Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 1

Name of topic/lesson – Concept, Definition and Introduction

Points –

1. It is a branch of pharmaceutics which deals with the utilization of information of absorption, distribution, metabolism and elimination for the optimal development of dosage form for the well being of human being and animals.
2. Drug movement within body is too complex; the drug will undergo Absorption, distribution, metabolism and elimination process. The Biopharmaceutics deals with the factors that influence the protection of the activity of the drug within the drug product (stability) the release of the drug from dosage form and rate of dissolution at absorption site and systemic movement of drug for therapeutic effectiveness.
3. The process of movement of drug from its site of administration to systemic circulation is called as absorption. The concentration of drug in plasma and onset of action, intensity and duration of action depends upon bioavailability of drug. Other process that play a role in therapeutic activity of a drug are distribution and elimination i.e. termination of drug therapy.

References

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 1-2.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 1-2.

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MODERN COLLEGE OF PHARMACY (FOR LADIES), MOSHI, PUNE-412105

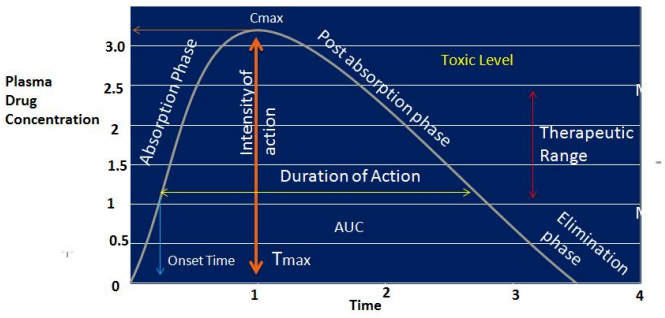
Class- Final Year B. Pharm. Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge- Dr. N. S. Kulkarni **Lecture Synopsis No. 2**

Name of topic/lesson – Concept, Definition and Introduction

Points –

1. Pharmacokinetics: is the mathematics of the time course of Absorption, Distribution, Metabolism, and Excretion (ADME) of drugs in the body. The biological, physiological, and physicochemical factors which influence the transfer processes of drugs in the body also influence the rate and extent of ADME of those drugs in the body.
2. Pharmacodynamics: It deals with the relationship between drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiological effects that influence the interaction of drug with receptor. Under pharmacodynamic we study the relationship between plasma concentration of drug and magnitude of biological effect it shows.
3. The rational use of the drug or therapeutic objective can only be achieved through a better understanding of pharmacokinetic (in addition to pharmacodynamic of drug) which helps in designing a proper dosage form.



References

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 1-2.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 3-4.

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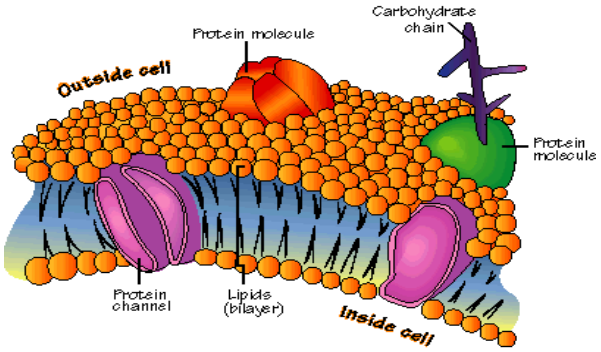
Class- Final Year B. Pharm. **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 3**

Name of topic/lesson – Absorption

1. It is movement of drug from the site of administration to the systemic circulation in unchanged form after administration. Absorption is prerequisite for a drug to show its pharmacological action.



Physiology of Cell Membrane

2. The cell membrane is the barrier that separates the inside of the cell from the outside. The cell membrane is made up of phospholipids, proteins, and other macromolecules.
3. The phospholipids' make up a bilayer. It contains hydrophilic and hydrophobic molecules.
4. The proteins in the cell membrane are located within the phospholipid bilayer. So, the biologic membrane is mainly lipid in nature but contains small aqueous channels or pores.

References

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 1-2.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 6-8.

Class- Final Year B. Pharm. Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 4

Name of topic/lesson – Absorption

Mechanism of drug Absorption

Three broad categories:

A. Transcellular/ intracellular transport: Passage of drug across GI epithelium.
   1. Passive Transport process
      a. Passive diffusion
      b. Pore transport
      c. Ion- pair transport
      d. Facilitated diffusion
   2. Active Transport
      a. Primary active
      b. Secondary active: (Symport and Antiport)

B. Parascellular/ intercellular transport: transport of drugs through junctions between GI epithelium.

C. Vesicular transport
   a. Pinocytsis
   b. Phagocytosis

References

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 10-22.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 24-26

Class- Final Year B. Pharm. Subject- Biopharmaceutics and Pharmacokinetics

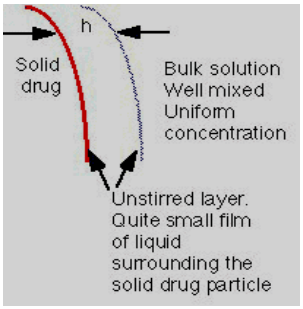
Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 5

Name of topic/lesson – Absorption

Factors affecting drug absorption:

Physicochemical Factors

1. Drug Solubility and Dissolution rate: Many drugs are given in solid dosage forms and therefore must dissolve before absorption can take place. If dissolution is the slow, it will be the rate determining step (the step controlling the overall rate of absorption) then factors affecting dissolution will control the overall process.



   Drug dissolution is considered to be diffusion controlled process through a stagnant layer surrounding each solid particle.
2. Particle size and Effective surface area of drug: Particle size and surface area of a drug are inversely related to each other. Smaller the dug particle, greater the surface area.
3. Polymorphism and Amorphism: Depending upon internal structure, a solid can exist either in a crystalline or amorphous form. When a substance exists in a more than one crystalline form, different forms are designated as polymorphs and the phenomena as polymorphism.

References

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 37-38.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 40-58.

Class- Final Year B. Pharm. Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 6

Name of topic/lesson – Absorption

Factors affecting drug absorption:

Physicochemical Factors

Salt form of Drug: Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base.

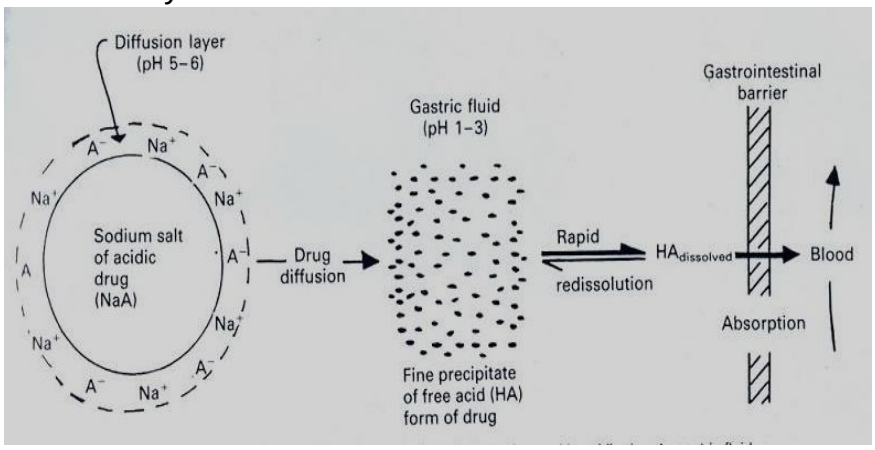


Figure: Improved solubility of weak acid when formulated as sodium salt

Drug pKa and lipophilicity and GI pH-pH Partition Hypothesis:

It is pH partition theory (Brodie et al) explains in simple term, process of drug absorption from the GIT and is distribution across all biological membranes. The theory states that for drug compounds of molecular weight greater than 100, which are primarily transported across the biomemebrane by passive diffusion, the process of absorption is governed by

1. Dissociation constant (pka)
2. Lipid solubility of unionized drug
3. pH at the absorption site

References

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 42-44.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 6-8.

Class- Final Year B. Pharm. Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 7

Name of topic/lesson – Absorption, Factors affecting drug absorption: Physicochemical Factors

The drug pka and gastrointestinal pH: The amount of drug that exists in unionized form is a function of dissociation constant pka of the drug and pH of the fluid at absorption site.

The lower the pka of an acidic drug, stronger the acid i.e. greater the proportion of ionized drug at particular pH, the highest the pka of a basic drug, stronger the base. Thus, from the knowledge of pka of the drug and pH at the absorption site the relative amount of ionized and unionized drug in solution at particular pH can be estimated using Henderson-Hasselbach equation.

Limitations of pH partition hypothesis:

1. Presence of virtual membrane pH
2. Absorption of ionized drug
3. Influence of GI surface area and residence time of drug
4. Presence of aqueous unstirred diffusion layer.

Physiological factors:

1. Age 2. Gastric Emptying 3. Intestinal Transit 4. Gastrointestinal pH
5. Disease state: Gastrointestinal disease, Cardiovascular disease, Hepatic disease
6. Blood flow to GIT

Reference:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 50-72.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 27-36.

Class- Final Year B. Pharm. Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 8

Name of topic/lesson – Absorption

Dosage form related factors that affect absorption:

The role of the drug formulation in the delivery of drug to the site of action should not be ignored. Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

Solution dosage forms:

In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

The role of the drug formulation in the delivery of drug to the site of action should not be ignored.

Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

Reference:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 50-72.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 61-80.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 09

Name of topic/lesson –Distribution

Two major disposition processes are

1. *Drug distribution:* means the reversible transfer of drug from one location to another within the body/ comapartment.
2. Elimination which causes irreversible loss of drug from body. It is Biotransformation and Excretion.

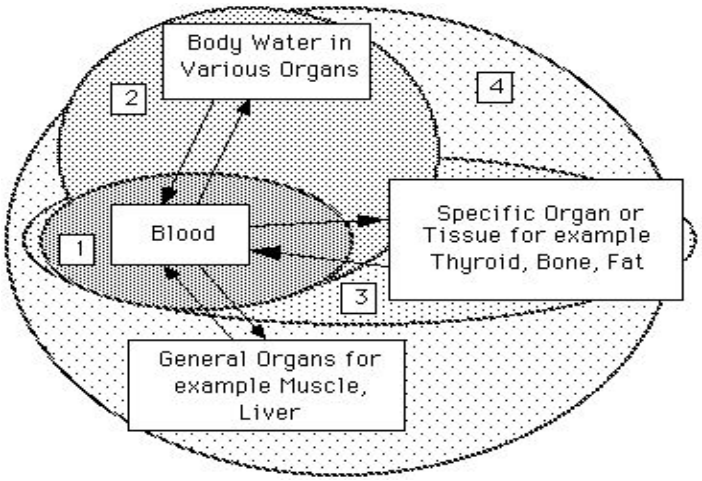


Figure Drug Distribution Pattern

Steps in Drug Distribution:

Movement from systemic circulation to extravascular tissues i.e. permeation of free drug present in blood through capillary wall and entry into interstitital/ extracellular fluid and further permeation of drug present in ECF into intracellular fluid.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 98-100.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 187-188.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 10

Name of topic/lesson –Distribution

Factors Affecting Drug Distribution:

1. Tissue permeability of drug
   a. Physicochemical properties of drug like molecular weight, pka and o/w partition coefficient
   b. Physiological Barriers to diffusion of drug like Simple capillary endothelial barrier, simple cell membrane barrier, Blood-brain barrier, blood-CSF barrier, Blood-placental barrier, Blood- testis barrier.

2. Organ size and Perfusion rate:
   Distribution is permeability rate-limited when drug under consideration is ionic, polar or water soluble and when highly selective barriers restrict diffusion of such drugs to the inside of cell.
   In contrast, distribution will be perfusion rate-limited when, drug is highly lipophilic and membrane across which drug is supposed to diffuse is highly permeable.

   Perfusion rate is defined as volume of blood that flows per unit time per unit volume of the tissue.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 98-100.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 192-194.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 11

Name of topic/lesson –Distribution

Factors Affecting Drug Distribution:

3. Binding of drug to tissue components: Several tissue components of which the two major categories are Blood and Binding of drug to extra vascular tissue.

The interacting molecules are generally macromolecules such as proteins, DNA or adipose. The proteins are particularly responsible for such interaction. The phenomenon of complex formation with protein is called as protein binding of drugs. Protein binding may be divided into intracellular binding and extracelluar binding.

- Mechanism of protein drug binding.

Binding of drug falls into 2 classes

1. Binding of drug to falls components like
   a. Plasma Proteins i.e. Human serum albumin, a1 acid glycoprotein, Globulins
   b. Blood cells i.e. Haemoglobine, Carbonic Anhydrase, and Cell membrane.

2. Binding of drug to extravascular tissues proteins, fats, bones, etc.

Tissue Localization of drug

For majority of drugs that binds to extravascular tisssues, order of binding is Liver > Kidney > Lung > Muscles

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 116-124.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 195-196.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 12**

Name of topic/lesson –Distribution

Concept Of Apparaent Volume Of Distribution

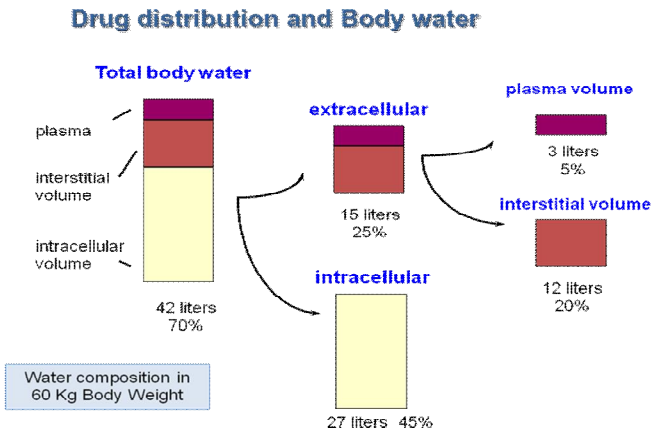
The concentration in plasma is achieved after distribution is complete is a function of dose and extent of distribution of drug into tissues.

This extent of distribution can be determined by relating the concentration obtained with a known amount of drug in the body

Concentration is related to the amount by a constant, VOLUME (V)

$$\text{Amount (mg)} = C\ (\text{mg/L}) * V_d\ (\text{L})$$

Plasma volume ~ 3 L; Extracellular water ~16 L; Total body water ~ 42 L.



References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 110-113.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 194-195.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 13**

Name of topic/lesson –Distribution

Factors affecting protein drug Binding:

1. Drug related factors: physicochemical properties of the drug, concentration of drug in body, affinity of drug for particular binding components.
2. Protein/ tissue related factor: physicochemical characteristics of protein or binding agent, concentration of protein, Number of binding sites
3. Drug Interaction (Displacement interaction and its significance)

Kinetics of Protein drug Binding

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 125-128, 134-136.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 197-198.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 14

Name of topic/lesson –Metabolism

Metabolism is defined as: The irreversible biotransformation of drug in the body → typically involves making it more polar to enhance renal excretion

Drug metabolism often converts lipophilic chemical compounds into:

more hydrophilic, more water soluble have their actions decreased (become less effective) or increased (become more effective) May be converted to less toxic or more toxic metabolites or to metabolites with different type of effect or toxicity

The metabolism of drugs takes place mainly in the liver (the smooth endoplasmic reticulum of the liver cell) . However, other organs such as the kidney, lung, intestine and placenta can also be involved in this process.

Introduction to Phase I and Phase II reactions.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 139-144, 180-184.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No.213-220.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 15

Name of topic/lesson –Metabolism

Factors affecting metabolism of drug:

1. Physicochemical properties of drug
2. Chemical factors
   a. Induction of drug metabolizing enzymes: Several drugs and chemicals have ability to increase the drug metabolising activity of enzymes called as enzyme induction.
   b. Inhibition of Drug Metabolising Enzymes: Contrary to metabolising enzyme induction, several drugs or chemicals have the ability to decrease the drug metabolising activity of certain enzymes called as enzyme inhibition.
   c. Auto induction
3. Biological factors: Species difference, Sex difference, Age, diet
4. Factors affecting metabolism of drug:
5. **Biological factors:** Strain difference, altered physiological factors as pregnancy, Hormonal imbalance, Disease state,
6. **Temporal factors:** Circadian rhythm.
7. **Bioactivation and tissue toxicity:** formation of highly reactive metabolite which interacts with the tissue to precipitate one or more of the several forms of toxicities such as carcinogenesis and teratogenesis is called bioactivation.
8. First pass effect: After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 125-128.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 197-198.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 16

Name of topic/lesson: Excretion

It is defined as the process whereby drugs and or metabolites are irreversibly transferred from internal to external environment.

Renal excretion of drugs-

Agents that are water soluble, non- volatile, small in molecular size (5oo daltons) and which are metabolized slowly are excreted in the urine.

1. Glomerular filtration
2. Active tubular secretion
3. Active or passive tubular reabsorption Fig. nephron showing excretion.

Renal clearance can be defined as the volume of blood or plasma which is completely cleared of the unchanged drug by the kidney per unit time.

4.

Cl_R= rate of urinary excretion/ plasma drug conc.

Cl_R= rate of filtration + rate of secretion – rate of reabsorption

Factors affecting renal clearance

1. Physicochemical properties of drugs
2. Plasma concentration of drugs

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No.196-206.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 131-136.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 17

Name of topic/lesson: Excretion

Factors affecting renal clearance

3. Distribution and binding characteristic of drugs
4. Urine pH
5. Blood flows to the kidney
6. Biological factors
7. Drug interaction
8. Disease state

Non renal routes of elimination

Biliary excretion , Pulmonary excretion ,Salivary excretion ,Mammary excretion, Skin excretion , Gastrointestinal excretions , Genital excretion

Biliary Excretion

some compounds are excreted in the bile. Bile is produced by the hepatic cell linings

It is secreted from liver after storage in gall bladder. It is secreted in duodenum

Classes into 3 groups

Group A – sodium, potassium and glucose

Group B – bile salts, creatinine, bilirubin

Group C – sucrose, inulin, phosphates

Factors influencing secretion of drug in bile

1. Physicochemical properties, Nature of biotransformation process
2. Other factors- Sex, Species, Protein drug binding

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No.206-209, 213-221
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No.144-145.
3. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 209-210.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 18**

Name of topic/lesson: Excretion

Salivary excretion

Excretion of drugs in saliva is passive diffusion processes pH of saliva is 5.8-8.4.

E.g.: caffeine, theophylline, phenytoin.

Pulmonary Excretion:

Gaseous and volatile substances such as the general anasthetics (e.g. halothene) are adsorbed through the lung by simple diffusion. Similarly, their excretion by diffusion into the expired air is possible.

Factors influencing pulmonary excretion of a drug include pulmonary blood flow, rate of respiration, solubility of volatile substance etc.

Mamillary Excretion

Milk consists of lactic secretions originating from the extracelluar fluid and rich in fat and protein. Excretion is a passive process and is dependent on a pH partition behaviour, molecular weight, degree of ionization.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No.213-221.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 211-214.

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Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 19

Name of topic/lesson –Dissolution studies

The process by which a solid or liquid forms a homogeneous mixture with a solvent OR mass transfer form solid phase to liquid phase

Tablet Dissolution is a standardized method for measuring the rate of drug release from a dosage form.

Historical development of dissolution testing:

It all started in 1897 with the first reference to dissolution:

Noyes and Whitney publish a paper on "The Rate of Solution of Solid Substances in Their Own Solution."

1904-Nernst and Brunner modified the Noyes-Whitney equation.

1931-Hixon and Crowell develop the cube-root law of diffusion.

1975-USP begins development of calibrators for dissolution testing.

Theories of dissolution:

1. Film theory or Diffusion layer model: It involves two steps, Solution of the solid to form stagnant film or diffusive layer which is saturated with the drug. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution; this is r.d.s in drug dissolution.

2. Interfacial barrier model / Limited Solvation: according to this an intermediate concentration can exist at interface as a result of salvation mechanism and is a function of solubility rather than diffusion.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 27-30.
2. Biopharmaceutics and clinical pharmacokinetics, 4th edition, Milo Gibaldi, pg. No. 47-50.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 20

Name of topic/lesson –Dissolution studies

3. Dankwerts Model: Dankwert takes into account the eddies or packets that are present in the agitated fluid which reach the solid-liquid interface, absorb the solute by diffusion and carry it into the bulk of solution.These packets get continuously replaced by new ones and expose to new solid surface each time, thus the theory is called as surface renewal theory.

Biopharmaceutics Classification System

A theoretical basis for correlating in-vitro drug solubility with in-vivo bioavailability was developed by Amidon and co-workers in 1995. This approach is based on aqueous solubility and permeability of the drug through gastrointestinal tract (Flicks First Law applied to cell membrane),

$J_W = P_W . C_W$

Jw: Drug flux across cell membrane

Pw: Permiability constant

Cw: concentration of drug at site of absorption site

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 29-30.
2. Amidon G. l., Lennernas H., Shah V. P., Crison J. R., A theorotical basis for a biopharmaceutic drug classificatgion: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharmaceutical research, 1995: 12(3). 412.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 21

Name of topic/lesson –Dissolution studies

According to BCS, drug substances are classified as:

Class I: High Solubility – High Permeability

Class II: Low Solubility – High Permeability

Class III: High Solubility – Low Permeability

Class IV: Low Solubility – Low Permeability

Different Approaches To Classify Drug Into Bcs Classification

Solubility determination:
Permeability determination:

Extent of absorption in humans:

1. Mass-balance pharmacokinetic studies.
2. Absolute bioavailability studies.

Intestinal permeability methods:

Application of BCS classification for the development of dosage form.

Dissolution Kinetics models: Zero order, first order, Higuchi

References:

1. Amidon G. l., A theorotical basis for a biopharmaceutic drug classificatgion: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharmaceutical research, 1995: 12(3). 412.
2. Paulo C., Modeling and comparison of dissolution studies, European journal of Pharmceutical Sciences, 123-133.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 22**

Name of topic/lesson –Dissolution studies
USP Dissolution test Apparatus

***In-Vitro-In-Vivo* Correlation**

In IVIVC, "C" denotes "Correlation", which means "the degree of relationship between two variables". This term does not limit a relationship to only the linear type, but allows for non-linear relationships as well.

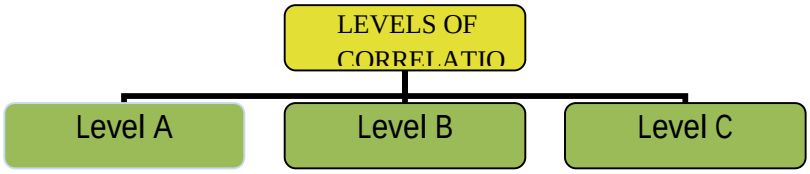
Conceptually, IVIVC describes a relationship between the in vitro dissolution / release versus the in vivo absorption.

FDA had defined IVIVC as "A predictive mathematical model describing relationship between in-vitro property of a dosage form and in-vivo response."

In-vitro properties are rate or extent of drug released under a given set of conditions. In-vivo properties are plasma drug conc. expressed in terms of Cmax, AUC.

LEVELS OF CORRELATION

There are four levels of IVIVC that have been described in the FDA guidance, which include



References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 29-30.
2. J-M Cardot In-vitro-In-vivo Correlation: Importance of Dissolution in IVIVC, Dissolution technology 2007.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 23

Name of topic/lesson: Non-linear Pharamcokinetics

Introduction

Linear Pharmacokinetics

At therapeutic doses, the change in the amount of drug in the body or the change in its plasma concentration due to absorption, distribution, binding, metabolism or excretion, is proportional to its dose, whether administered as a single dose or as multiple doses. **»** In such situation the rate processes are said to follw first order or linear kinetics and all semilog plots of C Vs t for different doses when collected for dose administered, are superimposable

NONLINEAR PHARMACOKINETICS

The rate process of drug's ADME is depending upon carrier or enzymes that are substrate specific, have definite capacities and are susceptible to saturation at a high drug concentration.

In such cases, an essentially first-order kinetics transform into a mixture of first-order and zero-order rate processes and the pharmacokinetic parameters are changed with the size of the administered dose.

Pharmacokinetics of such drugs are said to be dose-dependent. Terms synonymous with it are mixed-order, nonlinear and capacity-limited kinetics.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 305-314.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 3-4.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 24

Name of topic/lesson: Non-linear Pharamcokinetics

DETECTION OF NON-LINEARITY IN PHARMACOKINETICS

There are several tests to detect non –linearity in pharmacokinetics but the simplest ones are:

1) First test:- Determination of steady state plasma concentration at different doses.
2) Second test:- Determination of some important pharmacokinetic parameters such as fraction bioavailability, elimination half life or total systemic clearance at different doses of drug. Any change in these parameters is indicative to non-linearity which are usually constant.

CAUSES OF NON-LINEARITY

Drug absorption

Three causes:

I) Solubility / dissolution of drug is rate-limited.
II) Carrier - mediated transport system.
III) Presystemic gut wall / hepatic metabolism attains saturation.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 305-314.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 3-4.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 25

Name of topic/lesson: Non-linear Pharamcokinetics

Drug distribution

At high doses non-linearity due to

Two causes :- I) Binding sites on plasma proteins get saturated;

II) Tissue binding sites get saturated.

Drug metabolism

Non-linearity occurs due to capacity limited metabolism, small changes in dose administration - large variations in plasma concentration at steady state - large intersubject variability.

Two imp causes:-

I) Capacity - limited metabolism -

II) Enzyme induction - decrease in plasma concentration;

Drug excretion

Two active processes which are saturable,

I) Active tubular secretion - Penicillin G

II) Active tubular reabsorption - Water soluble vitamins & Glucose.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 305-314.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 3-4.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 26**

Name of topic/lesson: Non-linear Pharamcokinetics

MICHAELIS MENTEN ENZYME KINETICS

- ✓ It is also called as Capacity-limited metabolism or Mixed order kinetics.

$$E + D \rightleftarrows ED \rightarrow E + M$$

- ✓ Enzymes usually react with the substrate to form enzyme substrate complexes; then the product is formed. The enzyme can go back to react with another substrate to form another molecule of the product.

$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{K_M + C} \quad \ldots\ldots\ldots\ldots\ldots\ldots I$$

Where,

-dC/dt = rate of decline of drug conc. with time

V_{max} = theoretical maximum rate of the process

K_M = Michaelis constant

Three situations can now be considered depending upon the value of K_m and C.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 305-314.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 3-4.

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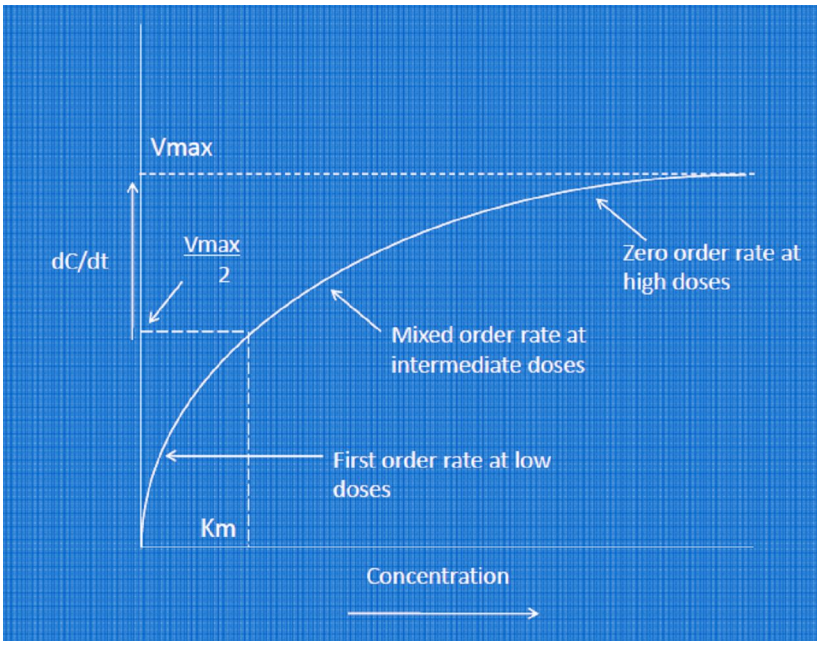
Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 27

Name of topic/lesson: Non-linear Pharamcokinetics

ESTIMATION OF V_{max} & K_m



Different approaches

1. Drug given as IV bolus
    a. Direct linear plot, b. Lineweaver-Burk Plot,
2. Dug Given as IV infusion
    a. Direct linear plot, b. Lineweaver-Burk Plot,

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 305-314.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 3-4.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No.28**

Name of topic/lesson –Introduction to Pharmacokinetic Models

The term "Pharmacokinetics" is derived from Greek words *Pharmakon* (drug) and *Kinesis* (movement).

Need of Pharmacokinetic Models: Drug movement within the body is a complex process. To understand the movement of drug in biological system pharmacokinetic models come under consideration.

Pharmacokinetic Models: Model is a hypothetical space bound by an unspecified membrane across which drugs are transferred in and out.

The two major approaches in the quantitative study of various kinetic process of drug disposition in body are

1. Model approach
2. Model-independent approach

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 245-255.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 4-5.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 29

Name of topic/lesson –Introduction to Pharmacokinetic Models

A. Model approach

In this approach, models are used to describe changes in drug concentration in the body with time.

1 Compartment Model (empirical model)
   (a) Mammillary Model
   (b) Catenary Model
2 Physiological Model Also know as *physiologically-based pharmacokinetic models* (PB-PK models). It describe the drug disposition in terms of realistic physiological parameters.
   (a) Perfusion-Limited Model
   (b) Diffusion-Limited Model
3 Distributed Parameter Model: Analogous to physiological model. Designed only for determining Variation in blood flow to an organ Variation in drug diffusion in an organ

B. Model-independent approach: Also know as model-independent-method. *Based on the assumption that the drugs or metabolites follow linear kinetics.*

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 245-255.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 4-5.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 30

Name of topic/lesson: Compartment Modeling

ONE COMPARTMENT OPEN MODEL (Instantaneous distribution model)

The body is considered as a single, kinetically homogeneous unit.
This model applies only to those drugs that distributes rapidly throughout the body.
Drugs move dynamically in an out of this compartment
Elimination is first order (monoexponential) process with first order rate constant.
Rate of input(absorption)> rate of output (elimination)

Depending on rate of input, several one compartment open models are :

1. One compartment open model, i.v. bolus administration
2. One compartment open model, continuous i.v. infusion.
3. One compartment open model, e.v. administration, zero order absorption.
4. One compartment open model, e.v. administration, first order absorption.

References:

1.Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 258-259.
1. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No.51-52.

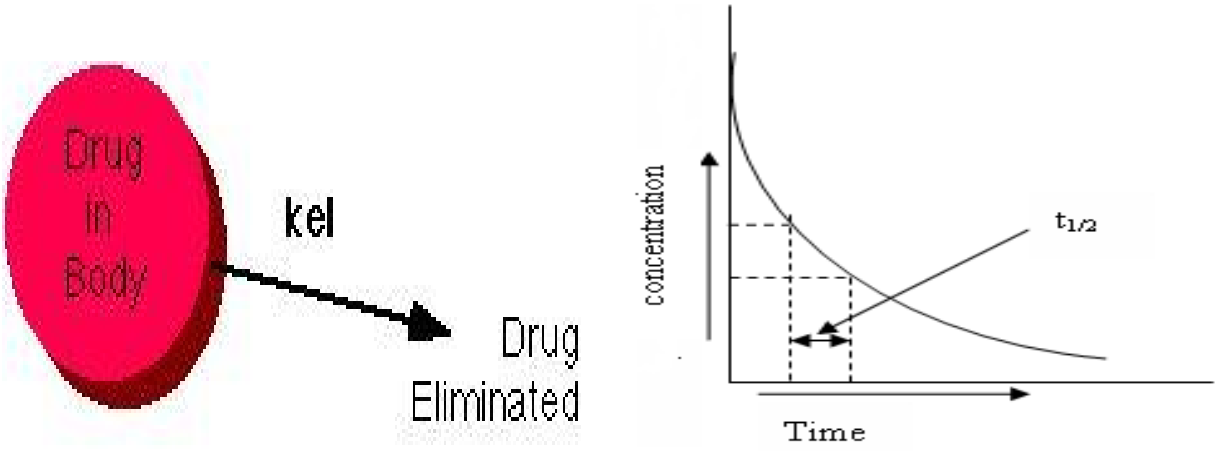
Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No.31**

Name of topic/lesson: Compartment Modeling

INTRAVENOUS BOLUS ADMINISTRATION

When drug is given in the form of rapid i.v. injection it takes about one to three Minutes for complete circulation and therefore the rate of absorption is neglected.



References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 259-267.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No.52-69.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 32

Name of topic/lesson: Compartment Modeling

ORGAN CLEARANCE Extraction Ratio

At an organ level, the rate of elimination can be written as:

Rate of elimination by an organ = Rate of presentation - Rate of exit from the organ to the organ

Rate of presentation (input) = Organ blood flow X Entering concentration

= QCin

Rate of exit (output) = Organ blood flow X Exiting concentration

= QC out of

Rate of elimination = rate of input –rate of output

=(QCin-QCout) = (QCin-Cout)

Rate of extraction =Clorgan = QCin-Qcout

Cin Cin

where, ER = (Cin – Cout)/Cin is called as **extraction ratio**.

1. It has no units and its value ranges from zero (no elimination) to one (complete elimination).
2. Based on ER values, drugs can be classified into 3 groups:
3. 1. Drugs with **high ER** (above 0.7),
4. 2. Drugs with **intermediate ER** (between 0.7 to 0.3),
5. 3. Drugs with **low ER** (below 0.3).

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 268-272.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No.105-115.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 33

Name of topic/lesson: Compartment Modeling

Estimation of pharmacokinetic parameters for IV bolus:

6. Elimination half life:
7. Apparent volume of distribution
8. Clearance

INTRAVENOUS INFUSION: Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity or when maintenance of a stable concentration or amount of the drug in body is desired. In such a situation, the drug is administered at a constant rate (zero ordered) by i.v. infusion.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 268-272.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No.105-115.

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Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

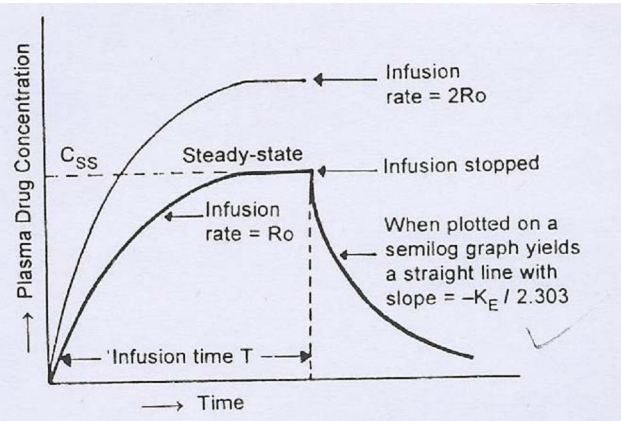
Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 34

Name of topic/lesson: Compartment Modeling

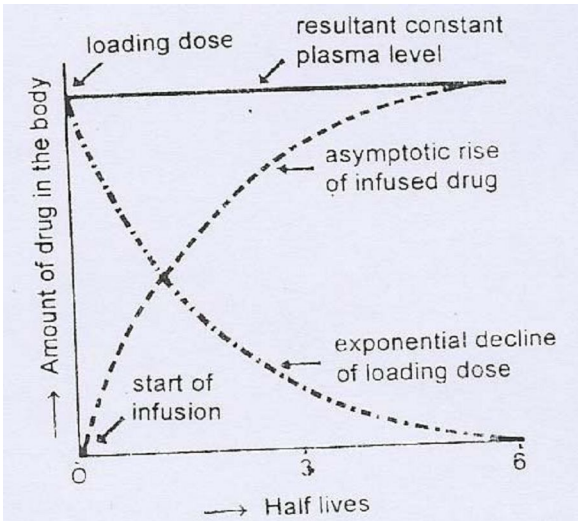
Infusion plus loading dose:

It takes very long time for the drugs having longer half lives before the steady state concentration is reached. An i.v. **loading dose is given** to yield the desired steady-state immediately upon injection prior to starting the infusion.

It should then be followed immediately by i.v. infusion at a rate enough to maintain this concentration.



ig. 10.3 Plasma concentration-time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates R_o and $2R_o$ for the same drug)



References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 268-272.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 105-115.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 35**

Name of topic/lesson: Compartment Modeling

Infusion plus loading dose:

It takes very long time for the drugs having longer half lives before the steady state concentration is reached. An i.v. **loading dose is given** to yield the desired steady-state immediately upon injection prior to starting the infusion.

It should then be followed immediately by i.v. infusion at a rate enough to maintain this concentration.

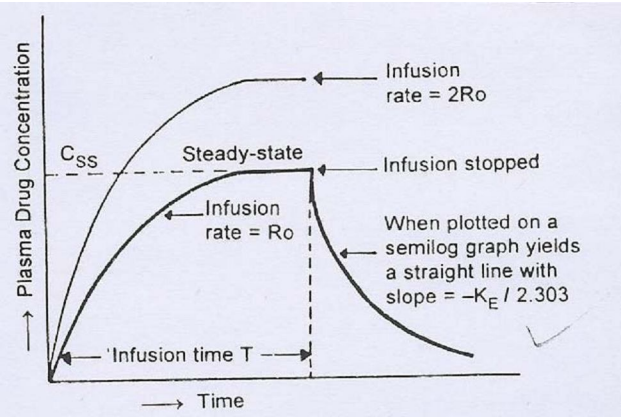
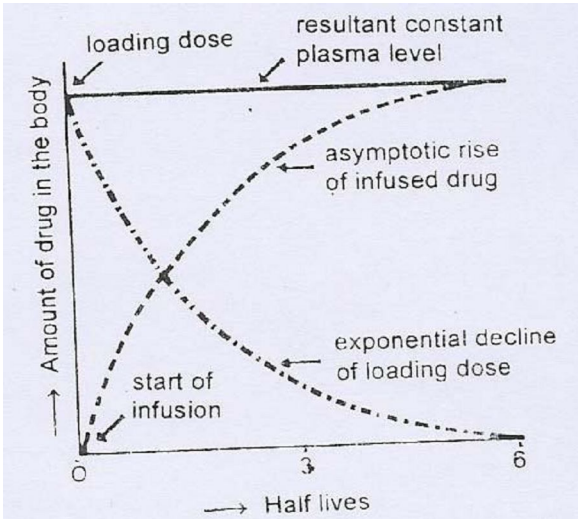


Fig. 10.3 Plasma concentration-time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates R_o and $2R_o$ for the same drug)



References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 268-272.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 105-115.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 36

Name of topic/lesson: Compartment Modeling

One compartment open model: extra vascular administration

When drug administered by extra vascular route (e.g. oral, i.m, rectal), absorption is prerequisite for its therapeutic activity.

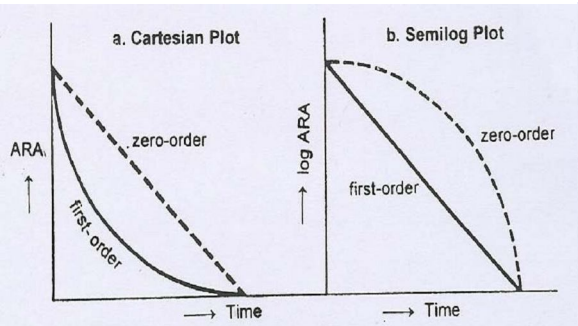
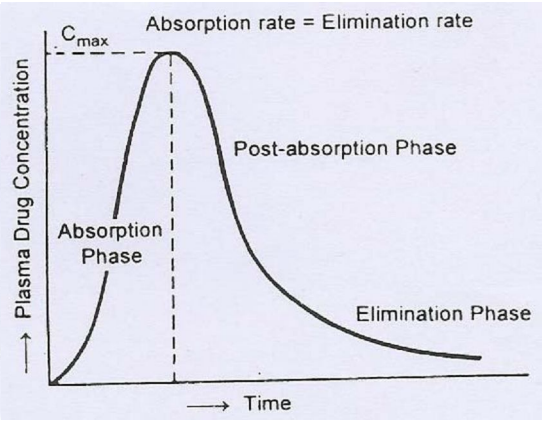


Fig. 10.6 Distinction between zero-order and first-order absorption processes. *Figure a* is regular plot, and *Figure b* a semilog plot of amount of drug remaining to be absorbed (ARA) versus time t.



It is of two types

1. One compartment open model: extra vascular administration (Zero order absorption).
2. One compartment open model: extra vascular administration (First order absorption).

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No.273-282.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 161-181.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 37**

Name of topic/lesson: Compartment Modeling

Determination of absorption rate constant:

Two approaches

1. METHOD OF RESIDUALS. Method is also known as Feathering, stripping.
2. Wagner Nelson Method

Estimation of Pharmacokinetic Parameters based on Urinary Excretion Data

Introduction Multi Compartment models:

One compartment is described by mono-exponential term i.e. elimination. For large class of drugs this term is not sufficient to describe its disposition. It needs a bi-or multi-exponential terms. 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 elimination.
Introduction to Two compartment open model

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No.273-282.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 161-181.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 38

Name of topic/lesson: Applications of Pharmacokinetics

NEED TO KEEP PLASMA CONCENTRATION IN THE THERAPEUTIC RANGE TO OPTIMIZE THERAPY (Therapeutic Drug Monitoring)

There exists a fundamental relationship between drug pharmacokinetics and pharmacologic response. The relationship between response and ln-concentration is sigmoidal. A threshold concentration of drug must be attained before any response is elicited at all. Therapy is achieved when the desired effect is attained because the required concentration has been reached. That concentration would set the lower limit of utility of the drug, and is called the Minimum Effective Concentration (MEC). Most drugs are not "clean", that is exhibit only the desired therapeutic response. They may also exhibit undesired side effects, sometimes called toxic effects at a higher, (hopefully a lot higher), concentration. At some concentration, these toxic side effects become become intolerable/and or dangerous to the patient.. That concentration, or one below it, would set the upper limit of utility for the drug and is called the Maximum Therapeutic Concentration or Minimum Toxic Concentration (MTC). Patient studies have generated upper (MTC) and lower (MEC) plasma concentration ranges that are deemed safe and effective in treating specific disease states. These concentrations are known as the "therapeutic range" for the drug.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 382-384.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 263-268.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 39**

Name of topic/lesson: Bioavailability and Bioequivalence

Concept of Bioavailability:

Easy to understand using intravenous route, No absorption phase, Simple to follow Concepts clear with less assumptions Need some math background algebra, log scale, Simple linear Equations etc complex math (differential equations, statistical concepts etc) for Modeling, Population PK, PK-PD etc.

The rate and extent to which the parent compound reaches the general circulation orThe rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. The evaluation of BA is made by data comparison of the BA from tested product and the BA data from a solution, suspension or IV dosage form.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 315-317.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 72-74

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 40

Name of topic/lesson: Bioavailability and Bioequivalence

ABSOLUTE BIOAVAILABILITY

Compares the bioavailability (estimated as area under the curve, or AUC) of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous administration), with the bioavailability of the same drug following intravenous administration(By definition, when a medication is administered intravenously, its bioavailability is 100%).

WHAT IS RELATIVE BIOAVAILABILITY

It is used to choice the best formulation in a group of different dosage forms. It measures the bioavailability of a certain drug when compared with another formulation of the same drug, usually an established standard (solution or other one), or through administration via a different route. The area under the curve (AUC), Cmax and Tmax are used to make comparisons.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 315-320.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 72-74.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 41**

Name of topic/lesson: Bioavailability and Bioequivalence

Single Dose Vs Multiple dose study for bioavailability

Single Dose

- ✓ Less tedious, Less exposure to drug
- ✓ In case of single dose study, Difficult to predict steady state characteristics of drug & intersubject variability with single dose study.

Multiple dose

- ✓ More tedious, More exposure to drug,
- ✓ Time consuming.

Measurement of bioavailability

Quantitative Estimation of Bioavailability

A) Pharmacokinetic:

a) Plasma-level time studies (Cmax, tmax, AUC)

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 319-321.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 72-73.

Name of topic/lesson: Bioavailability and Bioequivalence

b) Urinary Excretion data

B) Pharmacodynamic

a) Acute Pharmacologic response

When BA measurement is difficult, inaccurate, no reproducible by PK method, then acute pharmacologic effects such as change in electrocardiogram, change in pupil diameter is related with the time cuorse of given drug.

b) Therapeutic response

Observing clinical response to drug formulation given to patient suffering from disease to which it is intended to be used.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 319-324.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 460-464.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No.43

Name of topic/lesson: Bioavailability and Bioequivalence

Bioequivalence: Background

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Waxman-Hatch Act.

Definition: CFR 320.1

It is the absence of significance difference in the rate and extent to which active ingredient or active moiety in pharmaceutical equivalent or pharmaceutical alternative becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.
Following Aspects are important with respect to bioequivalence testing
Significance: Significant problem not observed in BA and BE of those drugs where 75 % drug is dissolved in water or 0.1 N HCl in 45 min. BA BE testing has significant importance in case of drugs which have a narrow theraputic index. E.g. digoxin, phenytoin, theophyllin.

The different experimental designs for BA BE studies are as follows,

Study Design:

1. Parallel design 2. Complete cross over design
2. b. Three period, three sequence cross over design

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 336-337
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 475-478.

Class- Final Year B. Pharm Subject- Biopharmaceutics and Pharmacokinetics

Subject Incharge-Dr. N. S. Kulkarni Lecture Synopsis No. 44

Name of topic/lesson: Bioavailability and Bioequivalence

The different experimental designs for BA BE studies are as follows,

Study Design:

3. Parallel design: Two groups -one group of subjects receives on formulations, one group receives other formulation which is to be compared.

   Drawback- intra subject and inter subject variations are not avoided, not recommended .

4. Complete cross over design: Generally, variability within the subject is higher than that between the subjects, Complete cross over design are used to overcome these variability. Each subject receives each formulation over a period separated by washout period.

a. Two period, two sequence cross over design

b. Three period, three sequence cross over design

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 339-342.
2. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 470-472.

Class- Final Year B. Pharm **Subject- Biopharmaceutics and Pharmacokinetics**

Subject Incharge-Dr. N. S. Kulkarni **Lecture Synopsis No. 45**

Name of topic/lesson: Bioavailability and Bioequivalence

c. Latin square design d. Balanced incomplete block design

Regulatory requirement of Bioavailability and Bioequivalence

For approved drugs bioequivalence studies are performed to compare the performance of different drug products of the same active ingredients. Abbreviated new drug application are permitted for duplicates of drug on condition that new drug product is shown to be bioequivalent to the originally approved drug products.

References:

Design and evaluation of bioequivalence Studies:

1. The Volunteers
2. Reference standard product
3. Study Design
4. Sampling Schedule
5. Sampling Analysis
6. Pharmacokinetic Parameters
7. Statistical Analysis

Criteria for Waiver of Bioavailability Requirements:

The *in-vivo* bioavailability requirements are waived by regulatory agencies if drug product meets one of criteria: e.g. preparation intended for the IV use or topical preparation for local effect.

References:

1. Biopharmaceutics and Pharmacokinetics a Treatise, D. M. Brahmankar, S. B. Jaiswal, Pg. No. 339-344.
2. CRC press Pharamcy education series, Basic Pharmacokinetics, MOhnish A. Hedaya, Pg. No. 79-81.
3. Applied Biopharmaceutics and Pharmacokinetics, 5th edition, Leon Shargel, Pg. No. 470-472.