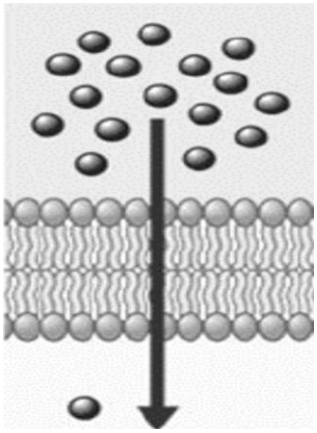
Pharmacokinetics: what the body does to the drug. This involves the processes of absorption, distribution, metabolism/biotransformation, and excretion. (ADME)

1. Absorption: is the movement of a drug from the site of administration into the blood stream .
2. Distribution: is the reversible transfer of drugs between body fluid compartments.
3. Metabolism: 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.

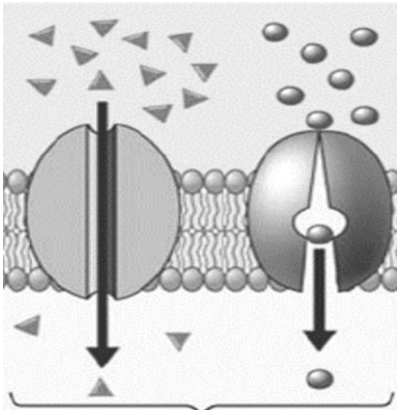
Mechanisms of absorption of drugs from the GI tract:

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

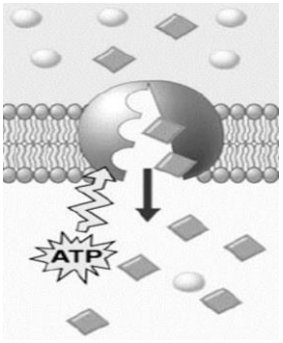
1. Passive diffusion: the drug moves from an area of high concentration to one of lower concentration across a membrane separating two body compartments. Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed by this 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.



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 by compounds that compete for the carrier.



3. Active transport: It involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs 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 cotransported 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 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, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and released by exocytosis.

Factors influencing absorption:

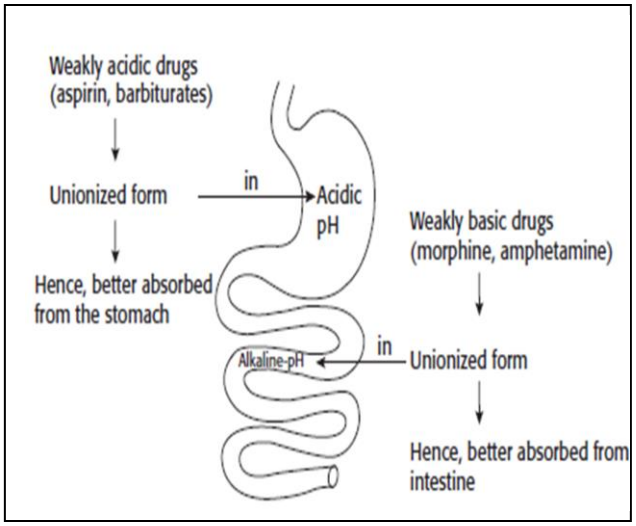
1. pH and ionization: Most drugs are either weak acids or weak bases. A drug passes through membranes more readily if it is uncharged. The degree of ionization (polarity) depends on the pKa of the drug and pH of the body fluid).

The pKa of a drug is the pH at which 50% of the drug is ionized and 50% is non-ionized.

Acidic drugs are better absorbed in acidic media (aspirin in the stomach).

Basic drugs are better absorbed in alkaline media (diazepam in the intestine).

Strongly acidic (heparin) and strongly basic (aminoglycosides) drugs usually remain ionized at all pH; hence they are poorly absorbed.



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.

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. Thus, in areas of high expression, P-glycoprotein reduces drug absorption.

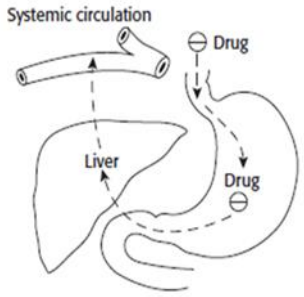
Bioavailability: Bioavailability is defined as the fraction of unchanged drug reaching the systemic circulation following administration by any route.

For an intravenous dose, bioavailability is assumed to be 100%. For a drug administered orally, bioavailability may be less than 100% for two main reasons: incomplete extent of absorption across the gut wall and first-pass elimination by the liver.

If two formulations of the same drug produce equal bioavailability, they are said to be **bioequivalent.**

Factors Affecting Bioavailability:

a. First-pass hepatic metabolism: When drugs are administered orally, they have to pass via gut wall →portal vein→ liver →systemic circulation. During this passage, certain drugs get metabolized and are removed or inactivated before they reach the systemic circulation. This process is known as first-pass metabolism. The net result is a decreased bioavailability of the drug and diminished therapeutic response.



b. Solubility of the drug: 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.

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.