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 dissolves in the GI fluid and then penetrates the epithelial cells of the intestinal mucosa, yet disease states or the presence of food may affect this process.

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.

Passive diffusion: the drug moves from a region of high concentration to one of lower concentration (Fick’s low). Passive diffusion does not involve a carrier. 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 bi-layers. 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. This process is known as facilitated diffusion. This type of diffusion does not require energy, can be saturated, and may be inhibited.

Active transport: This mode of drug entry also involves specific carrier proteins that cross the membrane. Active transport is energy-dependent and is driven by the hydrolysis of adenosine tri-phosphate. It is capable of moving drugs against a concentration gradient that is, from a region of low drug concentration to one of higher drug concentration.
**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, nor epinephrine) are stored in membrane-bound vesicles in the nerve terminal and are released by exocytosis.

**Factors affecting Drug absorption related to patient:**
- Route of administration.
- Gastric PH.
- Content of the GIT

**Factors affecting absorption in pediatric patients:**
- Gastrointestinal pH changes
- Gastric emptying
- Gastric enzymes
- Bile acids & biliary function
- Gastrointestinal flora
- Formula/food interaction

**Effect of pH on drug absorption** Most drugs are either weak acids or weak bases. A drug passes through membranes more readily if it is uncharged.

**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.
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. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

### IV. Bioavailability

Bioavailability is the fraction of administered drug that reaches 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 seventy percent.

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.
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.

2. Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, 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.

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.
**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.

**Capillary permeability**

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

**Capillary structure**: Capillary structure varies widely in the fraction of the basement membrane that is exposed by opening (slit) junctions between endothelial cells. In the brain, the capillary structure is continuous, and there are no slit junctions unlike liver and spleen.

**Blood-brain barrier**: To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported. By contrast, 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 arranged cells form tight junctions that constitute the so-called *blood-brain barrier (BBB)*.

**Drug structure**: The chemical nature of a drug strongly influences its ability to cross cell membranes, whether it is hydrophobic or hydrophilic drug, charged or uncharged. The major factor influencing the hydrophobic drug's distribution is the blood flow to the area. While hydrophilic drugs, do not readily penetrate cell membranes, and therefore, must go through the slit junctions.
Binding of drugs to plasma proteins

Reversible binding to plasma proteins keeps drugs in a non-diffusible form and slows their transfer out of the vascular compartment. 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 the 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.

Water compartments in the body

Once a drug enters the body, from any route of administration, it has the potential to distribute into any one of the following compartments of body water.

1- **Plasma compartment**: If a drug has a very large molecular weight or binds extensively to plasma proteins, it is trapped within the plasma (vascular) compartment.

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.

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.

4- **Other sites**: In pregnancy, the fetus may take up drugs and thus increase the volume of distribution.
Apparent volume of distribution

The volume into which drugs distributes. (Vd). Or it is the partition coefficient of a drug between the plasma and the rest of the body.

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, leading to a biologic response, and be available to the processes of elimination.