INTRODUCTION TO BIOPHARMACEUTICS

Abstract

Biopharmaceutics is the relationship among drug's all properties like organolaptic properties, hydrolysis, oxidation, reduction, racemization etc, and its dosage formulation, also administration route. 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. Biopharmaceutics consideration often determines the proper potency of formulation like local action drugs i.e. an ointment when apply topically, characterized as percentage or concentration of active ingredients of that preparation. But tablet form is always denoted in milligrams, now this dose depends upon the systemically absorbed quantity of drug when mixed with the proper quantity for getting required amount.

Keypoints: Biopharmaceutics: Biopharmaceutics is the relationship among drug's all properties like organolaptic properties, hydrolysis, oxidation, reduction, racemization etc, and its dosage formulation, also administration route.

Pharmacokinetics: It describes about absorption, distribution, metabolism and excretion of drug also its interaction to the therapeutic effect in human and animals. In short, what drugs does to the body.

Pharmacodynamics**:** At target site the interaction of amount of drug and its result along with time duration, desired effect and toxicological response .In short, what body does to the drug.

Absorption**:** When unchanged drug move from the administration site to the blood circulation.

Authors

Navneet Kaur
Assistant Professor
College of Pharmacy
RIMT University
Mandi Gobindgarh, Punjab, India
drnavneet3@gmail.com

Rajip Nepal
College of Pharmacy
RIMT University, Mandi
Gobindgarh Punjab, India.
rajivnepal777@gmail.com

Surg Lt Cdr (Dr) Prabhjot Singh
Resident Ophthalmology
Armed forces medical college
Pune, Maharastra,India

Distrubution: It is the process when drugs move in vice versa form from blood circulation and other body tissues.

Biotransfformation: This is an irreversible conversion of drugs from one chemical form to another, by the enzymes present in the body.

Elimanation: When drug and drug products gets eliminated from the body compartment.

Protein Drug Binding: -When there is a development of complex by proteins and drugs.

Bioavilability: It is the availability of drugs in the body (the amount of absorption of drug in the blood circulation).

Bioequivalence: When drug in its more similar forms act in the systemic circulation with similar rate and extent.

Minimum Effective Concentration (MEC): The least dose of drug material which needed at receptor site for action by producing desired pharmacological effect.

Minimum Toxic Concentration (MTC): The least dose when starts producing harmful effect.

On Set Of Time: The time taken by a drug to reach MEC.

Area Under Curve (AUC): It is that area between two given limits which calculated by integration.

Duration Of Action:- It is the difference between initial and final time for onset of action and to return back to its minimum effective concentration.

Cmax **(**Maximum Concentration**):** It is the highest amount of drug in blood, cerebrospinal fluid, or target organ after taking the drug.

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

(T 1/2): This is the time interval taken by a remedy to reduced by half in the body.

Volume Of Distrubution (Vd): It is that volume in which the quantity of the drug gets dissolved to supply the concentration which is present in the blood plasma

I. INTRODUCTION

Biopharmaceutics is the relationship among drug's all properties like organolaptic properties, hydrolysis, oxidation, reduction, racemization etc, and its dosage formulation, also administration route. Biopharmaceutics accomplish a relationship between in-vivo dosage form and manufacturing process parameters, drug efficient properties (tablet hardness, disintegration). In this we also study about those factors which determine the speed and extent of that dosage form which to reach to the systemic circulation and this data is used to manage the therapeutic effectiveness of that dosage form. It helps to obtain the drug concentration time profiles but it does not explain the desirable, pharmacological, toxicological or clinical response. Different kinds of manufacturing ways and techniques of efficiency of dosage form are involved in this branch of pharmacy. Theoretical model and quantitative techniques are used to check the efficacy value of drug substance, formulation and administration route in a physiological environment. It also determines the safety measure of the body by reducing side effect and delivers the right dosage form at right side of the body. 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. This study is done for in-vivo as well as in-vitro techniques. In-vivo techniques determines the measurements of bio-availability after administering the drug product. In-vitro methods involve test apparatus without involving laboratory animals or humans.
E.g., disintegration tests, dissolution tests etc.

Thus, biopharmaceutics deals with the following points:

1 Drugs stability and protective measure.
2 Release rate of drugs.
3 Dissolution rate of drugs.
4 Bio-availability of drugs.

This study involves pharmacokinetics and pharmacodynamics. Pharmacokinetics describes about absorption, distribution, metabolism and excretion of drug also its interaction to the therapeutic effect in human and animals. In short, what drugs does to the body. Pharmacodynamics explains at target site the interaction of amount of drug and its result along with time duration, desired effect and toxicological response. In short, what body does to the drug.

Pharmacokinetic description:

Absorption
Distribution
Metabolism

Excretion

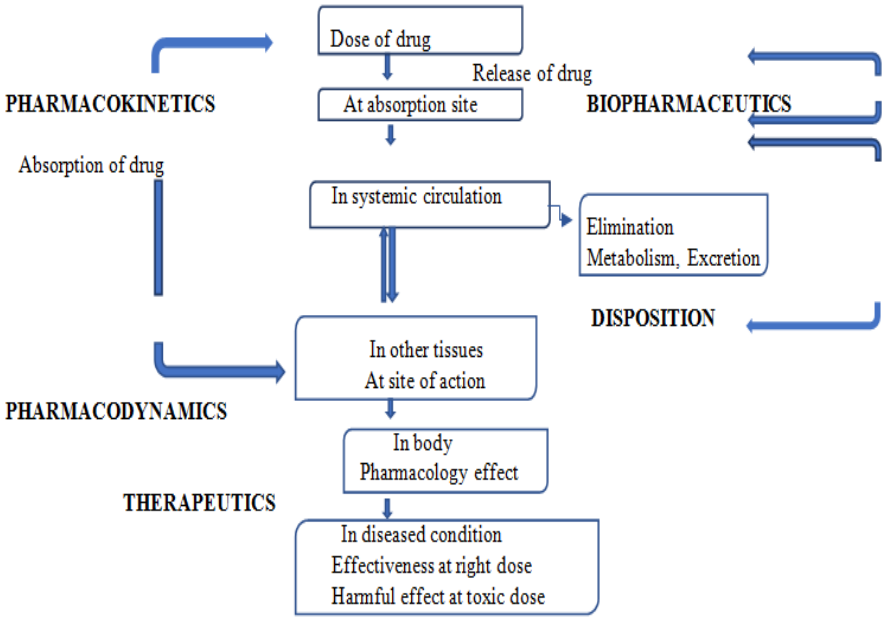


Figure 1: Arrangement showing drug therapeutic process

1. **Absorption:** This process involve when unchanged drugs move from the administration site to the blood circulation. Steps of drug absorption
   The main steps involved are:

   Transcellular or intracellular transportation
   Paracellular or intercellular transportation
   Vesicular transportation

- Transcellular /Intracellular Transportation is the process which describe the pass way through which drugs move across gastrointestinal epithelium. Drug transportation mostly follow this.
- Paracellular/Intercellular Transportation is the process which describes the drugs transportation across the junctions which are placed between the gastrointestinal epithelial cells. This is uncommon pathway.
- Vesicular or Corpuscular Transportation– At this stage much part of energy is require but transportation of products involve within vesicles and cells. So, it can also be describe as transcellular transportation.

- **Pharmaceutical Factors**

  Physical and chemical characteristics of drugs

  - Solubility and dissolution character of drugs
  - Size of particles and its surface area
  - Amorphism and polymorphism characteristics of drugs

- Pseudopolymorphism (hydrates/solvates)
- Drug's salt formation
- Drug's lipophilic parameter
- PK }pH-partition hypothesis
- Stability profile of drugs
- Drug's stereochemical nature

Characteristics and pharmaceutical ingredients of dosage form

- Tablets/ capsules disintegration time
- Dissolution study
- Manufacture variable parameters
- Adjuvents
- Dosage form
- Maintenance conditions of drug

- **Patient-related factors**

  - Age of the patient
  - Emptying time taken by gastric
  - Transit time taken by intestine
  - pH of GIT
  - Disease condition
  - Rate of blood flow across GIT
  - Presence of contents in GIT:
    Other drugs
    Food intake
    Fluids intake
  - Contact time with gastrointestinal mucosa
  - Presystemic metabolism occurs through:
    Enzyme present in luminal
    Enzyme present in Gut wall
    Enzyme including bacteria
    Enzyme present in liver

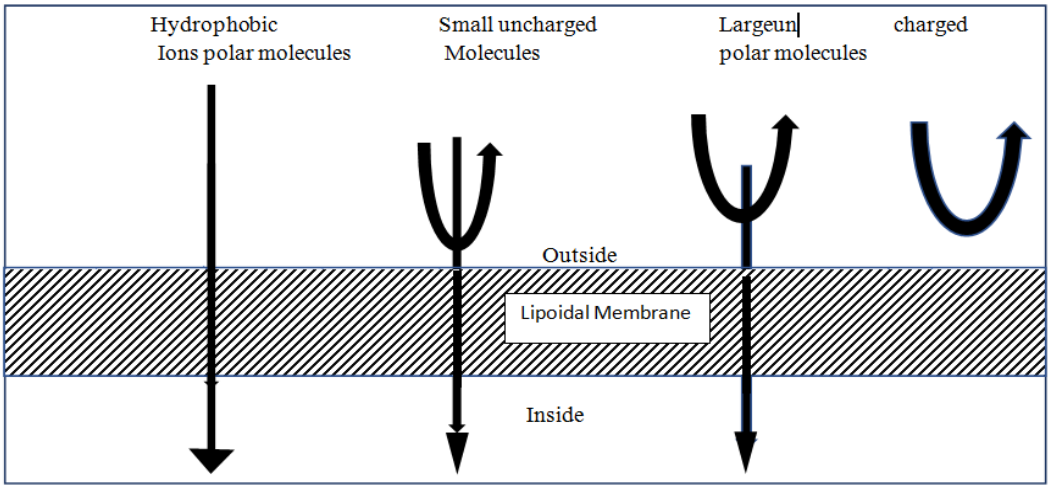


Figure 2: Schematic representation of Absorption.

2. **Routes for administering drugs:** It is the passage through which medicine/ remedy is taken to the body.

Classification

Topical: Medicine/ Remedy when rubbed onto the skin or mucosal membrane, mainly for the purpose of primary effect.
Buccal route: Drugs are introduced by buccal cavity or sublingual. Primarily used for systemic action (non local action).
Parenteral: It means injection is injected by a needle at varying depth i.e other than oral route.
Rectal: Drugs are introduced by rectum.
Inhalation: When the drug is absorbed through lung, either in aerosol form or super fine particulate form.

- **Topical route:** Drugs are applied externally on the skin surface for attaining primary action. In this, 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 lungs.

Advantage
- ➢ Convenient for use.
- ➢ Encouraging for patient.

- **Buccal route:** This route is used when substances are to be kept in the buccal cavity or under the tongue for the absorption purpose to the GIT through different epithelia and mucosal membrane.

Merits
- ➢ Easy amongst all routes.
- ➢ Sterilization is not required.3-Patient don’t feel pain while administered orally.

Demerits

- Sometimes unacceptable due to bitter taste.
- 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

- **Buccal/sublingual route:** In this, small size tablets are taken orally or kept under the tongue. Disintegration time of oral tablet is about 4 hour because of its hardness and design to dissolve at slower rate.

- **Parenteral route**

  Intravascular (IV, IA):- When medicine/remedy is given into blood stream directly. When drug is injected directly into vein is intravenous or in to artery is (intra arterial).

  Merits
  - Accuracy
  - Precision
  - 100% absorption

  Demerits
  - Sometime swelling at site of injection if administered wrongly.
  - An expert person is the basic requirement.
  - Occurrence of lumps at or around injection side.

  Intramuscular: Skeletal muscle is used to inject for this route.

  Merits
  - In case of solutions containing water absorption is fast.
  - Onset of action is always rapid as compare to all other routes.

  Demerits
  Bulky muscle**s** are preferred for better absorption.
  - **Subcutaneous:** To the deep layer of skin.
  - **Intradermal**: Skin layers are preferred, Beneficial of allergy testing.
  - **Intrathecal:** Spinal canal is chosen and required for final anaesthesia.

3. **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 absorbing, it reaches into the blood circulation. Now drug needs to reach interstitial space from plasma by crossing the capillary membrane. Finally, drug enters into intracellular fluid after crossing the cell membrane.

   Following points affects drug's distribution:

   - Physical and chemical properties of drug.
   - Physiological restriction for drugs diffusion.
   - Rate of perfusion.
   - Drug's binding ability to different tissues.
   - e. Drugs binding ability to different blood compounds.

- f. Drugs binding ability to other compounds of body.

Other Factors

- Age of patient
- Pregnancy condition
- High weight gain
- Food intake

A drug mainly interacts with blood as well as extra vascular tissues present in the body bur can also interact with tissue compartments other than blood and extra vascular tissues .The macromolecules interacting are generally adipose tissues, proteins and DNS. When proteins binds with the drug the process is known as protein binding of drugs. But bounded drug is inert because of pharmacokinetic and pharmacodynamically inactivation in the body.

Protein + drug ⇌ Protein-drug complex

Protein binding process may be classified as:

- Intracellular binding of drugs
- Extracellular binding of drugs

4. **Mechanisms of bindingn of drug:** Protein drug binding basically happens as reversible manner or irreversible manner.In reversible, there are weak chemical bonds like:

- Hydrogen bonds
- Hydrophobic bonds
- Ionic bonds
- Vander Waal's forces.

Irreversible binding of drug is uncommon, if there is involvement of covalent bond and often leads to tissue toxicity or carcinogenicity.

Factors affecting binding of drugs

- Factors related to a drug
  - Physical and chemical properties of the drug
  - Drugs concentration present in the body
  - Drug's affinity for specific binding compound

- Factors related to protein /tissue
  - Physical and chemical properties of the protein or binding agents
  - Protein or binding compound's concentration
  - Number of binding sites present on the binding agents
  - Interactions of drugs
    Competition of the drug and body compounds

- Factors related to a patient
  - Age of the patient
  - Other body variation
  - Diseased condition

Biotransformation: is also called metabolism, is described as biochemical change of drug into other chemical form. Biotransformation includes enzymatically driven chemical conversion, but selected drugs might be converted with a non-enzymatic procedure. Xenobiotics are foreign substances for the body, are, metabolized or converted to high level water-soluble components, because high level water soluble components are excreted more readily. This is the most important mechanism that the body attains for the purpose of detoxifying and to eliminate drugs and other foreign particles. Drugs absorbed through oral route have to pass through the hepatic site before these reaches to systemic circulation. Biotransformation now called as "first pass metabolism," and minimizes the drug's exposure to systemic results in good absorption. Chemical reactions such as oxidation, reduction, hydrolysis, and conjugation are commonly acquired metabolic pathways, provides more hydrophilic compounds which can be readily excreted. Cytochrome P450 (CYP-450) enzymes are responsible for the majority of drugs' metabolism and many other drug–drug interactions because these are metabolic enzymes. However the main role of metabolism is to help in elimination process of drugs out of the body, but also transfer drugs into other active or toxic species, which could be required for prodrugs and not required for toxic meterials.

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

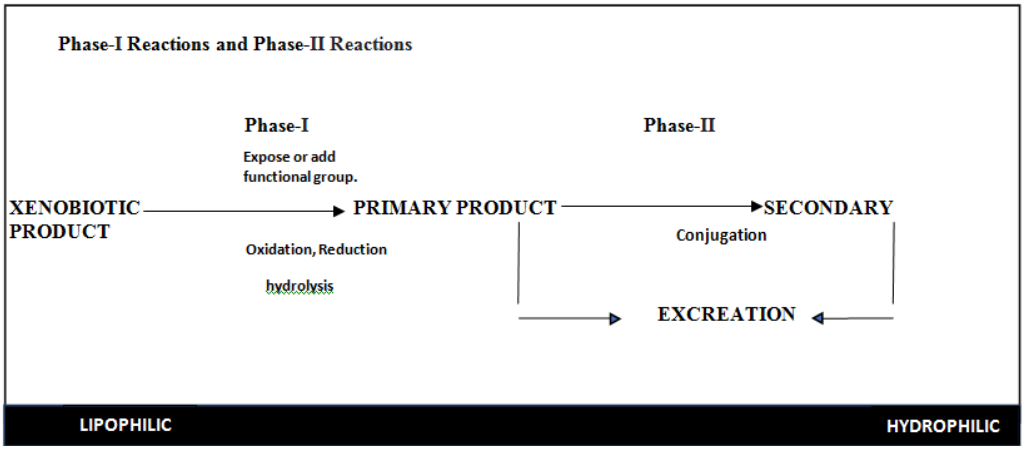


Figure 3: Schematic representation phases of drug metabolism

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 unit of renal and main parts are glomerulus, proximal tubule, loop of henle, distal tubule collecting duct.

Factors influencing renal excretion

- Physical and chemical properties of the drug
- Drug's concentration in plasma

- Drug's distribution and binding properties
  d. pH of urine
- Flow of blood to the kidneys
- In vivo factors
- Interactions of drugs
- Disease states

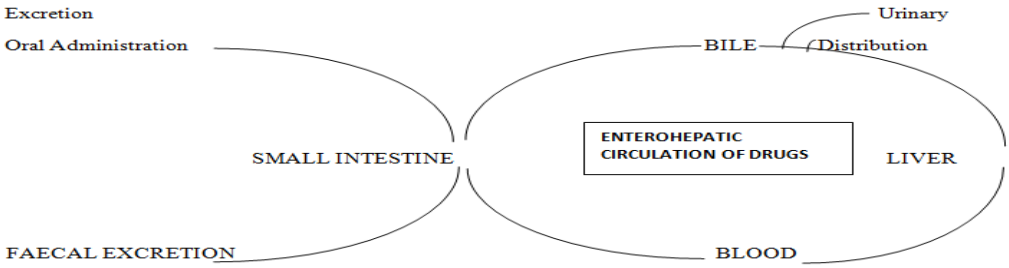


Figure 4: Diagrammatically representation of excretion processes.

- **Plasma concentration curve:** It is that curve which shows the concentration of drug that effectively reaches into the blood circulation in specific time that is influenced by the degree of bioavailability and by the rate at which elimination occurred.

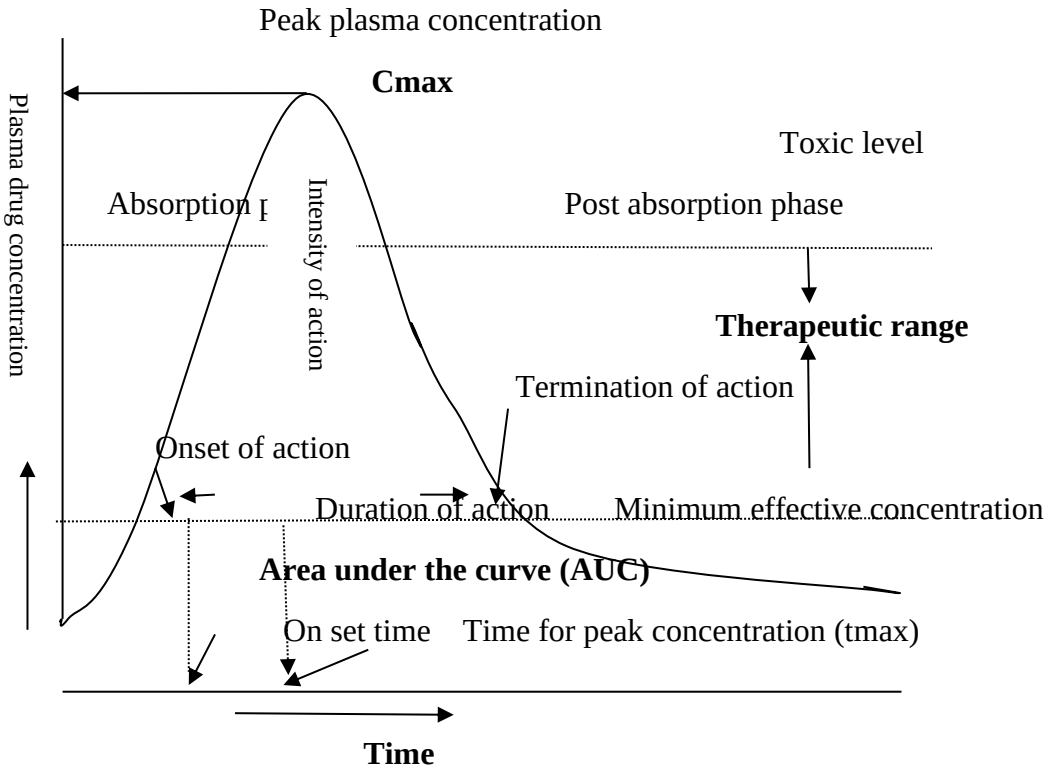


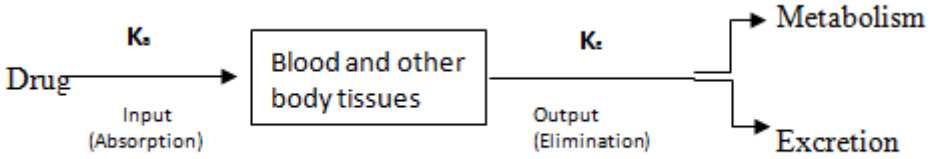
Figure 5: Schematic representation of plasma concentration curve.

5. **Compartment model system:** After administering the drug the time course of its concentration can be determined. Thus it is explained by considering the body as a single compartment with well mixed properties that follow first-order disposition processes.

Single-compartment open model (Instantaneous Distribution Model):- This model is based on these assumptions:

- The body is assumed as a single compartmental unit, kinetically homogeneous having no restrictions to the movement of drug.
- Resulting distribution equilibrium is attained and managed between the drug present in plasma and other body fluids (i.e., mixing) all the time. Thus this model is applicable to drugs that rapidly gets distributed throughout the body.
- Drugs move in this compartment for absorption and out for elimination.
- Elimination follows first order (monoexponential) process with first order rate constant.
- Input rate (absorption) > Output rate (elimination).
- 6 Anatomically reference compartment is plasma. Concentration of drug in plasma is the description of drug concentration in all body tissues.

Although, the model does not explain that the drug concentration in plasma is same to other body tissues. Here open means the input (availability) and output (elimination) are happening in same direction. Figure 5 indicates such a one-compartment open model. It is generally used to explain plasma level following administration of a single dose of a drug.



Single compartment models 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.

6. **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

- Central compartment consist of blood/plasma and tissues like brain, heart, lungs, liver and kidneys, which are highly prefused.
- Peripheral compartment consist of the tissues which have same distribution characters.
- Central compartment is the site where intravenously injection are injected directly .
- Again central compartment is the site where to and from elimination occur with the help of hepatic biotranformation or by renal excretion.
- Reversible distribution occurs between central and peripheral compartments, with a finite time required for distribution equilibrium to be attained.
- After drug equilibration between central and the peripheral compartments, elimination of drug follows first-order kinetics.
- 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.
- 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.

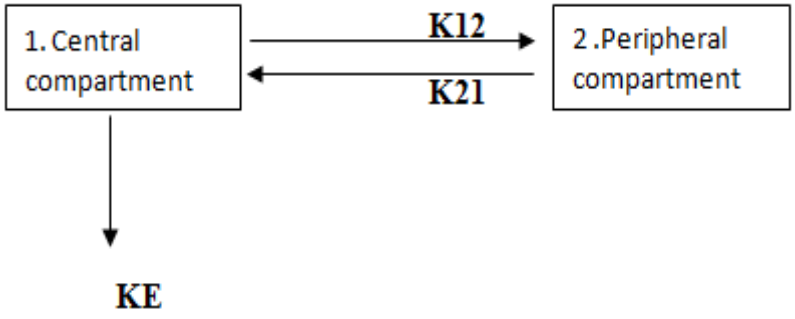
Two-compartment open model: The commonest of all multicompartment models is a two-compartment model. In such a model, the body tissues are broadly classified into 2 categories--

- **Central compartment** or **Compartment first:** consists of liver, kidney, lungs etc (highly perfused tissue). This is preferred compartment for elimination. It shows fast equilibrium.

- **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.



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

Objectives of bioavailability studies

- Bioavailability is done for determining the safety and effectiveness of the drug product which is used for in vivo clinical studies
- Bioavailability is helpful for labelling of drug.
- Bioavailability studies provide proper information about efficient and effectiveness of absorption of drug.
- 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

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

II. 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.

Figure 6: Schematic representation of BCS Classification of drugs.

III. 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

3. Drug product considerations

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

4. Patient considerations

- Acceptability & Compliance of drug product
- Cost

5. Manufacturing considerations

- Cost
- Availability of raw materials
- Stability

IV. 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
   - the physicochemical properties of the drug molecule,
   - the finished dosage form (e.g., tablet, capsule, etc.),
   - the nature of excipients in the drug product,
   - the manufacturing method, and
   - 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.

REFERENCES

[1] C V S Subrahmanyam, "Biopharmaceutics and Pharmacokinetics – concept and application", Vallabh Prakashan.
[2] D M Brahmankar Sunil B. Jaiswal, "Biopharmaceutics and Pharmacokinetics – A Treatise", Vallabh Prakashan.
[3] Dr. Anant Paradkar, "Biopharmaceutics and Pharmacokinetics", Nirali Prakashan.
[4] Robert E. Notari, "Biopharmaceutics and Clinical Pharmacokinetics: An Introduction", 4th Edition.
[5] Jasmin Kaur Randhawa, "Practical Guide Of Biopharmaceutics and Pharmacokinetics"

