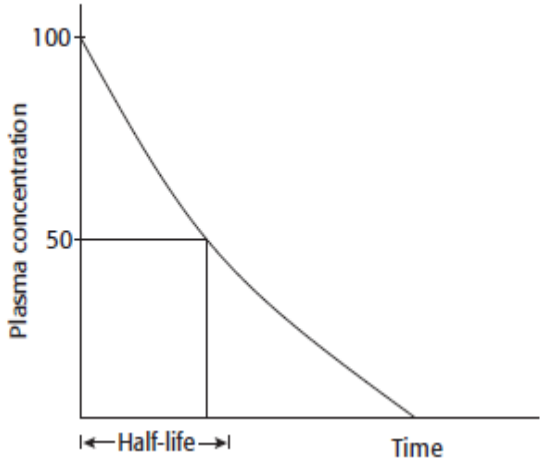
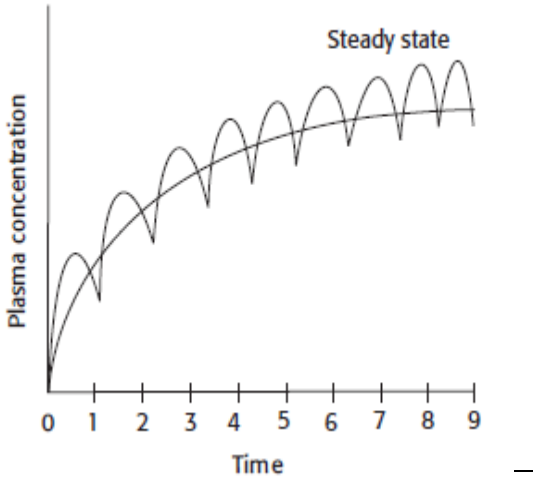
Half-life ($t_{1/2}$): It is the time required for the plasma concentration of the drug to decrease by 50% of its original value.

Clinical Importance of Plasma Half-life:

It helps to:

1. Determine the duration of drug action.
2. Determine the frequency of drug administration.
3. Estimate the time required to reach the steady state. At **steady state**, the amount of drug administrated is equal to the amount of drug eliminated in the dose interval. It takes approximately four-to-five half-lives to reach the steady state during repeated administration of the drug. A drug is almost completely eliminated in four-to-five half-lives after single administration.





Volume of distribution V_d: is defined as the theoretical volume of body fluid into which a drug is uniformly distributed at a concentration equal to that in plasma, assuming the body to be a single compartment.

$$V_d = \frac{\text{Total amount of drug in the body}}{\text{Concentration of the drug in plasma}}$$

- V_d reflects the extent to which the drug is present in the extravascular tissue but not in plasma.
- Lipid solubility can affect V_d, as highly lipid soluble drugs have good cell penetration, resulting in high V_d.
- Plasma-protein binding, particularly to albumin reduces the V_d, while tissue binding increases it.

Drug clearance: Clearance (CL) estimates the volume of plasma from which the drug is cleared per unit of time. Total CL reflects all mechanisms of drug elimination and is calculated as follows:

$$CL = 0.693 \times V_d / t_{1/2}$$

The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion. [Note: Elimination is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion. Excretion is removal of intact drug from the body.] Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug is eliminated in a given unit of time. Metabolism results in products with increased polarity, which allows the drug to be eliminated.

Factors affecting half-life $t_{1/2}$:

1. Volume of distribution (Vd) : half-life will increase as V_d increases.
2. Clearance (CL): half-life will increase as CL decreases.

Clinical Situations Resulting in Changes in Drug Half-life:

When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required.

- Patients who may have an **increase** in drug half-life include those with:

1) diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage;
2) decreased ability to extract drug from plasma, for example, in renal disease;
3) decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis.

These patients may require a **decrease in dosage or less frequent dosing intervals**.

- In contrast, the half-life of a drug may be **decreased** by:

1)increased hepatic blood flow,
2) decreased protein binding,
3) increased metabolism.

This may necessitate **higher doses or more frequent dosing intervals.**

Pharmacokinetics: what the body does to the drug. This involves the processes of absorption, distribution, metabolism/biotransformation, and excretion. (ADME)

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1. Absorption: First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.
2. Distribution: Second, the drug may reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
3. Metabolism: Third, the drug may be biotransformed through metabolism by the liver or other tissues.
4. Elimination: Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces

Drug Distribution: is the process by which a drug reversibly leaves the blood stream and enters the extracellular fluid and tissues.

For drugs administered IV, absorption is not a factor, and the initial phase immediately following administration represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues.

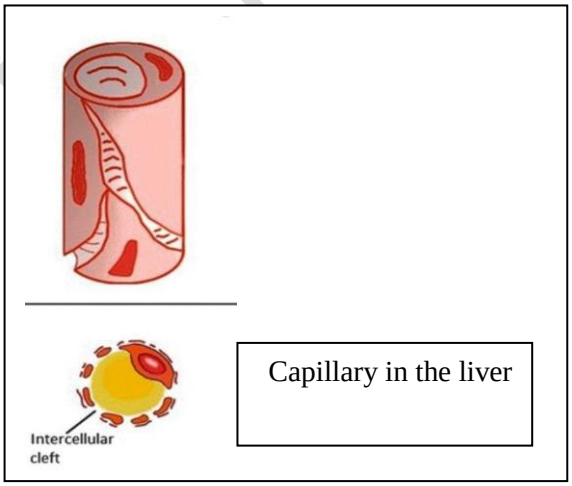
Factors Determining Drug Distribution:

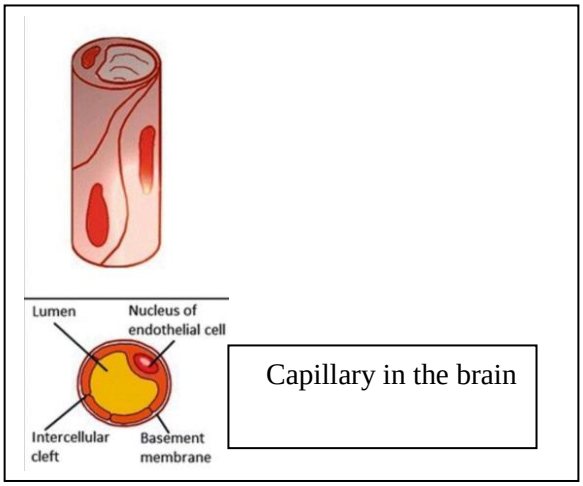
1. **Blood flow:** Blood flow to "vessel-rich organs" (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow.
2. **Capillary permeability:** is determined by
   a) capillary structure.
   b) the chemical nature of the drug.

   a. Capillary structure: In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.

   In the brain, the capillary structure is continuous, and there are no slit junctions.

   To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport.





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b. Chemical nature of the drug: Lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions. These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.

3. Binding of drugs to plasma proteins and tissues:

a- Binding to plasma proteins: Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows transfer out of the vascular compartment. Albumin is the major drug-binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin.

b- Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity.

4. Lipophilicity: Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

Distribution into the Water Compartments in the Body:

Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.

I. ***Plasma compartment:*** If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume, or about 4 L in a 70-kg individual. Heparin shows this type of distribution.

II. ***Extracellular fluid:*** If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14 L in a 70-kg individual). Aminoglycoside antibiotics show this type of distribution.

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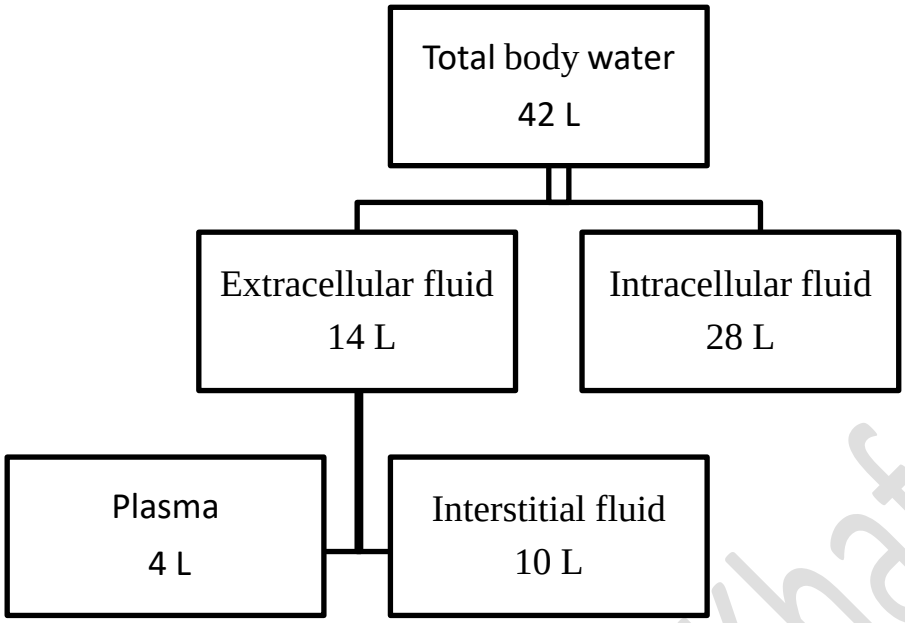
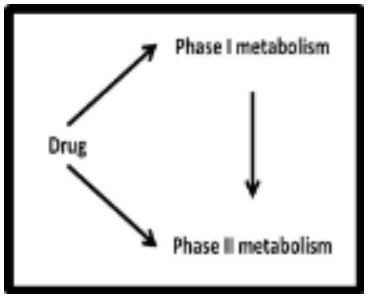


III. ***Total body water:*** If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. Ethanol exhibits this apparent V_d. [Note: In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid.]

Metabolism of drugs: it is the biotransformation or chemical alteration of the drug in the living system.

- The metabolism of a drug usually converts the lipid-soluble and unionized compounds into water-soluble and ionized compounds. They are not reabsorbed in the renal tubules and are excreted. If the parent drug is highly polar (ionized), it may not get metabolized and is excreted as such.
- Liver is the main site for drug metabolism; other sites are GI tract, kidney, lungs, blood, skin and placenta.
- The end result of drug metabolism is inactivation; but sometimes a compound with pharmacological activity may be formed.
- Drug metabolic reactions are grouped into two phases. They are phase I and phase II reactions.



Phase I reactions: are of two types

- utilizing the P450 (CYP) system.
- not involving the P450 system.

Phase II reactions: This phase consists of conjugation reactions.

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Factors Affecting Drug Metabolism

1. Age: Neonates and elderly metabolize some drugs to a lesser extent than adults. In both the cases, the impairment is due to diminished activity of hepatic microsomal enzymes.

2. Diet: Poor nutrition can decrease enzyme function.

3. Diseases: Chronic diseases of liver may affect hepatic metabolism of some drugs.

4. Genetic factors (pharmacogenetics): These factors also influence drug metabolism.

5. Simultaneous administration of drugs: This can result in increased or decreased metabolism of drugs.

a) CYP inducers: Certain drugs are capable of inducing CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, often with concurrent loss of pharmacologic effect.

b) CYP inhibitors: Certain drugs inhibit the activity of drug-metabolizing enzymes and this can lead to significant increases in plasma drug concentration and resultant adverse effects or drug toxicity.

Drug Excretion: Removal of the drug and its metabolite from the body is known as drug excretion. The main channel of excretion of drugs is the kidney; others include lungs, bile, feces, sweat, saliva, tears, milk, etc.

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