**INTRODUCTION TO BIOPHARMACEUTICS**

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**ABSTRACT**Biopharmaceutics is the relationship among physio-chemical properties of drug and its dosages form, also the route of administration and the rate and extent of drug absorption in the system. The sequence of events that predict elicitation, therapeutic effect of drug are important as a drug in its form and formulation of drug on the absorption and distribution to the target site. Initially the drug is absorbed orally or by any other route followed by release in predictable manner after that some portion of drug reaches to surrounding tissues finally reaches to the target site. Now we get required pharmacological response after achievement of minimum effective concentration by a drug product. Biopharnaceutics consideration often determines the ultimate dose of a drug product in a dosages form, e.g., local action drug i.e an ointment when apply tropically characterized as percentage or concentration of active drug in the formulation (e.g 0.5% w/w hydrocortisone ointments). But tablet form is always denoted in milligrams, now this dose depends upon the systemically absorbed quantity of drug and dissolved in an apparent volume of distribution to produce a desired concentration of drug at the target side.

**KEYPOINTS**

**BIOPHARMACEUTICS: -**The study of the relationships between the physical and chemical properties, dosage, and form of the administration of drug and its activity in the living body.**PHARMACOKINETICS: -**The kinetics of drug absorption, distribution, metabolism, and excretion (ADME) and their relationship with the pharmacological, therapeutics or toxicological response in man and animals.**PHARMACODYNAMICS: -**The relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects.

**ABSORPTION: -**The process of movement of unchanged drug from the site of administration to the systemic circulation.

**DISTRUBUTION**: - The reversible movement of the drug to and from the blood and various tissue of the body.

**BIOTRANSFFORMATION:-** It is an irreversible conversion of drugs from one chemical form to another, by the enzymes present in the body.**ELIMANATION:** - The process of removal of medication from the body.**PROTEIN DRUG BINDING**: - The phenomenon of complex formation of drugs with proteins. **BIOAVILABILITY: -** The rate and extent (amount) of absorption of unchanged drugs from its dosage form.**BIOEQUIVALENCE:** - It is a relative term which denotes that the drug substance in two or more identical dosage forms, reaches the systemic circulation at the same relative rate and to the same relative extent.

**MINIMUM EFFECTIVE CONCENTRATION (MEC) :** The minimum dose of drug required at the receptor site for action by producing desired pharmacological effect.

**MINIMUM TOXIC CONCENTRATION (MTC):** The minimum dose of drug which starts producing toxic effect.

**ON SET OF TIME:** The time taken by a drug to reach MEC.

**AREA UNDER CURVE (AUC):-** It is the sum total area between two given limits calculated by integration.

**DURATION OF ACTION:-** Difference occur between onset time and time taken for drug to reach back its MEC.

**Cmax (MAXIMUM CONCENTRATION) :** After administration of drug , the maximum concentration of that drug in blood, cerebrospinal fluid, or target organ.

**Tmax (MAXIMUM TIME) :** The time taken by a drug to attain its maximum concentration (Cmax).

**HALF LIFE (t 1/2) :** It is a time taken by amount of drug’s active substance to reduced by half in the body.

**VOLUME OF DISTRUBUTION (Vd) :** It is that apparent volume into which the drug is distributed to provide the concentration which is in the blood plasma.

**INTRODUCTION**

BIOPHARMACEUTICS involves the study of the interrelationship of the physiochemical properties of the drug, the dosage form in which the drug is given and the route of administration on the rate of extent of systemic drug absorption. It is also the study of factors influencing the rate and amount of drug that reaches the systemic circulation and the use of these information to optimize the therapeutic efficacy of drug products. It helps to obtain the drug concentration time profiles but it does not explain the desirable, pharmacological, toxicological or clinical response. Biopharmaceutics also consider the impact of the various manufacturing methods and technologies on the intended performance of the drug product. It uses quantitative methods and theoretical models to evaluate the effect of the drug substance, dosage form and the routes of drug administration on the therapeutic requirements of the drug and drug product in a physiological environment. It also allows for rational design of drug products to deliver the drug at specific rate to the body in order to optimize the therapeutic effect and minimize any adverse effects. The concept of biopharmaceutics and pharmacokinetics in pharmaceutical sciences was first induced in 1960s by DR. G. LEVY.It observed therapeutics response after its administration. Studies of biopharmaceutics involves both in-vivo and in-vitro methods. In-vivo methods involves the measurements of systemic drug availability after administering adrug product to an animal or human.In-vitro methods involve test apparatus without involving laboratory animals or humans.

E.g., disintegration tests, dissolution tests etc.

Thus, biopharmaceutics deals with the factors that influence the:

* Protection and stability of the drug within the product.
* The rate of drug release from the product.
* The rate of dissolution of the drugs at the absorption site.
* The availability of the drug at its site of action.

Biopharmaceutics involves pharmacokinetics and pharmacodynamics. Pharmacokinetics is the kinetics of drug absorption, distribution, metabolism, and excretion (ADME) and their relationship with the pharmacological, therapeutics or toxicological response in man and animals. Pharmacodynamics is defined as the body’s biological response to drugs.

Pharmacokinetics description; -

* Absorption
* Distribution
* Metabolism
* Excretion

Drug in dosage

Drug release

**PHARMACOKINETICS** Drug at absorption site **BIOPHARMACEUTICS**

Drug absorption

Drug in systemic circulation

Elimination

Metabolism, Excretion

**DISPOSITION**

Drug in extravascular tissues

Drug at site of action

**Pharmacodynamics**

In normal body

Pharmacology response

**Therapeutics**

In diseased body

Therapeutic effect at therapeutic dose

Toxic effect at toxic dose

**Fig.1 Schematic representation of the process involved in drug therapeutics**

**Absorption** is the process of movement of unchanged drug from the site of administration to the systemic circulation.

Mechanism of drug absorptionThe main mechanisms by which absorption occurs include:(a) Transcellular or intracellular transport(b) Paracellular or intercellular transport(c)Vesicular transport or endocytosis

1.Transcellular/Intracellular Transport is defined as the passage of drugs across the GI epithelium. It is the most common pathway for drug transport.2. Paracellular/Intercellular Transport is defined as the transport of drugs through the junctions between the GI epithelial cells. This pathway is of minor importance in drug absorption.3. Vesicular or Corpuscular Transport (Endocytosis) – Like active transport, these are also energy dependent processes but involve transport of substances within vesicles into a cell. Since the mechanism involves transport across the cell membrane, the process can also be classified as transcellular.

**A. PHARMACEUTICAL FACTORS:** include factors relating to the physicochemical properties of the drug, and dosage form characteristics and pharmaceutical ingredients.

**I. Physicochemical Properties of Drug Substances**

1. Drug solubility and dissolution rate.

2. Particle size and effective surface area

3. Polymorphism and amorphism

4. Pseudopolymorphism (hydrates/solvates)

5. Salt form of the drug

6. Lipophilicity of the drug

7. PK of the drug and gastrointestinal pH }pH-partition hypothesis

8. Drug stability

9. Stereochemical nature of the drug

**II. Dosage Form Characteristics and Pharmaceutical Ingredients**

(Pharmaco-technical Factors)

1. Disintegration time (tablets/capsules)

2. Dissolution time

3. Manufacturing variables

4. Pharmaceutical ingredients (excipients/adjuvents)

5. Nature and type of dosage form

6. Product age and storage conditions

**(B) PATIENT-RELATED FACTORS**: include factors relating to the anatomical, physiological and pathological characteristics of the patient

1. Age

2. Gastric emptying time

3. Intestinal transit time

4. Gastrointestinal pH

5. Disease states

6. Blood flow through the GIT

7. Gastrointestinal contents:

(a) Other drugs

(b) Food

(c) Fluids

(d) Other normal GI contents

8. Contact time with gastrointestinal mucosa

9. Presystemic metabolism by:

(a) Luminal enzymes (b) Gut wall enzymes

(c) Bacterial enzymes (d) Hepatic enzyme

Hydrophobic Small uncharged Large uncharged Ions

Molecules polar molecules polar molecules

Lipoidal Membrane

Outside

Inside

**Fig.2 Schematic representation of Absorption.**

**ROUTE OF DRUG ADMINISTRATION**

It is the path by which a drug/ medicine or any other substance is taken into the body.

**Routes of administration can broadly be divided into:**

**1. Topical:** Drugs are applied topically to the skin or mucous membranes, primarily for containing local action.

2. **Oral :** Drugs are introduced by buccal cavity or sublingual. Primarily for systemic action (non local action).

**3. Parenteral:** It means injection is injected by a needle at varying depth i.e other than oral route .

**4. Rectal:** Drugs are introduced by rectum .

**5. Inhalation:** When the drug is absorbed through lung., either in aerosol form or super fine particulate form.

**A. Topical Route:-**

When drugs are applied externally to the surface for attaining localized action. Drugs can be efficiently delivered to the localized lesions on skin, oro pharyngeal /nasal mucosa, eyes, ear canal, anal canal or vagina. In this, the drugs are in the form of powdered material, gaseous form, semi solid form or implants. But the drug which cannot be absorbed that needs to be provided orally (sucralfate, vancomycin) , or inhaled through bronchi (salbutamol, cromolyn sodium) and jellys (povidone iodine, lidocaine).

**Advantage:**

1. Convenient for use.
2. Encouraging for patient.

**B. Oral Route:-**

It is use by swallowing. It is intended for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract.

**Merits:**

1-Easy one amongst all route .

2-Sterilization is not required.

3-Patient don’t feel pain while administered orally.

**Demerits:**

1- Sometimes unacceptable due to bitter taste.

2- While absorbing by oral route, first pass mechanism occur then drug passes by liver to the general circulation and get metabolise there. E.g propranolol

**C. Buccal/Sublingual route:-**

In this, small size tablet are taken by mouth (buccal tablet) or kept under tongue (sublingual tablet). Disintegration time of buccal tablet is about 4 hour because of its hardness and are prepared all design to dissolve slowly. E.g, Nitroglycerin, as soft sublingual tablet.

**D. Parenteral Route:-**

**A- Intravascular (IV, IA):-** When drug is given directly into blood stream. Intravenous, when drug is injected directly into vein or artery( intra arterial).

**Merits**

Precise, accurate and immediate onset of action, 100% bioavailability.

**Demerits**

1. Sometime swelling at site of injection if admistered wrongly.
2. An expert person is the basic requirement.
3. Occurrence of lumps at or around injection side.

**B-Intramuscular :**(into the skeletal muscle).

**Merits**

1. In case of aqueous solution absorption is fast.
2. Onset of action is always rapid as compare to all other routes.

**Demerits**

Bulky muscleare preferred for better absorption.

**C-Subcutaneous** :- Under the deep layer of skin. e.g. insulin.

**D- Intradermal**,:- Into the layers of skin, Beneficial of allergy testing.

**E- Intrathecal** :- Spinal canal is chosen and required for final anesthesia .

**Drug distribution** :-

When the drug is transferred among the blood, extra vascular fluids and other tissue of the body occurs in reversible manner. Then after absorption the drug reaches into the circulation. Now the drug needs to reach interstitial space from plasma by crossing the capillary membrane. Finally, drug enter into intracellular fluid after crossing the cell membrane.

**FACTORS AFFECTING DISTRIBUTION OF DRUGS:**

**Tissue Permeability of the Drugs.** a**.** Physiochemical Properties of the drug like Molecular size, pKa and o/w Partition coefficient.b. Physiological Barriers to Diffusion of Drugs.c. Organ / Tissue Size and Perfusion Rate.d. Binding of Drugs to Tissue Components

e. Binding of drug to blood components

f.Binding of drug to extra cellular components**. Miscellaneous Factors.**

a. Age

b. Pregnancy

c. Obesity

d. Diet

e. Disease states, and Drug Interactions.

A drug in the body can interact with several tissue components of which the two major categories are blood and extravascular tissues. The interacting molecules are generally the macromolecules such as proteins, DNS and adipose tissue. The phenomenon of complex formation of drug with protein is called as protein binding of drugs. As a protein bound drug is neither metabolized nor excreted hence it is pharmacologically inactive due to its pharmacokinetic and Pharmacodynamic inertness.

**Protein + drug ⇌ Protein-drug complex**

**Protein binding may be divided into: –**1. Intracellular binding-2. Extracellular binding- **MECHANISMS OF PROTEIN DRUG BINDING:**  Binding of drugs to proteins is generally of reversible & irreversible.Reversible generally involves weak chemical bond such as: a. Hydrogen bondsb. Hydrophobic bondsc. Ionic bondsd. Van der Waal’s forces. Irreversible drug binding, though rare, arises as a result of covalent binding and is often a reason for the carcinogenicity or tissue toxicity of the drug.**FACTORS AFFECTING PROTEIN DRUG BINDING**1. Drug-related factorsa) Physicochemical characteristics of the drugsb) Concentration of drugs in the bodyc) Affinity of drug for particular binding components2. Protein / Tissue related factorsa) Physicochemical characteristics of the protein or binding agentsb) Concentration of protein or binding componentsc) Number of binding sites on the binding agents 3. Drug interactionsa) Competition between drugs for the binding site

b) Competition between the drug and normal body constituentsc) Allosteric changes in protein molecule

4. Patient-related factorsa) Ageb) Intersubjective variationsc) Disease state

**Biotransformation,** is also called metabolism, is defined as the biochemical conversion of drug into another chemical form. Biotransformation includes enzymatically driven chemical conversion, but some of the drugs may be chemically changed by a non-enzymatic process. Xenobiotics, which are substances foreign to the body, are, metabolized or biotransformed to more water-soluble compounds, because water soluble compounds are more readily excreted. It is one of the most important mechanisms that the body has for detoxifying and eliminating drugs and other foreign substances. Drugs delivered by the oral route must pass through the liver before reaching the general circulation. Biotransformation at this point is called “firstpass metabolism,” which can limit systemic exposure for drugs despite good absorption. Oxidation, reduction, hydrolysis, and conjugation are the most common metabolic pathways, generally leading to more hydrophilic compounds that can be readily excreted. Cytochrome P450 (CYP-450) enzymes are a family of drug metabolizing enzymes that are responsible for the majority of drugs’ metabolism as well as many drug–drug interactions. Although the primary role of metabolism is to facilitate elimination of drugs from the body, secondary effects include transformation of drugs into other active or toxic species, which could be desirable in the case of prodrugs or undesirable with respect to toxic metabolites.

**PHASES OF DRUGS METABOLISM**

**The biotransformation of drugs generally occurs in two phases. Phase- I reaction and Phase-II reactions.**  
 **Phase-I reaction and Phase-II reactions**

**Phase-I** **Phase-II**

**Expose or add functional group.**

**XENOBIOTIC PRIMARY PRODUCT SECONDARY PRODUCT**

**Conjugation**

**Oxidation, Reduction**

**hydrolysis**

**EXCREATION**

**HYDROPHILIC**

**LIPOPHILIC**

**Fig.3 Schematic representation phases of drug metabolism**

**Excretion** is an irreversible transfer process in which drug and its metabolites eliminate through out of the body. Water soluble or low molecular weight drugs are mostly excreted by kidney. Nephron act as the functional part of kidney and consists of glomerulus , proximal tubule, loop of henle, distal tubule and collecting tubule.

**FACTORS AFFECTING RENAL EXCRETION OF DRUGS** Different factors that affect renal excretion of drugs are a. Physical and chemical properties of the drug

b. concentration of the drug in plasma

c. Drug distribution and binding characteristics d. pH of urine

e. Flow of blood to the kidneysf. In vivo factorsg. Interactions of drugs

h. Disease states

Excretion Urinary

Oral Administration BILE Distribution

**ENTEROHEPATIC CIRCULATION OF DRUGS**

SMALL INTESTINE LIVER

FAECAL EXCRETION BLOOD

**Fig 2**. **Schematic representation of the process involved in Excretion.**

**Plasma concentration curve:-**

It is the curve which shows the concentration or amount of drug that effectively reaches into the systemic circulation in specific time that is influenced by the degree of bioavailability and by the rate at which elimination occurred.

Peak plasma concentration

**Cmax (** absorption rate =elimination rate **)**

Plasma drug concentration

Toxic level

Intensity of action

Absorption phase Post absorption phase

**Therapeutic range**

Termination of action

Onset of action

Duration of action Minimum effective concentration

**Area under the curve (AUC)**

On set time Time for peak concentration (tmax)

**Time**

**Fig.4 Schematic representation of plasma concentration curve.**

**COMPARTMENT MODELLING**

The time course of drug concentration determined after its administration can be satisfactorily explained by assuming the body as a single well-mixed compartment with first-order disposition processes.

**SINGLE-COMPARTMENT OPEN MODEL** (Instantaneous Distribution Model):- The single-compartment open model is the simplest model. Owing to its simplicity, it is based on following assumptions:-

1. The body is considered as a single, kinetically homogeneous unit that has no barriers to the movement of drug.

2. Final distribution equilibrium between the drug in plasma and other body fluids (i.e., mixing) is attained instantaneously and maintained at all times. This model thus applies only to those drugs that distribute rapidly throughout the body.

3. Drugs move dynamically, in (absorption) and out (elimination)of this compartment.

4. Elimination is a first order (monoexponential) process with first order rate constant.

5. Rate of input (absorption) > rate of output (elimination).

6. The anatomical reference compartment is plasma and concentration of drug in plasma is representative of drug concentration in all body tissues i.e., any change in plasma drug concentration reflects a proportional change in drug concentration throughout the body.

However, the model does not assume that the drug concentration in plasma is equal to that in other body tissues. The term open indicates that the input (availability) and output (elimination) are unidirectional and that the drug can be eliminated from the body. Fig. 9.1 shows such a one-compartment model. One-compartment open model is generally used to describe plasma levels following administration of a single dose of a drug.

Metabolism

**KE**

**Ka**

Blood and other body tissues

Drug

Output (Elimination)

Input (Absorption)

Excretion

Single compartment module are defined on basis of input rate:-

Single-compartment open model, i.v. bolus administration.

Single-compartment open model, continuous i.v. infusion.

Single-compartment open model, e.v. administration, zero-order absorption.

Single-compartment open model, e.v. administration, first-order absorption.

**MULTICOMPARTMENT MODELS:**

One-compartment model adequately describes pharmacokinetics of many drugs. Instantaneous distribution equilibrium is assumed in such cases and decline in the amount of drug in the body with time is expressed by an equation with a monoexponential term (i.e., elimination). Although, Rapid distribution is not acquire for most of drug and drug disposition is not monoexponential but bi- or multi-exponential. This is because the body is composed of a heterogeneous group of tissues each with different degree of blood flow and affinity for drug and therefore different rates of equilibration. Ideally, a true pharmacokinetic model should be the one with a rate constant for each tissue undergoing equilibrium, which is difficult mathematically.

Multicompartment models are thus based on following :-

1. Central compartment consist of blood/plasma and tissues like brain, heart, lungs, liver and kidneys, which are highly prefused.

2. Peripheral compartment consist of the tissues which have same distribution characters.

3. Central compartment is the site where intravenously injection are injected directly .

4. Again central compartment is the site where to and from elimination occur with the help of hepatic biotranformation or by renal excretion.

5. Reversible distribution occurs between central and peripheral compartments, with a finite time required for distribution equilibrium to be attained.

6. After drug equilibration between central and the peripheral compartments, elimination of drug follows first-order kinetics.

7. All rate processes involving passage of drug in and out of individual compartment are first-order processes and plasma level-time curve is best described by sum of series of exponential terms each corresponding to first-order rate processes associated with a given compartment.

8. The peripheral compartment is usually inaccessible to direct measurement and is not a site of drug elimination or clearance.

When drug is administered i.v bolus then its multicompartment characteristics are best explained. After that concentration in plasma decreases within time. The number of exponential which explain a plasma level time profile that describe the number of kinetically homogenous compartments for which the drug will be distributed.

**TWO-COMPARTMENT OPEN MODEL**

The commonest of all multicompartment models is a two-compartment model. In such a model, the body tissues are broadly classified into 2 categories--

1. **Central Compartment** or **Compartment First**  consists of liver, kidney, lungs etc ( Highly perfused tissue). This is preferred compartment for elimination. It shows fast equilibrium.

2. **Peripheral** or **Tissue Compartment** or **Compartment second** consists of muscles, skin, adipose tissue (poorly perfused tissue) . It participate in other physiological function. It shows slow equilibrium.

**Two-Compartment Open Model**

**Intravenous Bolus Administration**

The model can be depicted as shown below with elimination from the central compartment.

**K12**

1.Central compartment

2.Peripheral compartment

**K21**

**KE**

**Bioavailability**

The rate and extent (amount) of absorption of unchanged drugs from its dosage form.

**OBJECTIVES OF BIOAVAILABILITY STUDIES**1. Bioavailability is done for determining the safety and effectiveness of the drug product which is used for in vivo clinical studies

2. Bioavailability is helpful for labelling of drug.3. Bioavailability studies provide proper information about efficient and effectiveness of absorption of drug. 4. It also determines the quality of drug during processing, storage.

**Bioequivalence Studies**  It is a description of two or more identical dosages form, which reaches the circulation but at the same rate and same extent.

**Applications of bioequivalence studies**a**.** Equally effective substitution can be easily provided.b. Variables at formulation sate are also less.c. Also limits the bioequivalence studies. d. The plasma concentration time profiles of drug is identical without any difference.

**BIOPHARMACEUTICAL CLASSIFICATION SYSTEM:**

Biopharmaceutical classification system was first developed in the year 1995 by a group of scientists (Amidon and his team). It is a scientific frame work for classifying substances based on their aqueous solubility and intestinal permeability. It acts as predicting tool for bio equivalence study design through accurate invivo study.

High solubility and High permeability. E.g Metoprolol, Propranolol

CLASS- I

Low solubility and High permeability. E.g Naproxen, Nifedipine

CLASS-II

High solubility and Low permeability. E.g Cemitidine, Metformin

CLASS-III

Low solubility and Low permeability. E.g Taxol, Chlorthiazole

CLASS-IV

**Fig 3**. **Schematic representation of BCS Classification of drugs.**

**BIOPHARMACEUTICS CONSIDERATION IN DRUG PRODUCT DESIGN :**

1. **Pharmacodynamics consideration**

* Therapeutic objective
* Toxic effects
* Adverse effect

**2. Drug considerations**

* Particle size
* pka & pH profile
* Polymorphism
* Hygroscopicity
* Partition coefficient
* Excipient interaction
* pH stability profile
* Solubility

1. **Drug product considerations**

* Pharmacokinetics of drug
* Bioavailability consideration
* Route of administration
* Desired dose of drug
* Dosing frequency

1. **Patient considerations**

* Acceptability & Compliance of drug product
* Cost

1. **Manufacturing considerations**

* Cost
* Availability of raw materials
* Stability

**SIGNIFICANCE AND APPLICATIONS OF BIOPHARMACEUTICAL STUDIES**

1. The aim of biopharmaceutics is to adjust the delivery of a drug to the site of action to provide optimal therapeutic activity for the patient.2. Biopharmaceutical considerations in the design of a dosage form to deliver the active drug with the desired bioavailability characteristics and therapeutic objectives include

(I) the physicochemical properties of the drug molecule,

(II) the finished dosage form (e.g., tablet, capsule, etc.),

(III) the nature of excipients in the drug product,

(IV) the manufacturing method, and

(V) the route of drug administration.

3. Biopharmaceutical studies are done to check the irritation and energic level of drug . 4. Biopharmaceutic accomplish a relationship between invivo dosages form and manufacturing process parameter, drug efficient properties (tablet hardness, disintegration). For evaluation of dosages form in vivo method (bioavailability) and invitro method (dissolution) are used.

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