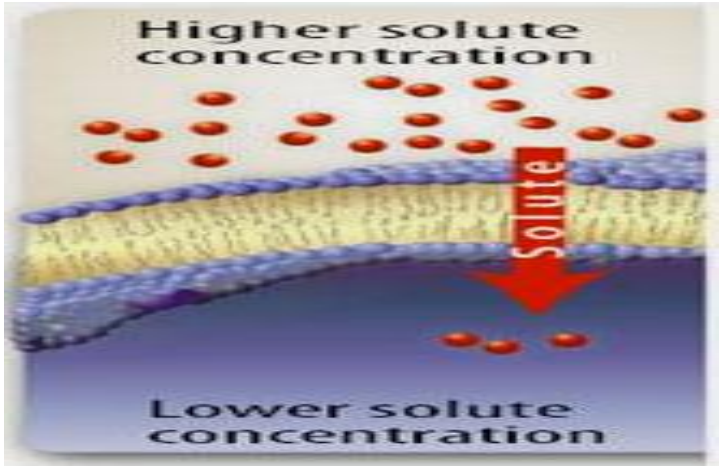
2-Transport across the membranes (Cont.):

2- Passive diffusion:

- Most drugs cross biologic membranes by passive diffusion.
- Diffusion occurs when the drug concentration on one side of the membrane is higher than that on the other side.
- The process is passive because no external energy is expended.
- The driving force for passive diffusion is the difference in drug concentrations on either side of the cell membrane.



2-Transport across the membranes (Cont.):

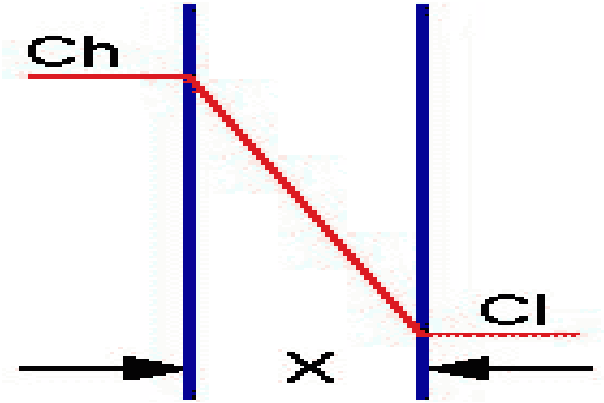


Diagram of Passive Transport with a Concentration Gradient

-The rate of transport of drug across the membrane can be described by Fick's first law of diffusion:-

$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{D \bullet A \bullet (Ch - Cl)}{x}$$

Fick's First Law, Rate of Diffusion

2-Transport across the membranes (Cont.):

- The parameters of this equation are:-

D: diffusion coefficient. This parameter is related to the size and lipid solubility of the drug and the viscosity of the diffusion medium.

As lipid solubility increases or molecular size decreases then D increases and thus dM/dt also increases.

A: surface area. As the surface area increases the rate of diffusion also increase.

The surface of the intestinal lining (with villae and microvillae) is much larger than the stomach. This is one reason absorption is generally faster from the intestine compared with absorption from the stomach.

2-Transport across the membranes (Cont.):

x: membrane thickness. The smaller the membrane thickness the quicker the diffusion process. As one example, the membrane in the lung is quite thin thus inhalation absorption can be quite rapid.

(Ch -Cl): concentration difference.

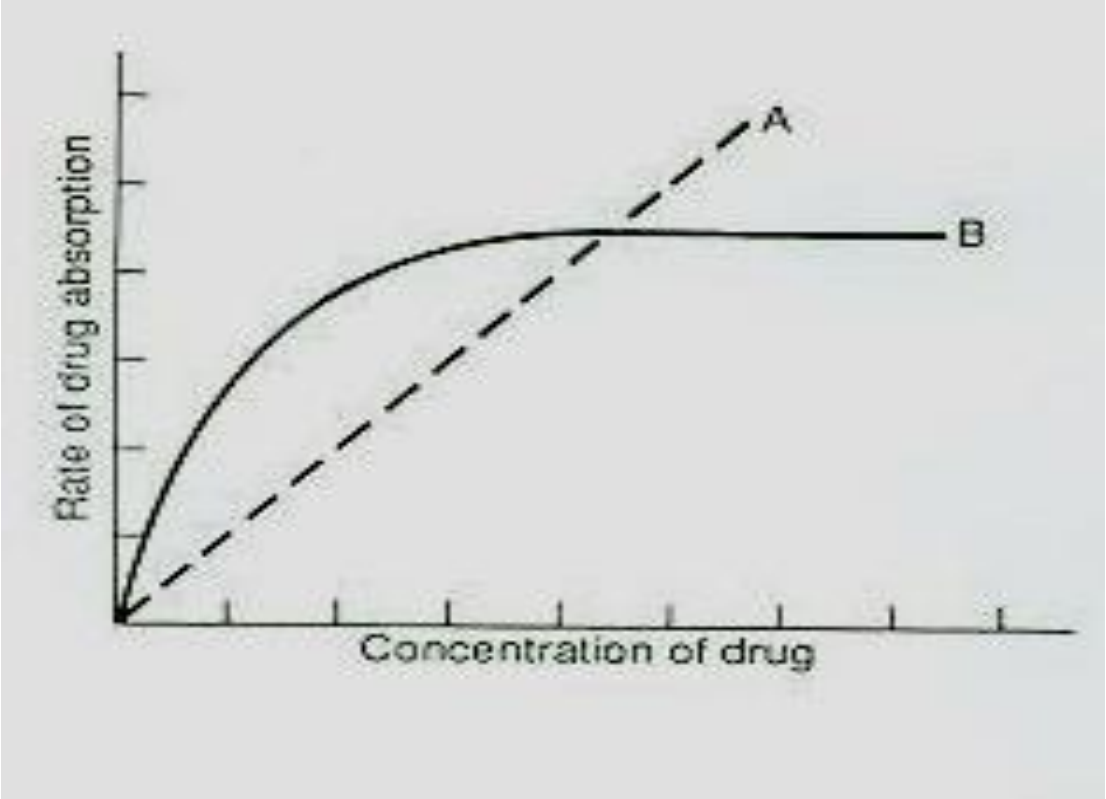
The drug concentration in blood or plasma will be quite low compared with the concentration in the GI tract. It is this concentration gradient which allows the rapid complete absorption of many drug substances.

- Normally Cl << Ch then:-

$$\frac{dM}{dt} = -\frac{D \bullet A \bullet Ch}{x}$$

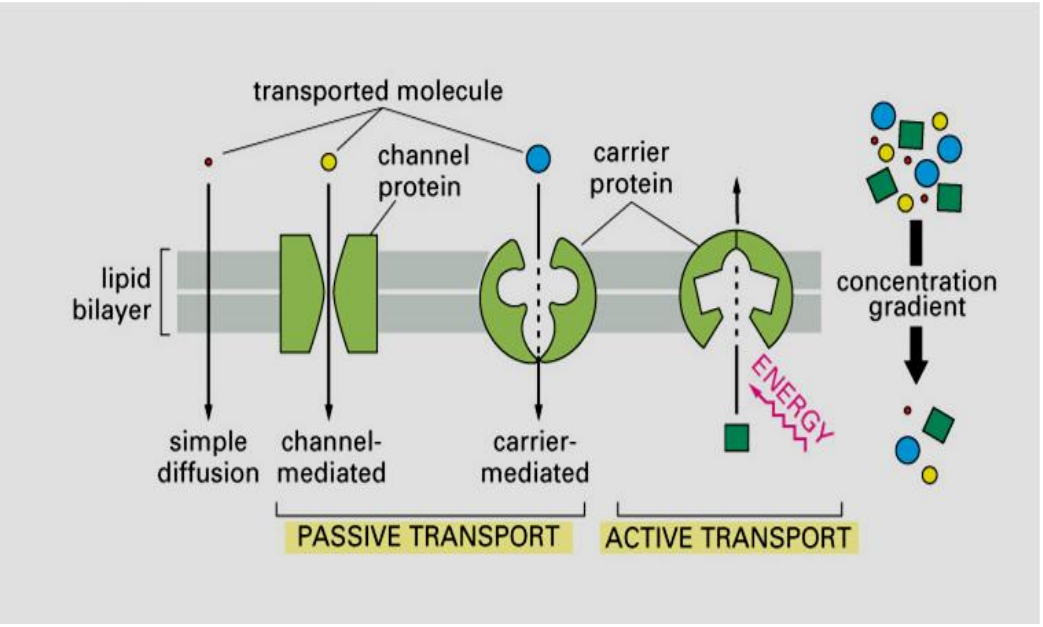
constant, ka

2-Transport across the membranes (Cont.):



Relationship between drug concentration and absorption rate For a passive process (Curve A) and for a carrier-mediated Process (Curve B).

2-Transport across the membranes (Cont.):



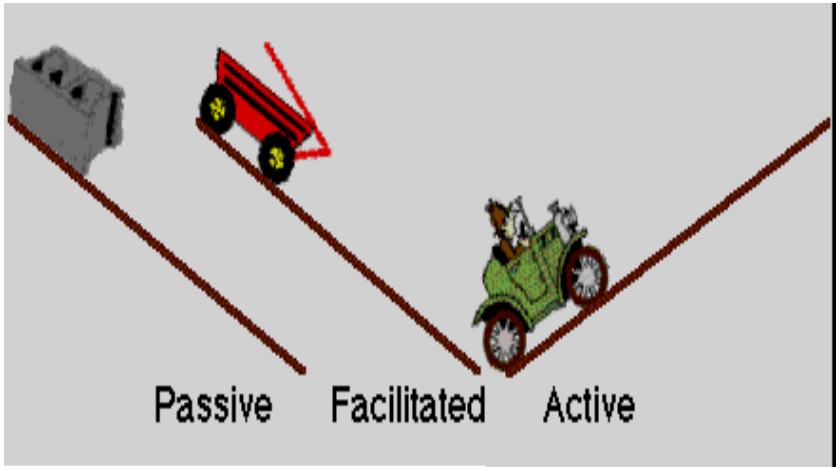


Illustration of Different Transport Mechanisms

2-Transport across the membranes (Cont.):

3- Vesicular transport:

- It is the process of engulfing particles or dissolved materials by the cell.

- Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested.

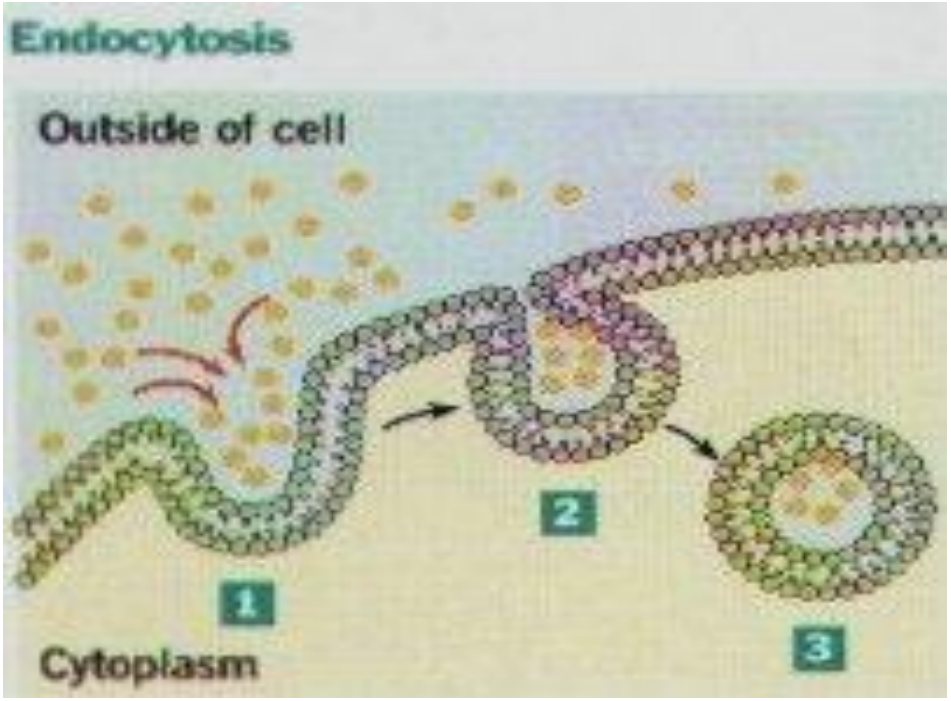
Pinocytosis: refers to the engulfment of small molecules or fluid.

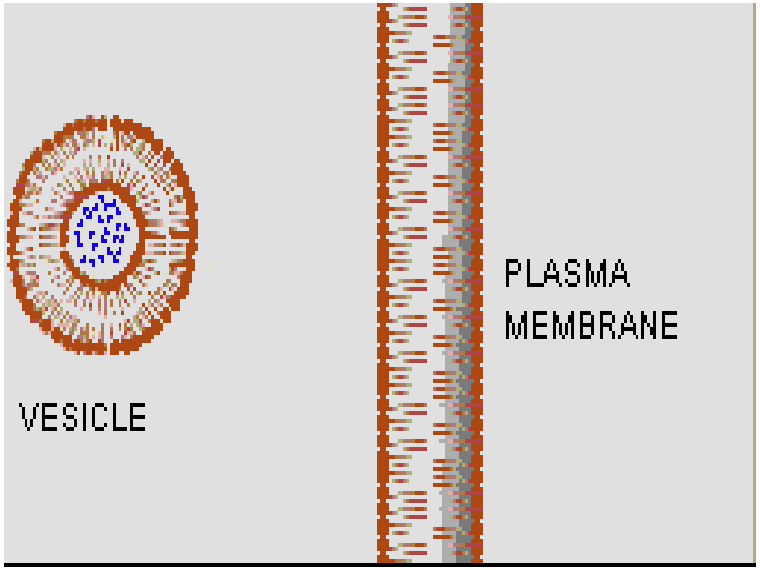
Phagocytosis: refers to the engulfment of larger particles or macromolecules.

- During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material, and then engulfs the material into the cell. Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell.

- Vesicular transport is the proposed process for the absorption of Vitamin A, D, E, and K, peptides in new born.

2-Transport across the membranes (Cont.):





2-Transport across the membranes (Cont.):

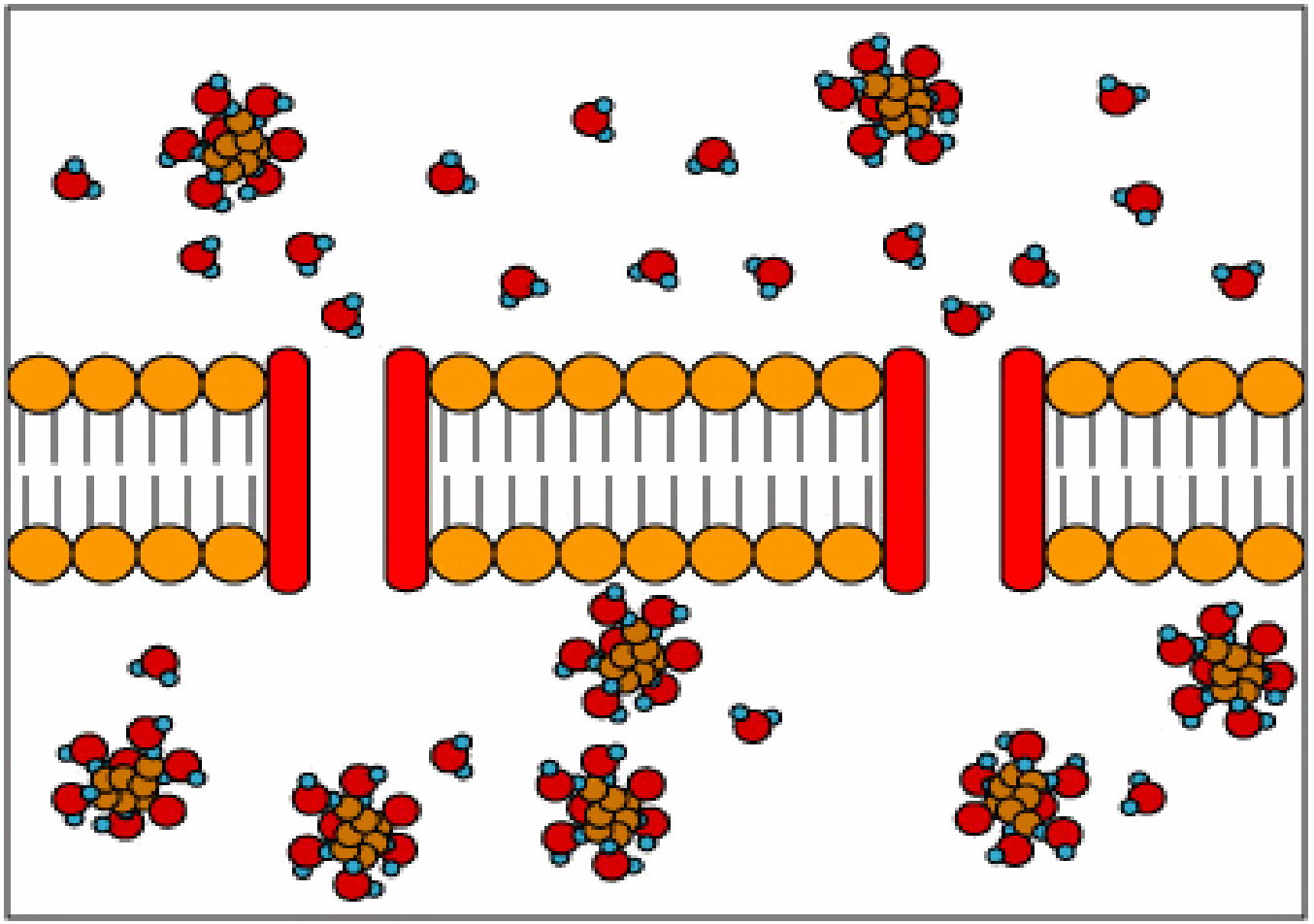
4- Pore (convective) transport:

- A certain type of protein called transport protein may form an open channel across the lipid membrane of the cell.
- Very small molecules, such as urea, water and sugars are able to rapidly cross the cell membrane through these pores.

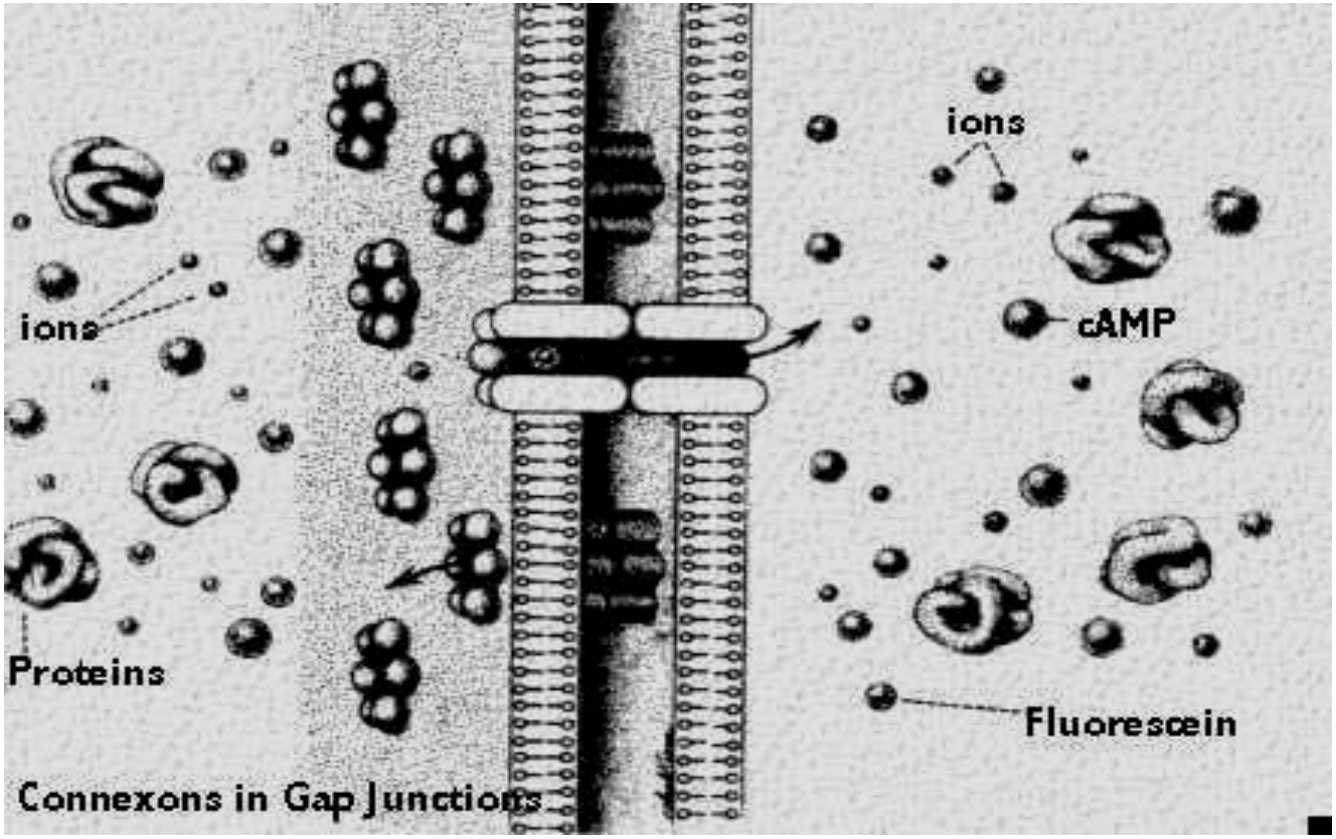
5- Ion pair formation:

- Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds.
- These drugs penetrate membranes poorly. When linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. This neutral complex diffuses more easily across the membrane.
- e.g. the formation of an ion pair for propranolol (basic drug) with oleic acid.

Transport of Substances Across a Membrane by Channel Proteins



2-Transport across the membranes (Cont.):



Mechanism of ion pair transport of drugs

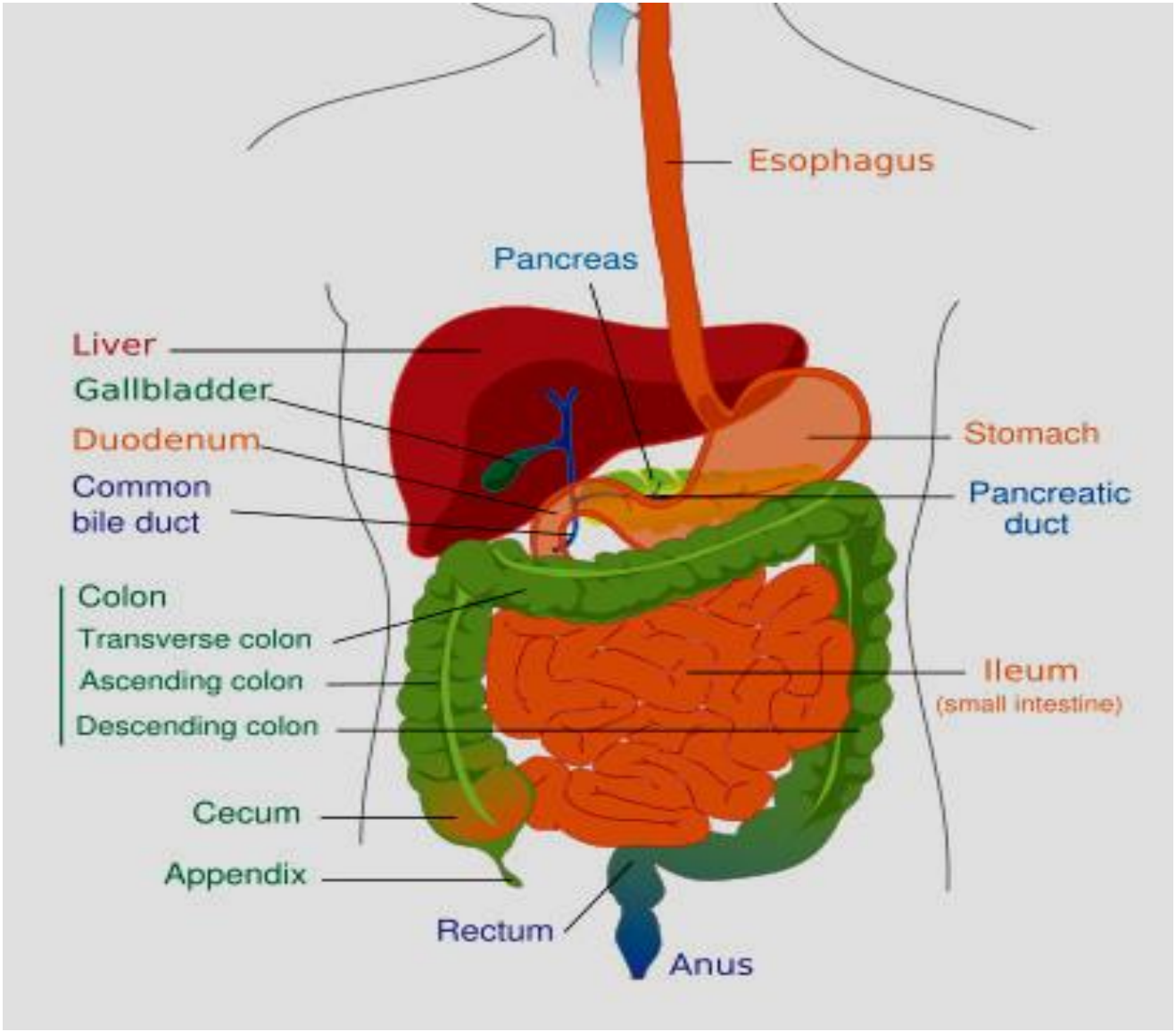
3- Gastrointestinal (GI) Physiology:

- The gastrointestinal tract is a muscular tube approximately 6 m in length with varying diameters.

- It stretches from the mouth to the anus and consists of four main anatomical areas: the oesophagus, the stomach, the small intestine and the large intestine or colon.

- The majority of the gastrointestinal epithelium is covered by a layer of mucous. This is a viscoelastic translucent aqueous gel that is secreted through out the GIT, acting as a protective layer and a mechanical barrier.

Gastrointestinal (GI) Physiology (Cont.):



Gastrointestinal (GI) Physiology (Cont.):

I. Characteristics of GI physiology and Drug Absorption:

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Buccal	approx 6	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
Oesophagus	5-6	Very thick no absorption	-	small	short, typically a few seconds, except for some coated tablets	-

I. Characteristics of GI physiology and Drug Absorption (cont.):

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Stomach	1.7-3.5	normal	good	small	30 min (liquid) - 120 min (solid food)	no
Duodenum	5 - 7	normal	good	Very large	very short,	no

I. Characteristics of GI physiology and Drug Absorption (cont.):

Organs	pH	Membrane	Blood Supply	Surface Area	Transit Time	By-pass liver
Small Intestine	6 – 7.5	normal	good	Very large	About 3 hours	no
Large intestine	6.8 - 7	-	good	Not very large	long, up to 24 hours	Lower colon, rectum yes

I. Characteristics of GI physiology and Drug Absorption (cont.):

The environment within the lumen:

Gastrointestinal pH

- As we observed from the previous tables, the pH of fluids varies along the length of the GIT.
- The gastrointestinal pH may influence the absorption of drugs in a variety of ways:

A- It may affect the chemical stability of the drug in the lumen e.g. penicillin G, erythromycin

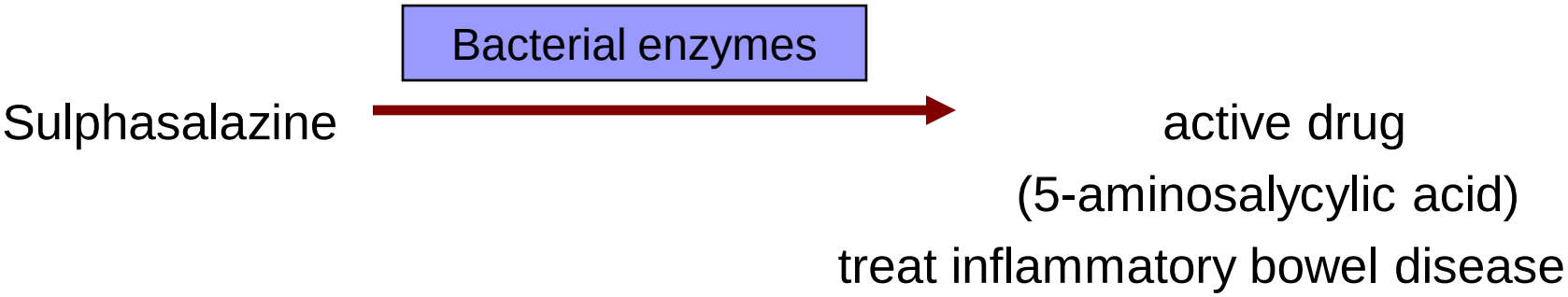
B- affect the drug dissolution or absorption e.g. weak electrolyte drug

Luminal enzymes

- The primary enzyme found in gastric juice is pepsin. Lipases, amylases and proteases are secreted from the pancreas into the small intestine.
- Pepsins and proteases are responsible for the digestion of protein and peptide drugs in the lumen.

I. Characteristics of GI physiology and Drug Absorption (cont.):

- The lipases may affect the release of drugs from fat / oil – containing dosage forms.
- Bacteria which are localized within the colonic region of the GIT secrete enzymes which are capable of a range of reactions.
- e.g. Sulphasalazine which is a prodrug used to target the colon.



I. Characteristics of GI physiology and Drug Absorption (cont.):

Disease state and physiological disorders

- Local diseases can cause alterations in gastric pH that can affect the stability , dissolution and absorption of the drug.
- Partial or total gastrectomy results in drugs reaching the duodenum more rapidly than in normal individuals. This may result in an increased overall rate of absorption of drugs that are absorbed in the small intestine.
- However, drugs that require a period of time in the stomach to facilitate their dissolution may show reduced bioavailability in such patients.

I. Characteristics of GI physiology and Drug Absorption (cont.):

The unstirred water layer

- It is a more or less stagnant layer of water and mucous adjacent to the intestinal wall.
- This layer can provide a diffusion barrier to drugs.
- Some drugs (antibiotics e.g. tetracycline) are capable of complexing with mucous, thereby reducing their availability for absorption.

II Gastric emptying and motility:

- The time a dosage form takes to traverse the stomach is usually termed: the gastric residence time, gastric emptying time or gastric emptying rate.

- Generally drugs are better absorbed in the small intestine (because of the larger surface area) than in the stomach, therefore quicker stomach emptying will increase drug absorption.

- For example, a good correlation has been found between stomach emptying time and peak plasma concentration for acetaminophen. The quicker the stomach emptying (shorter stomach emptying time) the higher the plasma concentration.

- Also slower stomach emptying can cause increased degradation of drugs in the stomach's lower pH; e.g. L-dopa.