CHAPTER 2-5

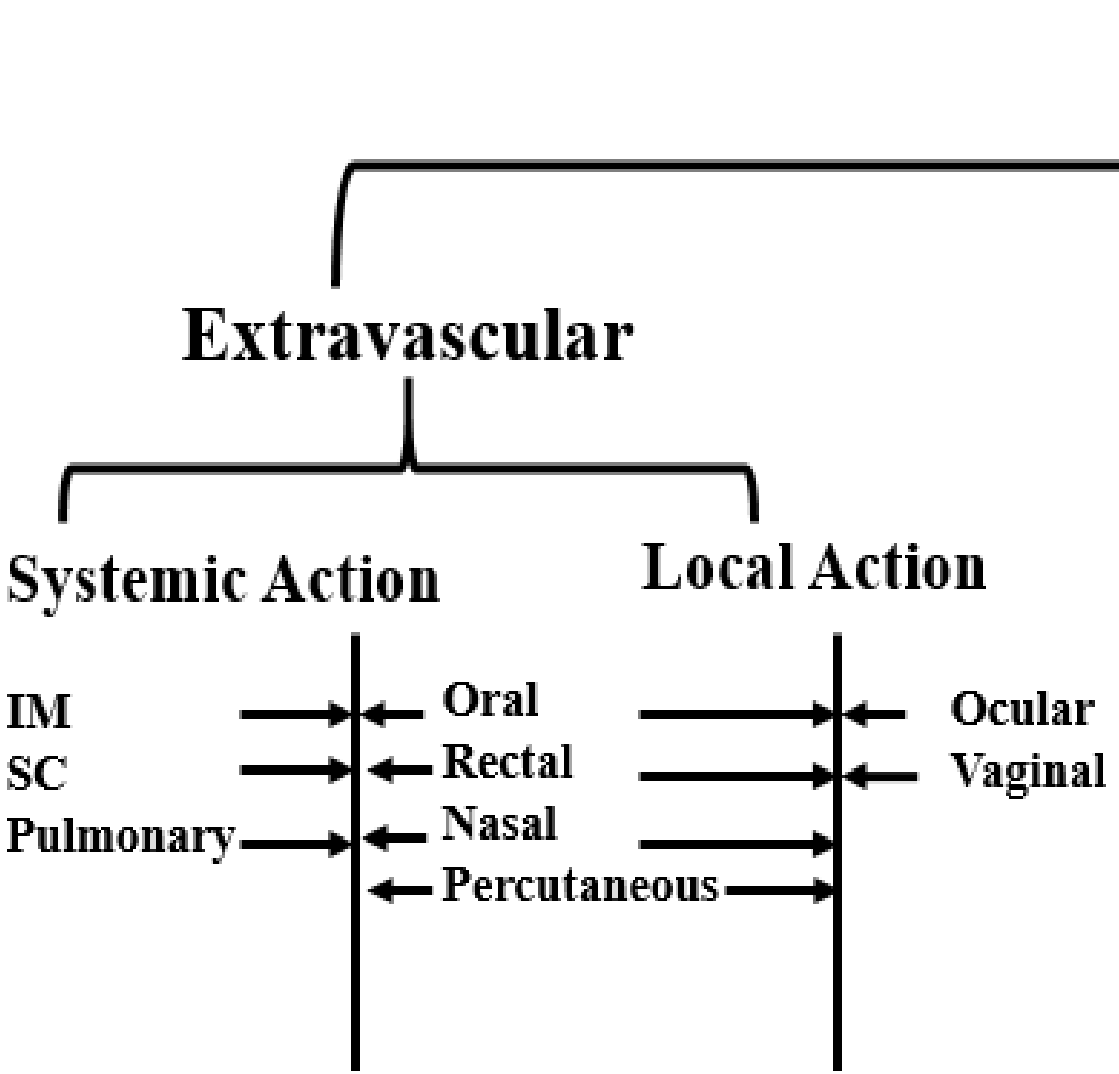
Gastrointestinal tract

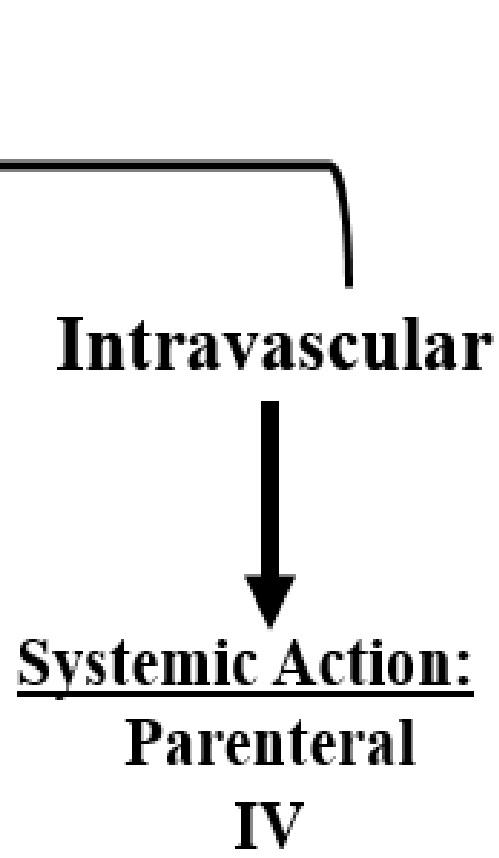
- **Buccal and Sublingual**
- **Oral route of Drug Administration.**
  - **-Stomach**
  - **-Small intestine**
- **Rectal route of administration**

Routes of administration

- **Enteral**
  - **Buccal & Sublingual**
  - **Gastrointestinal tract:**
    - **-Stomach,**
    - **-Small intestine& Large intestine**
    - **-Rectum**
- **Parenteral:**
  - **-Intravascular: IV bolus, IV infusion**
  - **-IM**
  - **-SC**
- **Others**
  - **-Percutaneous**
  - **-Vaginal**
  - **-Nasal and ear**
  - **-Ocular**
  - **-Pulmonary**

Routes of Administration





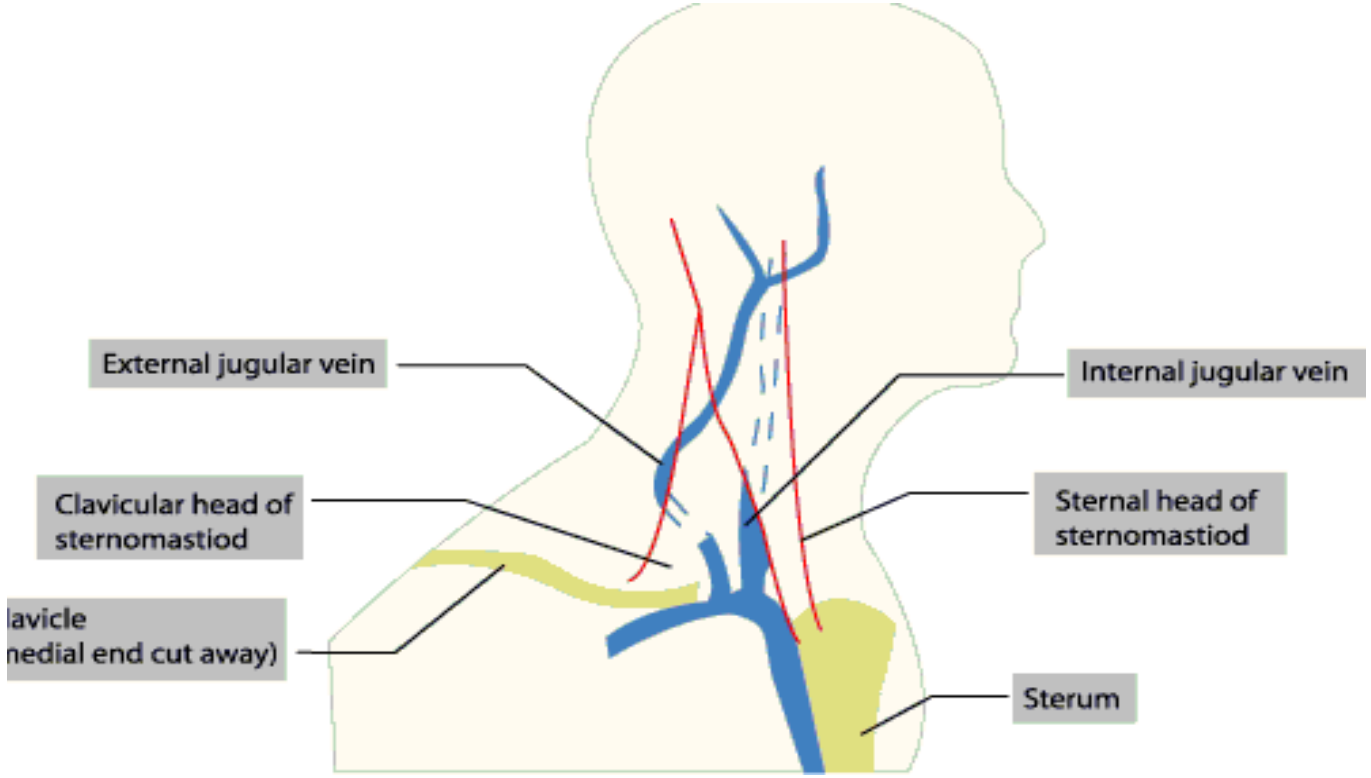
Buccal/Sublingual Absorption

In the oral cavity there are two regions:

* Buccal: Internal face of cheeks, External jugular Vein.
* Sublingual: Under the tongue, internal jugular vein.

Some drugs are taken as smaller tablets (special tablets) which are held in the mouth or under the tongue.

* Buccal or sublingual dosage forms may be used for **LOCAL** and/or **SYSTEMIC** effect.



Oral administration

Sublingual administration is where the dosage form is placed under the tongue

Buccal administration is where the dosage form is placed between gums and inner lining of the cheek

Buccal Route of administration

Buccal/Sublingual Administration

- **Buccal route:** *The medicament is placed between the cheek and the gum.*
- Dosage forms:
  - **Mouth washes.**
  - **Toothpastes.**
  - **Aerosols.**
  - **Chewable and sucking tablets.(15-45 min).**
- Buccal tablets are often hard (Disintegration time =4h), designed to dissolve slowly.
- Uses: Prophylactic and Antiseptic purposes.
- Also, Some steroids like testosterone and nicotine containing chewing gum.
- **Sublingual route:** *The drug is placed under the tongue and allowed to dissolve.*
- Nitroglycerin, as a softer sublingual tablet (Disintegration time=2min)→ Rapid relief of angina.

Drugs administered as buccal tablets

- Propranalol
- Nitrites and nitrates
- Nefidipine
- Fenoterol
- Estradiol
- Oxytocin
- Metoprolol
- Metoclopromide
- Insulin
- Nitro glycerine
- Codeine
- Morphine
- Diltiazem
- Chlorpheniramine maleate

Applications

1. Smoking cessation therapy.
2. Hormone replacement therapy .
3. Hypertension.
4. Angina pectoris.
5. Cancer.

- **Advantages of these routes are:**

1. Rapid absorption and higher blood levels due to high vascularization of the region (useful for administration of anti-anginal drugs).

2. No first-pass hepatic metabolism.

3. No degradation of drugs such as that encountered in the GIT (more stable than acidic stomach).

4. Presence of saliva facilitates both drug dissolution and its subsequent permeation by keeping the oral mucosa moist.

5. Quick termination.

6. Can be self administered.

- **Limitations of these routes (Disadvantages) are:**

1. Limited mucosal **surface area** (only a **small dose** can be administered).

2.Concern for **taste** of the medicament and **discomfort (irritation, holding in mouth, avoid drinking and eating).**

3.Technological concerns.

4. Holding the dose in the mouth is **inconvenient**. If any is swallowed that portion must be treated as an oral dose and subject to first pass metabolism.

- **Technological Requirements:**

1- Small with lenticular form.

2- Mwt 75-1000 Da.

3- Dose is small enough to deliver across the Buccal mucosa.

4- Drug should be hydrophilic/hydrophobic in nature.

5- Drug should be stable in Buccal pH (6.4-7.2).

6- No Sialogogic effect.

7-Tasteless (No aromatic and no flavor).

8- Excipients for rapid disintegration and rapid absorption.

9- Administered after eating.

- **Mechanism of Drug Absorption or Transport Routes**
- Mostly **drugs** are absorbed by **Passive Diffusion mechanism**.
- **Nutrients** Are absorbed by **Carrier Mediated mechanism**.

- There are two permeation pathways for passive drug transport across the oral mucosa:

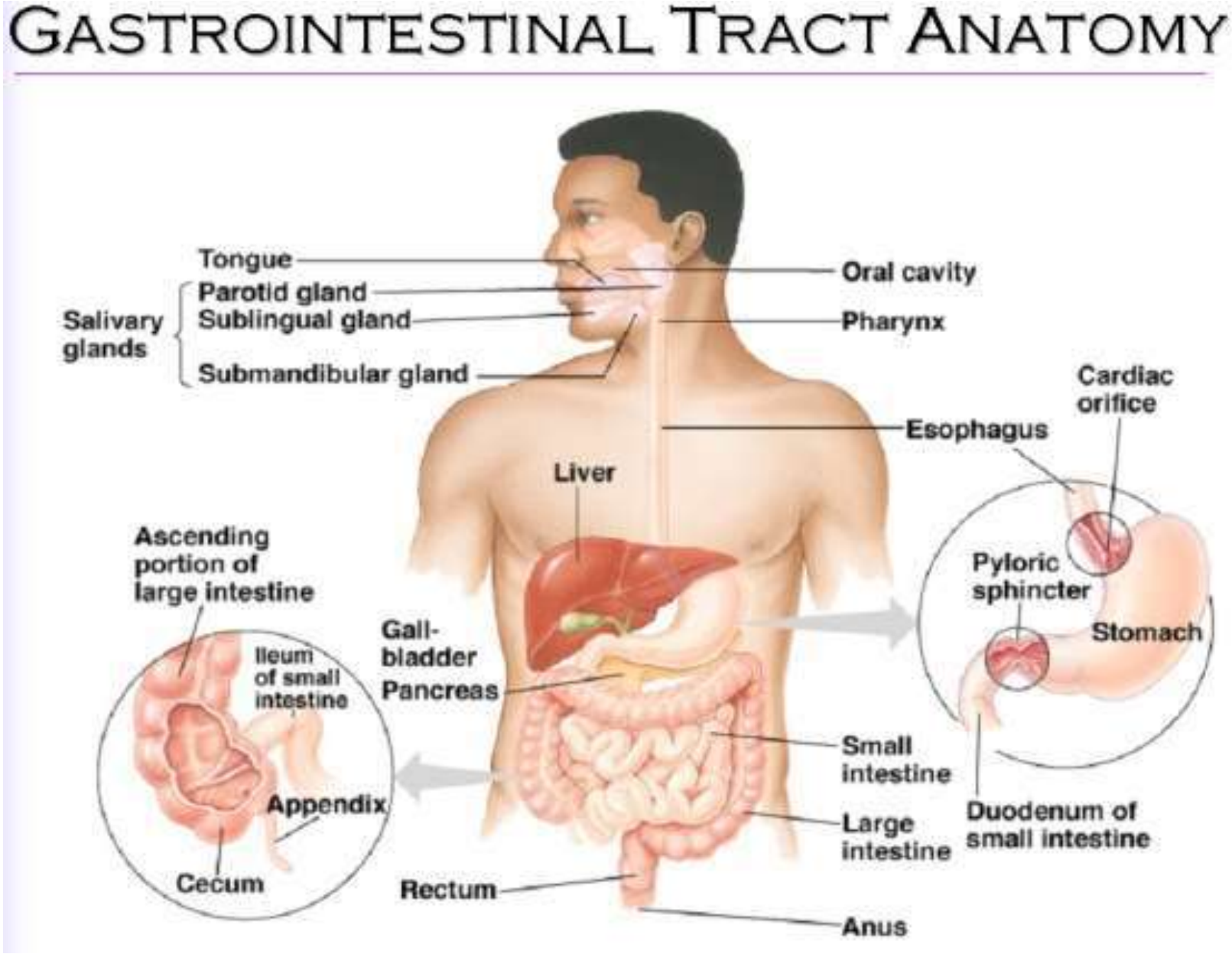
1.Transcellular route : Route for lipophilic compounds.

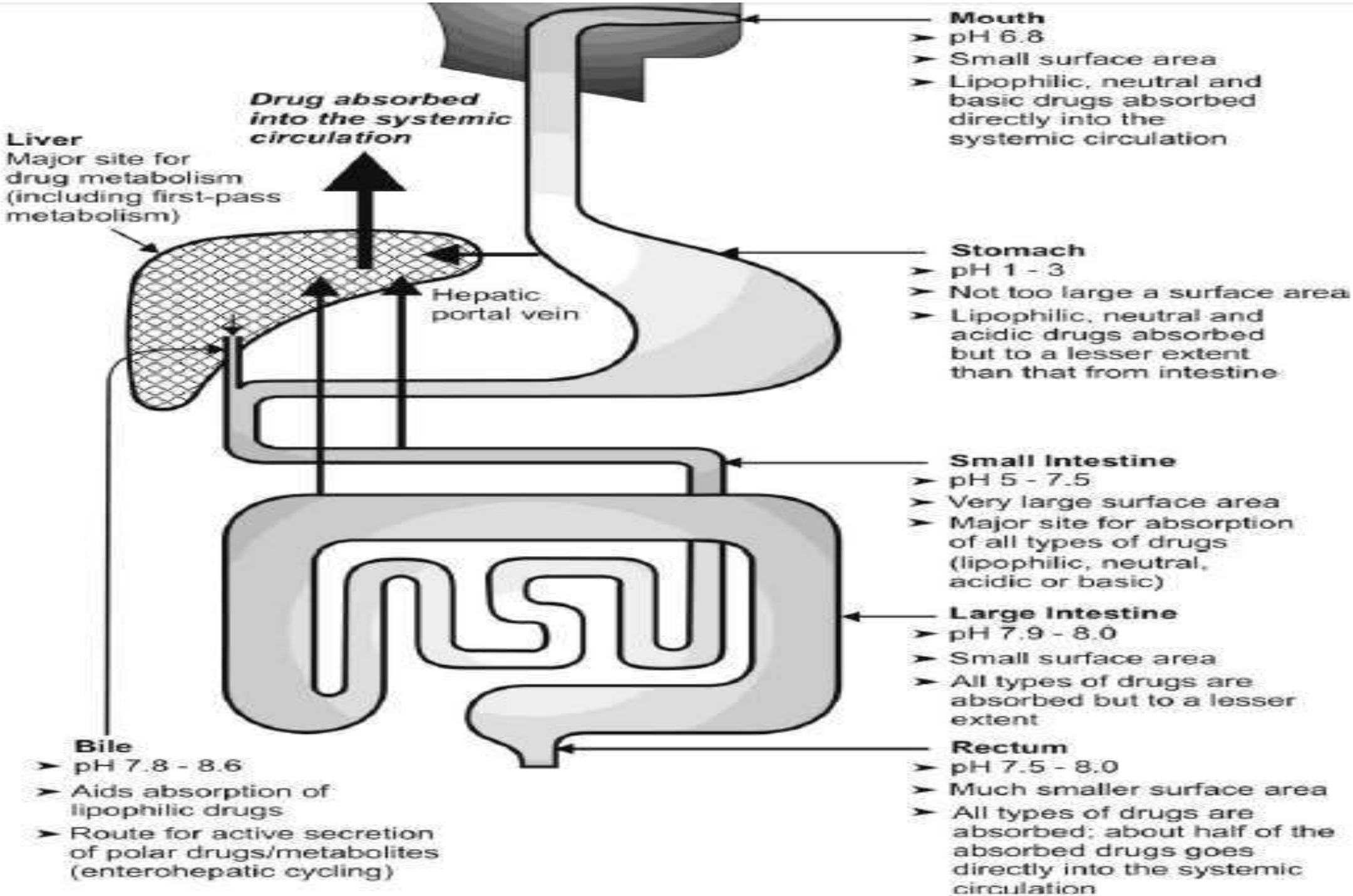
2. Paracellular route : Route for hydrophilic drug.

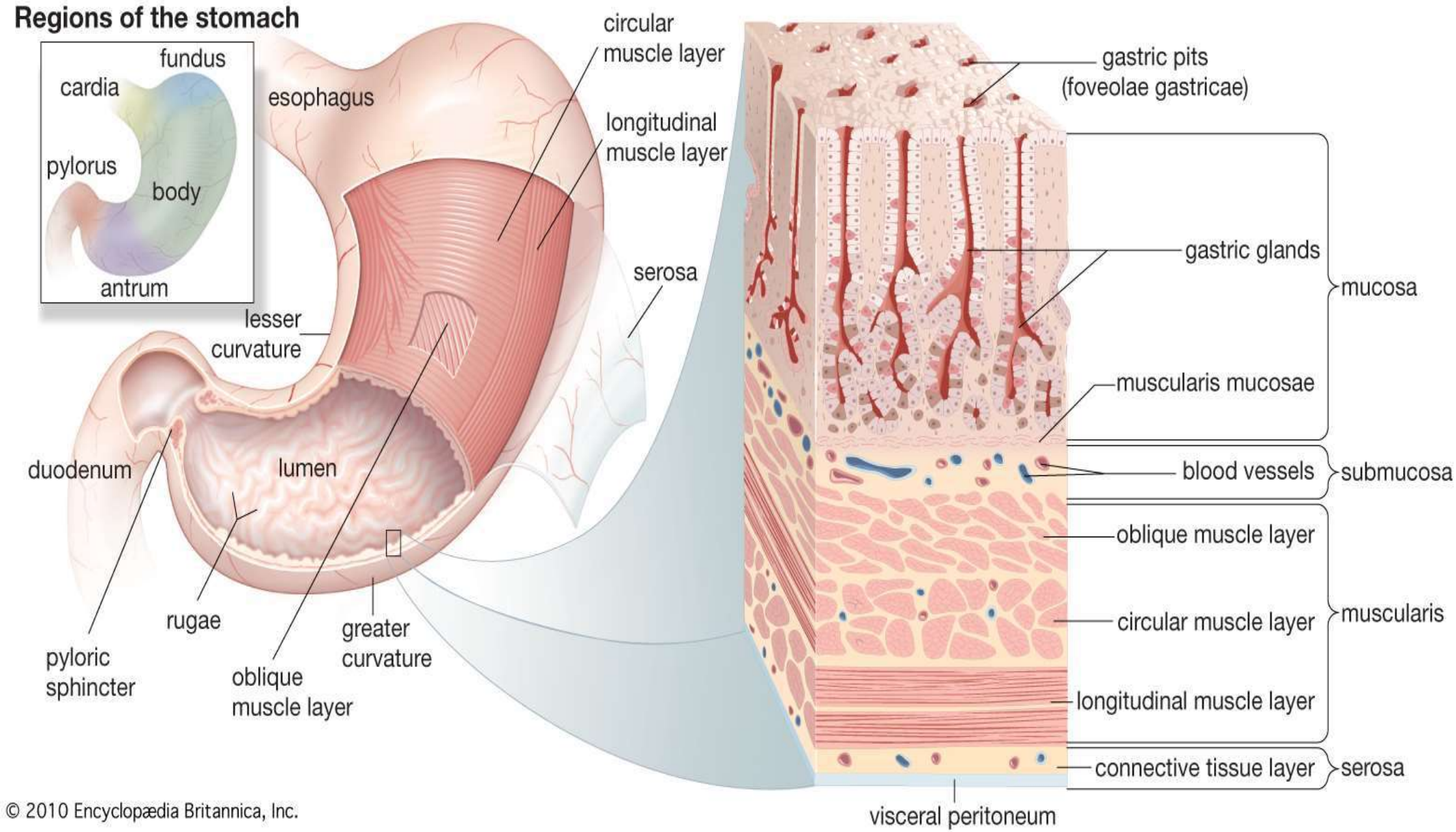
➢ Gastrointestinal (GI) Physiology:

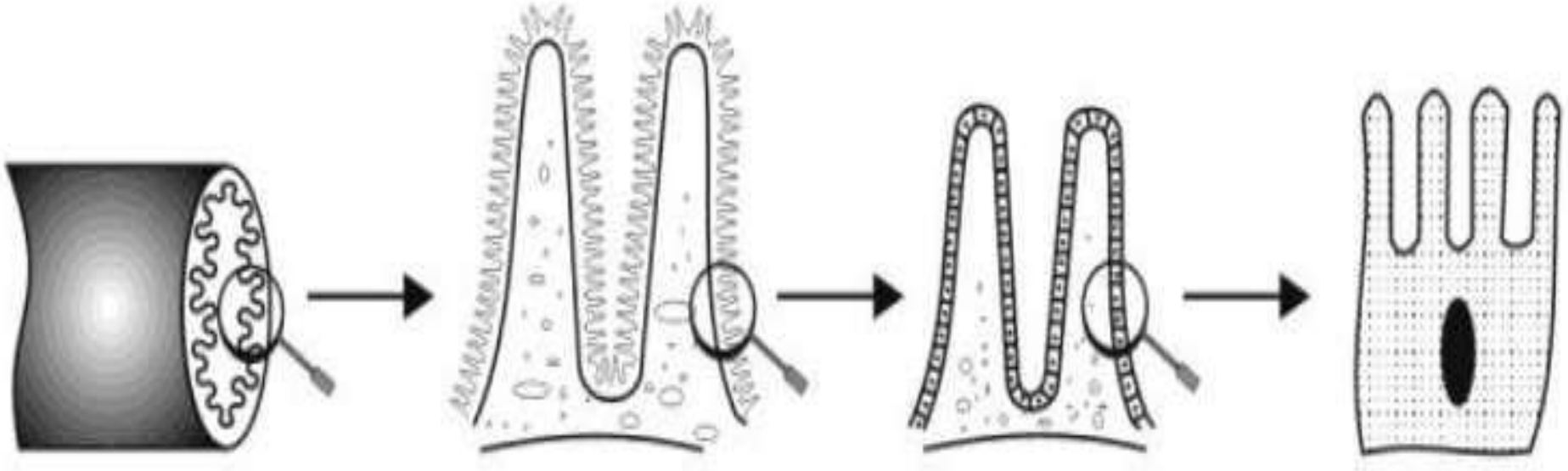
- Aproximately 6 m in length with varying diameters. It stretches from the mouth to the anus and consists of **four main** anatomical areas:
    - The esophagus,
    - The stomach,
    - The small intestine and
    - The large intestine or colon.
- The majority of the gastrointestinal epithelium is covered by a layer of **mucous**. This is a viscoelastic translucent aqueous gel that is secreted throughout the GIT, acting as a **protective** layer and a **mechanical** barrier.

Fig: Schematic representation of the GIT and different sites of drug absorption




Mouth
pH 6.8
Small surface area
Lipophilic, neutral and basic drugs absorbed directly into the systemic circulation
Drug absorbed into the systemic circulation
Liver
Major site for drug metabolism (including first-pass metabolism)
Hepatic portal vein
Stomach
pH 1 - 3
Not too large a surface area
Lipophilic, neutral and acidic drugs absorbed but to a lesser extent than that from intestine
Small Intestine
pH 5 - 7.5
Very large surface area
Major site for absorption of all types of drugs (lipophilic, neutral, acidic or basic)
Large Intestine
pH 7.9 - 8.0
Small surface area
All types of drugs are absorbed but to a lesser extent
Bile
pH 7.8 - 8.6
Aids absorption of lipophilic drugs
Route for active secretion of polar drugs/metabolites (enterohepatic cycling)
Rectum
pH 7.5 - 8.0
Much smaller surface area
All types of drugs are absorbed; about half of the absorbed drugs goes directly into the systemic circulation





	Small intestine as a cylinder	Folds of Kerckring	Villi	Microvilli
Surface area (m^2)	0.33	1	10	200
Relative increase in surface area	1	3	30	600

Fig: Representation of the components of intestinal epithelium that accounts for its large surface area

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	-

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

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

Oral Administration of Drugs

Oral Administration of Drugs

❑*Advantages of oral administration route:*

- ✓Safe.
- ✓Convenient- self- administered, pain free, non-invasive and easy to take.
- ✓Economical- compared to other parenteral routes.
- ✓Usually good absorption- takes place along the whole length of the GIT.
- ✓No need for sterilization.

❑*Disadvantages*:

1. Slow absorption, slow action → can not be used in emergency.
2. Irritable and unpalatable drugs→ nausea and vomiting.
3. Cannot be used in unconscious patients.
4. First-pass effect- due to Biotransformation.
5. Food–Drug interactions and Drug-Drug interactions.
6. Sometimes inefficient drug absorbed, some drugs are not absorbed like streptomycin.
7. Some drugs destroyed by gastric enzymes.
8. Local effect antibiotics may kill normal gut flora and allow overgrowth of fungal varieties.

Gastric Absorption

•The stomach does not act primarily as absorption organ, the drug can reside in the stomach from **30 min** up to **several hours** in contact with a stomach surface area and provide conditions for absorption of certain drugs as ***weak acid drugs*** and ***Alcohol.***

•***Factors affecting the gastric absorption:***

1. Gastric emptying time : The time a dosage form takes to traverse the stomach is usually termed (the gastric residence time).

•Decreased gastric emptying rate→ increased absorption.(in stomach)

•The rate of emptying of material from the stomach is proportional to the volume of material in the stomach.

- The emptying process obeys 1st order kinetics

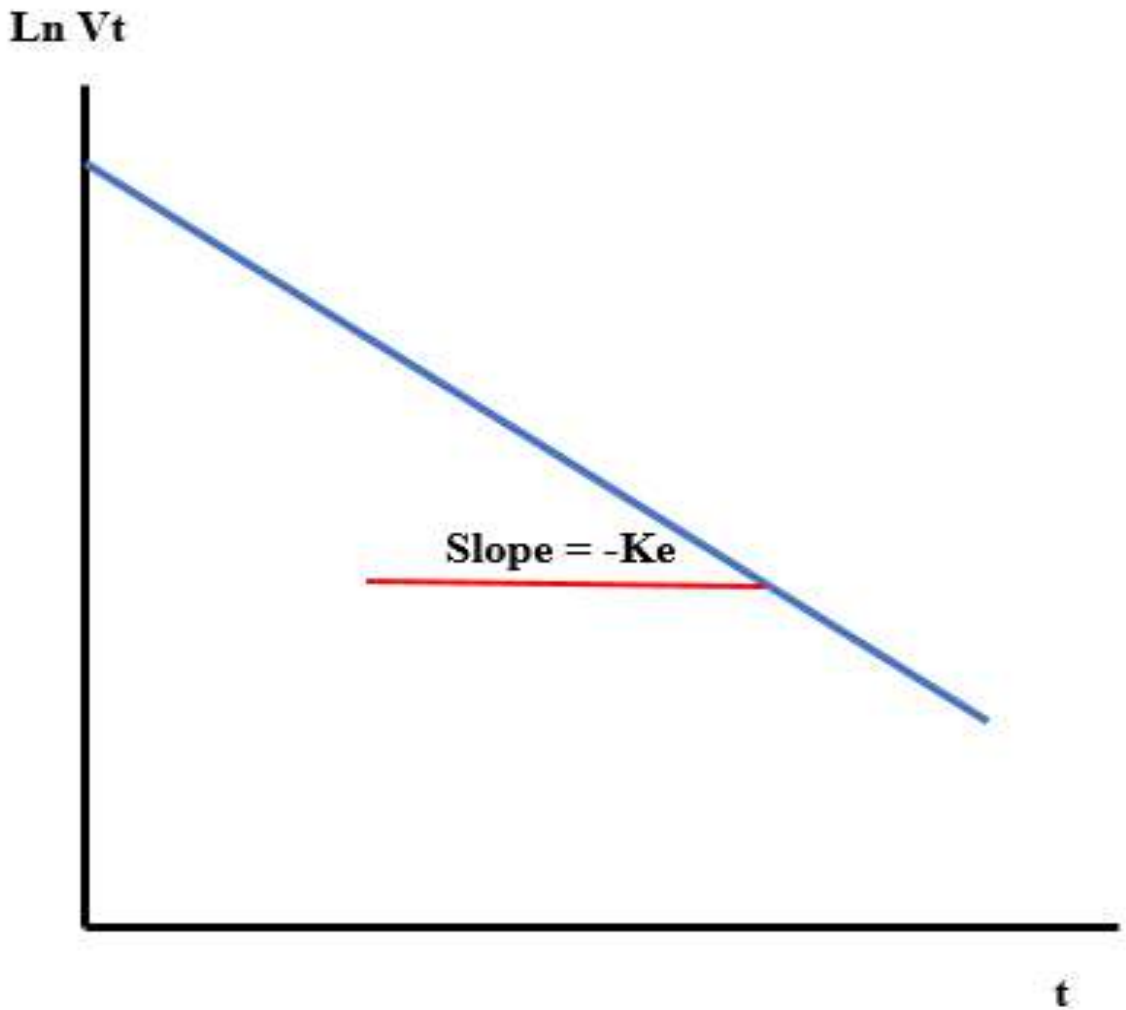
$V_t = V_o \cdot e^{-ke.t}$; $t_{½} = \frac{0.693}{Ke}$

V_t: The volume at time (t)

V_o : The volume at time (0)

K_e : Emptying rate constant

t : Interval of sampling



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

Factors affecting the G.E.R:

1. **Volume (Water) in stomach**. (More volume increases the GER).
2. **Temperature of the meal: (**High temperature increases the gastric emptying rate).
3. **Gastric content: (**Carbohydrates > Proteins > Fats (G.E.R))
4. **Viscosity of meal: (**More viscous less GER**).**
5. **Anticholinergic drugs. (**Decreases the GER**)**
6. **Pharmaceutical forms: (**liquids empty **more rapid than** solids).
7. **The mental state:**

- Stress and anxiety → **promote** gastric motility.
- Depression →**retards** gastric motility.

8. Hunger: (Promotes) the GER
9. Antiemetic drugs (Increases the GER).
10. Laying on the right side (Promotes the GER)
11. **Desease state as: Gastric ulcer, pyloric stenosis, Hypothyroidism** decreases the GER**.**
12. **Alcohol** (Decreases the GER)**.**

FACTORS INFLUENCING INTESTINAL DRUG ABSORPTION

Factors influencing GI Absorption of a Drug from its Dosage Form

A. DRUG RELATED (PHARMACEUTICAL) FACTORS

I. Physicochemical Properties of Drug Substances

1. Drug solubility and dissolution rate
2. Particle size and effective surface area
3. Polymorphism and amorphism
4. Pseudopolymorphism (hydrates/solvates)
5. Salt form of the drug
6. Lipophilicity of the drug
7. pKa of the drug and gastrointestinal pH
8. Drug stability
9. Stereochemical nature of the drug

II. Dosage Form Characteristics and Pharmaceutical Ingredients (Pharmaco-technical Factors)

1. Disintegration time (tablets/capsules)
2. Dissolution time :
   - Manufacturing variables
   - Pharmaceutical ingredients (excipients/adjuvants)
3. Nature and type of dosage form
4. Product age and storage conditions

B. PATIENT RELATED (PHYSIOLOGICAL) FACTORS

1. Age
2. Gastric emptying time
3. Intestinal transit time
4. Gastrointestinal pH
5. Disease states
6. Blood flow through the GIT
7. Gastrointestinal contents:
   - a. Other drugs
   - b. Food
   - c. Fluids
   - d. Other normal GI contents
8. Presystemic metabolism by:
   - a. Luminal enzymes
   - b. Gut wall enzymes
   - c. Bacterial enzymes
   - d. Hepatic enzymes

A. DRUG RELATED (PHARMACEUTICAL) FACTORS

I.Physicochemical Properties of Drug Substances

A. PHYSICOCHEMICAL FACTORS AFFECTING DRUG ABSORPTION

1. Drug Solubility and Dissolution Rate

- **Drug solubility directly** related to **dissolution rate** and hence to **Absorption**.

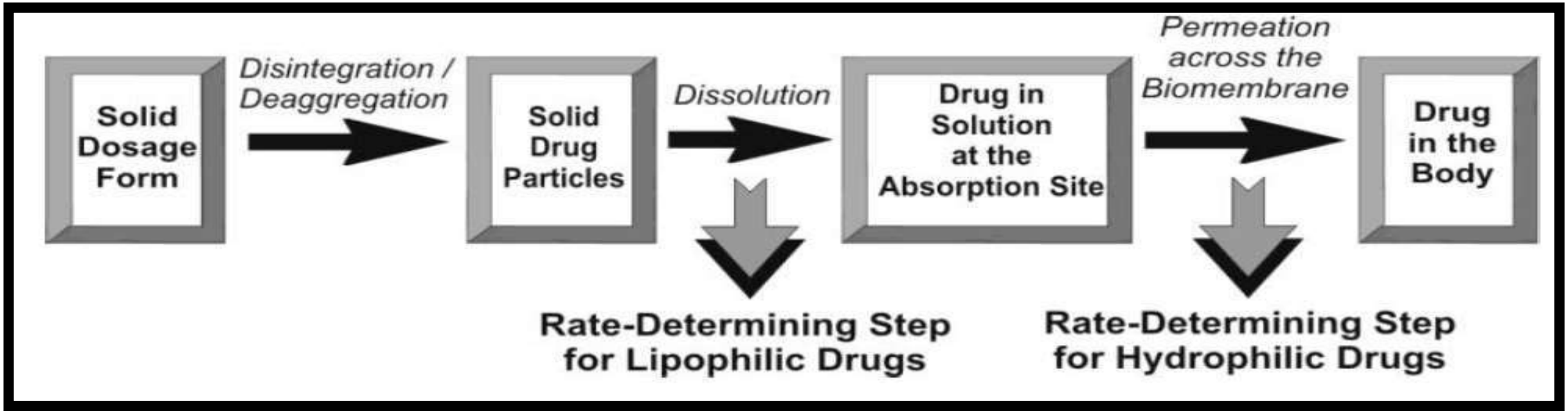


Figure: The two rate-determining steps in the absorption of drugs from orally administered formulations

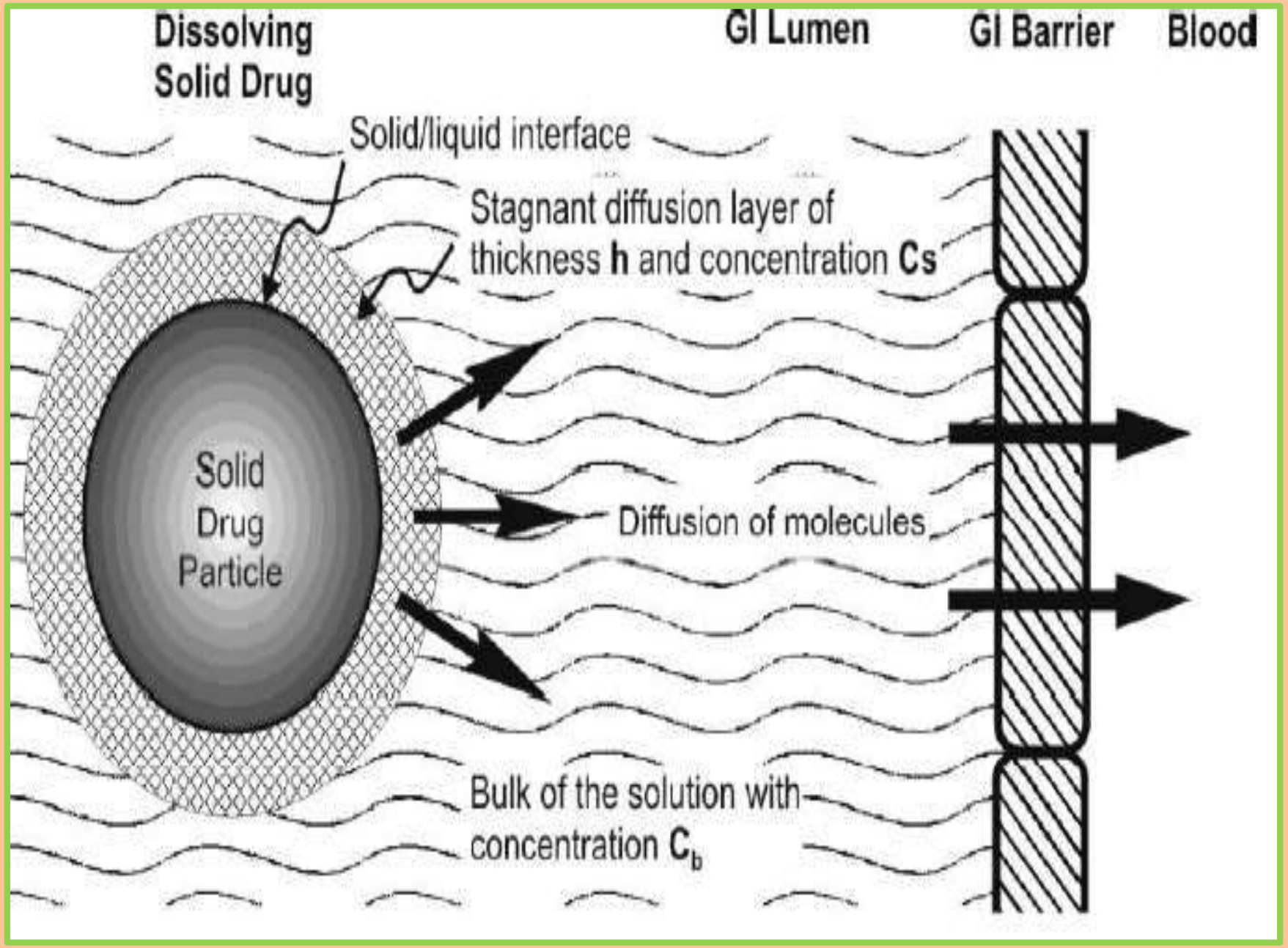
$$\frac{dc}{dt} = \frac{DA}{h}(Cs - C)$$ **Noyes and Whitney Equation**

where,

- dC/dt = dissolution rate of the drug,
- D = diffusion coefficient (*diffusivity*) of the drug
- A = surface area of the dissolving solid particle
- h = thickness of the stagnant layer.
- (Cs – Cb) = concentration gradient for diffusion of drug

  Cs = concentration of drug in the stagnant layer (also called as the **saturation or maximum drug solubility**), and

  Cb = concentration of drug in the bulk of the solution at time t.



The steps in dissolution include the process of drug dissolution at the surface of the solid particle, thus forming a saturated solution around the particle. The dissolved drug in the saturated solution, known as the ***stangant layer***, diffuses to the bulk of the solvent from regions of high drug conc. to regions of low drug conc.

Parameters	*Symbol*	*Influence on drug dissolution*
Diffusion coefficient	**D**	Greater the value, faster the dissolution of drug. Diffusion decreases as the viscosity of dissolution medium increases.
Surface area of solid	**A**	Greater the surface area, faster the drug dissolution; can be micronisation of drug.
Concentration gradient	**(Cs – b)**	Greater the concentration gradient, faster the diffusion and drug dissolution; can be increased by increasing drug solubility and the volume of dissolution medium.
Thickness of stagnant	**h**	More the thickness, lesser the diffusion layer and drug dissolution; can be decreased by increasing agitation.

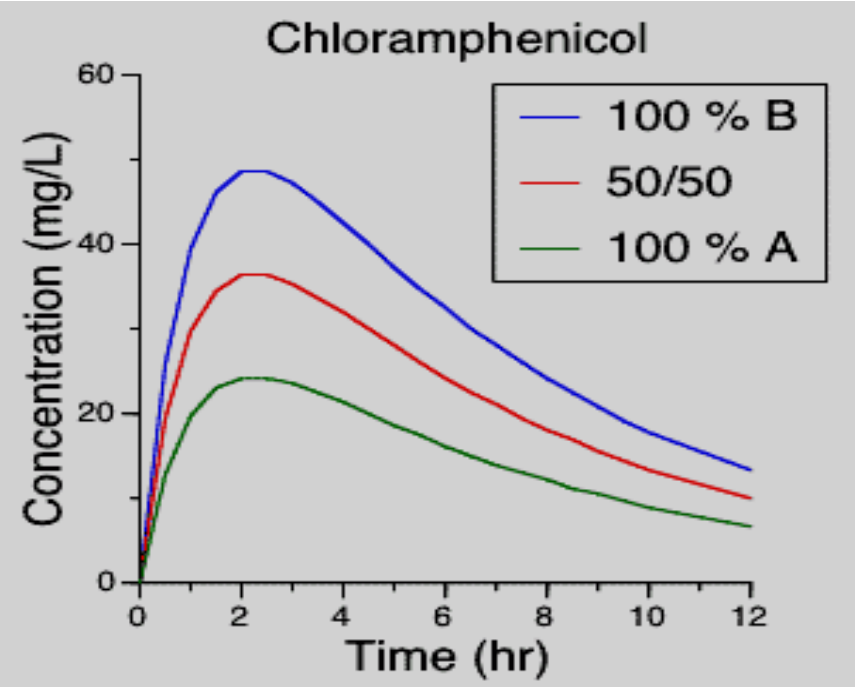
2. Particle Size and Effective Surface Area of the Drug

•Smaller the drug particle, greater the effective surface area higher the dissolution rate.

3. Polymorphism and Amorphism

•Polymorphism

Metastable > Unstable > Soluble (dissolution).



- ✓ Chloramphenicol palmitate is one example which exists in three crystalline forms A, B and C.

A Is the stable polymorph

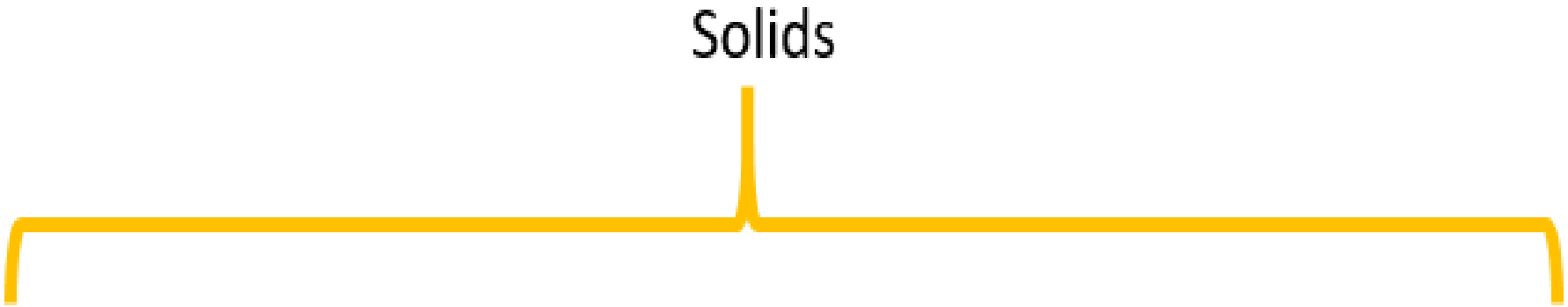
B Is the metastable polymorph (more soluble)

C Is the unstable polymorph

- ✓ Polymorphic forms A and B were investigated. The extent of absorption of Chloramphnicol increases as the proportion of the polymorphic form B is increased in each suspension.
- ✓ This is attributed to the more rapid Dissolution of the metastable Polymorphic form B.

- **Amorphous solid:**

The amorphous form dissolves more rapidly than the corresponding crystalline form.



Crystals		Amorphous
One step	Melting Point	various step
Regular	External shape	Irregular
Decrease	solubility	Increase
Increase	Stability	Decrease

4. Hydrates/Solvates (Pseudopolymorphism)

Anhydrous > hydrates (Solvate) (aqueous solubility).

•The faster-dissolving anhydrous form of ampicillin was absorbed to a greater extent from both hard gelatin capsules and an aqueous suspension than was the slower-dissolving trihydrate form.

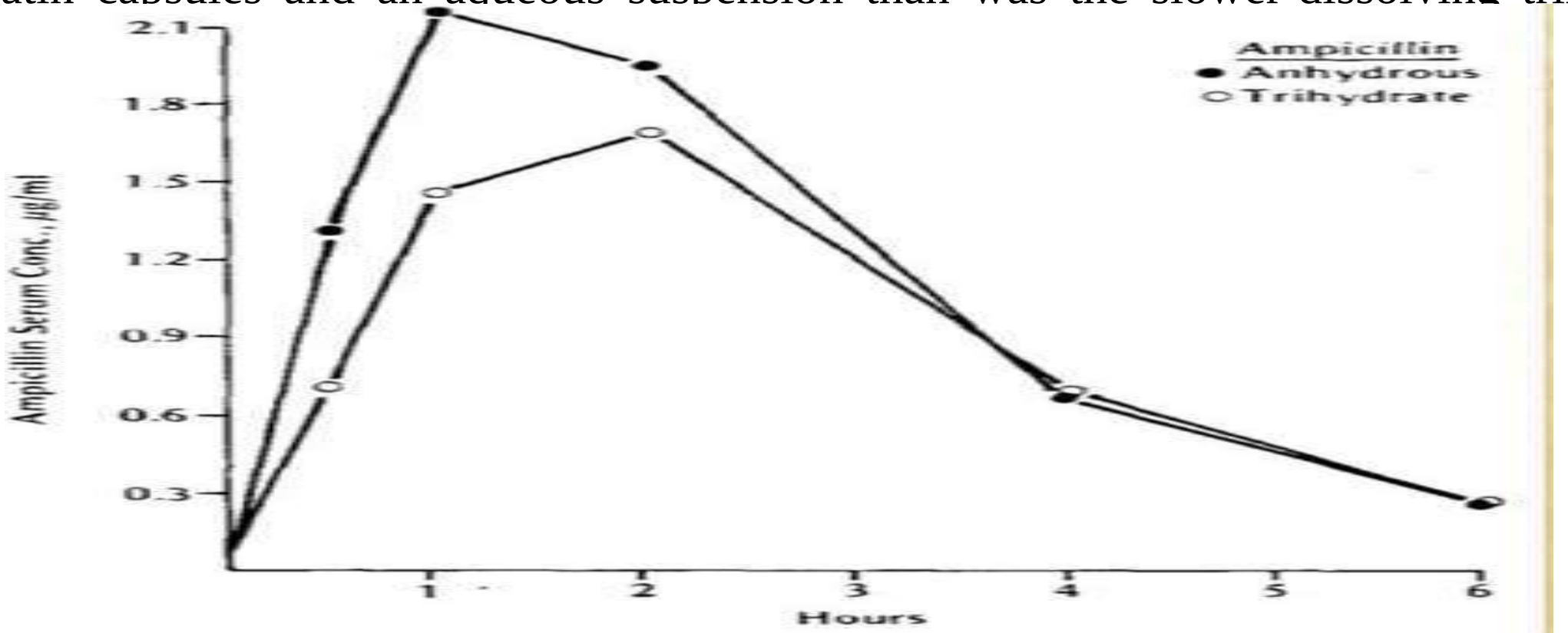


FIG. 8-9. *Mean serum concentrations of ampicillin in human subjects after oral administration of 250-mg doses of two solvate forms of the drug in suspension. Key: ●,*

5. Salt Form of the Drug

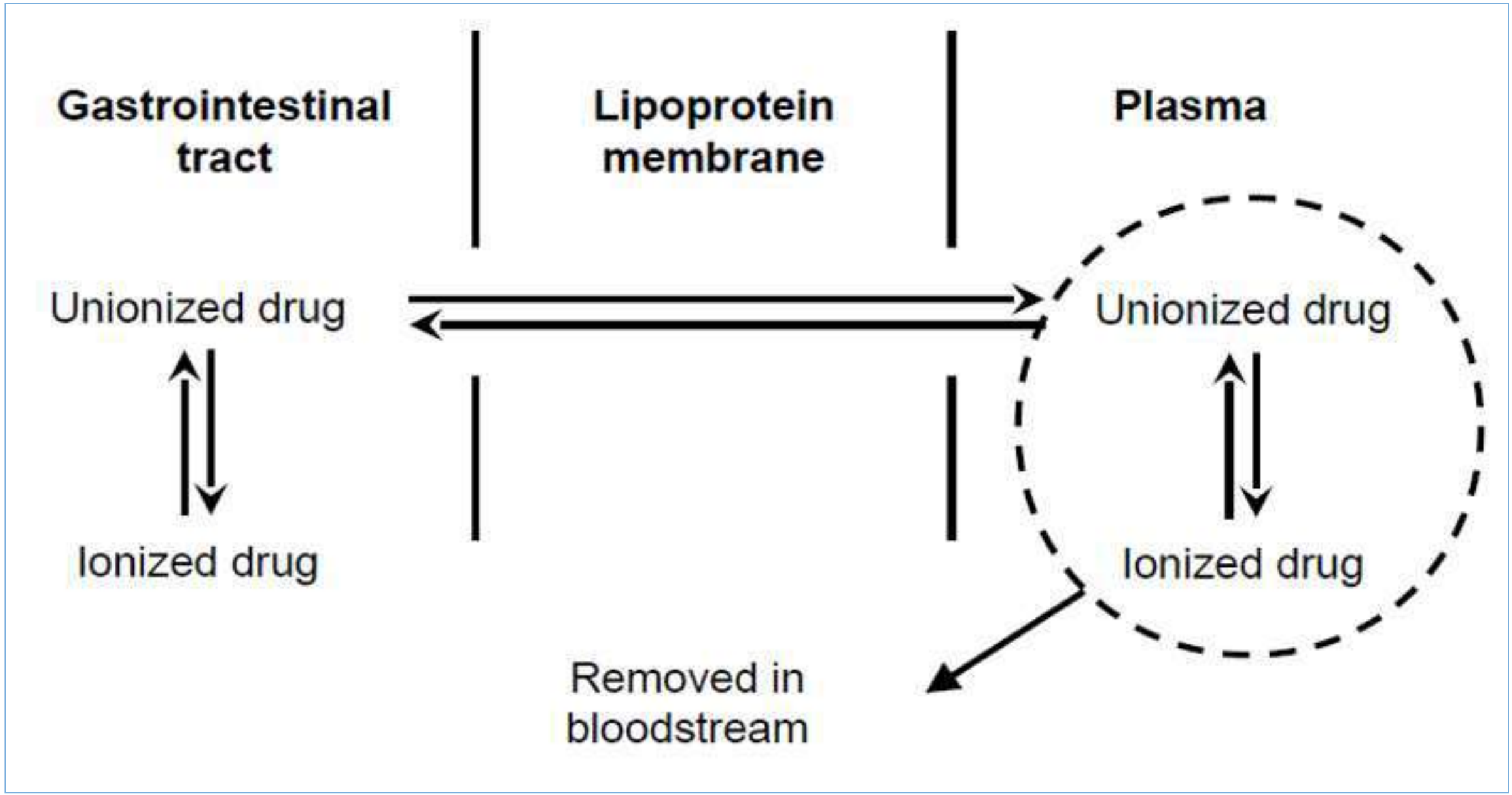
- Most drugs are either weak acids or weak bases.
- The solubility and dissolution rate of such drugs is enhanced by converting them into their salt forms.
- Weakly acidic drugs, a strong base salt is prepared such as the sodium and potassium salts of barbiturates and sulphonamides.
- Weakly basic drugs, a strong acid salt is prepared like the hydrochloride or sulphate salts of several alkaloidal drugs.

6. Drug pKa and Gastrointestinal pH

•According to the pH-partition hypothesis, the gastrointestinal epithelia acts as a lipid barrier towards drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier.

• As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (i.e. the lipid-soluble form) will pass across the gastrointestinal epithelia, whereas the gastrointestinal epithelia is impermeable to the ionized (i.e. poorly lipid-soluble) form of such drugs.

• Consequently, according to the pH-partition hypothesis, the absorption of a weak electrolyte will be determined chiefly by the extent to which the drug exists in its unionized form at the site of absorption


Gastrointestinal tract
Lipoprotein membrane
Plasma
Unionized drug
Unionized drug
Ionized drug
Ionized drug
Removed in bloodstream

- The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fluid may be calculated using the appropriate form of the
- **Henderson-Hasselbalch equation**
- For a weakly acidic drug having a single ionizable group (e.g. aspirin, phenylbutazone, salicylic acid) the equation takes the form of:

$$\log \frac{[A^-]}{[HA]} = pH - pK_a$$

- For a weakly basic drug possessing a single ionizable group (e.g chlorpromazine) the analogous equation is:

$$\log \frac{[BH^+]}{[B]} = pK_a - pH$$

- According to these equations a weakly acidic drug, pKa 3.0, will be predominantly unionized in gastric fluid at pH 1.2 (98.4%) and almost totally ionized in intestinal fluid at pH 6.8 (99.98%), whereas a weakly basic drug, pKa 5, will be almost entirely ionized (99.98%) at gastric pH of 1.2 and predominantly unionized at intestinal pH of 6.8 (98.4%).

- This means that, according to the pH-partition hypothesis, a weakly acidic drug is more likely to be absorbed from the stomach where it is unionized, and a weakly basic drug from the intestine where it is predominantly unionized. However, in practice, other factors need to be taken into consideration.

7. Lipophilicity and Drug Absorption

Ideally, for optimum absorption, a drug should have sufficient aqueous solubility to dissolve in the fluids at the absorption site and lipid solubility (Ko/w) high enough to facilitate the partitioning of the drug in the lipoidal biomembrane and into the systemic circulation.

• A perfect hydrophilic-lipophilic balance (HLB) should be there in the structure of the drug for optimum bioavailability.

8. Drug Stability

A drug for oral use may destabilize either during its shelf-life or in the GIT.

- Two major stability problems → **Poor bioavailability**
  - ➢Degradation of the drug into inactive form, and
  - ➢Interaction with one or more different component(s) either of the dosage form or those present in the GIT to form a complex that is poorly soluble or is unabsorbable.

9. Stereochemical Nature of Drug.

- Importanat only if drug is absorbed by carrier mediated system.

- 10. **Eutectic mixture:** Is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of the components.

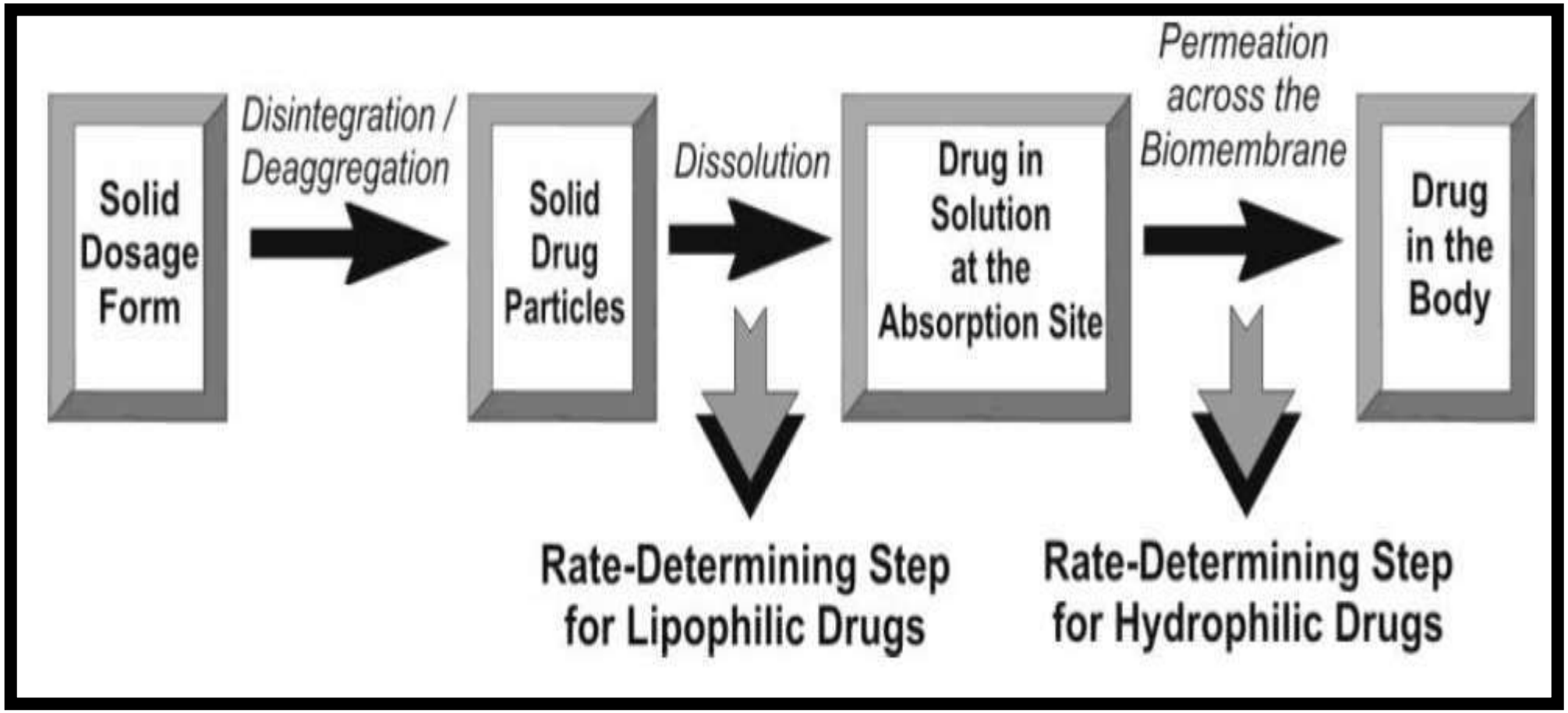


Figure: The two rate-determining steps in the absorption of drugs from orally administered formulations

A. DRUG RELATED (PHARMACEUTICAL) FACTORS

II.Dosage Form Characteristics and Pharmaceutical Ingredients (Pharmaco-technical Factors)

- Except in case of controlled-release formulations, disintegration and de-aggregation occur rapidly if it is a well-formulated dosage form. Thus, the two critical slower rate-determining processes in the absorption of orally administered drugs are:

    1. Rate of dissolution, and
    2. Rate of drug permeation through the bio-membrane.

- Dissolution is the **rate-limited step** for **hydrophobic**, poorly aqueous soluble drugs like griseofulvin and spironolactone; absorption of such drugs is often said to be **dissolution rate-limited**.

- If the drug is hydrophilic with **high aqueous solubility**—for example, cromolyn sodium or neomycin, then dissolution is rapid and **rate-limited step** in the absorption of such drugs is rate of permeation through the biomembrane. In other words, absorption of such drugs is said to be **permeation rate-limited** or **transmembrane rate-limited**

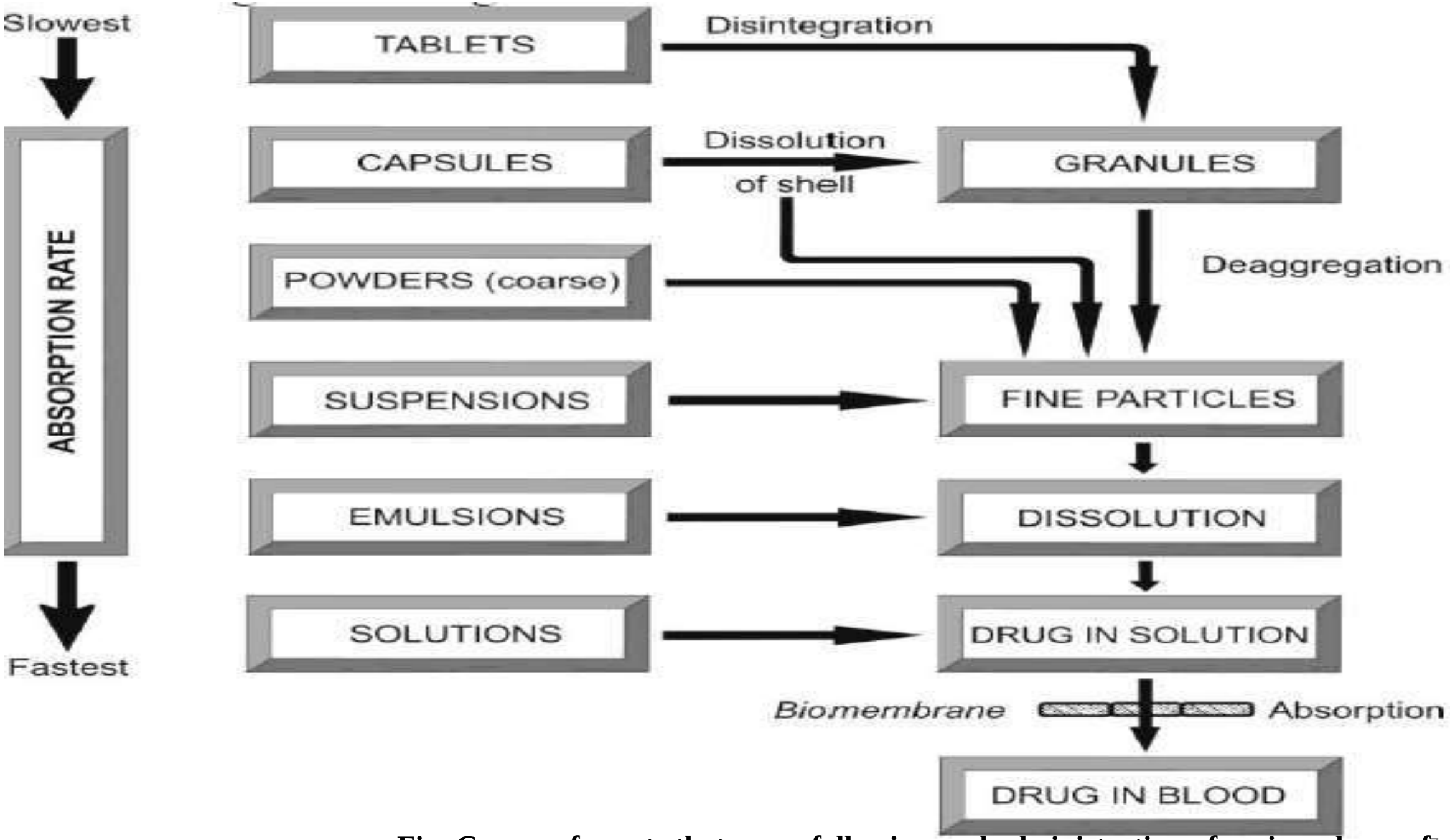


Fig: Course of events that occur following oral administration of various dosage forms

1. Disintegration time “DT” (tablets/capsules):

✓After disintegration of a solid dosage form into granules, the granules must deaggregate into fine particles, as dissolution from such tiny particles is faster than that from granules.

❖Coated tablets, especially sugar coated ones have long DT.

❖Rapid disintegration is thus important in the therapeutic success of a solid dosage form.

❖DT of a tablet is directly related to the amount of binder present and the compression force (hardness) of a tablet.

❖Disintegration can be aided by incorporating disintegrants in suitable amounts during formulation.

•

2-Dissolution time :

✓The dosage form related factors that influence dissolution and hence absorption of a drug from such formulations are:

1. ***Excipients*** (vehicles, diluents (fillers), binders and granulating agents, disintegrants, lubricants, coatings, suspending agents, emulsifiers, surfactants, buffers, complexing agents, colorants, sweeteners, crystal growth inhibitors, etc.)

2. Manufacturing processes :

Method of granulation (Wet granulation faster than other), compression force.

3. Dosage-form:

•Since a drug must be in solution to be absorbed from GIT, You may expect the bioavailability of a drug to decrease in the order

Solution > Susp > Cap > Tab > Coated Tab > Enteric Tab

❑Solution

•In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

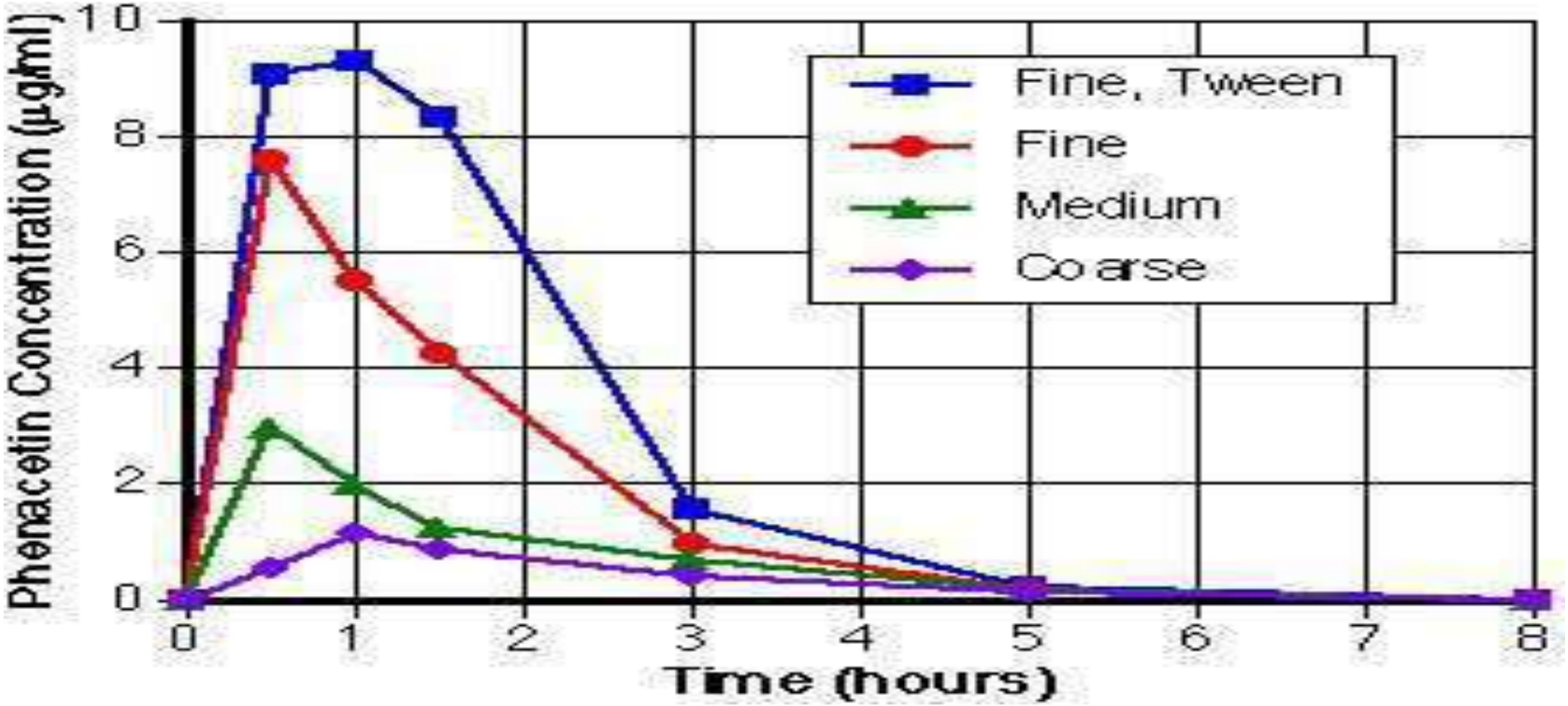
•***The rate limiting step is often the rate of gastric emptying***.???

❑Suspensions

•A well formulated suspension is second only to a in terms of superior bioavailability.

•Absorption may well be dissolution limited, however a suspension of a finely divided powder will maximize the potential for rapid dissolution.

- A good correlation can be seen for particle size and absorption rate. With very fine particle sizes the dispersibility o the powder becomes important.
- The addition of a surface active agent will improve dispersion of a suspension and may improve the absorption of very fine particle size suspensions (deflocculated), otherwise caking may be a problem.



❑Capsules

- In theory a capsule dosage form should be quite efficient.
- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.
- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation.
- These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.
- The rate at which a drug dissolves is dependent on the solubility of the drug.

❑Tablets

- The biggest problem is overcoming the reduction in effective surface area produced during compression.

- **Coated Tablets :**
  - **Used to mask an unpleasant taste, to protect the tablet ingredients during storage, or to improve appearance.**
  - The coating acts as yet another barrier which must first dissolve or disrupt to give way to disintegration and dissolution of tablet.
  - The enteric coated tablets which coated with polymer dissolved only in intestine pH.

4.Product age and storage conditions:

- Changes that occur during the shelf-life of a dosage form are affected mainly by large variations in **temperature** and **humidity.**
- With solution dosage form, precipitation of drug due to altered solubility, especially due to conversion of metastable into poorly soluble, stable polymorph can occur during the shelf-life of the product.
- Suspension dosage forms : Changes in particle size distribution resulting in decreased rate of drug dissolution and absorption.
- Solid dosage forms, especially tablets, disintegration and dissolution rates are greatly affected due to aging and storage conditions. An increase in these parameters of tablets has been attributed to excipients that harden on storage (e.g. PVP, acacia, etc.) while the decrease is mainly due to softening/crumbling of the binder during storage (e.g. CMC).

PATIENT RELATED (PHYSIOLOGICAL) FACTORS

B. PATIENT RELATED (PHYSIOLOGICAL) FACTORS

1. Age

- In infants, the gastric pH is high and intestinal surface and blood flow to the GIT is low resulting in altered absorption pattern in comparison to adults.
- In elderly persons, causes of impaired drug absorption include altered gastric emptying, decreased intestinal surface area and GI blood flow, higher incidents of achlorhydria and bacterial overgrowth in small intestine.

2. Gastric emptying time.

3. Intestinal transit time.

- long intestinal transit time is desirable for complete drug absorption.
- The residence time depends upon **the intestinal motility or contractions**.
- Peristaltic contractions → mixing movement → ↑drug absorption by:
  - ↑drug-intestinal membrane contact.
  - ↑drug dissolution (poorly soluble drugs).

4. Gastrointestinal pH

- The GI pH generally increases gradually as one move down the stomach to the colon and rectum.
- GI fluid pH influence drug absorption in several ways:

1. Disintegration
2. Dissolution
3. Absorption
4. Stability

5.Disease states

- Affects drug absorption by:

(a) Altered GI motility

(b) Malabsorption syndrome

(c) Gastrointestinal surgery

6. Blood flow through the GIT

•The GIT is extensively supplied by blood capillary network and the lymphatic system.

•The high perfusion rate of GIT→ Sink condition→ continued drug absorption.

7. Gastrointestinal contents:

1. Food-drug interactions

✓Presence of food may either delay, reduce, increase or may not affect drug absorption.

✓As a general rule, drugs are better absorbed under fasting conditions and presence of food retards or prevents it.

✓Food does not significantly influence absorption of a drug taken half an hour or more before meals and two hours or more after meals.

- ✓Delayed or decreased drug absorption by the food could be due to one or more of the several mechanisms:
    a. Delayed gastric emptying, affecting drugs unstable in the stomach e.g. penicillin.
    b. Formation of un-absorbable complex e.g. tetracycline-calcium.
    c. Increased viscosity due to food thereby preventing drug dissolution and/or diffusion towards the absorption site.

- ✓Increased drug absorption following a meal could be due to one or more of the under mentioned reasons –
    (a) Increased time for dissolution of a poorly soluble drug.
    (b) Enhanced solubility due to GI secretions like bile.
    (c) Prolonged residence time and absorption site contact of the drug e.g. water-soluble vitamins.
- ✓The specific meal components also have an influence on drug absorption.

2. Fluid volume:

Administration of a drug with large fluid volume → better dissolution, rapid gastric emptying →enhanced absorption.

•Example, erythromycin is better absorbed when taken with a glass of water under fasting condition than when taken with meals.

3. Interaction of drug with normal GI constituents:

•Mucin, bile salts and enzymes.

•Mucin, a normal component of gastrointestinal fluids, complexes with some drugs.

•The antibiotic streptomycin binds to mucin→ reducing the available conc. of the drug for absorption → poor bioavailability.

4. Drug-Drug interactions in the GIT:

- Adsorption .
- Complexation.
- pH change .

4. Drug-Drug interactions in the GIT:

Adsorption

✓The concurrent administration of drugs and medicines containing solid adsorbents **(e.g. antidiarrhoeal mixtures)** may result in the adsorbents interfering with the absorption of drugs from the gastrointestinal tract.

✓The adsorption of a drug on to solid adsorbents such as **kaolin or charcoal** may reduce its rate and/or extent of absorption, owing to a decrease in the effective concentration of the drug in solution available for absorption.

Complexation

- In general this only becomes an issue (with respect to bioavailability) where an irreversible or an insoluble complex is formed→ unavailable for absorption.
- However, if the complex formed is water soluble and readily dissociates to liberate the 'free' drug, then there may be little effect on drug absorption.
- For example:

  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.

8.Presystemic Metabolism/First-Pass Effects

For a drug administered orally, the 3 main reasons for its decreased bioavailability are:

- Decreased absorption (owing to adsorption, precipitation, complexation and poor solubility).
- Destabilization or destruction of drug.
- First-pass/presystemic metabolism

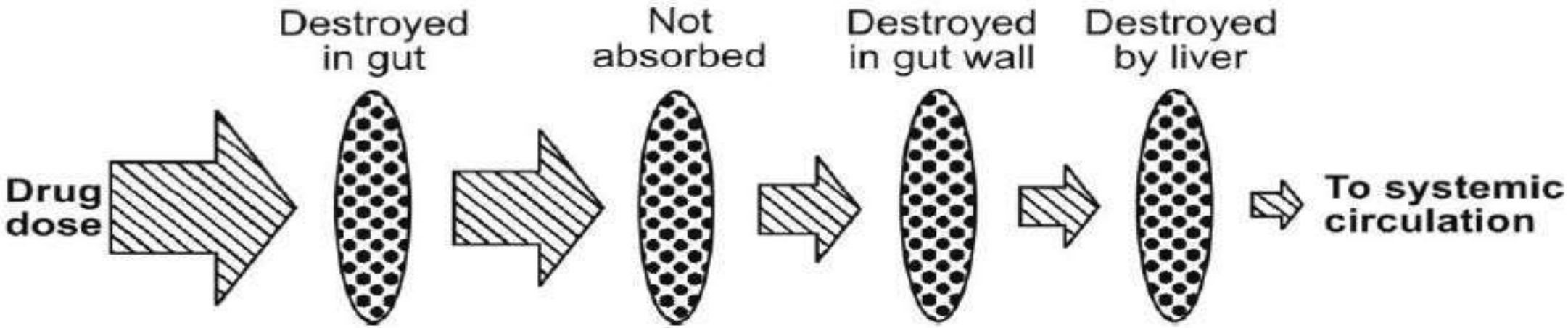


Fig. Processes that reduce the availability of orally administered drugs

- Before a drug reaches blood circulation, it has to pass for the first time through organs of elimination namely the GIT and the liver.
- The loss of drug through biotransformation by such eliminating organs during its passage to systemic circulation is called as ***first-pass or presystemic metabolism.***
- The 3 primary systems which affect presystemic metabolism of a drug are :

1. Luminal enzymes –
    (a) Digestive enzymes.
    (b) Bacterial enzymes.
2. Gut wall enzymes/mucosal enzymes.
3. Hepatic enzymes.

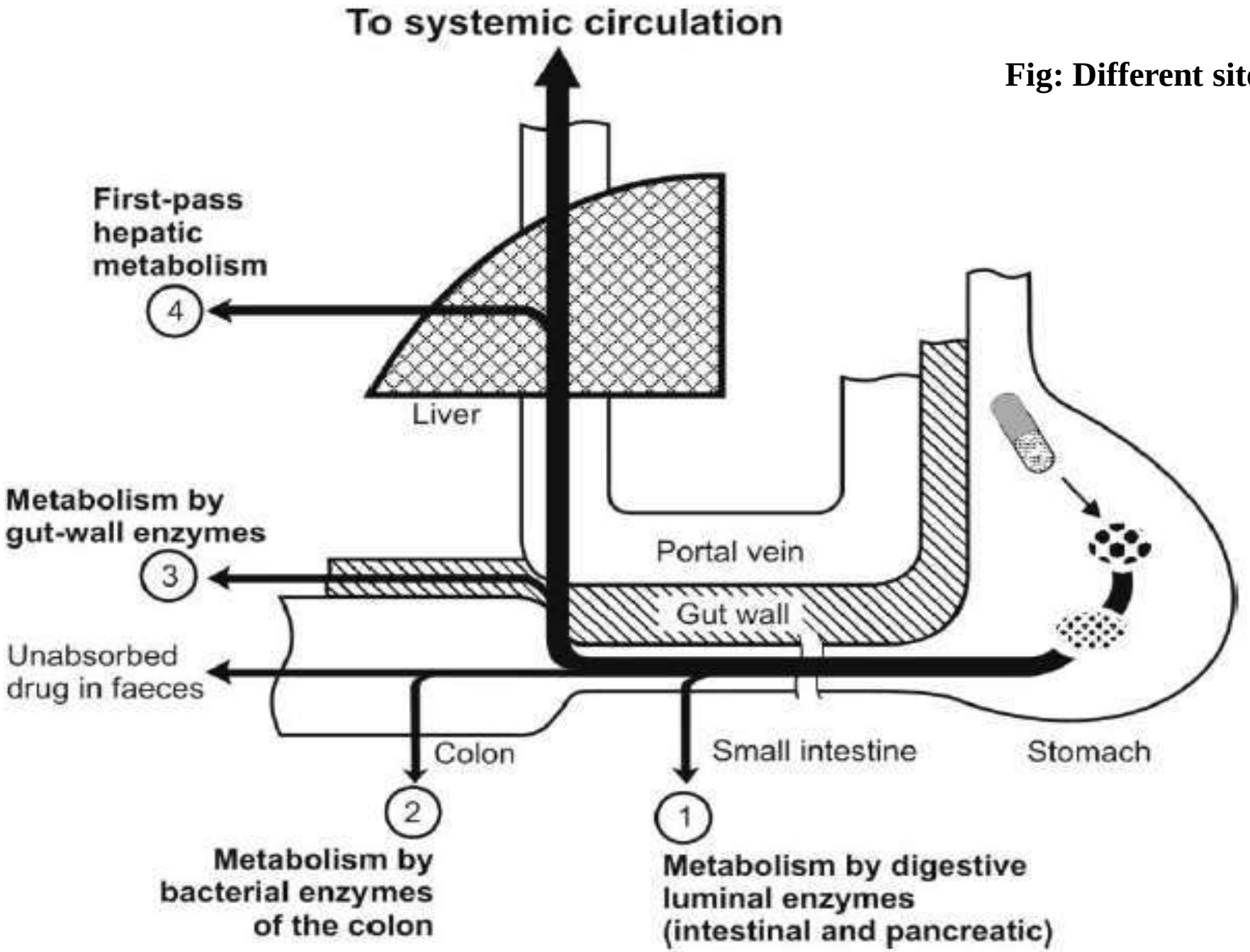


Fig: Different sites of presystemic metabolism

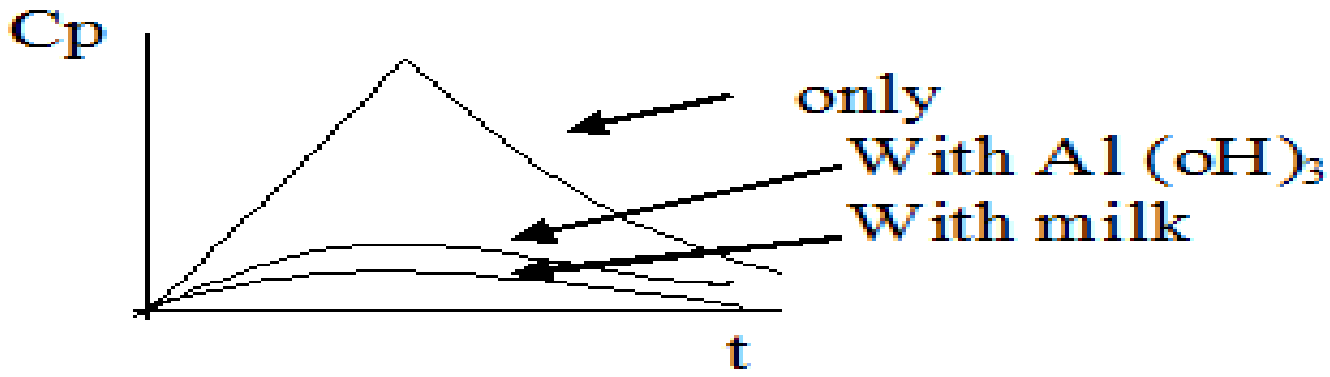
Interactions (drug-drug, drug-food, drug- components of GIT)

Mechanisms

- Alteration in the G.E.R
- Stimulation of the G.I. Secretions.
- Competition between food components and drugs for specialized absorption.
- Complexation of drug with components in the diet.
- Increased the viscosity of G.I.T Contents.
- Induced changes in blood flow to the liver.

a) Diets: The dissol. Rate decreased because increased η increased Complexation :

Tetracycline + Ca.



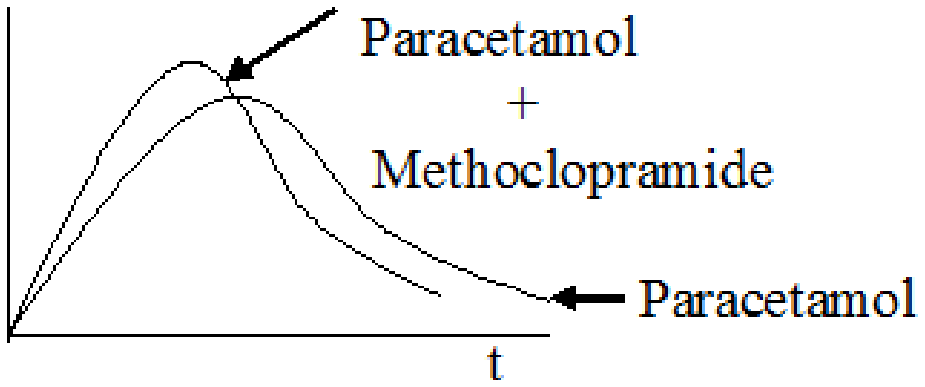
b) Drugs: 1- Adsorbents. And antacids (Neutralize) (active C; Kaolin)

2- Alteration of Gastro Int. Peristalsis.

- Cholinergic drugs: Increases G. E.R.
- Metoclopramide: Increses the abs. of Paracetamol
-Colestiramine. (Antihyperlypemic): C

Colestiramine + bile acids

of cholestero



Rectal Drug Delivery system

- **Definition:**

"Rectal drug delivery system means administration of drug or pharmaceutical preparations via rectum for **local** or **systemic** effect."

- **Rectal dosage forms:**

- Solid unit dosage form: Suppository.
- Liquid unit dosage form: Enema.
- Semi-solid dosage form: Ointment, Cream.

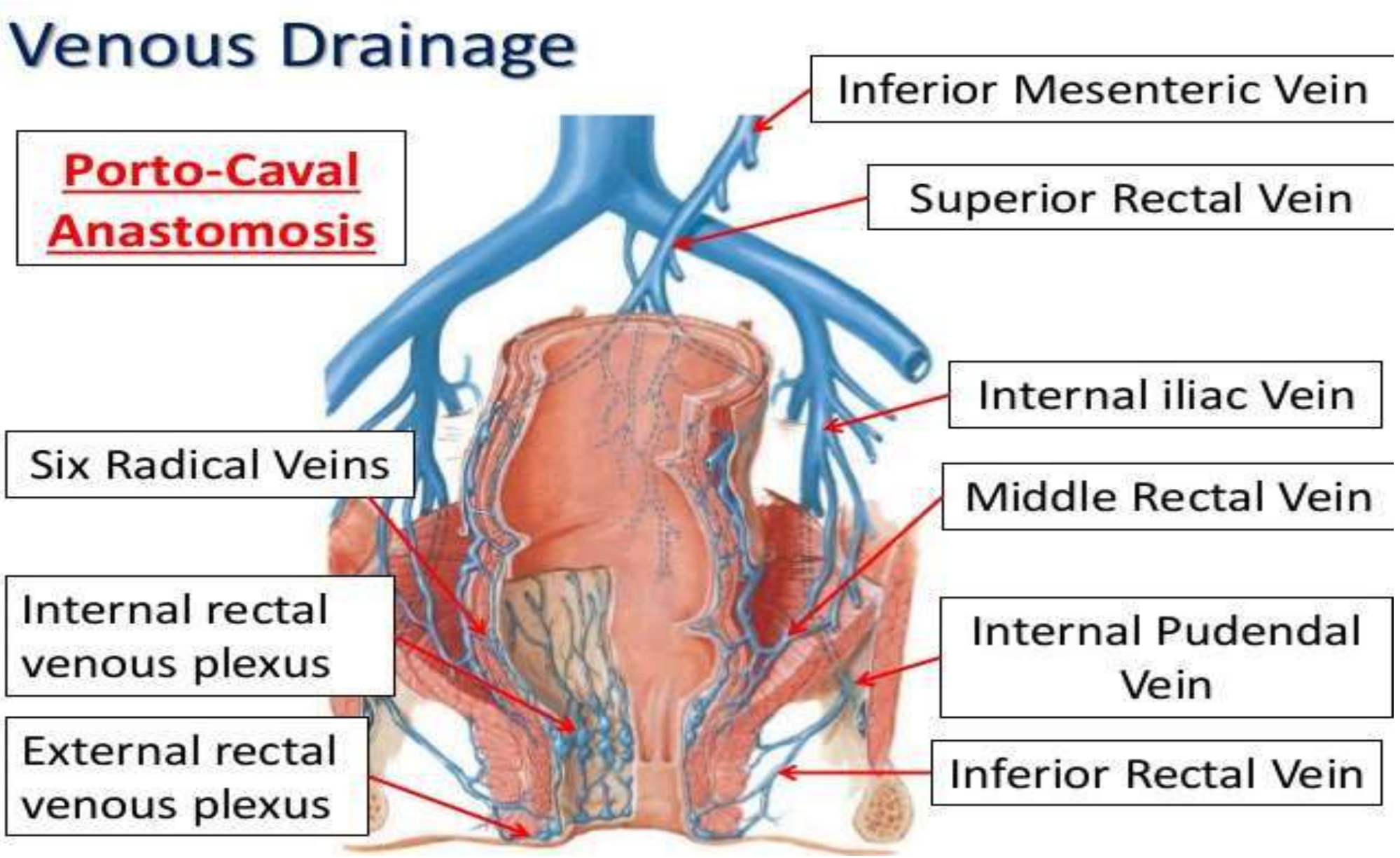


Fig. : Blood supply to the rectum and anus. The significance of the location of the superior and the inferior rectal veins is discussed in the text.

- **The therapeutic use of the rectal route:**
- **Local Effect:**

  - ✓**Pain, itching and hemorrhoids treatment.**
  - ✓**Locally acting drugs :**
    - ✓**Astringents,**
    - ✓**Antiseptics,**
    - ✓**Local anesthetics,**
    - ✓**Vasoconstrictors,**
    - ✓**Anti-inflammatory compounds,**
    - ✓**Soothing and protective agents, and**
    - ✓**Laxative to promote evacuation**
- **Systemic Effect:**

  - ✓**Analgesic, Anti-asthmatic, anti-rheumatic.**

❑ADVANTAGES:

1. The drug is less suited for oral route (GIT side effects, pH stability of GIT and enzymatic degradation).
2. The patient is unable to use the oral route (nausea and vomiting, unconscious patients, Post operative and Babies or old people who cannot swallow oral medication.
3. Minimize 1st pass metabolism and so enhance bioavailability.

❑DISADVANTAGES:

1. Absorption is less extensive and slower because of limited surface area of the rectal mucosa available for absorption.
2. Inter and intra subject variations.
3. The problem of patient acceptability. Suppositories are not suitable for patients suffering from diarrhea.
4. Microbial degradation may occur in rectum.
5. Technological requirements:
    - Choice of the suppository base.
    - Melting point.
    - Storage conditions.
    - Additives.

Remember (Pharmaceutics 1)

- **The ideal suppository base :**

1. **Inert** & **compatible with drug** → No chemical and/or physical interactions between the medicinal agent and the suppository base, which may affect the stability and/or bioavailability of the drug.
2. **Non toxic** & **non irritating** of the mucous membranes of the rectum, avoiding colonic response and prompt a bowel movement, eliminating the prospect of complete drug release and absorption.
3. Stable on storage → no color or odor change & no drug release pattern.
4. No metastable forms.
5. Can be easily manufactured by **compression** or **molding**.
6. Remain molten for a sufficient period of time → to allow pouring into molds.
7. Solidify sufficiently rapidly → to minimize sedimentation of dispersed solids.
8. Contract on cooling → to allow removing supp. easily from mold.
9. The base must be capable of **melting**, **softening at body temp.**, or **dissolving in the presence of mucous secretions** → to release its drug for absorption.
10. High water number (a high percentage of water can incorporated in it).
11. Wetting and emulsifying properties.

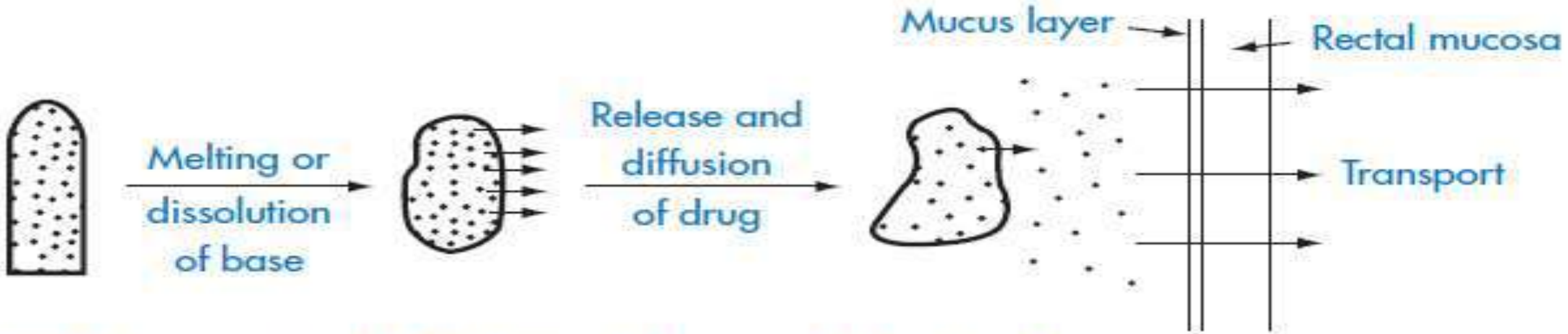


Fig. : Schematic representation of rectal absorption of an active principle from a suppository, and the factors at each stage likely to affect the bioavailability of the drug.
Modified from Jaminet F. In: Guillot BR, Lombard AP (eds) The Suppository. Paris: Maloine; 1973.

- Kinetics of the rectal absorption

The liberation is the rate limiting step and the absorption obeys first- order kinetics.

Ln Qt = Ln Q0 – Ka. T

$Qt = Q0 \,.\, e^{-ka.t}$

Qt: amount of the drug at time t.

Qo : Total amount of the drug.

Ka: absorption rate constant.

t : time.

- **Forms of absorbed drugs:**

  - Liposoluble drugs are the most readily absorbed.
  - Weak acids with pKa over 4.3 and below 8.5 are generally readily absorbed.
  - Un-ionized substances that are lipid insoluble are poorly absorbed.
  - Highly ionized compounds are poorly absorbed.
  - Completely ionized compounds like quaternary ammonium and sulphonic derivative are poorly absorbed.

➢Factors Influencing Rectal Drug Absorption:

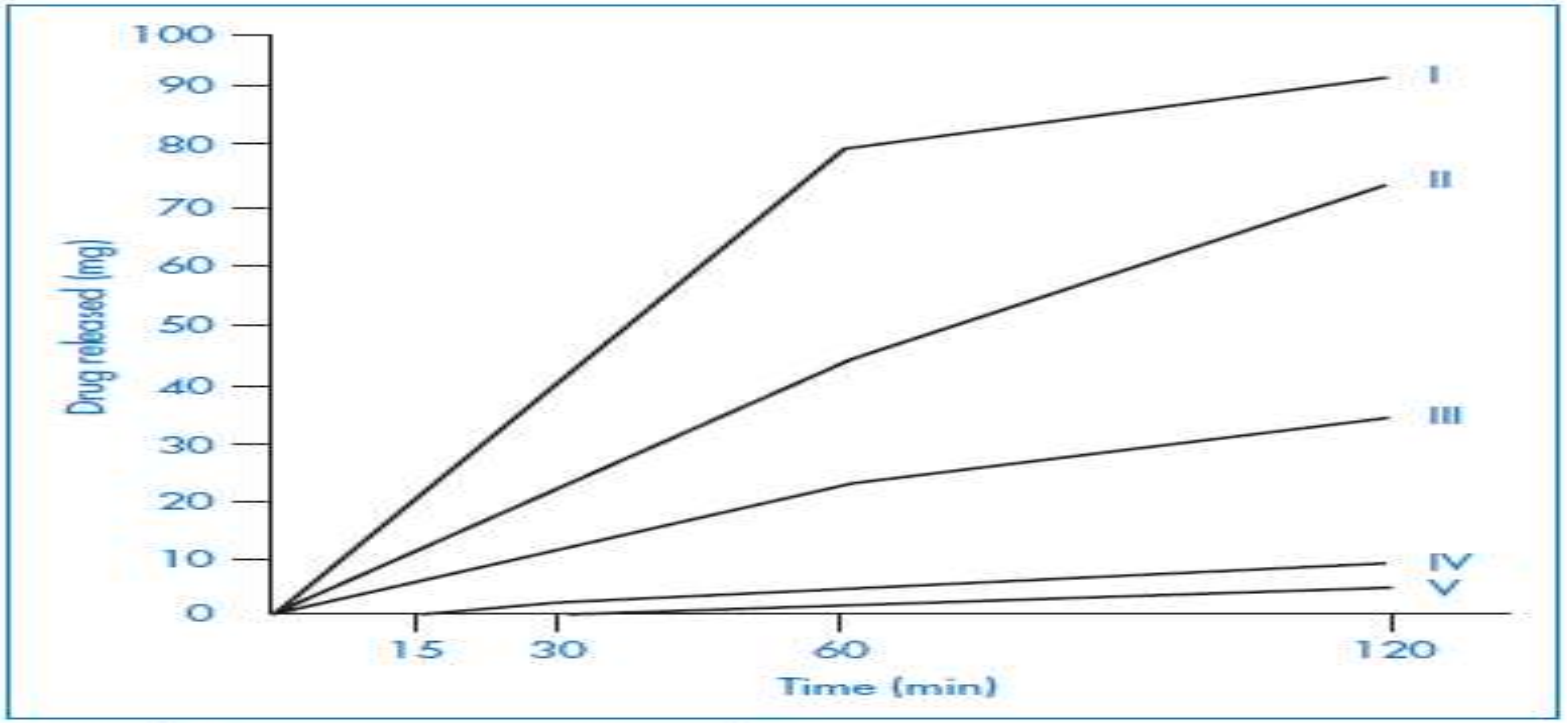
1. Physicochemical factors.

2. Formulation factors.

3. Physiological factors.

1. Physiochemical factors:

1. Solubility: Higher the solubility, consequently higher the dissolution rate and better is absorption.



Type	Solubility in water
I	1 in 1
II	1 in 10
III	1 in 10 to 1 in 100
IV	1 in 100 to 1 in 1000
V	1 in 1000 to 1 in 10 000

Fig. :Release of drugs of varying solubilities from fat-based suppositories of equal active agent content.

Continued……..

2. Degree of ionization

At the alkaline pH of rectal mucosa, basic drugs will exist in their unionized form and readily absorbed.

3. Particle size:

The smaller the size, the more readily the dissolution of the particle and the greater the chance for rapid absorption.

4. pH:

Rectal content is slightly alkaline (pH 7-8) , so alkaline drugs are quickly absorbed than acidic drugs.

5. Partition Coefficient (Lipid water solubility of a drug).

- The lipid water partition coefficient of a drug is important in selecting the suppository base and in anticipating drug release from that base.
- Lipophilic drug, in other word, distributed in a fatty suppository base has fewer tendencies to escape to the surrounding aqueous fluids. Thus water-soluble salt are preferred in fatty base suppository.
- Water-soluble base e.g: PEG, which dissolve in the rectal fluids, release both water-soluble and oil-soluble drugs.

Higher the partition coefficient of drug, more readily absorption of drug.

2. Formulation Factors

1) Nature of the Base:

- Suppository base capable of melting, softening or dissolving to release the drug for absorption.

-If the base irritating the colon, it will promote colonic response, lead to increase bowl movement and decrease absorption.

Types of Suppository Bases:

A- Fatty Bases.

B- Hydrophilic Suppository Bases.

Type of Bases

Hydrosoluble base
Polyoxyethylen glycol

Liposoluble base
Cacoa butter

System type

Homogenous

- **Hydrosoluble drug + Hydrosoluble base →**
  - **Slow release**
  - **Bad absorption**
  - **Local effect**
- **Liposoluble drug + Liposoluble base →**
  - **Slow release**
  - **Good absorption**
  - **Systemic effect**

Heterogeneous

- **Hydrosoluble drug + Liposoluble base →**
  - **Rapid release**
  - **Bad absorption**
  - **Local effect**
- **Liposoluble drug + Hydrosoluble base →**
  - **Rapid release**
  - **Good absorption**
  - **Systemic effect**

2) Presence of Adjuvant in Base :

• Adjuvant in a formula may affect drug absorption, change the rheological properties of the base at body temperature, or affected the dissolution rate of the drug.

• The important features of excipient materials are:

1. **Melting point.**
2. **Speed of crystallization and emulsifying capacity (Emulsifiers).**

• If the medicament dissolves in the base, it is likely that the melting point of the base will be lowered, so that a base with a melting point higher than 36–37°C has to be chosen.

• If the drug substance has a high density, it is preferable that the base crystallizes rapidly during production of the suppositories to prevent settling of the drug.

• Preservatives, hardening agents, emulsifiers, coloring agents and materials which modify the viscosity of the base after melting are common formulation additives.

3) Factors depending on the method of the preparation.

Molding or compression. (Inversely relationship between Absorption-Melting point)

3. Physiological factors:

1. Quantity of dissolution fluid available in rectum:

- Very small volume under normal conditions, thus, absorption of slightly soluble drugs will be dissolution rate limited. (e.g. Phenytoin).

2. Properties of rectal fluids

- Composition, Viscosity and pH of rectal fluids have great effects on drug bioavailability.

3. Contents of the rectum

- Faecal content → Drug will have greater opportunity to get absorbed when the rectum is empty.

4. Motility

- Upright position
- Wave of contraction from colon.