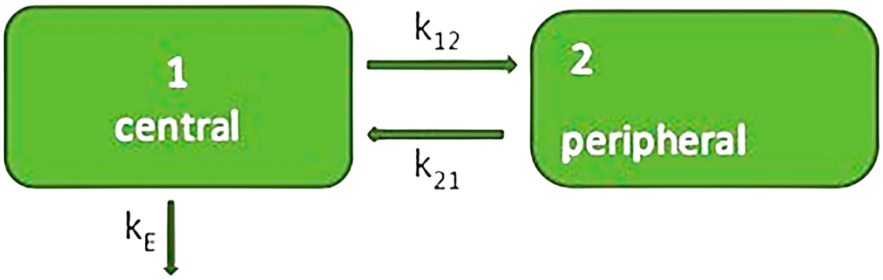
Multicompartment models

Two Compartment Open Model

Introduction to Multicompartment Models

- In pharmacokinetics, the body is often simplified into "compartments" to model how a drug is distributed and eliminated.
- A **two-compartment open model** assumes the body consists of two interconnected areas:
    - **Central compartment**: Represents the blood/plasma and organs with high blood flow (e.g., liver, kidney).
    - **Peripheral compartment**: Represents tissues/organs with lower blood flow (e.g., muscle, fat).



- **"Open"** means that drug can be eliminated from the system (unlike closed models where there's no elimination).

Key Components and Parameters

- **Drug Administration**: Usually via IV bolus or IV infusion.
- **Distribution phase (α-phase)**: Initially, the drug rapidly distributes from the central to the peripheral compartment.
- **Elimination phase (β-phase)**: The drug is eliminated primarily from the central compartment over time.
- **Rate constants**:
    - $\mathbf{k_{12}}$: rate constant for drug moving from central to peripheral compartment.
    - $\mathbf{k_{21}}$: rate constant for drug returning from peripheral to central.
    - $\mathbf{k_{10}}$: elimination rate constant from central compartment.

Mathematical Expression

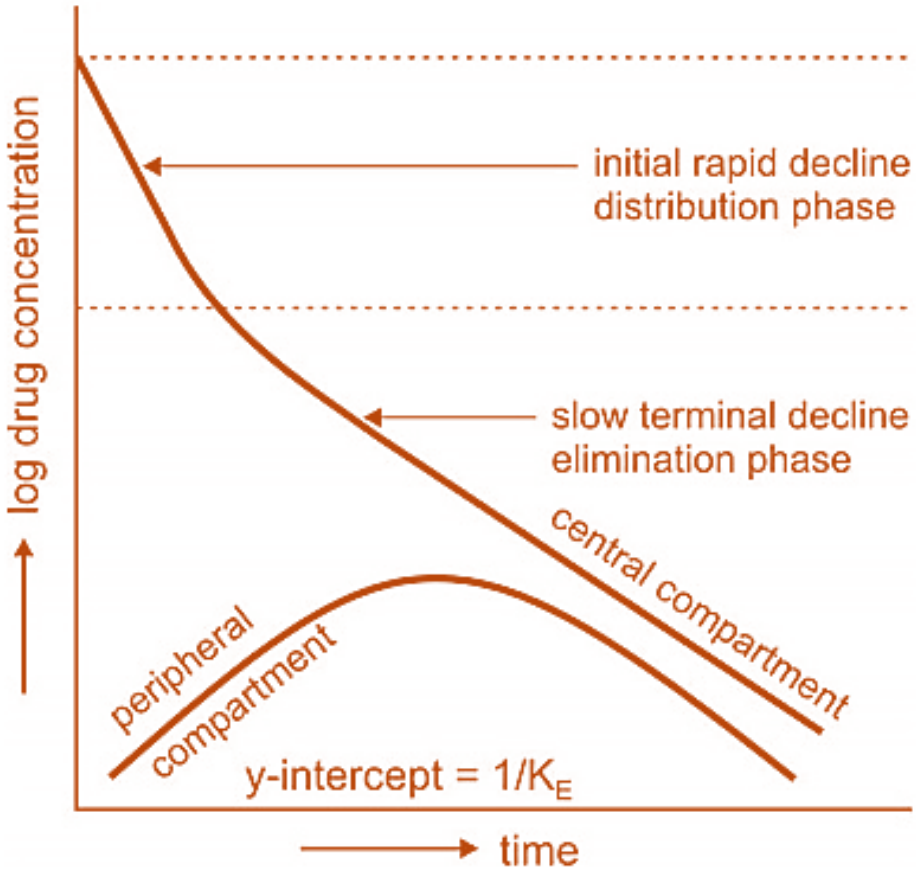
- After an **IV bolus injection**, the plasma concentration–time curve is biexponential and described as:

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

- **Where:**
    - A, B: intercepts (hybrid coefficients).

- α: distribution rate constant.
- β: elimination rate constant (slower phase).
- $C(t)$: plasma concentration at time t.

Graphical Interpretation



- The graph shows how drug concentration in plasma changes over time after an **IV bolus** in a **two-compartment model**. It has two phases:
  1. **Distribution Phase (initial steep drop):** Drug moves rapidly from the central to the peripheral compartment.
  2. **Elimination Phase (slower decline):** Drug is gradually eliminated from the central compartment.
- The curve is **biexponential**, meaning it has two distinct slopes, reflecting both distribution and elimination processes.

Clinical Significance

- **Understanding distribution kinetics** helps in predicting onset of action.
- **Dose calculation** becomes more accurate, especially in drugs with wide tissue distribution.
- **Drug monitoring**: Helps in interpreting plasma levels more accurately (e.g., in digoxin or aminoglycoside antibiotics).

Applications:

- Used when a drug shows:
    - **Rapid distribution to highly perfused organs**, followed by **slower distribution to tissues** like muscle and fat.
    - Complex kinetic behavior that single-compartment models can't describe.

IV Bolus Administration (Two-Compartment Model)

Definition

- **IV bolus** means the drug is injected directly into the bloodstream as a single, rapid dose.
- In this case, absorption is instantaneous, and the drug is assumed to enter the central compartment immediately at time = 0.

Key Assumptions:

- Entire dose enters the central compartment at once.
- Distribution between compartments and elimination begin immediately.
- First-order kinetics apply for distribution and elimination.

Model Behavior:

- Immediately after administration, plasma drug levels are highest.
- Drug starts redistributing from central → peripheral compartment and is also eliminated from the central compartment.

Plasma Concentration–Time Profile:

- This exhibits a **biexponential decline** and is described by the following function:

$$C(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

- Where:
    - **A** and **B** are y-intercepts for the distribution and elimination phases.
    - **α (alpha)** = rate constant for **distribution phase**
    - **β (beta)** = rate constant for **elimination phase**
- The curve has two phases:
    1. **Distribution phase (α-phase):** Rapid drop due to drug moving into tissues.
    2. **Elimination phase (β-phase):** Slower drop due to metabolism and excretion.

Volume of Distribution:

- You can calculate multiple volumes:
    - $\mathbf{V_1}$: Volume of the central compartment.

- **Vss (Steady-state volume)**: Total volume drug appears to distribute into.
- **Varea (based on AUC)**

IV Infusion (Two-Compartment Model)

What Is It?

- In **IV infusion**, the drug is administered **slowly over time**, not instantaneously.
- The drug enters the central compartment at a **constant rate (R_0)**.

Key Assumptions:

- Infusion rate is **zero-order** (constant rate).
- Distribution and elimination are **first-order**.
- At steady state, rate of input = rate of output.

Model Behavior:

- Plasma concentration gradually **increases** during the infusion.
- Drug redistributes between compartments and is eliminated at the same time.
- Once infusion stops, concentration declines in **biexponential** fashion.

Phases:

1. ### During Infusion:
   - Drug accumulates in the central and peripheral compartments.
   - Steady-state is approached asymptotically.
2. ### After Infusion Stops:
   - Concentration declines in two phases: distribution and elimination.

Equation During Infusion:

- The concentration at time **t** during infusion (before reaching steady state) is:

$$C(t) = R_0 \cdot \left(\frac{A}{\alpha(1 - e^{-\alpha t})} + \frac{B}{\beta(1 - e^{-\beta t})}\right)$$

- At **steady state**, the equation simplifies, and the total amount in body equals:

$$C_{ss} = \frac{R_0}{CL}$$

- Where **CL** is total clearance.

Clinical Importance:

- IV infusion allows **precise control** over plasma levels.

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