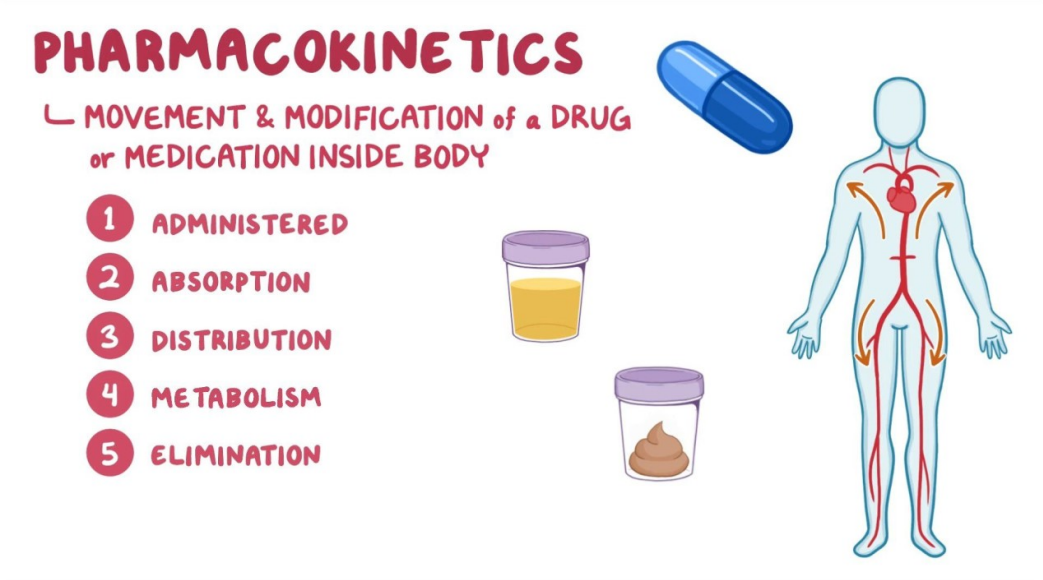
Basic concept of Pharmacokinetics

Pharmacokinetics is a fundamental branch of pharmacology concerned with the fate of drugs in the body. It describes what the body does to the drug, from the moment it is administered until it is completely eliminated. This discipline quantitatively evaluates the processes of Absorption, Distribution, Metabolism, and Excretion (ADME) and explains how these processes influence the onset, intensity, and duration of drug action.

An understanding of pharmacokinetics allows healthcare professionals to select the correct drug, determine an appropriate dose, choose the proper route of administration, and predict drug interactions and toxicity.

Basic Concepts in Pharmacokinetics

Pharmacokinetics involves studying changes in drug concentrations over time. The following four processes collectively determine the concentration of a drug in various tissues and biological fluids.



Absorption

Absorption refers to the transfer of a drug from its site of administration into the systemic circulation. For a drug to produce a therapeutic effect, adequate absorption is essential (except in the case of intravenous administration, which bypasses this step).

Drugs may cross biological membranes through various mechanisms:

- Passive Diffusion
- Facilitated Diffusion
- Active Transport
- Endocytosis and Exocytosis

Factors Affecting Absorption

1. **Physicochemical properties of the drug**
2. **Formulation factors**
3. **Physiological factors**
4. **Route of administration**
5. **First-pass metabolism**

Distribution -

Distribution refers to the **reversible transfer of a drug from the systemic circulation into the tissues and interstitial spaces**.

Factors Affecting Drug Distribution

- Blood Flow
- Plasma Protein Binding
- Tissue Binding
- Physiological Barriers

Volume of Distribution (Vd)

Volume of distribution is a **theoretical volume** that describes how widely a drug is distributed.

$$V_d = \frac{\text{Amount of drug in body}}{\text{Plasma drug concentration}}$$

Interpretation:

- **High Vd (>40 L)** → extensive tissue binding
- **Low Vd (<10 L)** → drug confined to plasma

Metabolism (Biotransformation)

Drug metabolism refers to the **chemical alteration of drugs** in the body, primarily to transform them into **more water-soluble metabolites** for easier excretion.

Sites of Metabolism

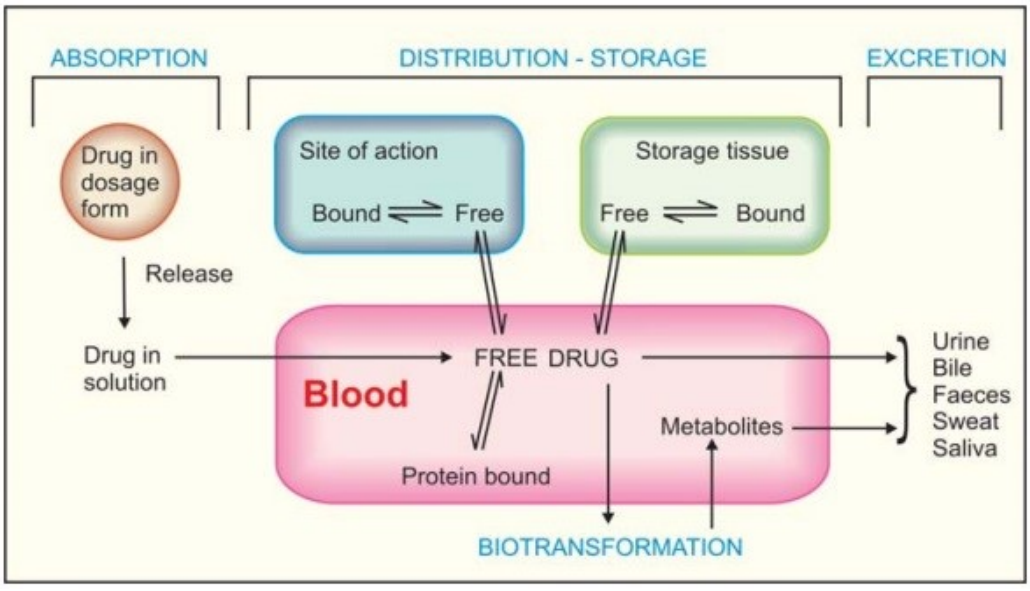
- **Liver** (primary)
- Also lungs, intestines, kidney, plasma

Drug metabolism occurs in two phases: Phase I reactions (functionalization) introduce or expose functional groups such as –OH, –NH_2, and –SH through oxidation, reduction, or hydrolysis, primarily mediated by CYP450 enzymes; while Phase II reactions (conjugation) involve attaching endogenous molecules like glucuronic acid, sulfate, acetyl groups, or glutathione to form inactive, water-soluble metabolites for easier excretion. Drug-metabolizing enzymes can be influenced by other substances: enzyme induction increases metabolic activity and lowers drug levels (e.g., rifampicin, phenobarbital, carbamazepine), whereas enzyme inhibition decreases metabolism and raises the risk of toxicity (e.g., cimetidine, erythromycin, ketoconazole).

Excretion

Excretion is the process by which the body removes drugs and their metabolites, ensuring the termination of their action. The major route is renal excretion, which involves glomerular filtration, tubular secretion, and tubular reabsorption. Drugs may also be eliminated through biliary excretion, where they pass into bile, enter the intestine, and are expelled in feces; some may undergo enterohepatic recycling, prolonging their action. Additional minor routes include the lungs (for volatile anesthetics), as well as sweat, saliva, and breast milk.

Two key pharmacokinetic parameters describe drug elimination: clearance (Cl), which is the volume of plasma cleared of a drug per unit time, and half-life (t½), the time needed for the plasma drug concentration to reduce by 50%. Half-life is clinically significant because it helps determine the dosing interval, and a drug typically reaches steady-state levels after 4–5 half-lives.



Pharmacokinetic process

Bioavailability

Bioavailability refers to the fraction of an administered drug dose that reaches the systemic circulation unchanged. It is 100% (F = 1) when given intravenously, while oral bioavailability is usually lower due to first-pass metabolism, degradation in the gut, and incomplete absorption.

Several factors influence bioavailability, including drug formulation, solubility, first-pass effect, and the influence of food or gastric pH.

Steady-state concentration

Steady-state concentration (Css) is achieved when the rate of drug administration equals the rate of elimination, typically after 4–5 half-lives. To reach therapeutic levels quickly, a loading dose (LD) may be given, calculated using the drug's volume of distribution and bioavailability. Afterward, a maintenance dose (MD) is used to sustain the desired concentration by accounting for clearance, dosing interval, and bioavailability.

Pharmacokinetic models

Pharmacokinetic models help describe drug distribution in the body. In the

- one-compartment model, the body is treated as a single uniform unit where the drug distributes instantly. In contrast,
- the two-compartment model divides the body into a central compartment (blood, heart, liver, kidney) and a peripheral compartment (muscle, fat), which is useful for drugs that distribute more slowly into tissues.

Clinical Importance of Pharmacokinetics

1. Ensures correct dosing in special populations
2. Prevents toxicity and subtherapeutic responses
3. Guides therapeutic drug monitoring (e.g., digoxin, phenytoin)
4. Helps anticipate drug interactions
5. Optimizes drug therapy in renal or liver disease