CHAPTER II
INTRODUCTION

LITERATURE ON BIOAVAILABILITY AND DISSOLUTION RATE

The most important property of a dosage form is its ability to deliver the active ingredients to its site of action in an amount sufficient to elicit the desired pharmacological response. This property of the dosage form has been variously referred to as its physiological availability, biologic availability or bioavailability. Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Accordingly, the absorption of an intravenously administered drug is instantaneous and complete. However, for reasons of convenience and stability, most drugs are administered orally after first being formulated into dosage forms, usually tablets or capsules. The rate and extent of absorption from such dosage forms is usually not precisely known as it is affected by a number of factors related to the drug, dosage form and patient.

Dosage form related factors which can produce profound differences in drug bioavailability include formulation and manufacturing variables such as, particle size, the chemical form and solubility of the drug, the type and quantity of the excipients used, the compaction pressure etc. Among the patient related factors those over which the physician and/or the patient can exert some control include the time of administration of the drug relative to food, co-administration of other drugs which may influence the absorption and compliance of the patient with the instructions of the physician, pharmacist or nurse. The patient related factors which normally cannot be controlled but for which some allowance (or) adjustment can be made include age, disease state, abnormal genital characteristics and/or gastro-intestinal physiology. The
active ingredient in a solid dosage form must undergo dissolution before it is available for absorption in the gastrointestinal tract. Dissolution forms the rate limiting step in the absorption of drugs from solid dosage forms especially when the drug is poorly soluble.

Methods to enhance bioavailability can be related to one of two approaches. The first is pharmaceutically dependent and involves improvement of the absorption attributes by increasing the dissolution rate of the drug preparation. This usually is achieved by changing certain ingredients in the formulation, optimizing the manufacturing process or by altering the physico-chemical properties of the drug substance without altering its molecular structure. The second approach is pharmacokinetically dependent and deals with resolving specific bioavailability problems that are intrinsic mainly to the drug chemical entity which includes, using salt or ester form of the drug or prodrugs or by increasing the non-polar portion of a molecule by extending the length of the chain. In certain cases, however, significant enhancement of bioavailability can be obtained by modulating the drug metabolic fate, its distribution characteristics or its excretion profile.

**Dissolution and Absorption of Drugs from Solid Dosage Forms:**

Before being absorbed into systemic circulation, drugs must dissolve in body fluids existing at the site of absorption and the dissolved drug molecules from solution absorb or cross the biological barriers by various drug transport mechanisms. Dissolution rate can be defined as the amount of solid substance that goes into solution per unit time under standard conditions of temperature, pH, solvent composition and constant solid surface area. It is a dynamic process and better related to drug absorption and bioavailability.
Wagner (Wagner, 1970) proposed the following scheme for the processes involved in the dissolution of solid dosage forms.

![Scheme](image)

**Scheme -1**

Scheme -1 indicates the processes involved in the absorption of drugs after oral administration in the form of a tablet or capsule. Dissolution of the drug occurs not only from the fine particles of the drug that are ultimately produced, but also to a small degree from intact dosage form before its disintegration and from fragments and agglomerates produced after disintegration. **In vivo**, process (Truitt and Morgan, 1964) (scheme - 1) involves the absorption of the drugs. The drug dissolved in the gastrointestinal contents must diffuse through the aqueous fluids to the gastrointestinal barrier and then be transported through the barrier to the systemic circulation. When the dissolution process is very much slower than the other processes, then the dissolution essentially and completely controls absorption rate. There is adequate evidence now available to conclude that the dissolution rate often partially or totally controls the rate of absorption. This is particularly true in the case of poorly soluble drugs. Examples of drugs for which dissolution rate limited absorption was observed include aspirin, tolbutamide, spiranolactone, prednisone, methyl prednisone,
ampicillin, griseofulvin, sulphamethiazine, salicylamide, etc. The rates of the process of disintegration, deaggregation and dissolution are all dependent upon the composition and method of preparation of the dosage form. These rates are all largely dependent upon pharmaceutical factors, which the formulator can alter.

A more quantitative description of the dissolution rate is given by the Noyes-Whitney (Noyes and Whitney, 1987) equation based on diffusion layer model:

$$\frac{dc}{dt} = \frac{D}{h} S (C_s - C)$$

Where dc/dt-rate of dissolution

S - Surface area

D - Diffusion coefficient

h - Thickness of the diffusion layer

C_s - Saturation solubility

C - Concentration of drug in solvent at time ‘t’

In dissolution rate limited absorption C is negligible compared to C_s. Under well defined conditions of use, D and h are relatively constant values that are not conveniently altered to any degree by product formulation. Hence,

$$\frac{dc}{dt} = K' S C_s$$

i.e. Dissolution rate α Surface area X Solubility

Thus, increasing either solubility or surface area or both can increase dissolution rate of poorly soluble drug. These two variables can be altered by the following techniques.
1. Controlling the solubility of weak acid or base drugs by buffering either the entire dissolution medium or the microenvironment i.e. the diffusion layer surrounding a particle through the use of buffers and salts.

2. Controlling the solubility of the drug through the choice of physical state such as crystal form, its hydrates, its amorphous form and so on.

3. Controlling the surface area of the drug through control of particle size.

**Methods to Enhance the Dissolution Rate and Absorption of Poorly Soluble Drugs:**

The different methods available to enhance the dissolution and absorption rates of poorly soluble drugs are summarized in Table 2.1

**Table-2.1**

<table>
<thead>
<tr>
<th>Method</th>
<th>Examples of drugs investigated</th>
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<td>I.</td>
<td>Methods which increase the solubility</td>
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ii. Use of salts of weak acids and weak bases

Na, K, Ca salts of p-aminosalicylic acid (Wan et al., 1974), Sod Tolbutamide (Nelson et al., 1962), tetracycline HCL (Nelson, 1959), Na and K salts of penicillin V (Juncher et al., 1957), Sod. Phenobarbitone (Nelson, 1958), theophylline (Vivino, 1954) and choline theophylline (Gagliani De Graff et al., 1954).

iii. Use of solvates and hydrates

Ampicillin anhydrate (Poole et al., 1968), caffeine and glutethimide anhydrous forms (Shefter and Higuchi, 1958), solvated forms of succinylsulphathiazole and hydrocortisone (Shefter and Higuchi, 1958).

iv. Use of selected polymorphic forms

Novobiocin (Mullins and Macek, 1958), chloramphenicol palmitate (Aguiar et al., 1967) and succinylsulphathiazole (Moustafa et al., 1974), (Moustafa et al., 1975).

v. Complexation

Benzocaine-caffeine (Higuchi et al., 1965), digitoxin-hydroquinine (Higuchi et al., 1974), caffeine-ergot alkaloids (Zoglio et al., 1969), PVP (Chowdary et al., 2006), Etoricoxib-β-cyclodextrin (Santoshkumar et al., 2006), Celecoxib-β and HPβ-cyclodextrin (Chowdary et al., 2008).

vi. Prodrug approach

Pivampicillin (Daehne et al., 1970), hectacillin (Schwartz et al., 1972), erythromycin-2'-N-alkylsuccinate (Sinkula, 1976), 2'-N-alkyl glutaramate, prodrugs of carbenicillin (Butter et al., 1971), lincomycin and clindamycin (Sinkula et al., 1973).
vii. Use of surfactants  Hydrocortisone-Tween80 (Hazratwala et al., 1974), amphotercin-B-biosurfactants (Goyal et al.1982), Sod.tauro cholate and sod.cholate), tolbudamide-Tween 20 and Tween 80 (Sanghvi et al., 1982), sulphathiazole, prednisolone and chloramphenenicol-polysorbate 80 (Chiou et al.,1976).

viii. Sublimation Technique  Etoricoxib-Menthol, Crosppvidone (Patel et al.,2008), Etoricoxib-camphor, menthol, thymol, low substituted hydroxylpropyl methyl cellulose, low substituted hydroxyl-propyl cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate(Patel et al., 2008).

II. Methods which increase the surface area

1. Micronization (particle size reduction to increase the surface area)  Griseofulvi (Bedford et al., 1960; Atkinson et al., 1962), digoxin (Shaw et al., 1974; Jounela et al., 1975), phenacetin(Finholt, 1974) and Sulphadiazine (Reinhold et al.,1945)

2. Use of surfactants (to increase effective surface area by facilitating proper wetting)  Phenacetin (Fiholt et al., 1968), ethinamate(Newton et al., 1971, sulfisoxazole (Kakemi et al., 1965).

4. Solid dispersions  Griseoflvin-PVP (Mayersohn et al., 1966), reserpine-PVP (dispersion of poorly soluble drug in a solid matrix of water soluble carrier) (Stupak et al., 1972), tolbutamide-PEG (Kaur et al., 1980) and chloramphenicolurea (Sekiguchi et al., 1964). Etoricoxib-croscarmellose sodium, crosspovidone carrier) (PrameelaRani et al., 2008). Aceclofenac-crosspovidone, PVP-K 30 (Thiyagarajan et al., 2009).

**NEWER TECHNOLOGIES** (Chowdary et al., 2005)

Newer and novel drug delivery technologies developed in recent years for bioavailability enhancement of insoluble drugs are listed below.

**Lipid Based Delivery Systems:**
- Lipid Solutions,
- Lipid Emulsions
- Microemulsions

**Self-Dispersing Lipid Formulations (SDLF):**
- Self-Emulsifying Drug Delivery Systems (SEDDS)
- Self-Microemulsifying Drug Delivery Systems (SMEDDS)

**Nanosizing by precipitation:**
- Evaporative Precipitation into Aqueous Solution (EPAS)
- Controlled Precipitation
- Cryogenic and Super critical fluid technologies.

**Biopharmaceutical Classification System:**

Biopharmaceutical Classification System (BCS guidance 2001) (BCS) guidance was provided by US Food and Drug Administration (FDA), to improve the efficiency of drug product development process. According to which drugs are grouped into four major classes basing on their solubility and permeability.
**Class I:** High Permeability and High Solubility

Propranolol, Metoprolol, Diltiazem, Verapamil

**Class II:** High Permeability and Low Solubility

Ketoconazole, Mefenamic acid, Nifedipine, Nicardipine, Felodipine, Piroxicam, Celecoxib

**Class III:** Low permeability and High solubility

Acyclovir, Neomycin B, Captopril, Enalapril maleate, Alendronate

**Class IV:** Low permeability and Low solubility

Chlorthiazide, Furosemide, Tobramycin, Cefuroxime

A drug substance is considered highly soluble when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5 and it is considered highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose. A drug product is considered to be rapidly dissolving when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

The rate limiting process for drug absorption and bioavailability (rate and extent of absorption) is either the release (or dissolution) of drug substances from the dosage form or its permeation through the intestinal membrane. If permeation through intestinal membrane is rate limiting, dissolution properties may be of negligible importance. Class I drugs behave *in-vivo* like an oral solution. Dissolution and bioavailability is very rapid for these drugs. If the Class I drug substance is released from the dosage form very rapidly *in-vivo*, gastric emptying will become the rate limiting process for drug absorption. Whereas for drugs having high permeability and low solubility (Class II), dissolution or release from the dosage form occurs slowly.
and the dissolution rate will become the rate limiting factor for drug absorption. These drugs exhibit variable bioavailability and need enhancement in dissolution rate for increasing bioavailability. Permeation through the intestinal membrane forms the rate-limiting step for absorption of drugs of Class III and bioavailability is independent of drug release from the dosage form. These drugs generally exhibit low bioavailability and need enhancement in permeability. Class IV drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability, gastric emptying form rate limiting steps for absorption of these drugs.