Introduction and general concepts

Pharmacology is the branch of science that studies the drug properties and its actions when binds with the specified biological receptors. Depending on a drug dose, different effects can be observed in living body, which either a desirable effect (the therapeutic effect) or an undesirable effect (the side effects of the drug).

A drug can be defined as a natural or synthetic substance that can affect a function or a structure of living body. It can be used in diagnosing, treating and/or preventing a disease or discomfort situations. Usually, the activation process of the drug inside the living body occurred by interacting with a **receptor** which is a specialised target macromolecule present on the cell surface or within the cell.

Clinical pharmacology can be defined as the science that studies the clinical actions and applications of the drugs, by exploring:

1- The drug pharmacokinetics (represents what the body dose to a drug).

2- The drug pharmacodynamics (represents what the drug dose to the body) of the drugs.

Pharmacokinetics:

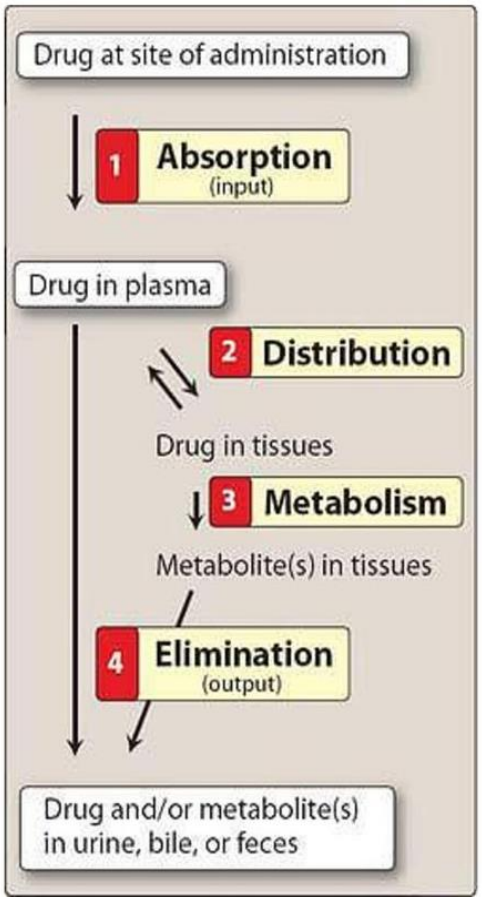
Four pharmacokinetic properties determine the onset, intensity, and duration of drug action.

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. Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, dose, frequency, and duration of treatment.



Routes of Drug Administration

The route of administration is determined by properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the need for a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical, with other routes.

A. Enteral

Enteral administration (administering a drug by mouth) is the most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual) or between the gums and cheek (buccal), facilitating direct absorption into the bloodstream.

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, heparin) or unstable in the GI tract (for example, insulin). Parenteral administration is also used for patients unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action. Parenteral administration provides the most control over the dose of drug delivered to the body. However, this route of administration is irreversible and may cause pain, fear, local tissue damage, and infections. The four major parenteral routes are intravascular (intravenous (IV) or intraarterial), intramuscular (IM), subcutaneous (SC), and intradermal.

C. Others: Oral inhalation and nasal preparations;Intrathecal; topical ointment and cream; transdermal patches and rectal suppositories and enema.

Drug pharmacokinetics

As was mentioned above the drug pharmacokinetics studies what the living body does to a drug i.e. how will it be absorbed, distributed, metabolised and excreted outside the body.

Absorption of the drugs:

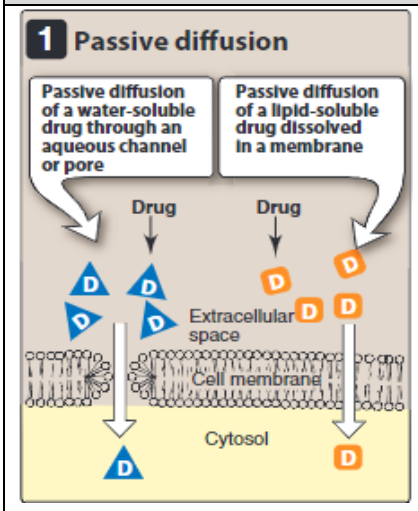
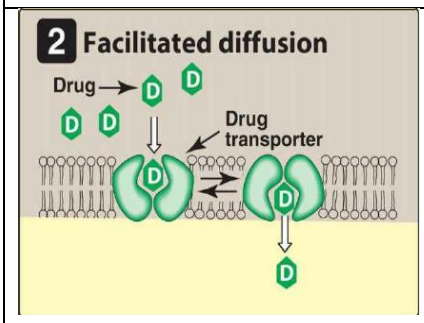
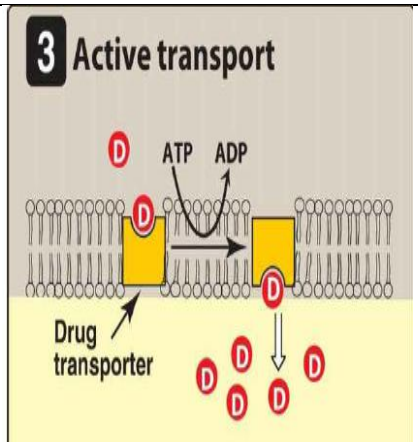
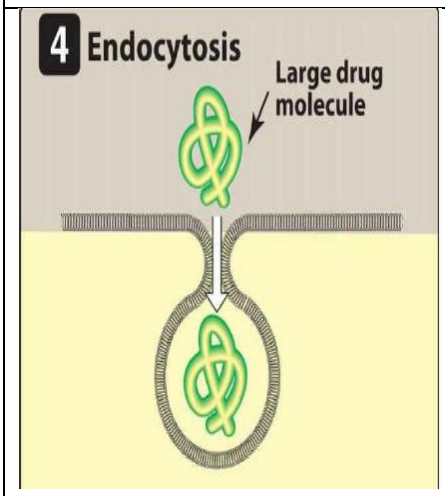
Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on:

1. The environment where the drug is absorbed
2. Chemical characteristics of the drug
3. Route of administration (which influences bioavailability).

Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

Mechanism of absorption	Characteristics features
	❖ The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. ❖ Drug moves from an area of high concentration to one of lower concentration. ❖ It does not involve a carrier, is not saturable, and shows low structural specificity. ❖ The vast majority of drugs are absorbed by this mechanism. ❖ Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.
	❖ Drug enters the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. ❖ These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. ❖ It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.
	❖ This mode of drug entry also involves specific carrier proteins that span the membrane. ❖ Active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). ❖ It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. ❖ The process is saturable. ❖ It is selective and may be competitively inhibited by other cotransported substances.
	❖ It is used to transport drugs of exceptionally large size across the cell membrane. ❖ Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. ❖ Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. ❖ Vitamin B12 is transported across the gut wall by endocytosis ❖ Norepinephrine are stored in intracellular vesicles in the nerve terminal and released by exocytosis.

Factors influencing on drug absorption

1- Effect of pH on drug absorption

Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H+), causing a charged anion (A−) to form:

$$HA \rightleftharpoons H^+ + A^-$$

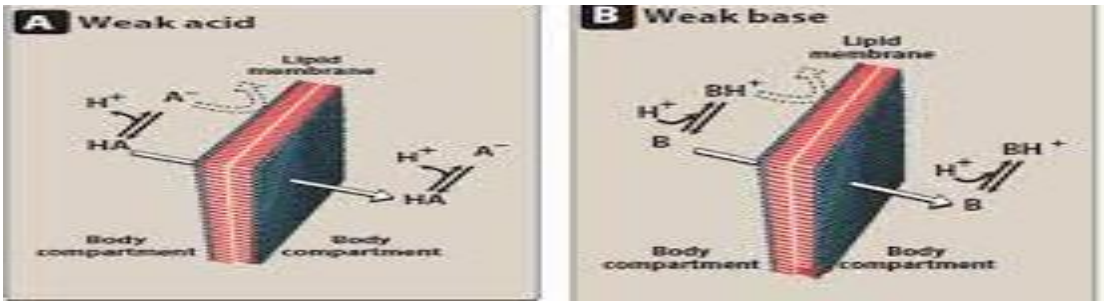
Weak bases (BH+) can also release an H+ . However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftharpoons B + H^+$$

A drug passes through membranes more readily if it is uncharged. Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A− cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pKa. .

The relationship between pH and pKa can be summarised in three cases:

1. pH = pKa, [HA] = [A–] and [BH+] = [B].
2. pH < pKa the protonated forms HA and BH+ predominate
3. pH > pKa the deprotonated forms A- and B predominate.



2. Blood flow to the absorption site

The intestines receive much more blood flow than does the stomach, so absorption from the intestine is favored over the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing absorption from SC administration.]

3. Total surface area available for absorption

With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4. Contact time at the absorption surface

If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption. [Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

5. Expression of P-glycoprotein

P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes. It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it "pumps" drugs out of cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

6- Age:

In children & Infants: Gastric pH is high, membrane permeability & BBB permeability is high, protein binding is less therefore it imparts drug absorption. While in Elderly patient there is altered gastric emptying, decrease intestinal surface area, decrease gastric blood flow & higher incidence of achlorhydria so it imparts drug absorption.

Clinical factors affecting on absorption

A) Diseases; B) Surgery ; C) Infection; D) Interaction of drug with food or other drug.

Disease condition

- Gastric diseases: –ACHLORHYDRIA Achlorhydria affects Aspirin absorption by increasing gastric emptying time & increasing stomach pH.
- Intestinal diseases like celiac disease, chrons disease.
- Cardio-vascular diseases: Several changes associated with congestive cardiac failure influence the bioavailability of the drug, edema of the intestine, decreases blood flow to GIT, etc.
- Hepatic diseases Disorders such as hepatic cirrhosis influence bioavailability mainly of drugs that undergo considerable first-pass hepatic metabolism e.g. Propranolol.

Interaction

- i) Food-Drug Interactions (Thyroxin and Tetracyclin should be administered before meal (mainly dairy products)
- ii) Drug-Drug Interactions (either physiochemical e.g. interaction of Tetracycline with antacid) or physiological interaction with drug that increase or decrease GIT motility)
- iii) Drug-GI contents interactions: Interaction with mucin, enzymes and bile salts influence drug absorption. Example: Bile salts Increase absorption of Vitamins (Solution) and decrease absorption of Neomycin and Kanamycin (Insoluble complex)

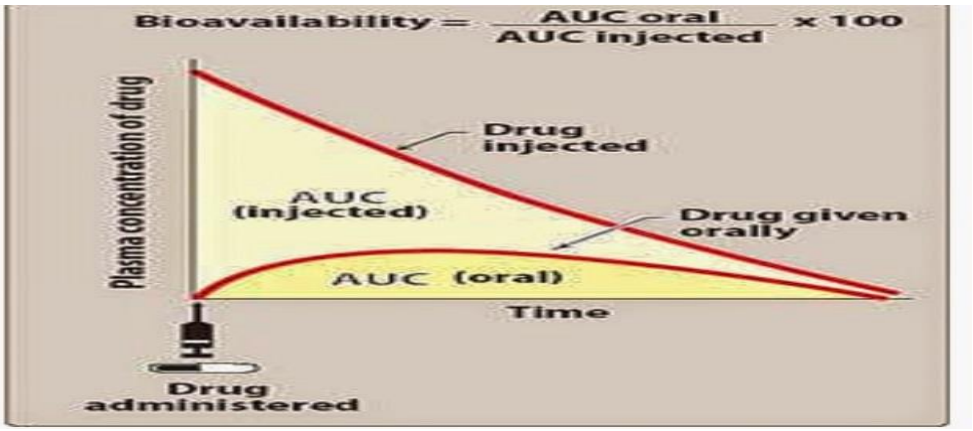
Bioavailability (F value)

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for nonintravenous routes of administration.

The bioavailability can be determined by the following equation:

$$\boldsymbol{Bioavailability} = \frac{\textbf{AUC oral}}{\textbf{AUC iIV}} \times \textbf{100}$$

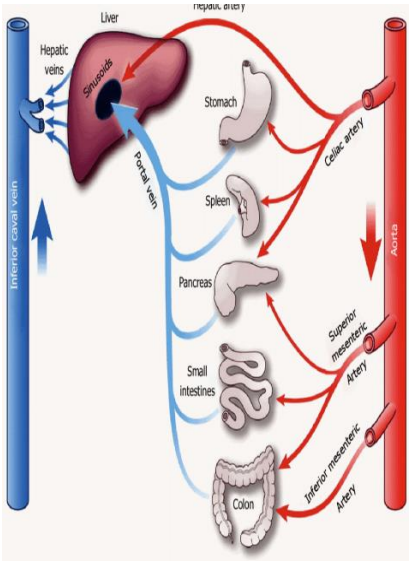
Where the AUC oral refers to the area under the blood concentration-time curve of orally administered drugs while the AUC injected represents the area under the blood concentration-time curve of intravenous (IV) injected drugs (figure 3). The F value of the IV drugs usually equals to 100%; however, for a drug given orally, its bioavailability < 100%. This may be due to incomplete extent of absorption and first pass effect.



Factors that influence on bioavailability (oral or other routes except IV)

a. First-pass hepatic metabolism

When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of nitroglycerin is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual, transdermal, or intravenous route.] **Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.**



b. Solubility of the drug

Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic with some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

c. Chemical instability

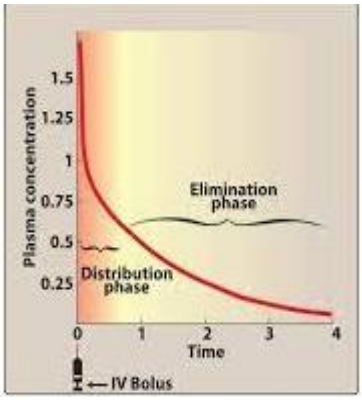
Some drugs, such as penicillin G, are unstable in the pH of gastric contents. Others, such as insulin, are destroyed in the GI tract by degradative enzymes.

d. Nature of the drug formulation

Particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Drug Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream 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. The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, tissue volume, degree of binding of the drug to plasma and tissue proteins, and relative lipophilicity of the drug.



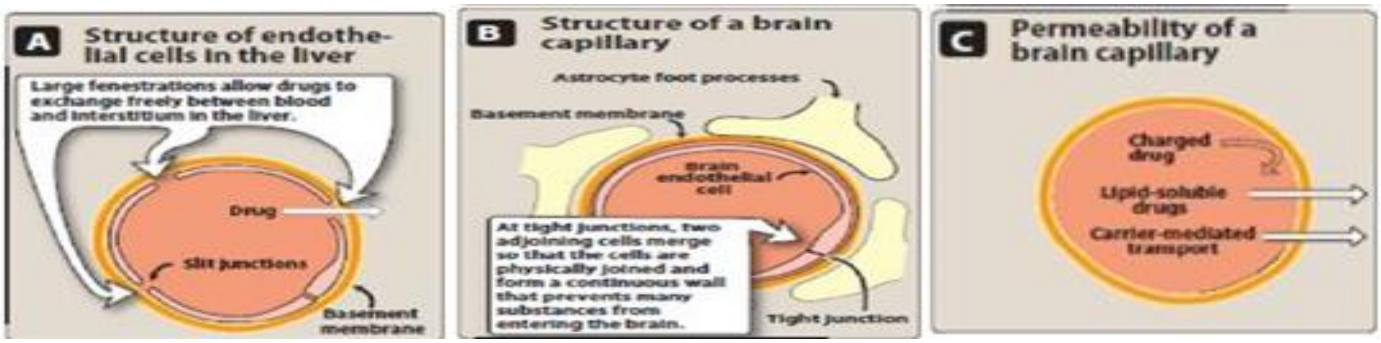
1- Blood flow

The rate of blood flow to the tissue capillaries varies widely. For instance, 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. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of propofol. High blood flow, together with high lipophilicity of propofol, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

2- Capillary permeability

Capillary permeability is determined by capillary structure and by the chemical nature of the drug. **Capillary structure** varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. **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. For example, a specific transporter carries levodopa into the brain.

Chemical nature: 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 protien

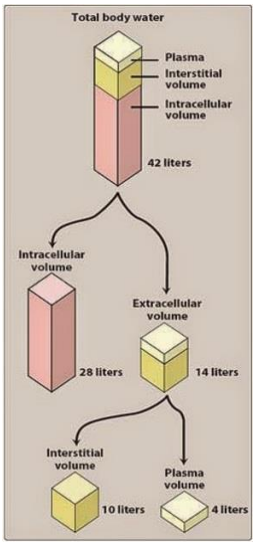
a. ***Binding to plasma proteins***: Reversible binding to plasma proteins sequesters drugs in a non-diffusible form and slows transfer out of the vascular compartment. Albumin is the major drug-binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination,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

b. *Binding to tissue proteins*: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of cyclophosphamide, can cause hemorrhagic cystitis because it accumulates in the bladder.)

4-Lipophilicity

Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

Volume of distribution



The apparent volume of distribution, Vd , is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_o).

$$Vd = \frac{Amount\ of\ the\ drug\ in\ the\ body}{\mathrm{Co}}$$

Although Vd has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

Distribution into the water compartments in the body

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

a. 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 Vd that approximates the plasma volume**, or about 4 L in a 70-kg individual. Heparin shows this type of distribution.

b. 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.

c.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 Vd .

[Note: In general, a larger Vd indicates greater distribution into tissues; a smaller Vd suggests confinement to plasma or extracellular fluid.]

d.Other sites: In pregnancy, the fetus may take up drugs and thus increase the volume of distribution.

Effect of Vd on drug half-life

Vd has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow but also on the fraction of drug in the plasma. If a drug has a large Vd , most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, **any factor that increases Vd can increase the half-life and extend the duration of action of the drug.** [Note: An exceptionally large Vd indicates considerable sequestration of the drug in some tissues or compartments.]

Metabolism (Biotransformation)

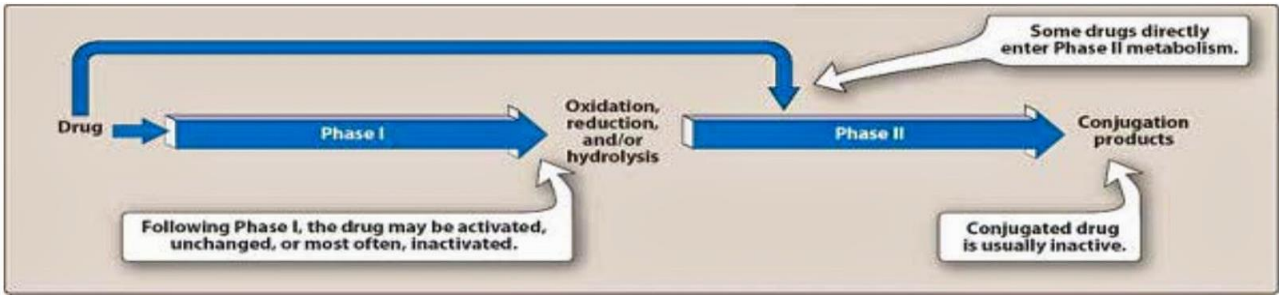
Drug metabolism may be defined as the biochemical modification of one chemical form to another, occurring usually through specialised enzymatic systems. It often involves the conversion of lipophilic chemical compounds (drugs) into highly polar derivatives that can be easily excreted from the body.

- Drugs are most often **eliminated** by biotransformation and/or excretion into the urine or bile. So, metabolism consider one process of elimination.

- The liver is the major site for drug metabolism, but specific drugs may undergo biotransformation in other tissues, such as the kidney, plasma, lung and the intestines.
- Some agents are initially administered as inactive compounds (pro-drugs) and must be metabolized to their active forms.
- The importance of metabolism is to terminate the action of the drug and to enhance the excretion of lipid soluble drug.

Reactions of drug metabolism

The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II.



1. Phase I

Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or –NH2 . Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity. It is classify into two types:

A) Utilize P450 system

1. Frequently involved in drug metabolism
2. Catalyze by Cytochrome P450 (cyp) system
3. Metabolizes both endogenous (such as steroid) and exogenous (such as drug and toxin) compound.
4. Four isozymes (CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2) are responsible for majority of reaction.
5. **Has Specificity**: Different P450 isoforms can metabolize a large number of structurally diverse drug and an individual drug may be a substrate for more than one isozyme.
6. Some of them found in intestinal mucosa, responsible for first-pass metabolism such as chlorpromazine and clonazepam.
7. P450 enzymes exhibit considerable **genetic variability** among individuals and racial groups. For example, some individuals obtain no benefit from the opioid analgesic codeine, because they lack the CYP2D6 enzyme that activates the drug. Also, clopidogrel carries a warning that patients who are CYP2C19 "poor metabolizers" have a diminished antiplatelet effect when taking this drug and an alternative medication should be considered.
8. Certain drugs (for example, phenobarbital, rifampin, and carbamazepine) 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. For example, rifampin, significantly decreases the plasma concentrations of human immunodeficiency virus (HIV), thereby diminishing the ability to suppress HIV replication.

9. Some drugs, however, are capable of **inhibiting CYP enzymes** for which they are not substrates (for example, ketoconazole), leading to drug interactions. Numerous drugs inhibit one or more of the CYP-dependent biotransformation pathways of warfarin. For example, omeprazole is a potent inhibitor of three CYP isozymes involved in warfarin metabolism. [Note: The more important CYP inhibitors are erythromycin, ketoconazole, and ritonavir, because they each inhibit several CYP isozymes.]

B) Not Utilize P450 system

These include:

1. Amine oxidation (for example, oxidation of catecholamines or histamine),
2. Alcohol dehydrogenation (for example, ethanol oxidation),
3. Esterases (for example, metabolism of aspirin in the liver)Hydrolysis (for example, of procaine).

Phase II

- This phase consists of conjugation reactions.
- Responsible for conversion of many phase I metabolites which are still too lipophilic into more water-soluble compounds.
- Conjugation reaction occur with endogenous substrate, such as glucuronic acid (most common), sulfuric acid, acetic acid, or an amino acid.
- Most of conjucated metabolite are pharmacologically inactive except morphine-6-glucuronide, which is more potent than morphine.
- The highly polar drug conjugates are then excreted by the kidney or in bile.

B) Excretion (elimination) by kidney

Excretion is the removal of drugs and their metabolites from the living bodies. There are several routes for drug elimination from the body; however, the main one is the renal system or the hepatic system as most of the drugs are eliminated by pathways that involve the kidneys or the liver. Renal excretion plays an important role in eliminating unchanged drugs or their metabolites into urine. A major characteristic of compounds excreted in urine is that they are polarized (i.e., charged) and water-soluble.

Factors influencing drugs excretion

1- Physico-chemical properties of drugs such as:

a. Molecular weight b. Lipid solubility c. Binding character d. Volume of distribution e. Degree of ionization

2- Urine pH.

3- Blood flow to the organs like kidneys and liver.

4- Biological factors e.g. age.

5- Diseases state.

A. Renal elimination of drug

A drug passes through several processes in the kidney before elimination: glomerular filtration, active tubular secretion, and passive tubular reabsorption.

1. Glomerular filtration

Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into the Bowman space as part of the glomerular filtrate. The glomerular filtration rate (GFR) is normally about 120 mL/min/1.73m2 but may diminish significantly in renal disease. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

2. Proximal tubular secretion

Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport systems: one for anions (for example, deprotonatedforms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system. [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the blood.]

3. Distal tubular reabsorption

As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion and increase the clearance of an undesirable drug. Generally, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called “ion trapping.” For example, a patient presenting with phenobarbital (weak acid) overdose can be given bicarbonate, which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

B. Excretion by Other Routes

Drug excretion may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs that are secreted directly into the intestines or into bile are excreted in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, desflurane). Elimination of drugs in breast milk may expose the breast-feeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity

Total body clearance

The total body (systemic) clearance, CLtotal, is the sum of all clearances from the drug-metabolizing and drug eliminating organs. The kidney is often the major organ of excretion. The liver also contributes to drug clearance through metabolism and/or excretion into the bile. Total clearance is calculated using the following equation:

$$CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + Cl_{other}$$

where CLhepatic + CLrenal are typically the most important.

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 increased hepatic blood flow, decreased protein binding, or increased metabolism. This may necessitate higher doses or more frequent dosing intervals.