Pharmacokinetics

Dr. Ahmed Faisal

Absorption of Drugs

Absorption is the transfer of a drug from its site of administration to the bloodstream.

The rate and efficiency of absorption depend on the route of administration.

For IV delivery, absorption is complete; that is, the total dose of drug reaches the systemic circulation.

Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability.

For example, the oral route requires that a drug dissolve in the GI fluid and then penetrate the epithelial cells of the intestinal mucosa, yet disease states or the presence of food may affect this process.

A. Transport of a drug from the GI tract

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

1. Passive diffusion:

The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments; that is, the drug moves from a region of high concentration to one of lower concentration.

Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity.

The vast majority of drugs gain access to the body by this mechanism.

Lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane bilayers.

Water-soluble drugs penetrate the cell membrane through aqueous channels or pores.

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, moving them from an area of high concentration to an area of low concentration.

This process is known as facilitated diffusion, does not require energy, can be saturated, and may be inhibited.

2. Active transport:

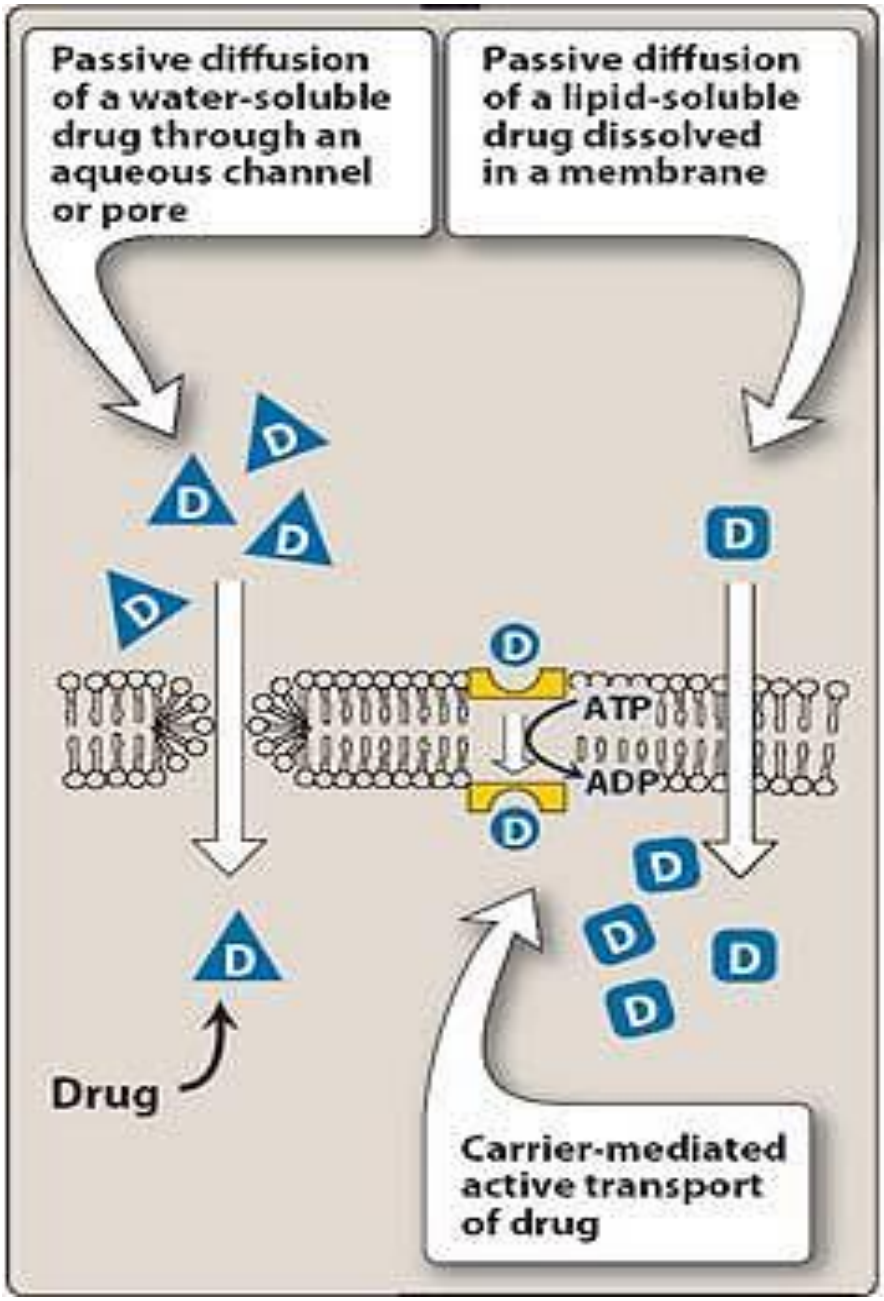
This mode of drug entry also involves specific carrier proteins that span the membrane.

A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins.

Active transport is energy-dependent and is driven by the hydrolysis of adenosine triphosphate.

It is capable of moving drugs against a concentration gradient (from a region of low drug concentration to a higher drug concentration.

The process shows saturation kinetics for the carrier.



Schematic representation of drugs crossing a cell membrane of an epithelial cell of the gastrointestinal tract

3. Endocytosis and exocytosis

This type of drug delivery transports drugs of exceptionally large size across the cell membrane.

Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug-filled vesicle.

Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process.

For example, vitamin B12 is transported across the gut wall by endocytosis.

Certain neurotransmitters (for example, norepinephrine) are stored in membrane-bound vesicles in the nerve terminal and are released by exocytosis.

B. Effect of pH on drug absorption

Most drugs are either weak acids or weak bases.

Acidic drugs (HA) release an 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):

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

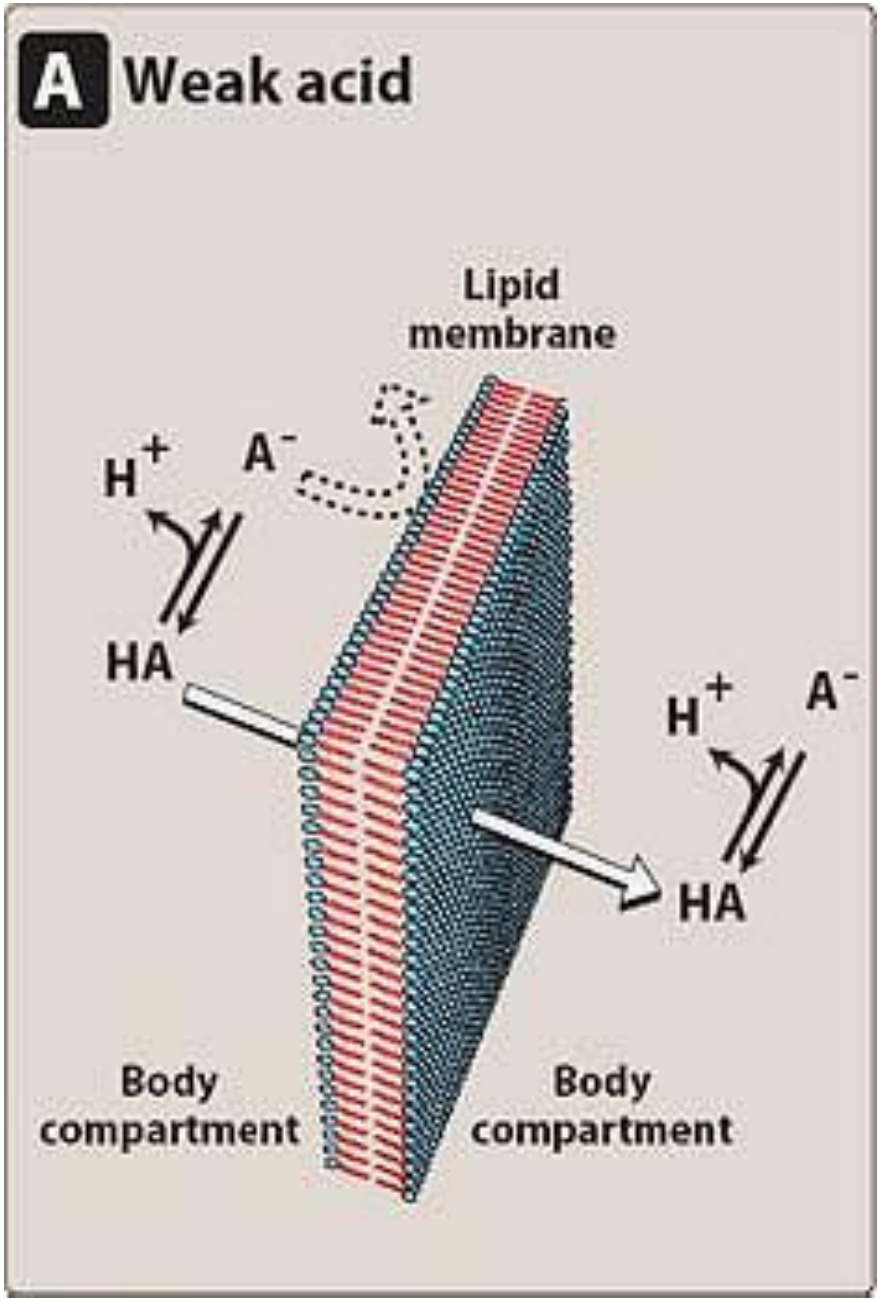
1. Passage of an uncharged drug through a membrane:

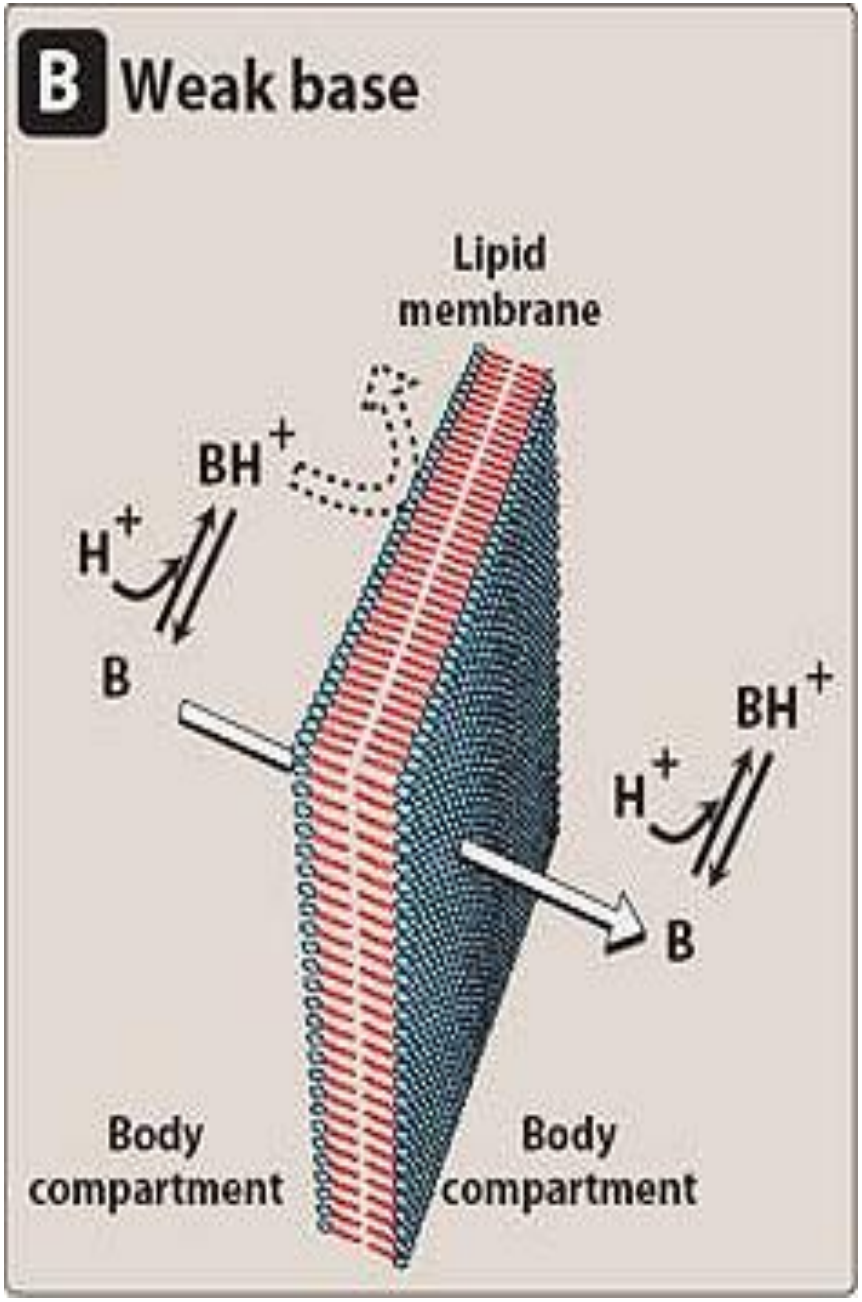
A drug passes through membranes more readily if it is uncharged.

Thus, for a weak acid, the uncharged form HA can permeate through membranes, and A^- cannot.

For a weak base, the uncharged form B can penetrates through the cell membrane, but BH^+ cannot.

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.





A. Diffusion of the non-ionized form of a weak acid through a lipid membrane.
B. Diffusion of the non-ionized form of a weak base through a lipid membrane.

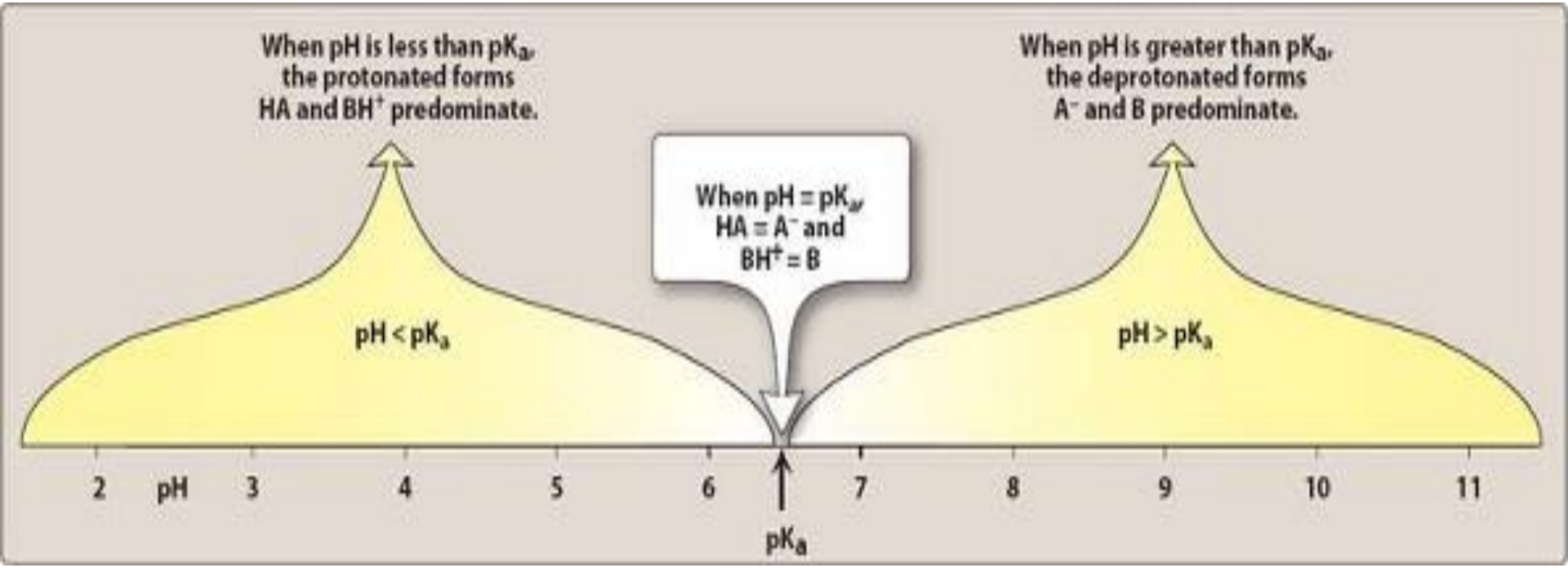
The ratio between the two forms is determined by the pH at the site of absorption and by the strength of the weak acid or weak base (pKa).

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 pKa, the more basic is the drug.

Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.



The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pKa of the drug.

For illustrative purposes, the drug has been assigned a pKa of 6.5.

C. Physical factors influencing absorption

1. Blood flow to the absorption site:

Blood flow to the intestine is much greater than the flow to the stomach; thus, absorption from the intestine is favored over that from the stomach.

Note: Shock severely reduces blood flow to cutaneous tissues, thus minimizing the absorption from SC administration.

2. Total surface area available for absorption:

Because the intestine has a surface rich in microvilli, it has a surface area about 1000-fold that of the stomach; thus, absorption of the drug across the intestine is more efficient.

3. Contact time at the absorption surface:

If a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed.

Anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

Note: Parasympathetic input increases the rate of gastric emptying, whereas sympathetic input as well as anticholinergics prolongs gastric emptying.

The presence of food in the stomach both dilutes the drug and slows gastric emptying.

A drug taken with a meal is generally absorbed more slowly.

Bioavailability

Bioavailability is the drug that reaches the systemic circulation.

Bioavailability is expressed as the fraction of administered drug that gains access to the systemic circulation in a chemically unchanged form.

For example, if 100 mg of a drug are administered orally and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7 or 70%.

A. Determination of bioavailability

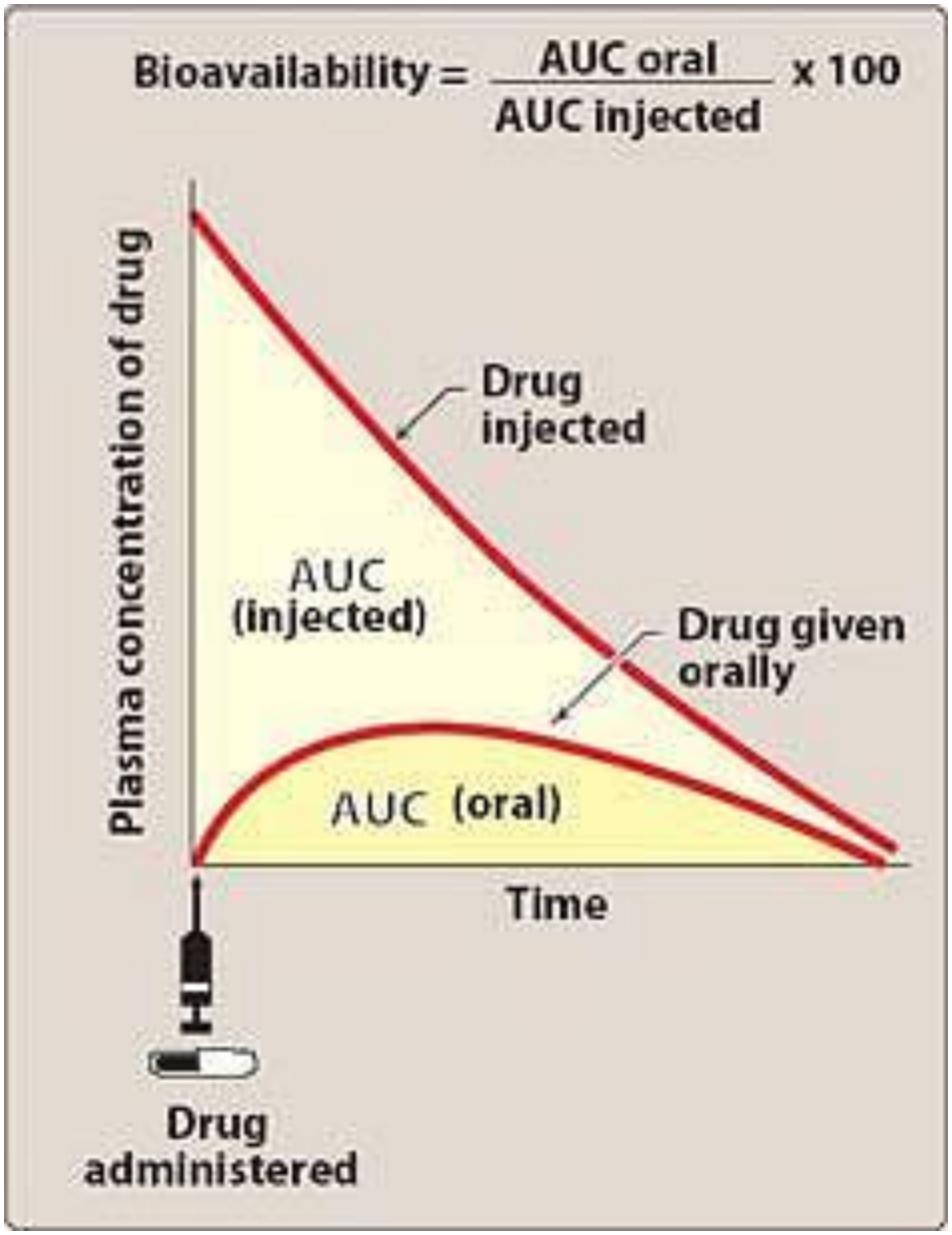
Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels achieved by IV injection in which all of the agent rapidly enters the circulation.

When the drug is given orally, only part of the administered dose appears in the plasma.

By plotting plasma concentrations of the drug versus time, one can measure the area under the curve (AUC).

This curve reflects the extent of absorption of the drug.

Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection.



Determination of the bioavailability of a drug

B. Factors that influence bioavailability

1. First-pass hepatic metabolism:

When a drug is absorbed across the GI tract, it enters the portal circulation before entering the systemic circulation.

If the drug is rapidly metabolized by the liver, the amount of unchanged drug that gains access to the systemic circulation is decreased.

Many drugs, such as *propranolol* or *lidocaine*, undergo significant biotransformation during a single passage through the liver.

2. Solubility of the drug:

Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes.

Drugs that are extremely hydrophobic are also poorly absorbed, because they are totally 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 hydrophobic, yet have some solubility in aqueous solutions.

This is one reason why many drugs are weak acids or weak bases.

There are some drugs that are highly lipid-soluble, and they are transported in the aqueous solutions of the body on carrier proteins such as albumin.

3. 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.

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 (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

C. Bioequivalence

Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.

Two related drugs with a significant difference in bioavailability are said to be bioinequivalent.

D. Therapeutic equivalence

Two similar drugs are therapeutically equivalent if they have comparable efficacy and safety.

Clinical effectiveness often depends on both the maximum serum drug concentrations and on the time required (after administration) to reach peak concentration.

Therefore, two drugs that are bioequivalent may not be therapeutically equivalent.

Drug Distribution

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

The delivery of a drug from the plasma to the interstitium primarily depends on blood flow, capillary permeability, the degree of binding of the drug to plasma and tissue proteins, and the relative hydrophobicity of the drug.

A. Blood flow

The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs.

Blood flow to the brain, liver, and kidney is greater than that to the skeletal muscles; adipose tissue has a still lower rate of blood flow.

This differential blood flow partly explains the short duration of hypnosis produced by a bolus IV injection of *thiopental*.

The high blood flow, together with the superior lipid solubility of *thiopental,* permit it to rapidly move into the CNS and produce anesthesia.

Slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration sufficiently so that the higher concentrations within the CNS decrease, and consciousness is regained.

Although this phenomenon occurs with all drugs to some extent, redistribution accounts for the extremely short duration of action of *thiopental* and compounds of similar chemical and pharmacologic properties.

B. Capillary permeability

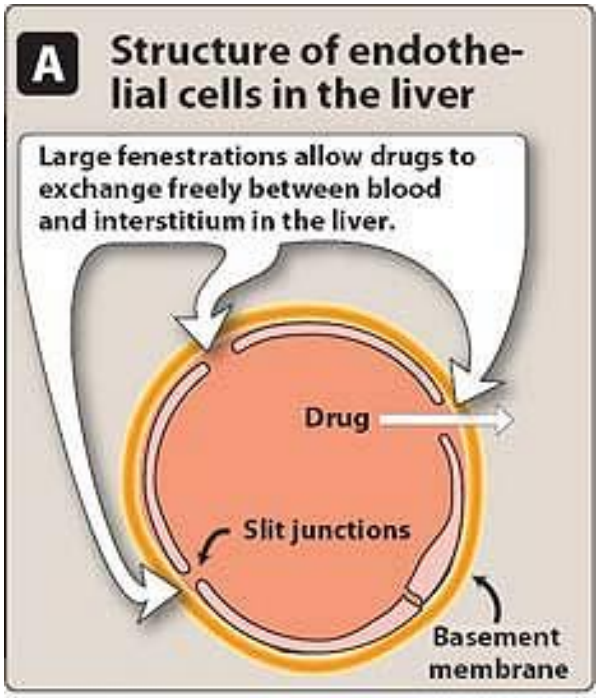
Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

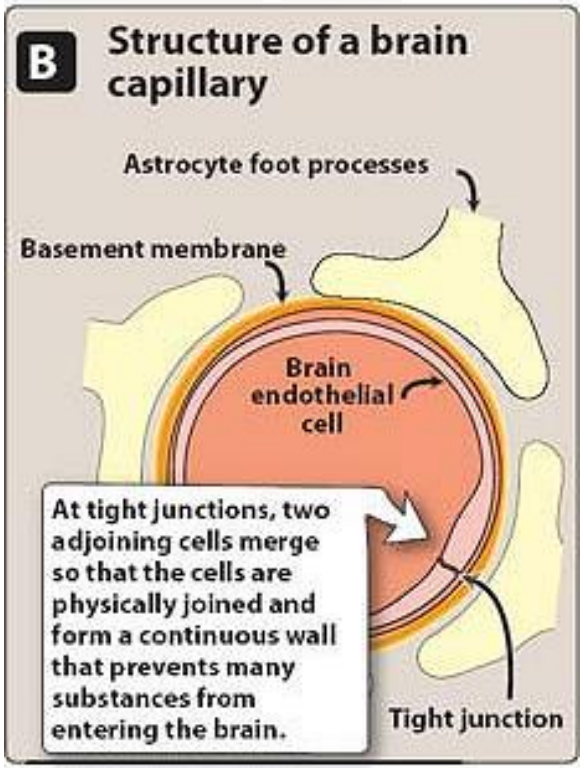
1. Capillary structure:

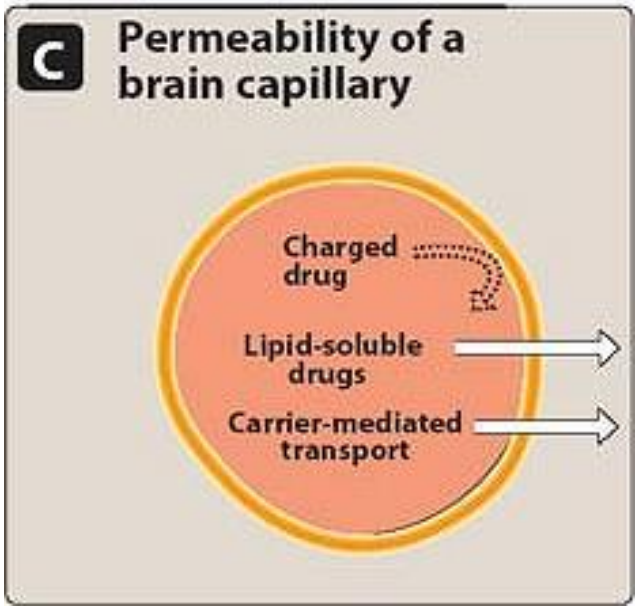
Capillary structure varies widely in terms of the fraction of the basement membrane that is exposed by slit junctions between endothelial cells.

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

This contrasts with the liver and spleen, where a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.







Cross-section of liver and brain capillaries

Blood-brain barrier: To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported.

For example, a specific transporter for the large neutral amino acid transporter carries *levodopa* into the brain.

Lipid-soluble drugs readily penetrate into the CNS because they can dissolve in the membrane of the endothelial cells.

Ionized or polar drugs generally fail to enter the CNS because they are unable to pass through the endothelial cells of the CNS, which have no slit junctions.

These tightly juxtaposed cells form tight junctions that constitute the so-called blood-brain barrier.

2. Drug structure:

The chemical nature of a drug strongly influences its ability to cross cell membranes.

Hydrophobic drugs, which have a uniform distribution of electrons and no net charge, readily move across most biologic membranes.

These drugs can dissolve in the lipid membranes and, therefore, permeate the entire cell's surface.

The major factor influencing the hydrophobic drug's distribution is the blood flow to the area.

By contrast, hydrophilic drugs, which have either a nonuniform distribution of electrons or a positive or negative charge, do not readily penetrate cell membranes, and therefore, must go through the slit junctions.

C. Binding of drugs to plasma proteins

Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment.

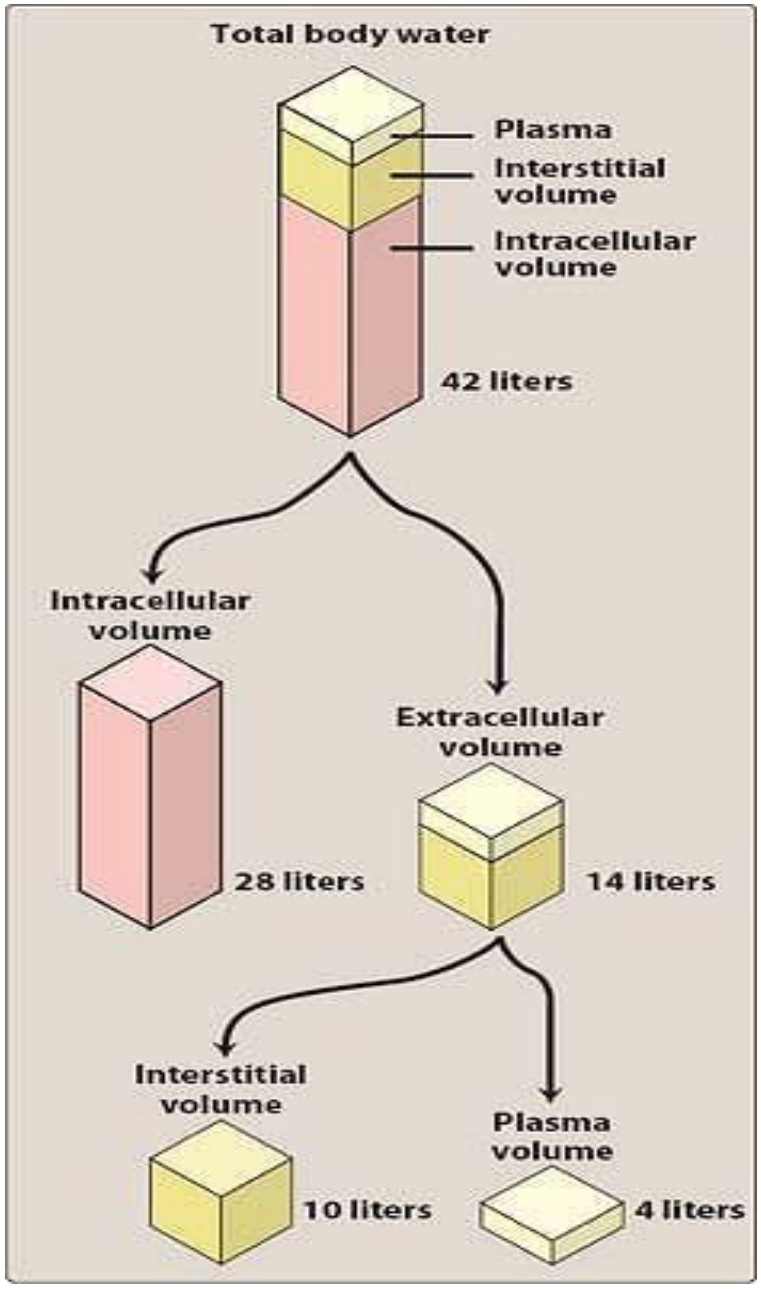
Plasma albumin is the major drug-binding protein and may act as a drug reservoir; that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein.

This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

Volume of Distribution

The volume of distribution is a hypothetical volume of fluid into which a drug is dispersed.

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



Relative size of various distribution volumes within a 70-kg individual

A. Water compartments in the body

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

1. Plasma compartment:

If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment.

As a consequence, the drug distributes in a volume (the plasma) that is about six percent of the body weight or, in a 70-kg individual, about 4 L of body fluid. *Heparin* shows this type of distribution.

2. Extracellular fluid:

If a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions of the capillaries into the interstitial fluid.

Hydrophilic drugs cannot move across the lipid membranes of cells to enter the water phase inside the cell.

Therefore, these drugs distribute into a volume that is the sum of the plasma water and the interstitial fluid, which together constitute the extracellular fluid.

This is about twenty percent of the body weight, or about 14 L in a 70-kg individual.

Aminoglycoside antibiotics show this type of distribution.

3. Total body water:

If a drug has a low molecular weight and is hydrophobic, not only can it move into the interstitium through the slit junctions, but it can also move through the cell membranes into the intracellular fluid.

The drug, therefore, distributes into a volume of about sixty percent of body weight, or about 42 L in a 70-kg individual.

Ethanol exhibits this apparent volume of distribution.

4. Other sites:

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

B. Apparent volume of distribution

A drug rarely associates exclusively with only one of the water compartments of the body.

Majority of drugs distribute into several compartments, often avidly binding cellular components; for example, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), or nucleic acids (abundant in the nuclei of cells).

Therefore, the volume into which drugs distribute is called the apparent volume of distribution, or Vd.

C. Determination of Vd

The concentration within the vascular compartment is the total amount of drug administered, divided by the volume into which it distributes, Vd:

$$\mathbf{C=D/Vd \quad or \quad Vd=D/C}$$

where C = the plasma concentration of the drug and D = the total amount of drug in the body.

For example, if 25 mg of a drug (D = 25 mg) are administered and the plasma concentration is 1 mg/L, then Vd = 25 mg/1 mg/L = 25 L.

Vd is useful because it can be used to calculate the amount of drug needed to achieve a desired plasma concentration.

For example, assume the arrhythmia of a cardiac patient is not well controlled due to inadequate plasma levels of *digitalis*.

Suppose the concentration of the drug in the plasma is C_1 and the desired level of *digitalis* (known from clinical studies) is a higher concentration, C_2.

The clinician needs to know how much additional drug should be administered to bring the circulating level of the drug from C_1 to C_2:

The difference between the two values is the additional dosage needed, which equals Vd (C2 - C1).

Binding of Drugs to Plasma Proteins

Drug molecules may bind to plasma proteins (usually albumin).

Bound drugs are pharmacologically inactive; only the free, unbound drug can act on target sites in the tissues, elicit a biologic response, and be available to the processes of elimination.

A. Binding capacity of albumin

The binding of drugs to albumin is reversible and may show low capacity (one drug molecule per albumin molecule) or high capacity (a number of drug molecules binding to a single albumin molecule).

Drugs can also bind with varying affinities.

Albumin has the strongest affinities for anionic drugs (weak acids) and hydrophobic drugs.

Most hydrophilic drugs and neutral drugs do not bind to albumin.

B. Competition for binding between drugs

When two drugs are given, each with high affinity for albumin, they compete for the available binding sites.

The drugs with high affinity for albumin can be divided into two classes, depending on whether the dose of drug (the amount of drug found in the body under conditions used clinically) is greater than, or less than, the binding capacity of albumin (quantified as the number of millimoles of albumin multiplied by the number of binding sites.

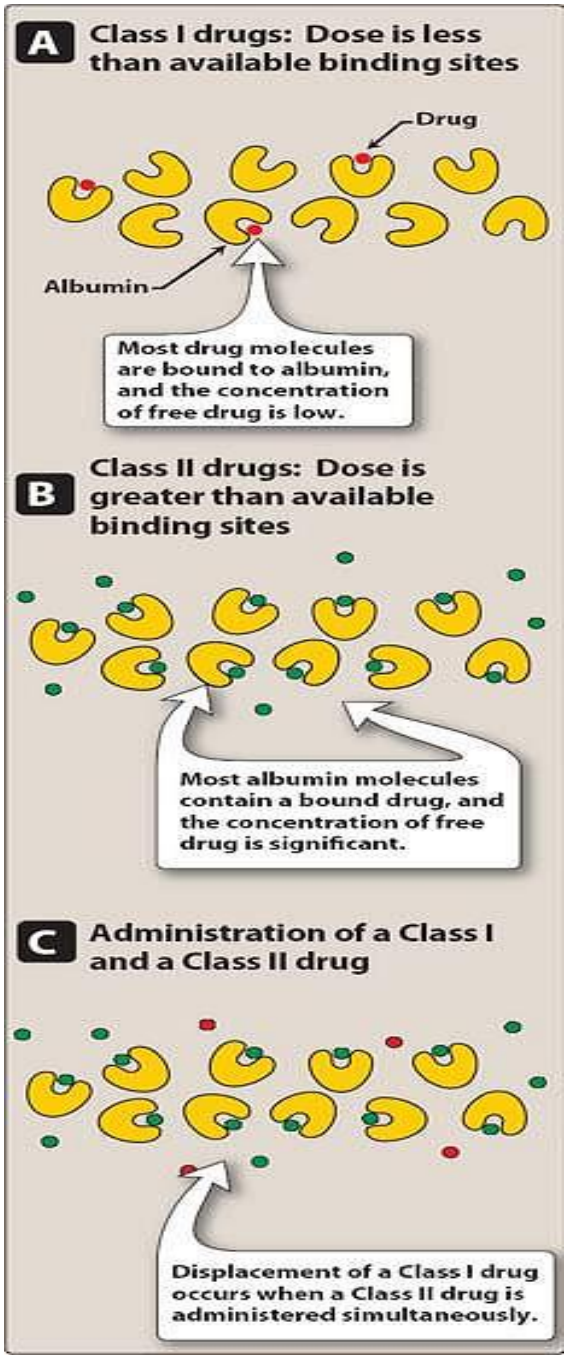
1. Class I drugs: If the dose of drug is less than the binding capacity of albumin, then the dose/capacity ratio is low.

The binding sites are in excess of the available drug, and the bound-drug fraction is high.

This is the case for Class I drugs, which include the majority of clinically useful agents.

2. Class II drugs: These drugs are given in doses that greatly exceed the number of albumin binding sites.

The dose/capacity ratio is high, and a relatively high proportion of the drug exists in the free state, not bound to albumin.



Binding of Class I and Class II drugs to albumin when drugs are administered alone (A and B) or together (C).

3. Clinical importance of drug displacement: This assignment of drug classification assumes importance when a patient taking a Class I drug, such as *warfarin*, is given a Class II drug, such as a *sulfonamide antibiotic*.

Warfarin is highly bound to albumin, and only a small fraction is free.

This means that most of the drug is bound to albumin and is inert in terms of exerting pharmacologic actions.

If a *sulfonamide* is administered, it displaces *warfarin* from albumin, leading to a rapid increase in the concentration of free *warfarin* in plasma, because almost 100 percent is now free, compared with the initial small percentage.

The increase in *warfarin* concentration may lead to increased therapeutic effects, as well as increased toxic effects, such as bleeding.