Unit-1

Biopharmaceutics and Pharmacokinetics

B.Pharma 6th Sem Notes

Unit: 1

Introduction to Biopharmaceutics

- **Absorption:** Mechanisms of drug absorption through GIT, factors influencing drug absorption though GIT, absorption of drug from Non per oral extra-vascular routes.
- **Distribution:** Tissue permeability of drugs, binding of drugs, apparent, volume of drug distribution, plasma and tissue protein binding of drugs, factors affecting protein-drug binding. Kinetics of protein binding, Clinical significance of protein binding of drugs.

Introduction to Biopharmaceutics

Definition:
Biopharmaceutics is the branch of pharmaceutical sciences that deals with the study of how the **physical and chemical properties of drugs**, the **dosage form**, and the **route of administration** affect the **rate and extent of drug absorption** in the body.

1. Bioavailability:

- Bioavailability refers to the **rate and extent** to which an administered drug reaches the **systemic circulation** in its **unchanged form**.

In simple words:
It shows **how much and how fast** the drug is absorbed into the blood.

Example:
If 100 mg of a drug is taken orally and only 70 mg reaches the bloodstream → bioavailability = 70%.

Factors affecting bioavailability:

- Drug solubility and stability
- First-pass metabolism
- Dosage form and route of administration
- Food and physiological conditions

2. Pharmaceutical Phase

Definition:
This is the **first phase** of drug action, involving the **disintegration** of the dosage form and **dissolution** of the drug in body fluids.

Steps:

1. **Disintegration** → Tablet breaks into smaller particles.
2. **Dissolution** → Drug particles dissolve in body fluids.
3. **Drug in solution** → Ready for absorption.

Example:
A tablet must dissolve in the stomach before the drug can be absorbed.

3. Pharmacokinetic Phase

Definition:
This phase deals with the **movement of the drug within the body** — what the **body does to the drug**.

It includes 4 major processes (ADME):

1. **Absorption** – Entry of drug into the blood.
2. **Distribution** – Transport of drug to tissues.
3. **Metabolism (Biotransformation)** – Chemical alteration of the drug (mainly in the liver).
4. **Excretion** – Removal of drug/metabolites (mainly via kidneys).

Example:
After oral administration, a drug is absorbed in the intestine, distributed via blood, metabolized in the liver, and excreted through urine.

4. Pharmacodynamic Phase

Definition:
This phase explains **what the drug does to the body** — how it produces its **therapeutic or toxic effects**.

Mechanism of Action:

- Drug binds to **receptors**, **enzymes**, or **ion channels**.
- Triggers a **biological response** (desired or adverse effect).

Example:
Paracetamol reduces fever by inhibiting prostaglandin synthesis in the brain.

5. Clinical Phase

Definition:
This is the **final phase**, where the **overall effect** of the drug is observed in the patient, including **therapeutic outcome** and **side effects**.

Involves:

- **Clinical evaluation** of drug response.
- Monitoring **efficacy, safety, and toxicity**.
- Used in **clinical trials** to test new drugs.

Example:
During clinical use, doctors observe if a patient's symptoms improve and if any adverse effects occur.

Processes in Biopharmaceutics

1. **Absorption** – Movement of the drug from the site of administration into the bloodstream.
2. **Distribution** – Transport of the drug through blood to different tissues and organs.
3. **Metabolism** – Chemical modification of the drug in the body, mainly in the liver.
4. **Excretion** – Removal of the drug and its metabolites from the body (mainly via kidneys).

Factors Affecting Biopharmaceutics

- **Physicochemical properties of drug:** solubility, particle size, pKa, stability, etc.
- **Dosage form:** tablets, capsules, suspensions, injections, etc.
- **Route of administration:** oral, intravenous, intramuscular, etc.
- **Physiological factors:** gastric emptying time, pH, enzyme activity, disease state, etc.

Scope of Biopharmaceutics

1. Understanding the relationship between drug formulation and its therapeutic effect.
2. Studying how different dosage forms (tablet, capsule, injection, etc.) affect drug absorption.
3. Designing dosage forms that deliver drugs effectively and safely.
4. Optimizing bioavailability (the amount of drug that reaches systemic circulation).

Importance of Biopharmaceutics

- Helps in designing dosage forms with optimal **therapeutic efficacy**.
- Reduces **toxicity** and **side effects**.
- Assists in achieving **consistent and predictable drug action**.
- Forms the foundation for **pharmacokinetics** and **drug development**.

Absorption: Absorption is the process of movement of drugs form its site of administration to the blood stream ,the therapeutics response of the drug depends on the rate as extent of drug absorption on and its concentration at the site of action.

Transport of Drug Across Biological Barriers:

For systemic absorption, a drug must pass from the absorption site through one or more layers of cells to gain access into the general circulation. For absorption into the cells, a drug must traverse the cell membrane.

Structure of Cell Membrane:

Cell membrane surrounds the entire cells and acts as a boundary between cell and interstitial fluid. Cell membrane acts as a selective barrier to the passage of molecules. Water, some small molecules, and lipid-soluble molecules pass through such membrane;

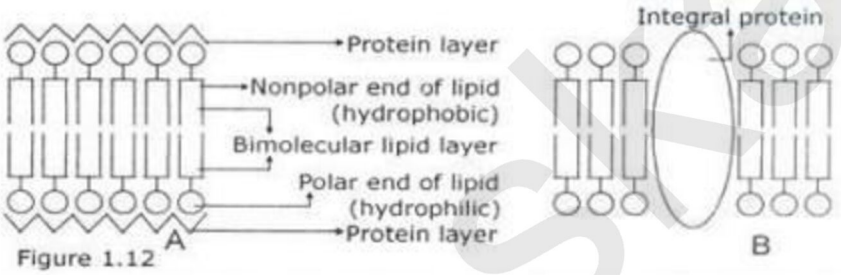
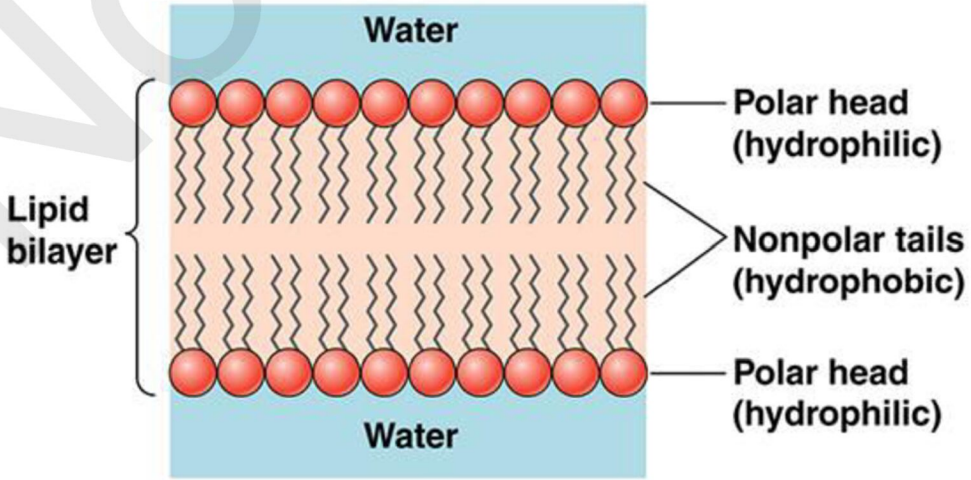


Figure 1.12

Structure:

- Cell membranes are generally thin, approximately 70 to 100 A in thickness.
- They are primarily composed of phospholipids in the form of bilayer. Some carbohydrates and proteins are inter dispersed within this lipid bilayer.



The principal mechanisms of transport of drug molecules across the cell membrane are:

1. Passive diffusion

2. Carrier mediated transport

    (a) Active transport
    (b) Facilitated transport

3. Vesicular transport

    a) Pinocytosis
    b) Phagocytosis

4. Pore transport

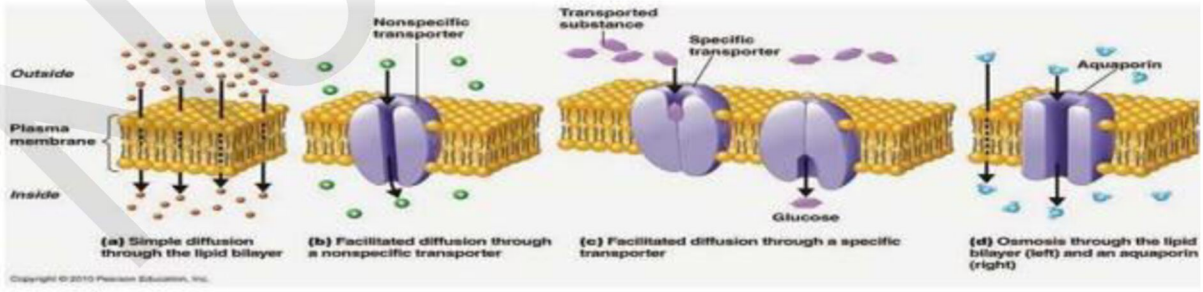
5. Ion pair formation Pore transport

Passive Transport:

Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is passive because no external energy is expended.

OR

Passive transport is the process of **drug movement across a biological membrane without using energy (ATP)**.
The drug moves from an area of **higher concentration to lower concentration** — i.e., **along the concentration gradient**.



Characteristics of passive transport:

- Drug molecules moves from a region of relatively high concentration to one of lower concentration.
- The rate of transfer is proportional to the concentration gradient between the compartments involved in the transfer.

- The transfer process achieves equilibrium when the concentration of the transferable species is equal on both sides of the membrane.

2. Carrier-Mediated Transport

This type of transport requires a **carrier protein** that helps move the drug molecules across the membrane.

(a) Active Transport

- Requires **energy (ATP)**.
- Drug moves **against the concentration gradient** (low → high).
- **Selective** and **saturable** (limited number of carrier proteins).
- May show **competitive inhibition** with similar molecules.

Examples:

- L-Dopa (via amino acid carrier)
- Certain vitamins and ions (Na^+, K^+, Ca^{2+})

(b) Facilitated Transport

- Requires **carrier proteins**, but **no energy**.
- Movement occurs **along the concentration gradient** (high → low).
- Process is **saturable** and **selective**.

Examples:

- Glucose and Vitamin B_{12} absorption in intestine.

3. Vesicular Transport

Large molecules (macromolecules, proteins, or particles) that cannot pass through membrane pores or carriers are transported by **vesicle formation**.

(a) Pinocytosis

- "Cell drinking" → Uptake of **fluids or small solute molecules** into vesicles.
- Requires **energy (ATP)**.
- Important for **large polar molecules**.

Example: Absorption of Vitamin B_{12} and fat-soluble vitamins.

(b) Phagocytosis

- "Cell eating" → Uptake of **solid particles or macromolecules** into vesicles.
- Common in **defense cells (macrophages)** rather than drug absorption.
- Example: Engulfing bacteria or dead cells.

4. Pore (Convective) Transport

- Transport of **small, water-soluble** drugs through **aqueous pores or channels** in the cell membrane.
- No energy required.
- Depends on **molecular size** and **hydrostatic pressure difference**.

Examples:

- Urea, water, small ions (Na^+, K^+).

5. Ion-Pair Formation

- Some **ionic drugs** (charged molecules) form **temporary neutral complexes (ion pairs)** with oppositely charged ions.
- These neutral ion-pairs are **lipid-soluble**, allowing them to cross the membrane by passive diffusion.
- After crossing, they dissociate back into ions.

Examples:

- Quaternary ammonium compounds with anions.
- Propranolol with fatty acids.

Factors Influencing GI Absorption of A Drug:

A) Pharmaceutical Factors: It include factores relating to the physicochemical properties of drug and dosage form characteristics and pharmaceutical ingredients.

Physico-chemical Properties of Drug substances:

- Drug solubility and dissolution rate
- Particle size and effective surface area
- Polymorphism and amorphism
- Pseudo polymorphism (hydrates / solvates)
- Salt form of the drug
- Lipophilicity of the drug – (pH partition hypothesis)
- pKa of the drug and pH – (pH partition hypothesis)
- Drug stability

Pharmaco- technical factors:

- Disintegration time (tablets / capsules)
- Dissolution time
- Manufacturing variables
- Pharmaceutical ingredients (excipients / adjutants)
- Nature and type of dosage form
- Product age and storage conditions

Patient –related factors:

- Age
- Gastric emptying time
- Intestinal transit time
- Gastrointestinal pH
- Disease states
- Blood flow through the GIT
- Gastrointestinal contents:

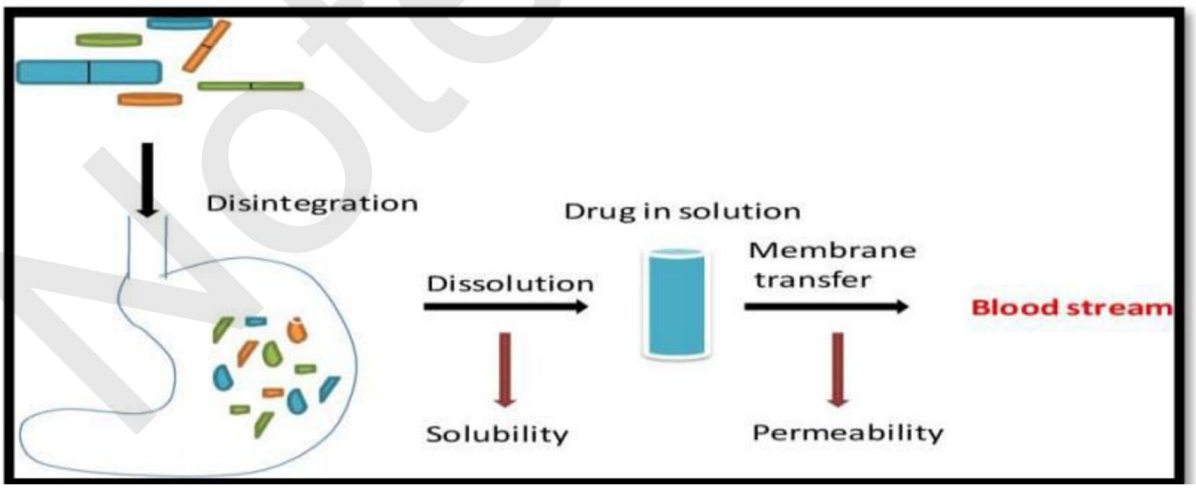
    (a) Other drugs
    (b) Food
    (c) Fluids
    (d) Other normal GI contents

- Pre-systemic metabolism by

    (a) Luminal enzymes
    (b) Gut wall enzymes
    (c) Bacterial enzymes
    (d) Hepatic enzymes

Drug solubility and dissolution rate:

Orally administered solid dosage form are first disintegrated or disaggregated, then the solid particles are dissolved drugs in solution then permeate across bio membrane to be absorbed in the body.



Their are two critical processes in which the absorption of orally administered drugs are:

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

Dissolution: is a sssprocess in which a solid substance solubilises in a given solvent

Their are several theories to explain drug dissolution they are following

1. Diffusion layer model
2. Danckwert model
3. Interfacial barrier model

1. Diffusion Layer Model (Film Theory or Noyes–Whitney Model)

Concept:

- Proposed by **Noyes and Whitney (1897)**.
- It assumes that when a solid drug is placed in a solvent, a **thin stagnant film (diffusion layer)** forms immediately around the solid surface.
- Drug molecules first dissolve in this layer and then **diffuse** through it into the bulk of the solvent.

Steps:

1. Drug molecules dissolve at the solid surface.
2. A **saturated solution** forms in the diffusion layer.
3. Drug diffuses from the diffusion layer → bulk solution (where concentration is lower).

Noyes–Whitney Equation:

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

Where:

- **dC/dt** = Rate of dissolution
- **D** = Diffusion coefficient
- **A** = Surface area of drug
- **C_s** = Solubility (concentration at surface)
- **C** = Concentration in bulk
- **h** = Thickness of diffusion layer

2. Danckwerts Model (Penetration Theory)

Concept:

- Proposed by **Danckwerts in 1951**.
- It modifies the diffusion layer model.
- It suggests that the **liquid at the solid surface is not stagnant** — instead, **fresh solvent molecules continuously replace** the liquid film due to turbulence.

Explanation:

- The surface of the solid drug is constantly being renewed by new layers of solvent.
- Each new layer becomes saturated, and the dissolved drug diffuses away.
- This continuous renewal maintains the concentration gradient.

Key Difference from Film Theory:

- The **film** in the diffusion layer model is **stationary**,
  while in the **Danckwerts model**, it is **constantly replaced**.

Equation (simplified form):

$$\frac{dC}{dt} = k(Cs - C)$$

Where **k** = dissolution rate constant.

3. Interfacial Barrier Model (Surface Barrier Theory)

Concept:

- Proposed by **R. H. Wagner**.
- It assumes that a **saturated layer or barrier** forms at the solid–liquid interface, which **controls the dissolution rate**.
- The barrier is formed due to **adsorbed impurities, solvation, or reaction products** at the surface.

Explanation:

- Drug molecules must cross this **interfacial barrier** to enter the bulk solution.
- The dissolution rate depends on how fast the drug can **cross or break** this barrier.

Patient-Related Factors Affecting Drug Absorption (GIT)

1. **Age:**
   Infants and elderly have slower and less predictable drug absorption due to immature or weakened GIT functions.
2. **Gastric Emptying Time:**
   Faster emptying increases absorption; delayed emptying slows it down.
3. **Intestinal Transit Time:**
   Longer transit allows more absorption; shorter transit reduces it.
4. **Gastrointestinal pH:**
   Weak acids absorb better in acidic pH, weak bases in alkaline pH.
5. **Disease States:**
   GIT or liver diseases can alter absorption rate and bioavailability.
6. **Blood Flow through GIT:**
   Increased blood flow enhances absorption; reduced flow decreases it.

Distribution

Definition:
Drug distribution refers to the **process by which a drug reversibly leaves the bloodstream** and enters the **interstitial (tissue) and intracellular fluids**.
It determines the **drug concentration at the site of action** and hence its **pharmacological effect**.

Tissue Permeability of Drugs

The ability of a drug to enter tissues depends on:

- **Lipid solubility:** Lipid-soluble drugs easily cross cell membranes (e.g., thiopental).
- **Molecular size:** Small molecules penetrate tissues faster than large ones.
- **Degree of ionization:** Only unionized (non-charged) drugs cross biological membranes easily.
- **Blood flow:** Highly perfused organs (liver, kidney, brain) receive drugs faster than poorly perfused tissues (fat, skin).

Binding of Drugs

Drugs can **bind to plasma proteins** (like albumin) or **tissue components**.
Only the **unbound (free) drug** is pharmacologically active and can cross membranes.

- **Plasma protein binding:** Usually reversible and affects drug distribution, metabolism, and excretion.
- **Tissue binding:** Drugs may accumulate in tissues, acting as reservoirs (e.g., chloroquine in liver).

Apparent Volume of Distribution (Vd)

Definition:
Vd is a theoretical volume that relates the amount of drug in the body to the plasma concentration.

$$Vd \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}}$$

- **High Vd:** Drug is widely distributed in tissues (lipophilic drugs).
- **Low Vd:** Drug remains mainly in the plasma (hydrophilic drugs or protein-bound drugs).

Example:

- Digoxin → high Vd
- Warfarin → low Vd

Plasma and Tissue Protein Binding of Drugs

Plasma Protein Binding:

- Mainly involves **albumin** (acidic drugs) and **α_1-acid glycoprotein** (basic drugs).
- Reversible process forming **drug-protein complex**.
- Bound drug is inactive; only free drug can diffuse and act.

Tissue Protein Binding:

- Drugs can bind to **tissue proteins, lipids, or nucleic acids**.
- Increases tissue concentration and duration of action.
- Example: Tetracyclines bind to bones and teeth.

Factors Affecting Protein-Drug Binding

1. **Drug concentration:** Higher concentration → more unbound drug.
2. **Affinity between drug and protein:** Stronger affinity → more binding.
3. **Protein concentration:** Reduced in liver/kidney disease → less binding.
4. **Competition with other drugs:** Two drugs may compete for the same binding site (e.g., sulfonamides displace warfarin).
5. **pH of plasma:** Alters drug ionization and binding extent.

Kinetics of Protein Binding

- **Reversible and rapid process:** Maintains equilibrium between bound and free forms.
- Represented as:

$$D + P \leftrightharpoons DP$$

where D = free drug, P = protein, DP = drug-protein complex.

- Changes in equilibrium affect **free drug concentration** and thus pharmacological response.

Clinical Significance of Protein Binding

1. **Drug action:** Only unbound drug produces therapeutic effect.
2. **Drug distribution:** Highly bound drugs have smaller Vd and slower distribution.
3. **Drug elimination:** Only free drug undergoes metabolism and excretion.
4. **Drug interactions:** Displacement by other drugs may cause toxicity.
5. **Disease conditions:** Hypoalbuminemia (low plasma protein) increases free drug → enhanced effect or toxicity.