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Chapter 1...

Introduction

The term biopharmaceutics was coined by Dr. G. Levy in 1960. *Biopharmaceutics* is the study of factors affecting bioavailability of a drug and use of this information to optimize pharmacologic or therapeutic activity of drug products in clinical applications. Thus, in other words we can say biopharmaceutics is the study of the relationship between physico-chemical properties of the drug in a dosage form and the various pharmacologic, toxicologic or therapeutic effects observed after the administration of the dosage form.

Pharmacokinetics is the term derived from Greek words, Pharmakon (drug) and Kinesis (motion or rate of change). Therefore, pharmacokinetics is application of kinetics in the study of absorption, distribution and elimination of drugs. It basically involves the study of time course of amounts and concentration of drug and its metabolites in different tissues in the body and interpretation of the data using suitable models. Pharmacokinetic studies are useful in the maintainance of therapeutic drug concentration in the body and preventing danger of toxicity. *Clinical Pharmacokinetics* deals with application of pharmacokinetic principles for the safe and effective therapeutic management of individual patients. *Toxicokinetics* i.e. kinetics of toxicity, is the study of kinetics of absorption, distribution, metabolism and excretion of drugs at high doses. In other words toxicokinetics is application of pharmacokinetics to toxicology.

Pharmacodynamics is the study of biochemical and physiological effects of drug and its mechanism of action. It deals with the relationship between concentration of drug at the site of action and the magnitude of the effect produced by the drug. Thus, in other words, pharmacodynamics deals with what a drug does to the body, whereas pharmacokinetics deals with what body does to a drug. *Pharmacogenetics* deals with the unusual drug responses due to genetic or hereditary differences. This genetic variability in pharmacokinetics is mainly due to differences in the drug metabolism and genes encoding enzymes or proteins.

Bioavailability is defined as the rate and extent of availability of drug to the systemic circulation. The process of movement of unchanged drug from the site of administration

to the systemic circulation is called as *absorption*. *Distribution* is the process of movement of drug from blood to various body fluids and tissues. *Metabolism* or *biotransformation* is the process of conversion of the drug to another chemical form i.e. metabolite, which may be therapeutically active or inactive. *Elimination* is a process of removal of drug from the body leading to termination of its action. The elimination of drug occurs either by excretion via various excretion pathways such as renal excretion, biliary excretion etc. or via by biotransformation as metabolities. *Excretion* is the means by which drug or its metabolites exit from the body. It occurs through one or more excretary processes such as via urine, bile, saliva, expired air, feces, milk, and sweat. *Drug disposition* includes both drug distribution and elimination.

QUESTIONS

1. Define following terms :
   (A) Biopharmaceutics
   (B) Pharmacokinetics
   (C) Clinical pharmacokinetics
   (D) Toxicokinetics
   (E) Pharmacodynamics
   (F) Pharmacogenetics
   (G) Bioavailability.

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Chapter 2...

Drug Absorption

Drug absorption is the process of movement of unchanged drug from the site of administration to the systemic circulation. Drug may be administered by various routes such as enteral routes i.e. oral, sublingual, buccal and rectal; parenteral i.e. intravenous, subcutaneous, intramuscular etc. and topical such as skin, ophthalmic etc.

The oral route is generally considered as the most convenient as compared to other non-oral alternatives. It is because of lower production cost, better suitability for self-medication, higher level of patient safety and better patient compliance. But, the orally administered drug must be sufficiently soluble in G.I. fluids, withstand acidic and enzymatic degradation in the G.I. tract and should have ability to permeate the epithelium of the intestinal mucosa which is the main absorptive area in G.I. tract.

Intestinal Epithelium :

The intestinal epithelium shows folds and villi, which increase the anatomical surface area of the mucosa approximately 600 fold in the small intestine. In between the villi there are crypts (Fig. 2.1), in which regeneration of the intestinal cells occurs. The functional unit of the intestinal epithelium is the crypt - villus axis. In the crypt-villus axis, proliferating cells are in the lower crypt and differentiating cells are present in the

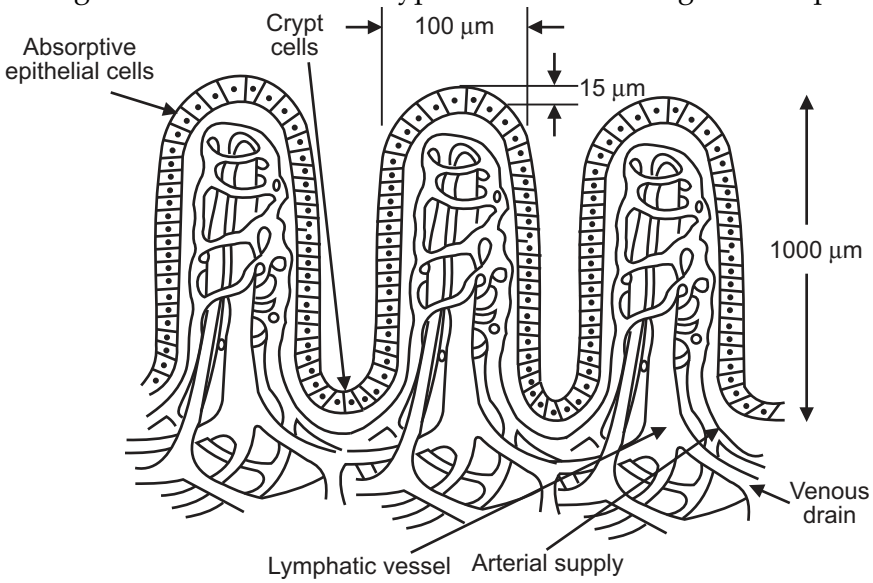

Fig. 2.1 : Scehmatic representation of the villi

upper crypt region. The absorptive epithelium consists of several types of cells which carry out endocrine, exocrine and absorptive functions. The endocrine cells secrete digestive hormonal peptides, the exocrine cells are goblet cells which secret mucus and the Paneth cells secreting antimicrobial peptides. About 80–90% of the epithelial cells are enterocytes which are real absorptive cells.

The cellular membranes are made-up of phospholipids arranged in bilayers that are intermingled with membrane proteins. It can be considered as a mayonnaise sandwich, where a double layer of lipids is sandwiched between two parallel monomolecular layers of proteins as shown in Fig. 2.2. The lipid layers contain amphiphillic lipid molecules with their hydrocarbon chains oriente d inside and polar heads outside. Thus it forms a hydrophobic lipid core with polar surface which is associated with a globular protein layer, with the aqueous filled pores of 4 to 10 $\mathring{A}$ size interspersed in between. Thickness of the lipid bilayer is 4 nm and each protein layer is 2 nm. The composition of phospholipids and proteins varies from cell type to cell type. The cell membrane of the intestinal enterocytes is polarised i.e. there are differences in membrane composition in the apical and basolateral membrane. The apical and basolateral membrane domains are separated by tight junctions, providing a seal between adjacent epithelial cells.

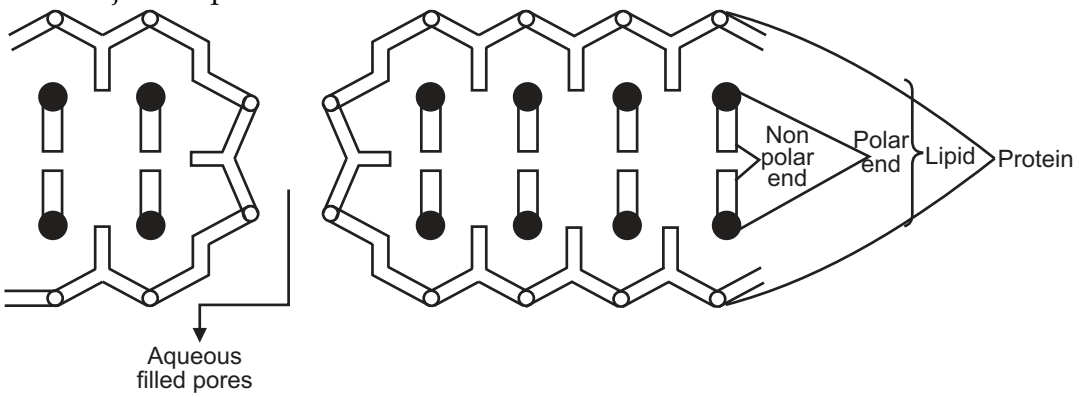

Fig. 2.2 : Structure of cell membrane

Mechanisms of Drug Absorption :

The absorption of drug across the absorptive epithelium occurs by one or several of the following mechanisms :

1. Transcellular passive diffusion.
2. Paracellular or convective transport.
3. Carrier-mediated transport.
4. Ion-pair transport.
5. Endocytosis.

1. Transcellular passive diffusion :

A drug molecule must penetrate the membrane surrounding the cell in order to transverse the cell. The first step in transcellular transport is the permeation of the apical membrane by the drug, which is followed by diffusion through the cytoplasm of the cell interior and subsequent permeation of the basolateral membrane.

Permeation through the apical membrane requires the drug molecule to be sufficiently lipophilic. Therefore, lipophilic drugs of moderate size are normally transported by the transcellular route. But molecules with very high lipophilicity may become trapped in the apical membrane, such molecules may permeate through lateral membrane. The apical membrane has lower permeability than the basolateral membrane.

Diffusion of small molecules in the cytoplasm is normally a rapid process, and therefore the apical membrane is usually considered as the rate limiting barrier to transcellular passive diffusion. Concentration gradient across the membrane acts as a driving force. Movement across the membrane occurs due to kinetic energy of the drug molecules. As membrane does not participate actively in the transport and just provides the physical barrier, the process is passive transport.

Process of passive diffusion follows Fick's law which states that 'the rate of passive diffusion across the membrane is directly proportional to the concentration gradient across the membrane'. It may be stated as :

$$\frac{dC}{dt} = \frac{DA\ K_{o/w}\ \Delta C}{h} \quad \text{... eq. (1)}$$

or $$\frac{dC}{dt} = P_c\ A\ \Delta C$$

where, $\frac{dC}{dt}$ = Rate of passive diffusion.

D = Diffusion coefficient of drug.

A = Surface area of the absorbing membrane.

$K_{o/w}$ = Partition coefficient of the drug between lipid portion of membrane and water.

ΔC = Concentration gradient across the membrane.

h = Thickness of the membrane.

P_c = Permeability coefficient.

In passive diffusion drug moves from higher to lower concentration. The rate of passive diffusion is directly proportional to absorbing surface area, partition coefficient, diffusion coefficient of the drug and inversely proportional to thickness of absorbing membrane. Diffusion coefficient is proportional to molecular weight, as molecular weight of the drug increases, rate of diffusion decreases. As non-ionic form of a drug can dissolve or partition in the membrane lipid, passive transcellular diffusion is also known as non-ionic diffusion. The extent of ionization of drug depends on the dissociation constant of drug and pH of the fluids on either side of the membrane. Drug absorption via transcellular route for polar molecules; if the polar surface area, which is the measure of hydrogen bonding capacity of the drug is more than 120 A^0 then molecule cannot pass by transcellular route.

Most of the rapidly and completely absorbed drugs are absorbed by transcellular passive diffusion. Weak organic acids, weak organic bases and organic non-electrolytes such as alcohol, urea, aminopyrine and some cardiac glycosides are absorbed by this mechanism.

The pH - Partition Hypothesis states that "for drugs with molecular weight greater than 100, absorption by passive diffusion is governed by pKa, lipid solubility and pH at absorption site".

2. Carrier-Mediated Transport :

In passive transport process discussed above the membrane does not actively participate in the transport process and acts as a physical barrier across which concentration gradient has been developed. In contrast to this, carrier-mediated transport involves participation of the membrane in the transfer of molecules. In this process, a 'carrier' may be an enzyme or some other component of the membrane. The carrier binds reversibly or non-covalently with the solute molecule and this carrier-solute complex traverses across the membrane. On the other side of the membrane the complex dissociates and discharges the solute molecule. The carrier again returns to the original site and is ready for next cycle.

Mechanisms of Drug Absorption

Intestinal membrane carriers are of three types.

Type I : These are located at the apical membrane of enterocytes and are responsible for transport in the absorptive direction (i.e. into the blood) .

Type II : These are located at the basolateral membrane of the enterocytes and transport drugs in secretory direction (i.e. out of the blood into the intestine).

Type III : These are located at both the apical and basolateral membranes of the enterocytes and are responsible for the drug passages across the enterocytes either the absorptive or secretory directions.

The characteristics of the carrier mediated transport are as follows :

1. **Rate :** Rate of carrier mediated absorption is significantly high as compared to passive diffusion.
2. **Structure specificity :** The carrier is designed to transport a specific chemical structure. Generally, carriers are designed to transport essential nutrients e.g. vitamins, such as niacin, vitamin B_{12}, building blocks for DNA and RNA.
3. **Competition :** Though it is structure specific, carrier may transport a chemical structure which is similar to the specific chemical transported by carrier. Thus, drugs having chemical structure similar to essential nutrients transported by carriers and are known as false nutrients. Antineoplastic drugs 5-bromouracil and 5-fluorouracil compete with uracil for carrier mediated transport.
4. **Absorption window :** In the G.I. tract there are limited areas in which carrier system is most dense and is referred as 'absorption window' where carrier mediated absorption occurs. Generally, it is in the upper portion of the intestine. Therefore, drugs which are absorbed at absorption window in the upper intestine should not be designed as sustained release. For example, conventional sustained release formulations of iron and vitamins show low bioavailability as the dose released after absorption window can not be absorbed.
5. **Capacity-limited absorption :** Since the number of carriers available are limited, the transport exhibit capacity limited absorption. When the number of carrier sites is more than the total number of transferable molecules the system is

unsaturated. Under unsaturated conditions the transport rate is directly proportional to the number of transferable molecules available i.e. first order kinetics. But, when number of transferable molecules exceeds the number of carrier sites the system becomes saturated. Under saturated conditions carrier system works at full capacity and transport occurs at constant rate, irrespective of concentration of transferable molecules i.e. zero-order kinetics.

Thus, in carrier mediated transport capacity limited absorption occurs which shows non-linear kinetics or also known as Michaelis-Menten Kinetics. It indicates deviation from first order kinetics at high doses of drug i.e. transferable molecules (Fig. 2.3).

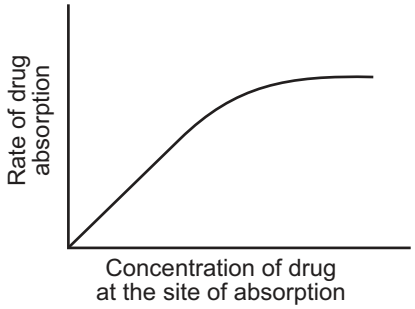

Fig. 2.3 : Plot of rate of absorption versus drug concentration for carrier mediated transport process

The carrier-mediated transport is further classified as facilitated diffusion and active transport.

(a) Facilitated passive diffusion : It is a carrier mediated process which occurs across the concentration gradient, i.e. from higher concentration to lower concentration. Facilitated passive diffusion is driven by an inside-negative membrane potential. Organic cation transporters OCT1, OCT2 and OCT3 are transporters causing facultative diffusion. But as it is carrier mediated, rate of transport is significantly higher than the passive diffusion. Absorption of Vitamin B_{12} occurs by facilitated diffusion. Intrinsic factor produced by the stomach wall acts as a carrier for vitamin B_{12}. Upto 1.5 µg of vitamin B_{12} is absorbed by facilitated diffusion.

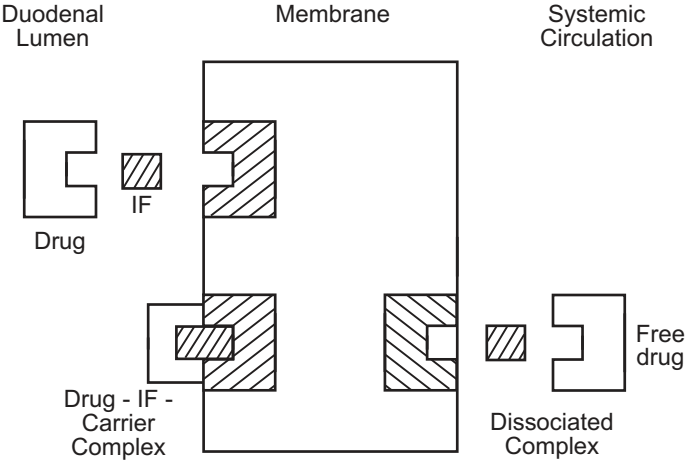

Fig. 2.4 : Facilitated diffusion of drug

(b) Active Transport : In this process the drug is transported against concentration gradient i.e. from lower concentration to higher concentration (Uphill transport). In active transport the drug-carrier complex moves across the membrane utilizing energy provided by adenosine triphosphate (ATP). Similarly, substances which interfere with the cell metabolism i.e. metabolic poisons such as cyanides, fluorides etc. can non-competitively inhibit the active transport of drugs.

Endogenous substances which are transported by active metabolism include pyrimidines, L-amino acids, monosaccharides, sodium, potassium, iron and vitamins like niacin, pyridoxin and ascorbic acid. Due to structural similarity many drugs are also absorbed by this mechanism. For example, methyldopa and levodopa are absorbed by L-amino acid transport system, 5-fluorouracil and 5-bromouracil are absorbed via pyrimidine transport system.

Recently, the mapping of human genome has identified nearly 1300 genes coding for ion channels and transporters, which might be directly or indirectly involved in the absorption process. Human jejunum indicated the presence of mRNA for approximately 200 transporters. These transporters contribute to significant extent (about 40 - 80%) total to the drug absorption. Different transporters and their substrates are given in Table 2.1.

Table 2.1 : Transporters in Drug Absorption

Transporter	Substrate/Drug
1. Monocarboxylate Transporter (MCT)	Salicylic acid, benzoic acid, pravastatin.
2. Organic Cation Transporter (OCT) : OCT N2 and OCT N1 Type.	Triethylammonium, pyrilamine, valproate, verapamil, guanidine, tributyl methylammonium.
3. Organic Anion Transporting Polypeptide (OATP)	Conjugated metabolites of steroid hormones, thyroid hormones, bile acids, bilirubin, pravastatin, benzylpenicillin and digoxin and other anionic drugs.
4. Human Peptide Transporter h Pep T1 and h Pep T2	β-lactum antibiotics, angiotensin converting enzyme (ACE) inhibitors, betastatin, δ-aminolevulinic acid, w-amino fatty acids, 5' amino acid esters of zidovudine and acyclovir.
5. Nucleoside Transporter	Adenosine, guanosine, purine and pyrimidine nucleoside, inosine.

3. Paracellular/Pore Transport :

Drugs of small to moderate molecular weights can permeate the intestinal epithelium through the water filled pores between the cells. This process is known as paracellular or pore transport or convective transport. This transport route is generally considered to be passive, although it appears to be more permeable to cationic drugs than anionic and neutral drugs. Drugs that are moderate in size and hydrophilic like atenolol, furosemide, cimetidine, ranitidine and famotdine (MW 200 - 270) are absorbed