therefore this surface is a polar.

Molecules or parts of that are hydrophobic and can fit into the cyclodextrin are in presence of water, include into the cyclodextrin cavity. In aqueous solution the polar cyclodextrin cavity is occupied by water molecules that are in an energetically unfavorable state (polar, a polar, repulsion) and are therefore readily replaced by an appropriate “guest molecule” that is phase polar than water. The cyclodextrin is the host molecule and driving force is the replacement of high enthalpy water molecules by an appropriate guest molecule. The cyclodextrin complexes are very stable and their solubility in water compared to pure cyclodextrin is strongly reduced so they are rapidly separated from the solution in crystalline form.

Advantages:

• Liquid compounds can be transformed into a crystalline from that is suitable the for the manufacture of the tablets.
• Volatile compounds can be stabilized against losses because of evaporation
• Protection against oxidation by air of oxidisable compounds.
• Bad taste and smell of some drugs can be masked by complex.
• It is useful to prevent interaction of two incompatible drugs by formation of Drug-β-CD complex for one drug.
• It is advantageous for improving solubility of poorly water soluble drugs.
Disadvantages:

- The complexation depends on an elementary nature of drug thus, i.e. the drug can or can not form any complex.
- Complexation is also dependent on molecule’s hydrophobicity and geometry in relation to those of the cyclodextrin cavity.
- The extent of the complex in an aqueous milieu is characterized by the stability constant of complex. Only those complexes with the stability constant between 100 to 20,000 M\(^{-1}\) seem to be suitable for practicable application. Too labile complexes result in premature release of drug.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Company/Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib / (\beta)-CD</td>
<td>Roff CD</td>
<td>Tablets</td>
<td>Unichem Guj Pure health</td>
</tr>
<tr>
<td>Piroxicam /(\beta)-CD</td>
<td>Cicladol Brexin</td>
<td>Tablets, sachets and suppository</td>
<td>Master Pharma, Chiesi, Italy</td>
</tr>
<tr>
<td>PGE(_2) /(\beta)-CD</td>
<td>Prostarmon-Edex</td>
<td>Sublingual Tablet</td>
<td>Ono, Japan</td>
</tr>
<tr>
<td>PGE(_2) /(\alpha)-CD</td>
<td>Prostavacin</td>
<td>Intraarterial</td>
<td>Ono, Japan, Schwarz</td>
</tr>
<tr>
<td>Itraconazole/H P-(\beta)-CD</td>
<td>Sporonox Clorocil</td>
<td>Liquids</td>
<td>Janseen, Belgium</td>
</tr>
<tr>
<td>Diclofenac/ HP-(\beta)-CD</td>
<td>Voltaren Opthal</td>
<td>Eye drop</td>
<td>Novatris, Switzerland</td>
</tr>
</tbody>
</table>

Table 1.5: Marketed Products of Cyclodextrin Drug Complex

Application in Pharmaceutical Formulation or Technology:

- Use to form an inclusion complex with a variety of drug molecule resulting in improvement in dissolution and bioavailability due to enhanced solubility and improved chemical and physical stability.
- For masking the unpleasant taste of active ingredients and to convert a liquid substance in to solid material.
- Modified cyclodextrin like Hydroxypropyl \(\beta\)-cyclodextrin, Methylated \(\beta\)-Cyclodextrin is becoming more important in pharmaceutical formulation because of their high intrinsic solubility.
- Cyclodextrin form inclusion complex with large molecules.Cyclodextrin tends to improve poor flow properties and require lubricants when directly compressed.
- Cyclodextrin are used in formulating solution, suppositories and cosmetics.
1.4 AIM OF THE PRESENT INVESTIGATION

The solubility behavior of drugs remains one of the most challenging aspects in formulation development. In recent years, with the advent of combinatorial chemistry and high throughput screening, the number of drugs with poor aqueous solubility has considerably increased. The driving force for oral absorption of most drugs across biological membranes is the concentration of drug in solution forming gastrointestinal fluid, thus drug efficacy can be severely limited by poor aqueous solubility. Consequences of poor solubility include low bioavailability, large inter and intra subject variation and variations in blood drug concentrations under fed and fasted conditions [11]. These sparingly water soluble drugs often show erratic dissolution profile in gastrointestinal fluids which consequently results in variable oral bioavailability[41].

Biopharmaceutical Classification System (BCS) classifies a new chemical entity (NCE) into four groups, Class I: Highly soluble-Highly permeable, Class II: Less soluble-highly permeable, Class III: Highly soluble-less permeable, Class IV: Less soluble-less permeable. Currently, 40% of the NCE’s fall under BCS Class II and Class IV [12]. Formulating such a molecule into a suitable oral dosage form for a desired therapeutic response poses a challenge to the formulation scientist. BCS Class II drugs exhibit low solubility and thereby slow release rates. These drugs exhibit variable bioavailability and need enhancement of dissolution rate for increasing bioavailability.

Rofecoxib (RXB), a Class II drug, is a potent cyclooxygenase-II inhibitor. It is used in osteoarthritis, rheumatoid arthritis and in management of acute pain in adults. It is a selective COX-2 inhibitor with 1000 fold selectivity for COX-2 relative to COX-1. It shows high anti-inflammatory and analgesic activities in addition to low toxicity, moderate incidence of gastric side effects and high therapeutic index [42]. However, it is practically insoluble in aqueous fluids; and its oral absorption is dissolution rate limited. Its aqueous solubility is reported to be 0.01 mg/ml [43]. Although the drug was withdrawn from the market in 2004 by its brand leader Merck Inc. due to its increased risk of acute myocardial infarction in patient’s receiving either high daily dose (>25 mg/day) or taking drug for longer period of time (>18 months) [44], it was used in present study as it provides a good model for other sparingly soluble drugs belonging to its class. Thus, it was selected as a model drug for the present investigation.
Several techniques have been suggested to improve the dissolution and bioavailability of the sparingly water soluble drugs like micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, alteration in pH, addition of surfactants and solid dispersion [19-23; 45-46]. Solid dispersion using various techniques (coprecipitates, melts and surface solid dispersion) and complexation using cyclodextrin were employed to enhance the dissolution of RXB in the present study for improving dissolution rate as they are simple, convenient, economic and advantageous in improving dissolution of sparingly soluble drugs. Hydrophilic carriers like polyethylene glycols, polyvinyl pyrolidone poloxamer, and cyclodextrin were employed to improve the dissolution of a poorly water soluble drug in present investigation and surface active carrier like gelucire was also explored to prepare surface solid dispersions for dissolution enhancement.

In pharmaceutical industries, the formulator is usually faced with the challenges of optimization of process and formulation factors aimed to prepare a product with the required characteristics. Experimental research methodology represents an efficient approach for solving such optimization problems. By adopting specific statistical experimental designs, one can optimize these factors systematically. Using these designs, an empirical model can be estimated approximating the response of dependent variables as a function of independent variables. Thus, experimental design approach was utilized for optimization of variables in present investigation as it helps in reaching the optimum point in the shortest time with minimum efforts [47-48].

Formulations were prepared and evaluated for dissolution profiles, yield and physical characteristics. Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), Thermal gravimetric analysis (TGA) and X-Ray diffractometry (XRD) were employed to characterize the formulations.

Solid dispersions/complex based formulations exhibit quick therapeutic effect compared to conventional formulations due to the enhancement of the drug dissolution rate [43, 49]. Thus, RXB solid dispersions/complex were also formulated as tablets and evaluated.
Carvedilol (\{1-carbazolyl-(4)-3-[2-methoxy-phenoxyethylamino] propranol-(2)\}), is used for the treatment of cardiovascular diseases (hypertension, congestive heart failure or myocardial infarction) [50]. It displays poor water solubility which prevents it from being absorbed well in the body. It also belongs to the BCS class II category. Hence, it was chosen as a model drug from the same BCS class for dissolution enhancement studies and to validate the approaches used in the above investigation.

Thus, the aim of the present investigation was to improve the dissolution of RXB using various techniques and to study systematically the effect of process and formulation variables on the dissolution rate. The study also included physicochemical characterization and stability studies of the solid dispersions/complexes. The development and evaluation of RXB tablets from RXB solid dispersions/complexes was also undertaken. The investigated approaches were also validated with another BCS class II drug, like carvedilol to assure the use of the optimized techniques and carriers for the drugs belonging to this class.
1.5 REFERENCES


