BIOPHARMACEUTICS

UNIT 4 NOTES

MULTI COMPARTMENT MODEL

- TWO COMPARTMENT OPEN MODEL
- CALCULATION OF IV BOLUS
- CALCULATION OF LOADING & MAINTAINCE DOSE

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Two Compartment Open Model: IV Bolus

- Two compartment open model for IV bolus administration is a pharmacokinetic model used to describe how a drug distributes and eliminated from the body after a single intravenous (IV) bolus route.
- It divides the body into two compartment:

① Central Compartment
② Peripheral Compartment

① Central Compartment

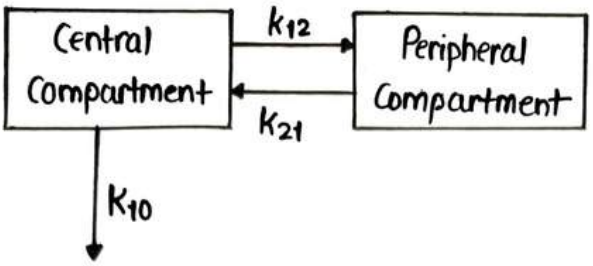
- Represents blood and highly perfused organs (heart, liver, kidneys).
- Drug is administered directly into this compartment.

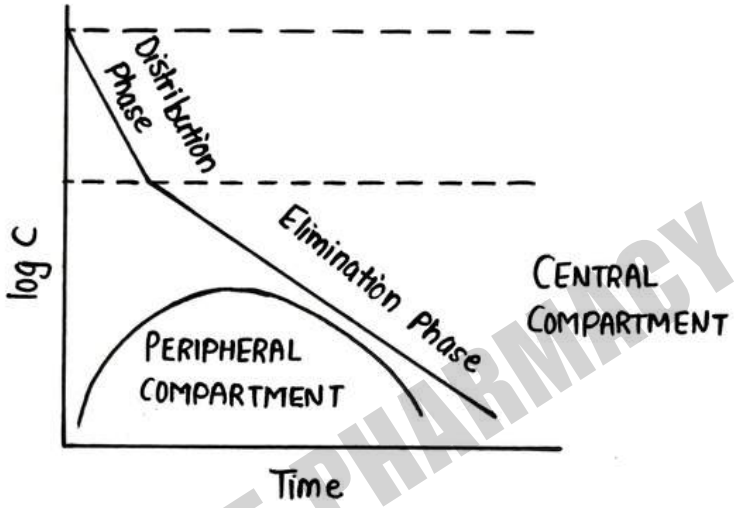
② Peripheral Compartments

- Represents less perfused tissues (e.g., muscle, fat).
- Drug distributes between the central and peripheral compartments.

Assumptions

- The drug is rapidly injected as a bolus into the central compartment.
- Drug elimination occurs only from the central compartment.
- Drug moves b/w compartments via first-order kinetics.





① Now rate of change in drug concentration is Central Compartment is given by :

$$\frac{dC_c}{dt} = K_{21} C_p - K_{12} C_c - K_{10} C_c \quad \text{---- ①}$$

Here, C_c = drug concentration in Central Compartment
C_p = drug concentration is in Peripheral Compartment
K_{12} = First order rate constant for rate of drug distribution from central to peripheral compartment
K_{21} = First order rate constant for rate of drug distribution from peripheral to central compartment
K_{10} = First order elimination rate constant.

② Similiarly rate of change of drug concentration in peripheral compartment :

$$\boxed{\frac{dC_P}{dt} = k_{12} C_C - k_{21} C_P} \quad \text{----} ②$$

Now we know $x = Vd \cdot C \Rightarrow C = \frac{x}{Vd}$

Substituting value of C in equation ① & ②, we get :

$$\frac{dC_C}{dt} = \frac{k_{21} X_P}{V_P} - \frac{k_{12} X_C}{V_C} - \frac{k_{10} X_C}{V_C} \quad \text{----} ③$$

$$\frac{dC_P}{dt} = \frac{k_{12} X_C}{V_C} - \frac{k_{21} X_P}{V_P} \quad \text{----} ④$$

Here, X_C & X_P = Amount of drug in Central & Peripheral compartment respectively

V_C & V_P = Apparent volumes of central & Peripheral compartment respectively

③ Integration of equations ③ & ④ yields :

$$C_C = \frac{X_0}{V_C}\left[\left(\frac{k_{21} - \alpha}{\beta - \alpha}\right) e^{-\alpha t} + \left[\frac{k_{21} - \beta}{\alpha - \beta}\right] e^{-\beta t}\right] \quad \text{---} ⑤$$

$$C_P = \frac{X_0}{V_P}\left[\left(\frac{k_{12}}{\beta - \alpha}\right) e^{-\alpha t} + \left(\frac{k_{21}}{\alpha - \beta}\right) e^{-\beta t}\right] \quad \text{----} ⑥$$

Where, X_0 = Dose given intravenously

t = Time after administration of dose, and

α and β = Hybrid first-order rate constants for the distribution phase and elimination phase respectively.

- α and β solely depend on k_{12}, k_{21} and k_{10}.
- Equation ⑤ and ⑥ describe the concentration of drug in central and peripheral compartments at any given time 't' respectively.

④ The mathematical relationships of α and β to the rate constants (k_{12}, k_{21} and k_{10}) are given by :

$$\alpha + \beta = k_{12} + k_{21} + k_{10}$$

$$\alpha\beta = k_{21}k_{10}$$

DOSAGE REGIMEN

- A dosage regimen refers to the systematic plan for administrating a drug in terms of:
  - Dose (how much)
  - Route (how its given)
  - Duration (how long)

- It ensures that the drug is administered in such a way that therapeutic levels are maintained in the body without causing toxicity.

COMPONENTS OF DOSAGE REGIMEN

① Dose : The amount of drug administered at a single time (e.g. 500 mg.)

② Dosing Interval (τ) : The time b/w two consecutive doses. (e.g., every 8 hours).

③ Frequency of administration : How many times a day the drug is administered (e.g., twice daily).

④ Duration of therapy : The total time the drug is administered (e.g., for 7 days).

⑤ Routes of Administration : How the drug is introduced into the body (e.g., oral, IV, IM)

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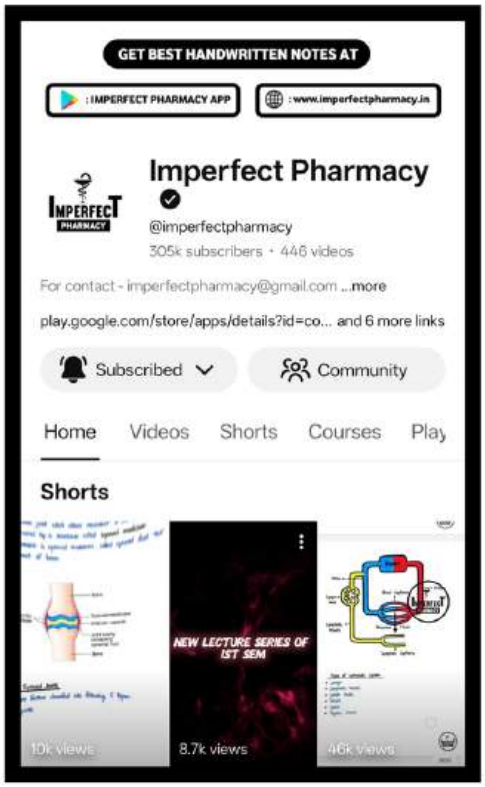

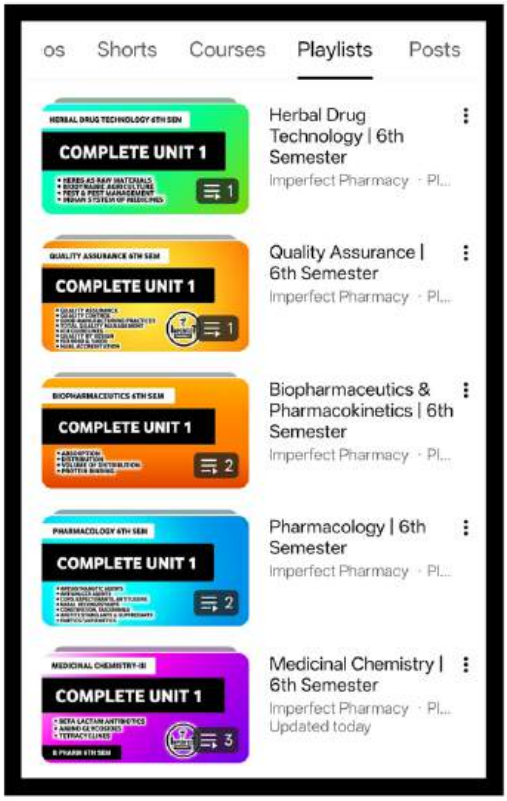

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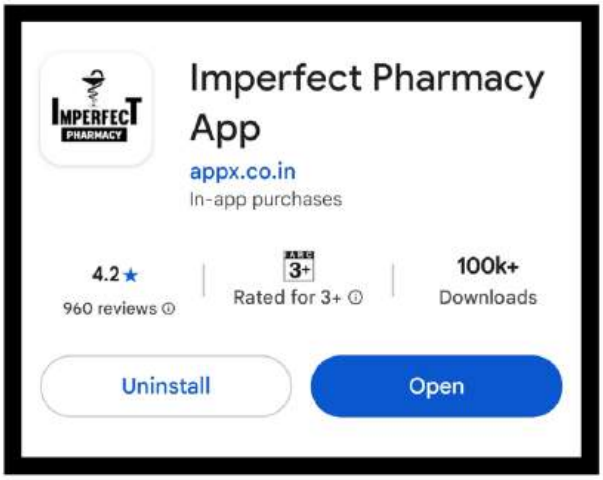
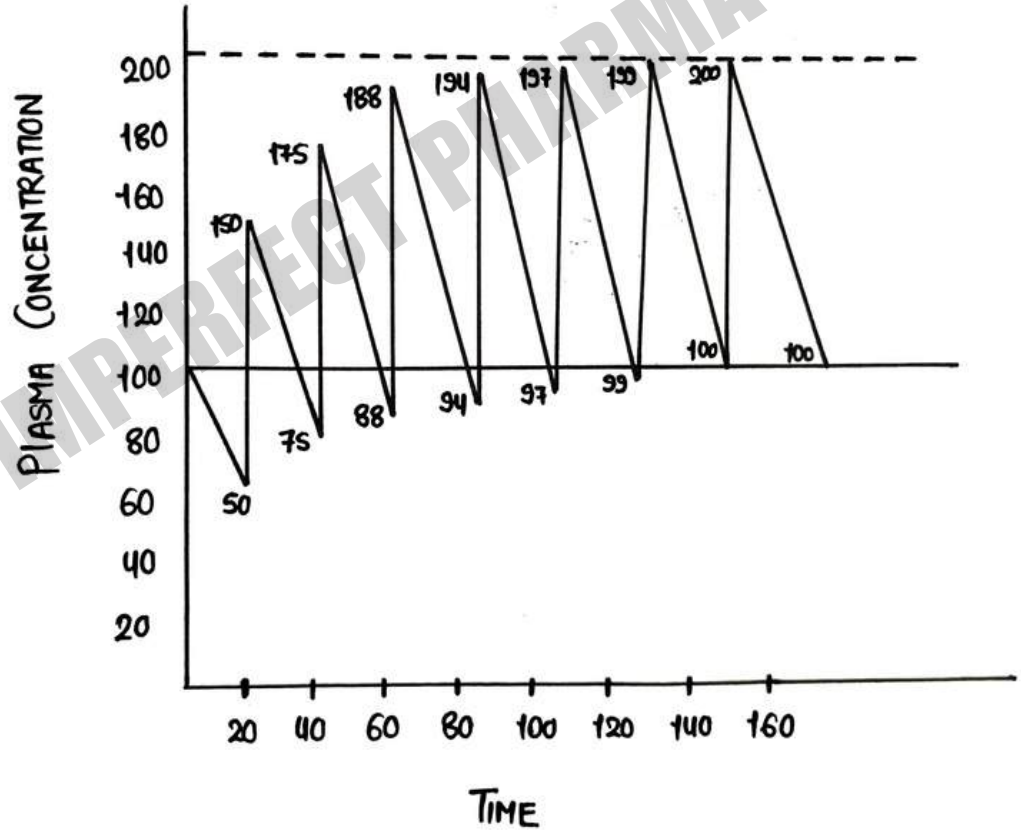


Objectives Of An Ideal Dosage Regimen

- Achieve and maintain steady - state plasma concentration (Css) within the therapeutic window.
- Avoid sub - therapeutic levels (ineffective) and toxic levels (dangerous).
- Ensure patients compliance (easy to follow).

STEADY STATE DRUG LEVELS

- If fixed dose of drugs is administered after regular interval, its plasma concentration starts increasing, However, as plasma concentration rises, rate of elimination also start increasing.
- When rate of administration becomes equal to rate of elimination, plasma concentration stabilizes and this is called **Steady state**.
- Typically reached after 4 to 5 half life of the drug.
- Important for maintaining therapeutic effect without toxicity.



CLINICAL SIGNFICANCE

- Used to determine the correct dosing regimen.
- Monitoring steady state levels is essential for drugs with narrow therapeutic windows (eg. digoxin, lithium)

LOADING DOSE

Loading dose is an initial higher dose of a drug given at the beginning of treatment to rapidly achieve a therapeutic concentration in the bloodstream.

FORMULA

$$\text{Loading Dose (LD)} = \frac{Css \times Va}{F}$$

Where, Css = desired steady-state plasma concentration
Va = Volume of distribution
F = Bioavailability (fraction of drug absorbed into systemic circulation)

PURPOSE

- Reduces the time required to reach therapeutic levels, especially important in emergencies.
- Quickly initiates drug action where they delay could be harmful (e.g., in siezures, arrhythmias or infections).

MAINTENANCE DOSE

A maintenance dose is the amount of drug administered at regular intervals to maintain a steady therapeutic concentration in the bloodstream after reaching that level with or without a loading dose.

FORMULA

$$\text{Maintenance Dose (MD)} = \frac{C_{ss} \times CL \times \tau}{F}$$

Where, C_{ss} = Desired steady-state plasma concentration
CL = Clearance (volume of plasma cleared of the drug per unit time).
τ = Dosing interval (time b/w doses)
F = Bioavailability

CLINICAL IMPORTANCE

- The clearance (CL) of the drug is crucial; higher clearance requires higher maintainence doses.
- If a drug has low bioavailability ($F < 1$), a larger dose may be needed compared to IV administration.
- Maintains efficacy without toxicity.
- Critical for drugs with long treatment durations (eg., antihypertensives, antiepileptics).

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