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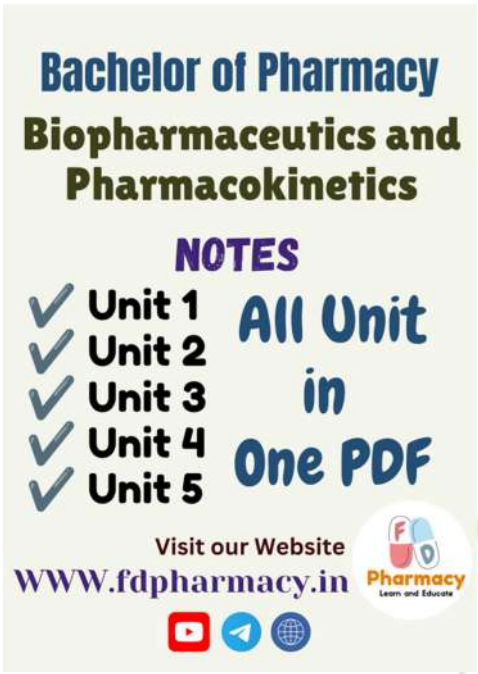
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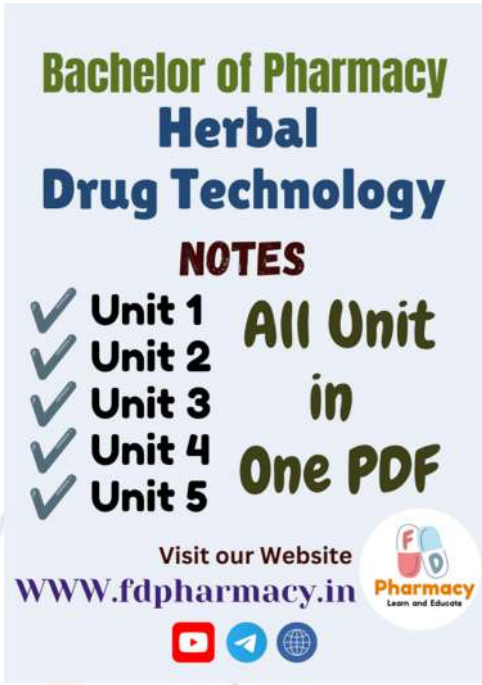
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BIOPHARMACEUTICS AND PHARMACOKINETICS

UNIT 4

TOPIC :

- **Multicompartment models :** Two compartment open model. IV bolus Kinetics of multiple dosing, steady state drug levels, calculation of loading and mainetnance doses and their significance in clinical settins.

Two Compartment Open Model : IV Bolus

The Two Compartment Open Model Is A Pharmacokinetic Model Used To Describe The Distribution And Elimination Of A Drug After A Single Intravenous (IV) Bolus Injection.

In this model, the body is divided into:

1. Central compartment
2. Peripheral compartment

Drug is injected directly into the bloodstream and distributes between both compartments.

Compartments of the Model

1. Central Compartment

Represents:

- Blood
- Plasma
- Heart
- Liver
- Kidneys
- Highly perfused organs

Characteristics:

- Drug enters directly into this compartment.
- Elimination occurs from this compartment.
- Distribution to tissues begins from here.

2. Peripheral Compartment

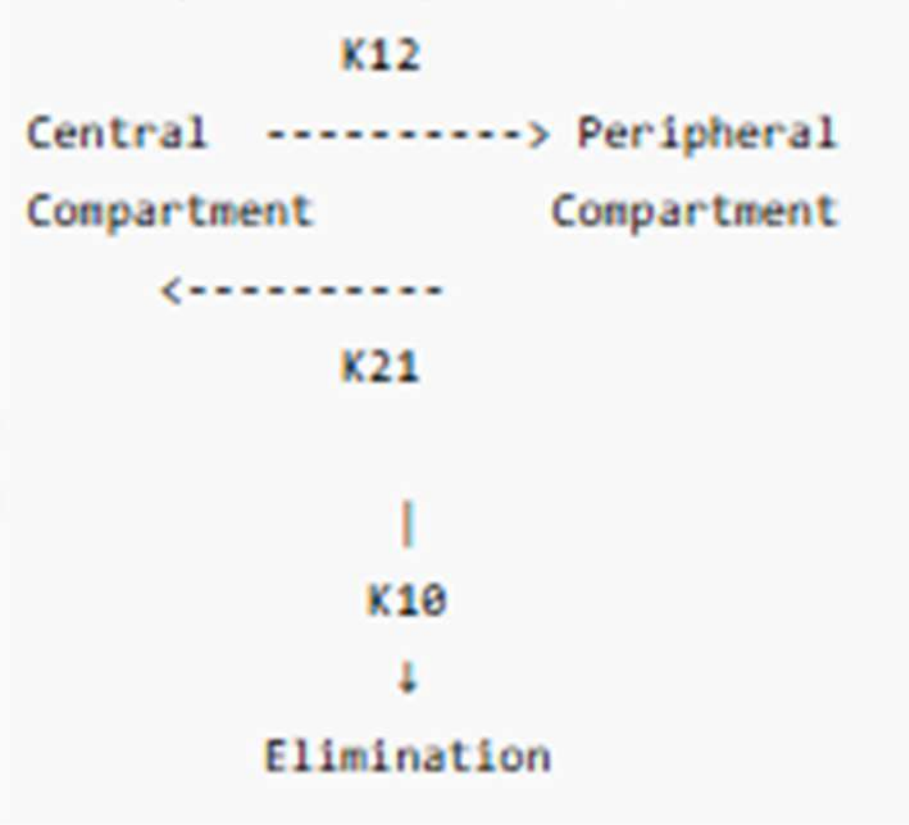
Represents:

- Muscle
- Fat
- Skin
- Less perfused tissues

Characteristics:

- Drug enters slowly from central compartment.
- No direct elimination occurs from this compartment.
- Drug can return back to central compartment.

Diagram of Two Compartment Model



Where:

- K12 = Rate constant for transfer from central to peripheral compartment
- K21 = Rate constant for transfer from peripheral to central compartment
- K10 = Elimination rate constant from central compartment

Rate of Change of Drug Concentration

In Central Compartment

The rate of change of drug concentration in the central compartment is:

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

Explanation

Where:

- C_c = Drug concentration in central compartment
- C_p = Drug concentration in peripheral compartment
- K_{12} = First-order transfer rate constant from central to peripheral compartment
- K_{21} = First-order transfer rate constant from peripheral to central compartment
- K_{10} = Elimination rate constant

Interpretation:

- Drug enters central compartment from peripheral compartment by $K_{21}C_p$
- Drug leaves central compartment by:
  - Distribution to tissues → $K_{12}C_c$
  - Elimination → $K_{10}C_c$

Rate of Change in Peripheral Compartment

The rate equation for peripheral compartment is:

$$\frac{dC_p}{dt} = K_{12}C_c - K_{21}C_p$$

Explanation

- Drug enters peripheral compartment from central compartment.
- Drug returns back to central compartment.

No elimination occurs directly from peripheral compartment.

Relationship Between Amount and Concentration

We know:

$$C = \frac{X}{V}$$

Where:

- C = Drug concentration
- X = Amount of drug
- V = Volume of distribution

Thus:

$$C_c = \frac{X_c}{V_c}$$

$$C_p = \frac{X_p}{V_p}$$

Where:

- X_c = Amount of drug in central compartment
- X_p = Amount of drug in peripheral compartment
- V_c = Apparent volume of central compartment
- V_p = Apparent volume of peripheral compartment

Equations in Terms of Amount of Drug

Substituting concentration equations into differential equations:

Central Compartment

$$\frac{dX_c}{dt} = K_{21}X_p\frac{V_c}{V_p} - K_{12}X_c - K_{10}X_c$$

Peripheral Compartment

$$\frac{dX_p}{dt} = K_{12}X_c\frac{V_p}{V_c} - K_{21}X_p$$

Plasma Drug Concentration Equation

After IV bolus administration, plasma concentration declines biexponentially:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

Where:

- C = Plasma drug concentration at time t
- A and B = Intercepts
- α = Distribution rate constant
- β = Elimination rate constant
- t = Time after dose administration

Meaning of α and β Phases

α (Alpha Phase)

Distribution phase:

- Rapid decline in plasma concentration
- Drug distributes from blood to tissues

β (Beta Phase)

Elimination phase:

- Slow decline in plasma concentration
- Drug eliminated from body

Hybrid Rate Constants

The hybrid constants α and β depend upon:

- K_{12}
- K_{21}
- K_{10}

Relationship:

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

Also:

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

Characteristics of Two Compartment Open Model

- Drug distributes rapidly first.
- Elimination occurs after distribution.
- Plasma concentration declines biexponentially.
- More realistic than one compartment model.

Applications

- Determination of dosage regimen
- Pharmacokinetic analysis
- Therapeutic drug monitoring
- Drug distribution studies
- Clinical pharmacokinetics

Dosage Regimen

A dosage regimen is the systematic schedule for administration of a drug to produce the desired therapeutic effect without causing toxicity.

It includes:

- Dose
- Frequency
- Dosing interval
- Route of administration
- Duration of therapy

The main purpose of dosage regimen is to maintain the plasma drug concentration within the therapeutic window.

Definition

A dosage regimen refers to the planned manner in which a drug is administered with respect to:

- How much drug is given
- How often it is given
- By which route it is given
- For how long it is given

Components of Dosage Regimen

1. Dose

The amount of drug administered at one time.

Example:

- 500 mg Paracetamol

Factors affecting dose:

- Age
- Body weight
- Severity of disease
- Renal function
- Hepatic function

2. Dosing Interval (τ)

The time interval between two consecutive doses.

Example:

- Every 6 hours
- Every 8 hours
- Once daily

Importance:

- Maintains therapeutic drug concentration
- Prevents accumulation and toxicity

3. Frequency of Administration

Number of times the drug is administered in one day.

Examples:

- Once daily (OD)
- Twice daily (BD)
- Three times daily (TDS)

Depends on:

- Half-life of drug
- Duration of action

4. Duration of Therapy

The total period for which the drug is administered.

Examples:

- Antibiotics for 5–7 days
- Antihypertensives for long-term use

Importance:

- Ensures complete treatment
- Prevents recurrence of disease

5. Route of Administration

The method by which the drug enters the body.

Examples:

- Oral
- Intravenous (IV)
- Intramuscular (IM)
- Subcutaneous
- Topical

Selection depends on:

- Drug properties
- Desired onset of action
- Patient condition

Objectives of an Ideal Dosage Regimen

1. Achieve Therapeutic Plasma Concentration

Drug concentration should reach effective level quickly.

1. Avoid Toxic Concentration

Drug concentration should not exceed toxic level.

High concentration may produce:

- Side effects
- Organ damage
- Toxic reactions

2. Avoid Subtherapeutic Levels

Concentration should not fall below minimum effective concentration.

Low concentration may cause:

- Treatment failure
- Drug resistance
- Poor clinical response

3. Improve Patient Compliance

Dosage regimen should be simple and convenient.

Example:

- Once daily dosing improves compliance compared to four times daily dosing.

Steady State Drug Levels

When a drug is administered repeatedly or by continuous infusion, the drug starts accumulating in the body. After some time, the rate of drug administration becomes equal to the rate of drug elimination. At this point, the plasma drug concentration becomes constant and is known as the steady state drug level.

Steady state is an important concept in pharmacokinetics and dosage regimen design.

Definition

Steady state drug level is the condition in which:

$$Rate\ of\ drug\ administration = Rate\ of\ drug\ elimination$$

At steady state:

- Average plasma concentration remains constant.
- Drug input equals drug output.

Characteristics of Steady State

- Drug concentration fluctuates within a fixed range.
- Average plasma concentration remains constant.
- Achieved during multiple dosing or continuous IV infusion.
- Depends mainly on biological half-life.

Clinical Importance of Steady State

1. Maintains Therapeutic Effect

Ensures continuous pharmacological action.

2. Prevents Toxicity

Avoids excessive drug accumulation.

3. Dose Optimization

Helps determine proper maintenance dose.

4. Useful in Chronic Therapy

Important for long-term treatment.

Examples:

- Hypertension
- Diabetes
- Epilepsy
- Cardiac diseases

Loading Dose (LD)

A loading dose is a large initial dose of a drug given to rapidly achieve the desired therapeutic plasma concentration.

It is mainly used for drugs:

- Having long biological half-life
- Requiring immediate therapeutic action

Purpose of Loading Dose

- Quickly reaches therapeutic concentration
- Reduces delay in onset of action
- Useful in emergency conditions

Formula for Loading Dose

$$LD = \frac{V_d \times C_{ss}}{F}$$

Where:

- LD = Loading dose
- V_d = Volume of distribution
- C_{ss} = Desired steady-state plasma concentration
- F = Bioavailability

For IV administration:

$$LD = V_d \times C_{ss}$$

Because:

- Bioavailability (F) = 1 for IV route

Steps in Calculation of Loading Dose

Step 1

Determine desired plasma concentration (Css)

Step 2

Determine volume of distribution (V_d)

Step 3

Know bioavailability (F)

Step 4

Substitute values into formula

Example of Loading Dose Calculation

Problem

Calculate loading dose for a drug having:

- $V_d = 40\ L$
- Desired plasma concentration = $10\ mg/L$
- Bioavailability = 0.8

Solution

Formula:

$$LD = \frac{V_d \times C_{ss}}{F}$$

Substitute values:

$$LD = \frac{40 \times 10}{0.8}$$

$$LD = 500\ mg$$

Significance of Loading Dose in Clinical Settings

1. Rapid Therapeutic Effect

Used when immediate action is required.

Example:

- Cardiac arrhythmia
- Status epilepticus

2. Useful for Drugs with Long Half-Life

Without loading dose, several days may be required to reach steady state.

3. Emergency Treatment

Provides quick relief in critical conditions.

4. Maintains Effective Drug Levels Early

Helps achieve therapeutic window rapidly.

Maintenance Dose (MD)

A maintenance dose is the dose required to maintain the desired therapeutic plasma concentration for a prolonged period.

It replaces the amount of drug eliminated from the body.

Purpose of Maintenance Dose

- Maintains steady-state concentration
- Prevents drug concentration fluctuation
- Maintains therapeutic response

Formula for Maintenance Dose

$$MD = \frac{Cl \times C_{ss} \times \tau}{F}$$

Where:

- MD = Maintenance dose
- Cl = Clearance
- C_{ss} = Desired steady-state concentration
- τ = Dosing interval
- F = Bioavailability

Steps in Calculation of Maintenance Dose

Step 1

Determine clearance (Cl)

Step 2

Determine desired plasma concentration (CssC_{ss}Css)

Step 3

Determine dosing interval (τ\tauτ)

Step 4

Know bioavailability (F)

Step 5

Substitute values into formula

Example of Maintenance Dose Calculation

Problem

Calculate maintenance dose for a drug with:

- Clearance = $5\ L/hr$
- Desired concentration = $10\ mg/L$
- Dosing interval = 12 hr
- Bioavailability = 0.5

Solution

Formula:

$$MD = \frac{Cl \times C_{ss} \times \tau}{F}$$

Substituting values:

$$MD = \frac{5 \times 10 \times 12}{0.5}$$

$$MD = 1200\ mg$$

Answer

Maintenance dose = 1200 mg every 12 hours

Significance of Maintenance Dose in Clinical Settings

1. Maintains Steady State

Keeps plasma concentration within therapeutic range.

2. Prevents Toxicity

Avoids excessive drug accumulation.

3. Maintains Long-Term Therapy

Important in chronic diseases.

Examples:

- Hypertension
- Diabetes
- Epilepsy

4. Dose Individualization

Maintenance dose can be adjusted based on:

- Renal function
- Liver function
- Age
- Weight