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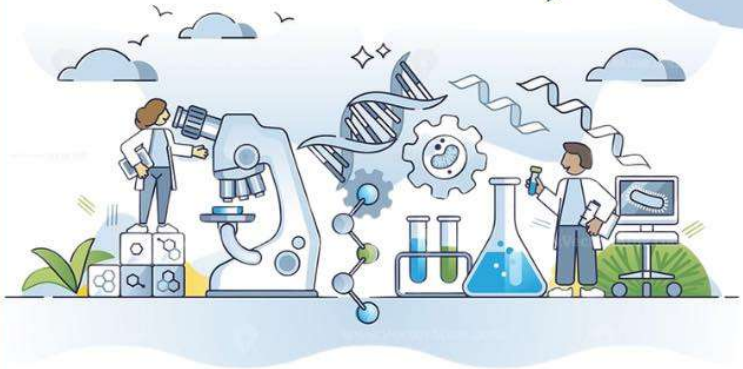

اسم الموضوع: *chapter 2 - drug absorption*

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لجان الدُّفعات

* intestine is the main site of absorption.
large surface area (villi & micro villi)

Drug Absorption

Presented by Dr. Muna Oqal

Absorption

Main factors affecting oral absorption:

I. **Physiological factors**

II. Physico-chemical factors

III. Formulation factors.

Absorption

I. Physiological factors affecting oral absorption:

1. **Membrane physiology**.
2. **Passage of drugs across membranes**.
3. **Gastrointestinal physiology**.

A. Characteristics of GIT physiology and drug absorption

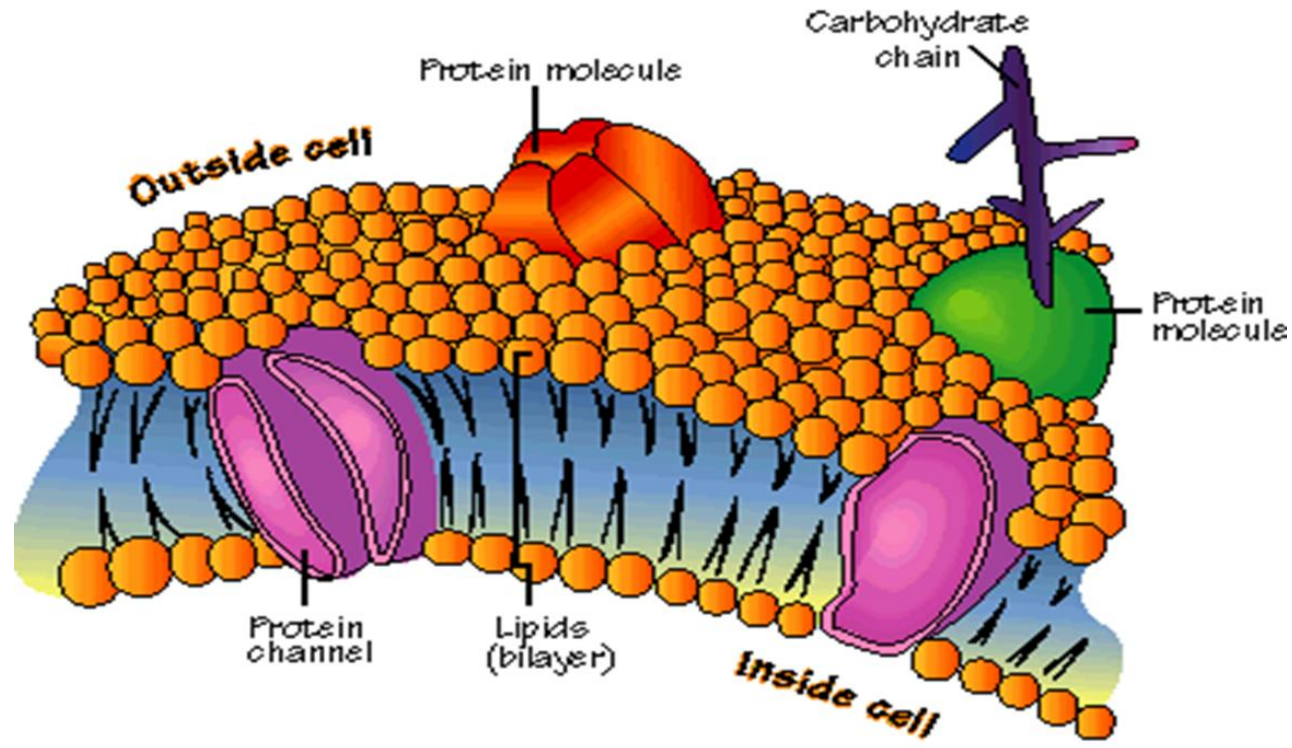
B. Gastric emptying time and motility

C. Effect of food on drug absorption

Physiological Factors Influencing Bioavailability

1. Membrane physiology:

- The cell membrane is the barrier that separates the inside of the cell from the outside.
- The cell membrane is made up of phospholipids, proteins, and other macromolecules.
- The phospholipids make up a bilayer. It contains hydrophilic and hydrophobic molecules.
- The proteins in the cell membrane are located within the phospholipid bilayer.
- So, the biologic membrane is mainly lipid in nature but contains small aqueous channels or pores.



Physiological factors affecting oral absorption

1. Membrane physiology

- Functionally, cell membranes are semipermeable partitions that act as selective barriers to the passage of molecules.

- For example: Water, some selected small molecules, and lipid-soluble molecules pass through such membranes, whereas highly charged molecules and large molecules, such as proteins and protein-bound drugs, do not.

2. Passage of drugs across cell membranes

1. **Carrier mediated transport:**
   A. Active transport → needs energy
   B. Facilitated diffusion
   C. P-glycoprotein
2. **Passive diffusion** (without carrier)
3. **Vesicular transport**
4. **Pore (convective) transport**
5. **Ion pair formation**

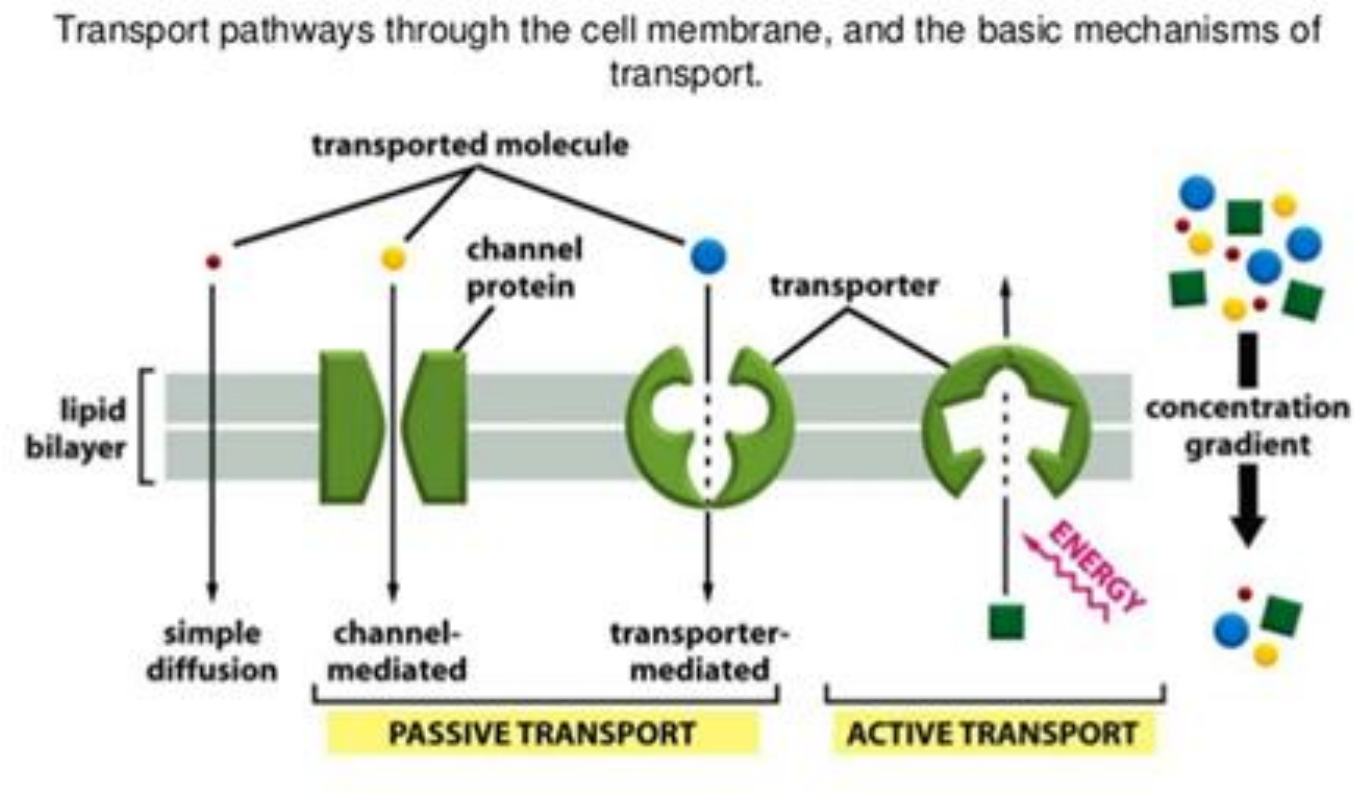
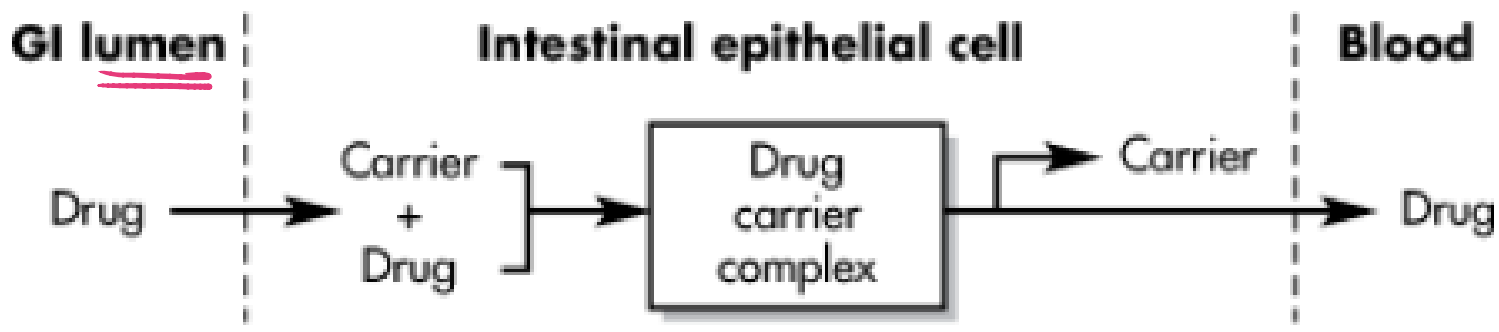


Illustration of different mechanisms of cell membrane transport

2. Transport across the membranes

1. Carrier mediated transport:

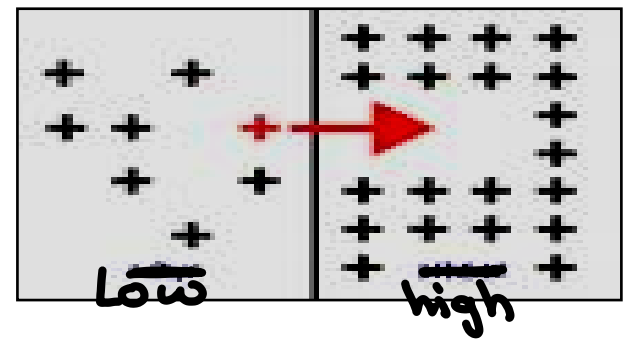


Scheme for the hypothetical carrier-mediated transport process

2. Transport across the membranes

A. Active transport:

- A few lipid-insoluble drugs (e.g.5-flurouracil, L-dopa) that resemble natural physiologic metabolites (e.g. glucose, amino acids) are absorbed from the GIT by this process.

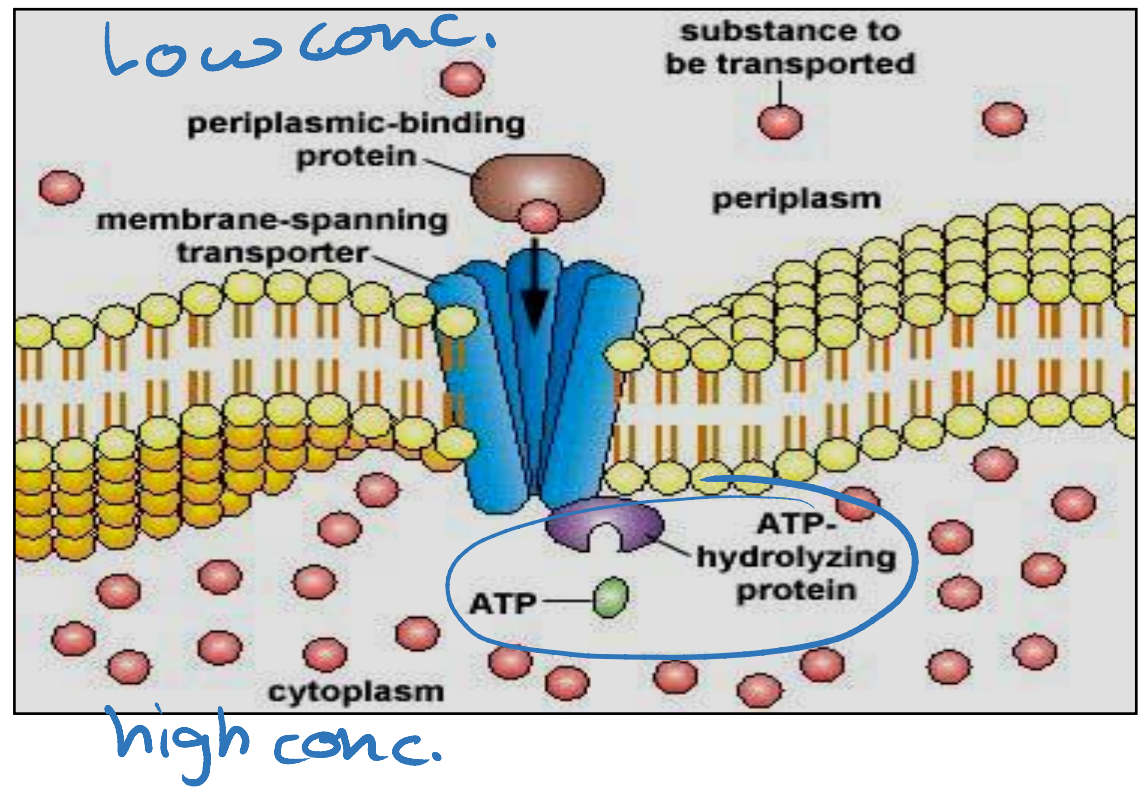


- Transport of a drug against concentration gradient (from regions of low drug concentrations to regions of high concentrations).

- It is an energy-consuming system.

- The carrier molecule may be highly selective for the drug molecule, therefore, drugs of similar structure may compete for sites of adsorption on the carrier (competitive inhibition is possible)

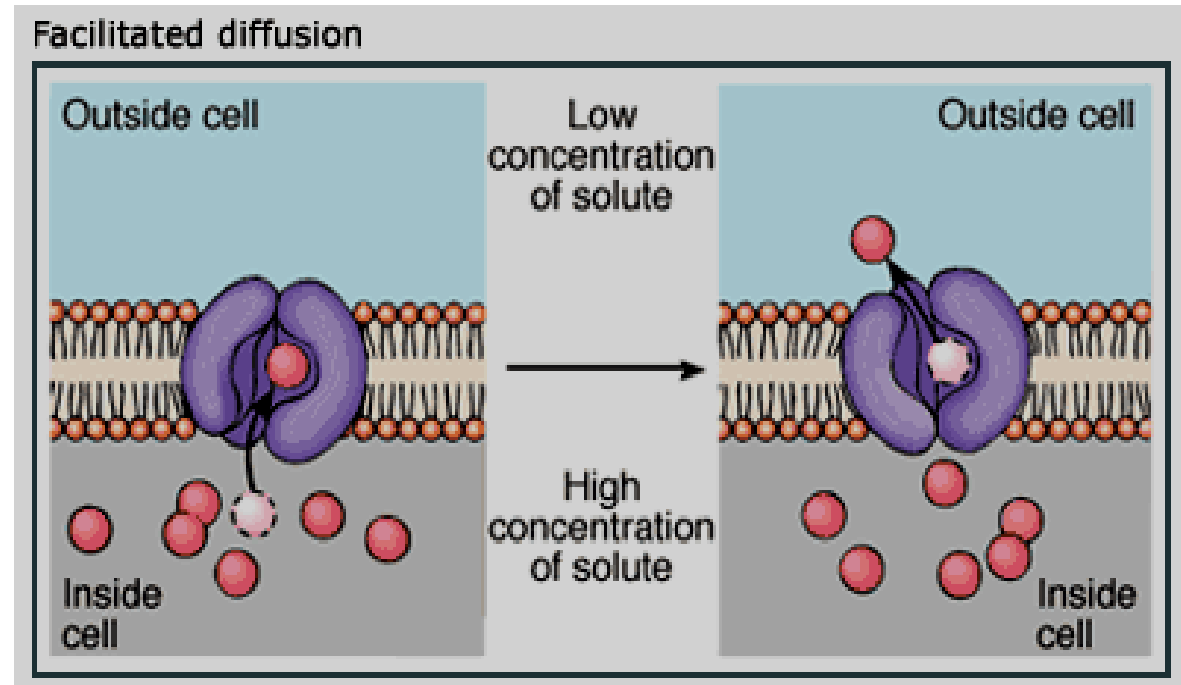
- Because only a certain amount of carrier is available, all the adsorption sites on the carrier may become saturated if the drug concentration gets very high.



2. Transport across the membranes

B- Facilitated diffusion:

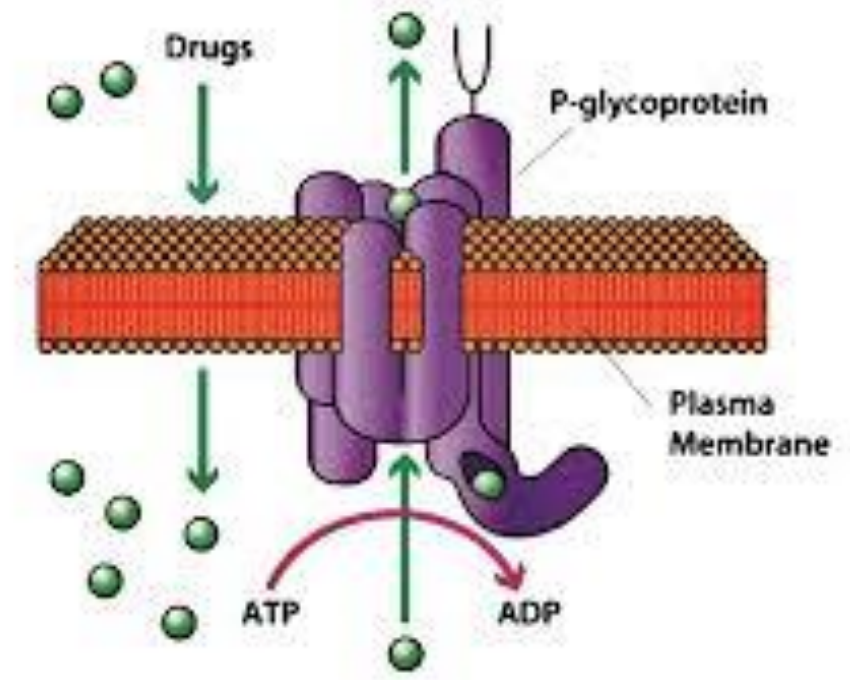
- Play a very minor role in absorption.
- A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport.
- Saturable if not enough carrier and structurally selective for the drug and shows competition kinetics for drugs of similar structure.
- No transport against a concentration gradient only downhill but faster.



2. Transport across the membranes

C. P-glycoprotein (PGP) transporters :

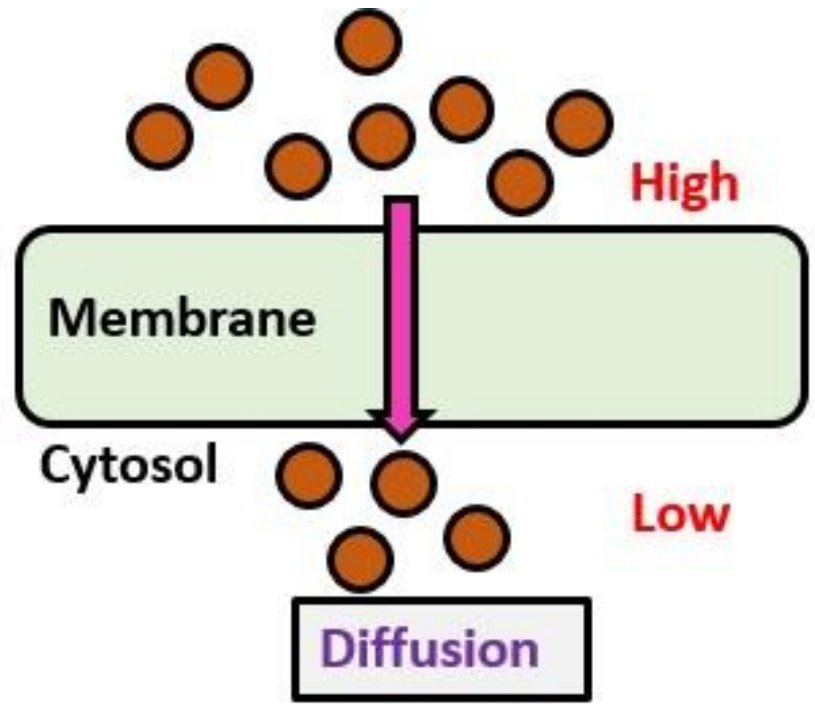
- P-glycoprotein are transmembrane proteins present throughout the body including liver, brain, kidney and the intestinal tract epithelia.
- This is an active, ATP-dependent process.
- Act as reverse pump generally inhibiting absorption (actively exporting drugs out of the cell).
- It is known as multidrug resistance protein 1 (MDR1).



2. Transport across the membranes

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 (higher drug concentrations on the mucosal side compared to the blood).
- So The rate of transport of drug across the membrane can be described by Fick's first law of diffusion. According to it, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.



2. Transport across the membranes

Fick's First Law, Rate of Diffusion

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

conc. in intestine

conc. in blood

membrane thickness

- The parameters of above 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 villi and microvilli) 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

✓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

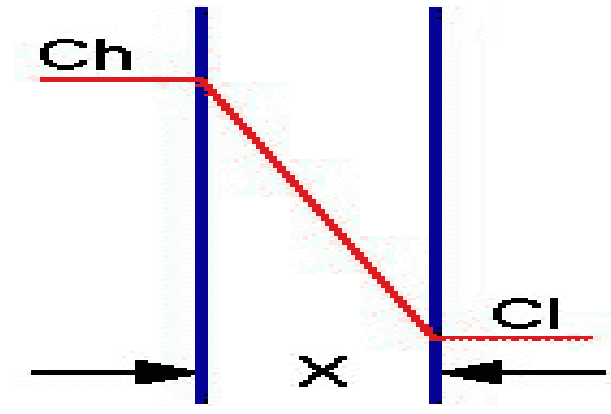
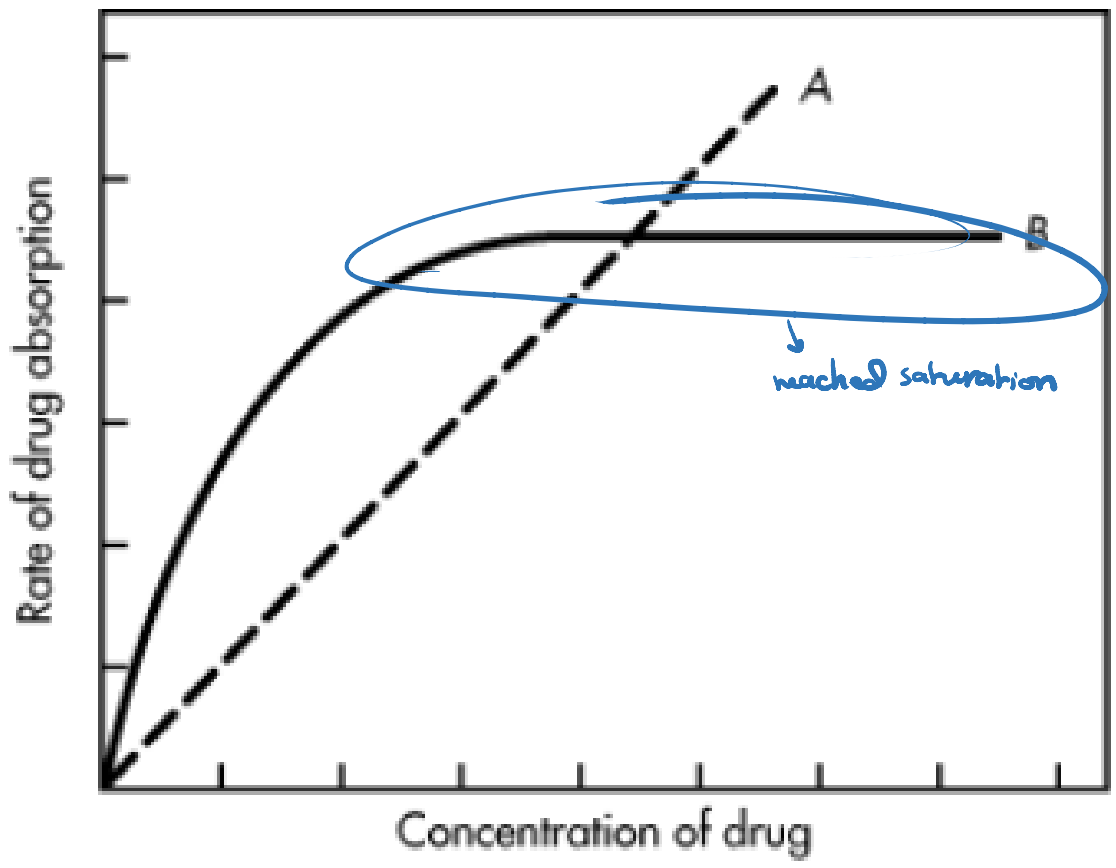


Diagram of Passive Transport with a Concentration Gradient

2. Transport across the membranes



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

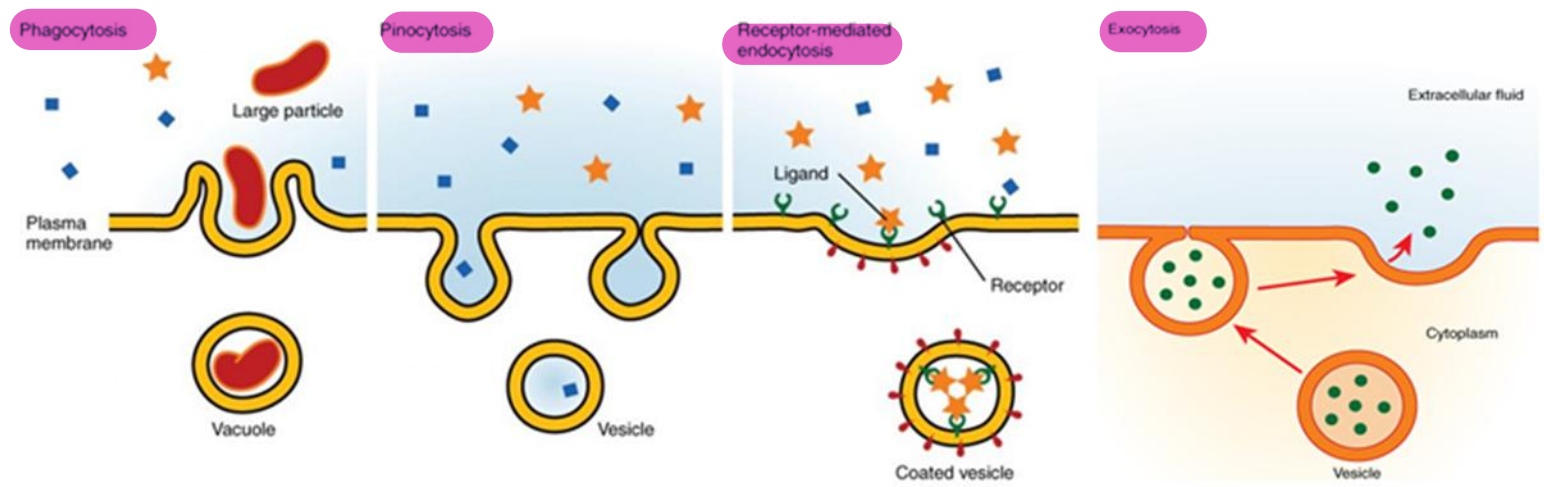
3. Vesicular transport:

- It is the process of engulfing particles or dissolved materials by the cell.
- Vesicular transport is the proposed process for the absorption of Vitamin A, D, E, and K, peptides in new born.
- 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. Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively.

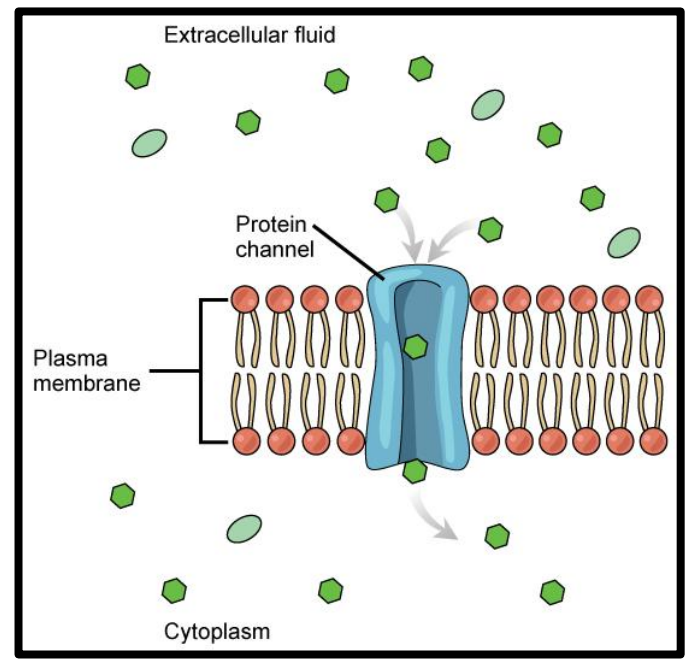


2. Transport across the membranes

4. Pore (convective) transport:

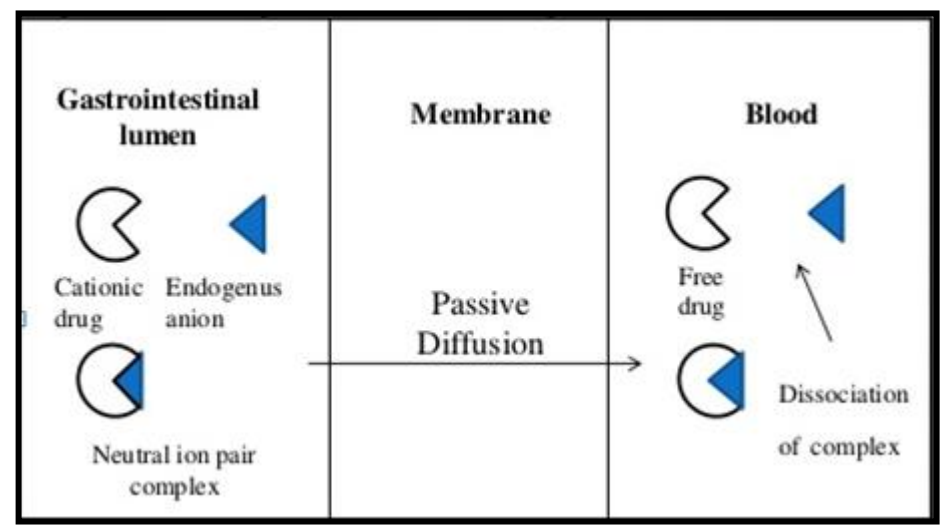
- A certain type of protein called transport protein may form an open channel across the lipid membrane of the cell.
- Very small molecules, such as urea, water and sugars are able to rapidly cross the cell membrane through these pores.
- Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of

the membrane.



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 (counter 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.

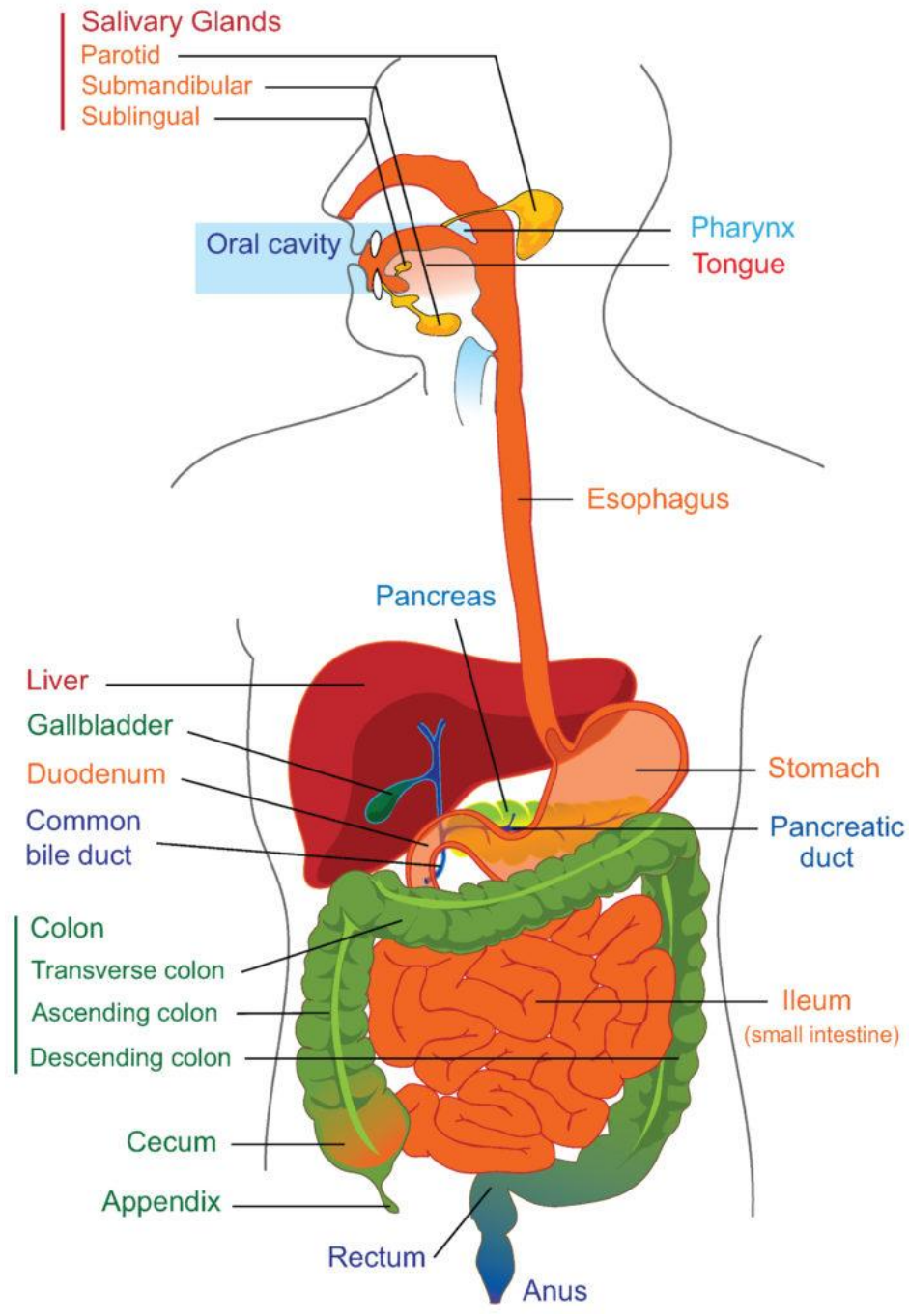


3. Gastrointestinal (GI) Physiology

- 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 esophagus, 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.



IMPORTANT INFORMATION

3.Gastrointestinal (GI) Physiology
A. 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
Esophagus	5 – 6	very thick , no absorption	-	small	,short, typically a few seconds except for some coated tablets	-
Stomach	1.7-3.5	normal	good	small	(solid food)min (liquid) - 120 min 30	no
Duodenum	5 –7	normal	good	Very large	very short	no
Small Intestine	7.5 – 6	normal	good	Very large	About 3 hours	no
Large intestine	7 - 6.8	-	good	Not very large	long, up to 24 hours	Lower ,colon rectum yes

A. Characteristics of GI physiology and Drug Absorption

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.

A. Characteristics of GI physiology and Drug Absorption

- emulsions

✓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 to treat the inflammatory bowel disease.

A. Characteristics of GI physiology and Drug Absorption

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.

A. Characteristics of GI physiology and Drug Absorption

The unstirred water layer

- It is a more or less stagnant layer of water and mucous adjacent to the intestinal wall.

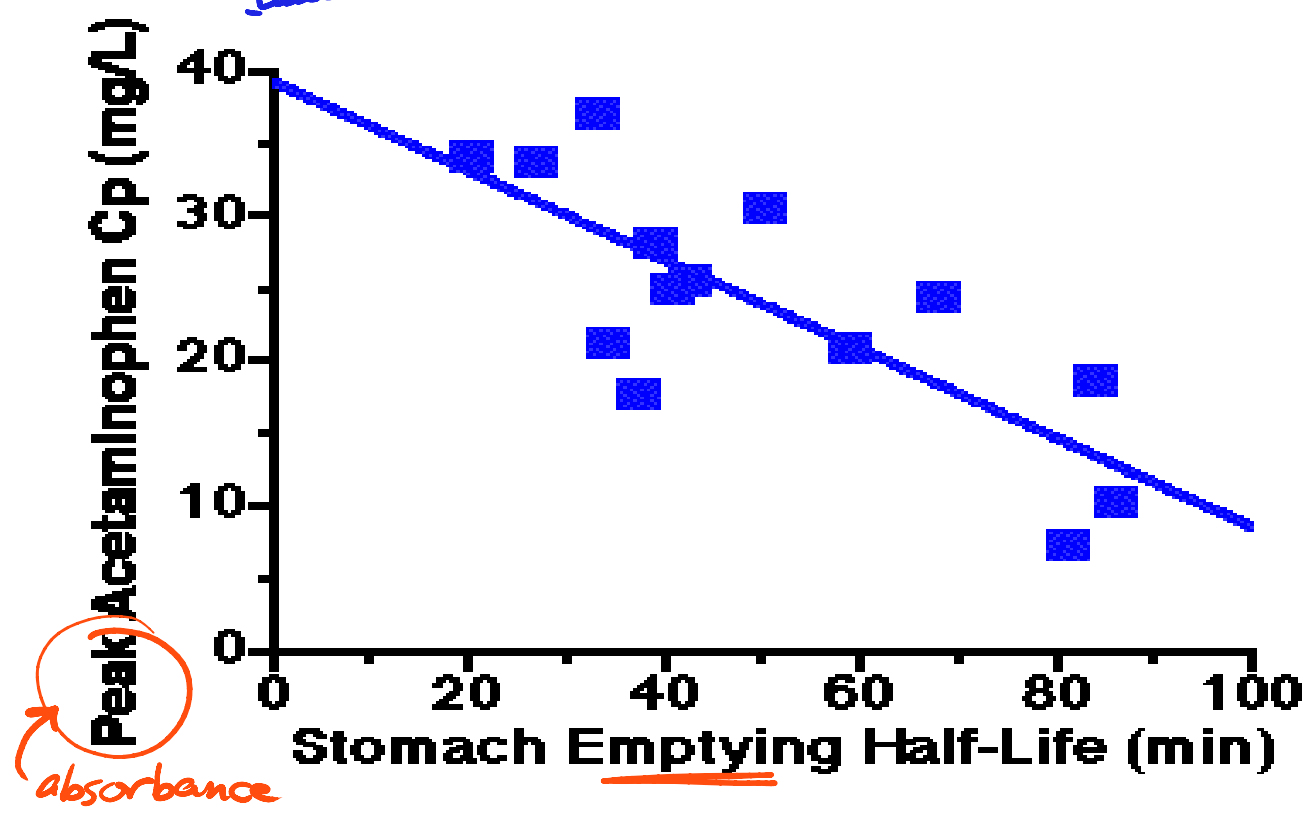
- This layer can provide a diffusion barrier to drugs.

- Some drugs (antibiotics e.g. tetracycline) are capable of complexing with mucous, thereby reducing their availability for absorption.

B. 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.



Dependence of peak acetaminophen plasma concentration as a function of stomach emptying half-life

B. Gastric emptying and motility

Factors Affecting Gastric Emptying

Factor	Effect on Gastric Empyting Rate
Volume of Ingested Material	As volume increases initially an increase then decrease Bulky material tends to empty more slowly than liquid
Type of Meal	Depend on type of food: fatty & carbohydrate foods decrease gastric empyting rate
Temperature of Food	Increase in temperature, increase in empyting rate
Drug	Anticholinergics (e..g. atropine), narcotics, analgesic (e.g aspirin) decrease empyting rate
Viscosity	Rate of emptying is greater for less viscous solutions
Emotional states	Stressful emotional states increase stomach contraction and emptying rate. Depression reduces stomach contraction and emptying
Disease states	Rate of emptying is reduced in: Some diabetic patients, hypothyrodism -Rate of emptying is increased in:hyperthyrodism
Excercise	Reduce emptying rate
Body Position	lying on the left side decreases emptying rate. standing versus lying (delayed).

C. Effect of Food

➢The presence of food in the GIT can influence the rate and extent of absorption, either directly or indirectly via a range of mechanisms.

A- Complexation of drugs with components in the diet

- e.g. Tetracycline forms non-absorbable complexes with calcium and iron, and thus it is advised that patients do not take products containing calcium or iron, such as milk, iron preparations or indigestion remedies, at the same time of day as the tetracycline.

B- Alteration of pH

- Food tends to increase stomach pH by acting as a buffer. This liable to decrease the rate of dissolution and absorption of a weakly basic drug and increase that of a weakly acidic one.

C- Alteration of gastric emptying

- Fats and some drugs tend to reduce gastric emptying and thus delay the onset of action of certain drugs.

C. Effect of Food

D- Stimulation of gastrointestinal secretions

- Gastrointestinal secretions (e.g. pepsin) produced in response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism, and hence a reduction in their bioavailability.
- Fats stimulate the secretion of bile. Bile salts are surface active agents which increase the dissolution of poorly soluble drugs (griseofulvin).
- Bile salts can form insoluble and non-absorbable complexes with some drugs, such as neomycin and kanamycin.

G- Food-induced changes in presystemic metabolism

- Certain foods may increase the bioavailability of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process.
- E.g. Grapefruit juice is capable of inhibiting the intestinal cytochrome P450 (CYP3A) and thus taken with drugs that are susceptible to CYP3A metabolism which result in increase of their bioavailability.

E-Competition between food components and drugs for specialized absorption mechanisms

There is a possibility of competitive inhibition of drug absorption in case of drugs that have a chemical structure similar to nutrients required by the body for which specialized absorption mechanisms exist.

C. Effect of Food

F- Increased viscosity of gastrointestinal contents

- The presence of food in the GIT provides a viscous environment which may result in:

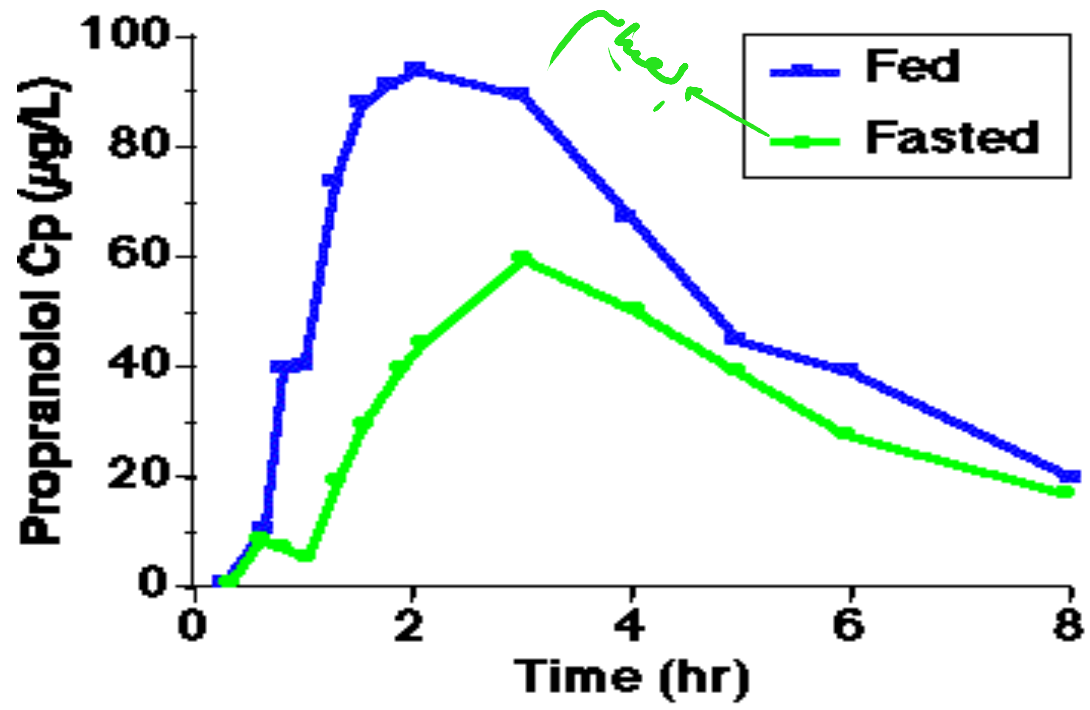
➢ Reduction in the rate of drug dissolution

➢ Reduction in the rate of diffusion of drug in solution from the lumen to the absorbing membrane lining the GIT.

Hence, there is reduction in drug bioavailability.

H- Food-induced changes in blood flow

- Food serve to increase the bioavailability of some drugs (e.g. propranolol) that are susceptible to first-pass metabolism.
- Blood flow to the GIT and liver increases after a meal. The faster the rate of drug presentation to the liver; the larger the fraction of drug that escapes first-pass metabolism. This is because the enzyme systems become saturated.



Effect of Fasting *versus* Fed on Propranolol Concentrations

C. Effect of Food

- Timing of drug administration in relation to meals is often important. **Pharmacists** regularly advise patients to take a medication either 1 hour before or 2 hours after meals to avoid any delay in drug absorption.

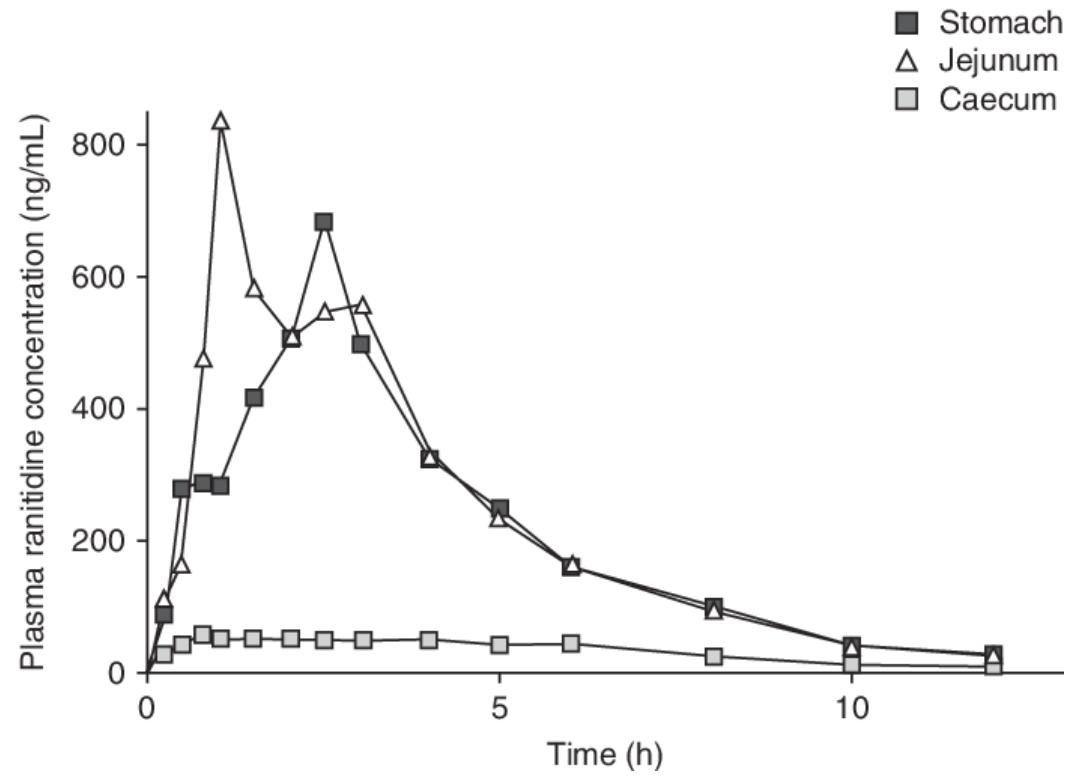
- Since fatty foods may delay stomach emptying time beyond 2 hours, patients who have just eaten a heavy, fatty meal should take these drugs 3 hours or more after the meal, whenever possible.

- Products that are used to curb stomach acid secretion are usually taken before meals, in anticipation of acid secretion stimulated by food. Famotidine (Pepcid), and cimetidine (Tagamet) are taken before meals to curb excessive acid production.

Double Peak Phenomena

- Some drugs such as cimetidine and ranitidine, after oral administration produce a blood concentration curve consisting of two peaks.

- The presence of double peaks has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic cycle or failure of a tablet dosage form.



The first pass effect (also known as first-pass metabolism or presystemic metabolism)

- **Definition:**

➢The metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount of unmetabolized drug reaching the systemic circulation.

- ***Gut wall metabolism***

➢This effect is known as first-pass metabolism by the intestine.

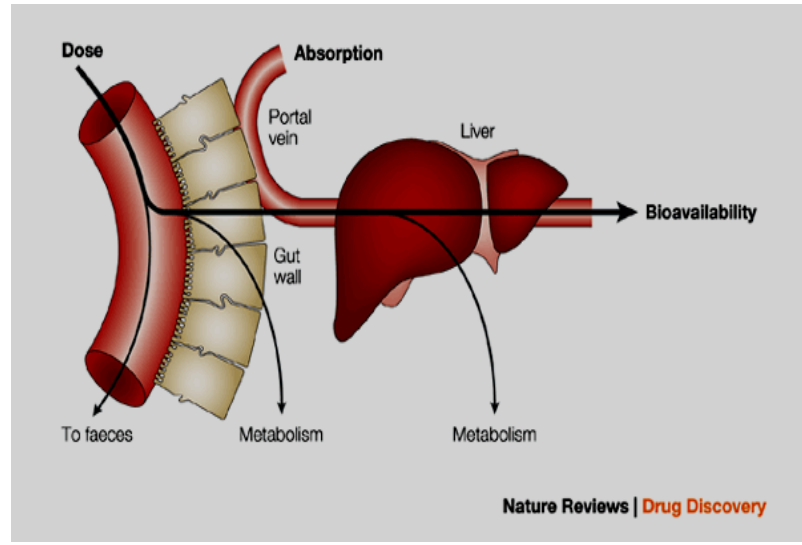
➢Cytochrome P450 enzyme, CYP3A, that is present in the liver and responsible for the hepatic metabolism of many drugs, is present in the intestinal mucosa and that intestinal metabolism may be important for substrates of this enzyme e.g. cyclosporin.

Presystemic metabolism

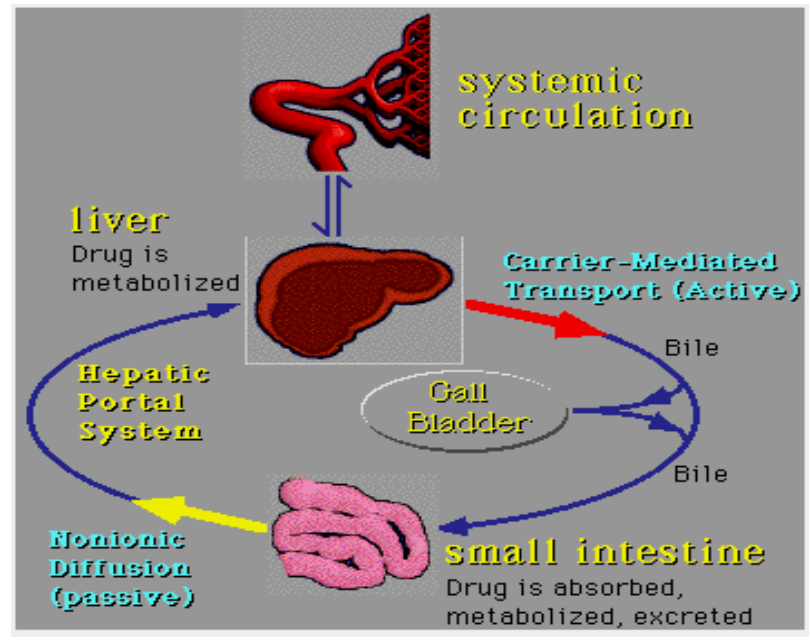
- ***Hepatic metabolism***
- After a drug is swallowed, it is absorbed by the digestive system and enters the hepatic portal system. It is carried through the portal vein into the liver before it reaches the rest of the body.

- The liver metabolizes many drugs (e.g. propranolol), sometimes to such an extent that only a small amount of active drug emerges from the liver to the rest of the circulatory system.

- This *first pass* through the liver thus greatly reduces the bioavailability of the drug.



Presystemic metabolism



Hepatic metabolism