CHAPTER 1

INTRODUCTION
1.1 BIOAVAILABILITY OF DRUG

Dosage forms are drug delivery systems. The activity of administered drug depends over the availability of drug in biophase. It is utmost essential to a drug, to have sufficient solubility in biological fluid, due to the permeability of biological barriers for dissolved molecules only. Post administration phase of the drug from various routes causes the drug molecule to undergo in several cyclic processes i.e. absorption, distribution, metabolism and excretion, the study of which is referred as biopharmaceutics. A brief scheme of the fate of the drug after its oral administration is (1,2) represented in fig.1 & 2.

For most of the practical purposes the complex jargon of drug traveling can be simplified as

```
  disintegration                        deaggregation
Solid dosage form ----------> Coarse particles ---------->

Absorption
G Drug in solution from dissolution
I gastrointestinal                    Fine particles <-
T fluid distribution
K4

Drug in blood ----------> Drug in tissues ---------->

K5                             K6

Excretion
Drug in urine + Metabolites in urine

V Metabolites <- Biophase
```

FIG 1:
FATE OF DRUG AFTER ORAL ADMINISTRATION

DRUG RECEPTOR INTERACTION  ➔ RESPONSE

DRUG IN TISSUES

DRUG IN SALIVA

METABOLITES IN OTHER FLUIDS

METABOLITES IN TISSUES

METABOLITE IN URINE

METABOLITE IN INTESTINAL TRACT

METABOLITE IN FECES

SOLID DRUG IN DOSAGE FORM

SOLID DRUG IN STOMACH

DRUG IN SOLUTION IN STOMACH FLUID

DRUG IN OTHER FLUIDS

DRUG IN EXTRACELLULAR FLUID

DRUG IN INTESTINAL FLUID

DRUG IN BILE

DRUG IN URINE

DRUG IN FECES

FIG 2:
The scheme depicts the biopharmaceutics of drug as a chain or sequential process, in which the extent of drug receptor interaction depends over large number of earlier processes namely, disintegration, deaggregation, dissolution, absorption and its distribution. The rate of absorption of a drug molecule is the characteristic of drug substances and permeability behavior of available barrier. In the above chain process, the intensity of therapeutic response is determined by the rate limiting step or the slowest process. Especially for poorly water soluble drug, dissolution will be obviously the rate determining step. Such drugs will yield poor biological response and inadequate utilization of administered drug for therapeutic purpose.

1.2 DISSOLUTION PHENOMENA

The logical way to resolve the bioavailability problem is to improve their dissolution. The phenomenon is illustrated in fig.3(a).

Dissolution is the act of dissolving a substance. For poorly soluble drug rate of dissolution \((3)\) determines the rate of absorption of drug. The rate at which a solid dissolves in a solvent is quantitatively expressed by well known Noyes-Witney equation as:

\[
\frac{dM}{dt} = D \times S (C_s - C) / V \times h
\]
Dissolution from solid matrix

(a) Representation of particle under dissolution

(b) Dissolution models
which can also be expressed in concentration terms as:

\[
\frac{dC}{dt} = \frac{D \times S \times (C_s - C)}{V \times h}
\]

where \( \frac{dM}{dt} \) is considered as rate of mass transfer from a solid surface to a solvent, \( D \) is the diffusion coefficient of the solute in solution (4), \( S \) is the surface area of exposed solid, \( h \) is the thickness of diffusion layer \( C_s \), is the concentration of solid at time \( t \), \( V \) is the volume of the solution. The quantity \( \frac{dC}{dt} \) is referred as dissolution rate.

Dissolution from a solid surface by solvent molecule occurs across a hypothetical aqueous diffusion layer or stagnant liquid film, having thickness 'h'. Across the stagnant layer a net concentration differential exists (5). At the solid surface - diffusion layer interface, \( x = 0 \), the drug in solid is in equilibrium with drug in diffusion layer. The gradient or change in concentration with distance across the diffusion layer, is constant. The declining slope of this gradient is expressed by \( C_s - C \) (6). Here Noyes - Witney equation resembles with Fick's first law; \( J = -D \times \left( \frac{dC}{dx} \right) \), where \( J \) is the flux, defined as;

\[
J = \frac{dM}{(S \times dt)}
\]

In case of \( C_s \gg C \) the condition is referred as sink condition and Noyes- Witney equation is reduced to:

\[
\frac{dM}{dt} = \frac{D \times S \times C_s}{h}
\]
For a powdered system having uniform sized particles, the
dissolution can be expressed as Hixson - Crowell cube root law
(7), which assumes the continuous decrease in particle radius as
the dissolution progresses. In a spherical particle the radius \( r \)
is reduced by \( dr \)(fig.3), through dissolution and the
infinitesimal volume lost is
\[
\frac{dv}{2} = 4\pi r^2 dr
\]
for \( N \) such particles.
The loss is
\[
\frac{dv}{2} = 4N\pi r^2
\]
and the surface area of \( N \) particles is
\[
S = 4N\pi r^2.
\]
The infinitesimal mass change as (8) is represented by the
equation
\[
dM = KSCs dt, \text{ where } K = D/h.
\]
The drug density multiplied by the volume change, \( pdV \) gives
\( dM \) or
\[
pdV = KSCs \frac{dv}{2} dt
\]
or from equation above
\[
-\frac{p}{4N\pi r^2} dr = KCS \frac{dv}{2} dt
\]
dividing the equation by \( 4\pi r^2 \) gives
\[
-\frac{pdr}{KCs} = dt.
\]
On integration between \( r = r_0 \) at \( t = 0 \) produces the expression
\[
r = r_0 - K(Cst/p).
\]
The volume of particles can be replaced by mass of \( N \) particles as
shown in fig.4. by using
\[
M = Np \left( \frac{\pi}{6} \right) d
\]
where \( d = 2r \) or
\[
1/3
\]
\[
M = \left[ Np \left( \frac{\pi}{6} \right) \right]^{1/3} d
\]
After substituting the value of \( 2r \) in integrated equation gives
\[
M - M^0 = Kt, \text{ in which } K = [N\pi/6] \times 2kCs/p
\]
Where \( M^0 = \text{Original Mass of drug particles} \)
\[
M^0 = \left[ 2KCs \right]^{1/3} d
\]
\[
= \frac{2KCs}{d}
\]
\[
\text{p}
\]
4
The drug release from matrices is most commonly expressed by Higuchi's approach (8,9,10). A drug passes out of a homogeneous matrix, in Fig 4, the boundary of drug (represented by dotted vertical line in Fig 3) moves to the left by an infinitesimal distance dh. The amount dQ of drug released because of this shift, expressed by the linear expression \( dQ = A \, dh - 1/2 \, Cs \, dh \).

This value of \( dQ \) is substituted in Fick's first law equation

\[
\frac{dM}{Sdt} = \frac{dQ}{dt} \times \frac{DCs}{h}
\]

the resulting equation is solved for \( h \), result

\[
( A - 1/2 \, Cs )dh = \frac{DCs}{h} \times dt
\]

\[
\frac{2A - Cs}{2 \, DCs} \times dh = \frac{dt}{h}
\]

or

\[
t = \frac{2A - Cs}{DCs} \times h^2 + C
\]

The integration constant \( C \) can be evaluated at \( t = 0 \) at which \( h = 0 \) gives

\[
t = \frac{(2A - Cs) \, h}{4 \, DCs}
\]

\[
= \frac{\sqrt{4 \, DCs \, t}}{2A - Cs}
\]

The amount of drug depleted per unit area of matrix Q, at time \( t \), is obtained (11), by integrating the linear equation, to yield:
\[ Q = hA - 1/2hCs, \] substituting above equation in this, produces:

\[
Q = \left( \frac{DCs \ t}{2A - Cs} \right)^{1/2}
\]

which is known as Higuchi's equation.

\[ Q = \left[ D \left( 2A - Cs \right) Cs t \right]^{1/2} \]

It indicates that the instantaneous release of a drug (12,13) at time \( t \) is proportional to square root of  \( A \), the total amount of drug, diffusion coefficient of drug in the matrix, \( Cs \) the solubility of drug and \( t \) the time - (fig 4).

1.3 METHODS OF SOLUBILITY ENHANCEMENT

Solubility alteration of solid drug is the area of primary interest of a formulator. It can be altered by anyone or the following approaches in single or in combinations (14,15).

1.31 USE OF AMPHIPHILES: Surfactants are popular agents to modify the solubility of the substances due to their capability to reduce interfacial tension. Several reports are published regarding the impact of surfactants in improving the bioavailability of medicament, but in some cases bioavailability is drastically decreased due to the entrapment of drug in poorly absorbable surfactant aggregates (micelles) (16,17).

1.32 COBOLVENCY: Cosolvency is one of the most popular approach of solubility enhancement which is mainly adopted in liquid formulations.
1.33 COMPLEXATION: Utilization of complex forming agent is also a popular mean to improve drug dissolution by forming a complex having higher solubility than the parent molecule.

1.34 PRODRUG APPROACH: Prodrug approach has gained the little popularity due to high cost involved in designing more soluble prodrug, as it generates an entirely new chemical species, which is subjected to similar clinical toxicity screening.

1.35 SOLID STATE MANIPULATION: It is one of the most fundamental way to alter drug dissolution and its solubility (18,19). The solubility phenomena can be treated as the melting of drug substance in liquid in which integrity of solid state structure is ruptured by external forces, generated by the drug-solvent interaction. The integriring force within the solid state structure can be modified by number of techniques, by disturbing the formation of stable crystal during its crystallization, leads to an increase in the lattice energy, which results in the faster dissolution of substances.

1.4 SOLID STATE STRUCTURE
The crystalline is that thermodynamically favored for solids. It is characterized by the three dimensional order of the molecules within its crystal lattice (fig 5).

1.41 POLYMORPHISM
The ability of many compounds to crystallize in more than one crystal form, each having a unique packing arrangement. Its relevance to pharmaceutical system has been the subject of
FIG. 5
SOLID STATE STRUCTURES

ORDER DISORDER
TYPES OF SOLIDS

SUBSTITUTIONAL INTERSTITIAL IMPERFECTIONS

FIG. 6 SPACE FIG. 7

TWO DIMENSIONAL REPRESENTATION OF SUBSTITUTIONS IN CRYSSTALINE MATERIALS
a number of reviews. (20, 21). If the transformation rate of one polymorph to another involves only a very small degree of alteration in the intermolecular bonding, one could find a rapid conversion of metastable form to the stable form (22). Polymorphs are sometimes classified according to the position of their transition temperature in relation to their melting points. Enantiotropic systems are those in which the transition point is below the melting point of either polymorph, while monotropism refers to those in which this temperature is above the melting point. The solubility of one monotropic polymorph will always be greater than the other at all temperatures below their melting point. The lower melting polymorph will always exhibit the greater solubility (23).

1.42 NONCRYSTALLINE SOLIDS

A pattern from a crystalline powder consists of many sharp diffraction maxima; in contrast, the pattern for a noncrystalline powder may show only a few diffuse diffraction peaks at low angle. The noncrystalline state is thermodynamically unstable and there will be tendency to entropically derive these solids to a stable crystalline state. The free energy of these noncrystalline solids is much higher than that of their corresponding crystalline polymorphic forms. Mullins and Macek (24) showed that amorphous novobiocin was much more soluble than crystalline material.
Rapid cooling of the melts of three sulfa drugs (25) results in the formation of noncrystalline materials (26,27). In an effort to obtain an indication of the maximum solubility achievable with a high-energy noncrystalline solids. Higuchi and coworkers (28) used point determination.

1.43 SOLVATES

The recrystallization of many compounds from solution will results in the formation of solids containing solvent molecules as an integral port of their crystal structure. The solvent is occluded in channels throughout the crystal lattice without any significant interaction between compound and solvent. Crystal structure determinations of these types of solvates show that the solvent is thermally labile and in many instances disordered in the solid (29). A model was developed (30) to explain the dissolution characteristics of crystalline solvents in aqueous system, where the bound solvent is not water.

The importance of solvate dissociation in the dissolution medium to obtain the benefits of increased dissolution was pointed out in experiments carried out by media are exceedingly important in comparing the dissolution rates of solvated forms to their respective stable crystalline modification.
1.44 RACEMATES - ENANTIOMERS
These forms of a compound differ not only in their ability to rotate plane-polarized light but also in their solubilities (32). Repta and co-workers (33) made use of the solubility difference between the optically active and inactive forms of a cytotoxic agent. Trace amount of a racemate can also alter the solubility of an enantiomer, which in term can result in dosage form problems (34).

1.45 DRUG DISPERSED IN MATRIX
Sekiguchi and co-workers (35,36) found that the use of eutectic mixtures formed by fusion could enhance dissolution and absorption rates of certain drugs. These studies were followed by others (37,38) which showed that the magnitude of the increase in dissolution rates was a function of the ratio of carrier to drug in the eutectic.

Two basic procedures are used to prepare solid dispersion: fusion and co-solvent techniques. Modification of these methods and combination of them have also been used (39,40) for the preparation of solid dispersions.

The cooling rate of a eutectic mixture can influence the physical state of the solid obtained and the particle size of the crystals formed (40,41). The physical and chemical characteristics of solid dispersions that have examined vary a great deal. They range from simple eutectic mixture to vitreous solutions. Extensive reviews of the subject have been published (39,42).
1.46 EUTECTIC

When two materials are completely miscible in their molten state they will solidify to form a eutectic mixture. A number of systems exhibiting eutectic behavior have been examined. Urea and succinic acid have been found to form simple eutectic with a wide variety of drugs (35 - 39, 43 - 45).

The particle size of the drug in eutectic formed by rapid solidification will be small (46). Extremely fine crystals, can exhibit much higher solubilities than large ones (47). The solubility of many compounds is known to be markedly increased in the presence of urea (48) and other organic compounds.

Substitutional solid solutions require a high degree of topological and chemical similarity between the molecules. Materials such as anthracene and acenaphthene form this type of solid solution (49).

1.47 POLYMERIC CARRIERS

Water soluble carriers have been extensively used to form solid dispersions. Most of the reported investigations have focused on dispersions made with polyethylene glycol (PEG) and polyvinyl pyrrolidones (PVP). The studies indicate that the ratio of drug to polymer should be low to maximize the increase in dissolution of the drug. Polyvinyl pyrrolidone is a noncrystalline polymer able in many instance to disperse a significant amount of a drug in a "high energy form". The high solubility achieved is maintained in solution for long period
of time (50,52). Rapidly cooled melts of Polyethylene glycol-
griseofulvin appear to contain 5-10% of the drug being
dispersed at a molecular level (39,53). The degree of molecular
dispersal in the polymer is influenced by the preparative
procedure and the handling of material (39,54) e.g. grinding
e tc..

1.48 GLASS DISPERSIONS
A number of water soluble compounds are known to form glasses
when their melts are rapidly solidified (55). Among these are
citric acid and a host of sugars. Drugs dispersed in glass
matrices of dextrose, galactose, and sucrose have been reported
to exhibit very rapid dissolution rates (56,57). Citric acid
has been shown to form glass dispersions systems with a number
of drugs (58,59).

1.49 SOLID SURFACE DISPERSIONS
The dissolution characteristics of drug can be altered by
dispersing it on the surface of certain materials. Monkhouse
and Lach (60) used water insoluble adsorbents, such as fused
silicon dioxide and silicic acid, as supports for the solvent
deposition of a number of drugs. The fast dissolution rates
of these systems were found to be dependent on the weight ratio
of drug to excipient. When low fractions of drug are used, the
rate is maximized (61).
Yamamoto and Co-workers (62) observed that griseofulvin was
ground with microcrystalline cellulose in a ball mill, its
dissolution and bioavailability were substantially enhanced.

1.5 METHODS OF PREPARATION OF SOLID DISPERSION

A number of modern therapeutic agents are poorly soluble in the aqueous media and dissolve only very slowly in gastro-intestinal fluids. Consequently the in vivo dissolution rate of these compounds is low, and their gastro intestinal absorption tends to be incomplete and erratic. Absorption of insoluble medicaments sometimes is a function of the dissolution rate of these solutions in aqueous medium, since the gastro intestinal absorption rates of drugs frequently is a function of their rate of dissolution, one often encounters difficulties related to undesirably slow absorption and / or incomplete availability of orally administered (relatively poorly soluble) pharmaceuticals. Since dissolution rate is directly proportional to surface area, one may increase the dissolution rate by decreasing the particle size of the drug. The greater the surface area of the drug in contact with the biological fluid, then will bring about more rapid dissolution and thereby more rapid gastro intestinal tract absorption, provided that absorption is rate limited by the dissolution process. For this reason slowly dissolving drugs and poorly soluble drugs are sometimes marketed in the micronized or microcrystalline forms. This may result in more rapid and more complete absorption of the administered dose in turn may cause an earlier, more extensive and more consistent pharmacological
response. The therapeutic dose of griseofulvin was reduced to 50% by micronization and it also produces a more constant and reliable blood levels (63).

The reduction in particle size can be achieved by several ways in which the drug be presented to the gastro intestinal fluid. The most direct method is to utilize microcrystalline. These may be incorporated into tablets, capsules, suspension and rarely in divided powder dosage form.

This can also be accomplished by grinding, milling, pulverization, fluid energy micronization, controlled precipitation by change of solvent temperature, application of ultra sonic waves and spray drying (67).

Although the reduction in particle size can be easily accomplished, the resultant fine particles may not produce the expected faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger Vander Wall's attraction between non-polar molecule (64,65) disadvantage of these pure fine powders of poorly water soluble drugs is their poor wettability. To dissolve or sometimes to disperse in fluids, wetting is the first step. They have more tendency to stick together, even if fine powders are produced by controlled precipitation (66).

The method of enhancing drug dissolution by incorporating a poorly water soluble drug in a soluble phase or carrier was first
proposed by Segikuchi and Obi in 1961 (68). Urea was used as the soluble carrier phase and melt formation as the method of incorporating the drug. This concept was subsequently applied in attempts to improve the biopharmaceutical properties of many drugs of low aqueous solubility. The enhancement in drug release reported as a result of solid dispersion formation relative to pure drug vary from as high as fur hundred fold (76) to less than two fold. An understanding of the mechanism of release from solid dispersion would allow to predict the potential gain in dissolution, resulting from a given solid dispersion.

A more unique way to obtain microcrystalline dispersion of a drug in gastro intestinal fluids is to administer a eutectic mixture composed of the drug and a soluble carrier which dissolves readily in water, and increase rate of dissolution and absorption was resulted (68), solid dispersions may function to increase dissolution rate by breaking down crystal lattice energy, concomitantly decrease the size of the medicament theoretically to the colloidal and even to the molecular level. Thus there is a subsequent increase in the rate of solution which is inversely proportional to particle size. If the dissolution process is the rate limiting step in absorption, the greater the surface area of drug has the faster and more complete should be the absorption.

The solid dispersions have numerous pharmaceutical applications
other than absorption enhancement as: to obtain a homogeneous distribution of a small amount of drugs at solid state, to stabilize unstable drugs, to dispense liquid medicament in solid dosage form. Methyl salicylate, vitamin E and benzyl benzoate was mixed by mechanical stirring with melted Polyethylene glycol 6000 at temperature below 70 %, to formulate a fast release priming dose in a sustained release form, and to formulate sustained release or prolonged-release regimens of soluble drugs by using poorly soluble or insoluble carriers (69).

Solid dispersion involves the incorporation of one or more active ingredients in an inert carrier or matrix at solid state prepared by the Eutectic mixtures, melting, solvent, melting solvent method, or physical mixture. Since the dissolution rate of a component from a surface is affected by the second component in a multicomponent mixture(70) influence on the dissolution characteristics;

1.5 EUTECTIC MIXTURES:

When two components form a completely miscible melt but solidify on cooling as two phases, existing as discreet particles of either component or an microfine mix of both, the melting point of the mix being below that of the either component.

The eutectic mixture is usually prepared from the rapid solidification of the fused liquid of two components which show complete miscibility and negligible solid-solid solubility.
Thermodynamically, such a system is regarded as an intimately blended physical mixture of its two crystalline components (71). When a eutectic composed of a poorly soluble drug is exposed to water or gastrointestinal fluids, the carrier may be released into aqueous medium in fine crystalline form (68). In addition to reduction of crystalline size, the factors stated below also contribute to the faster dissolution rate of a drug dispersed in the eutectic:

a) Increase in drug solubility since its solid crystallites are extremely small (72), b) Solubilization effect by the carrier may operate in the microenvironment immediately surrounding the drug particle in the early stage of dissolution since the carrier completely dissolves in a short time (73), c) Crystallites of hydrophobic drugs are devoid of any aggregation and agglomeration, which may play an important role in increasing dissolution rate since the aggregates held together by strong inter- or intramolecular or atomic cohesive forces (74), d) Dissolution rate of the drug in aqueous media is increased by excellent wettability and dispersibility of a drug from a eutectic or other solid dispersion (69) and e) If a drug crystallizes in a metastable form after solidification from the fused solution, then the increased rate of dissolution and absorption may be observed. A metastable crystalline form, according to Noyes–Witney equation has higher solubility, which ultimately leads to faster dissolution rate (75).
1.52 MELTING METHOD:
In this method the physical mixture of a drug and a water soluble carrier was heated directly until it melted. The melted mixture than cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized and sieved. Such a technique was subsequently employed with slight modifications by Goldberg et. al. (71, 76, 77, 78) and Chiou and Riegelman (79).

The advantages of this method includes, simplicity and economy. Supersaturation of solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under this condition the solute molecule is arrested in the solvent matrix. The disadvantage is that many substances either drugs or carriers, may decompose or evaporate during the fusion process at high temperature. (78).

1.53 SOLVENT METHOD:
A solid solution, mixed crystals of organic and inorganic compounds or mixed amorphous powder of drug and carrier may be resulted in finely subdivided state with the use of this method.

1.531 Coprecipitates:
It is prepared by dissolving the components separately in alcohol and distilled water. The aqueous solution is then poured into alcoholic solution with continuous stirring when
a clear solution was obtained. The system is then heated over water bath with vigorous stirring until co-precipitate is formed. The mass is filtered, dried and pulverized.

1.532 Co-evaporate:
The physical mixture of drug and carrier is dissolved in a common solvent, followed by evaporation, of the solvent, drying and pulverizing.

1.533 Controlled Crystallization:
The two components of solid dispersion are dissolved in the common solvent with the aid of gentle heat. The solution is then spontaneously cooled to room temperature then refrigerated at 5°C. The formed crystals are collected, dried and pulverized.

1.534 Melting Solvent Method:
Liquid components (5-15 % w/w) can be incorporated into Polyethylene glycol 6000 without significant loss of its solid property. The dispersions are prepared by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of Polyethylene glycol.

1.54 POLYETHYLENE GLYCOLS
Polyethylene glycols are water soluble synthetic polymers having repeated unit of oxyethylene (\(-\text{OCH}_2\text{CH}_2\) ) with either
end of the chain consists of hydroxyl group. They have the molecular weight ranging from 200-100000. The state of polyethylene glycols depend over its molecular weight fraction. Molecular weight below 700 has the liquid consistency at room temperature, 1000-2000 semisolid and waxy solids in the range of 3000-100000. A resinous thermoplastic(80) mass is obtained above average molecular weight 100000.

The useful carrier material for solid dispersion from this category is usually in between molecular weight range 3000-20000. In this range polymers are semicrystalline. The crystalline state consists of chains having double helices, arranged as lamellae from which the hydroxyl end groups are accommodated onto the surface. The interior chains may be extended or folded. The folded configuration of chain is relatively less stable. The lamellae are arranged in spherical structures termed as spherolytes(81,82). Higher molecular weight Polyethylene glycol posses more stable folded chain configuration. The extent of folding is affected by the thermal history of material. The useful range of Polyethylene glycol has a melting range of 55° to 65° C, the melting point bears a non-linear relationship with its chain length.

Differential Scanning Calorimetric studies indicated the endothermic change in transition at 56.1° and 60.7° C. It has the glass transition temperature in between 200°-230°K range.
Polyethylene glycols has unusually high aqueous solubility which is associated with the stearic compatibility with lattice. They are also soluble in a large number of organic solvents including acetonitrile, chloroform, dimethyl formamide (83).

In contact with water its particle swells to form gel like matrices, prior to dissolution. Dilute solutions of Polyethylene glycol exhibit Newtonian behavior. A 20 % w/w solution is capable to form an elastic gel, which, above this concentration becomes semi solid in which water acts as plasticizer. The dissolution rate of Polyethylene glycol is significantly affected by the degree of crystallinity, although the extant of chain folding does not have much impact(84,85). Polyethylene glycol is reported to have the tendency of forming week complexes with a large no of drugs. It also favors the formation of high energy metastable polymorphs of drug, which can affect the dissolution significantly.

1.6 DRUG PROFILES (86,87,88,89,90)

1.6.1 AMPICILLIN TRIHYDRATE

1.6.1.1 Description

1.6.1.1.1 Name

D-(2-amino-2-phenyl-acetamido)-3,3-dimethyl-oxo-4-thia
-1-azabicyclo,

[D(-)-α-aminophenyl acetamido] penicillanic acid,

D(-)-α-aminobenzylpenicillin and α-amino benzylpenicillin
1.6.112 Formula and Molecular Weight

\[
\text{C}_16\text{H}_{19}\text{N}_3\text{O}_4\text{S}_2\text{H}_2\text{O} = 403.75
\]

1.6.113 Isomers

Optical isomers are present due to symmetric C atom in the side chain, D-isomer is more active than L-isomer.

1.6.114 Appearance, color and odor

It is a white odorless, microcrystalline powder with a bitter taste. It contains 12-15% of water.

1.6.12 Physical Properties

1.6.121 Spectra

1.6.1211 Infrared Spectrum: Principle peaks at 1775, 1693, 1526, 1308, 1497, 1583.

1.6.1212 Ultra-violet absorption

<table>
<thead>
<tr>
<th>pH</th>
<th>Wave length, nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate buffer</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>1% E 1cm</td>
</tr>
<tr>
<td>Phosphate buffer</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>1% E 1cm</td>
</tr>
</tbody>
</table>
Phosphate buffer 9.5 258 268 ----
1% E 7.28 5.03 ----
saturated methanolic solution produces maximum absorption at 258, 262 and 268 nm.

1.6.122 Melting Range; 202-204°C with decomposition
1.6.123 Solubility
1 in 140 water, 1 in 150 methanol, 1 in 400 ethanol, freely soluble in cyclohexane, benzene, petroleum ether and carbon tetrachloride

1.6.124 Optical Rotation
\[
\beta \left(\frac{D}{20}\right) +287.9^\circ, \beta \left(\frac{D}{26}\right) +245.1^\circ (pH \ 8.0)
\]
\[
\beta \left(\frac{D}{27}\right) +249.5^\circ
\]

1.6.13 Stability; Mainly it is deteriorated by hydrolysis.

1.6.14 Pharmacokinetics; The absorption process is slower than the elimination process after intramuscular injection. Peak serum concentration after 500 mg. intramuscular injection was found within 20-30 minutes. Within the first 8 hrs 40% of this is eliminated through urine. Probenecid sustains the serum peak levels by delaying urinary excretion of urine.

1.6.15 Antimicrobial action; It's bactericidal action against most gram negative and gram positive bacteria, like spirochaetes and actinomycetes is due to interfering with the utilization of certain substances necessary for the synthesis of bacterial cell wall.
1.6.16 Therapeutic uses: Antibiotic, antitibacterial, acting against spirochaetes and actinomycetes.

1.6.17 Analytical methods: Benzoylation of the side chain and a-amino group converts it into benzamidobenzyl penicillin and treating this with mercuric chloride in acid solution forms a-benzamidobenzyl penicillinic acid which can be assayed spectrophotometrically. Degraded Ampicillin solution at pH 5.2 and 75°C can be measured at 320 nm. Aqueous acid solution can be measured at 257 nm (extinction coefficient \(-9.2\))(91,92,93,94):

A strong fluorescent yellow product in acid solution at elevated temperature is produced, which can be estimated fluorometrically.

Ampicillin trihydrate at p.p.m. levels can be determined using differential pulse polarography.

It can be detected by developing the chromatograms by zones of inhibition obtained with Bacillus subtilis or spraying the eluted plates with ninhydrin solution and eluting the drug in a solvent system containing butanol: ethanol: water (4:1:5).

The paper chromatograms are developed using water saturated mixture of butanol, ethanol and water (4:1:5). After descending chromatography papers were sprayed with ninhydrin solution.
1.6.2 CHLORPROPAMIDE

1.6.21 Description

1.6.211 Name: 1-(4-Chlorobenzene sulfonyl)-3-propyl urea.

1.6.212 Formula & Molecular weight.

\[
\begin{array}{cccc}
\text{C} & \text{H} & \text{Cl} & \text{N} & \text{O} & \text{S} \\
10 & 13 & 2 & 3 \\
\end{array}
\]

\[= 276.7\]

\[
\text{SO} \cdot \text{NH} \cdot \text{CO} \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{CH}
\]

\[2 \quad 2' \quad 3\]

1.6.213 Appearance color and odor. It is a white, odorless, almost tasteless, crystalline powder.

1.6.22 Physical Properties

1.6.221 Infra red spectrum; Principle peaks at wave numbers 1661, 1159, 1553, 757, 1086, 909

1.6.222 Ultra-voilet spectrum; A methanolic solution gives maximum absorption at 232 nm \( A = 598 \)

1.6.223 Solubility; Practically insoluble in water, soluble 1 in 12 of ethanol, 1 in 5 of acetone, 1 in 9 of chloroform and 1 in 200 mL of ether.

1.6.224 Melting Range; 126\(^\circ\) to 130\(^\circ\)C

1.6.23 Pharmacokinetics:

Rapidly and completely absorbed after oral administration. About 80% of the single dose is excreted in the urine in 7 days. During chronic therapy 100% is excreted in 24 hours. With 18% of unchanged drug. The main metabolic reactions are
hydroxylation at 2- and 3- position of the propyl substituent in the side-chain, N-dealkylation, and hydrolysis to form sulfonamide metabolite.

1.6.24 Therapeutic uses: Hypoglycemic agent for the treatment of diabetes mellitus.

1.6.25 Analytical methods:
It can be estimated by HPLC (124).

1.6.251 L.V. Spectrophotometric
Chlorpropanide can be estimated from its methanolic solution at 232 nm spectrophotometrically.

1.6.252 Thin-layer chromatography: The chromatograms are developed in a mobile phase, methanol; Strong ammonia solution (100:1.5) and ninhydrin is used as detecting reagent. The Rf value is 0.75.

1.6.3 PREDNISOLONE

1.6.31 Description

1.6.311 Name

11β,17α,21-Trihydroxypregna-1,4 diene-3,20-dione.

1.6.312 Formula and Molecular weight

\[
\text{C}_{21}\text{H}_{28}\text{O}_{5} = 360.4 \text{ CH}_{2}\text{OH}
\]

1.6.313 Appearance, odor and color: It is an odorless, white, crystalline hygroscopic powder with bitter taste.
1.6.32 Physical Properties

1.6.321 Melting Range
About 230° to 235°C, with decomposition.

1.6.322 Solubility
1 in 1300 of water, 1 in 30 of ethanol, 1 in 27 of dehydrated alcohol and 1 in 180 mL of chloroform, soluble in methanol and chloroform.

1.6.323 Ultra-violet spectrum;
Ethanol - 240nm (A₁ = 415a).

1.6.324 Infra-red spectrum
Principal peaks at wave numbers 1654, 1612, 1708, 887, 1112, 1085.

1.6.33 Pharmacokinetics;
Absorbed from gastro-intestinal tract. It is bound to plasma to a lesser extent than hydrocortisone and has a biological half-life of about 200 units. Free and conjugated metabolites are excreted in the urine as for hydrocortisone but over 20% of administered Prednisolone is excreted as conjugated Prednisolone.

1.6.34 Uses: Synthetic glucocorticoid, in Addison's disease, acute leukemia and in rheumatoid arthritis.

1.6.35 Analytical Methods;

1.6.351 Methods have been described for the spectrophotometric determination of a-ketolic steroids.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Solubility</th>
<th>U.V.</th>
<th>M.P.</th>
<th>LOD</th>
<th>Heavy Metals</th>
<th>Assay</th>
<th>Dose</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>1:150 in water, Insoluble in chloroform, alcohol, acetone, ether &amp; Fixed oils.</td>
<td>279 nm in NaOH</td>
<td>199-202</td>
<td>12-15%</td>
<td>---</td>
<td>90-105%</td>
<td>1-8G</td>
<td>Antibiotic daily</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Insoluble in water, 1:12 alcohol, 1:9 Chloroform, 1:200 Ether</td>
<td>232 nm in 0.1N HCl</td>
<td>126-130°C</td>
<td>1%</td>
<td>0.003%</td>
<td>97-103%</td>
<td>100-500 mg daily</td>
<td>Hypoglycemic agent</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1:1300 water, 1:27 dehydrated alcohol, 1:30 alcohol, 1:50 acetone, 1:180 Chloroform.</td>
<td>242 nm in methanol</td>
<td>230°C with 1%</td>
<td>---</td>
<td>97-102%</td>
<td>5-60 mg</td>
<td>Glucocorticoid daily</td>
<td></td>
</tr>
</tbody>
</table>
involving the use of 2,3,5-triphenyl tetrazolium chloride, 490 nm, 3,3'-dianisole-bis-4,4'(3,5-diphenyl)-tetrazolium chloride at 510 nm, 2,5-diphenyl-3-(p-iodophenyl) tetrazolium chloride at 495 nm, and 2-(p-iodophenyl)-3-(p-nitrophenyl)-5-phenyl tetrazolium chloride at 480 nm (95, 96). Prednisolone can be estimated by HPLC (125, 126). Colorimetric procedure for estimation is reported (127). Prednisolone dissolved in methanol is detected spectrophotometrically at 232 nm.

This layer chromatography. Mobile phase; methylene chloride; ether methanol; water (77:15:8:1.2). Detecting agent: Sulfuric acid-ethanol reagent Rf value 0.20.

1.6.4 MANNITOL (86, 87)

1.6.41 Description

1.6.411 Formula and molecular weight

\[
\begin{align*}
\text{C}_6\text{H}_6\text{O}_6 & = 182.17 \\
& \text{D - Mannitol}
\end{align*}
\]

1.6.412 Appearance Color and odor

A white, Colorless crystalline powder or granules with a sweetish taste, melting point. 166° to 169°C.

1.6.42 Toxic effect:

May cause diarrhoe when given by mouth. Intravenous injection may produce nausea vomiting, thirst, headache, dizziness, chill, fever, or chest pain.
1.6.43 Abortion and Fate: It is not absorbed through gastrointestinal tract. After intravenous injection, it is not significantly metabolized. It is filtered by the glomeruli in the kidney and is not reabsorbed. About 80% of a dose is excreted in urine is 3 hours.

1.6.44 Uses: Mannitol in used as an osmotic diuretic when injected intravenously.

1.6.45 Solubility: 1:6 water, 1:10 glycol, slightly soluble in alcohol and pyridine and insoluble in ether.

1.6.46 Loss on Drying: 0.3%.

1.6.5 POLY ETHYLENE GLYCOL 6000(86,87)

1.6.51 Description

1.6.511 Formula and molecular weight

\[ O(\text{OCH}_2\text{CH}_2)_n\text{OH} = 7000 - 9000 \]

1.6.512 Appearance, color and odor: It is odorless, creamy-white, hard, wax-like solid or flakes. Freezing point about 60°C. Viscosity at 20°C is 700-900 centistokes.

1.6.52 Solubility: 1 in 2 of water, 1 in 2 mL chloroform, slightly soluble in alcohol and insoluble in ether.

1.6.53 Toxic effect: Non-toxic.

1.6.54 Absorption and Fate: Not absorbed significantly through gastrointestinal tract. After intravenous injection quickly excreted in urine.

1.6.55 Use: Strongly hydrophillic, o/w emulsifying agent, in the preparation of ointment and suppository etc.
1.6.6 POLY VINYL PYRROLIDONE (86,87).

1.6.61 Description

1.6.611 Formula and Chemical Name

(C H N O )

6 9 n

1.6.612 Appearance, color and odor

A white or creamy-white, odorless or almost odorless, tasteless powder. It is hygroscopic and significant moisture is absorbed at low humidities.

1.6.62 Solubility: Soluble in alcohol, water, chloroform and isopropyl alcohol.

1.6.63 Toxic effect: Lung damage when used with hair spray, intravenous injection increases sedimentation time.

1.6.64 Absorption and Fate: It is not metabolized following injection. Low molecular weight are excreted in the urine about 60-70% within 24-72 hrs. Small amount is excreted in the faces.

1.6.65 Use: As suspension and dispersion agent, tablet binding and granulating agent.

1.6.7 UREA (86,87)

1.6.71 Description

1.6.711 Formula and molecular weight

CH N O = 60.06

4 2

1.6.712 Appearance, color and odor

Colorless, slightly hygroscopic, odorless or almost odorless, prismatic crystal with a cooling saline taste.
1.6.72 Melting point: 132°C - 135°C
1.6.73 Solubility: 1 in 1 mL water, 1 in 10 mL alcohol, 1 in 1 mL boiling alcohol, 1 in 20 mL absolute alcohol, 1 in 6 mL methanol and 1 in 2 mL glycol.
1.6.74 Heavy metals: Not more than 0.002%.
1.6.75 Toxic effect: May cause gastric irritation with nausea and vomiting when given by mouth. Intravenous administration may cause headache, nausea and vomiting, confusion and a fall in blood pressure.
1.6.76 Precaution: Should not be given to the patients with marked impairment of hepatic or renal function or with dehydration.
1.6.77 Absorption and Fate: Rapidly absorbed from the gastrointestinal tract and is excreted in the urine.
1.6.78 Use: Osmotic diuretic with a low renal threshold. In the treatment of acute increase in intracranial pressure due to cerebral oedema.

1.7 ANALYTICAL METHODS OF SOLID DISPERSION

Many methods are available that can contribute information regarding the physical nature of a solid dispersion system. In many instances, a combination of two or more methods is required to study its complete picture (97,98).

1.7.1 THERMAL ANALYSIS

1.7.1.1 Cooling Curve Method:

In this method the physical mixture of various compositions
are heated until a homogenous melt is obtained. The temperature of the mixture is then recorded as a function of time. From a series of temperature-time curves, the phase diagram can be established (99,100). It is time consuming, it requires a relatively large amount of sample and changes in slopes can be missed, if cooling takes place rapidly (101,102).

1.712 Thaw Melt Method
The thaw point is referred to a temperature crossing a solidus line (99). This simple method was used by Rheinboldt (103), Rheinboldt and Kircheisen (104,105). A stirring device in the capillary tube was employed for more accurate results by Sekiguchi et al. (106). A range of six degrees of variation was reported in the study of thaw points of a chloramphenicol-urea system (107).

1.713 Thermomicroscopic Method
Goldberg et al. (108) used polarized microscope with a hot stage to study phase diagrams of binary systems. The melting of isotropic crystals often cannot be detected accurately under a polarizing microscope (109). The existence of a limited solid solution of griseofulvin in succinic acid determined by this method (110).

1.714 Differential Thermal Analysis
Differential effects, associated with physical or chemical changes are automatically recorded as a function of
temperature or time as a substance is heated at a uniform rate (111). Apparatus permitting direct observation of samples during heating were used to facilitate the observation of any physical-chemical changes (112). This technique was first introduced in 1952 (113). The phase diagram can be constructed. This method is limited to compounds with high terminal stability and low volatility (114).

1.72 X-RAY DIFFRACTION METHOD
The intensity of the x-ray diffraction from a sample is measured as a function of different angles. The advantages and disadvantage of these two methods were well discussed (115,116). It was used to study binary eutectic system of chloromphemicol-urea(117,118).

1.73 MICROSCOPIC METHOD:
Microscopy has been used quite often to study polymorphism (119) and morphology of solid dispersion (46,100,107). The fine particles of crystallization in the glassy Polyvinyl pyrrolidone matrix can be readily detected by the polarizing microscope (111).

1.74 SPECTROSCOPIC METHOD
Visible absorption spectroscopy was used to study the low concentration dispersion of β-carotene in Polyvinyl pyrrolidone. These results indicated that β-carotene is dispersed molecularly in the polymer. IR spectroscopy was also used to study the solid solution.
1.75 DISSOLUTION -RATE METHOD
The dissolution -rate method was proposed by Allen and Kwan (120). The dissolution-rate method has been shown to be applicable to simulated systems of Indomethacin-Polyethylene glycol 6000 and sulphathiazole-urea (121, 122, 123). The validity of this principle however, needs further confirmation by other methods.

1.76 THERMODYNAMIC METHODS
The phase diagrams of eutectic and solid solution systems can be constructed on the basis of same thermodynamic parameters (49,100). A knowledge of heats of fusion entropies, and partial pressure at various compositions enables one to determine the solubility gap below the solid-liquid equilibrium.
RESEARCH ENVISAGED

1. Standardization of Drugs & Carriers
2. Preparation of Standard Curves
3. Preparation of Solid Dispersions
4. Characterization of Solid Dispersions
5. Dissolution Rate Studies
6. Biopharmaceutical Study
7. Statistical Techniques Used
   a) Drug & Carrier Standardization
   b) Standard Curves
   c) Dissolution Studies
   d) Percent Dissolution Plot
   e) Log Transformation of Dissolution Data
   f) Higuchi's Plot
   g) Blood Plasma Level Curve