

# PHARMACOKINETICS

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# Introduction

- **Pharmacokinetics**
- Pharmacokinetics is the field of science that deals with the **kinetics** of drug absorption, distribution and elimination
- After oral administration:
  - The drug is **absorbed (A)** from the site of administration to the systemic circulation
  - The drug is **distributed (D)** to all parts of the body
  - And the drug is eliminated from the body by **metabolism and/or excretion (ME)**

- Each process is associated with one or more parameters that are dependent on the drug, drug product and the patient
- These are the pharmacokinetic parameters and they determine the rate of the different processes

# The pharmacokinetic Applications

- The pharmacokinetic principles have many applications in biomedical sciences:
  - **Pharmacological testing**
  - The pharmacokinetic principles are used to assess the relationship between the drug concentration and pharmacological activities. This is important to determine how much and how often the drug should be given

- **Toxicological Testing**

- The pharmacological principles are used to assess tissue accumulation of drug and how it is related to tissue toxicity

- **Evaluation of Organ function**

- The pharmacokinetic principles are used to evaluate the function of eliminating organs. For example inulin is eliminated entirely by the kidney and the rate of inulin elimination can be used to assess the kidney function

- **Dosage regimen design**
  - The pharmacokinetic principles are used to design the dosing regimen (dose and dosing interval of a specific drug product) that can achieve the maximum therapeutic effect with minimal toxicity

## Rates and orders of reactions

- The **rate** of a chemical reaction or pharmacokinetic process is the **velocity** with which it occurs
  - The **order** of a reaction is the way in which the **concentration** of a drug or reactant in a chemical reaction **affects** the **rate**
- A. Zero-order reaction.** The drug concentration changes with respect to time at a constant rate, according to the following equation:



$$\frac{dc}{dt} = -k_0$$

Integration of this equation yields the linear (straight-line) equation:

$$C = C_0 - k_0 t$$

[..zero order.jpeg](#)

## **B. First-order reaction**

- The change in drug concentration with respect to time equals the product of the rate constant and the concentration of drug remaining, according to the following equation:

$$\frac{dC}{dt} = -k_1 C$$

- Integration and subsequent transformation of this equation yields the following mathematically equivalent equations:

$$C = C_0 e^{-k_1 t}$$

[..\first order.jpeg](#)

$$\ln C = \ln C_0 - k_1 t$$

$$\log C = \log C_0 - \frac{k_1 t}{2.303}$$

- A plot of  $\log C$  vs Time yield straight line and slope of the line will give  $k_1$
- Half life can be calculated by:

$$t_{1/2} = 0.693/k_1$$

# Pharmacokinetic Models

- Pharmacokinetics models provide concise means of expressing **mathematically** or quantitatively, the **time course of drug(s)** throughout the body and **compute meaningful** pharmacokinetics parameters
- **Types of Pharmacokinetics Models**
  1. Compartment Model
  2. Non – compartment Analysis
  3. Physiological Models

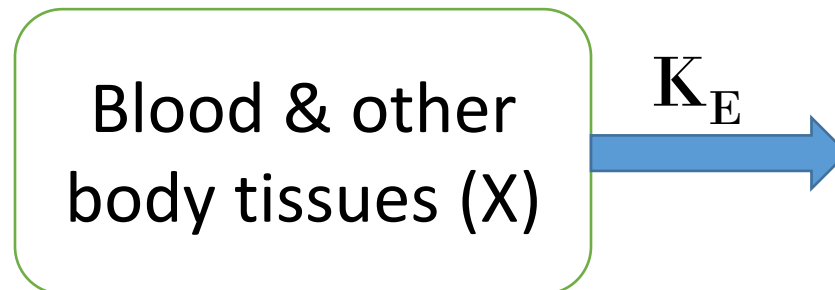
- A **model** is a mathematic description of a biologic system and is used to express quantitative relationships
- A **compartment** is a group of tissues with similar blood flow and drug affinity. A compartment is not a real physiologic or anatomic region (**Kinetically homogeneous**)

## Compartmental Models

- Mammillary model – Satellite like connection
- Caternary model – train compartment like connection
- Central compartment – Rapid distributed & highly perfused
- Peripheral compartment – tissues and muscles

# One compartment open Model - IV Bolus administration

- The entire drug dose enters the body **instantaneously**, and the rate of absorption is therefore assumed to be negligible in calculations
- The entire **body** acts as a **single** compartment, and the drug **rapidly equilibrates** with all of the **tissues** in the body
- Elimination follow **first** order kinetics



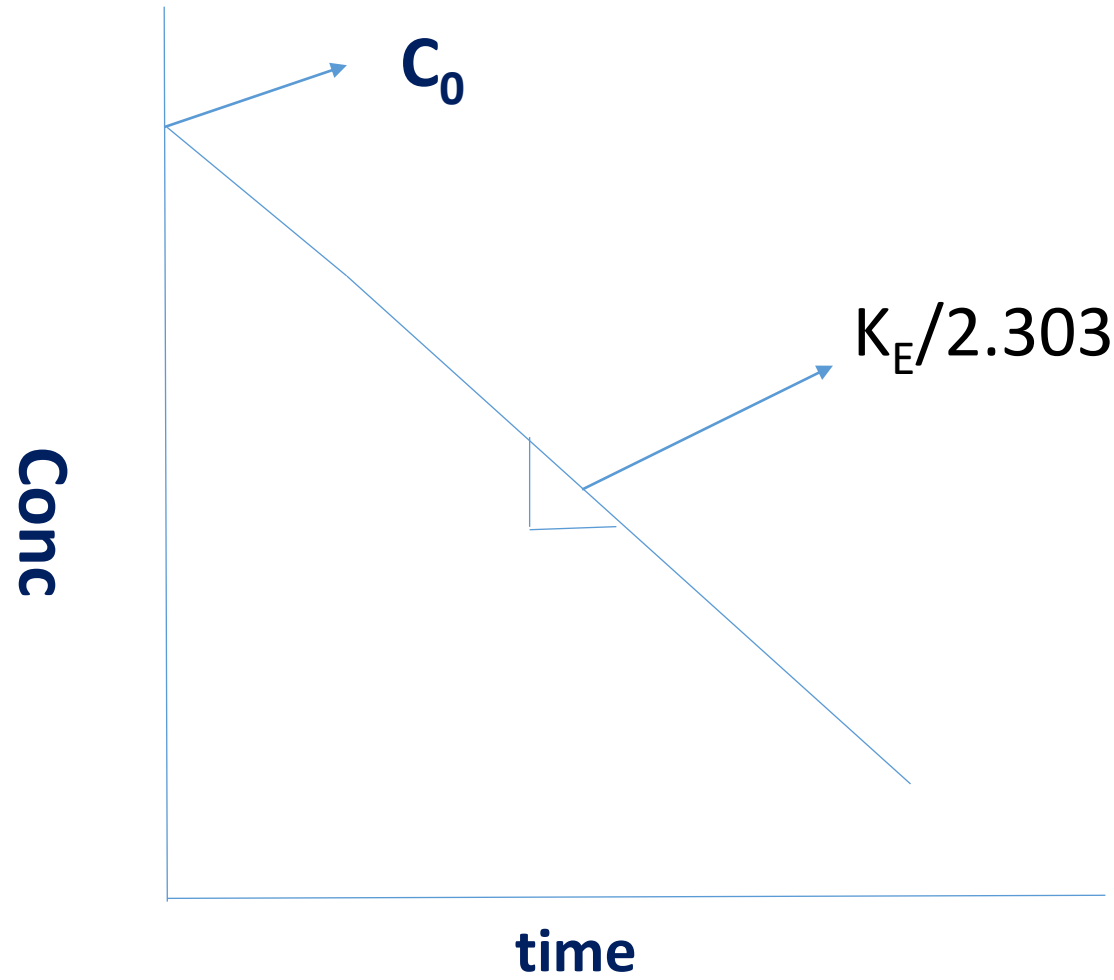


## Mathematical treatment

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

$$\ln C = \ln C_0 - K_E t$$

$$\log C = \log C_0 - \frac{K_E t}{2.303}$$



## Important Formulae

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

$$V_d = \frac{x_0}{c_0}$$

$$Cl_T = K_E V_d$$

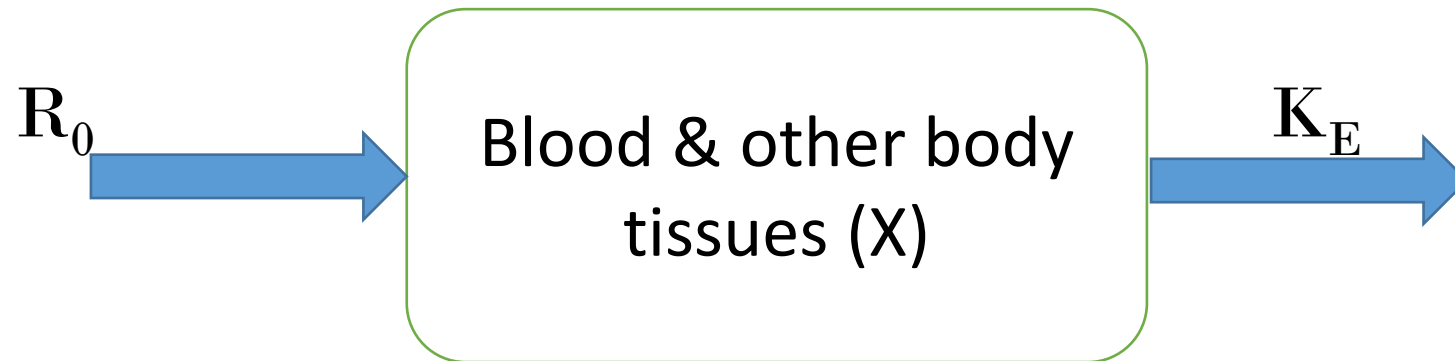
$$AUC = \frac{C_0}{k_E}$$

# Urinary Excretion data

1. Rate of excretion method
2. Sigma-Minus method

# One compartment open Model - IV Infusion

- Drug is introduced into body at constant rate over a period of time
- $R_0$  is assumed as constant (zero order) rate of infusion
- Elimination is assumed to be following First order kinetics



- Intravenous infusion is an example of zero-order absorption and first-order elimination
- If the intravenous infusion is discontinued, the plasma drug concentration declines by a first order process
- As the drug is infused, the plasma drug concentration increases to a plateau, or **steady-state concentration** ( $C_{ss}$ )

$$C_{ss} = \frac{R_0}{K_E V_d}$$

- Under steady-state conditions, the fraction of drug absorbed equals the fraction of drug eliminated from the body

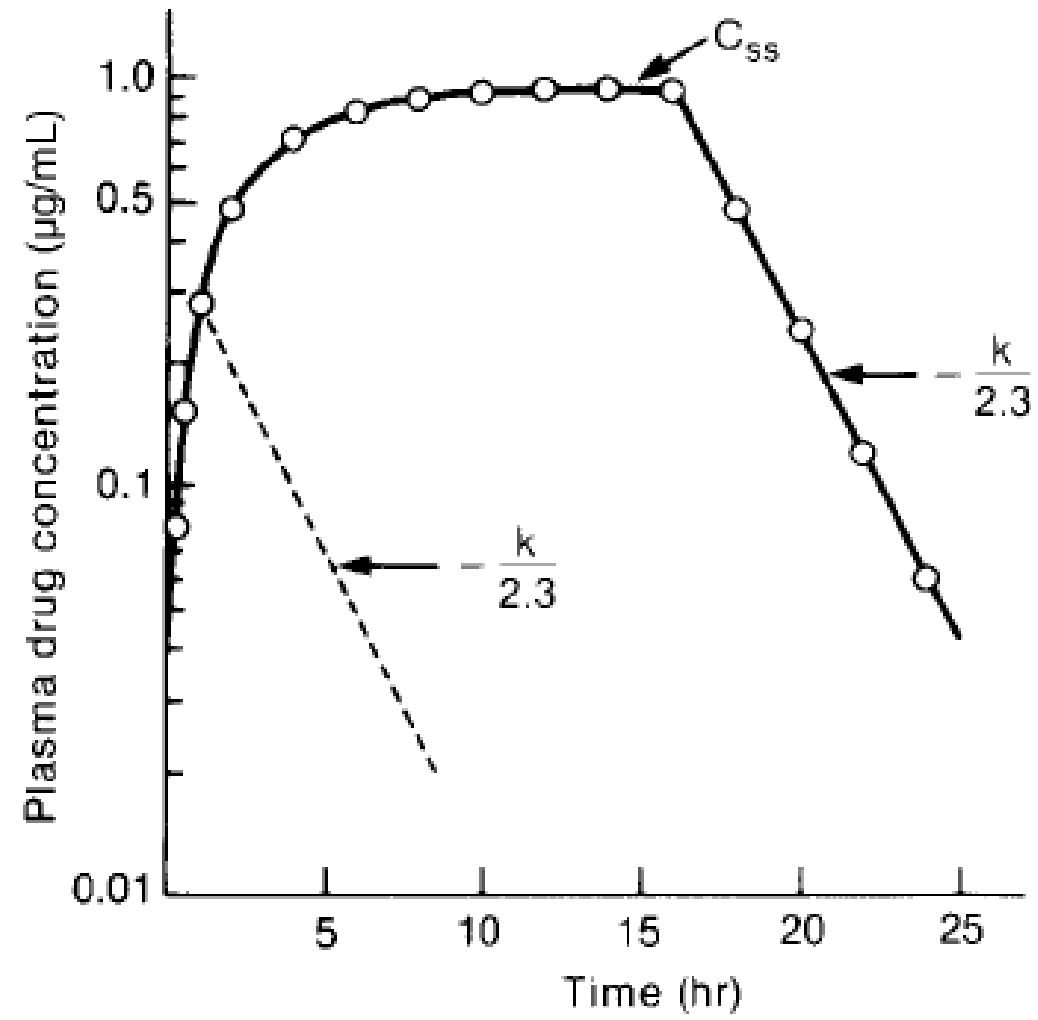
## Mathematical Treatment

$$\frac{dx}{dt} = R_0 - k_E X$$

$$C = \frac{R_0}{K_E V_d} [1 - e^{-K_E t}]$$

$$C = \frac{R_0}{CL_T} [1 - e^{-K_E t}]$$

$$C = C_{ss} [1 - e^{-K_E t}]$$





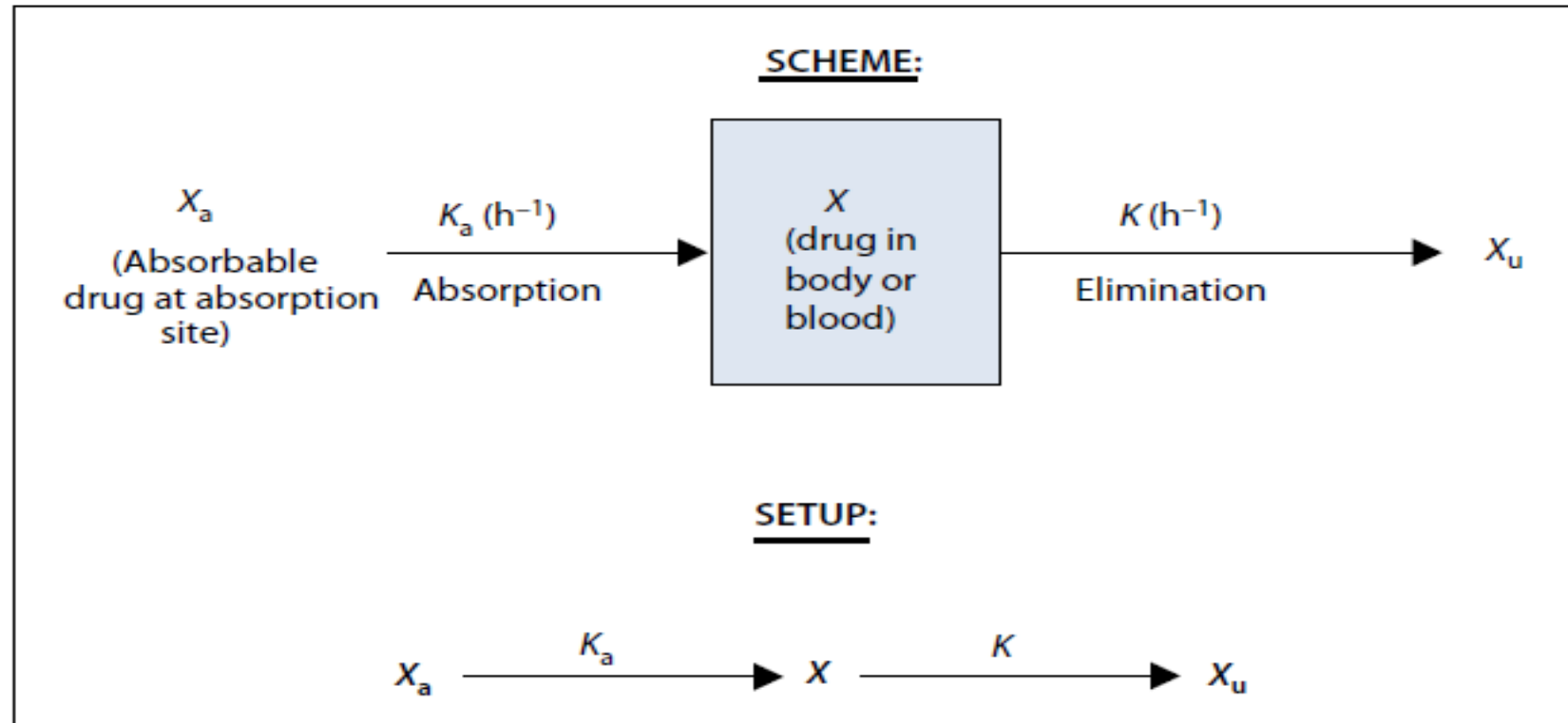
- A **loading dose** ( $D_L$ ) is given as an initial intravenous bolus dose to produce the  $C_{ss}$  as rapidly as possible
- The intravenous infusion is started at the same time as the  $D_L$
- The time to reach  $C_{ss}$  depends on the **elimination half-life** of the drug
- Reaching **90%, 95%, or 99%** of the  $C_{ss}$  **without** a  $D_L$  takes **3.32, 4.32, or 6.65** half-lives, respectively
- Loading dose ( $D_L$ ) can be estimated by:

$$D_L = C_{ss} \cdot V_d$$

$$D_L = \frac{R_0}{K_E}$$

# One compartment open Model - EV administration

- The drug is generally absorbed by first-order kinetics
- Elimination of the drug also follows the principles of first-order kinetics
- In normal cases Absorption rate constant  $\gg$  Elimination rate constant
- If Elimination rate constant  $\gg$  Absorption rate constant, then the drugs are said to be following **Flip-Flop** model



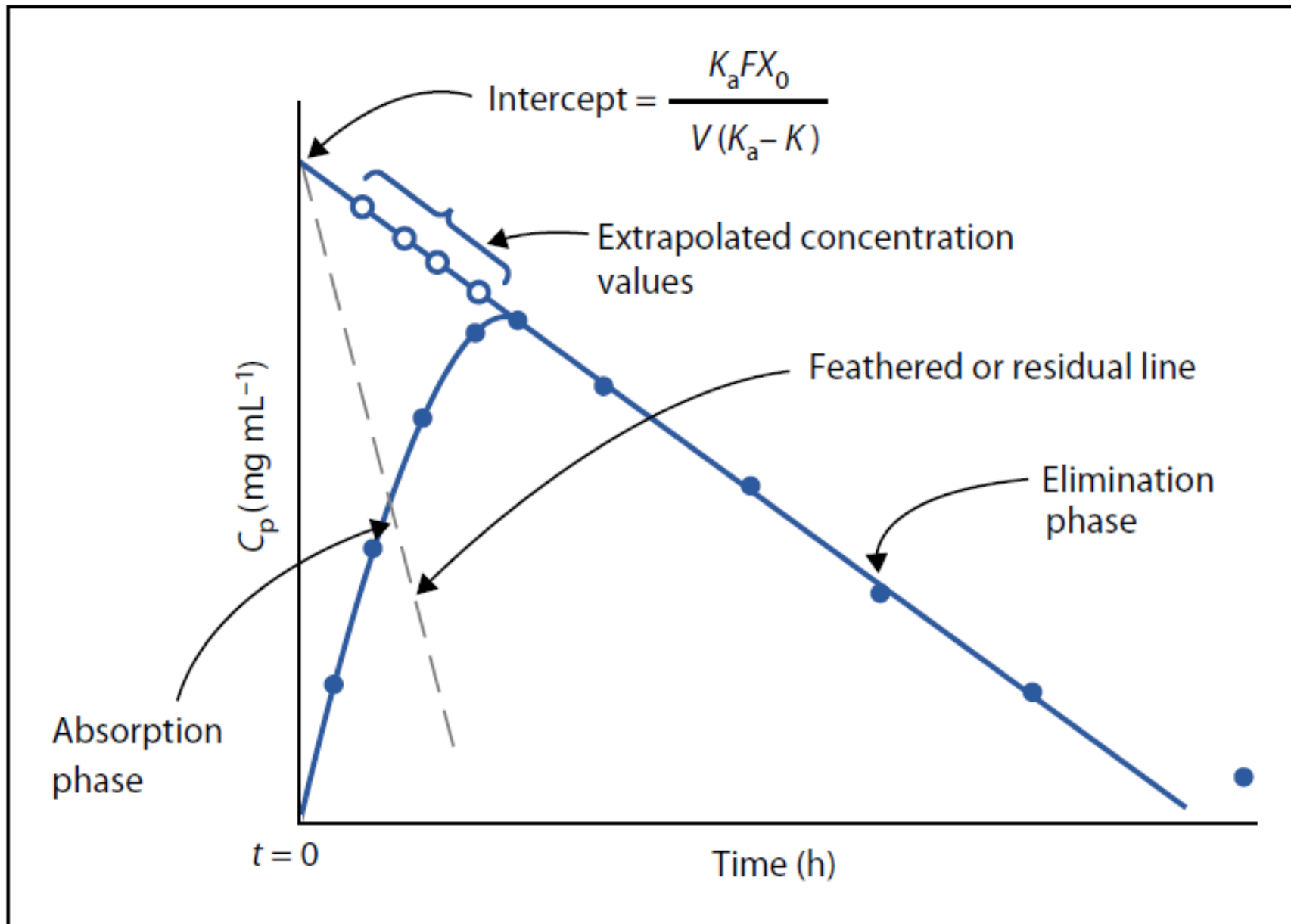
$$C_P = \frac{FD_0 k_A}{V_D(k_A - k)} (e^{-kt} - e^{-K_A t})$$

- Time for peak plasma concentration ( $t_{\max}$ ) can be estimated by:

$$t_{\max} = \frac{2.3 \log (k_A/k)}{k_A - k}$$

- Area under the curve can be estimated by:

$$[\text{AUC}]_0^\infty = \int_0^\infty C_P dt = \frac{FD_0}{V_D k}$$



# Multiple dose administration

- Administered in chronic therapy
- After 7 – 8, doses at half life time period administration, the concentration reaches steady state
- The average steady state concentration can be calculated by:

$$C_{Av}^{\infty} = \frac{FD_0}{kV_D\tau}$$

# Non compartmental Analysis

- It is also called as Model independent method
- Non-compartmental models describe the pharmacokinetics of drug disposition using **time and concentration** parameters
- Can be applied to any compartment model provided the drugs or metabolites follow linear kinetics

- This approach based on **statistical moments theory**, involves the collection of experimental data following a single dose of drug
- If one considers the time course of drug concentration in plasma as a statistical distribution curve, then

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



- **Mean residence time (MRT)** is the average time for the drug molecules to reside in the body
- MRT is also known as the *mean transit time* and *mean sojourn time*

$$\text{MRT} = \frac{\text{total residence time for all drug molecules in the body}}{\text{total number of drug molecules}}$$

$$\text{MRT}_{\text{iv}} = \frac{1}{K_E}$$

- **Mean absorption time (MAT)** is the difference between MRT and  $MRT_{IV}$  after an extravascular route is used

$$MAT = MRT_{ev} - MRT_{iv}$$

- **Clearance** is the volume of plasma cleared of drug per unit time and may be calculated without consideration of the compartment model

$$Cl = \frac{FD_0}{AUC_{0-\infty}}$$

# Nonlinear Pharmacokinetics

- It is also known as **capacity-limited, dose-dependent, or saturation** pharmacokinetics
- At lower dose, drug shows first order kinetics but at higher dose, it shows zero order due to saturation, so it is also known as **Mixed Order Kinetics**
- Nonlinear pharmacokinetics **do not follow first-order kinetics** as the dose increases
- Nonlinear pharmacokinetics may result from the **saturation** of an **enzyme-** or **carrier-**mediated system

## Characteristics of nonlinear pharmacokinetics

- The AUC is **not proportional** to the dose
- The amount of drug excreted in the urine is not proportional to the dose
- The elimination half-life may increase at high doses
- The ratio of metabolites formed changes with increased dose

## Tests to detect non-linearity

- Determine  $C_{ss}$  (steady state plasma concentration) at different doses and if  $C_{ss}$  is directly proportional to the doses then it is linear pharmacokinetics else it is nonlinear pharmacokinetics
- Determine some of important pharmacokinetic parameters such as fraction bioavailable  $F$ ,  $t_{1/2}$ , total clearance at different doses. Any change in parameters which are usually constant, means non-linear pharmacokinetics

# Causes of non-linearity

## 1. Drug Absorption

- When the absorption is **solubility or dissolution rate limited** eg., Griseofulvin
- When absorption involve **Carrier mediated transport**: saturation at higher dose result in nonlinearity eg., Ribofalvin, Ascorbic acid
- When **pre systemic** gut wall or hepatic metabolism attains saturation eg., Propranolol
- Changes in gastric blood flow and gastric emptying eg., various diseases, time of administration (**Chronopharmacokinetics**)

## 2. Distribution

- Saturation of plasma protein binding e.g., in case of Phenylbutazone
- Saturation of tissue binding sites e.g., in case of Imipramine
  - a. In both the cases, **increase in free plasma drug concentration and increase in  $V_d$  in the former case** where as **decrease in  $V_d$  in latter case**
  - b. Clearance of a drug with high ER is greatly increases due to saturation of binding site

### 3. Drug Metabolism

- **Capacity limited metabolism** due to the enzyme or cofactor saturation. Example include Phenytoin, theophylline, alcohol.  
Increase  $C_{ss}$ , decrease CL
- **Enzyme induction** example in case of carbamazepine where decrease in plasma concentration is observed on repetitive administration over a period of time. Increase CL, decrease  $C_{ss}$
- Hepatotoxicity, change in hepatic blood flow and inhibitory effects of metabolites on enzymes



## 4. Drug Excretion

- **Active tubular secretion** as in penicillin. Decreases renal clearance
- **Active tubular reabsorption** as in water soluble vitamins and glucose. Increases renal clearance
- Forced diuresis, change in urine pH, nephrotoxicity

## Michaelis–Menten kinetics

- It is used to describe nonlinear pharmacokinetics
- The **Michaelis–Menten equation** describes the rate of change (velocity) of plasma drug concentration:

$$\frac{dc}{dt} = -\frac{V_{max}C}{k_m + C}$$

**Where**  $V_{max}$  is the maximum velocity of the reaction

$C$  is the substrate or plasma drug concentration

$K_m$  is the Michaelis constant equal to the  $C$  at  $0.5 V_{max}$

- At low  $C$  values, where  $C \ll K_m$ , this equation reduces to a first-order rate equation because both  $K_m$  and  $V_{\max}$  are constants

$$\frac{dc}{dt} = -\frac{V_{\max}C}{k_m + c} = k^1 C$$

- At high  $C$  values, where  $C \gg K_m$ , this equation reduces to a zero-order rate equation

$$\frac{dc}{dt} = -V_{max}$$

- Show **zero-order** elimination rates at **high** drug concentrations, **fractional-order** elimination rates at **intermediate** drug concentrations, and **first-order** elimination rates at **low** drug concentrations

# Time to recap

1. The earliest evidence that a drug is stored in tissue is
  - A. An increase in plasma protein binding
  - B. A large apparent volume of distribution ( $V_D$ )
  - C. A decrease in the rate of formation of metabolites by the liver
  - D. An increase in the number of side effects produced by the drug

Ans is **B**

2. The intensity of the pharmacologic action of a drug is most dependent on the
- A. Concentration of the drug at the receptor site
  - B. Elimination half-life ( $t^{1/2}$ ) of the drug
  - C. Onset time of the drug after oral administration
  - D. Minimum toxic concentration (MTC) of the drug in plasma

Ans is **A**

3. Drugs that show nonlinear pharmacokinetics have which property?
- A. A constant ratio of drug metabolites is formed as the administered dose increases
  - B. The elimination half-life ( $t_{1/2}$ ) increases as the administered dose increases
  - C. The area under the plasma drug concentration versus time curve (AUC) increases in direct proportion to an increase in the administered dose
  - D. Both low and high doses follow first-order elimination kinetics

Ans is **B**

4. Creatinine clearance is used as a measurement of
- A. Renal excretion rate
  - B. Glomerular filtration rate (GFR)
  - C. Active renal secretion
  - D. Passive renal absorption

Ans is **B**



5. The e loading dose ( $D_L$ ) of a drug is usually based on the
- A. Total body clearance ( $Cl_T$ ) of the drug
  - B. Percentage of drug bound to plasma proteins
  - C. Fraction of drug excreted unchanged in the urine
  - D. Apparent volume of distribution ( $V_D$ ) and desired drug concentration in plasma

Ans is **D**

6. Creatinine clearance is used as a measurement of
- A. Renal excretion rate
  - B. Glomerular filtration rate (GFR)
  - C. Active renal secretion
  - D. Passive renal absorption

Ans is **B**

7. Drugs that show nonlinear pharmacokinetics have which property?
- A. A constant ratio of drug metabolites is formed as the administered dose increases
  - B. The elimination half-life ( $t_{1/2}$ ) increases as the administered dose increases
  - C. The area under the plasma drug concentration versus time curve (AUC) increases in direct proportion to an increase in the administered dose
  - D. Both low and high doses follow first-order elimination kinetics

Ans is **B**

8. The biological half-life of procaine in a patient was 35 min and its  $V_d$  was estimated to be 60 litres. The total clearance rate of procaine is

- A. 1.88 litres/min
- B. 0.115 litres/min
- C. 11.5 litres/min
- D. 5.57 litres/min

Ans is **A**

9. Compartment modelling is explained by assuming
- A. Rate of drug presentation is first order
  - B. Drug disposition is first order
  - C. Rate of drug absorption is constant
  - D. Both (a) and (b)

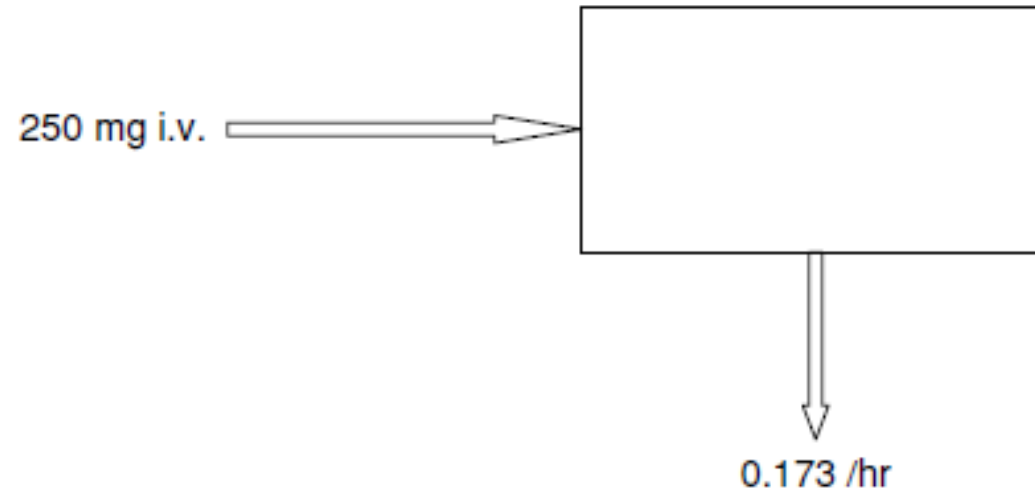
Ans is **B**

10. In Michaelis–Menten equation when  $K_m = C$

- A. The rate of process is equal to half of maximum rate
- B. Equation becomes identical to first order elimination of drug
- C. Indicates zero-order process
- D. The rate process occurs at a constant rate

Ans is **A**

11. In a pharmacokinetic model depicted in the following scheme, what is the half-life of the drug if the apparent volume of distribution of the drug is 25 L?



(A) 1.7 hr

(C) 4 hr

(B) 2 hr

(D) 3 hr

Ans is **C**

12. What will be the maintenance dose of a sustained release 12 hour formulation of drug X exhibiting one compartment kinetics with a half-life of 6 hours, plasma concentration (steady state) 6 mg/ml, volume of distribution 30 L, and an oral bioavailability of 80%?

- A. 249.48 mg
- B. 225.48 mg
- C. 311.85 mg
- D. 281.85 mg

Ans is **C**



13. What will be the approximate  $T_{\max}$  of a drug exhibiting  $K_a$  of 2  $\text{hr}^{-1}$  and  $K$  of 0.2  $\text{hr}^{-1}$ ?

A. 1.2 hr

B. 2.4 hr

C. 4.8 hr

D. 2.0 hr

Ans is **A**

14. It is required to maintain a therapeutic concentration of 10 microgram/mL for 12 hours of a drug having half life of 1.386 h and  $V_d$  of 5 L. The dose required in a sustained release product will be

- A. 600 mg
- B. 300 mg
- C. 30 mg
- D. 60 mg

Ans is **A**

15. A drug (200 mg dose) administered in tablet form and as intravenous injection (50 mg dose) showed AUC of 100 and 200 microgram h/mL, respectively. The absolute availability of the drug through oral administration is

- A. 125%
- B. 250%
- C. 12.5%
- D. 1.25%

Ans is **C**

16. The volume of distribution of a drug administered at a dose of 300 mg and exhibiting 30 microgram/mL instantaneous concentration in plasma shall be

A. 10 L

B. 100 L

C. 1.0 L

D. 0.10 L

Ans is **A**

17. What will be the dose required to maintain therapeutic concentration of 20 microgram/ml for 24 h of a drug exhibiting total clearance of 2 L/h?

- A. 96 mg
- B. 480 mg
- C. 960 mg
- D. 48 mg

Ans is **C**

18. Which of the following parameters from plasma concentration time profile study gives indication of the rate of drug absorption?

A.  $C_{\max}$

B.  $T_{\max}$

C. AUC

D.  $t_{1/2}$

Ans is **B**