BIOPHARMACEUTICS

UNIT 3 NOTES

PHARMACOKINETICS

- DEFINITION
- COMPARTMENT MODELS
- NON COMPARTMENT MODELS
- PHYSIOLOGICAL MODELS
- ONE COMPARTMENT MODEL
- PHARMACOKINETIC PARAMETERS
- METHODS OF ELIMINATION

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PHARMACOKINETICS

- Pharmacokinetics is the branch of science that studies what the body does to a drug after it is taken.
- It explains how a drug moves through the body from the moment you take it until it leaves your body/ system.
- Pharmacokinetics is often called "ADME", which stands for :

i) Absorption - How the drug gets into the bloodstream.
ii) Distribution - How the drug spread through the body.
iii) Metabolism - How the body breaks down the drug.
iv) Excretion - How the drug is removed from the body.

OBJECTIVES

- To determine how the body absorb the drug, how distributed the drug, how the drug is metabolized, and how the drug is eliminated.
- To calculate drug concentration in blood over time.
- To optimize drug dosing for maximum effect and minimum side effects.
- To support safe, and effective therapeutic drug monitoring.
- To predict onset, intensity and duration of drug action.

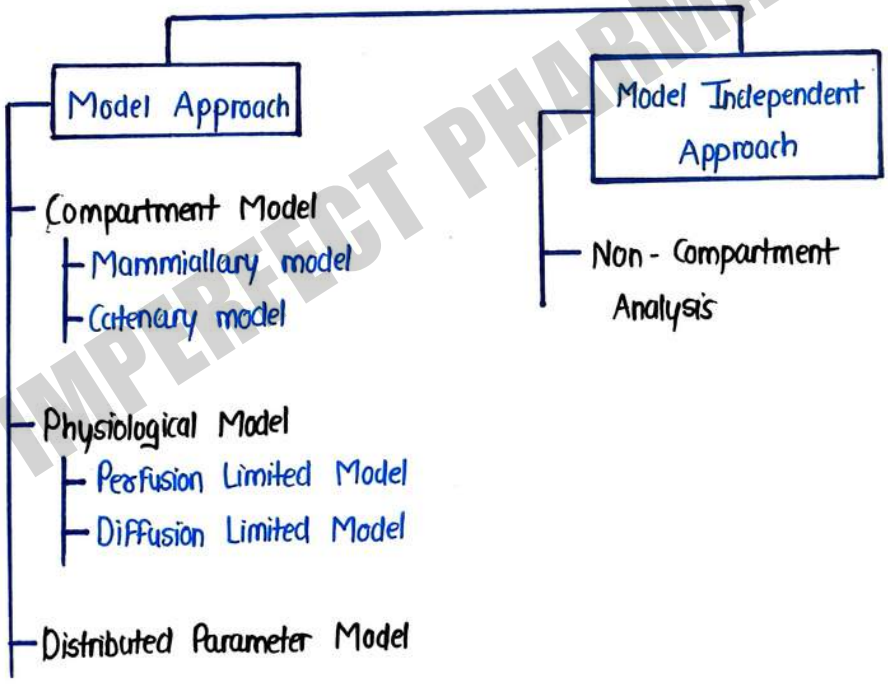
APPLICATIONS

- Help to decide how much medicine to give.
- Helps avoid side effects and drug problems.
- Helps make treatments more personal for each patient.
- Helps doctors treat overdoses or high drug levels safely.
- Support safe use of drug during research and trials.

PHARMACOKINETIC MODELS

- Pharmacokinetic models are like maps or diagrams that help us understand and predict how a drug moves through the body over time.
- They are tools that scientists use to describe what happens to a medicine after it enters the body and how it gets in, how it's broken down and how it leaves.
- These models use math and pictures to represent the body as different compartments (like boxes), such as blood, liver or other organs.

- Basically, there are two methods for analysis of pharmacokinetic data:



COMPARTMENT MODEL

- Compartment models are simple ways to understand how a drug moves in the body by dividing the body into sections or compartments.
- Think of compartment like boxes that represents different parts of the body, like bloodstream, organs, or tissues.
- These models don't show real body parts help us understand how the drug enters, moves around and leaves the body.
- A compartment is not a real physiological or ant anatomic region but an imaginary or hypothetical grouping of tissues with similiar blood flow & affinity.

ADVANTAGES

- Simple to use and understand.
- Helps predict drug levels in the body over time.
- Useful for estimating drug absorption, distribution and elimination.
- Can be adapted to fit different types of drugs.
- Requires fewer data to create a model.
- Help design proper dosing schedule.

DISADVANTAGE

- Do not represent actual organs or tissues.
- Less accurate for drugs with irregular distribution.
- Not suitable for all types of drugs or conditions.
- May require adjustments to fit real-life data.
- Assume uniform drug concentrations within compartments.

Types Of Compartment Model

- Compartment models are devided into two categories :

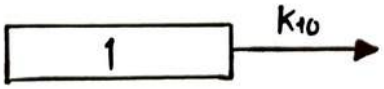
a) Mammillary Model
b) Catenary Model

① Mammillary Model

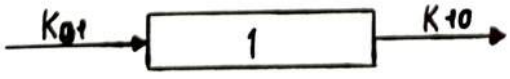
- This compartment model is most commonly used in pharmacokinetic studies.
- It has central compartment and peripheral compartment, in which the peripheral compartments are connected centeral compartment.
- The central compartments consists of plasma and organs like lungs, liver and kidneys, and the peripheral compartmens consist of less vascularized tissues with lower blood flow.
- The rate of movement of drug b/w compartments is called rate constant and denoted by 'K'.

- Various mathematical equations are used to describe the models and evaluate various pharmacokinetic parameters :

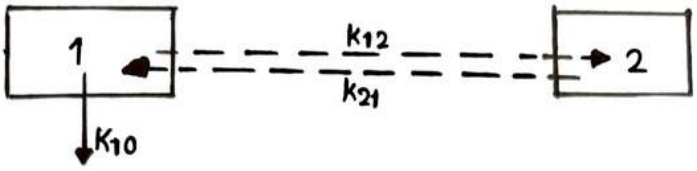
- Model 1 : One - compartment open model I.V. injection.



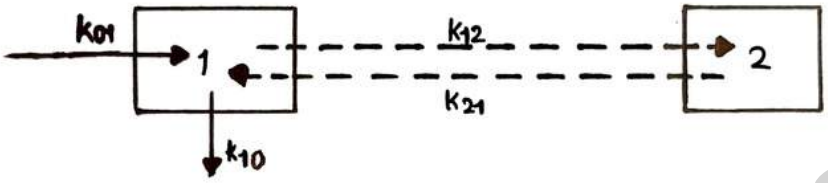
- Model 2 : One - compartment open model with first - order absorption.



- Model 3 : Two compartment open model I.V. injection

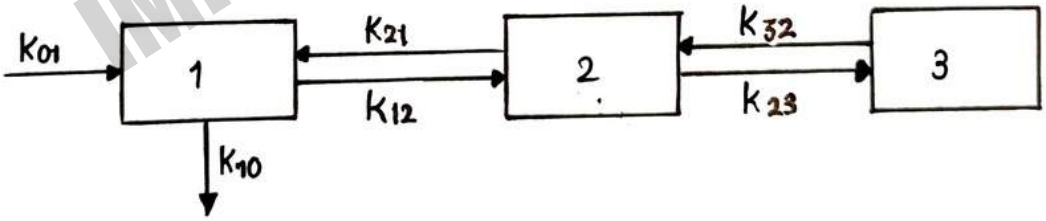


- Model 4 : Two - compartment open model with first - order absorption.



② CATENARY MODELS

- The catenary models is another way to understand how a drug moves through the body, but it's a bit difference from mammillary model.
- It is model of imagination a chain of compartments linked one after the others.
- This model is used rarely.



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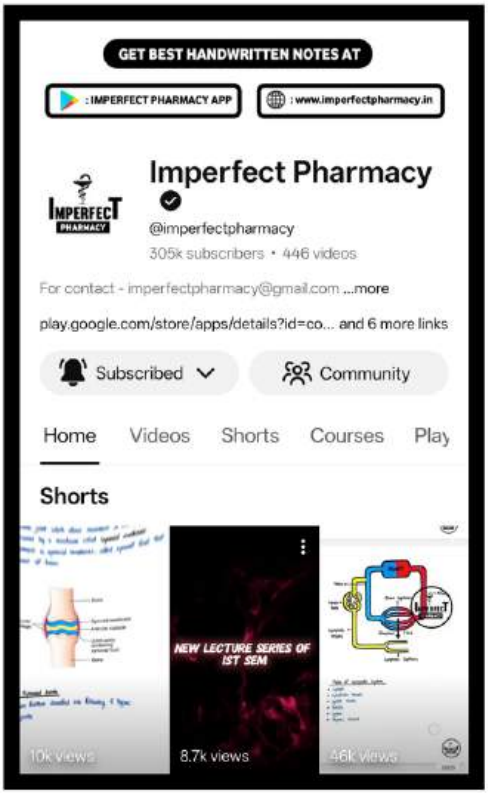

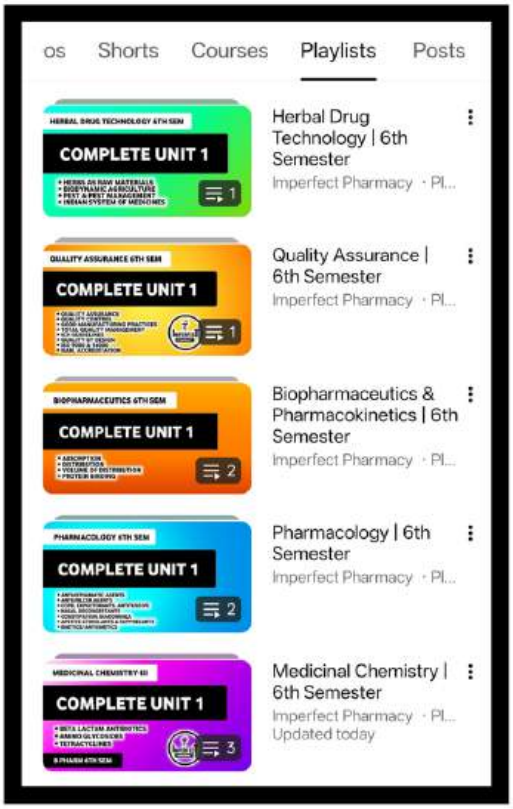

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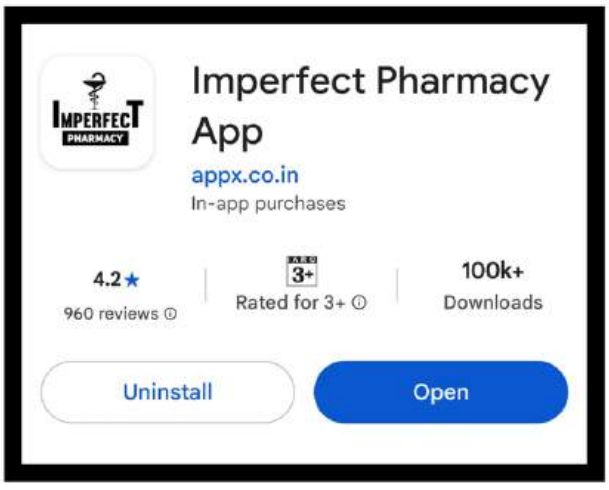
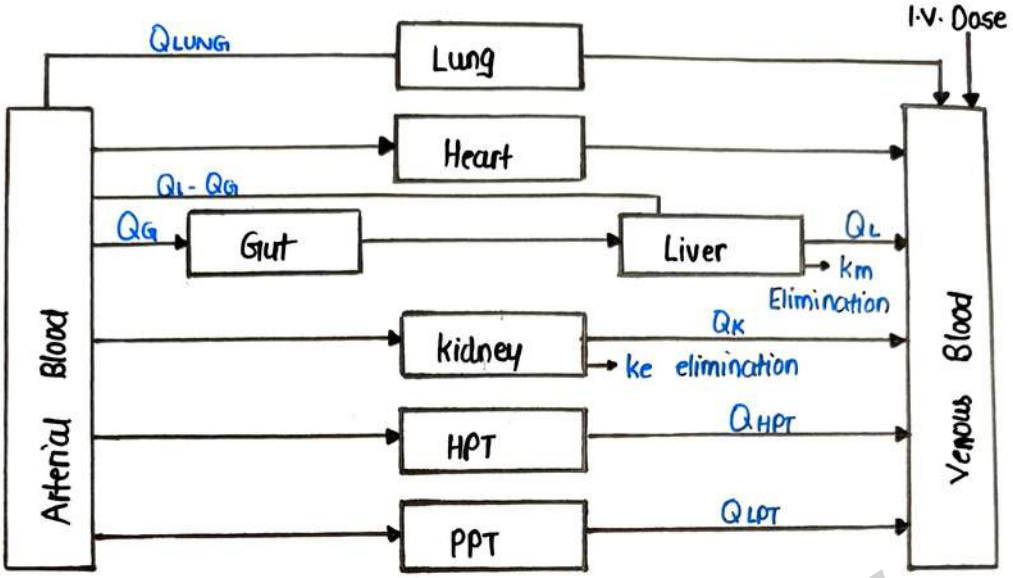


Physiological Models

- Physiological models also known as physiologically-based pharmacokinetic Models (PB-PK models).
- Its understanding of drug distribution in the body as realistic way.
- These models are based on an anatomical and physiological data. These models potentially predicts the accurate tissue drug concentration, which the compartment models fails to do.

Structure of Model

- The no. of compartments are based on the drug's characteristics in the model.
- Describe each tissue / organ with mathematic equations makes the model complex, tissues with similiar perfusion properties are grouped into a single compartment.
- For example lungs, liver, brain and kidney are grouped as Rapidly equilibrating tissues (RET) while muscles and others like adipose (Fat) grouped as Slowly equilibrating tissues (SET).



Where, Q = Blood flow rate to body region

HPT= Highly Perfused Tissue

PPT= Poorly Perfused Tissue

Km = Rate constant for hepatic elimination

Ke = First - order rate constant for urinary excretion.

FACTORS AFFECTING DRUG DISTRIBUTION

- In physiological models, the rate of drug delivery to an organ depends on :
- Blood flow to tissues / organs.
- Tissue permeability like Lipid solubility and membrane transport affect entry.
- Fat and water content affect drug solubility and storage.

Types of Physiological Models :

I) Blood Flow rate- Limited Models (Perfusion Limited Model)

II) Membrane Permeation rate - Limited Models (Diffusion Limited Model)

① Blood Flow rate - Limited Models

- This model assume that the drug which is mov in the blood within a body region is faster than blood flow.

② Membrane Permeation rate- Limited Models

- They are complex and applicable to highly polar, ionised and charged drugs.
- In this the cell membrane act as barrier for the drug, which permeates gradually through diffusion.

Model Independent Approach

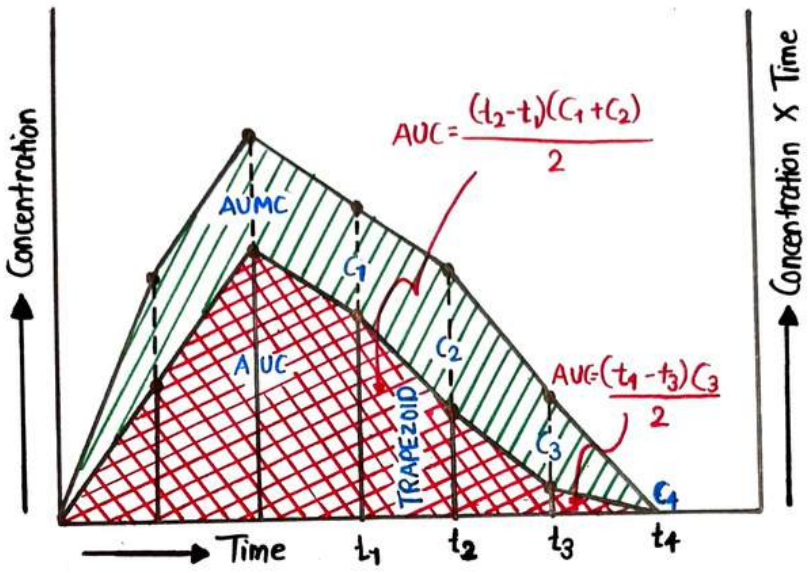
Non Compartment Analysis

- This compartment doesn't require assumption or imagination of specific compartment model.
- This compartment known as model - independent method.
- It assumes the drugs or metabolites follow linear kinetics.
- It's involve collecting the data after administrating the single dose of the drug.
- The non compartment analysis approach, based on statistical moments theory, involves accumulation of experimental data with a single dose of drug.
- The drug concentration in plasma as a statistical distribution curve

$$MRT = \frac{AUMC}{AUC}$$

Where, MRT = Mean residence time
AUMC = Area under the first - moment curve
AUC = Area under the zero - moment curve

- To calculate AUMC and AUC from the graphs, devided the curve into trapezoids, find the area of each trapezoids separately and add them together.



ADVANTAGES

- This mathematical treatment can be used for almost any drug or metabolite, provided that they follow - first order kinetics.
- Not required detailed description of drug disposition characteristics.
- Simple algebric equation, used for derivation of the pharmacokinetic parameters.

DISADVANTAGES

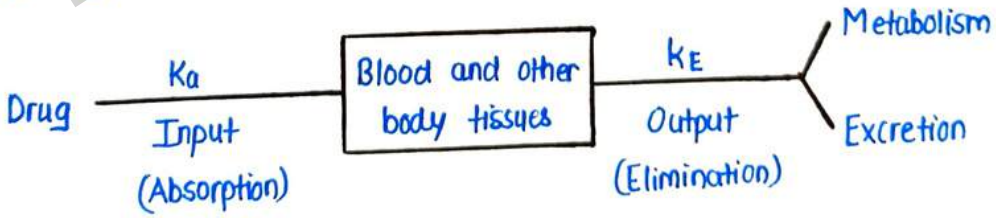
- Provides limited information regarding the plasma drug concentration time profile.
- This method does not used for non-linear kinetics.

One Compartment Open Model

- In this compartment, we assumed whole body in an one compartment.
- The one compartment open model is simplest model, also known as Instantaneous Distribution Model.
- One compartment open model operates on some following assumptions:

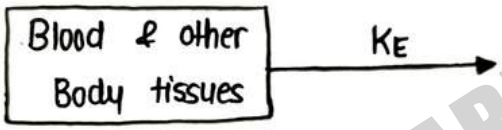
i) Whole body assumes as single compartment without barriers to drug movement.
ii) The drugs quickly spread throughout the body, maintaining instant distribution equilibrium between plasma and other body fluids.
iii) Drugs move dynamically, in (absorption) and out (elimination) of this compartment.
iv) Elimination of drugs are at constant rate.
v) Rate of absorption/input greater than rate of output/elimination.
vi) Plasma shows drug levels in all body tissues, after it they might not be same.

- They generally used to describe plasma levels following administration of single dose of drug.



One Compartment Model For IV Bolus

- The one compartment Open model for IV (intravenous) Bolus injection is a pharmacokinetic model where the entire body is considered as a single, uniform compartment and the drug is administered instantly into the systemic circulation (via IV bolus).
- The drug then gets eliminated from the body following first-order kinetics, through an open system.



Key Features

- **One Compartment :** Drug distributes instantly & uniformly.
- **Open Model :** Drug is eliminated (mostly via liver or kidneys).
- **IV Bolus :** Entire dose is given at once, no absorption phase.
- **First Order Elimination :** Rate of elimination is proportional to drug concentration.

- The rate of drug presentation in body is expressed as:

$$\frac{dx}{dt} = \text{Rate in (availability)} - \text{Rate out (elimination)}$$

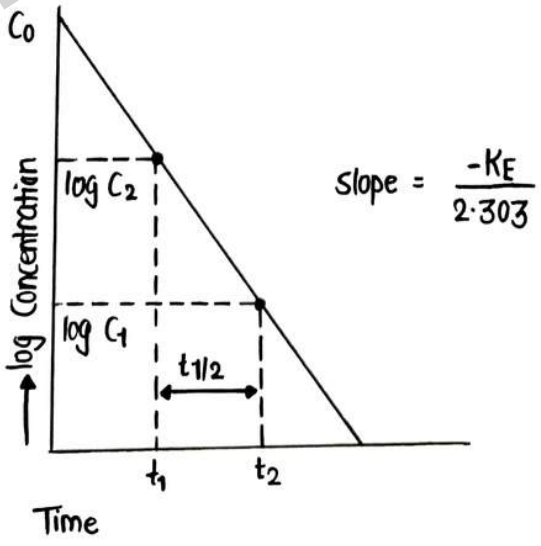
- Now since in IV Bolus there is no absorption phase, Hence we can write the equation as:

$$\frac{dx}{dt} = - \text{Rate in (availability)}$$

$$\frac{dx}{dt} = - K_{EX}$$

Here,

- K = First order elimination rate constant
- X = Amount of drug in body at any time t.
- Negative sign indicates that drug is being last from the body.



Estimation of Pharmacokinetic Parameters

- Elimination rate constant
- Elimination Half-life
- Clearance

① Elimination Rate Constant

From General equation, we have

$$\frac{dx}{dt} = -K_E X$$

On, Integrating above equation we get

$$x = x_0 \cdot e^{-kt}$$

Taking $\log_{10}$ on both side, we get

$$\log x = \log x_0 - \frac{K_E t}{2.303}$$

Changing the equation into concentration form, it can be written as (because $x = Vd \cdot C$)

$$\boxed{\log C = \log x_0 - \frac{K_E t}{2.303}}$$

Here, C = Concentration of drug in the body at time t
K_E = Elimination rate constant

② Elimination Half-life

- It is defined as time taken for the amount of drug in the body as well as plasma concentration, to decrease to 50 % of its initial value due to elimination.
- It is related to elimination rate constant.

$$t_{1/2} = \frac{0.693}{K_E}$$

Here,

$t_{1/2}$ = Half life

K_E = Elimination Rate Constant

③ Clearance

- Clearance is the volume of plasma from which the drug is completely removed per unit time.
- It is an important parameter that relates plasma drug concentration with rate of drug elimination from below equation

$$\text{Clearance} = \frac{\text{Rate of Elimination}}{\text{Plasma drug concentration}}$$

$$Cl = \frac{dx/dt}{C}$$

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