

# **BIOPHARMACEUTICS**

**Wollo University**  
**Department of pharmacy**  
**Pharmaceutics unit**

# Session Objectives

✍️ @ the end of this session you will be able to:

- 👍 Define terms related with **bp** and **pk**
- 👍 Describe the physiology of GI system
- 👍 Recognize the mechanisms of transport across the GI membrane

# Definitions (1)

- ✍ **Biopharmaceutics** is the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacological and therapeutic activity of drug products”
- ✍ **Pharmacokinetics** is the science of the kinetics of drug absorption, distribution, and elimination (i.e., excretion and metabolism).

# Definitions (2)

- ✍ **Clinical pharmacokinetics:** is the application of pharmacokinetic methods to drug therapy
- ✍ **Population pharmacokinetics:** is the study of pharmacokinetic differences of drugs in various population groups
- ✍ **Pharmacodynamics:** refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with the receptor

# Definitions (4)

- ✍ **Toxicokinetics** is the application of PK principles to the design, conduct, and interpretation of **drug safety evaluation** studies and in validating dose-related exposure in animals
- ✍ **Clinical toxicology** is the study of adverse effects of drugs and toxic substances (poisons) in the body

# OVERVIEW OF BIOPHARMACEUTICS

- ✍ **Biopharmaceutics:** the study of how the physicochemical properties of drugs, dosage forms and routes of administration affect the rate and extent of drug absorption.
- ✍ The relationship between the drug, its dosage form and the route by which it is administered governs how much of the drug and how fast it enters the systemic circulation.

# BIOPHARMACEUTICS

- ✍ For a drug to be effective, enough of it needs to reach its site(s) of action and stay there long enough to be able to exert its pharmacological effect.
- ✍ If a drug is given IV it is administered directly into the blood, the entire drug reaches the systemic circulation (**100% bioavailable**).
- ✍ If a drug is given by another route there is no guarantee that the whole dose will reach the systemic circulation intact.
- ✍ The fraction of an administered dose of the drug that reaches the systemic circulation in the unchanged form is known as the **bioavailable dose**.

✍ The relative amount of an administered dose of a particular drug that reaches the systemic circulation **intact** and the rate at which this occurs is known as the **bioavailability**.

✍ This definition would not be valid in the case of **prodrugs**, whose therapeutic action normally depends on their being converted into a therapeutically active form prior to or on reaching the systemic circulation.



✍ A given drug may exhibit differences in its bioavailability if it is administered:

- ➡ In the same type of dosage form by different routes of administration, e.g. an **aqueous solution** administered by the **oral** and **intramuscular** routes;
- ➡ By the same routes of administration but different types of dosage form, e.g. a tablet, a hard gelatin **capsule** and an aqueous **suspension** administered by the peroral route;

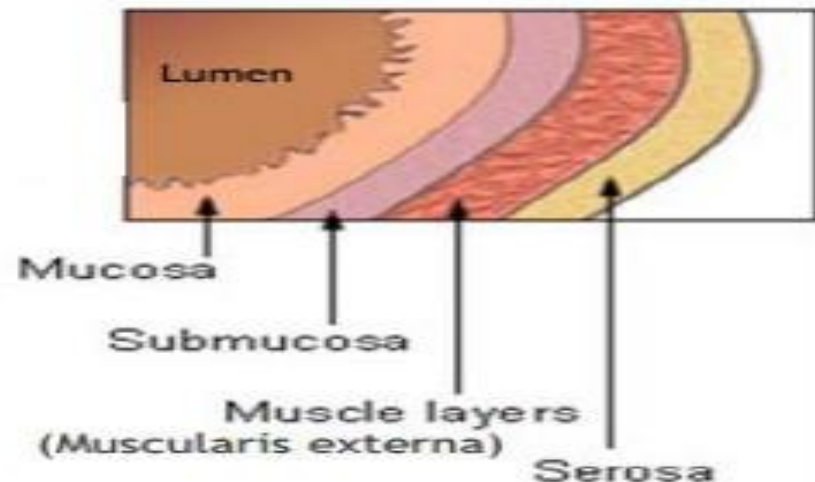
⇒ In the same type of dosage form by the same route of administration but with different formulations of the dosage form, e.g. different formulations of an oral aqueous suspensions

# Physiology of the GIT

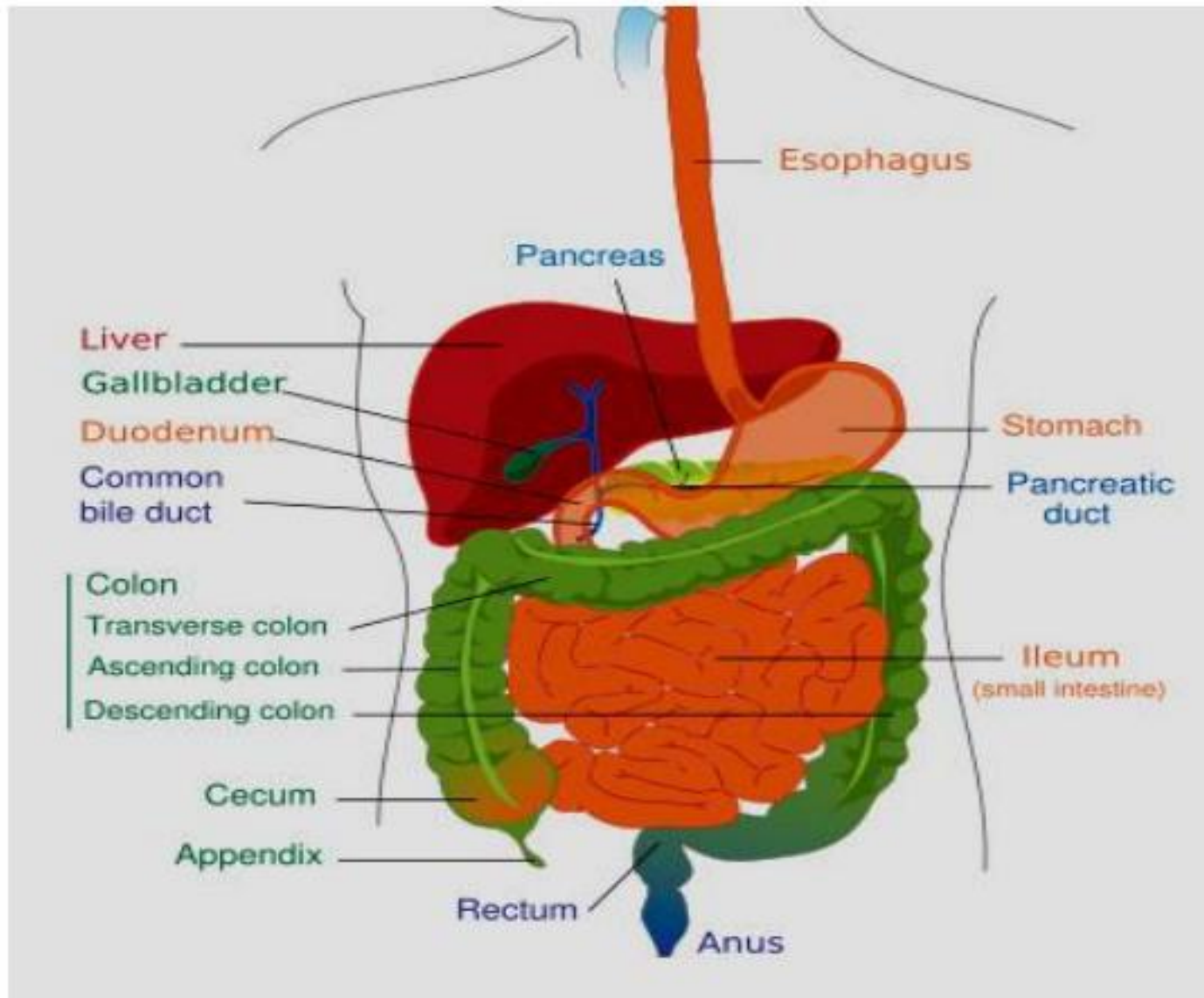
- ✍ The GIT is a muscular tube approximately 6 m in length with varying diameters.
- ✍ It stretches from the mouth to the anus
- ✍ Consists of four main anatomical areas:
  - ⇒ Oesophagus
  - ⇒ Stomach
  - ⇒ Small Intestine and
  - ⇒ Large intestine or colon.

✍ The wall of the GIT is essentially similar in structure along its length, consisting of four principal histological layers:

- ➡ Serosa
- ➡ Muscularis
- ➡ Sub mucosa
- ➡ Mucosa



- ✍ The majority of the gastrointestinal epithelium is covered by a layer of **mucus**.
- ✍ This is a viscoelastic translucent aqueous gel that is secreted throughout the gastrointestinal tract, acting as a protective layer and a mechanical barrier.



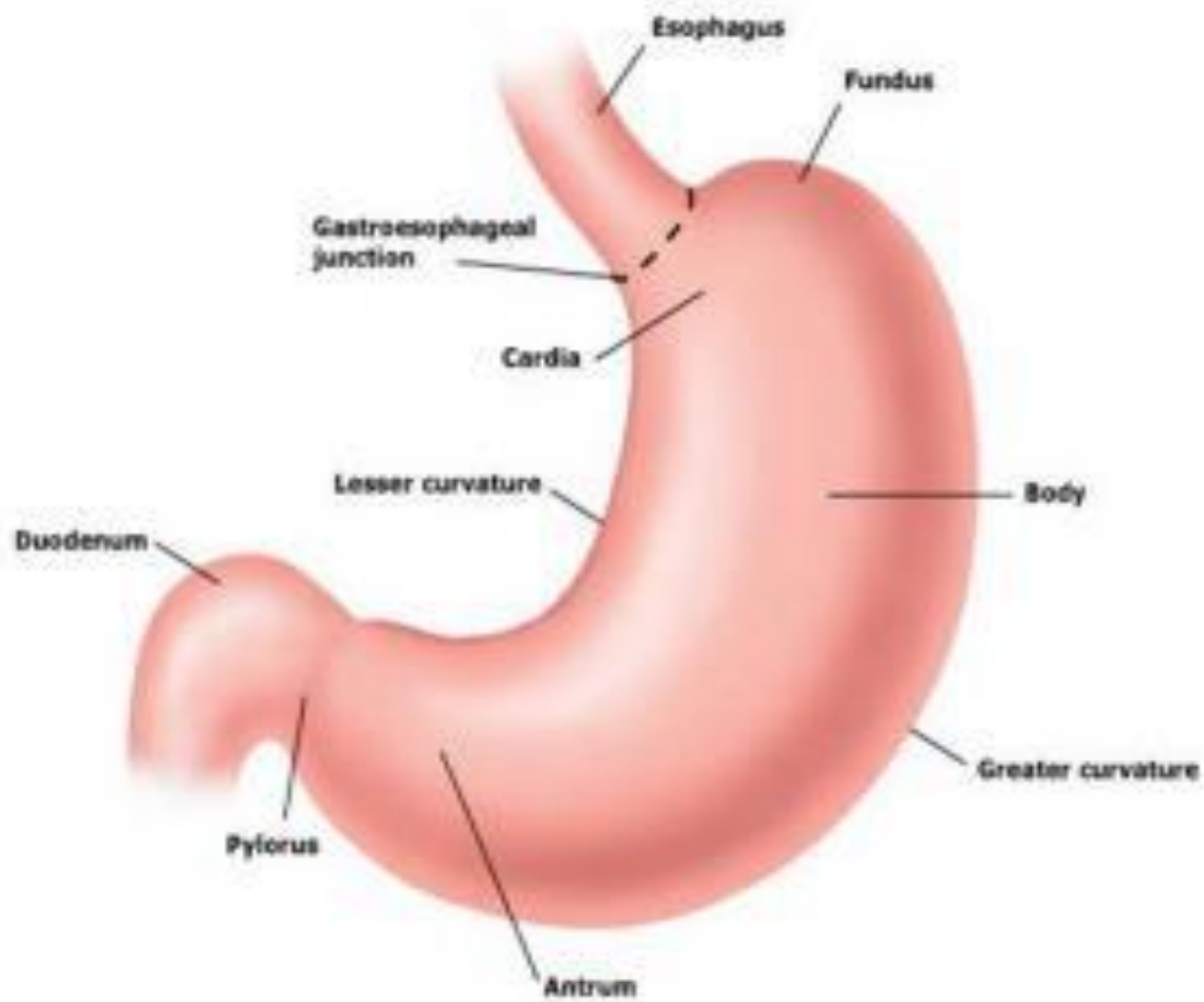
## The oesophagus

- ⇒ Links the oral cavity with the stomach, approximately **250 mm** long
- ⇒ Joins the stomach at **gastroesophageal junction**
- ⇒ pH of esophageal lumen is 5 to 6

## The Stomach

- ➡ It is the most dilated part of the GIT and is situated between the lower end of the oesophagus and the small intestine.
- ➡ Its opening to the duodenum is controlled by the pyloric sphincter.
- ➡ The stomach can be divided into four anatomical regions, namely fundus, body, antrum and pylorus.





✍ The two major functions of the stomach are:

1. To act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate;
2. To reduce ingested solids to a uniform creamy consistency, known as **chyme**, by the action of acid and enzymatic digestion.

➡ This enables better contact of the ingested material with the mucous membrane of the intestines and thereby facilitates absorption.

✍ The stomach has a capacity of approximately 1.5 L

✍ Under fasting conditions it usually contains no more than 50 mL of fluid, which is mostly gastric secretions

# Gastric secretions:

## ⇒ Acid

- ◆ Secreted by the **parietal cells**
- ◆ **parietal cells** also secrete intrinsic factor
- ◆ Maintains the pH of the stomach between 1 and 3.5 in the fasted state;

## ⇒ The hormone **gastrin**

- ◆ Secreted by **G cells**
- ◆ Is a potent stimulator of gastric acid production.

## ⇒ Pepsins

- ◆ Are secreted by the **peptic cells (Chief cells)** in the form of its precursor pepsinogen.

## ⇒ Mucus

- ◆ Is secreted by the surface **mucosal cells**
- ◆ Lines the gastric mucosa.

- Very little drug absorption occurs
- High biopharmaceutical importance:
  - Gastric emptying can dictate drug absorption from SI

## The small intestine

- ➡ The small intestine is the longest (5 m)
- ➡ Most convoluted part of the gastrointestinal tract
- ➡ Extends from the **pyloric sphincter** of the stomach to the **ileocaecal junction** where it joins the large intestine.

✍ Its main functions are:

➡ **Digestion:** the process of enzymatic digestion, which began in the stomach, is completed in the small intestine.

➡ **Absorption:** the small intestine is the region where most nutrients and other materials are absorbed

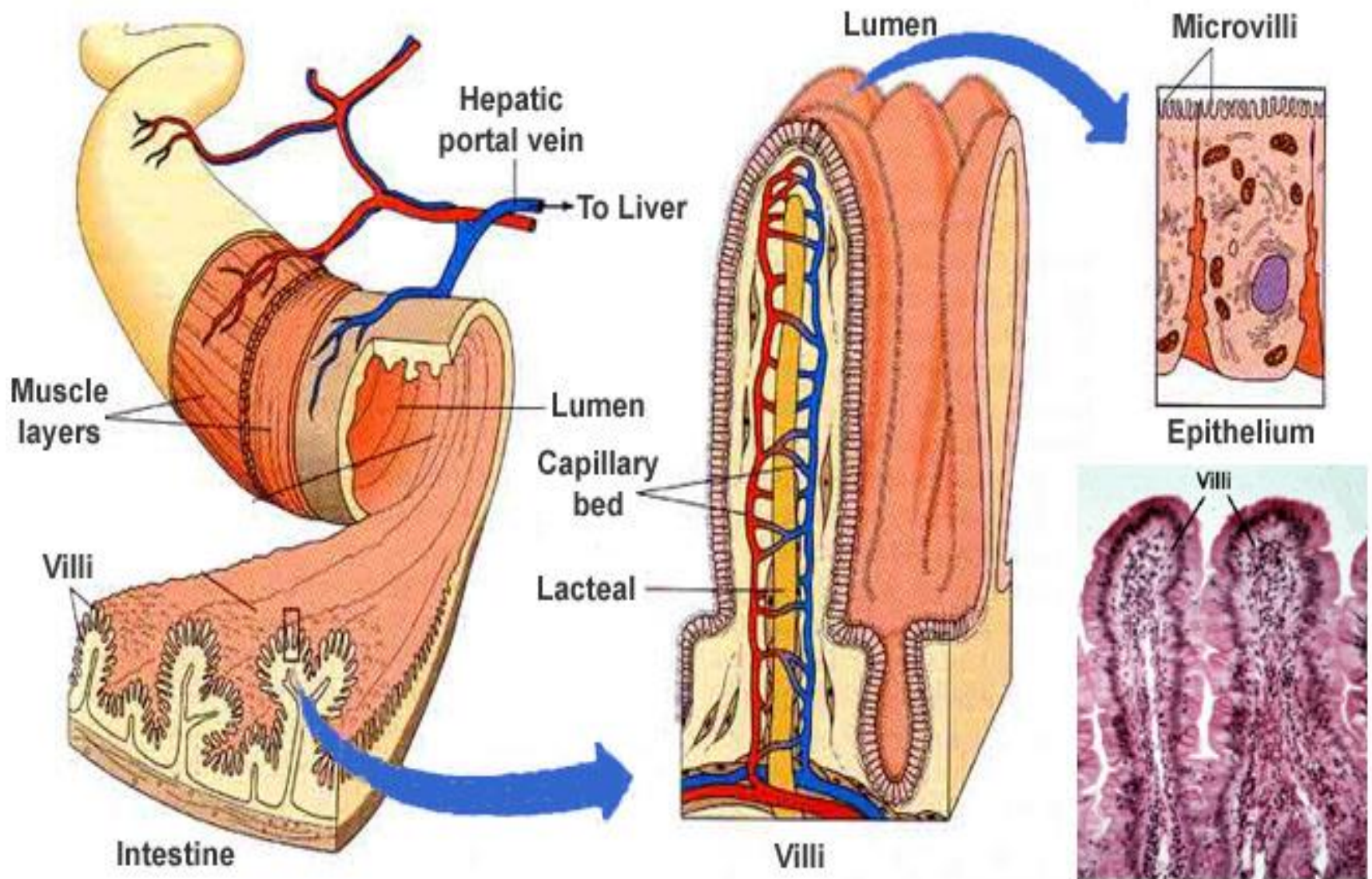
✍ The small intestine is divided into the

➡ Duodenum (20-30 cm)

➡ Jejunum (1.5 m)

➡ Ileum (3 m)

- ✍ The wall of the small intestine has a rich network of both blood and lymphatic vessels.
- ✍ The surface area of the small intestine is increased by about 600 times that of a simple cylinder, to approximately  $200 \text{ m}^2$  in an adult, by several adaptations → a good absorption site: folds of **villi** and **microvilli**





✍ The luminal pH of the small intestine increases to 6 and 7.5 due to:

1. Brunner's glands in the duodenum: secret **bicarbonate**
2. Intestinal cells in the small intestine: secret mucus and enzymes like **hydrolases** and **proteases**

### 3. Pancreatic Secretions:

➡  $\text{NaHCO}_3$  and

➡ Enzymes like:

● Proteases (trypsin, chymotrypsin and carboxypeptidases),

● Lipase

● Amylase

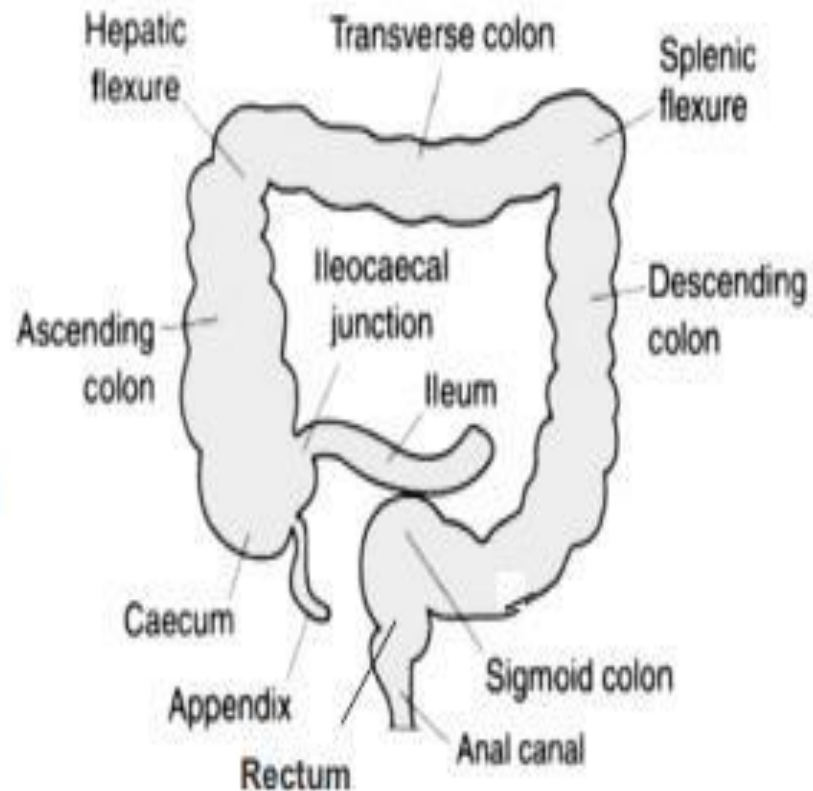
### 4. Hepatocytes (liver): secret bile

- SI has significant biopharmaceutical importance:
  - Most nutrients and drugs absorbed from SI

# Large intestine

- Final part-ileocaecal junction to anus ( $\sim 1.5\text{m}$  long)
- The large intestine has greater diameter (6cm)

→ caecum ( $\sim 8.5\text{ cm}$ )  
→ ascending colon ( $\sim 20\text{ cm}$ )  
→ transverse colon ( $> 45\text{ cm}$ )  
→ descending colon ( $\sim 30\text{ cm}$ )  
→ sigmoid colon ( $\sim 40\text{ cm}$ )  
→ rectum ( $\sim 12\text{ cm}$ )



- From a functional point of view, the large intestine may be divided into two.
- The proximal half, concerned primarily with absorption
- The distal half, concerned with storage and mass movement of fecal matter
  - Storage and compaction of fecal material

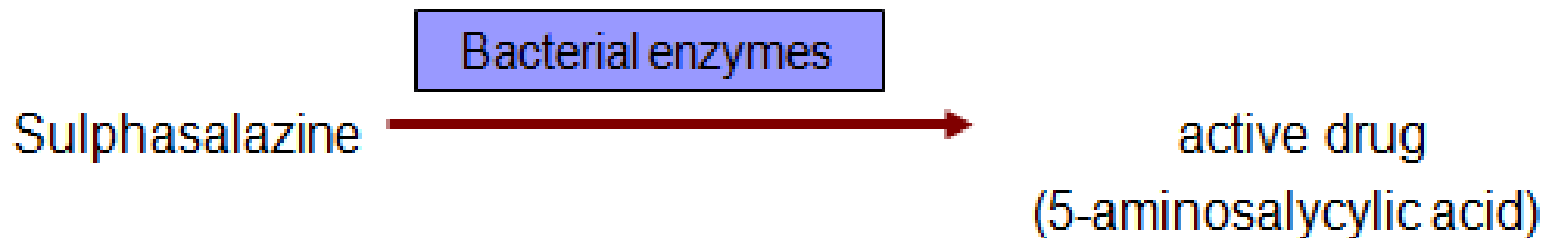
# The Colon

- ✍ It is the last 1.5 m of the 6 m of the GIT.
- ✍ The colon, unlike the small intestine has **no specialized villi**.
- ✍ The surface area is approximately  $(1 / 30)^{\text{th}}$  that of the small intestine.

✍ The main functions of the colon are:

1. The absorption of  $\text{Na}^+$ ,  $\text{Cl}^-$  and  $\text{H}_2\text{O}$  in exchange for **bicarbonate** and **potassium ions**. Thus the colon has a significant homeostatic role in the body.
  2. The storage and compaction of faeces.
- The colon is permanently colonized by extensive number and variety of bacteria.
  - Capable of several metabolic reactions

- Although some drugs may be rendered inactive, bacterial metabolism of other drugs may give rise to more active or toxic products.
- Sulfasalazine, which is used in the treatment of ulcerative colitis, provides an interesting example of a drug whose metabolites represent the active pharmacological species.



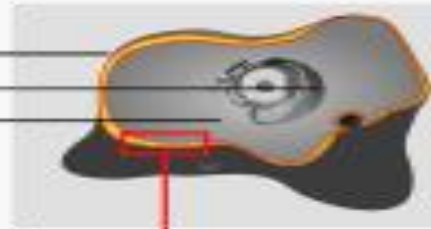
# THE GASTROINTESTINAL MEMBRANE

- ✍ The gastrointestinal membrane separates the lumen of the stomach and intestines from the systemic circulation.
- ✍ It is the main cellular barrier to the absorption of drugs from the GIT.
- ✍ The membrane is complex in nature, being composed of lipids, proteins, lipoproteins and polysaccharides, and has a bilayer structure

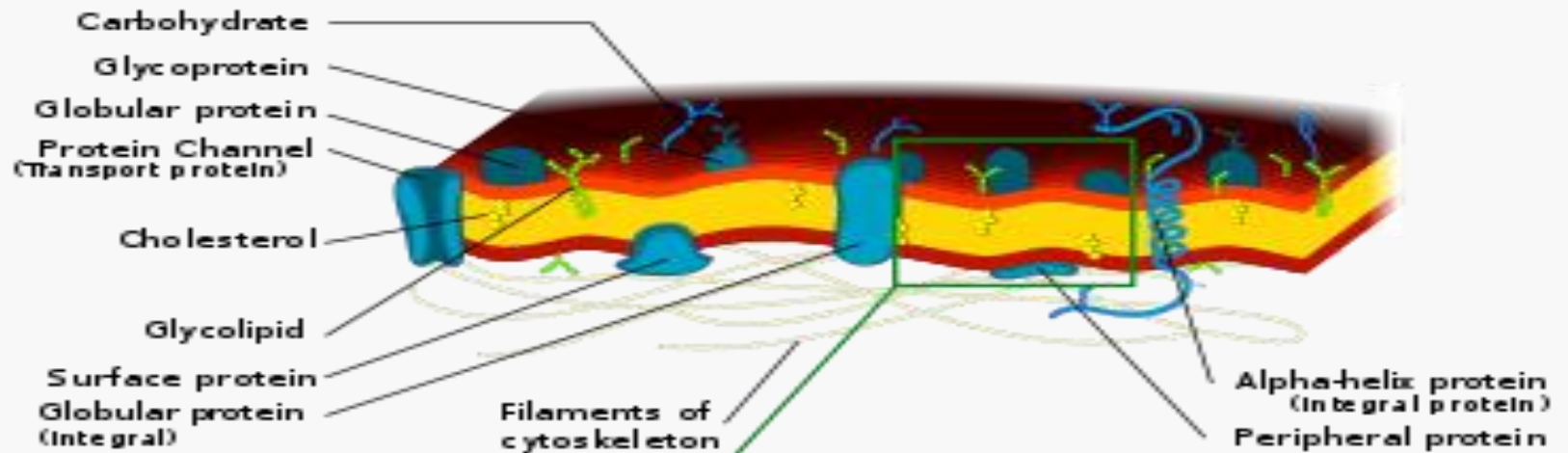


## Cell

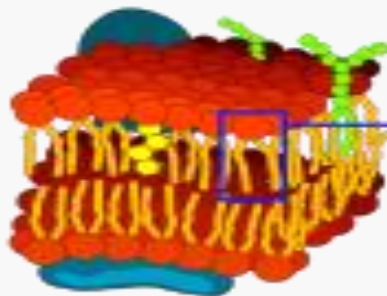
Extracellular fluid  
Nucleus  
Cytoplasm



## Cell membrane



## Phospholipid bilayer



## Phospholipid (Phosphatidylcholine)



Hydrophilic head

Hydrophobic tail

✍ The barrier has the characteristics of a **semipermeable membrane**, allowing the rapid transit of some materials and impeding or preventing the passage of others.

✍ It is **permeable** to amino acids, sugars, fatty acids and other nutrients, and **impermeable** to plasma proteins

✍ The membrane is viewed as a semipermeable lipoidal sieve

➡ Allows the passage of **lipid-soluble** molecules across it

➡ The passage of **water and small hydrophilic molecules** through its numerous aqueous pores.

➡ In addition there are a number of **transporter proteins** or **carrier molecules** that exist in the membrane and which, with the help of energy, transport materials back and forth across it

# Mechanisms of Transport across the Membrane

✍ There are two main mechanisms of drug transport across the GI epithelium:

➡ **Transcellular**: across the cells

➡ Simple passive diffusion

➡ Carrier-mediated transport

➡ Active transport

➡ Facilitated diffusion

➡ Endocytosis

➡ **Paracellular**: between the cells.

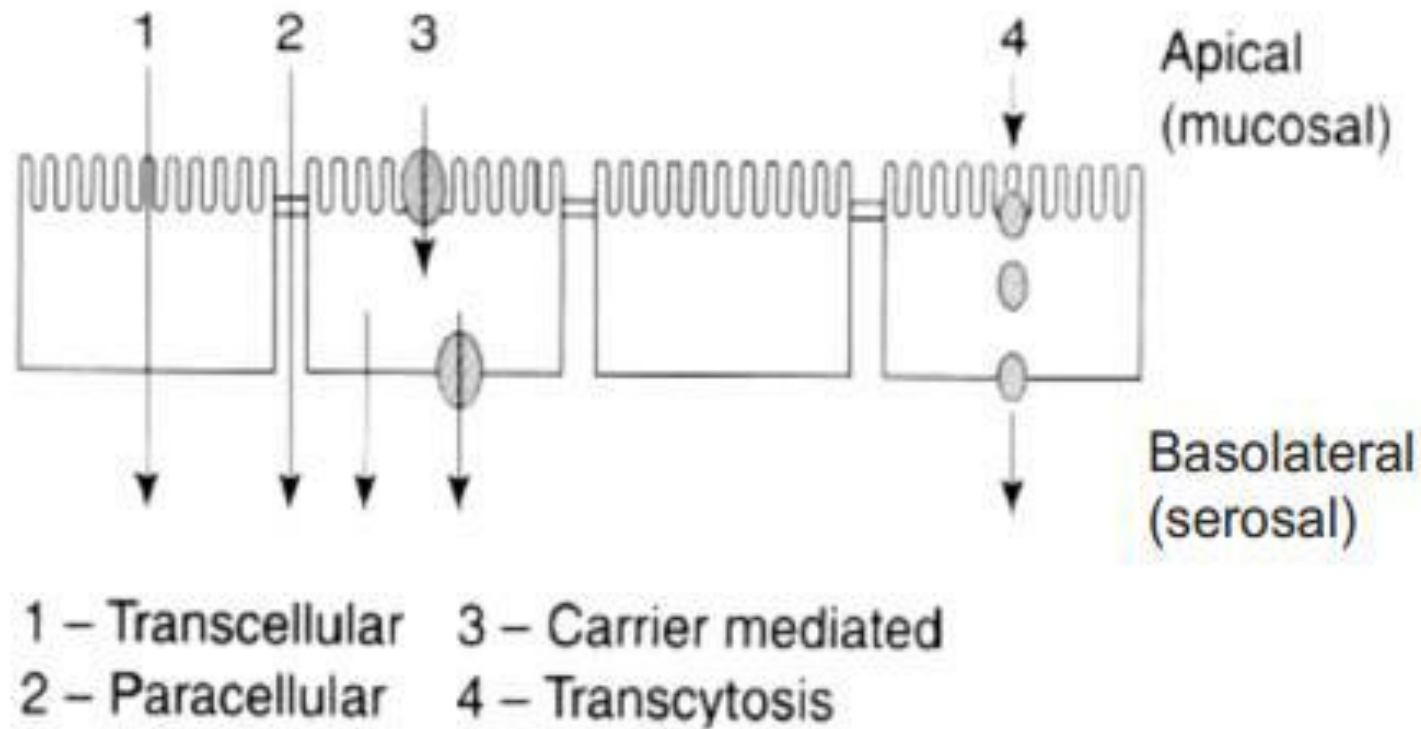


Fig. Summary of intestinal epithelial transport mechanisms

# Passive Diffusion

- ✍ The preferred route of transport for relatively **small lipophilic molecules** and thus many drugs.
- ✍ Drug molecules pass across the lipoidal membrane from a region of high concentration in the lumen to a region of lower concentration in the blood.
- ✍ This lower concentration is maintained primarily by **blood flow**.

# Passive Diffusion

- ✍ The rate of transport is determined by
  - ➡ The physicochemical properties of the drug
  - ➡ The nature of the membrane
  - ➡ The concentration gradient of the drug across the membrane.
- ✍ The process initially involves the partitioning of the drug between the aqueous fluids within the GIT and the lipoidal-like membrane of the lining of the epithelium


- ✍ The drug in solution in the membrane then diffuses across the epithelial cell/cells within the GI barrier to blood in the capillary network
- ✍ Upon reaching the blood the drug will be rapidly distributed, so maintaining a much lower concentration than that at the absorption site.



## fick's first law of diffusion

⇒ States that the rate of diffusion across a membrane ( $dC/dt$ ) is proportional to the difference in concentration on each side of that membrane.

$$dC/dt = k(C_g - C_b)$$

 The **proportionality constant  $k$**  incorporates the diffusion coefficient of the drug in the GI membrane ( $D$ ), and the thickness ( $h$ ) and surface area of the membrane ( $A$ ).

$$k = \frac{DA}{h}$$

✍ These equations indicate that the rate of GI absorption of a drug by passive diffusion depends on the **surface area** of the membrane that is available for drug absorption.

✍ Thus the small intestine, primarily the duodenum, is the major site of drug absorption, owing principally to the presence of **villi** and **microvilli** which provide such a large surface area for absorption

✍ This equation also indicates that the rate of drug absorption depends on a large **concentration gradient** of drug across the GI membrane.

✍ This concentration gradient is influenced by the apparent **partition coefficients** exhibited by the drug with respect to the GI membrane/fluid interface and the GI membrane/blood interface.

✍ It is important that the drug has **sufficient affinity (solubility) for the membrane phase** that it can partition readily into the gastrointestinal membrane.

✍ In addition, after diffusing across the membrane the drug should exhibit **sufficient solubility in the blood** such that it can partition readily out of the membrane phase into the blood.

✍ On entering the blood in the capillary network, the drug will be:

- ➡ Carried away from the site of absorption by the rapidly circulating GI blood supply
- ➡ Diluted by distribution into a large volume of blood (i.e. the systemic circulation),
- ➡ Distributed into body tissues and other fluids,
- ➡ Bind to plasma proteins in the blood which will further lower the concentration of free (i.e. diffusable) drug in the blood
- ➡ Metabolized and excreted.

✍ Consequently, the blood acts as a 'sink' for absorbed drug and ensures that the concentration of drug in the blood at the site of absorption is low in relation to that in the GI fluids at the site of absorption, i.e.  $C_g \gg C_b$ .

✍ The 'sink' conditions provided by the systemic circulation ensure that a large concentration gradient is maintained across the GI membrane during the absorption process.

✍ The passive absorption process is driven solely by the concentration gradient of the diffusible species of the drug that exists across the gastrointestinal blood barrier.

✍ Therefore the GI absorption of most drugs follows **first-order kinetics**.

$$\frac{dC}{dt} = \frac{DA C_g}{h} = k C_g$$

# Carrier-mediated Transport

- ✍ Certain compounds and many nutrients are absorbed transcellularly by a carrier-mediated transport mechanism, of which there are two main types:
  - ➡ Active transport and
  - ➡ Facilitated diffusion or transport.

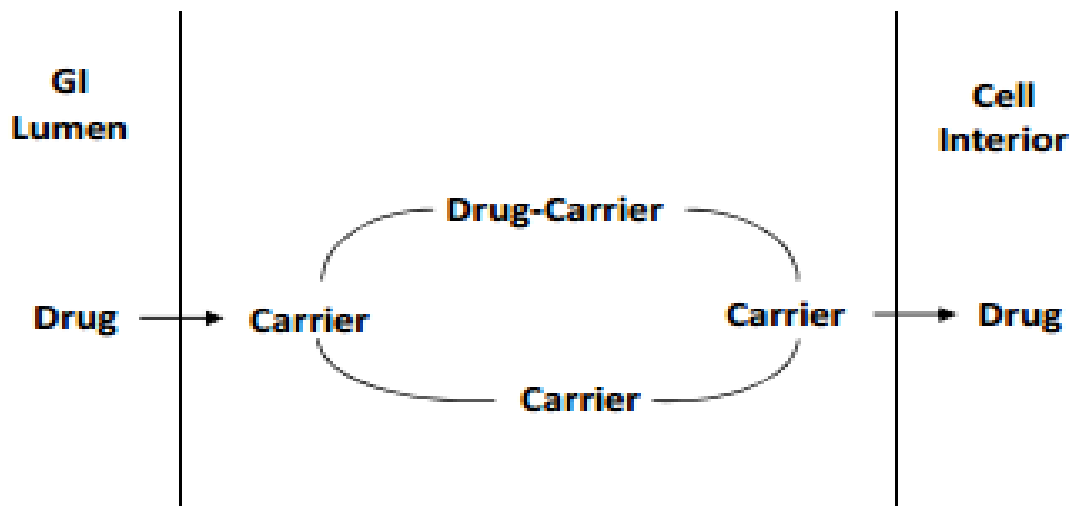


# Active Transport (1)

- ✍ Active transport is a process whereby materials are transported **against a concentration gradient** across a cell membrane, i.e. transport can occur from a region of lower concentration to one of higher concentration.
- ✍ Active transport is an **energy-consuming** process.

## Active Transport (2)

- Explained by shuttling process across epithelial membrane
  - Drug forms complex with carrier
  - Drug-carrier complex moves across membrane
  - Drug liberated on other side
  - Free carrier returns to initial position In cell membrane adjacent to GI lumen



# Active Transport (3)

✍ Various membrane transporters in the small intestine include:

- ➡ Peptide transporters: penicillins, cephalosporins, ACEIs and renin inhibitors
- ➡ Nucleoside transporters: Nucleosides and their analogue
- ➡ Sugar transporters

# Active Transport (4)

- ⇒ Bile acid transporters
- ⇒ Amino acid transporters: L-dopa and methyldopa
- ⇒ Organic anion transporters
- ⇒ Vitamin transporters

# Active Transport (5)

- ✍ Active transport proceeds at a rate that is proportional to the drug concentration only at low concentrations
- ✍ At higher concentrations the carrier mechanism becomes **saturated**
  - ➡ Further increases in drug concentration will not increase the rate of absorption.
- ✍ **Competition** between two similar substances for the same transfer mechanism,
  - the inhibition of absorption of one or both compounds.

# Facilitated Diffusion

- ✍ Carrier-mediated process
- ✍ It cannot transport a substance against concentration gradient.
- ✍ Does not require an energy input
- ✍ Is **saturable** and is subject to **inhibition** by competitive inhibitors

# Vesicular transport

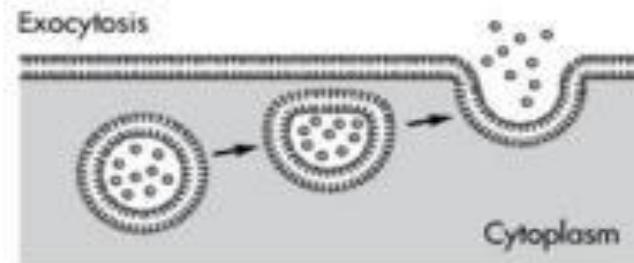
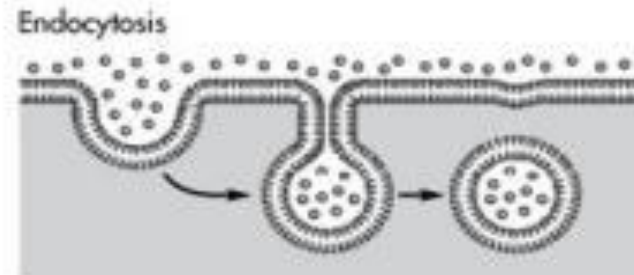
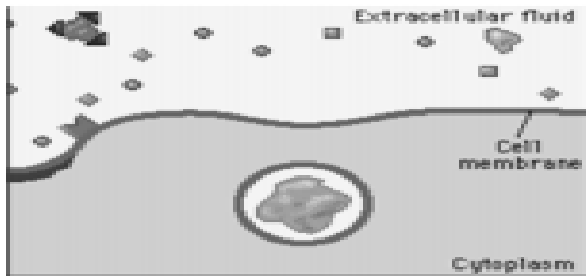
- The process of engulfing particles or dissolved materials by the cell.
- **Pinocytosis and phagocytosis** are forms of vesicular transport that differ by the type of material ingested.
- Pinocytosis refers to the engulfment of small solutes or fluid,
- Phagocytosis refers to the engulfment of larger particles or macromolecules, generally by macrophages.
- Endocytosis and exocytosis.

# Vesicular transport...

- During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material and then engulfs the material, incorporating it into the cell.
- The cell membrane containing the material becomes pinched off, forming small intracellular membrane-bound vesicle or vacuole within the cell.
- Material migrate to basolateral surface of cell and exocytosed
- The fat-soluble vitamins A, D, E and K are absorbed via pinocytosis.



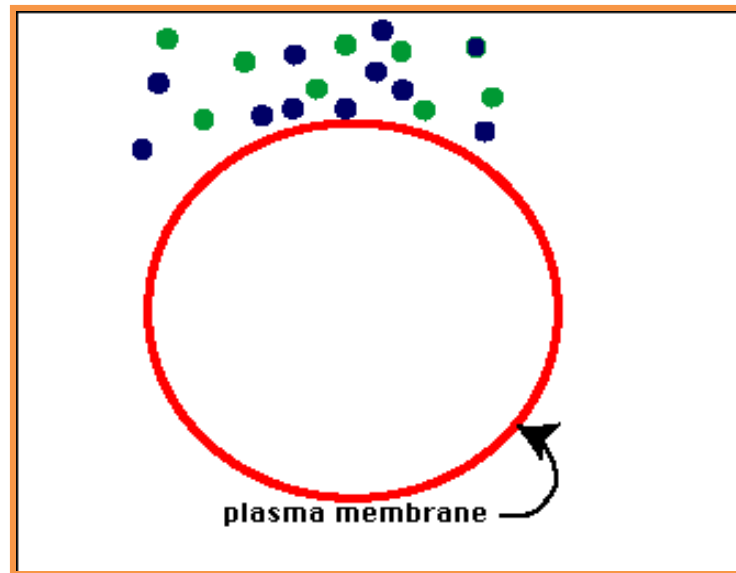
# Vesicular transport...



Diagrams showing vesicular transport: *endocytosis and exocytosis*

# Vesicular transport...

- ✍ **Phagocytosis:** is engulfment by the cell membrane of particles larger than 500 nm.
- ✍ This process is important for the absorption of polio and other vaccines from the GIT.



# Paracellular Pathway

- ✍ It is the transport of materials in the aqueous pores between the cells rather than across them.
- ✍ Is important for the transport of **ions** such as calcium and for the transport of **sugars, amino acids** and **peptides** at concentrations above the capacity of their carriers.
- ✍ **Small hydrophilic and charged drugs** that do not distribute into cell membranes cross the GI epithelium via the paracellular pathway

# Presystemic Metabolism

- ✍ **Def:** The metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount drug reaching the systemic circulation.
- ✍ An oral dose of drug could be completely absorbed but incompletely available to the systemic circulation because of first-pass or presystemic metabolism by the gut wall and/or liver
  - ➡ Gut-wall metabolism
  - ➡ Hepatic metabolism

## *Gut wall metabolism*

- Mucosal cells lining the gut wall represent a significant potential site for drug metabolism.
- Many drugs have been shown to undergo metabolism in the gut wall, including those that are substrates for the *CYP3A4* isozyme.
  - e.g. *aspirin, acetaminophen, morphine*

## *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
- This first pass through the liver Thus greatly reduces the BA of The drug.
  - Propranolol, lidocaine, imipramine

