BIOPHARMACEUTICS

UNIT 1 NOTES

ABSORPTION

- MECHANISM OF ABSORPTION
- FACTORS INFLUENCING ABSORPTION
- ABSORPTION FROM NON PER ORAL

DISTRIBUTION

- APPARENT VD
- PROTEIN DRUG BINDING

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Introduction to Biopharmaceutics

- Biopharmaceutics is the study of how the drug's properties, dosage form and route of administration affect the rate and amount of drug absorbed into the bloodstream.
- It helps in designing effective and safe dosage forms.

- Pharmacokinetics is the study of how the body absorbs, distributes, metabolizes and excretes a drug.
- It explains how the drug moves through the body over time.

- Together, Biopharmaceutics focuses on how the drug enters the body, while pharmacokinetics explains what the body does to the drugs after it enters.

Applications Of Biopharmaceutics & Pharmacokinetics

- Helps in designing suitable dosage forms like tablets, capsules or injections.
- Improves drug absorption and ensures that drug reaches the blood-stream effectively.
- Predicts the concentration of the drug in the blood over time.
- Helps avoid side effects and toxicity by determining safe dose limits.
- Explains how the drug behaves through different routes like oral, injections or inhalations.
- Provides scientific data for clinical trials and new drug development.

ABSORPTION

- Absorption is defined as movement of drugs from its site of administration to the systemic circulation (Bloodstream)
- This process is essential for the drug to exert its therapeutic effects (except in the case of direct administration into the bloodstream such as intravenous (IV) injection).
- For a better absorption, the drugs should be lipid soluble in nature because only lipid soluble drugs can cross the biological membranes
- If a drug is administered from Oral route, it has to cross the membranes of git and blood vessels to reach the blood. Therefore, it should be in ✓ Lipid Soluble form.

NATURE OF DRUGS

- Most of the drugs available in the market are either :

① Weak Acids
② Weak Bases

- This is because they are generally in unionized form, hence more lipid soluble in nature :
- But to maintain their unionized nature, they must be absorbed from their respective medium
- Weak Acidic Drugs absorbed from Acidic Medium (i.e. Stomach)
- Weak Basic Drugs should absorbed from Basic Medium (i.e. Inteshine)

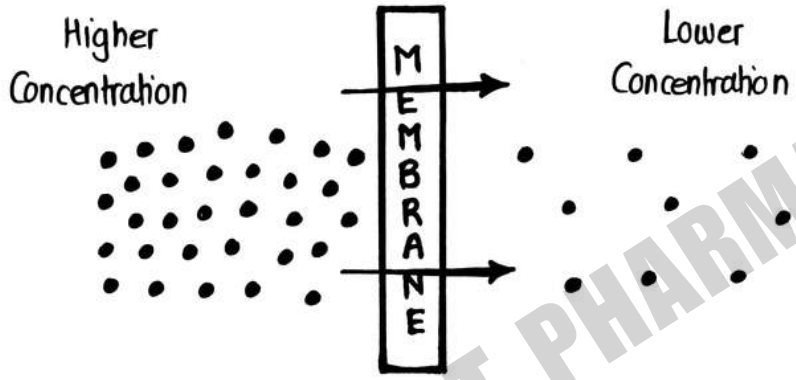
Mechanism Of Drug Absorption Through GIT

- Drug absorption through the gastrointestinal tract (GIT) primarily refers to how a drug moves from the site of administration into the systemic circulation :
- It involves following mechanism :

① Passive Diffusion
② Facilitated Diffusion
③ Active Transport
④ Pore Transport / Filtration
⑤ Ion Pair Transport
⑥ Endocytosis

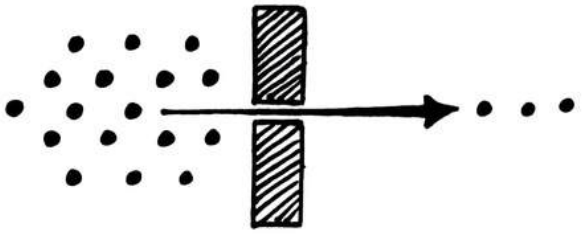
① PASSIVE DIFFUSION

- Passive Diffusion is the process by which drugs moves across a membrane from an area of high concentration to the area of low concentration.
- The movement is driven by Concentration Gradient.
- This is the most important mechanism for majority of drugs.
- The movement continues until equillibrium reached.
- It depends on factors like drugs lipophilicity and molecular size.



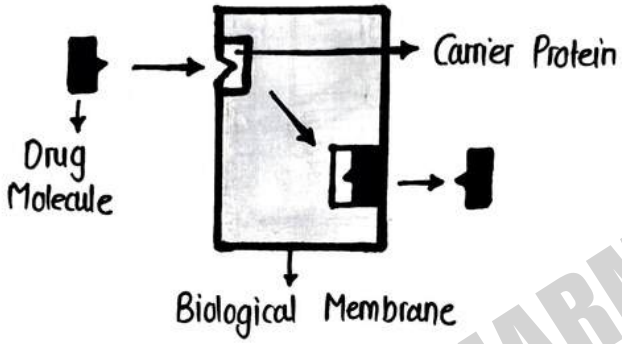
② PORE TRANSPORT

- It is also known as Filtration.
- Pore transport is a mechanism of drug movement wher drug molecules transport through aqueous pores or channels in the cell membrane.
- Through Filtration, Lipid Insoluble drugs can also cross biological membranes but their size should be small



③ FACILITATED DIFFUSION

- It is similar to Passive Diffusion but requires some specific carrier proteins.
- It is also known as Carrier Mediated Transport.
- This process does not require energy and relies on the concentration gradient of the drug.
- This mechanism is crucial for larger or less lipophilic molecules.



④ ACTIVE TRANSPORT

- In Active Transport drug moves against the concentration gradient (i.e., from low concentration to high concentration).
- In this energy is required in the form of ATP and it also needs carrier proteins.

⑤ ION PAIR TRANSPORT

- Ion pair transport is a mechanism of drug transport in which drugs are transported across cell membrane as part of a paired complex with an ~~ion~~ endogenous ion.
- It particularly relevant for drugs that are poorly soluble and have low membrane permeability.

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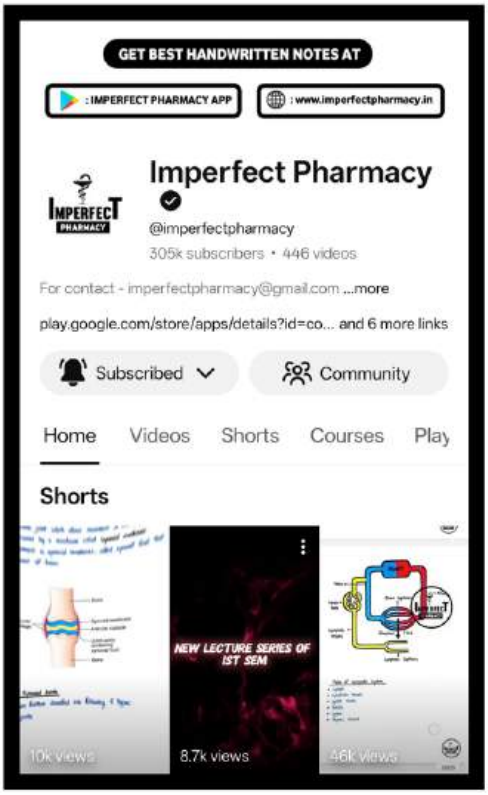

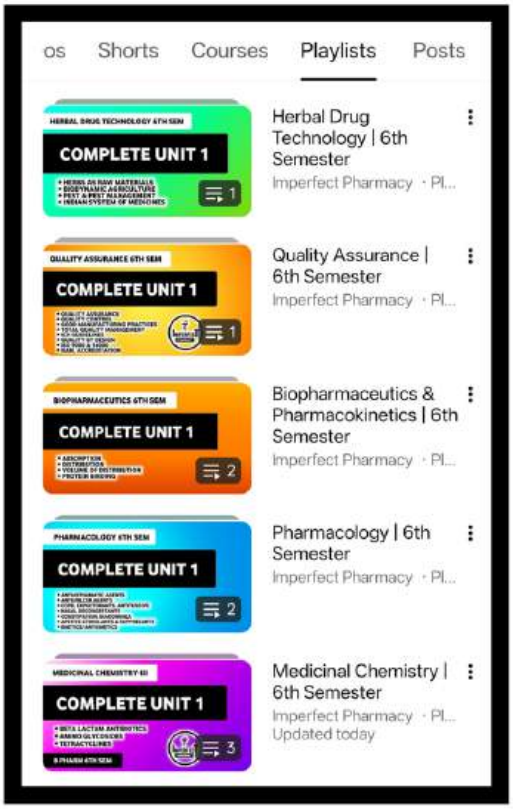

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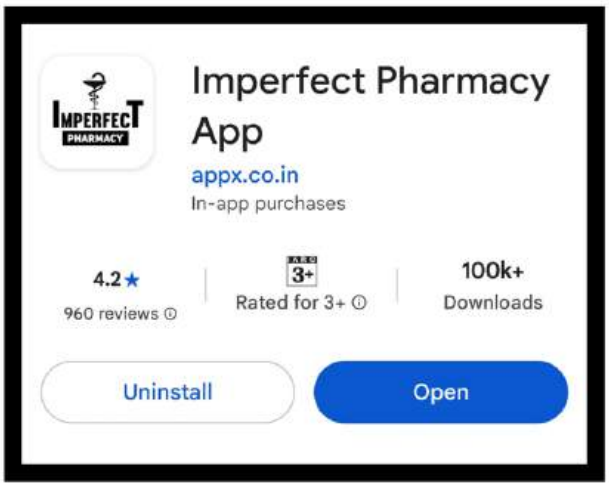
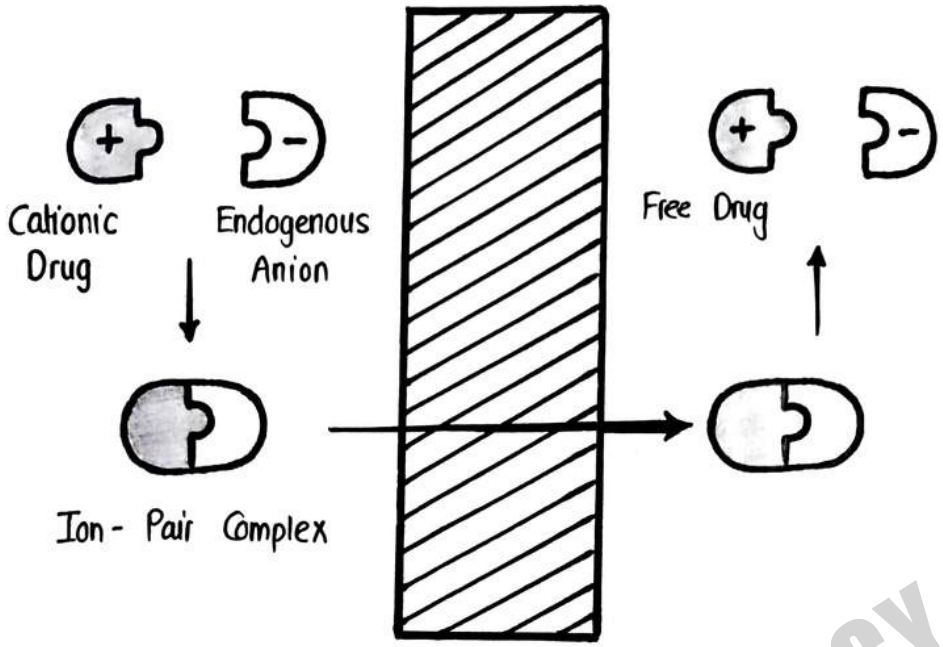
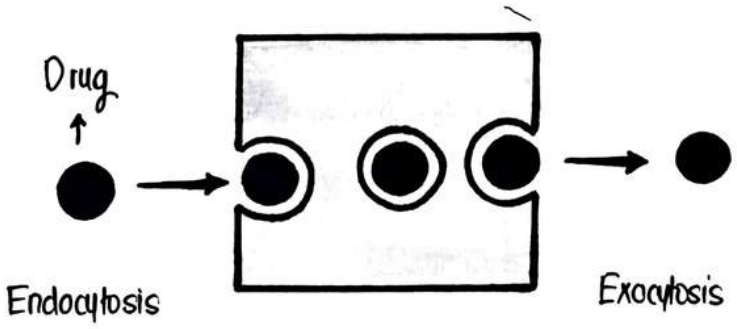




⑥ ENDOCYTOSIS

- It is also known as 'Vessicular Transport'
- Endocytosis is a process where a cell engulf substances from its surroundings by wrapping them in its cell membrane and forming a vessicle
- It is of two types

ⓐ Phagocytosis (Engulfment of Solid Particles)
ⓑ Pinocytosis (Engulfment of Liquid Particles)



FACTORS AFFECTING DRUG ABSORPTION

Drug Absorption is influenced by various factors as follows:

① Physicochemical Factors
② Physiological Factors
③ Pharmaceutical Factors

① PHYSICOCHEMICAL FACTORS

These relate to drug's physical & chemical properties. It includes:

- Solubility
- Drug Ionization & pH
- Particle Size
- Drug Stability

① Solubility :
- Drug must dissolve in biological fluids before absorption.
- Lipophilic drugs (fat soluble) cross cell membranes easily
- Hydrophilic drugs (water soluble) requires specific carrier proteins.

② Drug Ionization & pH :
- Most drugs are weak acids or weak bases
- Non-ionized drugs are more lipid soluble and easily absorbed.
- Ionized drugs are water soluble & less absorbed.

③ Particle Size :
- Smaller particles dissolve faster and absorbed more quickly.

④ Drug Stability : • Some drugs degrade in acidic environments.
• Enteric coatings help protect acid-sensitive drugs.

② PHYSIOLOGICAL FACTORS

These are biological factors that influence drug absorption.

- Gastric Emptying
- Surface Area
- First Pass Metabolism

ⓐ Gastric Emptying : • Fast gastric emptying leads to faster absorption.
• Slow gastric emptying leads to delayed absorption.

ⓑ Surface Area : • The small Intestine has a large surface area, making it the primary site for drug absorption.

ⓒ First Pass Metabolism : • Some drugs are metabolised in the liver before reaching systemic circulation, reducing Bioavailibility.

③ PHARMACEUTICAL FACTORS

These factors depend on drug formulation and route of administration.

- Dosage form
- Route of Administration
- Drug Interactions.

ⓐ **Dosage Form :** • Liquid forms absorbed faster than solid forms

ⓑ **Route of Administration :** • Oral : Most common but involves first-Pass Metabolism
- Sublingual : Avoids first pass metabolism
- Parenteral : Bypasses Absorption barriers
- Topical : Depends on Skin Permeability

ⓒ **Drug Interaction :** • Presence of other drugs can also affect absorption efficiency.

Absorption Of Drug From Non Per Oral Extra Vascular Routes

- Absorption from non per oral extravascular to the process by which a drug administered outside the gastrointestinal tract (excluding the oral route).
- There are non per oral extravascular routes :

① Intramuscular (IM) Route
② Subcutaneous (SC) Route
③ Transdermal (Topical) Route
④ Inhalation Route
⑤ Rectal Route
⑥ Vaginal Route
⑦ Ocular Route

① Intramuscular (IM) Routes

- Drug is injected deep into a large muscle (e.g. deltoid, gluteus).
- Absorbed into systemic circulation through capillary present in muscle tissues.
- Increased blood flow (e.g. during exercise) enhances absorption.
- Aqeous solutions absorbs faster than oily or depot preparations.
- Large volume may reduce absorption efficacy.
- It's little Painful & Requires trained personnel.

ⓑ Subcutaneous (SC) Route

- Drug is injected into fatty larger layer beneath the skin (eg. upper arm, abdomen, thigh).
- Drug absorb through lymphatic and capillary vessels into systemic circulation.
- Absorbtiop is slower than IM due to less blood supply.
- Massage or heat can increase absorption.
- Solution from absorb faster than suspensions or implants.
- Suitable for self-administration (e.g. insulin).
- Provides slow, sustained absorption.
- Less painful than IM.

© Transdermal (Topical) Routes

- In this Drug applied on the skin surface for systemic effect via skin absorption (e.g. patches).
- Drug penetrates stratum corneum (outermost skin layer), then into dermis and enters systemic capillaries.
- More lipid-soluble drugs absorb better.
- Broken or inflammed skin increases absorption.
- Provides sustained and controlled release (e.g. fentanyl, nicotine)
- Avoid first-pass metabolism.

ⓓ Inhalation Route

- Drugs are administered in gaseous or aerosol form via mouth or nose (e.g. Salbutamol, Anesthetic gases).
- Absorbed rapidly through the thin alveolar membrane into pulmonary capillaries.
- Asthma, infections can affect absorption.
- Deep and slow inhalation improves delivery.
- Very rapid onset (due to large surface area and high viscosity).

ⓔ Rectal Route

- Drugs are administered in the rectum as suppositories or enemas.
- Absorbed through rectal mucosa.
- Suppository base Affects melting and drug release.
- Useful when oral route is not possible (vomiting, unconcious).
- Although this route this inconvenient and can patient discomfort.
- Risk of mucosal irritation.

ⓕ Vaginal Route

- Drugs administered via vaginal suppositories, tablets, or creams.
- Drug absorb through vaginal epithellium into systemic circulation or local tissue.
- Harmonal changes may alter absorption.
- Formulation base affects drug release.
- Having limited patient acceptability.

⑧ Ocular Route

- Drugs applied as eye drops, ointments or inserts.
- Use mostly for local effect.
- Blinking and tearing can wash away drug.
- Higher viscousity improves retention.

DISTRIBUTION

- Distribution refers to the process by which a drug, after being absorbed into the bloodstream, transported to various tissues and organs in the body.
- It determines where the drug goes, how much reaches the target site and how long it stays in the body.

FACTORS AFFECTING DRUG DISTRIBUTION

There are various factors that affect Drug distribution as follows:

- Blood Flow To Tissues
- Plasma Protein Binding
- Lipid Solubility of Drug
- Tissue Permeability
- Volume of Distribution

① Blood Flow To Tissues

- Organs with high blood flow (e.g., liver, kidneys, Brain) receive drugs faster compare to those with low blood flow (e.g., fat, skin, muscle).

② Plasma Protein Binding

- Drugs in the blood binds to plasma proteins.
- Now only the free drug is available for distribution to various tissues.
- Highly protein bound drugs have limited distribution.

③ Lipid Solubility Of Drugs

- Lipophilic drugs easily cross cell membranes and accumulate in tissues.
- Hydrophilic drugs stay mostly in the blood and extracellular fluid.

④ Tissue Permeability

- Highly permeable tissues (e.g., liver, kidney) allow drugs to pass easily.
- Barriers like Blood-Brain Barrier (BBB) or placental barrier limit drug entry.

⑤ Volume Of Distribution (Vd)

- Vd is a pharmacokinetic parameter that describes how widely a drug is distributed in body fluids and tissues.
- High Vd : Drug is widely distributed in tissues.
- Low Vd : Drug stays mainly in the blood.

VOLUME OF DISTRIBUTION

- The apparent volume of distribution (V_d) is a theoretical pharmacokinetic parameter that describes the extent to which a drug distributes throughout the body relative to its concentration in plasma.
- It does not represent a real physiological volume but rather an indication of how widely a drug spreads in body tissues.

$$V_d = \frac{\text{Dose Administered (IU)}}{\text{Plasma Concentration}}$$

Tissue Permeability Of Drugs

- Tissue permeability describes how easily a drug molecule can pass from the bloodstream into the instestinal or interacellular fluid of tissues.
- It is influenced by the drug's physiochemical properties and the characteristics of the tissue or membrane barrier.

Factors Affectng Tissue Permeability

ⓐ Physiochemical properties of Drug

- Molecular size : Smaller molecules pass more easily through membranes.
- Lipid solubility (Lipophilicity) : Lipid-soluble drugs diffuse readily through lipid layers of cell membranes.
- Ionization (pKa) : Non ionized (uncharged) drugs penetrate membranes more easily than ionized form.
- Polarity : Non-polar molecules cross lipid membranes more efficiently than poler ones.

ⓑ Characterstics of the Tissue

- Perfusion rate : Highly perfused tissue (e.g. liver, kidney, brain) recieved drugs more quickly.
- Membrane Composition : Tissues with tight junctions (e.g. blood-brain barrier) select drug permeability.
- Presence of transporters : Active or Facilliated transport proteins can enhance or limit drug entry.

Protien Binding Of Drugs

- After administration, drugs may bind to plasma proteins or tissue proteins.
- Only the free (unbound) form of drugs is pharmacologically active.

Types Of Protein Binding

It is mainly of two types:

① Plasma - Protein Binding
② Tissue Drugs Binding

Plasma - Protein Binding

- Plasma - proteins binding refers to the reversible interaction b/w drug molecules and proteins present in the plasma.
- Only the unbound (free) drug is pharmacologically active and can:
  - Cross membranes
  - Exert therapeutic effects
  - Be metabolized or excreted

Nature Of Binding

- Reversible and non- covalent (via -hydrogen bonds van der Waals forces, ionic interaction)
- Form a dynamic equilibrium: Drug + Protien ⇌ Drug - Protein complex
- Acts as a drug reservoir that maintains plasma concentration over time.

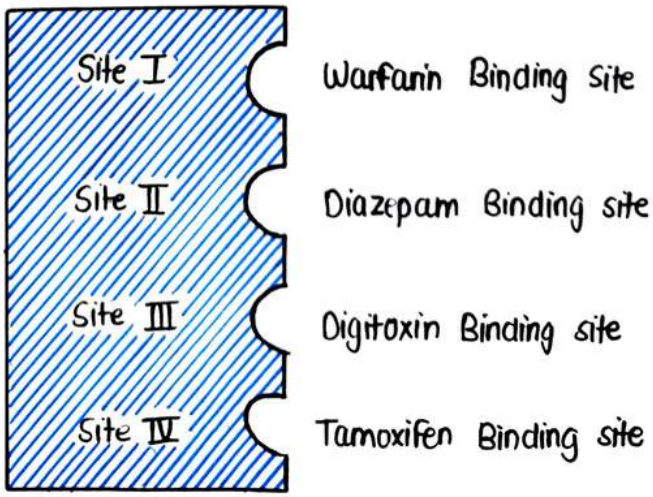
Types Of Plasma Protien

There are mainly 4 types of Plasma Proteins involve in binding:

1. Albumin
2. Globulin
3. α1 Acid Glycoprotein
4. Lipoprotein

① Albumin

- Most abundant plasma protein (3.5 - 5 g/dL)
- Synthesized in the liver.
- Binds acidic and neutral drugs
- Example : Warfarin, Phenytoin, Diazepam.
- Binding is reversible via hydrogen bonds and van der walls forces.
- Has 4 major drug - binding sites :
  - Site I (Warfarin site)
  - Site II (Benzodiazepene site)
  - Site III Digixin Site)
  - Site IV (Tamoxifen site)



ⓑ GLOBULIN

- Includes alpha, beta and gamma globulins.
- Bind hormones, metals and specific molecules.
- Thyroxine binds to TBG (thyroxine-binding globulin).
- Estrogens and testosterone binds to SBHG (Sex hormone-binding globulin).
- Levels change in endocrine disorders, pregnancy or with hormone therapy.

ⓒ α1-ACID GLYCOPROTIEN (AAG)

- Bind basic (positively charged) drugs.
- Synthesized in liver; found in low amounts (~0.4 – 1.2 mg/mL).
- Has one high-affinity site.
- Examples: Propanolol, lidocaine, Imipramine, Morphine.
- Levels increase in critically ill pateints → Lower free drug availability.

ⓓ LIPOPROTEINS

- Transport lipids like cholesterol and triglycerides.
- Bind highly lipophillic (fat-soluble) drugs.
- Types included VLDL, LDL and HDL.
- Examples: Cyclosporine, Tacrolimus, Amphotericin B, Propofol.
- In hyperlipidemia, lipoprotein levels rise → more drug binding.

TISSUE DRUG BINDING

- Tissue drug binding refers to the reversible binding of drug to tissue components (like proteins, lipids or structural elements) after it leaves the bloodstream and enters body tissues (like liver, kidneys, muscle, fat etc.)
- Tissue drug binding occurs in various tissues such as:
  - Fat tissue (Adipose)
  - Muscles
  - Organs like liver, kidney, lungs
  - Bones (for drugs with high affinity for calcium).
  - Melanin rich tissues (like eyes)

MECHANISM OF BINDING

- Non covalent and reversible interactions — mainly via hydrogen bonding, van der walls forces or ionic bonds.
- Drugs binds to tissue components such as:
  - Structural Proteins (like collagen)
  - Lipoproteins
  - Mitochondrial components
  - Phospholipids in cell membranes

EXAMPLE

- Thiopental - binds to fat; Rapid redistribution causes short anesthesia.
- Tetracyclines - binds to calcium in bones and teeth.
- Chloroquine - binds to melanin in eyes, can cause retinopathy.

FACTORS AFFECTING PROTIEN BINDING OF DRUGS

- Drug molecules can reversibly bind to proteins found in plasma like albumin and α1 - glycoprotein acid) and tissues (like muscle, fat, and organ proteins).
- This binding significantly influences the drug's distribution, free concentration, efficacy, duration of action, metabolism, and excretion.
- Only the unbound (free) drug is pharmacologically active.

- Below are the key combined factors that affect protein binding of drugs :

① PHYSIOCHEMICAL PROPERTIES OF DRUG

- Affinity for proteins : Drugs with higher affinity will bind more extensively to plasma or tissue proteins.
- Lipophilicity : Lipophilic drugs bind strongly to both plasma lipoproteins and tissue components, especially fat.
- Ionization and pKa : The ionization state of a drug (affected by body pH) influences how it binds to proteins and penetrates tissues.
- Moleculer size and structure : Larger or more complex drugs may have more binding sites and stronger binding.

② Concentration Of Drug And Binding Proteins

- Drug Concentration: When the binding sites are saturated (especially at high drug concentrations), more free drug becomes available in plasma or tissues.
- Protein Concentration: Low levels of plasma proteins (e.g. albumin or α1-acid glycoprotein) or tissue proteins reduce binding, increasing free drug levels.

③ Type And Nature Of Proteins

ⓐ Plasma proteins:

- Albumin: Binds mainly acidic and neutral drugs.
- α1-acid glycoproteins: Binds mainly basic drugs.
- Lipoproteins: Bindl Highly lipophilic drugs.

ⓑ Tissue proteins:

- Include structural proteins, enzymes, and cell membrane components that can bind drugs → especially in liver, kidneys, fat and musde.

④ Drug Interactions

- Competitive Binding: When two drugs have affinity for the same binding site, one can displace the other, increasing the free concentration of the displace drug.
- Endogeneous Substances: Substances like bilirubin, urea, and fatty acids can also complete for binding sites, especially in pathological conditions.

⑤ Physiological And Pathological Conditions

- Age : Neonates have lower albumin and immature tissue proteins, leading to reduced binding.
  Elederly may have altered protein levels and drug metabolism.
- Liver disease : Reduces synthesis of albumin and other proteins, decreasing plasma binding.
- Kidney disease : Accumulation of waste products can iterfare with binding.
- Inflammation / Trauma : Increases α1- acid glycoprotein, which can enhance binding of basic drugs.
- Malnutrition : Leads to lower plasma protein levels, affecting binding.
- Obesity : Increases fat tissues, which may enhance tissue binding of lipophilic drugs.

⑥ Tissue Characteristics

- Perfusion (blood flow) : Well- perfused tissues (liver, kidney) get more drug and potentially more binding.
- Binding site availability : Some tissues have more abundant proteins or cellular targets.
- Fat content : Lipophillic drugs can accumulate and bind in adipose tissue, prolonging drug action.
- pH differences : Variations in pH between blood and tissues can lead to ion trapping, altering tissue binding.

KINETICS OF PROTIEN DRUG BINDING

- Kinetics of Protein-drug binding refers to the study of the rate at which a drug binds to and dissociate from its target protein.
- This process is characterized by two main parameters :

① **ASSOCIATION RATE CONSTANT**

This describes how quickly the drug (D) binds to the protein (P) to form a drug - protein complex (PD).

$$P + D \longrightarrow PD$$

② **DISSOCIATION RATE CONSTANT**

This describes how quickly the drug protein complex dissociates back into free drug & protein.

$$PD \longrightarrow P + D$$

Now let's apply law of mass action an association rate constant

$$P + D \longrightarrow PD$$

$$ka = \frac{[PD]}{[P][D]}$$

or we can write $[PD] = ka\,[P][D]$ ..... ①

Here, [P] = Concentration of free protein , [PD] = Concentration of Protein Drug complex
[D] = Concentration of free Drug
ka = Association Rate constant

- Now If P_T is the total number of protein present, both bound & Unbound, then

$$P_T = [PD] + [P] \quad \text{..... (2)}$$

- Now If r is number of moles of drug bound to total number of proteins, then

$$r = \frac{[PD]}{P_T}$$

$$r = \frac{[PD]}{[PD]+[P]} \quad \text{..... from eq. (2)}$$

$$r = \frac{ka[P][D]}{ka[P][D] + [P]}$$

$$r = \frac{\cancel{[P]}\, ka[D]}{\cancel{[P]}\,(ka[D] + 1)}$$

$$r = \frac{ka[D]}{ka[D] + 1}$$

- The above equation holds when there is only one binding site on protein, if more than 1 or N number of binding sites are available, then :

$$\boxed{r = \frac{Nka[D]}{ka[D]+1}}$$

Clinical Significance Of Protien Drug Binding

- Protein drug binding refers to the reversible interaction between a drug and plasma proteins (mainly albumin, α_1 - acid glycoprotein and lipoproteins) in the blood.
- This interaction significantly influences the drug's distribution, pharmacological activity, metabolism and excretion.

① Drug Distribution And Storage

- Only free (unbound) drug molecules are pharmacologically active and can cross cell membranes to reach target tissues.
- Bound drugs are temporarily inactive, serving as reservoir that maintains plasma drug levels.

Clinical Significance :

- Highly protein - bound drugs have a longer duration of action.
- Drug release from protein - binding sites sustains therapeutic levels over time.

② Pharmacological Activity

- The free drug concentration determines the intensity and duration of a drug's effect.
- Binding reduces the immediate pharmacologic effect since only free drug is active.

Clinical Significance :

- Altered protein binding can lead to toxicity or therapeutic failure if not monitored.

③ Drug - Drug Interactions

- Two drugs that are highly protein- bound may compete for bonding sites.
- One drug may displace another, increasing the free concentration of the displace the drug.

Clinical Significance :

- Risk of toxicity with drugs having a narrow therapeutic index (e.g. warfarin, phenytoin).

④ Metabolism And Elimination

- Only free drugs are filtered by the kidney's and metabolized by liver.
- Protein - bound drugs are protected from immidiate elimination.

Clinical Significance :

- High protein binding prolongs half - life and reduces clearance.

⑤ Disease States Affecting Protein Binding

- Liver disease, Kidney disease, Malnutrition, and burns can reduce plasma protein levels.
- This increases the free drug concentration, potentially enhancing drug effect or causing toxicity.

Clinical Significance :

- Dose adjustment is often needed in such conditions.

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