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Chapter Two

Pharmacokinetics
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2.1 Overview

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics.

Four pharmacokinetic properties determine the onset, intensity, and duration of drug action which includes **absorption** (**A), distribution (D), metabolism (M) and excretion (E).**

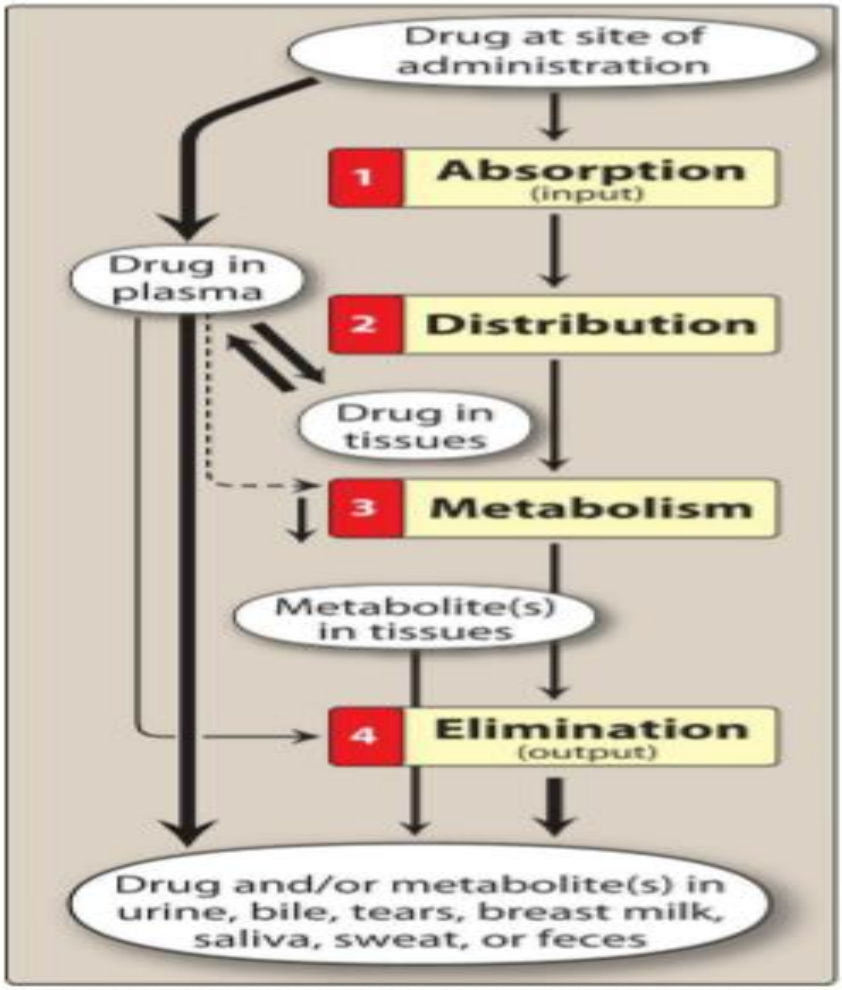


Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

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 bio transformed 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.

2.2 Routes of 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)

Major routes of drug administration include enteral, parenteral, and topical.

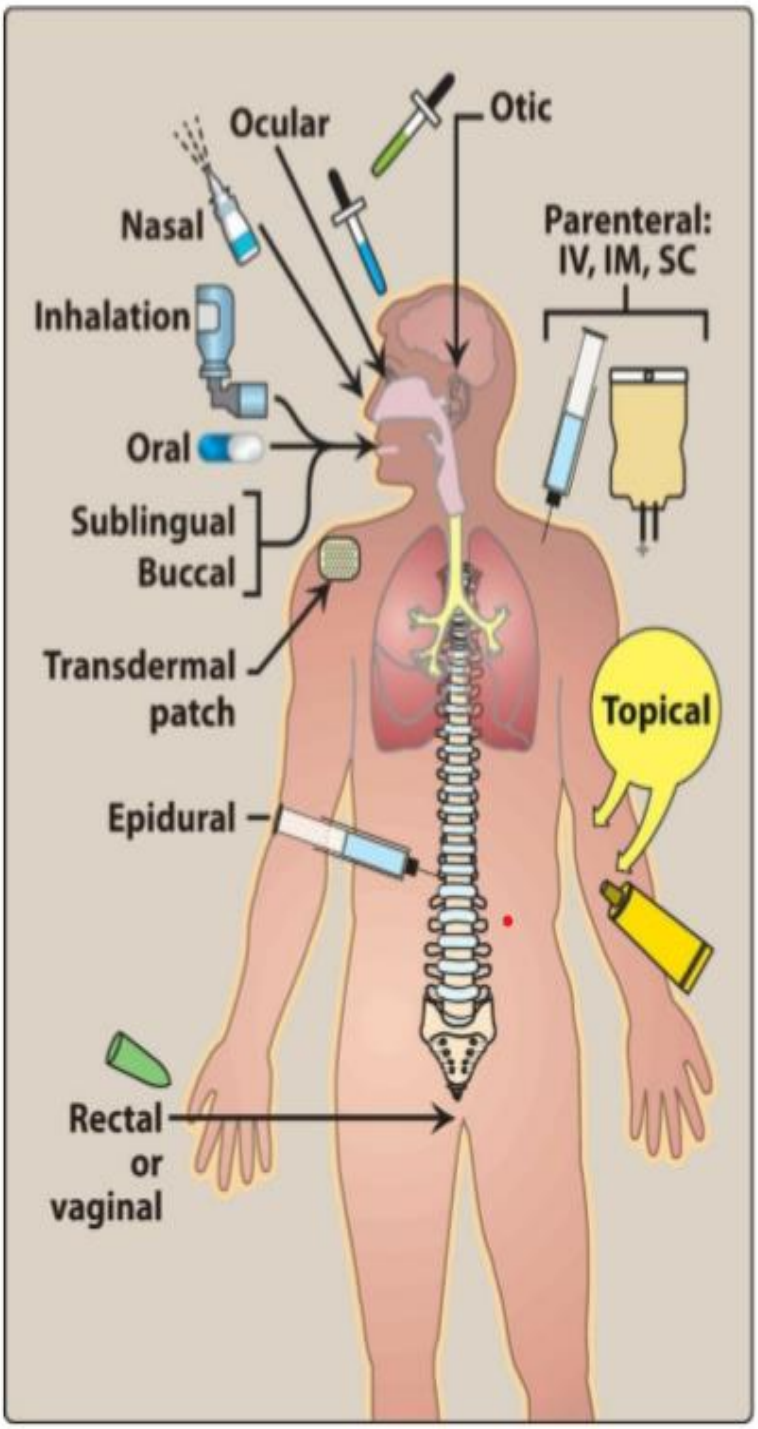


Figure 1.2 Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

1A) 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.

Oral administration provides many **advantages,** such as easy self-administered and you can stop and overcome drug toxicities and/or overdose of oral drugs with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs.

A wide range of oral preparations is available including **enteric-coated and extended-release preparations**

A) Enteric-coated preparations: an enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug.

Enteric coating is useful for certain drugs (for example, omeprazole) that are acid labile, and for drugs that are irritating to the stomach, such as aspirin.

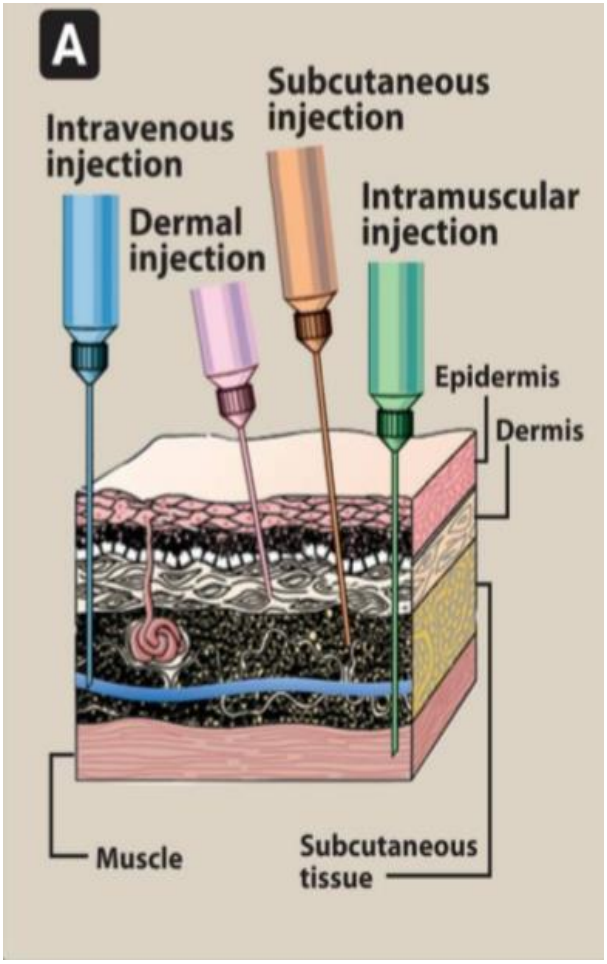
B) Extended-release preparations: Extended-release (abbreviated ER, XR, XL, SR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral morphine is very short, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used.

1B) Sublingual/buccal: the sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh

gastrointestinal (GI) environment, and avoidance of first-pass metabolism.

2) Parenteral administration

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 or intraarterial), intramuscular, subcutaneous, and intradermal**.



1. Intravenous (IV): IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally.
IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.

2. Intramuscular (IM): Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of drug in a nonaqueous vehicle.
As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over a long period of time.

3. Subcutaneous (SC): SC injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of haemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.

4. Intradermal (ID): The intradermal (ID) route involves injection into the dermis, the more vascular layer of skin under the epidermis. Agents for diagnostic determination and desensitization are usually administered by this route.

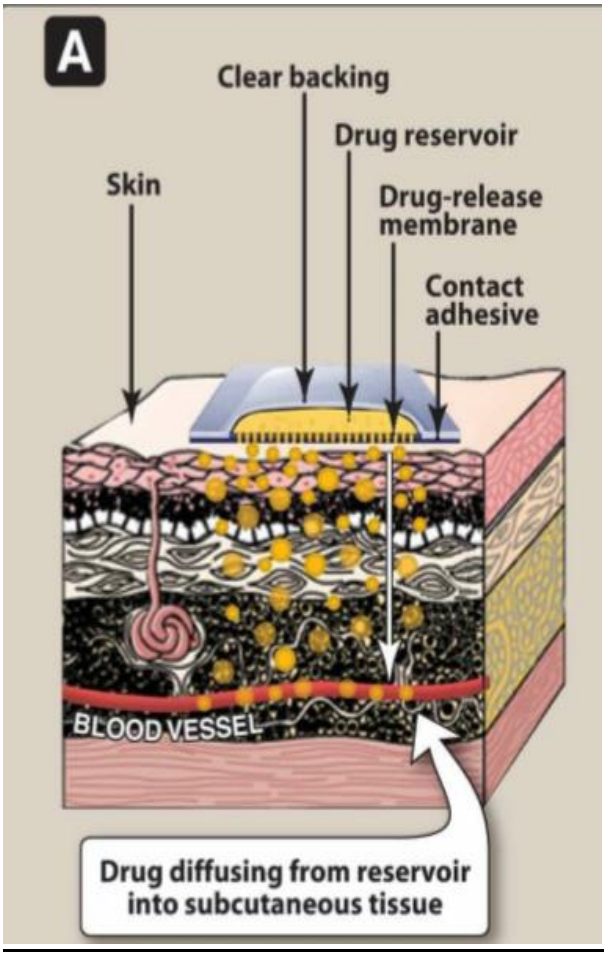
3) Other routes of administration:

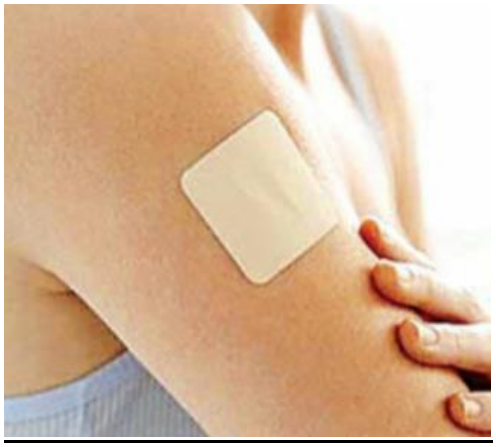
1. Oral inhalation and nasal preparations: Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as are those with IV bolus. Drugs that are gases (for example, some anaesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because drug is delivered directly to the site of action, thereby minimizing systemic side effects.
The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

2. Intrathecal/intraventricular: the introduction of drugs directly into the cerebrospinal fluid.

3. Topical: Topical applications are used when a local effect of the drug is desired.

4. Transdermal This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch.
The rate of absorption is different, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug.


A
Clear backing
Drug reservoir
Skin
Drug-release membrane
Contact adhesive
BLOOD VESSEL
Drug diffusing from reservoir into subcutaneous tissue



5.Rectal: The biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa.

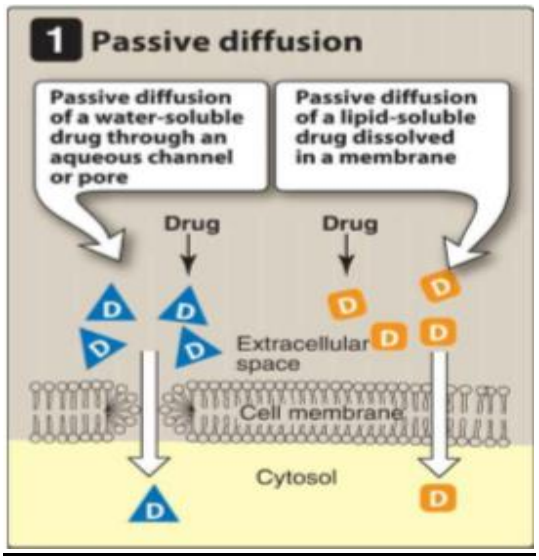
2.3 Absorption of Drugs

Absorption: is the transfer of a drug from the site of administration to the bloodstream.
The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability).

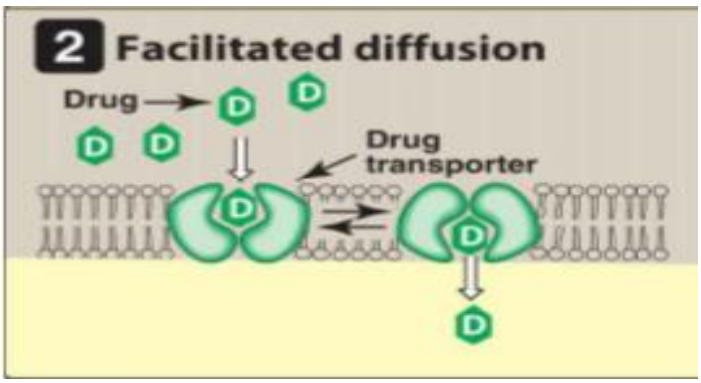
A. Mechanisms of absorption of drugs from the GI tract

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

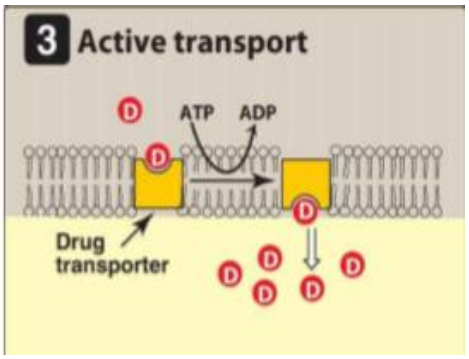
1. Passive diffusion: The drug moves from an area of high concentration to one of lower concentration. Passive diffusion does not involve a carrier. Most drugs are absorbed by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, while lipid-soluble drugs readily move across most biologic membranes due to solubility in the membrane lipid bilayers.



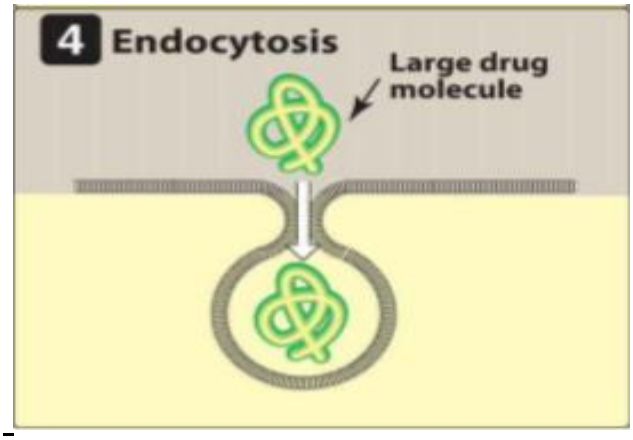
2. Facilitated diffusion: Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited.



3. Active transport: 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. Active transport systems are selective and may be competitively inhibited by other cotransporter substances.



4. Endocytosis and exocytosis: This type of absorption 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. Exocytosis is the reverse of endocytosis. Vitamin B12 is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.



2.4 Absorption Factors

1) Effect of pH on drug absorption: Drug absorption is determined by the pH at the site of absorption and by the strength of the weak acid or base.

2) Blood flow to the absorption site: The intestines receive much more blood flow than does the stomach, so absorption from the intestine is more superior over the stomach.

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.

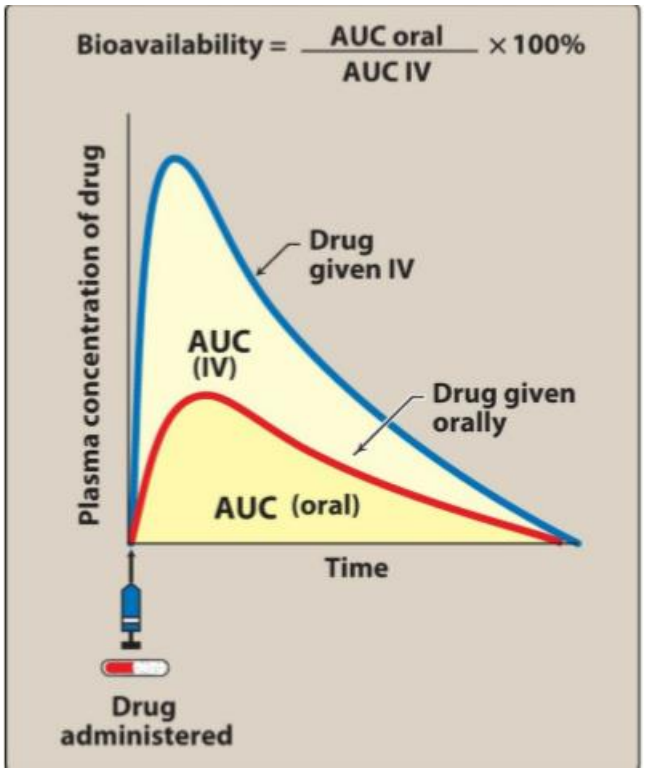
4)Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhoea, it is not well absorbed.
The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more 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.

2.5 Bioavailability

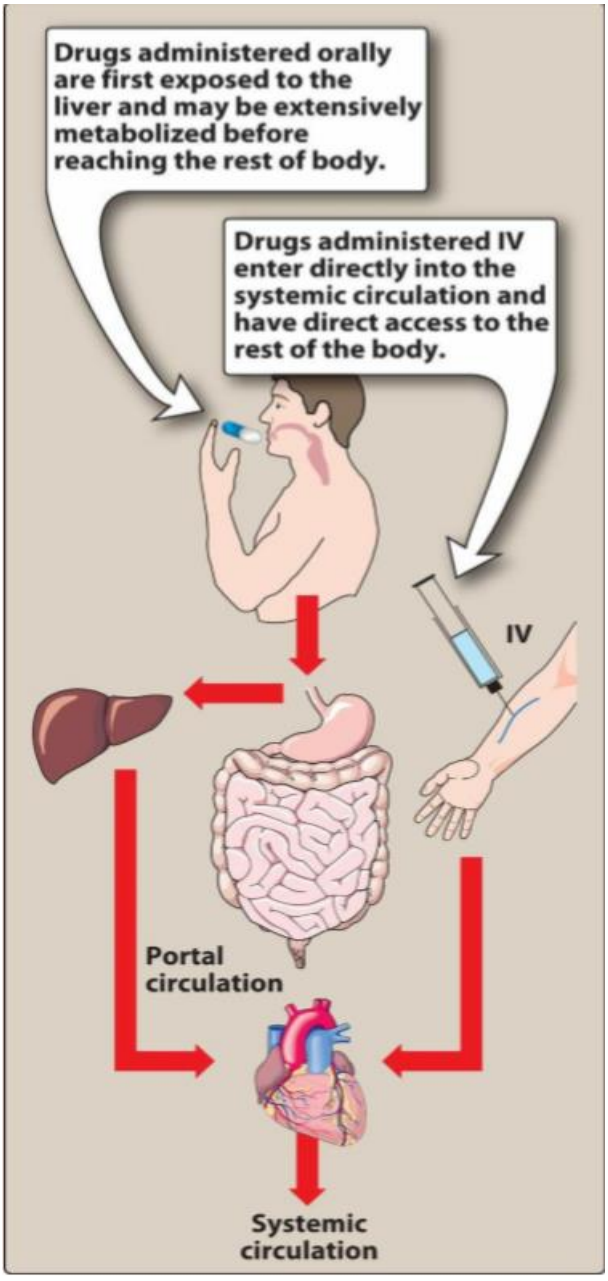
Bioavailability: is the rate and extent to which, an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for no intravenous routes of administration.

Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration. After IV administration, 100% of the drug rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma.



2.5.1 Factors that influence bioavailability

In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.



1) 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 active drug entering the systemic circulation is **decreased**. This is referred to as first-pass metabolism.

2) Solubility of the drug Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes, 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, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

3) 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.

4) Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients.

2.6 Distribution

Drug distribution: is the process by which a drug leaves the bloodstream and enters the extracellular fluid and tissues. For drugs administered IV, absorption is not a factor. The distribution of a drug from the plasma to the interstitium depends on:

1) Cardiac output and local blood flow: The rate of blood flow to “vessel-rich organs” (brain, liver, and kidney) is greater than that to the skeletal muscles, adipose tissue and skin.

2) Capillary permeability: Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

3) Binding of drugs to plasma proteins and tissues: Binding to plasma proteins puts the drug in a non- diffusible form and slows its transfer out of the vascular compartment.
While binding to tissue proteins, will accumulate the drug in the tissues leading to a higher concentration 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.

4) Lipophilicity: The chemical nature of a drug strongly influences its ability to cross cell membranes. 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 cell junctions.

5) Volume of distribution: The V_D of a drug represents the degree to which a drug is distributed in body tissue rather than the plasma. **V_D** is directly correlated with the amount of drug distributed into tissue; **a higher V_D indicates a greater amount of tissue distribution**

Volume of distribution has an important influence on the half-life of a drug, any factor that increases **V_D** can increase the half-life and extend the duration of action of the drug.

2.7 Metabolism

Drug metabolism: is the metabolic breakdown of drugs usually through specialized enzymatic reactions, in order to increase the polarity of the drug, so it can be ready for elimination from the body.

Reactions of drug metabolism include the following:

1) Phase I reactions: It converts lipophilic drugs into more polar molecules by introducing or removing 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.

Phase I reactions most frequently involved in drug metabolism are catalysed by the cytochrome **P450 (CYP) system**. The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (drugs, carcinogens, and environmental pollutants).

2) Phase II reactions: Phase II This phase consists of conjugation reactions. If the metabolite from phase I is sufficiently polar, it can be excreted by the kidneys.
Glucuronidation is the most common and the most important conjugation reaction.

2.8 Elimination

Elimination: is the process of the removing the drug outside the body.

A drug must pass through several processes in the kidney before elimination:

A) 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 (Figure 1.19). 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.

B) Proximal tubular secretion: Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles,

C) Distal tubular reabsorption: As a drug moves toward the distal convoluted tubule, its concentration increases. a drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation, Manipulating the urine pH to increase the clearance of an undesirable drug. Generally, weak acids can be eliminated by alkalinisation of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called **“ion trapping.”**

Other Routes of Elimination (Excretion)

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 faeces.
The lungs are primarily involved in the elimination of aesthetic 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 occur only to a small extent.