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# PHARMACOLOGY - I

## UNIT 1

TOPIC :

- **General Pharmacology**

  a. **Introduction to Pharmacology-** Definition, historical landmarks and scope of pharmacology, nature and source of drugs, essential drugs concept and routes of drug administration, Agonists, antagonists( competitive and non competitive), spare receptors, addiction, tolerance, dependence, tachyphylaxis, idiosyncrasy, allergy.

  b. **Pharmacokinetics-** Membrane transport, absorption, distribution, metabolism and excretion of drugs .Enzyme induction, enzyme inhibition, kinetics of elimination

# General Pharmacology

- The word *Pharmacology* is derived from two Greek words:
  - **Pharmakon** → Drug
  - **Logos/Logy** → Study
- **Definition**: Pharmacology is the branch of science that deals with the study of drugs, their sources, chemical properties, biological effects, mechanisms of action, and therapeutic uses.
- In simple terms: *It studies how drugs interact with biological systems and how the body handles drugs.*

## Branches of Pharmacology

Pharmacology is broadly divided into two major branches:

1. **Pharmacokinetics** – It is a Greek word which means the " the action of body on the drugs
   - Processes involved:
     - **Absorption** – entry of drug into blood
     - **Distribution** – transport of drug to tissues
     - **Metabolism** – biotransformation of drug
     - **Excretion** – elimination of drug from body
2. **Pharmacodynamics** – It is also a Greek word which means " the action of drugs on the body
   - Includes:
     - Mechanism of action (MOA)
     - Therapeutic (desired) effects
     - Side effects and adverse effects

# Historical Landmarks in Pharmacology

Pharmacology has evolved from the use of crude natural substances to modern biotechnology-based drugs. Its development can be divided into different periods:

### 1. Ancient Period

- Use of natural substances like plants, minerals, and animal products as medicine.
- Traditional systems:
  - Ayurveda in India
  - Traditional Chinese Medicine
  - Unani in Middle East
- Example: Use of opium (pain relief), garlic (antimicrobial), turmeric (anti-inflammatory).

### 2. Middle Ages

- Paracelsus (1493–1541), known as the *Father of Toxicology*, introduced the dose-response concept:
  - *"All substances are poisons; only the dose makes a thing not a poison."*
- This highlighted the importance of dose in determining therapeutic vs toxic effects of drugs.

### 3. 18th – 19th Century (Isolation of Active Principles)

- Scientists began to isolate pure active compounds from natural sources:
  - Morphine (1806) → from *opium* (analgesic)
  - Quinine (1820) → from *cinchona bark* (antimalarial)
  - Atropine (1833) → from *belladonna* (anticholinergic)
  - Cocaine (1855) → from *coca leaves* (local anesthetic)
- This era marked the shift from crude extracts to pure chemical substances.

### 4. Modern Era (20th Century – Present)

- Development of synthetic drugs (e.g., Aspirin, Barbiturates, Sulfonamides).
- Discovery of antibiotics:
  - *Penicillin* (1928, Alexander Fleming)
  - *Streptomycin* (1943, Selman Waksman)
- Introduction of vaccines for prevention of infectious diseases.
- Biotechnology and genetic engineering:
  - Recombinant human insulin
  - Monoclonal antibodies (e.g., for cancer therapy)
  - Gene therapy drugs

## Scope of Pharmacology

The scope of pharmacology covers the complete study of drugs, including their discovery, action, therapeutic uses, and safety.

**Main areas include:**

1. **Pharmacokinetics** – Study of how the body absorbs, distributes, metabolizes, and excretes drugs.
2. **Pharmacodynamics** – Study of how drugs act on the body, including their mechanism of action.
3. **Pharmacotherapeutics** – Application of drugs in prevention, diagnosis, and treatment of diseases.
4. **Toxicology** – Study of harmful and toxic effects of drugs and poisons.
5. **Clinical Pharmacology** – Study of drugs in humans, including clinical trials and safety evaluation.
6. **Neuropharmacology** – Study of the effects of drugs on the central and peripheral nervous system.
7. **Pharmacogenomics** – Study of how genetic variations affect drug response in individuals.

# Nature & Sources of Drugs

## Nature of Drugs

- The nature of drugs refers to their characteristics and properties.
- **Physical properties**:
  - Drugs may exist in different states –
    - Solid drugs: e.g., Aspirin, Paracetamol
    - Liquid drugs: e.g., Nicotine
    - Gaseous drugs: e.g., Nitrous oxide
- **Chemical properties**:
  - Drugs may be organic (carbon-containing, e.g., morphine, aspirin) or inorganic (e.g., ferrous sulfate, sodium chloride).
- Thus, the nature of drugs is defined by their physical form, chemical composition, and biological activity.

## SOURCES OF DRUGS

Drugs are obtained from different natural and artificial sources:

***1. Natural Sources***

- **Plant origin**:
  - *Vincristine, Atropine, Morphine*
- **Animal origin**:
  - *Heparin, Insulin*
- **Mineral origin**:
  - *Ferrous sulphate, Calcium carbonate*
- **Microbial origin**:
  - *Penicillin, Gentamicin*
- **Human origin**:
  - *Human Chorionic Gonadotropin (hCG), Human Insulin*

### *2. Semi-Synthetic Sources*

- These are chemically modified natural drugs to improve efficacy, reduce toxicity, or increase stability.
- Examples: *Amikacin*, *Cefuroxime axetil*, *Hyoscine butylbromide*

### *3. Synthetic Sources*

- Drugs prepared entirely by chemical synthesis in laboratories.
- Examples: *Aspirin*, *Paracetamol*, *Phenytoin*, *Diclofenac sodium*

### *4. Biotechnology / Recombinant DNA Technology*

- Drugs produced using genetic engineering and biotechnology.
- Examples: *Recombinant Human Insulin*, *Recombinant Erythropoietin*

# Essential Drug Concept

- The Essential Drug Concept is a global health strategy introduced by the World Health Organization (WHO) to promote rational use of medicines.
- Its aim is to ensure that safe, effective, and affordable medicines are available to all people, especially for priority healthcare needs.
- WHO Definition (1977): *"Essential medicines are those that satisfy the priority healthcare needs of the population."*

## Key Principles of Essential Drugs

Essential medicines must fulfill the following criteria:

1. **Availability** – Should be available at all times in adequate quantities.
2. **Accessibility & Affordability** – Must be cost-effective and affordable to individuals and health systems.
3. **Safety & Efficacy** – Must be proven safe, effective, and based on sound clinical evidence.
4. **Quality Standards** – Should meet high standards of purity, stability, and bioavailability.
5. **Rational Selection** – Chosen according to the prevalent health needs of the population.

## WHO Model List of Essential Medicines (EML)

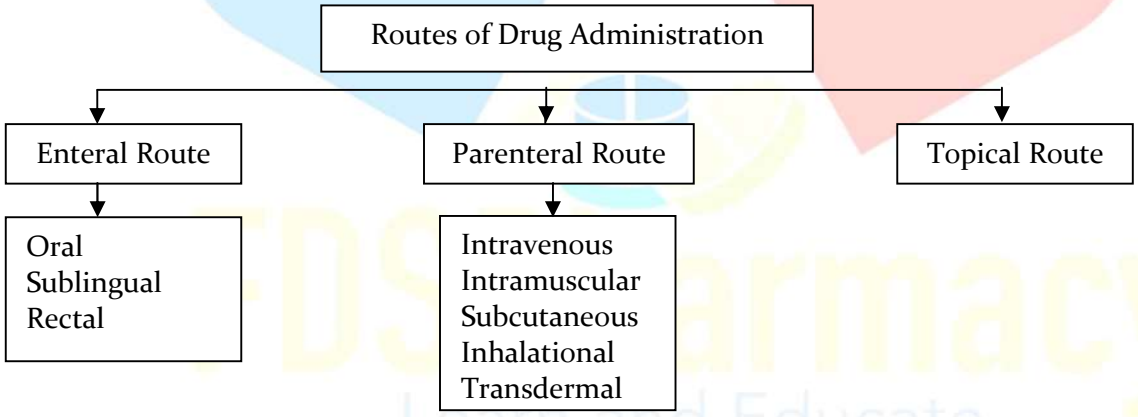
- The first WHO Model List was published in 1977.
- It provides a reference list of essential medicines with their dosage forms and strengths.
- The list is revised every 2 years.
- Latest 22nd List (2021):
    - Contains 489 medicines, including 41 Fixed-Dose Combinations (FDCs).

# National List of Essential Medicines (NLEM) – India

- India published its first NLEM in 1996.
- Revised in 2003, 2011, 2015, and latest in 2021.
- NLEM 2021 includes:
  - 384 medicines (including 23 FDCs).
- Purpose: To ensure availability of essential medicines at affordable cost through government health facilities.

# Various Route of Drug Administration

- Route of drug administration is the path by which the drug is introduced into the body.
- For the treatment of a disease, the drug is introduced into the body through a specific site.
- The choice of route for the drug administration depends on:
  - Properties of the drug like water or lipid solubility, ionisation, etc.
  - Therapeutic objectives, i.e., rapid onset of action or long-term administration or restricted to a local site.




## Enteral Route

- It is the safest, most economical, and convenient route of drug administration.
- Tablets, capsules, powders, mixtures, emulsions and gels are taken orally.
- Solution form of drug gets rapidly absorbed through enteral route.

## Oral Route

- In this route the drug is placed in oral cavity and is swallowed along with water or milk etc.
- Drug is administered through mouth.
- It is also known as per oral (p.o.).
- The main advantages of this route are that the patient is able to self-administer drug and chances of systemic infection are reduced.
- Activated charcoal (antidote) is used in the treatment of toxicities or overdose related problems of oral route.

### Advantages

- Safe, convenient and painless method therefore most preferred.
- Economical, sterilisation is not required.
- For oral drug administration any assistance is not required.
- Less chances of acute drug reaction.

### Disadvantages

- Sometimes complete drug is not absorbed.
- First-pass metabolism takes place in liver where drug reaches through the portal vein.
- Gastric mucosa irritation by certain drugs leads to nausea and vomiting.
- Not effective in emergencies.
- Unpleasant taste of drugs.
- Route not preferred in unconscious and uncooperative patients.

- Low gastric pH, digestive and liver enzymes destroy drug, before its distribution into circulation.

**Sublingual/Buccal Route**

- Drug (small size tablet) is kept beneath the tongue (without water) to disintegrate and get absorbed in mouth, e.g., nitroglycerine tablets.
- The drug enters the systemic circulation through diffusion into the capillary network.
- In buccal route drug kept within the mouth around the cheeks or buccal cavity, where it disintegrates and get absorbed.

**Advantages**

- Rapid absorption of drugs due to highly vascularised site therefore fast onset of action.
- Stomach enzymes and acids are not involved so the drug remains stable.
- Drugs do not undergo first-pass metabolism.
- In case of any side effects drug can be withdrawn.
- Drugs can be administered easily.
- Less chances of infection.
- No involvement of GI environment.

**Disadvantages**

- It is sometimes inconvenient to keep drug in mouth.
- Small doses are required to keep in mouth.

- Drugs having high molecular weight cannot be absorbed (e.g., insulin).
- Unpleasant, distasteful, irritant drugs cannot be administered through this route.

**Rectal Route**

- Suppositories are drugs that are administered through rectal route.
- Drug is formulated with waxy additives in which drug is dissolved or liquefy on insertion into the rectum.
- Drug absorbance occurs directly through thin, highly vascularised wall of rectum.
- This route is used to avoid the destruction of drug by intestinal enzymes or by low pH of stomach.
- The drug is administered in the form of suppositories, through rectal route, when patient is not able to take drug orally (due to vomiting, in consciousness) or have restrictions on eating (mostl after surgery).

**Advantages**

- Useful when patient is suffering from nausea and vomiting.
- By-pass first pass metabolism can be avoided, since absorption occurs from external haemorrhoidal veins.
- Gastric irritant drugs are administered through this route.

**Disadvantages**

- Rectal inflammation.
- Irregular absorption.

**Parenteral Route**

→ All the route of drug administration other than the enteral route comes under parenteral route.

→ but this route mainly includes subcutaneous, intramuscular, an intravenous injections.

→ This route is useful when:

1) Drug is poorly absorbed from the gut,
2) Digestive enzymes destroy the drug,
3) To avoid first pass metabolism by liver
4) Rapid action of drug desired.

**Intravenous (IV) Route**

- In this Route the drug is directly injected into Vein through injection.
- Which absorbed directly into blood stream.
- Injection Inject at a angle of $25^{0}$

**Advantages**

- 100% bioavailability.
- Large quantities.
- Emergency situations.
- Diarrhoea and vomiting.
- No first-pass metabolism.

**Disadvantages**

- Inconvenient and painful causing irritation, cellulitis and thrombophlebitis.
- Repeated injections not suitable.
- Safety level is very low.
- Technical and trained person required.
- Infection may occur.

- Costly.

**Intramuscular (IM) Route**

- The drug is injected into muscles than the drug reach into Blood Circulation.
- Injection Inject at a angle of 90°

**Advantages**

- Uniform absorption.
- Onset of action is fast.
- Prevent first pass metabolism.
- No GIT related factors.

**Disadvantages**

- Only 10ml drug may be administered.
- Local pain and infection.
- Expensive.

**Subcutaneous (SC) Route**

- Drug is deposited into loose subcutaneous tissue which is richly supplies by nerves.

**Advantages**

- Self-administering.
- Onset of action is fast.
- Prevent first pass metabolism.
- No GIT related factors

**Disadvantages**

- Painful.
- Irritant drugs cause tissue damage.
- Maximum 2ml of dose may be injected.

**Inhalational Route**

- It delivers drug throughout the respiratory tract, mucous membranes and pulmonary epithelium, as well as giving fast effect as intravenous injections.
- Gases or aerosol forms of drugs like anaesthetics are administered through this route.
- This route is effective in treatment of patients with respiratory complications such as asthma, or chronic obstructive pulmonary disease.
- Systemic side effects related to drugs (e.g., albuterol and corticosteroids fluticasone) can be minimised in this route.

**Advantages**

- Surface area of the respiratory endothelium is large causing rapid absorption.
- Instant absorption of drug and rapid onset of action.
- No hepatic first-pass metabolism of drug.

**Disadvantages**

- Specialised equipment required for drug delivery, e.g., inhalers.
- Bioavailability of drug depends on the patient's inhaler technique and drug particle size of drug.
- Due to use of inhaler dose regulation is difficult.

**Transdermal Route**

- Transdermal patches are employed to deliver systemic effect of drug through skin.
- The rate of absorption depends on physical characteristics of the skin and application site.
- Transdermal patch provides sustained delivery of drugs,
- e.g., antianginal drug (nitro-glycerine), antiemetic (scopolamine), and contraceptive patch.

**Advantages**

- Sustained effect.
- No hepatic first-pass metabolism.
- Convenient and good patient compliance.

**Disadvantages**

- Relatively slow onset.
- Excessive absorption may give inflamed, rough, abraded on skin.
- This route is preferred for highly lipophilic drugs.

## Topical Route

- → In topical route drug is applied on the surface of skin (epidermis) or mucous membrane, by means of special formulations, e.g., creams, ointments, gels, lotions, sprays, powders, and aerosols.
- → By the topical route local (affecting a small area) to systematic (affecting the entire body) effects can be obtained.
- → The drug is absorbed through the pores present in skin (e.g., sweat glands and hair follicles, etc.).
- → These dosage forms treat skin infections, minimise inflammation, and protect skin.

### Advantages

- Drug can be applied easily.
- Less complication than oral delivery as drugs poorly absorbed systemically.
- Fast action on application site.

### Disadvantages

- Skin irritation
- Improper absorption of certain drugs.
- Ointments have longer duration of action due to sticky and oily texture.

# Some Important Terms in Pharmacology

## Agonist

- An agonist is a drug or substance that binds to and activates a receptor, producing a biological response.
- It mimics the action of natural chemicals (endogenous ligands) to stimulate specific body functions.
- Example: Morphine is an opioid receptor agonist.

## Antagonist

- An antagonist is a drug or substance that blocks a receptor and prevents a biological response.
- It works by inhibiting the action of natural chemicals or other drugs.
- **Types of Antagonists:**
  - **Competitive Antagonist** → Competes with agonist for the same receptor site. (e.g., Atropine against acetylcholine)
  - **Non-competitive Antagonist** → Binds to a different site and prevents receptor activation even if the agonist is present. (e.g., Ketamine on NMDA receptors)

## Spare Receptors

- Spare receptors are extra receptors present in a cell that are not required to produce the maximum drug effect.
- Even if only a fraction of receptors are occupied, a full response can occur.
- Significance: Explains why low drug concentrations may still produce maximal effects.

## Addiction

- Addiction is a strong, compulsive, and uncontrollable craving to use a drug, despite harmful consequences.
- It occurs due to neurochemical changes in the brain that create drug-seeking behavior.

- **Example:** Addiction to opioids, alcohol, or nicotine.

## Dependence

- Dependence is a state in which the body adapts to a drug, leading to withdrawal symptoms when the drug is stopped.
- **Types:**
  - **Physical dependence** → Withdrawal symptoms like sweating, tremors, nausea.
  - **Psychological dependence** → Emotional need/craving for the drug.

## Tolerance

- Tolerance means that over time, increasing doses of a drug are required to produce the same effect.
- It develops due to adaptation of the body to the drug.
- **Example:** Tolerance to morphine analgesia.

## Tachyphylaxis

- Tachyphylaxis is a rapid decrease in response to a drug after repeated short-term use, even if the dose is unchanged.
- It occurs due to fast receptor desensitization or depletion of mediators.
- **Example:** Ephedrine loses effect quickly on repeated dosing.

## Idiosyncrasy

- Idiosyncrasy is an unusual, abnormal, or unexpected reaction to a drug that occurs in certain individuals.
- It is unrelated to dose or allergy, but due to genetic or metabolic differences.
- **Example:** Hemolysis after taking primaquine in patients with G6PD deficiency.

## Allergy

- An allergy is an immune-mediated hypersensitivity reaction to a drug.
- The immune system treats the drug as harmful, leading to symptoms such as:
  - Rash, itching, swelling
  - Severe cases: difficulty in breathing, anaphylaxis
- **Example:** Penicillin allergy.

# Pharmacokinetics

- Pharmacokinetics is the branch of Pharmacology that studies what the body does to the drug, i.e., how drugs move through the body over time.
- It describes the processes of ADME:
    1. Absorption – Entry of drug into systemic circulation.
    2. Distribution – Transport of drug to different tissues and organs.
    3. Metabolism (Biotransformation) – Chemical modification of drug, mainly in liver.
    4. Excretion – Removal of drug from the body, mainly via kidneys.

# Membrane Transport

- Membrane transport is the **movement of drugs across biological membranes**, such as:
    - Cell membrane
    - Intestinal epithelium
    - Blood–brain barrier
    - Renal tubules
- Since most drugs must cross membranes to reach their site of action, understanding these mechanisms is important.

## Types of Membrane Transport

### *1. Passive Diffusion*

- Movement of drugs from high concentration → low concentration.
- No energy required.
- Driven by concentration gradient until equilibrium is reached.
- Most common mechanism of drug absorption.
- **Factors affecting:**
    - Lipid solubility (lipophilic drugs diffuse faster)
    - Molecular size (smaller molecules diffuse faster)
- **Example:** Absorption of alcohol, steroids.

### *2. Pore Transport (Filtration)*

- Also called aqueous diffusion.
- Drugs pass through aqueous pores or channels in membranes.
- Important for small, water-soluble, lipid-insoluble drugs.
- Example: Urea, water, electrolytes.

### *3. Facilitated Diffusion*

- Similar to passive diffusion, but requires specific carrier proteins.
- No energy required; movement is still along concentration gradient.
- Used by drugs that are large or less lipophilic.
- Example: Transport of glucose and some vitamins.

### *4. Active Transport*

- Movement of drugs against concentration gradient (low → high).
- Requires energy (ATP) and carrier proteins.
- Highly selective and saturable process.
- Example: Levodopa transport across intestinal mucosa.

### *5. Ion-Pair Transport*

- Poorly lipid-soluble drugs form ion-pair complexes with endogenous ions (cation or anion).
- The neutral complex can cross membranes more easily.
- Example: Transport of cationic drugs paired with endogenous anions.

### *6. Endocytosis (Vesicular Transport)*

- The cell engulfs drug molecules by enclosing them in vesicles formed from the cell membrane.
- Important for large or macromolecular drugs.
- Types:
  - Phagocytosis → Uptake of solid particles.
  - Pinocytosis → Uptake of fluids or dissolved substances.
- Example: Transport of proteins, immunoglobulins.

# Absorption of Drugs

- Absorption is the process by which a drug moves from its site of administration into the systemic circulation (bloodstream).
- It is a crucial step for a drug to produce its therapeutic effect, except in cases where the drug is administered directly into the bloodstream (e.g., intravenous injection).

## General Principles

- For better absorption, a drug should be lipid-soluble, because only lipid-soluble drugs can easily cross biological membranes.
- Example: When a drug is given orally, it must cross the membranes of the GIT epithelium and blood vessels before reaching systemic circulation.

## Nature of Drugs and Absorption

- Most drugs are weak acids or weak bases.
- The degree of ionization affects lipid solubility and absorption:
  - Unionized (non-charged) form → more lipid-soluble → better absorbed.
  - Ionized (charged) form → more water-soluble → less absorbed.
- Thus, absorption depends on the pH of the medium and the pKa of the drug (Henderson–Hasselbalch principle).

## Absorption of Weak Acids and Weak Bases

1. **Weak Acidic Drugs**
   - Best absorbed in an acidic medium (stomach).
   - Because they remain mostly in the unionized (lipid-soluble) form.
   - **Example:** Aspirin, Phenobarbital.
2. **Weak Basic Drugs**
   - Best absorbed in a basic medium (intestine).
   - They remain largely in the unionized form in alkaline pH.
   - **Example:** Morphine, Diazepam.

# Bioavailability

- Bioavailability is defined as the fraction (percentage) of an administered drug dose that reaches the systemic circulation in its unchanged (active) form.
- It is an important pharmacokinetic parameter that determines the efficiency of drug absorption.

**Key Points**

1. **IV Route** → Bioavailability is **100%** because the drug is directly introduced into the bloodstream without absorption barriers or metabolism.
2. **Oral Route** → Bioavailability is usually **less than 100%** due to factors like incomplete absorption, drug degradation in GIT, and **first-pass metabolism**.
3. **Expression** → Bioavailability is expressed in **percentage (%)**.

**Example:**
If 100 mg of a drug is taken orally and only 50 mg reaches the systemic circulation → Bioavailability = 50%.

## Calculation (Oral vs IV)

Bioavailability is measured using the Area Under the Curve (AUC) from a plasma drug concentration-time graph.

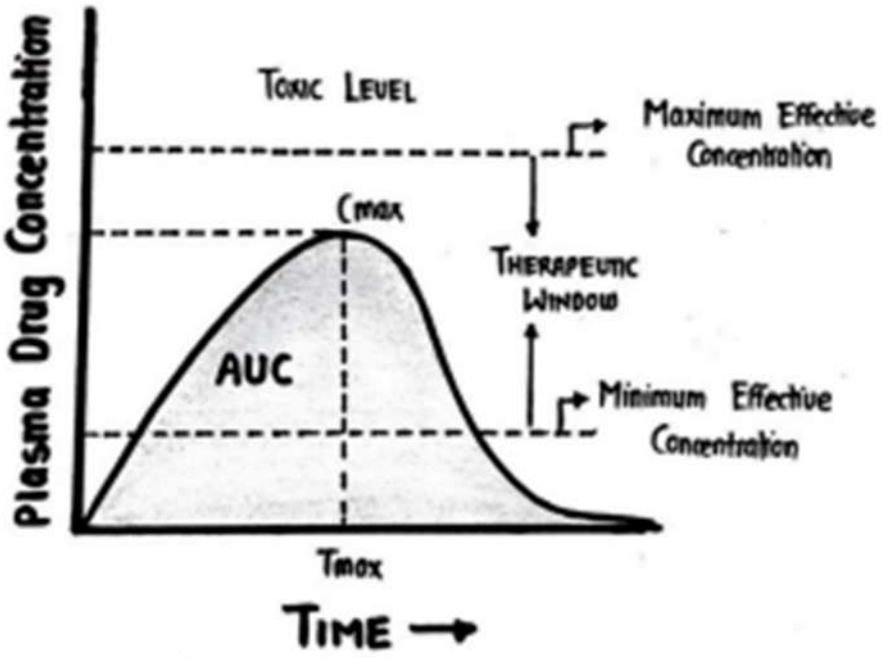
$$F = \frac{AUC_{oral}}{AUC_{IV}} \times 100$$

Where:

- F = Bioavailability
- AUC (Area Under Curve) = Represents total drug exposure over time.

## Plasma Drug Concentration-Time Curve

- **Cmax** = Maximum plasma concentration achieved after drug administration.
- **Tmax** = Time required to reach **Cmax**.
- **MEC (Minimum Effective Concentration)** = Minimum plasma concentration required to produce therapeutic effect.
- **MTC (Maximum Tolerated Concentration)** = Plasma concentration above which adverse/toxic effects appear.
- **Therapeutic Window** = Range between MEC and MTC.



# FIRST PASS METABOLISM (First Pass Effect)

- First-pass metabolism is the metabolic breakdown of a drug before it reaches systemic circulation, usually after oral administration.
- This reduces the bioavailability of the drug.

**Process**

1. **Oral administration** → Drug enters stomach and intestine.
2. **Absorption** → Drug is absorbed into the portal circulation.
3. **Liver metabolism** → The absorbed drug passes through the liver where enzymes (mainly CYP450) metabolize a significant portion.
4. **Systemic circulation** → Only the **remaining fraction** of the active drug enters the blood and reaches the target organs.

**Drugs with High First Pass Effect**

- Propranolol
- Nitroglycerin
- Morphine
- Verapamil

**Ways to Bypass First Pass Metabolism**

- Parenteral routes: IV, IM, SC
- Sublingual route (e.g., Nitroglycerin)
- Rectal route (partially bypasses)
- Transdermal patches

# Factors Affecting Drug Absorption

- Drug absorption is the process by which a drug moves from its site of administration into the systemic circulation.
  The efficiency of absorption is influenced by Physicochemical factors, Physiological factors, and Pharmaceutical factors.

# Physicochemical Factors

(Related to drug's physical and chemical properties)

- **Solubility**
  - A drug must first dissolve in biological fluids before absorption.
  - Lipophilic (fat-soluble) drugs → cross cell membranes easily.
  - Hydrophilic (water-soluble) drugs → require transport proteins.
- **Drug Ionization (pH effect)**
  - Most drugs are weak acids or weak bases.
  - Non-ionized (unionized) drugs → more lipid-soluble → better absorbed.
  - Ionized drugs → more water-soluble → less absorbed.
  - Example: Weak acids absorbed in acidic medium (stomach), weak bases in alkaline medium (intestine).
- **Particle Size**
  - Smaller particles dissolve faster and are absorbed more quickly.
  - Micronization increases surface area and enhances absorption.
- **Drug Stability**
  - Some drugs degrade in acidic gastric fluid (e.g., penicillin, erythromycin).
  - Enteric coatings protect acid-sensitive drugs until they reach intestine.

## Physiological Factors

(Related to body conditions influencing absorption)

- **Gastric Emptying**
  - Faster gastric emptying → quicker drug absorption.
  - Delayed emptying (due to fatty food, disease, drugs) → slower absorption.
- **Surface Area**
  - Small intestine has large absorptive surface (villi & microvilli).
  - Therefore, it is the primary site of drug absorption.
- **First-Pass Metabolism**
  - Drugs absorbed from GIT pass through the liver via portal vein.
  - Significant metabolism may occur before reaching systemic circulation.
  - This reduces bioavailability (e.g., propranolol, nitroglycerin).

## Pharmaceutical Factors

(Related to formulation and administration of the drug)

- **Dosage Form**
  - Liquids (syrups, solutions) → absorbed faster than solids (tablets, capsules).
  - Controlled-release forms → slower but prolonged absorption.
- **Route of Administration**
  - Oral → most common, but subject to first-pass metabolism.
  - Sublingual → avoids first-pass effect, rapid absorption.
  - Parenteral (IV, IM, SC) → bypass absorption barriers, rapid action.
  - Topical/Transdermal → depends on skin permeability and formulation.
- **Drug Interactions**
  - Presence of other drugs or food may alter absorption.
  - Example: Tetracycline + milk (calcium) → reduced absorption.

# Distribution

Distribution is the process by which a drug, after being absorbed into the bloodstream, is transported to different tissues and organs of the body.
It determines:

- Where the drug goes in the body
- How much of it reaches the target site
- How long it remains active in the system

## FACTORS AFFECTING DRUG DISTRIBUTION

### 1. Blood Flow to Tissues

- Organs with high blood flow (e.g., liver, kidneys, brain, lungs, heart) → receive drugs rapidly.
- Organs with low blood flow (e.g., fat, skin, muscles) → receive drugs slowly.
- Clinical note: This explains why highly perfused organs show faster drug action.

### 2. Plasma Protein Binding

- Drugs in plasma can bind to albumin, α1-acid glycoprotein, lipoproteins.
- Only free (unbound) drug is pharmacologically active and available for distribution.
- Highly protein-bound drugs (e.g., warfarin, phenytoin) → limited distribution, longer duration of action.
- Drug interactions can occur if two drugs compete for the same binding sites.

### 3. Lipid Solubility of Drugs

- Lipophilic drugs → easily cross cell membranes, accumulate in tissues, especially fatty tissues and brain.
- Hydrophilic drugs → remain mostly in plasma and extracellular fluids, limited tissue penetration.

### 4. Tissue Permeability

- Distribution also depends on the ability of drug molecules to cross tissue barriers.
- Highly permeable tissues (e.g., liver, kidney, lungs) → allow easy entry of drugs.
- Protective barriers like:
    - Blood–Brain Barrier (BBB): restricts entry of many polar/hydrophilic drugs into CNS.
    - Placental barrier: partially restricts drug passage to fetus, though many lipophilic drugs can cross.

### 5. Volume of Distribution (Vd)

- A pharmacokinetic parameter that describes the extent of drug distribution in body fluids and tissues.
- High Vd: drug widely distributed in tissues (lipid-soluble drugs).
- Low Vd: drug remains mainly in blood/plasma (water-soluble or protein-bound drugs).

Formula:

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

# Plasma Protein Binding

Plasma protein binding refers to the reversible interaction between a drug and plasma proteins such as albumin, α1-acid glycoprotein, and lipoproteins. This process significantly influences drug distribution, metabolism, elimination, and pharmacological action.

**Key Aspects**

**1. Bound vs. Free Drug**

- Bound Drug → Inactive, cannot cross biological membranes, stored in plasma.
- Free Drug → Active form, can cross membranes, bind to receptors, and produce pharmacological effects.
- Only free drug determines therapeutic activity.

**2. Plasma Proteins Involved**

- Albumin → Binds mainly acidic drugs (e.g., Warfarin, Phenytoin, Aspirin).
- α1-Acid Glycoprotein → Binds mainly basic drugs (e.g., Propranolol, Lidocaine).
- Lipoproteins → Bind lipophilic drugs (e.g., Cyclosporine).

**3. Clinical Importance of Binding**

- Highly protein-bound drugs → Less free drug available, longer duration of action, higher risk of drug–drug interactions.
- Weakly protein-bound drugs → More free drug available, shorter duration, rapid clearance.
- Conditions like liver disease, kidney disease, or malnutrition (low albumin levels) increase free drug → risk of toxicity.

# VOLUME OF DISTRIBUTION (Vd)

The apparent volume of distribution (Vd) is a theoretical pharmacokinetic parameter that indicates the extent to which a drug distributes in body tissues relative to plasma concentration.

It does not represent an actual physiological volume, but an index of drug distribution.

Formula

$$V_d = \frac{\text{Dose of drug administered}}{\text{Plasma drug concentration}}$$

**Interpretation of Vd**

- **Low Vd (<10 L)** → Drug remains mostly in plasma (e.g., warfarin).
- **Moderate Vd (10–40 L)** → Drug distributes in extracellular fluid (e.g., aminoglycosides).
- **High Vd (>40 L)** → Drug widely distributes into tissues, including fat and intracellular compartments (e.g., digoxin, chloroquine).

**Clinical Significance**

- Helps in deciding loading dose of a drug:

$$\text{Loading Dose} = \frac{\text{Desired plasma concentration} \times \text{Vd}}{\text{Bioavailability}}$$

High Vd → drug may accumulate in tissues, long half-life.

Low Vd → drug confined to plasma, short half-life.

# Drug Metabolism (Biotransformation)

Metabolism (also called Biotransformation) is the process by which the body chemically alters drugs into more water-soluble and easily excretable forms.

## Sites of Drug Metabolism

- Primary site → Liver (major organ with drug-metabolizing enzymes).
- Other sites → Kidney, intestine, lungs, plasma, skin.

## Purpose of Metabolism

- Convert lipid-soluble drugs → water-soluble drugs (for easier excretion).
- Convert unionized drugs → ionized forms.
- Modify drug activity and toxicity.

## Outcomes of Drug Metabolism

1. Active drug → Inactive metabolite
    - Example: Procaine → PABA.
2. Active drug → Active metabolite
    - Example: Codeine → Morphine.
3. Inactive drug (prodrug) → Active metabolite
    - Example: Enalapril → Enalaprilat.

## Clinical Importance

- Determines duration and intensity of drug action.
- Affects drug safety by detoxifying harmful compounds.
- Sometimes, metabolism may produce toxic metabolites (e.g., acetaminophen overdose → hepatotoxic metabolite).

# Cytochrome P450 Enzymes (Cyp Enzymes)

Cytochrome P450 (CYP450) enzymes are a superfamily of heme-containing proteins that play a major role in the metabolism of drugs, toxins, and endogenous substances.

- "Cytochrome P" → "P" stands for Pigment (characteristic absorption peak at 450 nm when bound with carbon monoxide).
- They are mainly located in the liver endoplasmic reticulum, but also found in intestine, kidney, lungs, and brain.

**Nomenclature**

CYP enzymes are named as CYP + number + letter + number

- Number (family): e.g., *3* → CYP3
- Letter (subfamily): e.g., *A* → CYP3A
- Number (specific isoform): e.g., *4* → CYP3A4

**Example:** CYP3A4

- Family: 3
- Subfamily: A
- Isoform: 4

**Major CYP Families in Drug Metabolism**

- CYP3A4 → Most abundant (≈ 30–35% of hepatic CYP content); metabolizes the largest proportion of drugs (~35%).
- CYP2D6 → Responsible for metabolism of many CNS and cardiovascular drugs (e.g., antidepressants, beta-blockers, codeine).
- CYP2C19 → Metabolizes proton pump inhibitors (omeprazole), antiepileptics, clopidogrel.
- CYP2C9 → Important for metabolism of NSAIDs (diclofenac, ibuprofen), warfarin.
- CYP1A2 → Metabolizes caffeine, theophylline, some antidepressants.

## Clinical Importance

- Drug–drug interactions: Inhibition or induction of CYP enzymes can alter drug metabolism.
    - Example: Ketoconazole inhibits CYP3A4 → ↑ plasma levels of many drugs.
- Genetic polymorphism: Some enzymes (e.g., CYP2D6, CYP2C19) show genetic variations → differences in drug response among individuals.
- Drug safety: Helps predict metabolism, clearance, and risk of adverse effects

# Types of Metabolism (Biotransformation) Reactions

There are **two main phases**:

- **Phase I Reactions (Functionalization Reactions)**
- **Phase II Reactions (Conjugation Reactions)**

## Phase I Reactions (Functionalization Reactions)

In these reactions, functional groups such as –OH, $–NH_2$, –SH, or –COOH are introduced or unmasked in the drug molecule.
This usually converts lipophilic drugs into more polar metabolites.
Mainly mediated by microsomal enzymes (Cytochrome P450 system).

### Types of Phase I Reactions

1. **Oxidation**
   - Addition of oxygen / removal of hydrogen.
   - Most common type of reaction.
   - Enzyme: CYP450 (Mixed function oxidases).
   - **Examples:** Phenytoin, Phenobarbital, Propranolol.
2. **Reduction**
   - Addition of hydrogen / removal of oxygen.
   - Less common than oxidation.
   - **Examples:** Chloramphenicol, Warfarin.
3. **Hydrolysis**
   - Breakdown of drug molecule by addition of water.
   - Common in esters and amides.
   - Enzymes: Esterases, Amidases, Peptidases.
   - **Examples:** Procaine (ester hydrolysis), Lidocaine (amide hydrolysis).
4. **Cyclization**
   - Conversion of a straight-chain compound into a ring structure.
   - **Example:** Cycloguanil from Proguanil.
5. **Decyclization (Ring Opening)**
   - Opening of a cyclic structure to form a straight-chain compound.
   - **Example:** Barbiturates.

# Phase II Reactions (Conjugation Reactions)

These reactions involve the conjugation (attachment) of the drug (or its Phase I metabolite) with an endogenous substrate.
The product formed is highly polar, water-soluble, and inactive, hence easily excreted.
Mediated by transferase enzymes (mostly non-microsomal).

**Types of Phase II Reactions**

1. **Glucuronide Conjugation**
    - Addition of glucuronic acid.
    - Enzyme: UDP-glucuronosyl transferases (UGTs).
    - Examples: Chloramphenicol, Aspirin, Paracetamol.
2. **Acetylation**
    - Addition of an acetyl group.
    - Enzyme: N-acetyl transferases.
    - Examples: Sulfonamides, Isoniazid.
3. **Methylation**
    - Addition of a methyl group.
    - Enzyme: Methyl transferases.
    - Examples: Methyldopa, Epinephrine.
4. **Sulfate Conjugation**
    - Addition of sulfate group.
    - Enzyme: Sulfotransferases.
    - Examples: Chloramphenicol, Methyldopa.
5. **Glycine Conjugation**
    - Addition of glycine.
    - Enzyme: Glycine N-acyltransferases.
    - Examples: Salicylic acid, Nicotinic acid.
6. **Glutathione Conjugation**
    - Addition of glutathione (tripeptide).
    - Enzyme: Glutathione-S-transferases.
    - Example: Paracetamol (detoxification pathway).

## Factors Affecting Drug Metabolism

Drug metabolism (biotransformation) can vary widely between individuals due to physiological, genetic, pathological, and environmental factors. These factors influence how quickly or slowly a drug is metabolized, which in turn affects its **efficacy, toxicity, and duration of action.**

### 1. Age

- **Newborns and Infants:**
  - Metabolic enzyme systems are immature.
  - Phase I and Phase II reactions are underdeveloped, leading to slower drug metabolism**.**
  - Example: Chloramphenicol → causes "Gray baby syndrome" due to poor glucuronidation.
- **Elderly:**
  - Liver size, hepatic blood flow, and enzyme activity decline with age.
  - Results in slower metabolism and prolonged drug action**.**
  - Example: Benzodiazepines accumulate more in elderly patients.

### 2. Genetics

- Genetic variations (polymorphisms) affect enzyme activity, leading to fast or slow metabolizers.
- Example:
  - **Isoniazid** metabolism varies due to differences in **N-acetyltransferase** (slow vs fast acetylators).
  - **CYP2D6 polymorphism** → affects metabolism of drugs like codeine, antidepressants, and beta-blockers.
- Hence, genetics can greatly influence drug response and toxicity.

### 3. Liver Health

- Liver is the primary site of drug metabolism.
- Conditions like hepatitis, cirrhosis, fatty liver, or cancer impair liver function.
- Damaged liver → slower metabolism, drug accumulation, and toxicity.
- Example: Patients with liver disease require dose adjustment for drugs like warfarin, phenytoin.

### 4. Gender (Sex Differences)

- Hormonal differences between men and women affect enzyme activity.
- Women may metabolize some drugs slower or faster than men.
- Example: Certain benzodiazepines and alcohol show different metabolic rates in men vs women.
- During pregnancy, enzyme activity may also be altered.

### 5. Diet and Lifestyle

- **Dietary factors:**
  - Grapefruit juice inhibits CYP3A4, slowing metabolism and increasing blood levels of drugs like statins, calcium channel blockers.
- **Lifestyle habits:**
  - **Smoking** induces CYP1A2, increasing metabolism of theophylline, caffeine.
  - **Chronic alcohol** → induces enzymes (↑ metabolism of some drugs).
  - **Acute alcohol** → inhibits metabolism (↑ toxicity).

# Enzyme Induction

- Enzyme induction is the process by which a drug increases the synthesis (expression) or activity of metabolic enzymes in the liver or other tissues.
- **Mechanism:**
  - Inducing drugs bind to nuclear receptors (e.g., PXR, CAR).
  - This stimulates transcription of CYP genes → increased enzyme production.
  - More enzyme activity → faster metabolism of drugs.
- **Effects:**
  - **Decreased plasma concentration** of the drug.
  - **Reduced therapeutic effect** (treatment failure possible).
  - May also enhance metabolism of endogenous substances (e.g., steroids, bilirubin).
- **Examples of Enzyme Inducers:**
  - **Rifampin** → induces CYP3A4 → reduces effectiveness of oral contraceptives.
  - **Carbamazepine, Phenytoin, Phenobarbital** → increase metabolism of warfarin and other drugs.

# Enzyme Inhibition

- Enzyme inhibition is the process by which a drug reduces the activity of metabolic enzymes, leading to slower drug metabolism**.**
- **Mechanism:**
  - Inhibiting drugs may bind to the enzyme (competitive or non-competitive).
  - Prevents metabolism of substrate drugs.
  - Leads to accumulation of drugs in plasma.
- **Effects:**
  - Increased plasma concentration of drug.
  - Enhanced pharmacological effect or toxicity.
- **Examples of Enzyme Inhibitors:**
  - **Ketoconazole, Itraconazole** → inhibit CYP3A4 → increase levels of statins → risk of muscle toxicity.

- **Erythromycin, Clarithromycin** → inhibit CYP3A4 → increase theophylline, warfarin toxicity.

## Excretion of Drugs

Excretion is the process by which drugs and their metabolites are removed from the body.
It is an essential pharmacokinetic step that determines:

- Drug half-life (t½)
- Clearance (Cl)
- Duration of action

The major route is renal (kidneys), but other organs like liver, lungs, sweat glands, saliva, and breast milk also contribute.

### 1. Renal Excretion (Major Route)

The kidney is the most important organ for drug elimination. Drugs are excreted through urine in three main steps:

#### a) Glomerular Filtration

- Only free/unbound drugs (not protein-bound) are filtered from plasma into the renal tubules.
- Example: Aminoglycosides.

#### b) Tubular Secretion

- Active transport of drugs from blood into the renal tubule.
- Occurs mainly in the proximal tubule.
- Example: Penicillin, Probenecid.

#### c) Tubular Reabsorption

- Some drugs can be reabsorbed back into blood from renal tubules.
- Reabsorption depends on lipid solubility and urine pH.

- Example:
  - Weak acids like aspirin are reabsorbed in acidic urine.
  - Alkalinization of urine (e.g., sodium bicarbonate) increases excretion of weak acids (used in aspirin overdose).

**2. Hepatic (Biliary) Excretion**

- Drugs and their metabolites are secreted into bile and eliminated via feces.
- In some cases, drugs undergo enterohepatic circulation (reabsorption from intestine, prolonging action).
- Examples: Digoxin, Steroids, Chloramphenicol.

**3. Pulmonary Excretion**

- Volatile drugs and gases are eliminated via exhalation through lungs.
- Rate depends on respiratory rate and blood solubility of the drug.
- Examples: Inhalational anesthetics (halothane, nitrous oxide), alcohol.

**4. Sweat and Saliva Excretion**

- Minor route of drug elimination.
- Not clinically significant for most drugs but useful in drug testing (saliva).
- Examples: Heavy metals, alcohol, lithium.

**5. Breast Milk Excretion**

- Drugs may pass into breast milk due to its slightly acidic pH.
- Lipid-soluble and weakly basic drugs accumulate more.
- This is important because drugs in breast milk may affect infants.
- Examples: Tetracyclines (cause teeth discoloration), Opioids (respiratory depression in infant).

# Kinetics of Elimination

The elimination kinetics of a drug describes how the body removes drugs over time. It includes two key concepts**:** Clearance and Order of Kinetics.

## 1. Clearance (Cl)

- Clearance is the *theoretical volume of plasma from which a drug is completely removed per unit time.*
- It reflects the efficiency of the body (kidneys, liver, lungs) in eliminating a drug.

**Formula:**

$$Cl = \frac{\text{Rate of Elimination}}{\text{Plasma Drug Concentration}}$$

- Units: **mL/min** or **L/hr**
- High clearance → drug eliminated quickly.
- Low clearance → drug persists longer in plasma.



## 2. Order of Kinetics

Drugs are eliminated from the body in specific kinetic patterns:

### a) First-Order Kinetics

- Most common type.
- Rate of elimination ∝ plasma drug concentration.
- A constant *fraction* of drug is eliminated per unit time.
- As drug concentration decreases → elimination rate slows.

Example: Most drugs (e.g., aspirin at therapeutic dose, penicillin, theophylline).

Graph: Exponential decline in plasma concentration vs time.

**b) Zero-Order Kinetics**

- Elimination rate is constant and independent of plasma concentration.
- A fixed *amount* of drug is eliminated per unit time.
- Seen when elimination pathways become saturated.

Examples: Alcohol (ethanol), Phenytoin, High-dose aspirin.

Graph: Linear decline in plasma concentration vs time.

**3. Plasma Half-Life (t½)**

- Plasma half-life is the time required for the drug concentration in plasma to decrease by 50%.
- It is a crucial parameter to determine dosing interval, duration of action, and steady-state levels.

**Formula:**

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

Where:

- 0.693 = natural logarithm of 2
- Vd = Volume of distribution
- Cl = Clearance

**Interpretation:**

- Long half-life → drug stays longer in body (e.g., Diazepam ~ 30 hrs).
- Short half-life → requires frequent dosing (e.g., Penicillin G ~ 30 min).