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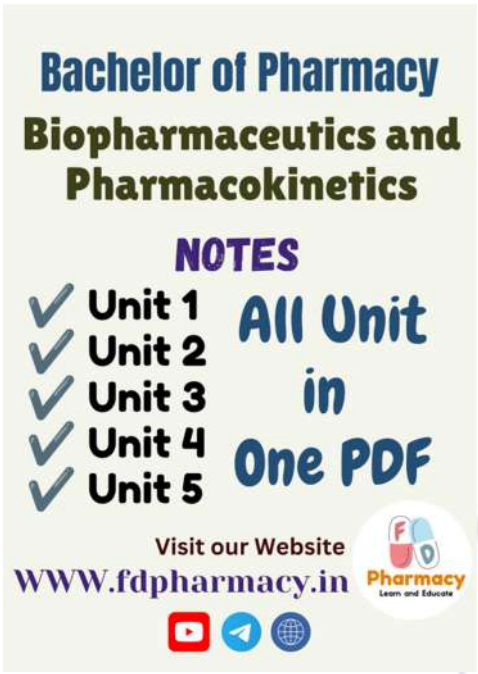
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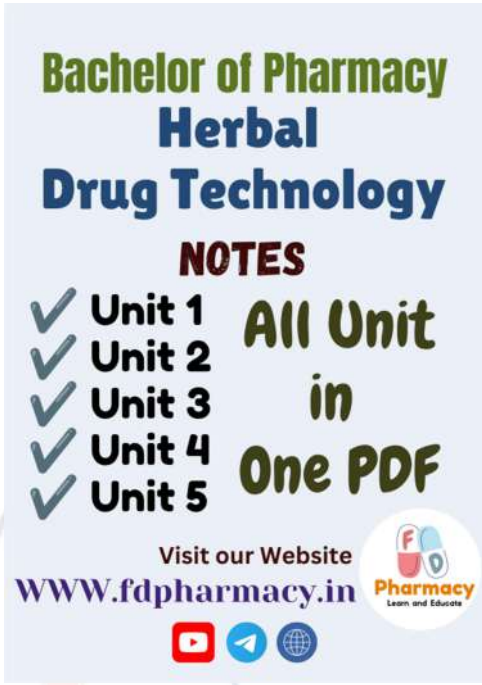
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BIOPHARMACEUTICS AND PHARMACOKINETICS

UNIT 1

TOPIC :

- **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

Distribution of Drugs

Distribution is the process by which a drug is transported from the bloodstream to different tissues, organs, and body fluids after absorption.

After entering systemic circulation, the drug gets distributed throughout the body to produce its therapeutic action.

Distribution depends on:

- Blood flow to tissues
- Permeability of membranes
- Binding of drug to plasma proteins
- Lipid solubility of drug

Drug distribution may be defined as:

"The reversible transfer of a drug from the bloodstream to body tissues and fluids."

Process of Drug Distribution

After absorption:

1. Drug enters bloodstream
2. Drug circulates through body
3. Drug crosses capillary membranes
4. Drug reaches tissues and organs
5. Drug produces pharmacological action

Some drugs distribute rapidly while others distribute slowly.

Factors Affecting Drug Distribution

1. Blood Flow to Tissues

Organs with high blood supply receive drugs rapidly.

Highly perfused organs:

- Brain
- Heart
- Liver
- Kidneys

Poorly perfused tissues:

- Fat
- Skin
- Bones

2. Lipid Solubility of Drug

Lipid soluble drugs cross cell membranes easily and distribute rapidly.

Water soluble drugs distribute slowly.

3. Plasma Protein Binding

Many drugs bind with plasma proteins such as albumin.

- Bound drug cannot cross membranes
- Only free drug produces action

High protein binding reduces distribution.

Example:

- Warfarin strongly binds to plasma proteins

4. Tissue Binding

Some drugs bind to tissue proteins and accumulate in tissues.

Example:

- Tetracycline accumulates in bones and teeth

5. Molecular Size

- Small molecular size drugs distribute easily.
- Large molecules cross membranes slowly.

6. pH and Ionization

- Unionized drugs distribute more easily than ionized drugs.
- pH differences between blood and tissues influence distribution.

Tissue Permeability of Drugs

Tissue permeability refers to the ability of a drug to cross biological membranes and enter tissues.

Drug molecules must pass through:

- Capillary walls
- Cell membranes
- Tissue barriers

Permeability determines the extent and rate of distribution.

Factors Affecting Tissue Permeability of Drugs

1. Lipid Solubility

Highly lipid soluble drugs penetrate tissues easily.

Reason:

- Cell membranes are lipid in nature

Example:

- Diazepam crosses blood-brain barrier rapidly

2. Degree of Ionization

- Unionized drugs penetrate membranes more effectively.
- Ionized drugs are less permeable.

3. Molecular Size

- Small molecules pass easily through membrane pores.
- Large molecules show poor permeability.

4. Blood Supply to Tissue

- Tissues with rich blood supply receive drugs rapidly.
- Poor blood supply decreases permeability and distribution.

5. Nature of Biological Membrane

Different tissues have different permeability characteristics.

Examples:

- Blood-brain barrier is highly selective

6. Presence of Transport Systems

Some drugs require carrier proteins for movement across membranes.

Example:

- Glucose transport

Apparent Volume of Drug Distribution (Vd)

→ Apparent volume of distribution is the hypothetical volume in which the total amount of drug would need to be uniformly distributed to produce the observed plasma concentration.
→ It indicates the extent of distribution of a drug in the body.

Formula of Volume of Distribution

$$V_d = \frac{Amount\ of\ drug\ in\ body}{Plasma\ drug\ concentration}$$

Where:

- V_d = Volume of distribution
- Amount of drug in body = Total quantity of drug administered
- Plasma drug concentration = Concentration of drug in plasma

Binding of Drugs

Drug binding refers to the attachment of drugs to proteins present in plasma or tissues after entering the bloodstream.
Binding is usually reversible in nature.
Drugs mainly bind with:

- Plasma proteins
- Tissue proteins

Only the free or unbound drug can produce pharmacological action.

Types of Drug Binding

1. Plasma Protein Binding

In this type, drugs bind with proteins present in blood plasma.
Major plasma proteins involved:

- Albumin
- Globulin
- Lipoproteins

Characteristics

- Reversible process
- Bound drug becomes inactive temporarily
- Free drug produces therapeutic effect

Binding of Drugs

- Acidic drugs mainly bind to albumin
- Basic drugs mainly bind to globulin

Examples

- Warfarin, Phenytoin, Aspirin

Importance of Plasma Protein Binding

- Increases duration of action
- Acts as drug reservoir
- Reduces drug elimination
- Affects distribution of drugs

Disadvantages

- Delays onset of action
- May cause drug displacement interactions

2. Tissue Binding

→ Some drugs bind to proteins or components present in tissues.
→ This causes accumulation of drugs in certain organs.

Examples

- Tetracycline binds to bones and teeth
- Chloroquine accumulates in liver

Factors Affecting Drug Binding

1. Drug Concentration

- Higher drug concentration may increase binding.

2. Protein Concentration

- Low plasma protein levels reduce binding.

Example:

- Liver disease
- Malnutrition

3. Affinity of Drug

- Some drugs have stronger attraction toward proteins.

4. Presence of Other Drugs

- One drug may displace another from protein binding sites.

Factors Affecting Protein-Drug Binding

1. Drug Concentration

Higher drug concentration may saturate protein binding sites.

- At low concentration → more binding
- At high concentration → free drug increases

2. Protein Concentration

Protein deficiency decreases drug binding.

Conditions causing low proteins:

- Liver disease
- Malnutrition
- Kidney disease
- Burns

Result:

- Increased free drug concentration
- Increased toxicity risk

3. Affinity of Drug for Protein

Drugs with high affinity bind strongly to proteins.

Example:

- Warfarin shows high protein binding

4. Presence of Other Drugs

Two drugs may compete for same binding site.

One drug can displace another drug from protein.

Example:

- Aspirin displaces warfarin from albumin

Result:

- Increased free warfarin
- Risk of bleeding

5. pH of Blood

- Changes in blood pH alter ionization of drugs and proteins, affecting binding.

6. Age

Protein binding differs with age.

- Neonates have low plasma proteins
- Elderly patients may have reduced albumin levels

Kinetics of Protein Binding

→ Protein-drug binding is generally a reversible process represented as:

$$Drug + Protein \rightleftharpoons Drug\text{-}Protein\ Complex$$

In this equilibrium:

- Drug molecules continuously bind and unbind
- Free drug concentration determines pharmacological action

Characteristics of Protein Binding Kinetics

1. Reversible Process

Binding and dissociation occur continuously.

2. Dynamic Equilibrium

A balance exists between:

- Bound drug
- Free drug

3. Saturable Process

Proteins have limited binding sites.

At high drug concentration:

- Binding sites become saturated
- Free drug concentration rises

4. Law of Mass Action

Binding depends on:

- Drug concentration
- Protein concentration
- Affinity of drug

Clinical Significance of Protein Binding of Drugs

Protein binding has major importance in pharmacology and therapeutics.

1. Influences Drug Action

Only free drug produces therapeutic effect.
Highly bound drugs act slowly because less free drug is available.

2. Affects Duration of Action

Bound drug acts as a reservoir and releases slowly.

Result:

- Prolonged duration of action

Example:

- Diazepam

3. Influences Drug Distribution

Highly protein-bound drugs remain mainly in bloodstream.
This decreases tissue distribution.

4. Affects Drug Elimination

Only free drug undergoes:

- Metabolism
- Excretion

Highly bound drugs are eliminated slowly.

5. Causes Drug Interactions

One drug may displace another from protein binding sites.
This increases free drug concentration and toxicity.

Example:

- Aspirin + Warfarin

6. Important in Dose Adjustment

Dose modification may be needed in:

- Liver disease
- Kidney disease
- Elderly patients
- Neonates