Biopharmaceutics

4th Stage

College of Pharmacy

Lecture 2: Factors Affecting Absorption

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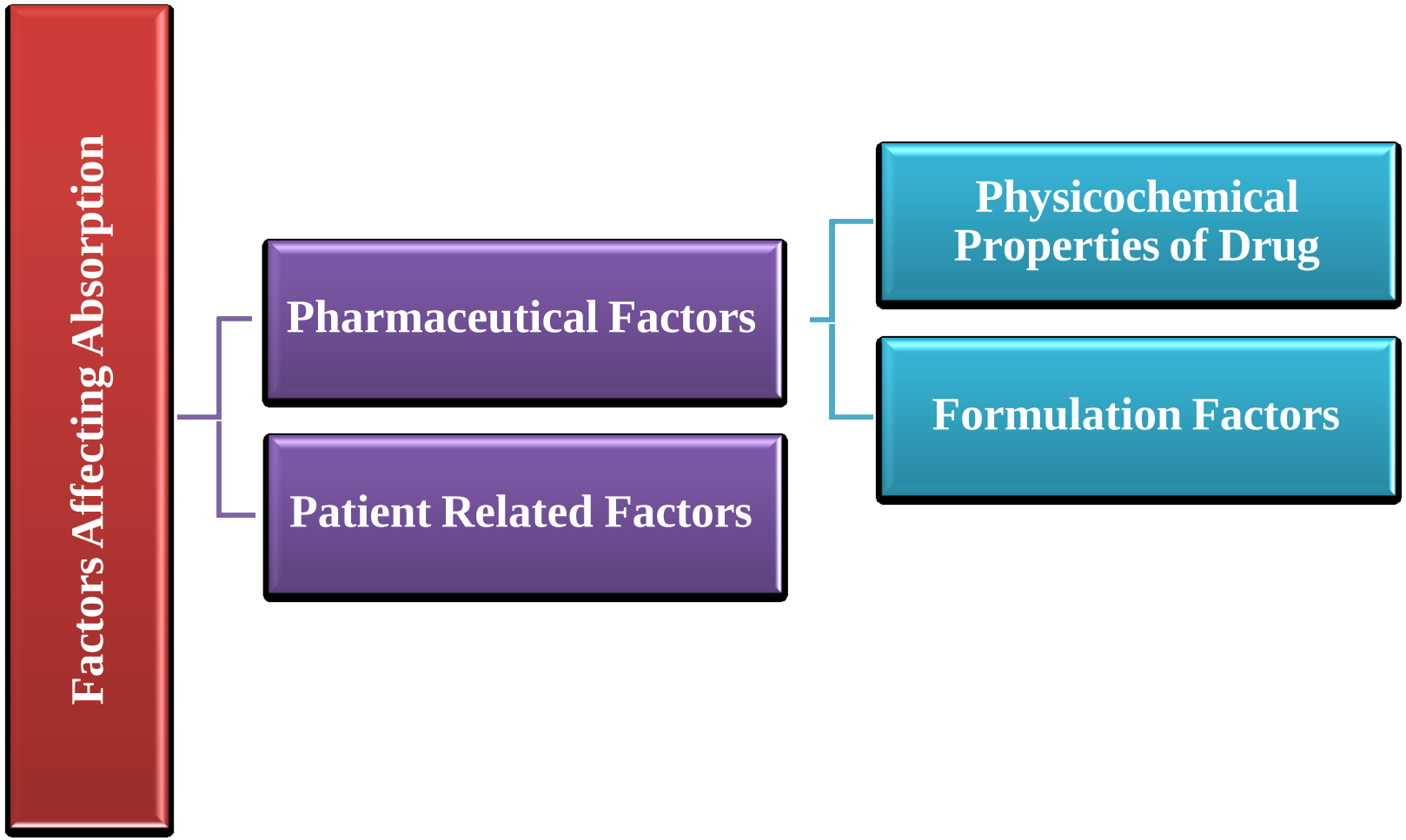
FACTORS AFFECTING ABSORPTION



Factors Affecting Absorption

Pharmaceutical Factors

I. Physicochemical Properties of Drug

1. Drug solubility and dissolution rate
2. Particle size
3. Polymorphism and amorphism
4. Pseudopolymorphism
   - Hydrates
   - Solvates
5. Salt form of the drug
6. Drug pka & lipophilicity & GI pH-partition hypothesis.

II. Formulation Factors

1. Nature and type of dosage form
2. Disintegration Time
3. Manufacturing process:
   A. Method of granulation
   B. Compression force
4. Pharmaceutical ingredients (excipients)
5. Product age and storage conditions.

Patient Related Factors

1. Gastric emptying
2. First pass metabolism by:
    a) Luminal enzymes
    b) Gut wall enzymes
    c) Bacterial enzymes
    d) Hepatic enzymes
3. Gastrointestinal pH
4. Diseased states
5. Blood flow through the GIT



Physicochemical properties of drug substances

1-Dissolution and solubility of drug.

- **Dissolution** is a process in which a solid substance solubilizes in a given solvent i.e. mass transfer from the solid surface to the liquid phase.
- **Solubility** is defined as the maximum amount of solute dissolved in a given solvent under standard conditions of temp, pressure and pH.
- **Rate of dissolution** is the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

The **dissolution rate** is described by the Noyes and Whitney (1897) equation.

$$\frac{dC}{dt} = \frac{DA}{h}(C_s - C)$$

dC/dt is the rate of drug dissolution at time t
A is the surface area of the particle
C_s is the concentration of drug in the stagnant layer (solubility)
C is the concentration of drug in the bulk solvent
D is the diffusion coefficient of the drug
h is the thickness of the stagnant layer

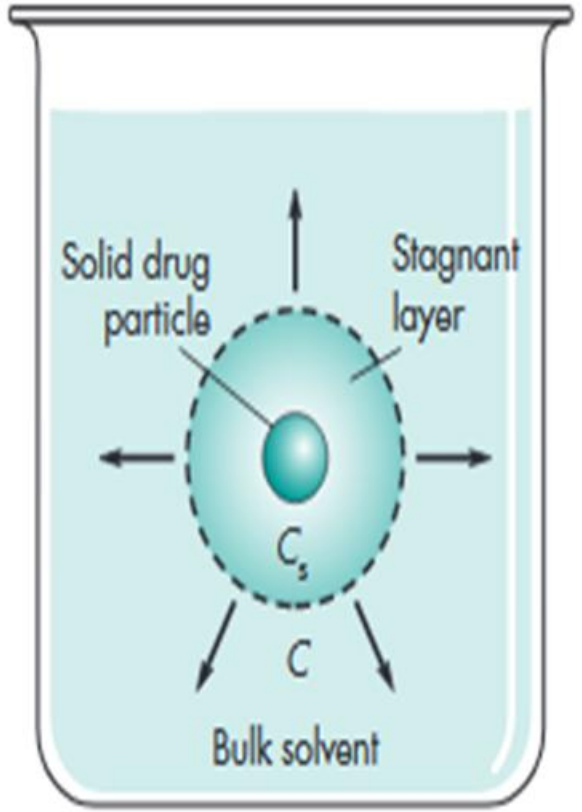
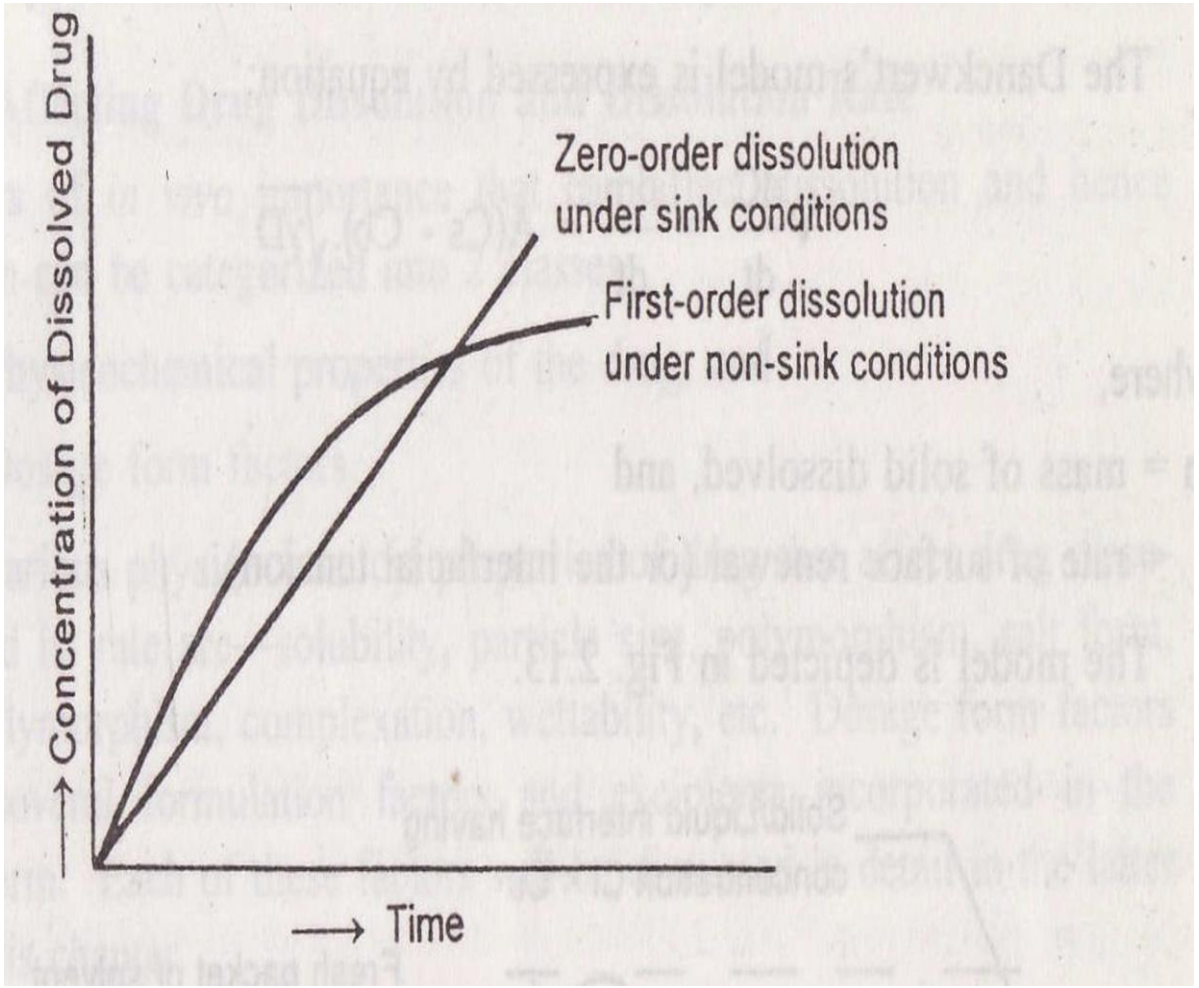


FIGURE 15-3 Dissolution of a solid drug particle in a solvent. (C_s = concentration of drug in the stagnant layer, C = concentration of drug in the bulk solvent.)

- This is first order dissolution rate process, for which the driving force is concentration gradient.
- The *in-vivo* dissolution is rapid as sink conditions are maintained by absorption of drug in systemic circulation i.e. C_b=0 and rate of dissolution is maximum.
- Sink conditions mean that the dissolution medium contains enough volume and has enough capacity to dissolve the drug so that the drug concentration remains far below its saturation solubility throughout the dissolution test.
- Under sink conditions, the concentration of dissolved drug does not approach saturation.



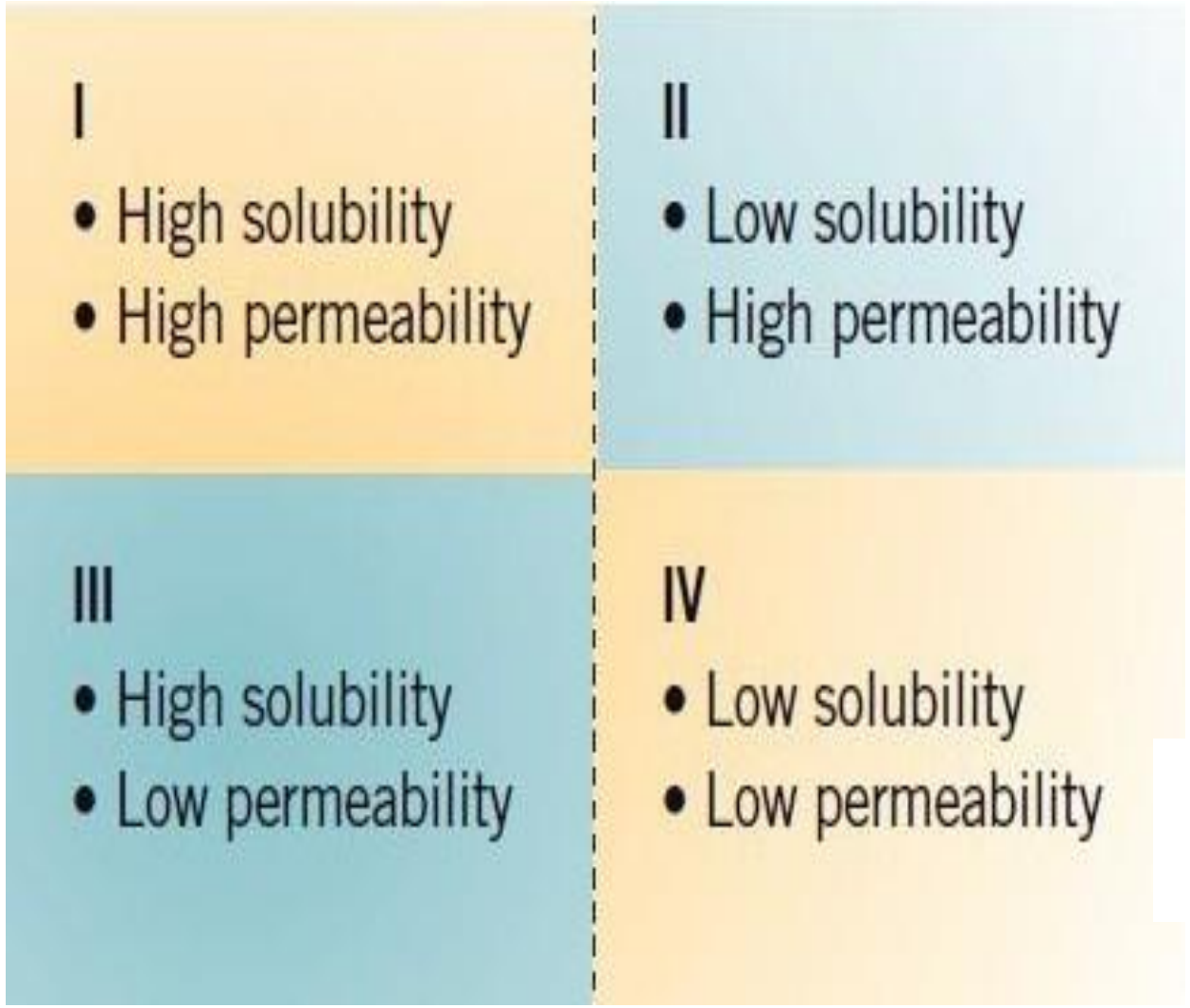
Dissolution rate under non-sink and sink conditions.

The rate limiting steps in oral absorption of drugs :

1. **Dissolution rate** is step for **lipophilic drugs** because the dose may incomplete dissolve
    - e.g. Griseofulvin.
2. **Permeation rate** of the membrane is step for **hydrophilic drugs**
    - e.g. Neomycin.

Biopharmaceutics Classification System (BCS)

propranolol
verapamil



naproxen,
ketoprofen

cimetidine
ranitidine
atenolol
captopril

furosemide,
hydrochlorothiazide

Physicochemical properties of drug substances

2-particle size and effective surface area.



- Particle size and surface area are inversely related to each other.
- Two types of surface area –
  - Absolute surface area which is the total surface area of any particle.
  - Effective surface area which is the area of solid surface exposed to the dissolution medium.
- Particle-size reduction usually increases the surface area of a drug and therefore can increase its dissolution rate according to the Noyes–Whitney equation

When Is Particle Size Reduction NOT Beneficial?

- Particle-size reduction usually increases the surface area of a drug and therefore can increase its dissolution rate according to the Noyes–Whitney equation.
- However, smaller particles are NOT ALWAYS BETTER. Extremely fine particles may create formulation problems:

1. **Very fine particles may agglomerate**
   - Hydrophobic drug particles tend to adsorb air onto their surfaces.
   - This decreases their wettability and may cause the particles to float on the dissolution medium rather than becoming dispersed.
     - Example: Micronized hydrophobic drugs such as phenobarbital and aspirin
2. **Electrostatic charge can interfere with wetting**
   - Fine particles have a large surface area and may develop electrostatic charges during milling.
   - This can reduce dispersion and wetting, limiting the expected increase in dissolution.
3. **Excessive surface area may reduce drug stability**
   - ➢ This may increase:
     - Chemical degradation, such as oxidation or hydrolysis and Physical instability
     - Ex. of such drugs are Penicillin G & Erythromycin
4. **Faster dissolution may sometimes increase adverse effects**
   - For some drugs, increasing dissolution or the rate at which drug becomes available in the gastrointestinal tract can increase local GI irritation.
     - Examples: nitrofurantoin may produce increased local GI irritation in some formulations.

Physicochemical properties of drug substances

3- Polymorphism and Amorphism

- A drug can exist in different **solid forms**, and these forms can affect its **solubility, dissolution, and absorption**.
- **Polymorphism** means that the same drug can have **more than one crystalline form**.
- Polymorphs have the **same chemical structure** but different physical properties.
  - ➢ They may differ in:
    - Solubility
    - Density
    - Hardness
    - Melting point
    - Dissolution rate
- **Example: Chloramphenicol**
  - It has several crystal forms.
  - The **β-polymorph is more soluble**.
  - Therefore, it is **better absorbed** when administered orally.

Classification of polymorphs

➢ Amorphous Form

- An **amorphous drug** has **no regular internal crystal structure**.
- Because the molecules are less tightly organized, amorphous forms generally have:
  - **Higher aqueous solubility**
  - Faster dissolution
  - Potentially better absorption
- **Example:**
  - The amorphous form of **novobiocin** is about **10 times more soluble** than its crystalline form. However, the amorphous form mentioned in the lecture was therapeutically ineffective.

➢ crystalline：depending on their relative stability

- **A stable polymorph** has highest melting point and least aqueous solubility.
- The remaining polymorphs are called as **metastable** forms

Stable vs. Metastable Forms

- **Stable polymorph**
  - Most thermodynamically stable
  - **Highest melting point**
  - **Lowest aqueous solubility**
  - Usually dissolves more slowly
- **Metastable polymorph**
  - Less stable
  - Lower melting point
  - **Higher aqueous solubility**
  - Dissolves faster
  - Can eventually change into the stable form.

- **Solubility/Dissolution: Amorphous > Metastable > Stable**

4-Pseudopolymorphs

- **Hydrates and Solvates**
  - Sometimes **solvent molecules become trapped inside the crystal structure** of a drug. This is called **pseudopolymorphism**.
  - ➢ **Solvate**
    - A **solvate** contains solvent molecules within the crystal structure.
    - Organic solvent molecules may be present.
    - They can be undesirable because **residual organic solvents may be toxic**.
  - ➢ **Hydrate**
    - When the solvent incorporated into the crystal is **water**, it is called a **hydrate**.

✓ **Anhydrous form > Hydrous form in solubility**

- Example: Anhydrous ampicillin has greater aqueous solubility than **ampicillin trihydrate**.

Physicochemical properties of drug substances

5- Salt Forms of Drugs

- Converting a drug into a **salt form** is one of the common ways to improve its:
  - **Solubility**
  - **Dissolution rate**
  - Potentially its **absorption**
- The salt can modify the **pH of the diffusion layer** around the drug particle, rather than substantially changing the pH of the entire solution.
  - **Weak acidic drugs**
    - For a **weak acid**, conversion to an appropriate salt can increase the pH around the drug particle (**diffusion layer**).
    - This can: **Increase solubility → increase dissolution → promote absorption**

pH – Partition Hypothesis

- **Brodie et al** 1957
- It states that in case of drugs with molecular weight greater than **100 Dalton** and drugs that move across the cell membrane by the process of **passive diffusion**, the absorption is **dependent** upon:
  1. **pKa** value of drug.
  2. **pH** of absorption site.
  3. **Lipid** solubility of unionized drug (lipophilicity "$K_{w/o}$").
- Most of the drugs are **weak acid** or **weak base**, thus the degree of **ionization** will depend on the **pH** of the media.

pH – Partition Hypothesis

- For **passive diffusion**, the drug should be **unionized** and had a sufficient **lipid solubility**, as explained by Henderson-hesselbach equation: -

For Weak Acids:

Henderson-Hasselbalch Equation:

$$pH = pK_a + \log\left(\frac{[\text{Ionized drug}]}{[\text{Unionized drug}]}\right)$$

Percent Drug Ionized:

$$\%\text{Drug Ionized} = \frac{10^{pH-pK_a}}{1+10^{pH-pK_a}} \times 100$$

For Weak Bases:

Henderson-Hasselbalch Equation:

$$pH = pK_a + \log\left(\frac{[\text{Unionized drug}]}{[\text{Ionized drug}]}\right)$$

Percent Drug Ionized:

$$\%\text{Drug Ionized} = \frac{10^{pK_a-pH}}{1+10^{pK_a-pH}} \times 100$$

pH – Partition Hypothesis

- This hypothesis is **true** assuming that:

1. The **GIT** is a **simple lipid barrier** for drug transport.
2. **Larger** the **unionized** fraction, **faster** the **absorption**.
3. The **greater lipophilicity** of the unionized fraction, **better** the **absorption**.

pK_a and pH

- The amount of the unionized drug is a function of pKa and pH "Henderson-hessel bach equation".
- If pKa = pH, the concentration of unionized = ionized.

pH – Partition Hypothesis

Lipophilicity [partition coefficient "$K_{o/w}$"

- For optimum absorption, the drug should have:

1. Hydrophilicity to dissolve
2. Lipophilicity of unionized fraction to permeate

- Thus, the drug should have a hydrophilic-lipophilic balance (HLB).
- According to the pH – partition hypothesis, an increase in the partition coefficient (Po/w) *(more is the lipid solubility)* will associated with an increase in absorption.

$$P_{o/w} = \frac{Distribution\ of\ drug\ in\ organic\ phase\ (octanol)}{Distribution\ of\ drug\ in\ aq\ phase}$$

For example, consider the concentration of salicylic acid (pKa = 3.0) in the stomach (pH = 1.2) compared with its concentration in plasma (pH = 7.4).

According to the Henderson–Hasselbalch equation:

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

In plasma, pH 7.4:

$$\text{Ratio} = \frac{(RCOO^-)}{(RCOOH)} = 10^{(1.2-3.0)} = 1.58 \times 10^{-2}$$

In gastric juice, at pH 1.2

- However, the movement of a drug is not always affected significantly by pH.
  - **Very weak acids and bases remain** largely nonionized at physiological pH values.
    - Therefore, their transfer across membranes is generally rapid and relatively independent of pH.
  - In contrast**, strong acids and bases** are largely or completely ionized under physiological conditions.
    - Consequently, their transfer across lipid membranes is usually slow and relatively pH-independent.

Q- Given below in the table are three basic drugs together with some of physicochemical and biological properties

Property	diazepam	loratidin	guanethidine
Pk a	3.7	5	11.7
Agues solubility	slight	insoluble	high
$K_{o/w}$	high	27	low

1-determine the percent drug ionization in stomach pH 3 and intestine pH 5?

2- Assuming that only the unionized drug is absorbed what percent of drug will be absorbed from the intestine pH 7.4?

II. Formulation Factors

1. Nature and type of dosage form
2. Disintegration Time
3. Manufacturing process:
    A. Method of granulation
    B. Compression force
4. Pharmaceutical ingredients (excipients)
5. Product age and storage conditions.

1. Nature and Type of Dosage Forms (DF)

- The **physical state** of a drug affects the rate of absorption.
- The dosage form affects the rate of absorption.
- The dosage form affects the route of administration and bioavailability.
  - Tablets can be classified into:

    Conventional Tablets > Coated Tablets > Enteric Coated Tablets > Sustained Release **tablets/products**
- The **dosage form** determines how quickly and where the drug is released, which can consequently influence its **absorption, bioavailability, and duration of action**.

2. Disintegration Time

- **Disintegration** is the process by which a solid dosage form, such as a tablet, breaks down into smaller particles after administration.
- Faster disintegration generally allows the drug to become available for dissolution and subsequent absorption more quickly.
- Therefore, **a shorter disintegration time (D.T.)** is generally desirable for immediate-release tablets.
- Sequence:

  Rapid disintegration → faster drug dissolution → faster availability for absorption → potentially faster absorption
- A shorter disintegration time does not necessarily mean greater total absorption or higher bioavailability. It primarily tends to affect **the rate at which the drug becomes available for absorption.**

3. Manufacturing Process

A. Method of granulation

- **Wet granulation** produces tablets that **dissolve faster** than tablets made by other granulation methods.

B. Compression force

- **Higher compression force** produces tablets with:
  - **Greater hardness**
  - **Reduced wettability**
  - Therefore, a **longer disintegration time (D.T.)**
    - Wet granulation → faster dissolution.
    - Higher compression force → harder tablet → lower wettability → **longer disintegration time.**

4. Pharmaceutical Excipients

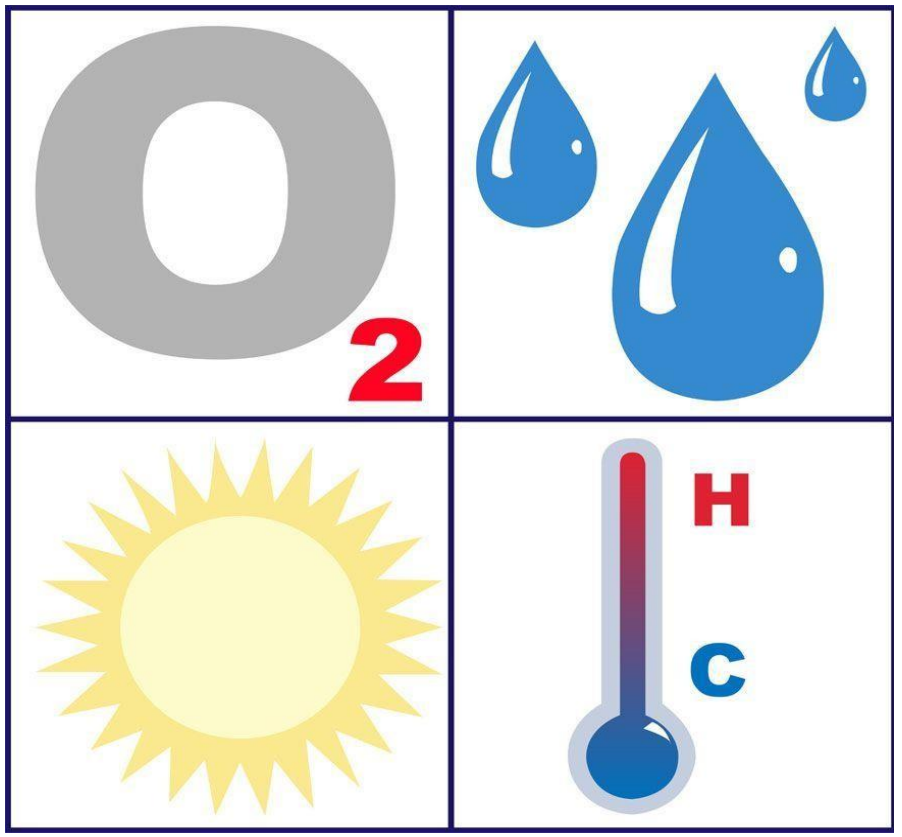
- When increase no. of excipients in dosage form, more complex & greater the potential for absorption and bioavailability problems.
- Example: Absorption of tetracycline from capsules is reduced by calcium phosphate due to complexation.
- More amount of binder → increases hardness of tablet → decrease dissolution & disintegration rate.
- **Surfactants :**Widely used in formulation as wetting agent, solubilizer …etc. Their effect on absorption is very complex may **enhance or retards** drug absorption by interacting **with drug or membrane or both**.

5. Product aging and storage conditions

✓ Product aging and improper storage conditions adversely affect bioavailability.

Examples :

- Precipitation of drug in solution.
- Change in particle size of suspension.
- Hardening of tablet.



Patient Related Factors

1. Gastric emptying
2. First pass metabolism by:
    a) Luminal enzymes
    b) Gut wall enzymes
    c) Bacterial enzymes
    d) Hepatic enzymes
3. Gastrointestinal pH
4. Diseased states
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Patient Related Factors

1. Gastric Emptying (GE)

- The discharge gastric content from stomach to small intestine, called as gastric emptying (1-5 hr)
- GE is rate limiting step in absorption because the major site of drug absorption is intestine.
- Several parameters used to quantify gastric emptying :

✓ **Gastric Emptying Rate (GER)**: speed at which stomach contents empties into intestine.

✓ **Gastric Emptying Time (GET)**: time required for gastric contents to empty into the small intestine.

➢ Rapid GER is recommended when :

- When **rapid onset** of action is desired, e.g., with **sedatives**.
- When the **drug is unstable in gastric fluids**, e.g., **penicillin G**.
- When the drug should **dissolve in the intestine**, e.g., **enteric-coated formulations**.
- When the drug is **best absorbed from the distal small intestine**, e.g., **vitamin B_{12}**.

➢ Delay GER is recommended :

- **Food promotes** drug **dissolution** and absorption
- The drugs **dissolve slowly** e.g. griseofulvin.
- **Disintegration** and dissolution of dosage form is promoted by **gastric fluids**.

Factors Affecting Gastric Emptying

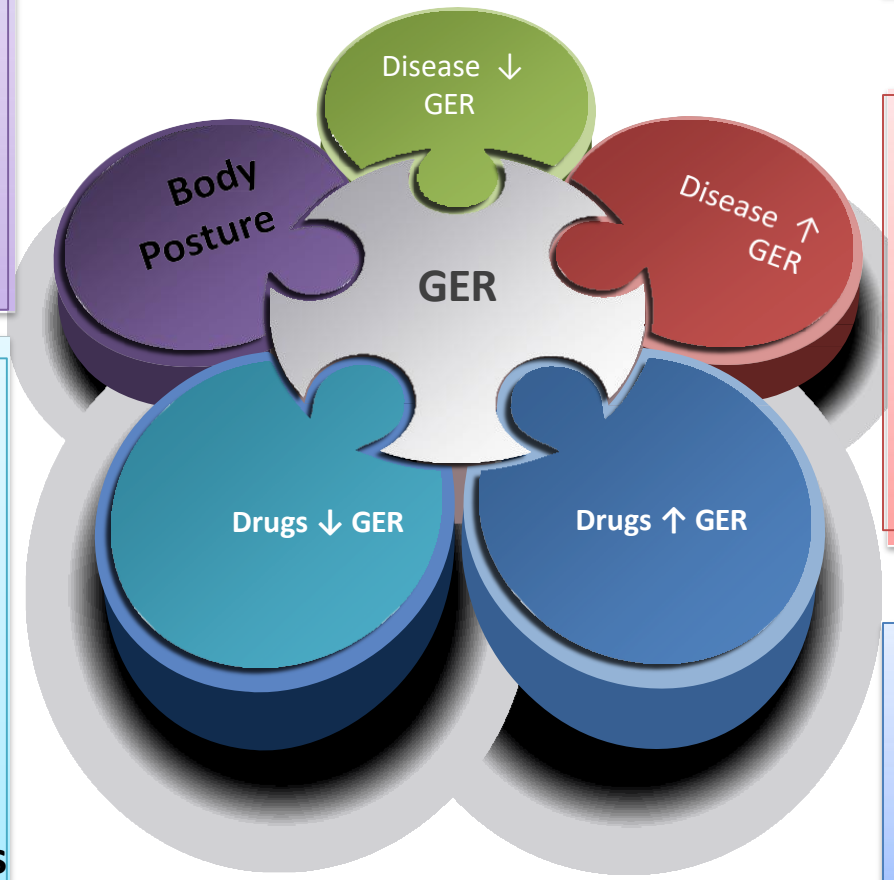
Body Posture:

↑ GER

- Standing
- Lying on right side

↓ GER

- Supine
- Lying on left side



Disease ↓ GER :

- Gastroenteritis
- Gastric ulcer

Disease ↑ GER :

- Partial or total gastrectomy
- Duodenal ulcer
- Hyperthyroidism

Drugs ↓ GER include:

- **Poorly soluble antacids**
  aluminum hydroxide
- **Anticholinergics:**
  atropine
- **Narcotic analgesics**
  morphine
- **Tricyclic antidepressants**
  imipramine

Drugs ↑ GER include:

- Metoclopramide.
- Domperidone

2. First pass metabolism

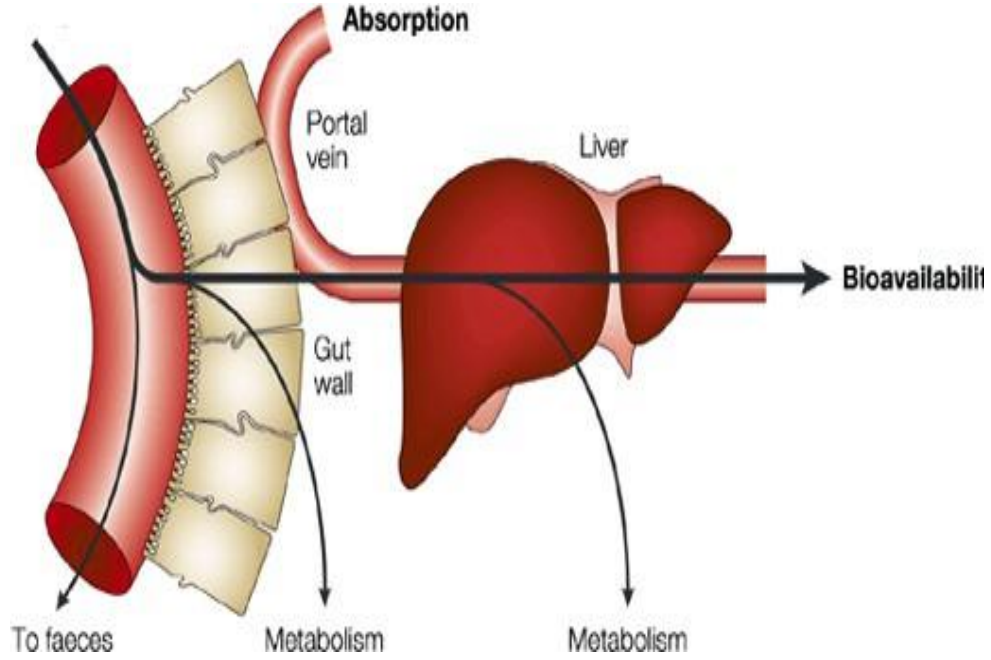
- For a drug administration orally, the main reasons for its **decreased bioavailability** are:

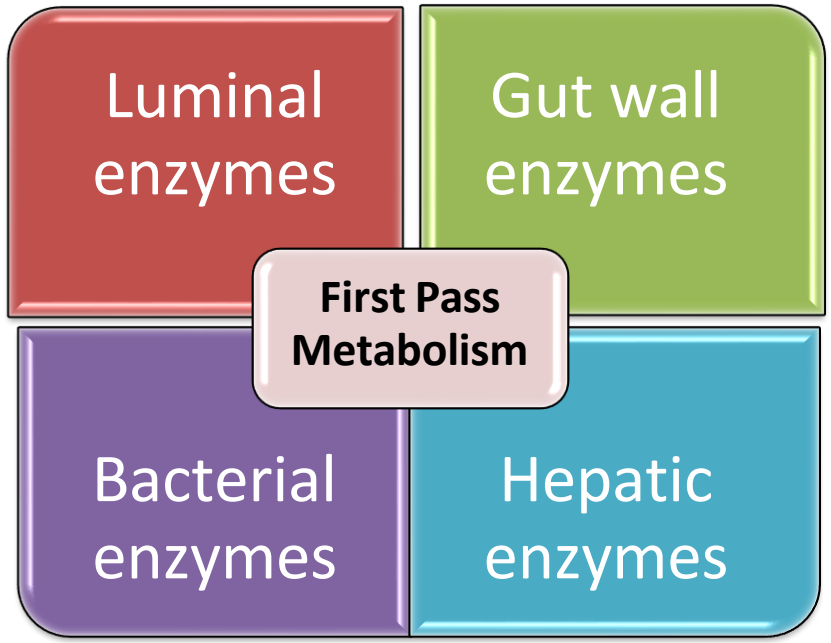
    A. Decreased absorption

    B. First pass metabolism

- The loss of drug through metabolism by eliminating organs during its passage to systemic circulations called as first pass or presystemic metabolism.

    The 4 primary systems which effect presystemic metabolism of a drug are:





A. Luminal enzymes:

- These are present in GIT fluids and include enzymes from intestinal and pancreatic secretions.
- They contain **estrase** which hydrolyse ester drugs
- For example:
  - chloramphenicol palmitate convert to active form.

B. Gut wall enzymes:

- They are called as mucosal enzymes present in stomach, intestine and colon. For example :
- **Alcohol dehydrogenase** : enzyme of stomach mucosa inactivates ethanol.

C. Bacterial enzymes :

For example :

- Sulfasalazine (drug for ulcerative colitis)

D. Hepatic enzymes:

- Several drugs suffer **first pass hepatic** metabolism like propranolol, nitroglycerine, diltiazem, lidocaine, morphine etc.

3. Gastrointestinal pH

- **GI fluid pH influence drug absorption in several ways**

1. Disintegration pH dependent:

- Enteric coated formulations:
- The coating dissolves only in intestine followed by disintegration.

2. Dissolution:

- Weakly acidic drugs: dissolve rapidly in alkaline pH of intestine.
- Weakly basic drugs: dissolve in acidic pH of stomach

3. Absorption:

- Depends on drug pKa and whether its an acidic or basic drug, GI pH influences drug absorption by determining amount of drug that would exist in unionized form at the site of absorption.

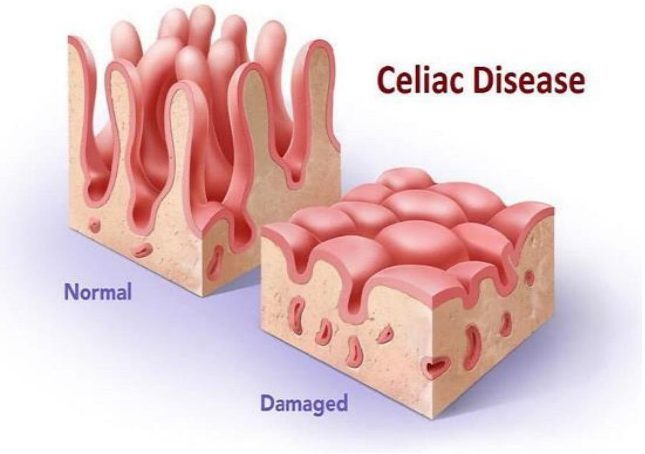
4. Stability: (GI pH also affect chemical stability of drug)

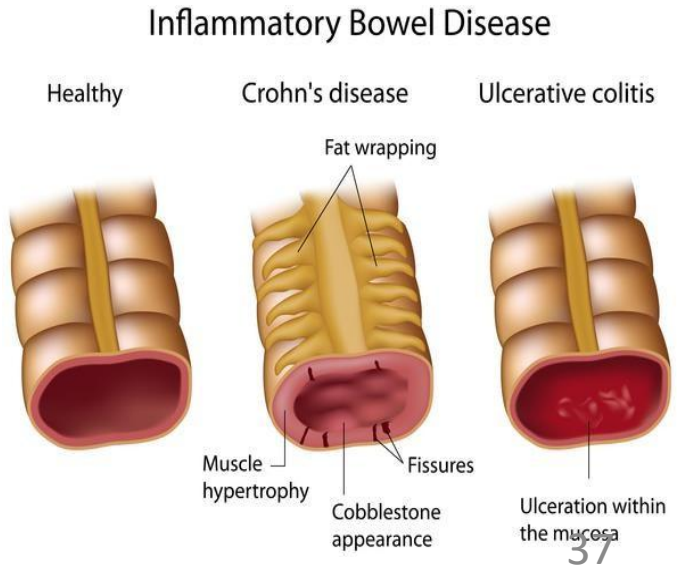
- ✓ **acidic** stomach pH- affect degradation of **pencillin G and erythromycin.**
- ✓ Can be overcome by preparing **prodrugs** of such drug e.g. erythromycin estolate.

4. Diseased states

Gastrointestinal diseases and infections:

- Two disorders of the intestine related with malabsorption syndrome that influence drug availability are
  - Celiac disease (destruction of villi and microvilli).
  - Crohn's disease
- GI infections like shigellosis, gastroenteritis, cholera and food poisoning also result in malabsorption.





5. Blood flow through the GIT

- The GIT is extensively supplied by blood capillary network

- Most drugs reach the systemic circulation via **blood**.
- Few drugs (**low MW, lipid soluble**) removed by lymphatic system.
- High perfusion rate of GIT helps in maintaining **sink conditions** and concentration gradient for drug absorption by rapidly removing drug from the site of absorption.