UNIT

II

DRUG ABSORPTION & ITS MECHANISM

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INTRODUCTION

The process of transporting the drug from the site of administration to systemic circulation is referred to as drug absorption.

The drug concentration should be high enough to produce the desired effect. A drug that is completely but slowly absorbed may fail to produce a therapeutic response because the therapeutic level is not reached. As a result, the rate and extent of absorption of drug are two critical factors to be considered. This type of absorption pattern has several advantages:

The drug is absorbed very rapidly, so is very less susceptible to degradation or interaction with other components.

- Drug levels in the blood rapidly rise, resulting in a quicker onset of action.
- The drug's therapeutic response is more consistent, higher, and repeatable.

COMMON ROUTES OF DRUG ADMINISTRATION

The drugs for showing response can be administered in one of three ways:

The Enteral Route: Peroral, gastric, sublingual/buccal, and rectal routes are all part of the enteral route. The bulk of medications are administered through the gastrointestinal tract.

The Parenteral Route: The drug is dispensed through one or more layers of skin in this route of administration. While absorption is not required when the medication is administered intravenously, it is required for other parenteral routes (extravascular like the subcutaneous and intramuscular).

The Topical Route: The skin is the first major organ involved in this route of administration, followed by other organs like the eyes and mucous membranes for other parts.

The intranasal, inhalation, intravaginal, and transdermal routes may be considered enteral or topical, according to the above discussion.

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DRUG ABSORPTION MECHANISMS

The three major types of systems of drug transport that play a role in absorption are:

1. Transcellular/intracellular transport
2. Paracellular/intercellular transport
3. Vesicular transport

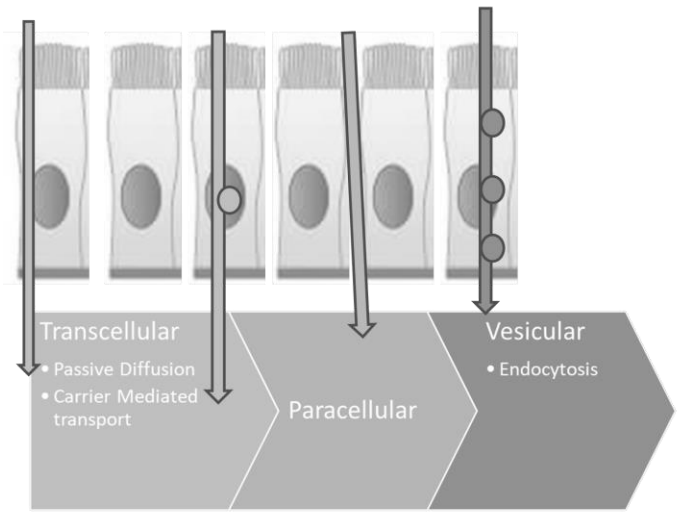

Figure 2.1: Illustration showing comparison of intracellular, intercellular and vesicular processes of transport.

INTRACELLULAR/TRANSCELLULAR TRANSPORT

It is known as medication transit through the GI epithelium. It is the most common method of medication delivery. The following are the various intracellular transport processes involved in medication absorption:

Passive Transport Processes

Apart from the energy required for molecular mobility, these transport systems require no additional energy (Brownian motion). There are several types of passive transport processes that can be distinguished:

- Process of passive diffusion.

- Pore transport procedure.
- Transport of ion pairs.
- Facilitated or mediated diffusion.

Active Transport Processes

This transport pathway requires ATP energy to move drug molecules from the extracellular to intracellular environment. These are classified into two types: primary active transport and secondary active transport. The secondary transport is further classified into two types:

- Symport (co-transport)
- Antiport (counter-transport)

Paracellular/Intercellular Transport

This is defined as drug transport across GI epithelial cell junctions. This route has a minor impact on medication absorption. Drug absorption is mediated by two paracellular transport pathways:

Permeation through epithelial cell tight junctions

This process essentially occurs through openings slightly larger than aqueous pores. This mechanism is used by compounds such as insulin and cardiac glycosides.

Persorption

Drug permeation through temporary openings formed by the shedding of two adjacent epithelial cells into the lumen.

VESICULAR OR CORPUSCULAR TRANSPORT (ENDOCYTOSIS)

These are energy-dependent processes that involve the engulfment of extracellular components within a segment of the cell membrane to form a saccule or vesicle (hence also called as corpuscular or vesicular transport). Fat and starch absorption, oil soluble vitamins like E, K, and water soluble vitamins like vitamin C are a few examples. Drug vesicular transport can be divided into two types:

a) **Pinocytosis:** The other name of process is cell drinking. In this process fluid solute are uptake.

b) **Phagocytosis** also known as cell eating. This process involves solid particulate adsorptive uptake.

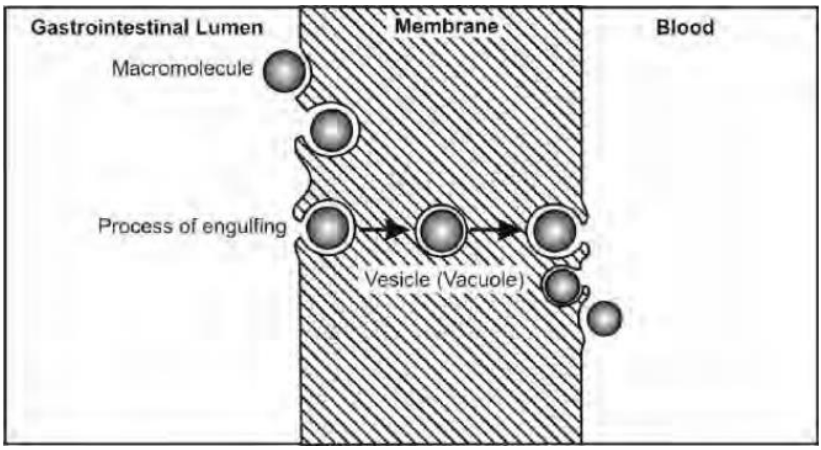

Figure 2.2: Endocytic uptake of macromolecules.

Few important drug absorption pathways

Passive Diffusion / Non-ionic diffusion

It is one of the most important step in the absorption of more than 90 percent of medications and requires no energy. This activity is propelled by the concentration gradient.

Fick's first law of diffusion best expresses passive diffusion, which states that the rate of diffusion is directly proportional to the concentration gradient across the membrane, and drug molecules diffuse from a higher concentration area to a lower concentration area until equilibrium is reached. The following equation can be used to express it mathematically:

$$\frac{dQ}{dt} = \frac{DAK_{m/w}}{h}(C_{GIT} - C)$$

dQ/dt = drug diffusion rate (amount/time). It also represents the rate at which the drug appears in the blood.

D = drug diffusion coefficient through membrane (area/time)

A = absorbing membrane surface area for drug diffusion (area)

Km/w = the drug's partition coefficient between the lipoidal membrane and the aqueous GI fluids (no units)

(CGIT – C) = difference in drug concentration between GI fluids and plasma, also known as the concentration gradient (amount/volume).

The medication is absorbed passively into the bloodstream, where it is quickly whisked away and disseminated across a larger volume of body fluids. As a result, the absorption site drug concentration (CGIT) remains higher than the plasma concentration (C). This is known as a sink state in terms of drug absorption.

Because D, A, Km/w, and h are constants under normal absorption conditions, the expression DAKm/w/h can be replaced by a single constant P known as the permeability coefficient. Furthermore, due to sink conditions, the drug concentration in plasma C is much lower than in CGIT (CGIT >> C). As a result, the above equation can be reduced to:

$$\frac{dQ}{dt} = PC_{GIT}$$

The above equation represents a first-order process expression. As a result, passive diffusion exhibits first-order kinetics.

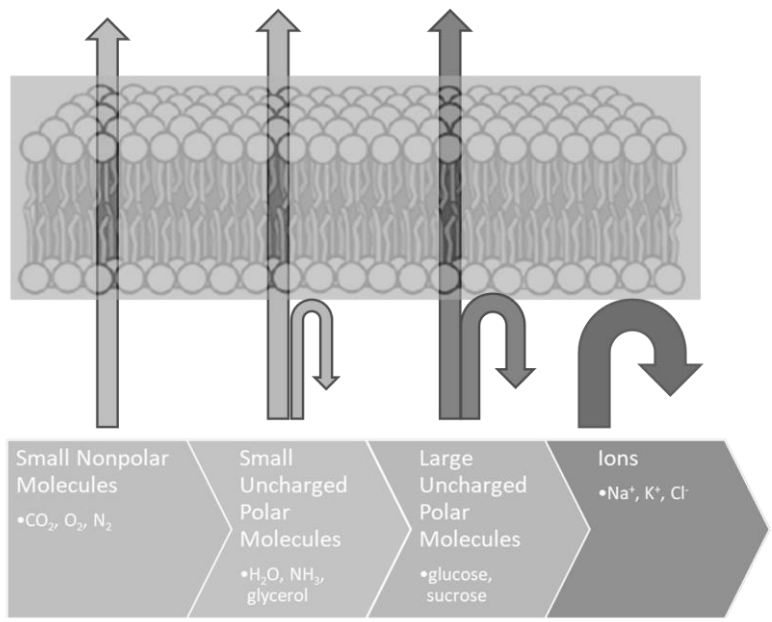

Figure 2.3: Shows the relative permeability of various molecules to a lipid bilayer.

Convective transport = Pore transport = Bulk flow

This mechanism is in charge of transporting chemicals through the aqueous protein channels in the cell membrane. The driving force is provided by the hydrostatic pressure or osmotic variations across the membrane. This mechanism absorbs drugs with low molecular weight (less than 100), tiny molecular size (smaller than the diameter of the pore), and are frequently water-soluble (such as urea, water, and sugars).

Transport of Ion Pairs

Ion-pair transport is used to transport medications like quaternary ammonium compounds and sulphonic acids that ionise at all pH levels. These ionic compounds form a reversible neutral combination with endogenous ions of the GIT, such as mucin. Passive diffusion necessitates the presence of both lipophilicity and water solubility, both of which are present in such neutral compounds. For example, propranolol forms an ion pair with oleic acid.

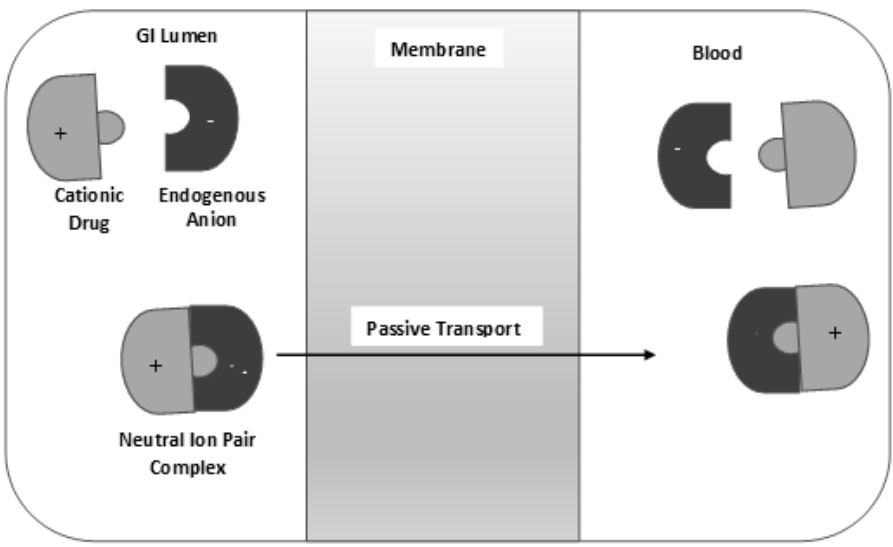

Figure 2.4: A cationic drug's ion-pair transport.

Transport via Carrier

Some polar substances, such as mono-saccharides, amino acids, and vitamins, pass through the membrane more easily because they form a

reversible or non-covalent carrier-solute complex with the solute molecules. This carrier-solute complex crosses the membrane, discharges the solute molecule, and then returns to its original location to restart the cycle by absorbing a new solute molecule. Membrane carriers are proteins (transport proteins) and may be enzymes.

The following are important characteristics of carrier-mediated transport:

- The outer surface of a carrier protein is always uncharged (non-polar).
- The carriers have no directionality;
- The transport process is structure-specific; fake nutrients with a structure similar to essential nutrients are absorbed by the same carrier system.
- The system is capacity-limited because the number of carriers is limited, which means that at higher drug concentrations, the system becomes saturated and approaches an asymptote.
- The absorption window is the area with the highest density of the carrier system.

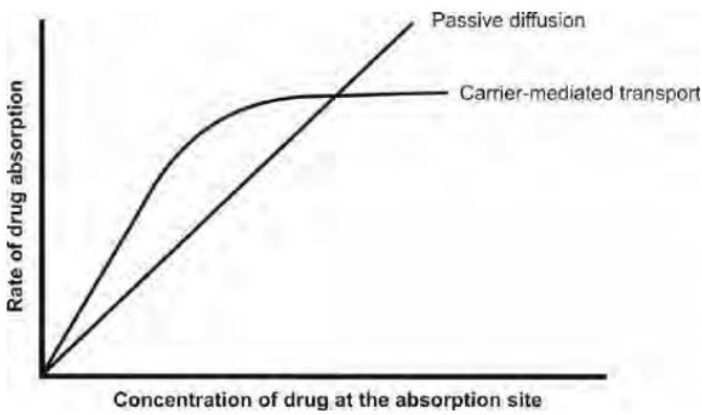

Figure 2.5: Curve showing relationship between passive diffusion & carrier-mediated transport

Carrier-mediated transport systems are classified into two types. They are known as facilitated diffusion and active transport.

1. Diffusion Facilitated

It is a carrier-mediated transport system that moves down the concentration gradient at a much faster rate than basic passive diffusion can account for. The gradient in concentration is the driving force (hence a passive process). It is primarily used in the intestine during glucose entry into RBCs and vitamin B_{12} absorption.

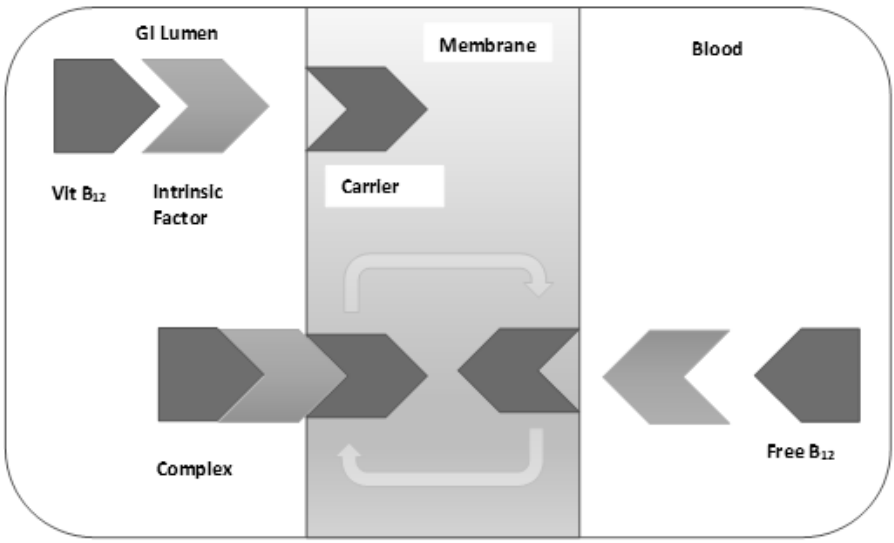

Figure 2.6: Facilitated diffusion of vitamin B_{12}

2. Active Transportation

This mode of transportation necessitates the use of ATP as an energy source. Active transportation systems are further classified as follows:

a) Primary Active Transport – As with glucose absorption, this mechanism requires direct ATP and occurs in only one direction. In primary active transport, two types of carrier proteins are involved:

1. Ion Transporters – These are in charge of moving ions into and out of cells. The proton pump is a well-known example of an ATP-powered ion pump. Ion transporters are classified into two types:

- **Organic anion transporters,** such as pravastatin and atorvastatin;
- **Organic cation transporters,** such as diphenhydramine.

2. **ABC transporters** – P-glycoprotein (P-gp) is a well-known ABC transporter that is responsible for pumping anticancer medications out of cells and causing multi-drug resistance.

b) Secondary active transport: Secondary active transport does not require direct ATP and instead relies on a previously established concentration gradient. As a result, this procedure is divided further into:

1) **Symport (co-transport) –** occurs when two molecules move in the same direction, such as the Na+-glucose symporter and the H+-coupled peptide transporter (PEPT1).

2) **Antiport (counter-transport) –** involves the movement of molecules in the opposite direction, such as the expulsion of H+ ions in the kidneys using the Na+ gradient.

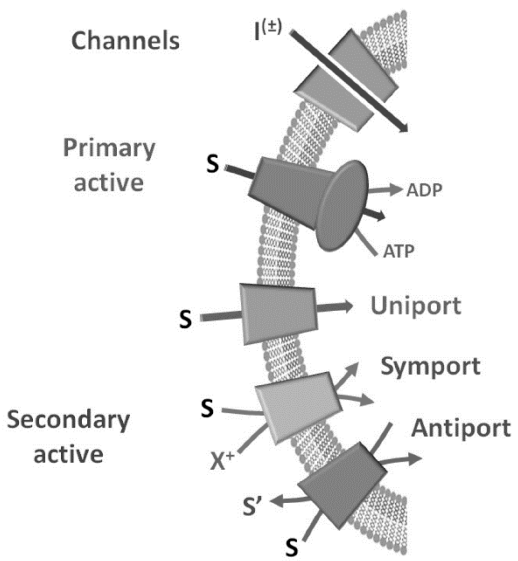

Figure 2.7: Schematic representation of primary and secondary active transport

Stages of Drug Transfer from the Gastrointestinal Absorption Site to Systemic Circulation

Drug absorption via the GI epithelium can be divided into three stages:

1) **Pre-uptake Phase:** The two most important pre-uptake processes are a) drug dissolution in GI fluids and b) drug metabolism in the GI lumen.

2) **Uptake phase:** This phase includes drug delivery to the absorption site in the GIT, drug metabolism by enzymes in the GI epithelium, and drug passage through the GI epithelium.

3) **Post-uptake phase:** The three major post-uptake processes are as follows:

    - Drug metabolism via the liver on the way to systemic circulation (first-pass hepatic metabolism).
    - Drug enterohepatic circulation — the drug may be excreted in bile, re-enter the GIT via the gallbladder, and be reabsorbed during the first pass through the liver.
    - Absorption of drugs into the circulatory system.

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