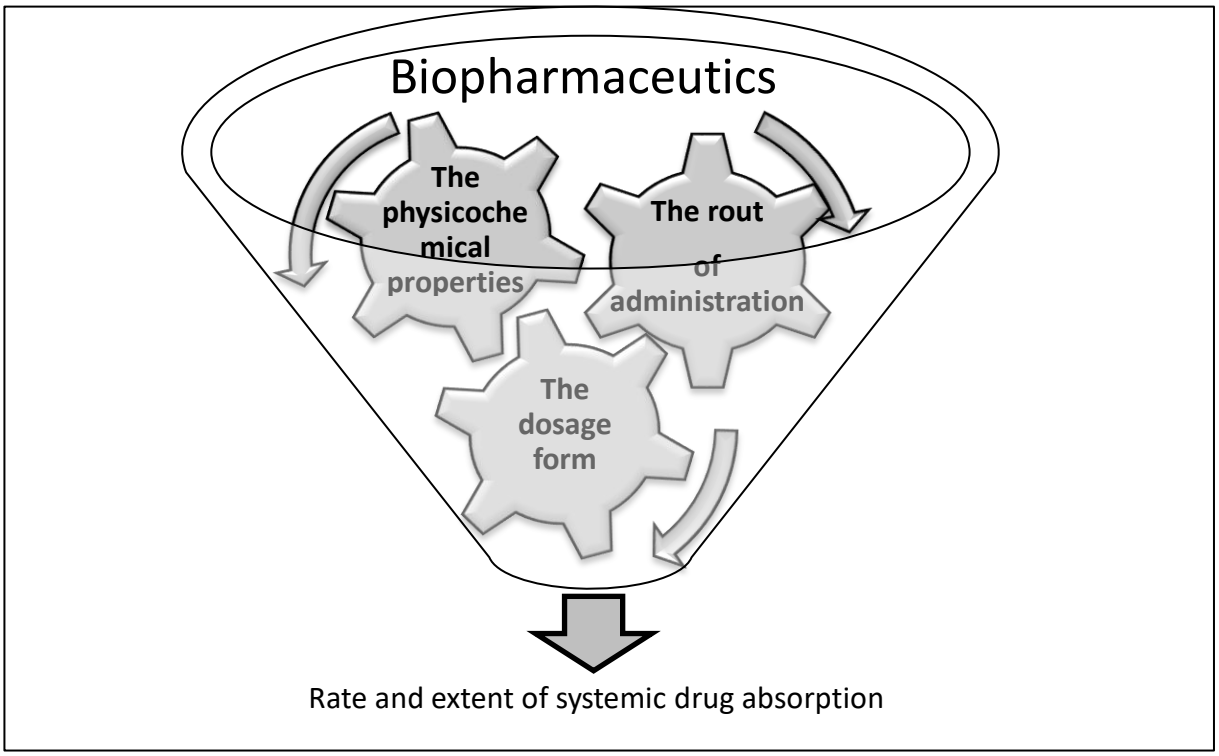
General concepts in biopharmaceutics and pharmacokinetics

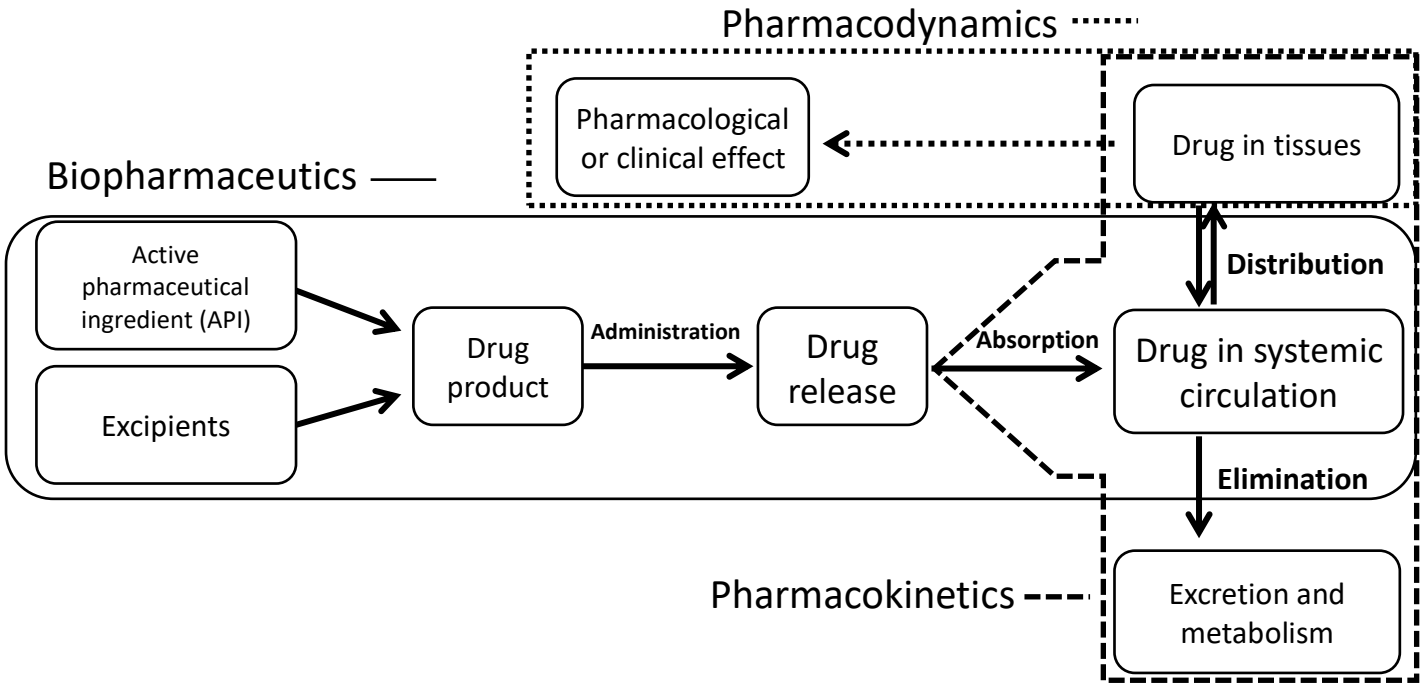
Biopharmaceutics

In biopharmaceutics we will study the factors that affect the entry of the drug to the body

Pharmacokinetics

In pharmacokinetics we will study the kinetics (rate and extent) of drug movement in the body (both





BIOPHARMACEUTICAL ASPECTS OF PRODUCTS

Drugs are not generally given as pure chemical drug substances but are formulated into finished dosage forms (drug products) before being administered to patients for therapy. Formulated drug products usually include the active drug substance and selected ingredients (*excipients*) that make up the dosage form. Drug products are designed to deliver drug for local or systemic effects. Common drug products include liquids, tablets, capsules, injectables, suppositories, transdermal systems, and topical products such as creams and ointments.

Biopharmaceutics directly correlates with the bioavailability of the drug. **Bioavailability** represents the fraction of the administered dose that reaches the systemic blood circulation. Because the systemic blood circulation delivers therapeutically active drug to the tissues and to the site of action of the drug, changes in bioavailability affect changes in the pharmacodynamics and toxicity of a drug. The aim of biopharmaceutics is to adjust the delivery of drug from the drug product in such a manner as to provide optimal therapeutic activity and safety for the patient.

DRUG ABSORPTION

Major considerations in the design of a drug product include the therapeutic objective, the application site, and systemic drug absorption from the application site.

Absorption can be defined as the transfer of a drug from its site of administration to the blood stream.

If the drug is intended for systemic activity, the drug should ideally be completely and consistently absorbed from the application site. In contrast, if the drug is intended for local activity, then systemic absorption from the application should be minimal to prevent systemic drug exposure and possible systemic side effects. For extended-release drug products, the drug product should remain at or near the application site and then slowly release the drug for the desired period of time.

The systemic absorption of a drug is dependent on **(1)** the physicochemical properties of the drug, **(2)** the nature of the drug product, and **(3)** the anatomy and physiology of the drug absorption site.

Route of drug administration

Table 1. Common routes of drug administration

Route	Bioavailability
Parenteral Routes	
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion rate.
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.
Intradermal injection	Drug injected into surface area (dermal) of skin.
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.
Intra-arterial injection	100% of solution is absorbed.
Intrathecal Injection	100% of solution is absorbed
Intraperitoneal injection	In laboratory animals, (eg, rat) drug absorption resembles oral absorption.
Enteral Routes	
Buccal or sublingual (SL)	Rapid absorption from lipid soluble drugs.
Oral (PO)	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).
Other Routes	
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.
Inhalation and intranasal	Rapid absorption. Total dose absorbed is variable.

Nature of cell membrane

Drugs that are administered by extravascular routes (eg, oral, topical, intranasal, inhalation, rectal) are either designed for local effect or designed to be absorbed from the site of administration into the systemic circulation. For systemic drug absorption, the drug has to cross cellular membranes to reach the site of action. The general principles and kinetics of absorption from these extravascular sites follow the same principles as oral dosing, although the physiology of the site of administration differs.

The permeability of a drug at the absorption site into the systemic circulation is mainly related to (1) the molecular structure and properties of the drug and to (2) the physical and biochemical properties of the cell membranes. Once in the plasma, the drug may act directly or have to cross biological membranes (biomembranes) to reach the site of action. Therefore, biological membranes represent a significant barrier to drug delivery. Epithelial and endothelial membrane barriers separate the body from its environment and individual body compartments from each other.

- The **epithelium** is a membrane tissue that covers almost all body surfaces such as the skin, lungs, nasal cavity, buccal cavity, intestine, and other body cavities.
- The **endothelium** consists of thin layer of cells that lines the interior surface of blood vessels.

The basic structure of cellular membranes is the lipid bilayer, composed of double layer of phospholipids, with occasional proteins, some of these proteins function as channel formers, drug transporters, or drug-metabolizing enzymes **(Figure 1).**

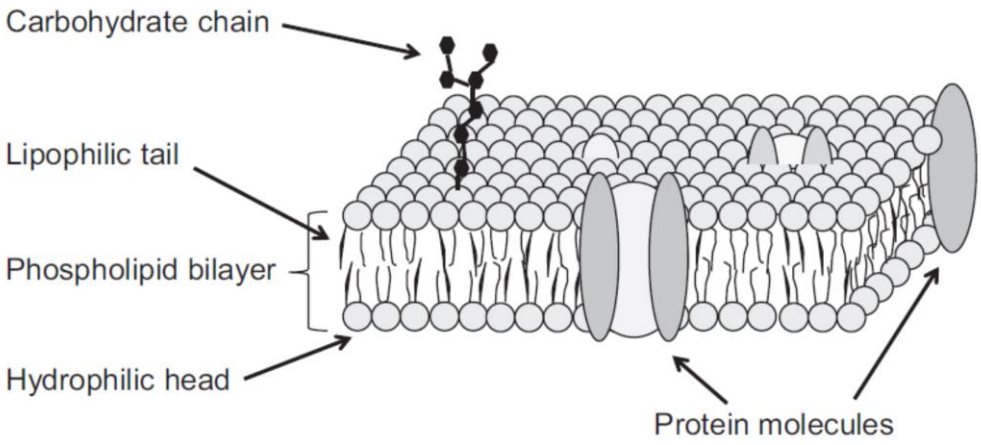


Figure 1. Schematic representation of a cell membrane.

Transport mechanisms of drugs through biomembranes

- **Transcellular transport** is the process of drug movement across a cell.
- **Paracellular transport** is the process of drug movement through gaps or tight junctions between cells. Usually limited to drug molecules smaller than 500 MW.

Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

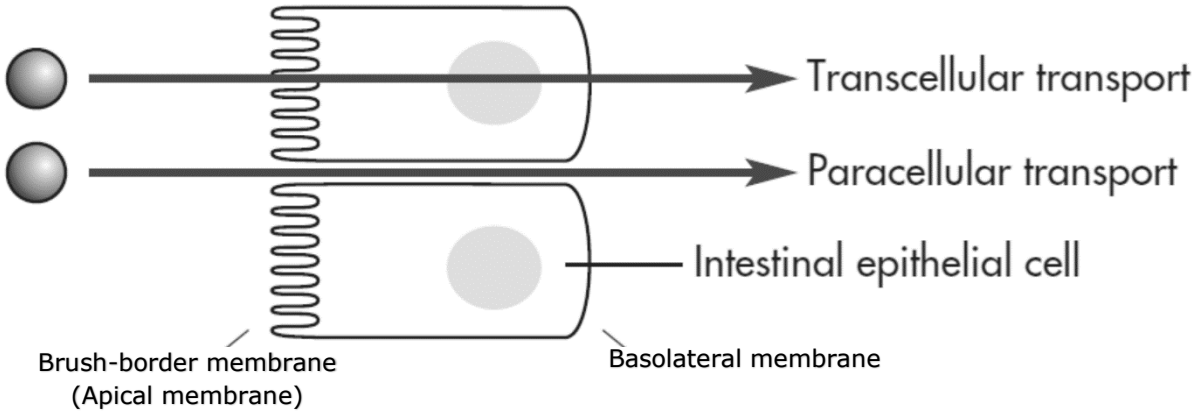


Figure 2. Transport mechanisms across cell membranes, epithelial cells (enterocytes) of the GIT as an example.

PASSAGE OF DRUGS ACROSS CELL MEMBRANE

1. PASSIVE DIFFUSION

Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is *passive* because no external energy is expended. Drug molecules can move forward and back across a membrane; the net movement of molecules depends on the concentration differences on both sides of the membrane.

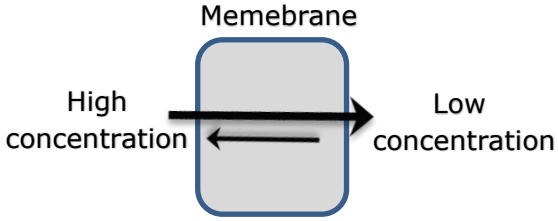


Figure ٣. Schematic representation for net movements of molecules across cell membrane based on passive diffusion law.

Passive diffusion is the major absorption process for most drugs. The driving force for passive diffusion is higher drug concentrations, typically on the mucosal side compared to the blood as in the case of oral drug absorption. According to ***Fick's law of diffusion***, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

$$\frac{dQ}{dt} = \frac{DAK}{h} (C_{GI} - C_p) \text{ ..... } \textit{Fick's law of diffusion}$$

Where dQ/dt = rate of diffusion, D = diffusion constant, A = surface area of membrane, K = lipid-water partition coefficient of the drug in the biologic membrane that controls permeation, h = membrane thickness, and $C_{GI} - C_p$ = difference between the concentration of the drug in the gastrointestinal tract and in the plasma.

Notes:

- Once the drug is absorbed to the blood it distributes rapidly into a large volume. The concentration in the blood will be quite low with respect to the concentration at the site of drug administration. For example, a drug is usually given in milligram doses, whereas plasma concentrations are often in the µg/mL or ng/mL range. If the drug is given orally, then $C_{GI} >> C_p$ and a large concentration gradient is maintained until most of the drug is absorbed, thus driving drug molecules into the plasma from the gastrointestinal tract.
- Drugs that are more lipid soluble have a larger value of *K.*
- The surface area, *A*, of the membrane also influences the rate of absorption. The duodenal area of the small intestine shows the most rapid drug absorption, due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are less abundant in other areas of the gastrointestinal tract.
- The thickness of the membrane, *h*, affects the diffusion. Drugs usually diffuse very rapidly through capillary plasma membranes in the vascular compartments, in contrast to diffusion through plasma membranes of capillaries in the brain (the brain has a thicker lipid membrane).
- The diffusion constant, *D*, is constant for each drug.
- Because *D*, *A*, *K*, and *h* are constants under usual conditions for absorption, a combined constant ***P*** or **permeability coefficient** can be used instead.

$$P = \frac{DAK}{h}$$

- The drug concentration in the plasma, C_p, is extremely small compared to the drug concentration in the gastrointestinal tract, C_{GI}. If C_p is negligible and P is substituted into the equation, the following relationship for *Fick's law* is obtained:

$$\frac{dQ}{dt} = P\,(C_{GI})$$

Factors affecting the drug diffusion across biomembranes

- **Effect of pH and the extent of ionisation on diffusion**

Many drugs act as weak electrolytes, such as weak acids and bases, the extent of ionization influences the drug's diffusional permeability. Weak electrolytes exist in both unionised and ionised form, the ratio of the two forms varying with pH.

- The ionized form of the drug contains a charge and is water soluble and has very low lipid solubility.
- The non-ionised form of the drug is more lipid soluble and in most cases this lipid solubility is sufficient for membrane permeation.

The extent of ionisation depends on the pKa of the drug and the pH of the medium according to ***Henderson and Hasselbalch*** **equation.**

For weak acids,

$$AH \overset{Ka}{\rightleftharpoons} A^- + H^+$$

$$\text{Ratio} = \frac{[\text{Salt}]}{[\text{Acid}]} = \frac{[A-]}{[HA]} = 10^{(\text{pH-p}Ka)}$$

For weak bases,

$$BH^+ \overset{Ka}{\rightleftharpoons} B + H^+$$

$$\text{Ratio} = \frac{[\text{Base}]}{[\text{Salt}]} = \frac{[B]}{[BH+]} = 10^{(\text{pH-p}Ka)}$$

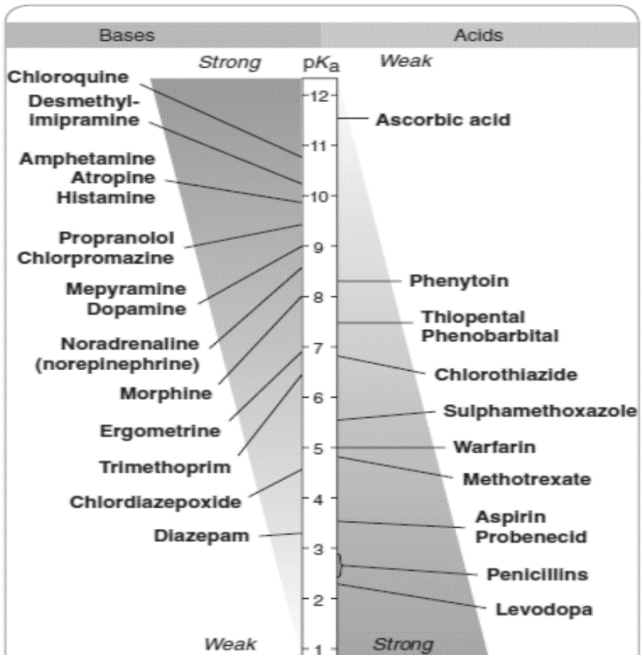


Figure ٤ . pKa values for some acidic and basic drugs

Examples;

- Calculate the extent of ionisation for salicylic acid (pKa = 3.0) in plasma.

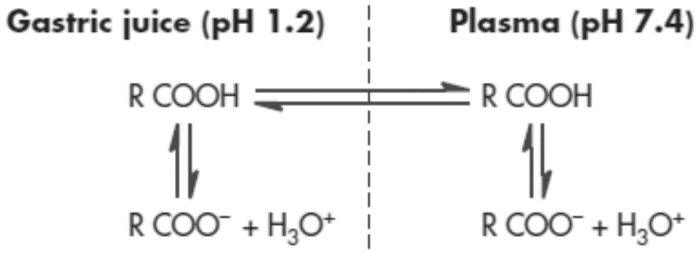
  The pH of plasma is 7.4

  - Ratio = $\frac{[\text{Salt}]}{[\text{Acid}]} = 10^{(7.4 - 3)}$
  - Log $\frac{[\text{Salt}]}{[\text{Acid}]} = 7.4 - 3 = 4.4$
  - $\frac{[\text{Salt}]}{[\text{Acid}]} = 2.51 \times 10^4$

  At plasma pH, salicylic acid exists mostly in its ionized or water-soluble form.

Note: For nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium. However, for electrolyte drugs or drugs that ionize, the total drug concentrations on either side of the membrane are not equal at equilibrium if the pH of the medium differs on respective sides of the membrane.

For example, the concentration of salicylic acid (pKa = 3.0) in the stomach (pH 1.2) as is different from its concentration in the plasma (pH 7.4) as shown in the following figure.



In the plasma, at pH 7.4

Ratio = $\frac{[\text{RCOO}-]}{[\text{RCOOH}]} = 2.51 \times 10^4$

In gastric juice, at pH 1.2

Ratio = $\frac{[\text{RCOO}-]}{[\text{RCOOH}]} = 1.58 \times 10^{-2}$

If the pH on one side of a cell membrane differs from the pH on the other side of the membrane, then
(1) the drug (weak acid or base) will ionize to different degrees on respective sides of the membrane;
(2) the total drug concentrations (ionised plus nonionised drug) on either side of the membrane will be unequal; and
(3) the compartment in which the drug is more highly ionized will contain the greater total drug concentration.

- **The affinity of the drug for a tissue component**

Binding or uptake of the drug by a tissue component prevents the drug from moving freely across the membrane.

Examples of binding include:

1. Binding to plasma or tissue proteins;
    - Dicumarol binds to plasma proteins.
    - Digoxin binds to tissue proteins.
2. Partitioning to the adipose tissues;
    - Chlordane is a very lipid soluble drug and will partition to adipose (fat) tissues.
3. Complexation with a tissue component;
    - Tetracycline forms a complex with calcium in the bones and teeth.
4. Active transport uptake by the tissue;
    - Uptake of iodide by the thyroid tissue.
    - Some catecholamines into adrenergic storage sites.

Such drugs may have a higher **total drug** concentration on the side where binding occurs, yet the **free drug** concentration that diffuses across cell membranes will be the same on both sides of the membrane.

2. CARRIER-MEDIATED TRANSPORT

This mechanism of drug transport across the cell membrane involve the use of drug transporter (carrier).

- Uptake (influx) transporters move drug to the blood and increase plasma concentration.
- Efflux transporters move drug back to the lumen (GIT for example) and decrease plasma concentration.

Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

A. Active Transport

Active transport is a type of carrier mediated transport and it is characterized by the ability to transport drug against a concentration gradient ie, from regions of low drug concentrations to regions of high drug concentrations.

- The carrier molecule may be highly selective for the drug molecule.

- It is an energy consuming process.
- If a drug is structurally similar to the natural substance that is actively transported by the carrier, then it is likely to be transported by the same carrier.
- Only a fixed number of carriers are available, the biding sites may become saturated if high concentration of the is applied.
- The rate of drug absorption increases with the increase in the concentration of the drug until all the carrier molecules are saturated. At higher concentrations, the rate of absorption remains constant (zero order).
- For the passive diffuse the rate of absorption is directly related to the concentration of the drug at the site of administration (first order rate).

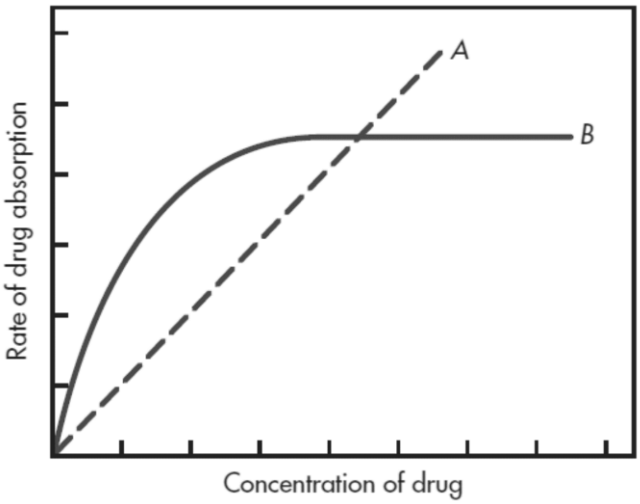


Figure 5. Comparison of the rate of absorption for a drug absorbed by passive diffusion (Line A) and drug absorbed by carrier mediated absorption (Line B).

B. Facilitated Diffusion

Facilitated diffusion is also a carrier-mediated transport system, differing from active transport in that the drug moves along a concentration gradient (ie, moves from a region of high drug concentration to a region of low drug concentration).

- This system does not require energy input.
- It is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure.
- In terms of drug absorption, facilitated diffusion seems to play a very minor role.

Transporters and Carrier-Mediated Intestinal Absorption

Both influx and efflux transporters are present in the brush border and basolateral membrane that will increase drug absorption (influx transporter) or decrease drug absorption (efflux transporter). Please refer to **Figure 6** for examples.

Many drugs are absorbed by carrier systems because of the structural similarity to natural substrates. The small intestine expresses a variety of **uptake transporters** for amino acids, peptides, hexoses, organic anions, organic cations, nucleosides, and other nutrients.

P-glycoprotein (P-gp or called MDR1)) is an example of **efflux transporters**. MDR1 is one of the many proteins known as *multidrug-resistance associated protein*. It is important in pumping drugs out of cells and causing treatment resistance. P-gp is also present in various human tissues like the kidney, brain, adrenal medulla, and the prostate.

The expression of P-gp is often triggered in many cancer cells making them drug resistant due to drug efflux.

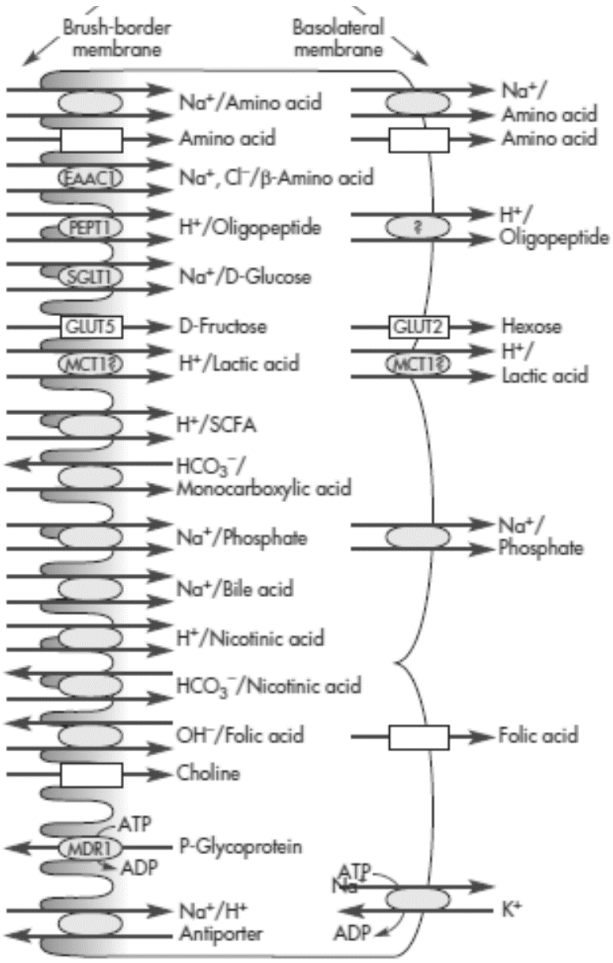


Figure ٦ . Summary of intestinal epithelial transporters. Transporters shown by a square represent ***active transporters***. Oval transporters represent ***facilitated transporters***.

3. VESICULAR TRANSPORT

Vesicular transport is the process of engulfing particles or dissolved materials by the cell.

A. *Pinocytosis* refers to the engulfment of small solutes or fluid.
B. *Phagocytosis* refers to the engulfment of larger particles or macromolecules, generally by macrophages.
C. *Endocytosis* and *exocytosis* are the processes of moving specific macromolecules into and out of a cell, respectively.

During pinocytosis and phagocytosis the cell membrane invaginates to surround the material and then engulfs the material, incorporating it inside the cell. Subsequently, the cell membrane containing the material forms a vesicle within the cell.

D. *Transcytosis* is the process by which various macromolecules are transported across the interior of a cell. In transcytosis, vesicles are employed to intake the macromolecules on one side of the cell, draw them across the cell, and eject them on the other side. Transcytosis (sometimes referred to as vesicular transport) is the proposed process for the absorption of orally administered various large proteins.

4. PORE (CONVECTIVE) TRANSPORT

Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores. A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell (see **Figure 1** in this lecture notes). Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.