FirstHope Notes | B.Pharm Semester 4

General Pharmacology

Introduction to Pharmacology

Definition of Pharmacology

- Pharmacology is the branch of science that deals with the study of drugs, including their origin, nature, properties, actions, and effects on living organisms.
- It is primarily divided into two major branches:
    - **Pharmacodynamics** – What the drug does to the body (mechanism of action, therapeutic effect).
    - **Pharmacokinetics** – What the body does to the drug (absorption, distribution, metabolism, excretion).
- Pharmacology helps to understand the interaction between drugs and biological systems, guiding therapeutic applications and safety considerations.

Pharmacokinetics (PK)

- Pharmacokinetics is the study of what the body does to the drug.
- It involves the movement of drugs through the body and is typically divided into four key processes:
    1. **Absorption**
    2. **Distribution**
    3. **Metabolism (Biotransformation)**
    4. **Excretion**
- These processes determine the onset, intensity, and duration of a drug's action.

Historical Landmarks in Pharmacology

- Pharmacology has evolved from traditional herbal remedies to a highly scientific discipline.
- Here are important historical milestones:
    1. **Ancient Era:**
        - Early use of medicinal plants and minerals in civilizations such as Egypt, India (Ayurveda), China (Traditional Chinese Medicine), and Greece.
    2. **Dioscorides (1st Century):**
        - Authored *De Materia Medica*, cataloging medicinal substances from nature.
    3. **Paracelsus (16th Century):**

- Introduced the principle "the dose makes the poison," emphasizing dose-response relationships.

4. **18th–19th Century:**
   - Isolation of active principles like morphine (from opium), quinine (from cinchona bark), and digitalis (from foxglove).
5. **20th Century:**
   - Discovery of antibiotics (e.g., penicillin by Alexander Fleming in 1928).
   - Development of vaccines, anesthetics, and chemotherapeutic agents.
   - Establishment of pharmacology as an experimental and clinical science.
6. **Modern Era:**
   - Introduction of biotechnology, genetic engineering, targeted therapy, and pharmacogenomics.

Scope of Pharmacology

- Pharmacology intersects with multiple disciplines:
  - **Pharmacognosy:** Study of drugs derived from natural sources (plants, animals, minerals).
  - **Pharmaceutics:** Formulation and dispensing of drugs.
  - **Pharmacokinetics and Pharmacodynamics:** Essential sub-disciplines focusing on how the body handles drugs and how drugs act on the body.
  - **Toxicology:** Study of harmful effects of chemicals on living organisms.
  - **Clinical Pharmacology:** Application of pharmacological principles in the clinical setting.
  - **Pharmacovigilance:** Monitoring and evaluating drug safety post-marketing.
- The ultimate scope is to improve the use of drugs to optimize therapeutic outcomes and minimize adverse effects.

Importance:

- Development of safer and more effective drugs.
- Rational and evidence-based drug therapy.
- Regulation and monitoring of drug use.

Nature of Drugs

Definition of a Drug:

- A drug is any substance (natural or synthetic) that, when administered to a living organism, produces a biological effect.
- Drugs are used for diagnosis, prevention, treatment, or cure of diseases.

Chemical Nature of Drugs

1. Organic vs. Inorganic

- **Organic**: Most drugs are organic compounds (carbon-based), often containing nitrogen, oxygen, sulfur.
- **Inorganic**: Some drugs are made of metal ions or salts (e.g., lithium carbonate, magnesium sulfate).

2. Acids and Bases

- Most drugs are weak acids or weak bases.
- Their ionization affects absorption, distribution, and excretion.
- Ionized (charged) drugs are water-soluble but poorly lipid-soluble → poor absorption.
- Non-ionized (uncharged) drugs are lipid-soluble → better absorption.

3. Physical States

- Drugs may exist as:
  - **Solids**: Tablets, capsules, powders.
  - **Liquids**: Syrups, emulsions.
  - **Gases or volatile liquids**: Anesthetics like nitrous oxide.

4. Stereoisomerism

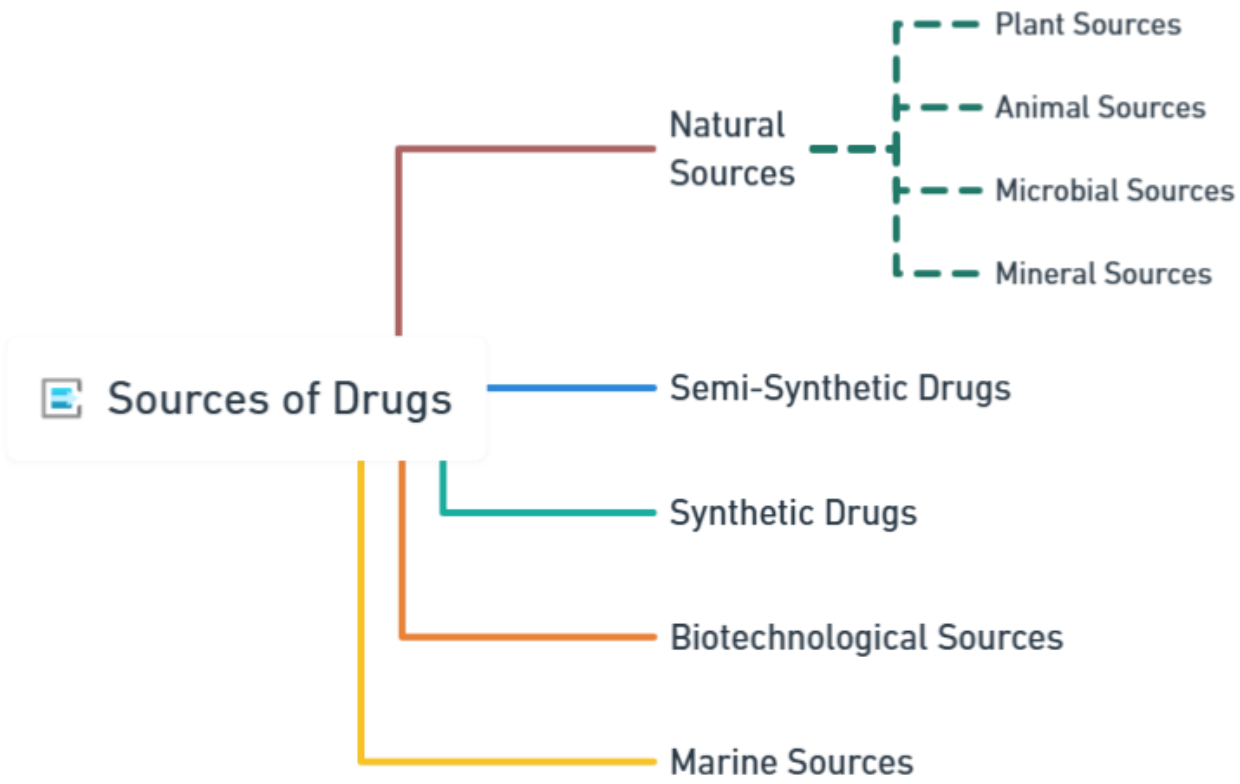
- Some drugs have optical isomers (enantiomers) with different biological activities.
- Example: L-isomer of propranolol is active; D-isomer is less active.

5. Prodrugs

- Inactive compounds that become active after metabolic conversion inside the body.
- Example: Enalapril (inactive) → Enalaprilat (active).

Source of Drugs

- Drugs can be obtained from various natural, semi-synthetic, synthetic, and biotechnological sources.



1. Natural Sources

➢ These are substances directly obtained from **nature** – plants, animals, microorganisms, or minerals.

A. Plant Sources

- Many traditional and modern medicines originate from plants.
- Parts used: leaves, bark, roots, seeds, flowers.
- **Examples**:
  - Morphine – Opium poppy (*Papaver somniferum*)
  - Atropine – Belladonna plant (*Atropa belladonna*)
  - Quinine – Cinchona bark
  - Digoxin – Foxglove plant (*Digitalis purpurea*)

B. Animal Sources

- Some drugs are extracted from animal tissues, fluids, or hormones.
- **Examples**:
  - Insulin – Pancreas of pigs or cattle (now replaced by recombinant insulin)
  - Heparin – Intestinal mucosa of pigs

- Thyroid extract – From animal thyroid glands

C. Microbial Sources

- Antibiotics and other drugs produced by bacteria and fungi.
- **Examples**:
  - Penicillin – *Penicillium notatum*
  - Streptomycin – *Streptomyces griseus*
  - Erythromycin – *Streptomyces erythraeus*

D. Mineral Sources

- Drugs derived from inorganic minerals.
- **Examples**:
  - Magnesium sulfate – Used as a laxative and anticonvulsant.
  - Iron – For treating anemia.
  - Lithium – Mood stabilizer in bipolar disorder.

2. Semi-Synthetic Drugs

- These are natural substances that have been chemically modified to enhance properties such as efficacy, stability, or safety.
- **Examples**:
  - Ampicillin – Modified from penicillin.
  - Heroin – Derived from morphine.
  - Hydrocortisone – From natural cortisol.

3. Synthetic Drugs

- Entirely man-made using chemical synthesis in laboratories.
- Allows precise control over drug structure and properties.
- Often cheaper and more stable than natural sources.
- **Examples**:
  - Paracetamol (acetaminophen)
  - Omeprazole
  - Sulfonamides
  - Benzodiazepines

4. Biotechnological Sources (Recombinant DNA Technology)

- Use of genetic engineering, cell cultures, or recombinant DNA to produce complex biologics.

- Allows for the production of human-identical proteins and hormones.
- **Examples**:
  - Recombinant insulin (human insulin) – Produced by inserting human insulin gene into *E. coli*.
  - Erythropoietin – Stimulates red blood cell production in anemia.
  - Monoclonal antibodies – For autoimmune diseases and cancers.

5. Marine Sources

- A growing area of pharmacology, drugs are isolated from marine organisms like sponges, algae, and sea snails.
- **Examples**:
  - Ziconotide – From cone snail venom (used for chronic pain).
  - Trabectedin – From sea squirt, used in cancer treatment.

Essential Drugs Concept

Definition

- Essential drugs (or essential medicines) are those that:
  - Satisfy the priority health care needs of the population.
  - Should be available at all times, in adequate amounts, appropriate dosage forms, with assured quality and affordable cost.

WHO Model List of Essential Medicines (EML)

- First published in 1977 with 208 drugs.
- Updated every 2 years by WHO experts.
- Divided into two categories:
  - **Core List**: Minimum medicines needed for a basic healthcare system.
  - **Complementary List**: Drugs for more specialized or complex situations (e.g., cancer, rare diseases).

Examples from the WHO list:

- Paracetamol – for pain and fever
- Amoxicillin – antibiotic
- Metformin – for diabetes
- Salbutamol – for asthma
- ORS (Oral Rehydration Salts) – for diarrhea

Criteria for Selection

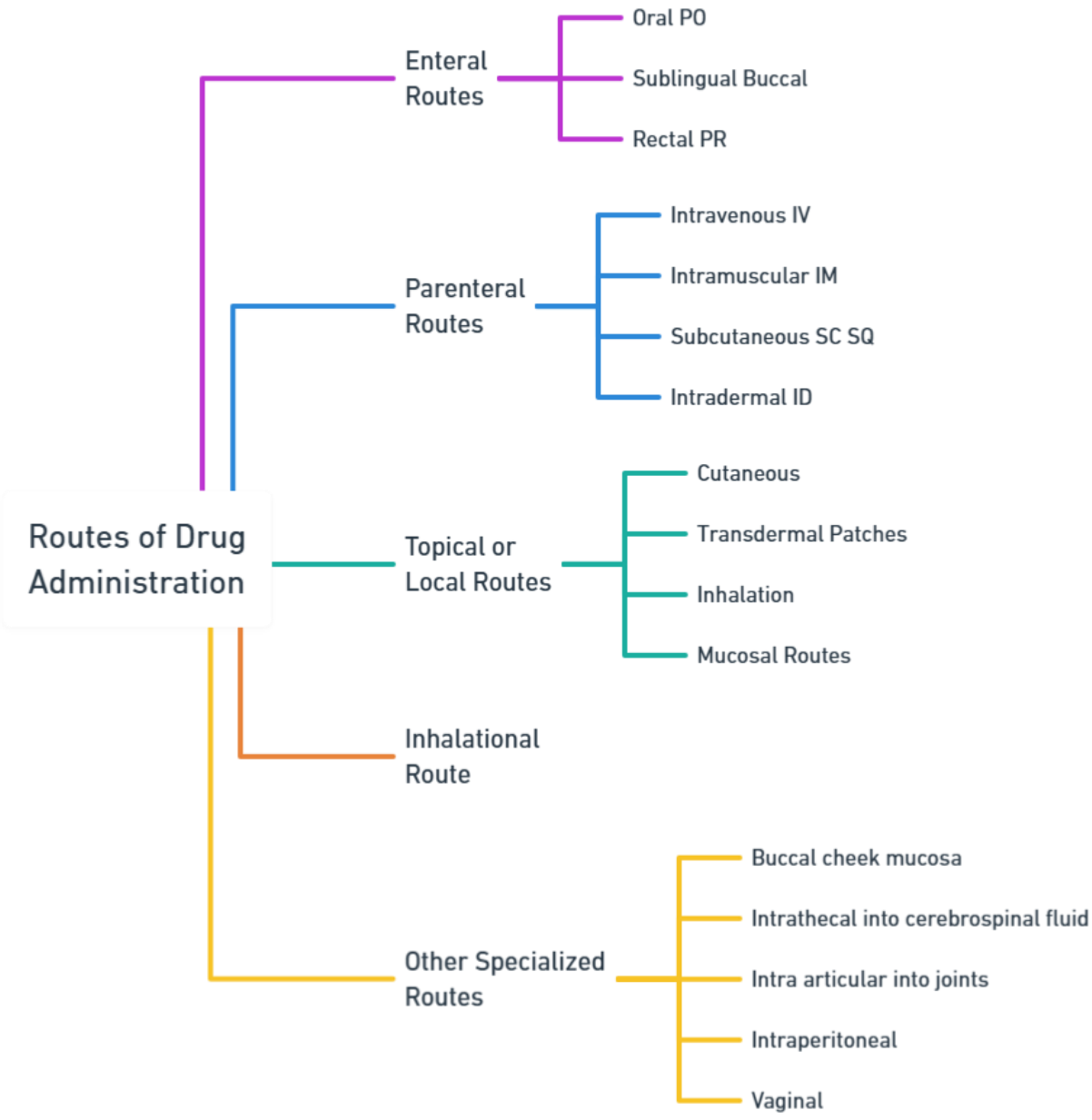
- Public health relevance.
- Efficacy and safety.
- Cost-effectiveness.
- Scientific evidence.

Benefits

- Promotes rational use of drugs.
- Ensures accessibility and affordability.
- Helps in budget planning and procurement by governments and health organizations.

Routes of Drug Administration

- The route of administration affects the **onset, intensity, and duration** of drug action.



A. Enteral Routes

1. **Oral (PO):**
   - Most common, safest, and convenient route.
   - Subject to first-pass metabolism in the liver and variable absorption.
2. **Sublingual/Buccal:**
   - Absorbed through the oral mucosa (e.g., nitroglycerin).
   - Avoids first-pass metabolism.
3. **Rectal (PR):**
   - Partially avoids first-pass effect.
   - Useful when patients cannot take oral medications (unconscious, vomiting).

B. Parenteral Routes

1. **Intravenous (IV):**
   - Delivers drug directly into the bloodstream.
   - Rapid onset, 100% bioavailability.
   - Higher risk of adverse reactions.
2. **Intramuscular (IM):**
   - Injected into muscle (e.g., deltoid, gluteus).
   - Absorption depends on blood flow to the muscle.
3. **Subcutaneous (SC/SQ):**
   - Injection into subcutaneous tissue (e.g., insulin administration).
   - Slower absorption compared to IM.
4. **Intradermal (ID):**
   - Injected into the dermis.
   - Example: skin testing for allergies, Mantoux test for TB.

C. Topical or Local Routes

1. **Cutaneous:**
   - Applied to the skin for local effect (creams, ointments).
2. **Transdermal Patches:**
   - Systemic effect through skin absorption (e.g., nicotine patch).
3. **Inhalation:**
   - Rapid absorption via the pulmonary route (e.g., bronchodilators, volatile anesthetics).

4. **Mucosal Routes:**
    - Drops for eye/ear/nasal issues.
    - Vaginal administration.

D. Inhalational Route

- Direct delivery to the lungs.
- Rapid onset.
- Useful for anesthetics and bronchodilators.

E. Other Specialized Routes

- Buccal (cheek mucosa)
- Intrathecal (into cerebrospinal fluid)
- Intra-articular (into joints)
- Intraperitoneal
- Vaginal, etc.

Factors influencing route selection:

- Desired speed of action.
- Site of action.
- Patient condition (conscious/unconscious).
- Drug properties (e.g., stability, solubility).

Agonists

Definition:

- An agonist is a drug (or any chemical) that binds to a receptor and activates it, producing a biological response.
- Agonists mimic the action of endogenous (natural) ligands like hormones or neurotransmitters.

Types of Agonists:

1. Full Agonist:

- Produces maximum possible response when it binds to the receptor.
- **Example**: Morphine (a full opioid receptor agonist).

2. Partial Agonist:

- Produces a less than maximal response even if all receptors are occupied.
- **Example**: Buprenorphine (partial agonist at opioid receptors).

3. Inverse Agonist:

- Binds to the same receptor as an agonist but produces the opposite effect.
- **Example**: Beta-carbolines at GABA-A receptors.

Antagonists

Definition:

- An antagonist is a drug that binds to a receptor without activating it.
- It blocks the action of agonists (both drugs and endogenous substances).

Types of Antagonists:

1. Competitive Antagonist:

- Binds reversibly to the same site as the agonist on the receptor.
- Competes with the agonist for binding.
- The effect of a competitive antagonist can be overcome by increasing the concentration of the agonist.
- **Example:** Naloxone competes with opioids at opioid receptors.

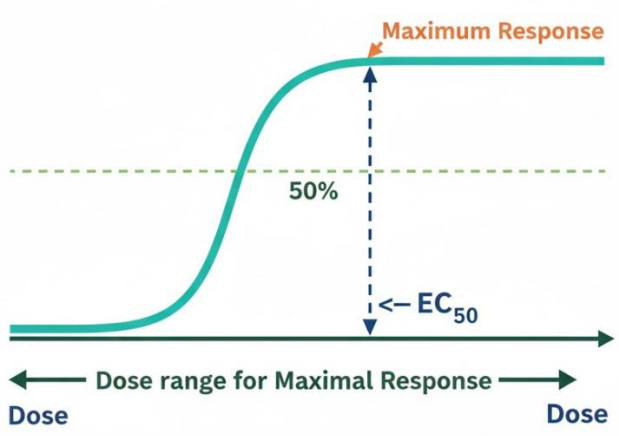
2. Non-competitive Antagonist:

- Binds either irreversibly to the receptor or to a different (allosteric) site.
- Reduces the maximum response of the agonist, regardless of its concentration.
- **Example:** Phenoxybenzamine, an irreversible α-adrenergic blocker.

Spare Receptors

Definition:

- Spare receptors are receptors that are not required to be occupied by a drug to produce the maximum response.



Significance:

- A full response can be achieved even when only a small fraction of total receptors are occupied.
- This is due to signal amplification in certain receptor systems (especially those involving G-proteins and enzymes).

Implication:

- Presence of spare receptors increases sensitivity to agonists.
- It explains why low concentrations of a drug can sometimes still produce a full effect.

Addiction

Definition:

- Addiction is a chronic, relapsing disorder characterized by:
  - **Compulsive drug-seeking behavior**
  - **Loss of control** over drug use
  - **Continued use despite harm**
- It is mainly psychological and involves reward pathways in the brain (dopamine system).

Drugs Commonly Causing Addiction:

- Opioids (heroin, morphine)
- Nicotine
- Alcohol
- Cocaine
- Amphetamines

Addiction leads to **craving** and high risk of **relapse** even after long periods of abstinence.

Tolerance

Definition:

- Tolerance is a condition where increasing doses of a drug are required to produce the same effect previously achieved with a lower dose.

Types of Tolerance:

1. ### Pharmacokinetic Tolerance:
   - ➢ Due to increased drug metabolism (e.g., enzyme induction).

- **Example**: Barbiturates increase liver enzymes that metabolize drugs.

2. **Pharmacodynamic Tolerance:**
   - Due to cellular changes at the receptor level (e.g., receptor downregulation or desensitization).
3. **Cross Tolerance:**
   - Tolerance to one drug leads to tolerance to another **similar drug**.
   - **Example**: Tolerance to alcohol can lead to tolerance to benzodiazepines.

Dependence

Definition:

- Dependence is a state where the body has adapted to the presence of a drug, and withdrawal symptoms occur if the drug is stopped.

Types of Dependence:

1. **Physical Dependence:**
   - Withdrawal symptoms are physical (e.g., tremors, seizures).
   - **Example**: Withdrawal from alcohol or opioids.
2. **Psychological Dependence:**
   - Characterized by **craving** and emotional distress without the drug.
   - **Example**: Cocaine, cannabis.

Important Note:

- Dependence does not always mean addiction, though the two often coexist.

Tachyphylaxis

Definition:

- Tachyphylaxis is a rapid decrease in drug response after repeated administration in a short time.

Key Features:

- Occurs quickly (within minutes to hours).
- Further dosing does not restore the effect.

Mechanism:

- Possible depletion of neurotransmitter stores.

- Desensitization or inactivation of receptors.

Example:

- Ephedrine (indirect sympathomimetic): Causes tachyphylaxis due to depletion of norepinephrine.

Idiosyncrasy

Definition:

- Idiosyncrasy refers to an unusual or unexpected response to a drug that is:
  - **Unpredictable**
  - **Not dose-dependent**
  - **Often genetically determined**

Example:

- Primaquine can cause hemolysis in people with G6PD deficiency.
- Reaction may be harmless in most, but dangerous in susceptible individuals.

Allergy (Drug Hypersensitivity)

Definition:

- A drug allergy is an immune system-mediated adverse drug reaction.
- It can occur at low doses, is unpredictable, and is not related to the pharmacologic action of the drug.

Types of Hypersensitivity Reactions (Gell and Coombs classification):

1. **Type I (Immediate, IgE-mediated):**
   - Rapid onset (within minutes).
   - Examples: Anaphylaxis, urticaria.
   - Drugs: Penicillin, vaccines.
2. **Type II (Cytotoxic, IgG/IgM-mediated):**
   - Affects blood cells.
   - Example: Hemolytic anemia.
3. **Type III (Immune complex-mediated):**
   - Causes vasculitis, serum sickness.
   - Occurs after 1-3 weeks.

4. Type IV (Delayed, T-cell mediated):

- Occurs after 48–72 hours.
- Example: Contact dermatitis from topical drugs.

Management:

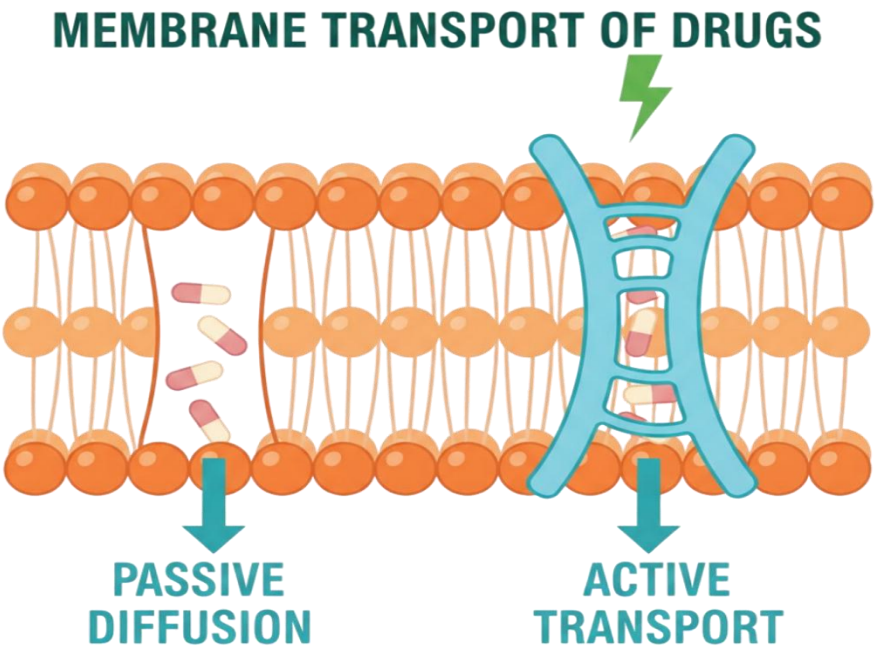
- **Avoidance** of the offending drug.
- **Antihistamines**, **corticosteroids**, or **epinephrine** (in case of anaphylaxis).

Pharmacokinetics

Membrane Transport of Drugs

- Understanding how drugs cross biological membranes is crucial to all processes of pharmacokinetics (ADME).
- Biological membranes are primarily **lipid bilayers** interspersed with proteins.

Several mechanisms allow drugs to traverse these membranes:



1. **Passive Diffusion**
   - Most common mechanism for many drugs.
   - Dependent on the concentration gradient (high → low).
   - Does not require energy.
   - Best suited for lipid-soluble (lipophilic) drugs that can easily pass through the hydrophobic core of the membrane.
   - **Rate is influenced by** lipid solubility, degree of ionization (pKa), molecular size, thickness of the membrane, and the area of absorption.
2. **Facilitated Diffusion**
   - Utilizes a **carrier protein** or a specific transporter embedded in the membrane.
   - Moves drugs **down** the concentration gradient (no direct energy required).
   - **Saturable** and subject to competition (different substances may use the same transporter).
3. **Active Transport**
   - Also uses carrier proteins but can move drugs against their concentration gradient.
   - Requires energy (ATP) directly or indirectly.

- Saturable and can be inhibited by substances competing for the same transporter.
- **Example**: transport of levodopa across the blood-brain barrier via amino acid transporters.

4. Endocytosis and Exocytosis

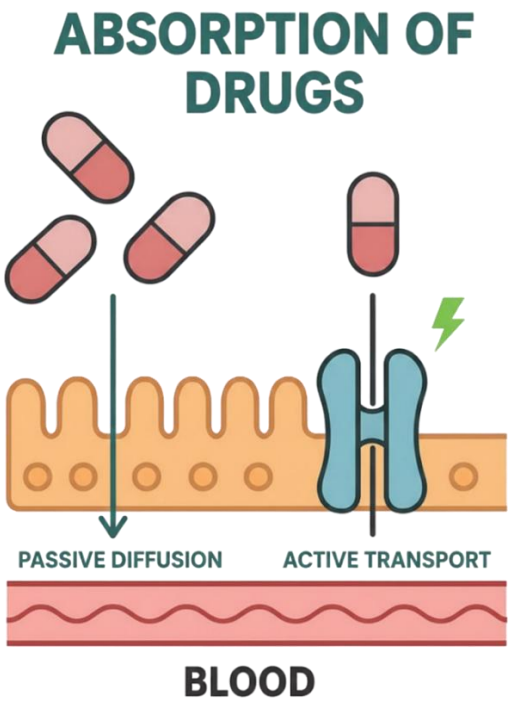
- **Endocytosis:** The cell membrane engulfs the drug particle (often larger molecules like protein drugs) forming a vesicle.
- **Exocytosis:** The vesicle fuses with the cell membrane to release its contents outside the cell.
- **Examples**: Vitamin B12 absorption in the gut involves receptor-mediated endocytosis.

5. Ion-Pair Transport

- Some highly ionized drugs can form neutral complexes (ion pairs) with endogenous substances that facilitate passive transport across membranes.

Absorption of Drugs

- **Absorption** refers to the process by which a drug enters the bloodstream from its site of administration.



Factors Affecting Absorption:

- **Route of Administration:** Oral, IV, IM, subcutaneous, transdermal, inhalational, etc.
  - IV route bypasses absorption as the drug is delivered directly into the bloodstream.
- **Physicochemical Properties of the Drug:**
  - Solubility (lipid vs. water solubility)
  - Stability in gastric pH

- Molecular size

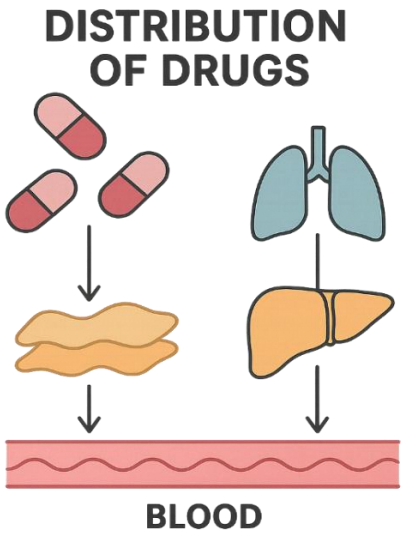
- **Formulation Factors:** Tablet vs. capsule, coatings, sustained-release formulations, etc.
- **Blood Flow at the Site of Administration:** Better blood flow → better absorption (e.g., deltoid muscle has faster absorption than gluteal).
- **Surface Area:** Larger surface area (e.g., small intestine) generally leads to higher absorption.
- **pH and Ionization:** Drugs are better absorbed in the part of the GI tract where they remain unionized. For instance, weak acids (like aspirin) are better absorbed in the more acidic stomach environment, though the majority of drug absorption still occurs in the small intestine due to its huge surface area.
- **First-Pass Effect (Hepatic Metabolism):** Some drugs are significantly metabolized in the liver (and/or gut wall) before reaching systemic circulation. This reduces bioavailability.

Bioavailability

- The **fraction** (percentage) of a dose that reaches systemic circulation in its **active** form.
- For IV drugs, bioavailability is 100%.
- For oral drugs, it can vary significantly depending on first-pass metabolism, solubility, stability in GI fluids, and more.

Distribution of Drugs

- Distribution is the reversible transfer of a drug from the bloodstream to various tissues and organs.
- Once absorbed, drugs distribute throughout the body, moving into different tissues and fluids.



Distribution depends on:

1. Blood Flow (Perfusion Rate)

- Organs with higher blood flow (brain, liver, kidneys) get drug supply more rapidly.
- Skeletal muscle, adipose tissue, and skin receive the drug more slowly.

2. Plasma Protein Binding

- Many drugs bind to **albumin** (acidic drugs) or **α1-acid glycoprotein** (basic drugs).
- Bound drugs are **not** free to exit capillaries or exert a pharmacological effect; only **unbound (free) drug** is active.
- Protein binding is reversible, and changes in binding (e.g., due to hypoalbuminemia, displacement by other drugs) can alter the free drug concentration.

3. Tissue Binding

- Drugs can accumulate in certain tissues (fat, bone, muscle) due to various affinities.
- **Example**: Tetracyclines accumulate in bones and teeth because they bind to calcium.

4. Specialized Barriers

- **Blood-Brain Barrier (BBB):** Tight junctions in the cerebral endothelium limit penetration to more lipophilic drugs or those using specific transport mechanisms.
- **Placental Barrier:** Less selective than the BBB, yet still restricts some drugs; many cross, so fetal drug exposure is a concern.

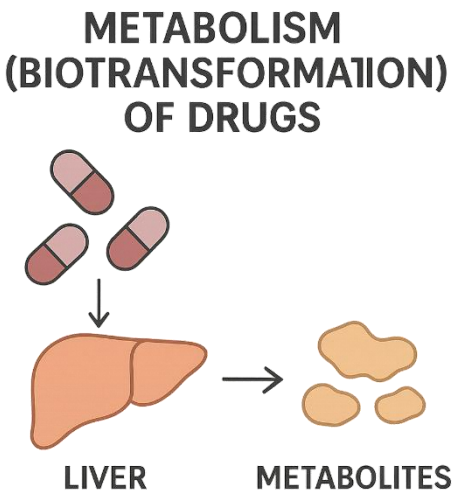
5. Volume of Distribution (Vd)

- A theoretical volume that relates the amount of drug in the body to the concentration of drug in the blood/plasma.
- If a drug has a high Vd, it indicates extensive distribution into tissues.
- A low Vd indicates the drug is largely contained in the vascular compartment.

Metabolism (Biotransformation) of Drugs

Definition:

- Metabolism is the process by which drugs are chemically altered (usually in the liver) to make them more water-soluble for excretion.



Sites:

- **Primary**: Liver (most important).
- **Others**: Kidney, lungs, intestines, plasma.

Phases of Metabolism:

Phase I (Functionalization reactions):

- **Reactions**: Oxidation, reduction, hydrolysis
- Introduce or expose a functional group (–OH, –NH2, –SH).
- **Enzymes**: Mainly Cytochrome P450 enzymes (CYP450).

- Converts lipophilic drugs to more polar forms.

Phase II (Conjugation reactions):

- Drug or metabolite from phase I is conjugated with another compound (e.g., glucuronic acid, sulfate, glycine).
- These reactions increase water solubility and promote excretion.
- **Example:** Glucuronidation of morphine.

Significance of Metabolic Enzymes

- **Cytochrome P450 Enzymes:**
  - Large family (CYP3A4, CYP2D6, CYP2C9, etc.).
  - Responsible for the metabolism of many drugs.
- Genetic polymorphisms can affect the expression of these enzymes (fast vs. slow metabolizers).

Enzyme Induction and Inhibition

Enzyme Induction:

- Certain drugs increase the activity of CYP450 enzymes.
- Leads to faster metabolism of the drug and/or other drugs.
- **Effect**: Reduced plasma levels and therapeutic effect.

Examples of Enzyme Inducers:

- Rifampin
- Phenobarbital
- Carbamazepine
- Phenytoin

Enzyme Inhibition:

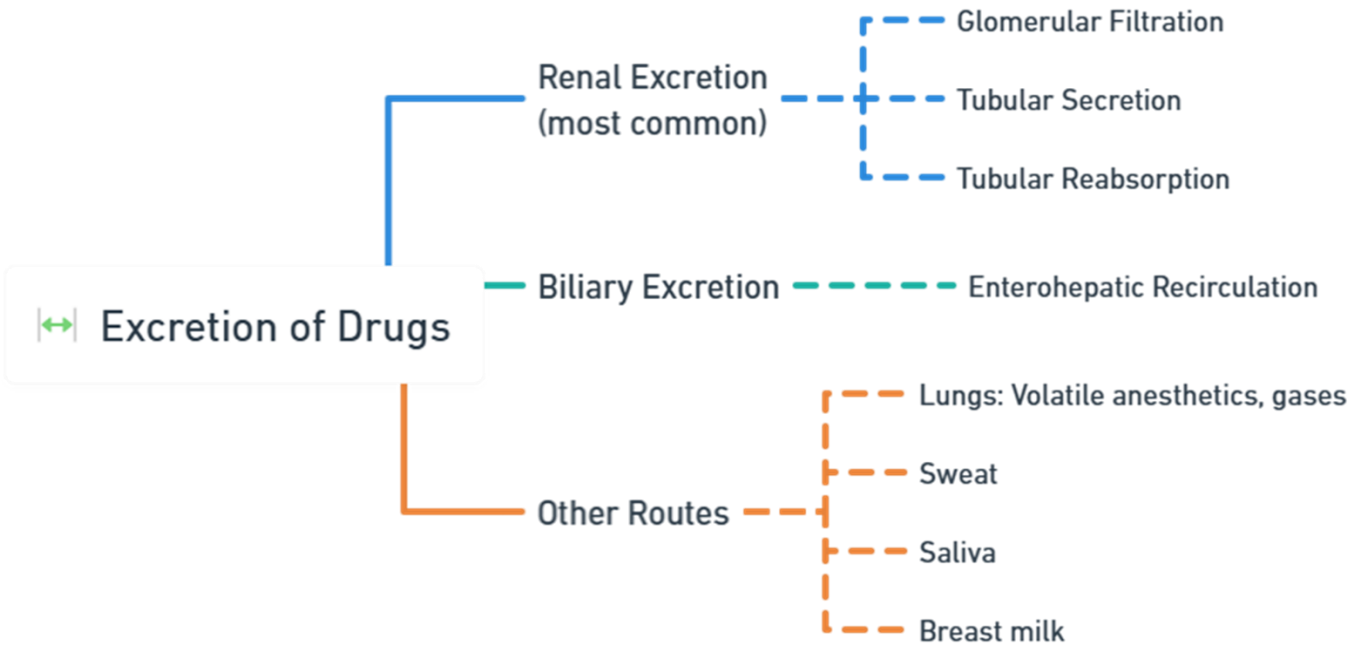
- Some drugs inhibit CYP450 enzymes.
- Leads to **slower metabolism** → increased drug levels → possible toxicity.

Examples of Enzyme Inhibitors:

- Cimetidine
- Ketoconazole
- Erythromycin
- Grapefruit juice

Excretion of Drugs

- Excretion is the process by which the drug or its metabolites are **removed from the body**.



1. Renal Excretion (most common)

- **Glomerular Filtration:** Depends on the free drug fraction in plasma (unbound drug is freely filtered).
- **Tubular Secretion:** Active transport in the proximal tubule (e.g., secretion of acidic drugs by organic anion transporters, basic drugs by organic cation transporters).
- **Tubular Reabsorption:** Passive diffusion of lipid-soluble unionized drugs from the renal tubule back into the bloodstream.

2. Biliary Excretion

- Drugs or metabolites secreted into bile, then into the intestine.
- **Enterohepatic Recirculation:** Some drugs get reabsorbed from the gut, prolonging their half-lives (e.g., certain oral contraceptives).

3. Other Routes

- **Lungs:** For volatile anesthetics and gases.
- **Sweat, Saliva, Breast Milk:** Minor routes but can still be clinically significant (e.g., drug exposure in nursing infants).

Kinetics of Drug Elimination

- **Drug elimination kinetics** describe how the concentration of a drug decreases over time.

Clearance and Half-Life

- **Clearance (CL):** The volume of plasma completely cleared of drug per unit time (mL/min or L/hr).

- Total body clearance is the sum of individual clearances via each route (e.g., hepatic + renal + others).

- **Half-life (t½):** Depends on **volume of distribution (Vd)** and **clearance (CL)**:

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$

- Knowing half-life helps determine **dosing intervals** and time to reach **steady-state** (usually 4–5 half-lives under first-order kinetics).

Types of Drug Elimination Kinetics

A. First-Order Kinetics (Exponential Elimination):

- Most drugs follow this.
- A constant fraction of drug is eliminated per unit time.
- Rate of elimination is proportional to drug concentration.
- Drug concentration decreases exponentially.

Half-life (t½):

- Time taken for the plasma concentration to decrease by 50%.
- Independent of dose in first-order kinetics.

B. Zero-Order Kinetics (Linear Elimination):

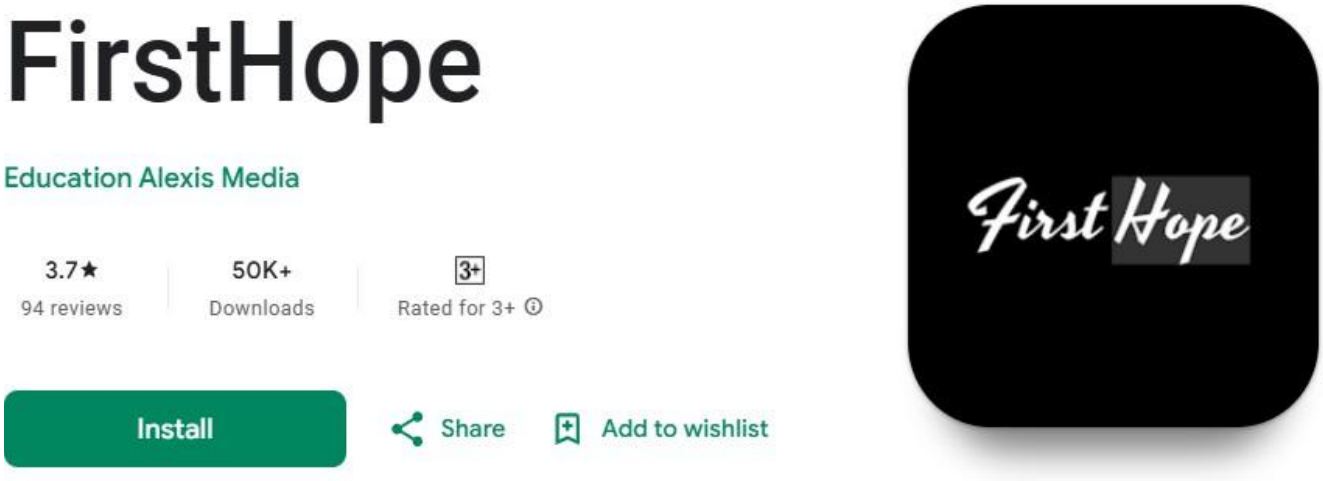
- **A constant amount** of drug is eliminated per unit time (not a fraction).
- Occurs when elimination mechanisms are **saturated**.
- Small dose increases can lead to **toxicity**.

Examples:

- Ethanol
- Phenytoin
- High doses of aspirin

First Hope

Easy Short Notes Designed to Help You Score Better



Android Users:

👉 Download on Google Play

iOS Users (Org Code- DYFFUX):

👉 Download on App Store

Connect With FirstHope

Visit Our Official Website ↗

Watch Free Videos on YouTube ↗

Join Our WhatsApp Community ↗

Join Our Telegram Channel ↗