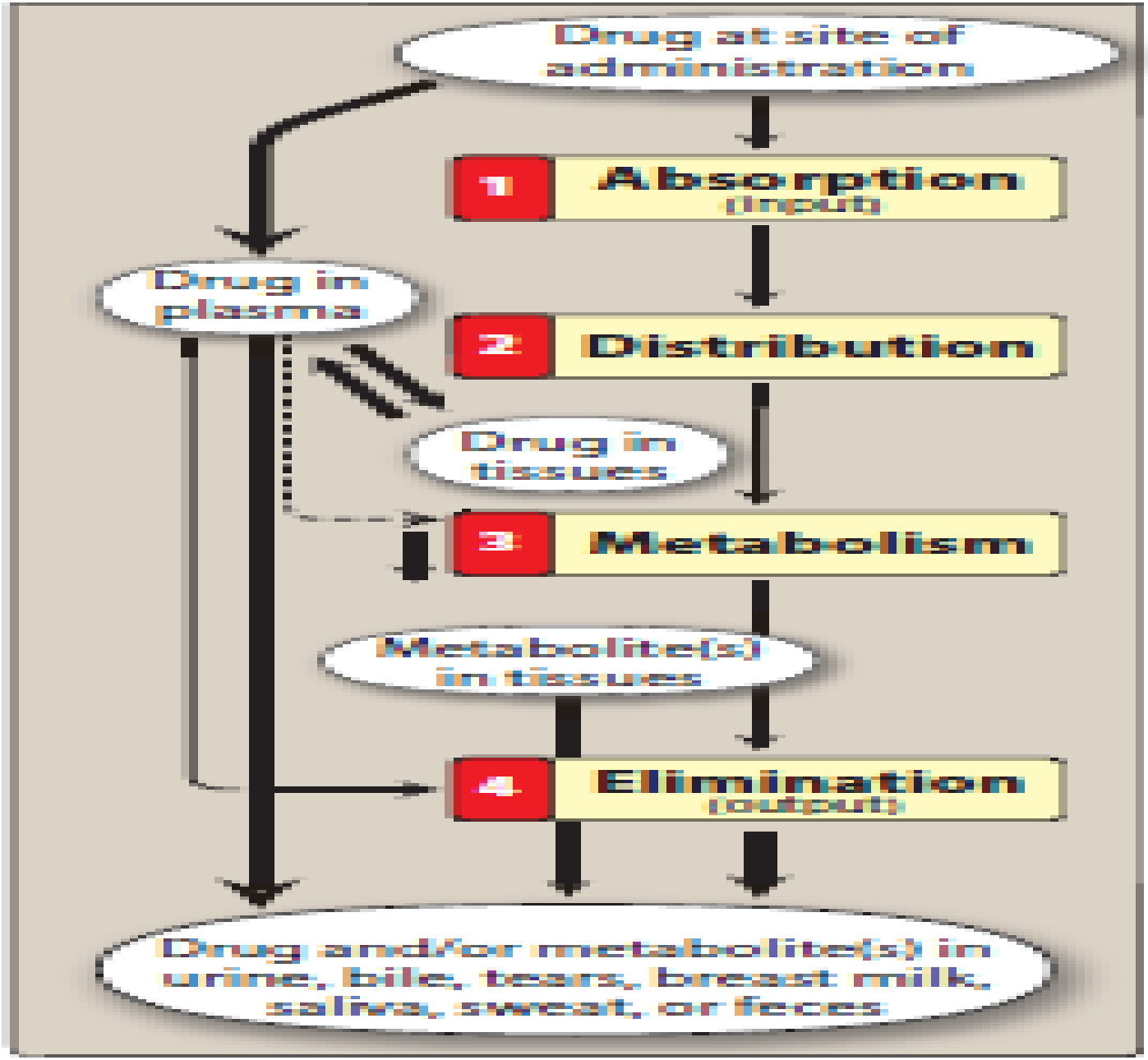
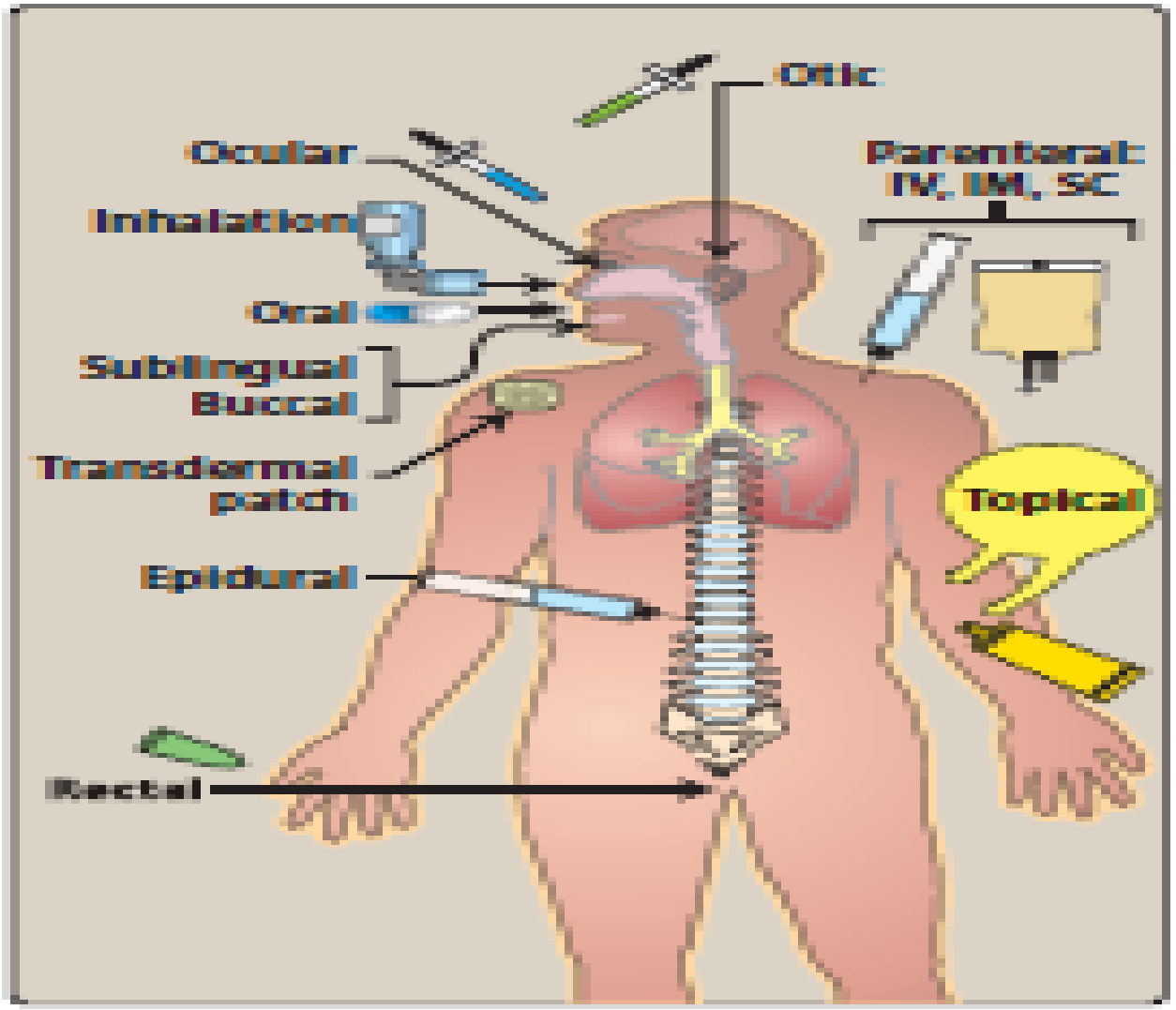
Pharmacokinetics

- refers to what the body does to a drug
- pharmacodynamics: describes what the drug does to the body.
- *Four pharmacokinetic properties determine the onset, intensity,and the duration of drug action


Drug at site of administration
1 Absorption (input)
Drug in plasma
2 Distribution
Drug in tissues
3 Metabolism
Metabolite(s) in tissues
4 Elimination (output)
Drug and/or metabolite(s) in urine, bile, tears, breast milk, saliva, sweat, or feces

- • **Absorption**
- • **Distribution**
- • **Metabolism**
- • **Elimination**
- Using knowledge of pharmacokinetic to know the route of administration, the dose,the frequency, and the duration of treatment.

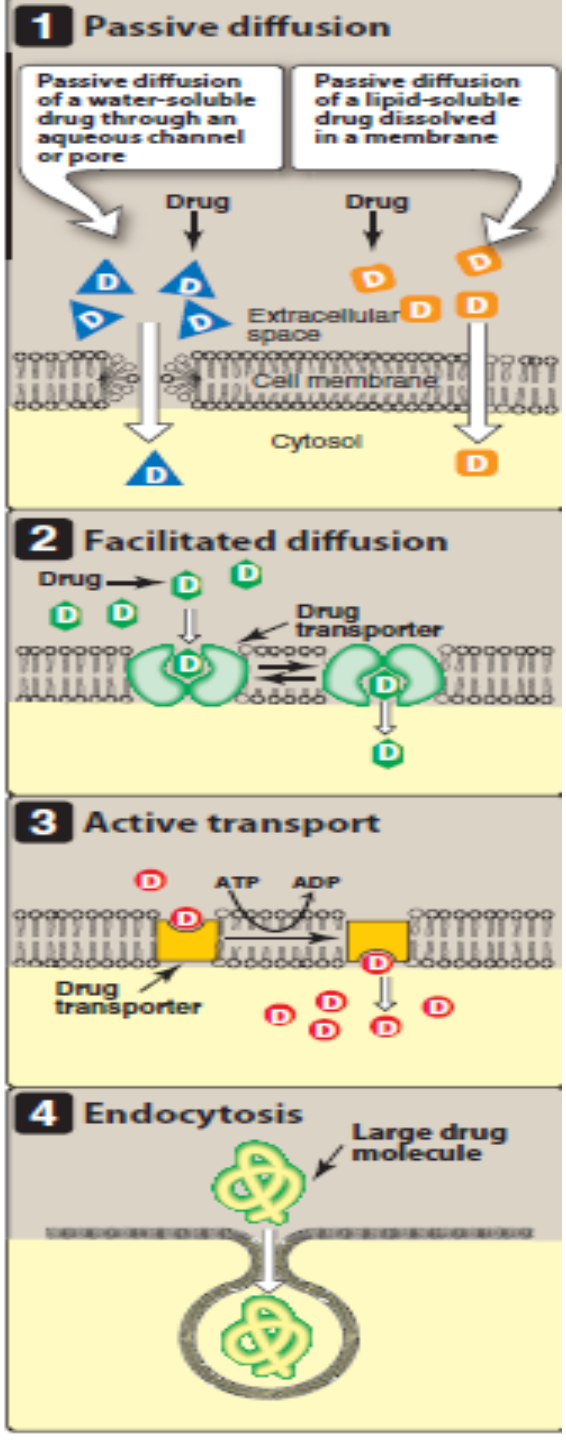
ROUTES OF DRUG ADMINISTRATION



ABSORPTION OF DRUGS :

Absorption is the transfer of a drug from the site of administration to thebloodstream

- **A.Mechanisms of absorption of drugs from the GI tract**
- Depending on their chemical properties, drugs may be absorbed from the GI tract by
- 1 :passive diffusion 2:facilated diffusion
- 3:active transport 4:endocytosis & exocytosis

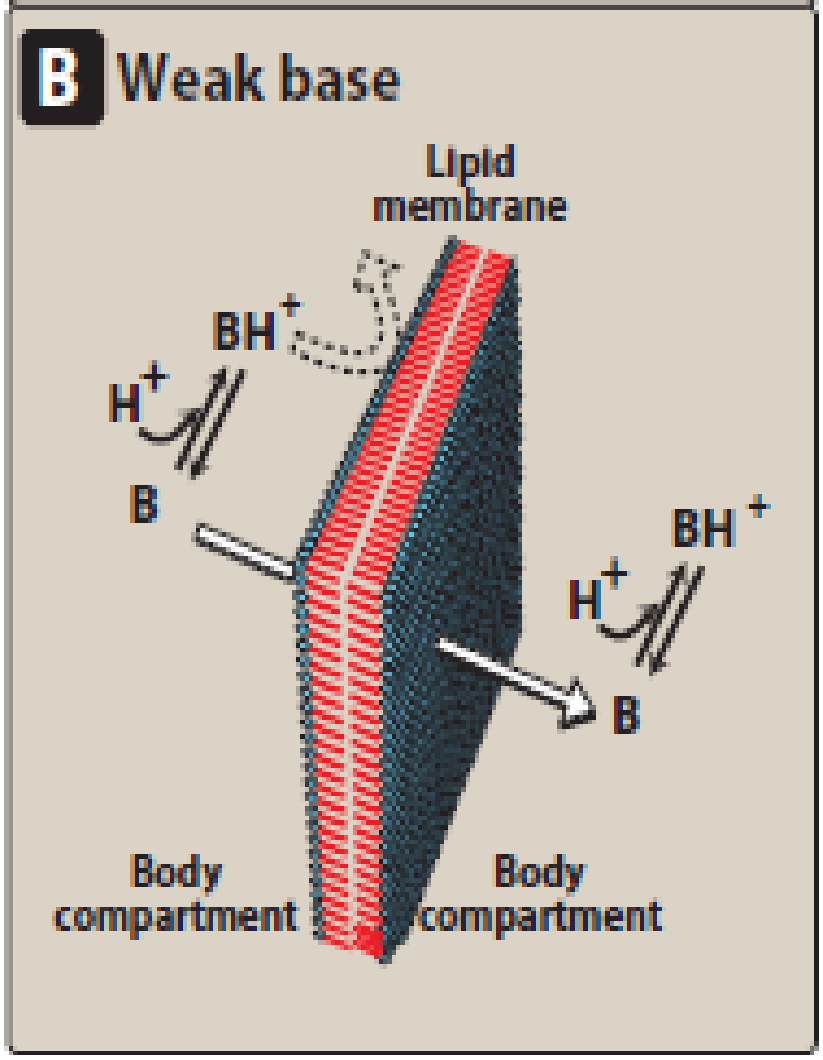

1 Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
Extracellular space
Cell membrane
Cytosol
2 Facilitated diffusion
Drug
Drug transporter
3 Active transport
ATP
ADP
Drug transporter
4 Endocytosis
Large drug molecule

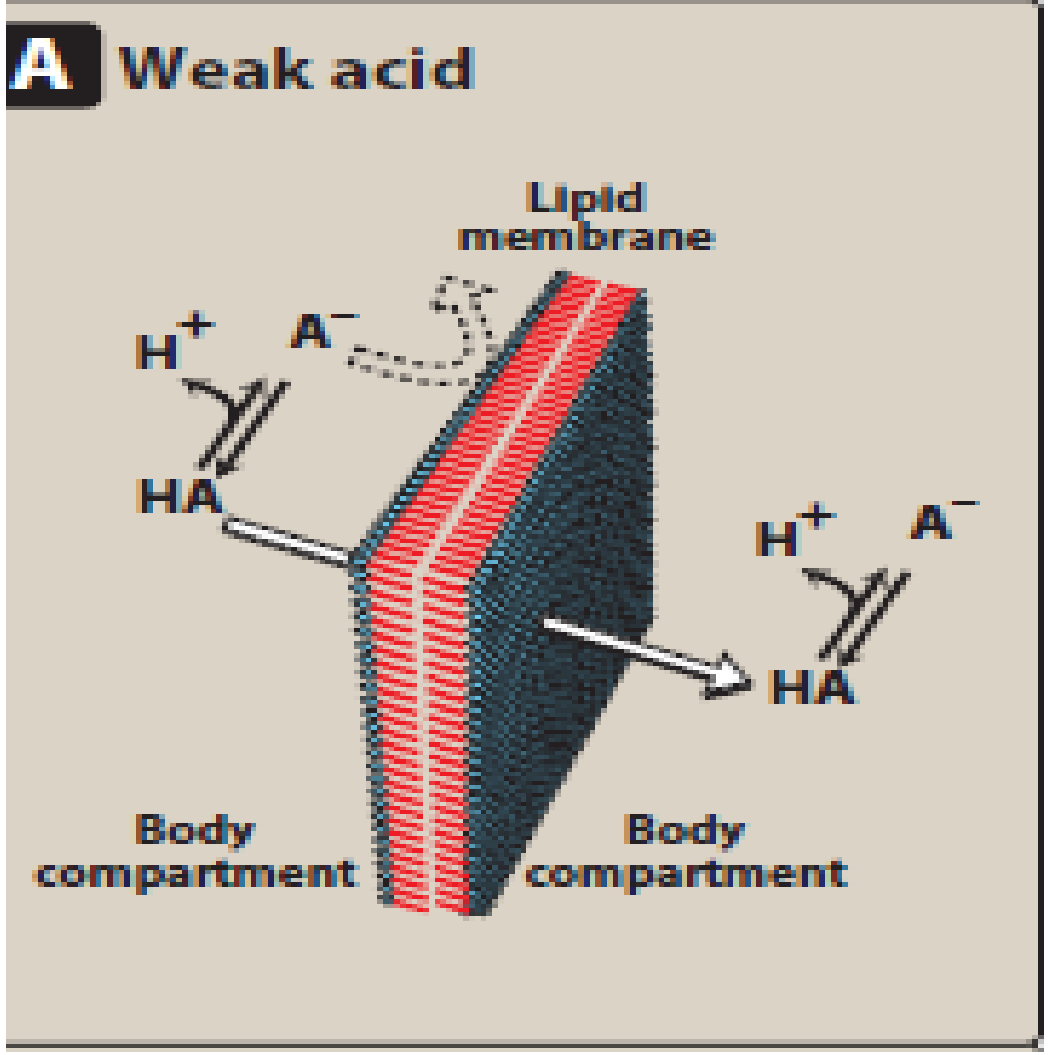
A . Factors influencing absorption

1. **Effect of pH on drug absorption:** Most drugs are either weak acids or weak bases

- 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):

- drug passes through membranes more readily if it is uncharged The pKa is a measure of the strength of the interaction of a compound with a proton.The lower the pKa of a drug, the more acidic it is. Conversely, the higher the pK8 , the more basic is the drug.]


B Weak base
Lipid membrane
BH+
H+
B
BH+
H+
B
Body compartment
Body compartment


A Weak acid
Lipid membrane
H+
A−
HA
H+
A−
HA
Body compartment
Body compartment

2.Blood flow to the absorption site:
The intestines receive much more blood flow than the stomach

- **3. Total surface area available for absorption:** With a surface rich in brush borders containing microvilli, the intestine has a surface

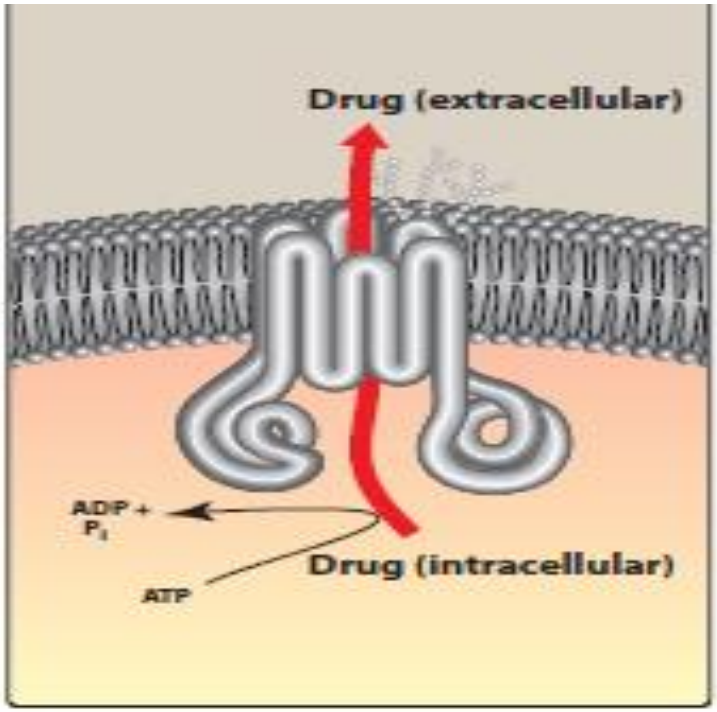
area about 1000-fold that of the stomach •

4.Expression of P-glycoprotein

- transporter protein responsible for transporting various molecules

*Its involved in transportation of drugs from tissues to blood

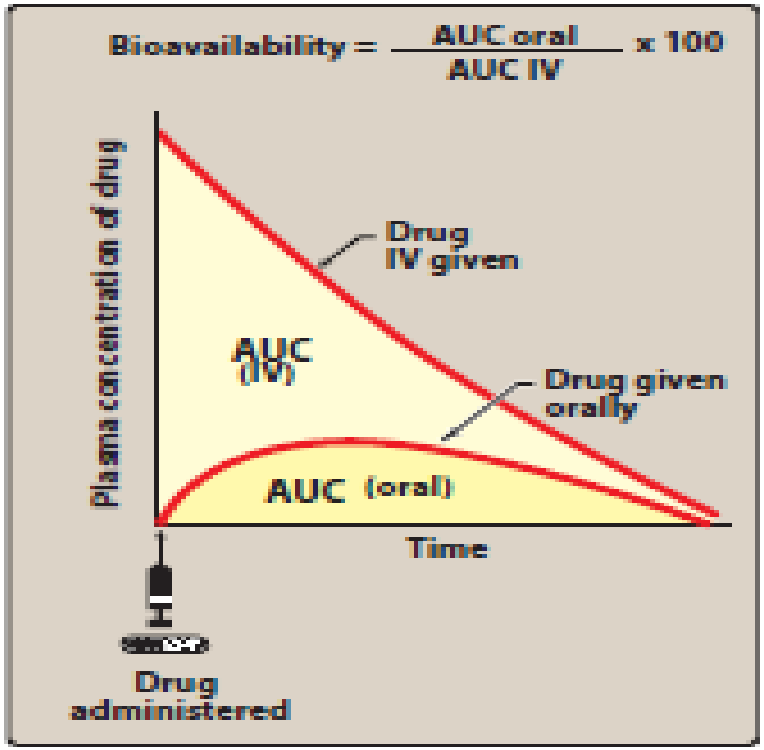
-



C. 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 nonintravenous routes of administration.

- **1. Determination of bioavailability:** 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.



2. Factors that influence bioavailability

- **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

**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

-

b. Solubility of the drug

- *Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes
- *drugs that are extremely lipophilic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells

- **c. Chemical instability:**
- Some drugs, such as *penicillin G,* are unstable in the pH of the gastric contents. Others, such as*insulin,* are destroyed in the GI tract by degradative enzymes
- **d. Nature of the drug formulation:** Drug absorption may be altered by factors unrelated to the chemistry of the drug

. DRUG DISTRIBUTION

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

- The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, the tissue volume, the degree of binding of the drug to plasma and tissue proteins, and the relative lipophilicity of the drug

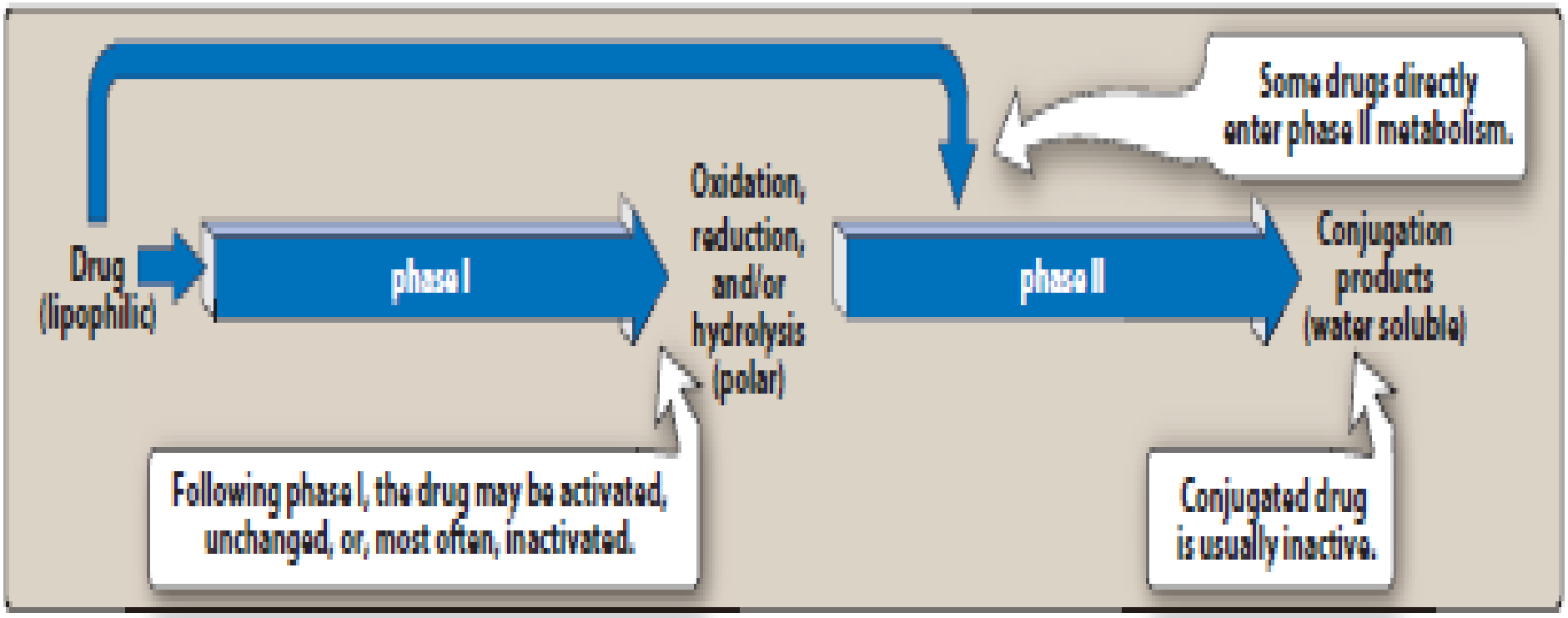
- **Volume of distribution**
- The apparent volume of distribution, Vd, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma

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.

Metabolism :

- Once a drug enters the body, the process of elimination begins.
- It’s a process of chemical alteration of drugs in the body and converted to inactive them by various biochemical reaction
- (it’s a process convert drug into more polar water soluble compounds so that they are easily excreted throught kidney)

Reactions of drug metabolism



Reactions of drug metabolism

- The kidney cannot efficiently eliminate lipophilic drugs that readily
- cross cell membranes and are reabsorbed in the distal convoluted
- tubules. Therefore, lipid-soluble agents are first metabolized into morepolar (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.

2.Phase II: This phase consists of conjugation reactions

*If the metabolite from phase I metabolism is sufficiently polar, it can be excreted by the kidneys

*many phase I metabolites are still too lipophilic to be excreted. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar

*some drug may enter phase II directly and become conjugated without prior phase I metabolism the highly polar drug conjugates are then excreted by the kidney or bile

excretion of drugs

its the process of removing a drug and its metabolites from the body

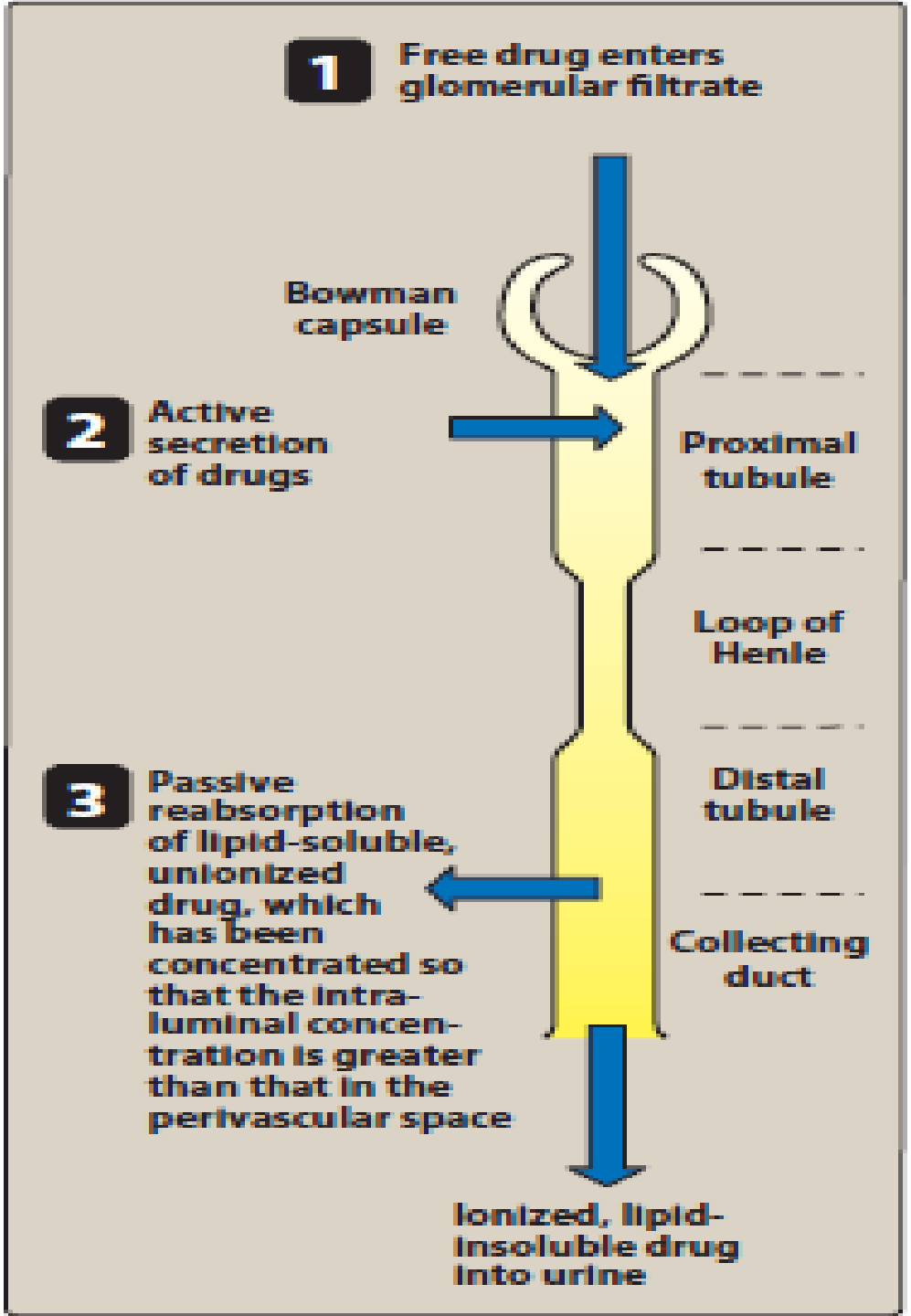
*the most important being elimination through the kidney into the urine.

*Drug clearance may also occur via the intestines, bile, lungs, and breast

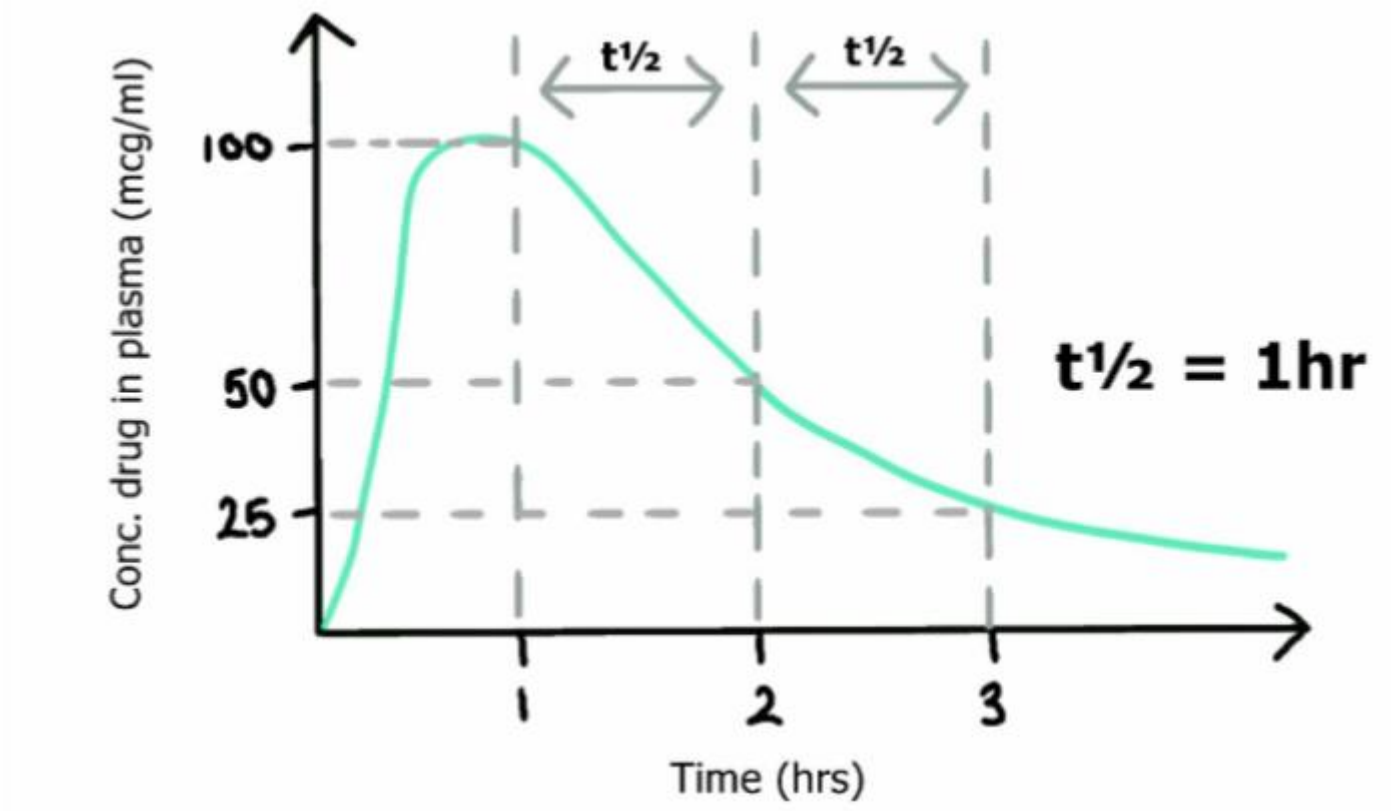
Milk sweat, saliva, tears

Renal elimination of a drug

- Elimination of drugs via the kidneys into urine involves the processes
- of glomerular filtration, active tubular secretion, and passive tubular
- reabsorption.


1
Free drug enters glomerular filtrate
Bowman capsule
2
Active secretion of drugs
Proximal tubule
Loop of Henle
Distal tubule
3
Passive reabsorption of lipid-soluble, unionized drug, which has been concentrated so that the intra-luminal concen-tration is greater than that in the perivascular space
Collecting duct
Ionized, lipid-insoluble drug into urine

Half-life is the time it takes for the drug concentration to reduce by half. This depends on both metabolism and excretion, and so each drug will have a different half-life.


t½
t½
100
50
25
Conc. drug in plasma (mcg/ml)
1
2
3
Time (hrs)
t½ = 1hr


thank
you