PHARMACOLOGY - I

UNIT 1 NOTES

- INTRODUCTION
- ROUTES OF DRUG ADMINISTRATION
- PHARMACOKINETICS
  - ABSORPTION
  - DISTRIBUTION
  - METABOLISM
  - EXCRETION

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GENERAL PHARMACOLOGY

- The word Pharmacology derived from two greek words : 'Pharmakon' means 'Drug' and 'Logy' means 'Study'
- In simple words we can say It is the branch of science that studies drugs, their sources, chemical properties, biological effects and therapeutic uses.
- It explores how drugs interact with biological systems, including how they are absorbed, distributed, metabolized and excreted by the body.

BRANCHES OF PHARMACOLOGY

Pharmacology is mainly divided into two parts :

① Pharmacokinetics
② Pharmacodynamics

PHARMACOKINETICS

- It is simply defined as what the body does to the drug.
- It simply deals with :
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

PHARMACODYNAMICS

- Pharmacodynamics is simply defined as what a drug does to the body.
- It basically deals with Mechanism of Action, Therapeutic effect and side effects of drug.

SCOPE OF PHARMACOLOGY

The scope of Pharmacology covers everything related to drugs, from how they work in the body to their medical use and safety.
It includes :

- Pharmacokinetics : How the body processes drugs
- Pharmacodynamics : ~~Use~~ How drugs work
- Pharmacotherapeutics : Use of medicines in treatment
- ~~Side Eff~~ Toxicology : Side effects and toxic effects
- Clinical Pharmacology : Study of how drugs work in humans.
- Neuropharmacology : Effect of drugs on brain.
- Pharmacogenomics : How genes affect drug response.

NATURE & SOURCES OF DRUGS

The nature of drugs refers to their characteristics, properties like their Physical properties such as state of drugs i.e., solid drugs like aspirin, liquid drugs like nicotine and gaseous drugs like nitrous oxide and chemical properties like whether they are organic or inorganic in nature.

SOURCES OF DRUGS

Drugs can be obtained from various sources as follows :

① NATURAL SOURCES

- Plant : Vincristine, Atropin. Morphine
- Animal : Heparin, Insulin
- Mineral : Ferrous Sulphate. Calcium Carbonate
- Microbial : Penicillin, Gentamicin
- Human : Chorionic Gonadotropin, Human Insulin

② SEMI- SYNTHETIC SOURCES

- Amikacin
- Cefuroxime Axetil
- Hyoscine Butyl Bromide

③ SYNTHETIC SOURCES

- Aspirin, Paracetamol, Phenytoin
- Diclofenac Sodium

④ BIOTECHNOLOGY

- Human Insulin, Recombinant Erythropoietin

ESSENTIAL DRUG CONCEPT

- The Essential Drug Concept is a global health strategy introduced by the World Health Organization (WHO) to ensure that safe, effective and affordable medicines are available to all people.
- The WHO has defined Essential Medicines (drugs) as "those that satisfy the priority healthcare needs of the population".

KEY PRINCIPLES OF ESSENTIAL DRUGS

- Essential medicines should be available at all times in sufficient quantities.
- They should be cost-effective and affordable.
- They must be safe and effective
- Essential drugs must meet high standards of purity, stability and bioavailibility.

WHO MODEL LIST OF ESSENTIAL MEDICINES

- The WHO brought out its first Model List of Essential Drugs along with their dosage forms and strength in 1977.
- This has been revised from time to time and the current is the 22nd list of 2021 having:
  - 439 entries including 41 FDCs (Fixed Dose Combinations).

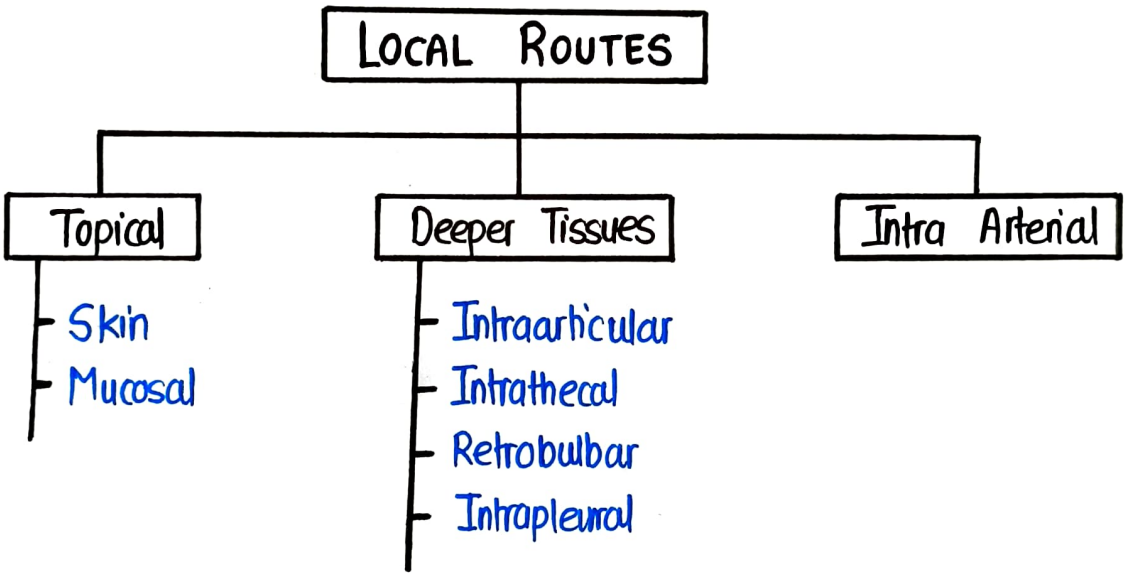
NATIONAL LIST OF ESSENTIAL MEDICINES

- India released its 'National Essential Drug List' in 1996, and revised it in 2011 and in 2015 with the title 'National List of Essential Medicines' (NLEM)
- The latest list has been brought out in September 2022, which includes:
  - 384 Medicines including 23 FDCs

Routes Of Drug Administration

- The Route of drug administration refers to the path by which a drug is taken into the body to achieve its desired effect.
- The choice of routes depends on factors like drug properties, desired effect and patient condition.
- These routes can be mainly classified into two major types:

① Local Routes
② Systemic Routes



① Topical

- The topical route of drug administration involves applying medications directly to the skin or mucous membranes to treat localized conditions.
- This method allows the drug to act at the site of application, making it effective for conditions affecting specific areas.

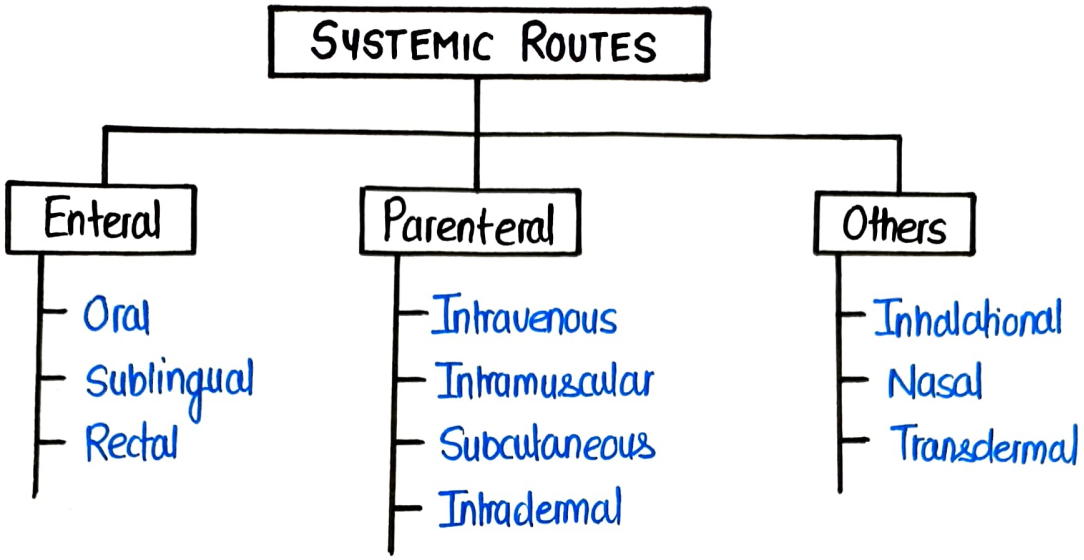
② Deeper Tissues

- The deeper tissue route of drug administration refers to the direct delivery of medication into tissues beneath the skin by using a syringe and needle
- Certain deeper tissue include :

ⓐ Intra Articular : Medication injected directly into the knee.
ⓑ Intrathecal : The drug is injected into spinal fluid around spinal cord.
ⓒ Retrobulbar : Medications injected behind the eyeball.
ⓓ Intrapleural : The drug is injected into the pleural cavity.

③ INTRA - ARTERIAL

- The intra - arterial route involves injecting medication directly into an artery to deliver the drug to a specific organ or tissues.
- This method ensures a high concentration of drug reaches the target area quickly while minimizing the effect on rest of the body.



SYSTEMIC ROUTES

The Drug administered through systemic routes is intended to be absorbed into the bloodstream and distributed all over the body, including the site of the action.

① ENTERAL ROUTES

- The enteral route refers to the administration of drugs through the gastrointestinal tract (GIT) for systemic absorption.
- It is the most common and convenient route of drug administration.
- It includes :

(a) Oral
(b) Sublingual
(c) Rectal

@ **Oral Route** :
- The oral route is the most common and convenient method of drug administration, where the drug is taken by mouth and absorbed through the gastrointestinal (GI) tract into the bloodstream.
- Both solid & liquid dosage forms can be given orally.

Limitations

- Slower Rate of Action
- Cannot be used for unconscious / vomiting patient.
- May cause nausea and vomiting
- First Pass Metabolism

ⓑ **Sublingual Route** :
- The sublingual route involves placing a drug under the tongue, where it dissolves and is absorbed directly into the bloodstream through a rich network of blood vessels in ~~buccal mucosa~~. sublingual mucosa.
- In this first pass metabolism is avoided.
- Drugs shows rapid absorption & action.
- Drugs must be lipid-soluble.

© **Rectal Route** :
- The rectal route involves the administration of drugs into the rectum.
- Use for irritant and unpleasant drugs
- Useful for vomiting and unconscious patients.
- However, it is rather inconvenient & embarassing.

② PARENTERAL ROUTE

- The parenteral route often refers to the administration of drugs by Injection, bypassing the gastrointeshinal tract.
- The word Parenteral made from two words :
  - Par - Beyond
  - Enteral - Inteshinal
- Some most important parenteral routes are :

(a) Intravenous
(b) Intramuscular
(c) Subcutaneous
(d) Intradermal

ⓐ Intravenous (IV) :

- The intravenous route involves injecting a drug directly into a vein, allowing it to enter the bloodstream immediately.
- Intravenous route has 100% Bioavailibility.
- It is the fastest way to deliver medication
- The drug is given at 25° Angle.

ⓑ Intramuscular (IM) :

- The intramuscular route involves injecting a drug directly into a muscle, where it is absorbed into the blood stream
- Muscles having a good bloodsupply, allowing the drug to be absorbed faster than subcutaneous injections but slower than intravenous administration.

© Subcutaneous :
- In this drug is deposited in the loose subcutaneous tissue which have rich nerve supply.
- This method provides a gradual and sustained drug release, making it useful for long-acting medications
- In this drug is given at 45° angle.

ⓓ Intradermal :
- The drug is injected into the skin raising a bleb of the epidermis
- In this drug is given at 10-15° angle.

③ Other Routes

Some other routes include :

ⓐ Inhalational
ⓑ Nasal
ⓒ Transdermal
ⓓ Transmucosal

ⓐ Inhalational :
- The inhalational route involves administering drugs in the form of gases, vapours or aerosols into the respiratory tract, primarily absorbs through lungs into the bloodstream.

ⓑ Nasal :
- The nasal route of drug administration involves delivering medications through nasal cavity, typically via sprays, drops or inhalers.
- This method allows the drug to be absorbed through the mucous membranes in the nose, directly into the bloodstream

ⓒ Transdermal :
- The transdermal route of drug administration involves delivering drugs through the skin, typically via patches, creams or gels.
- These medications are absorbed into the bloodstream through the skin's layers and provide a controlled, sustained release over time.

ⓓ **Transmucosal** :

- The transmucosal route of drug administration involves delivering medications through the mucous membranes, which are found in areas such as mouth, nose, eyes etc.
- Drugs are absorbed through the mucosa directly into the bloodstream.

SOME IMPORTANT TERMS

① AGONIST

- An Agonist is a drug or substance that activates a receptor in the body and produces a biological response.
- It works by mimicking natural chemicals to stimulate specific functions in the body.

② ANTAGONIST

- An Antagonist is a drug or substance that blocks a receptor in the body and prevents a response
- It works by stopping natural chemicals or other drugs from activating the receptor.
- It is of two types :

① Competitive Antagonist
② Non- competitive Antagonist

③ SPARE RECEPTORS

- Spare Receptors are extra receptors in a cell that are not needed to produce the maximum effect of a drug.
- This means that even if only some of the receptors are activated, the full response still happens.

④ ADDICTION

- Addiction is a strong and uncontrollable desire to use a drug, even when it causes harm.
- It happen because the drug changes the brain, making the person crave it and feel unable to control their use.

⑤ DEPENDENCE

- Dependence means the body gets used to a drug and a person feels unwell or has withdrawl symptoms if they stop taking it.
- It can be physical or psychological

⑥ TOLERANCE

- Tolerance means over the time , a person needs a higher dose of a drug to get the same effect.
- This happens because the body gets used to the drug, making it less effective at the usual dose.

⑦ TACHYPHYLAXIS

- Tachyphylaxis is when a drug stops working as well just after being used for a short time , even if the dose stays the same.
- It happens because the body rapidly adapts to the drug.

⑧ IDIOSYNCRASY

- Idiosyncrasy is when a person has an unusual or unexpected reaction to a drug that most people don't experience.
- This reaction is not related to the drug dose or an allergy ; it happens because of a person's unique body chemistry

⑨ ALLERGY

- An allergy is when the body's immune system reacts badly to a drug, thinking it is harmful.
- This can cause symptoms like rash, itching, swelling or even serious reactions like difficulty in breathing.

PHARMACOKINETICS

- Pharmacokinetics is the branch of Pharmacology that studies how drugs move throughout the body over time.
- It describe the process of ADME :

① Absorption
② Distribution
③ Metabolism
④ Excretion

- Now all the Pharmacokinetic processes involves transport of drug across biological membranes.

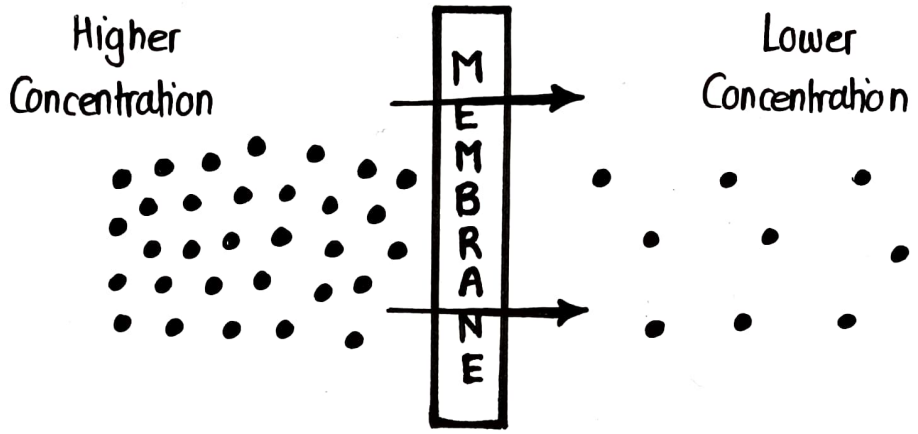
MEMBRANE TRANSPORT

- Membrane Transport is defined as transport of drugs across biological membranes, such as cell membrane, intestinal lining, blood-brain-barrier and renal tubules.
- It can be of following types :

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

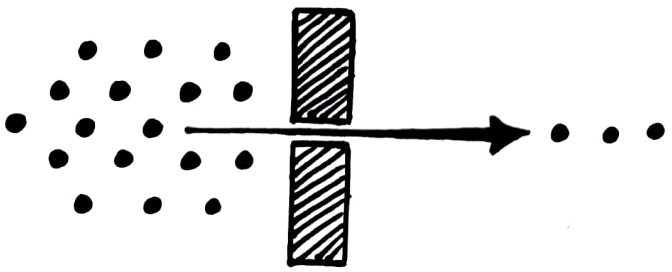
① Passive Diffusion

- 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.



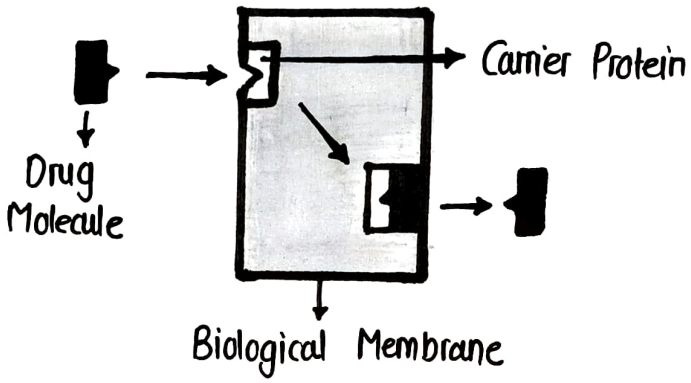
② Pore Transport

- 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.

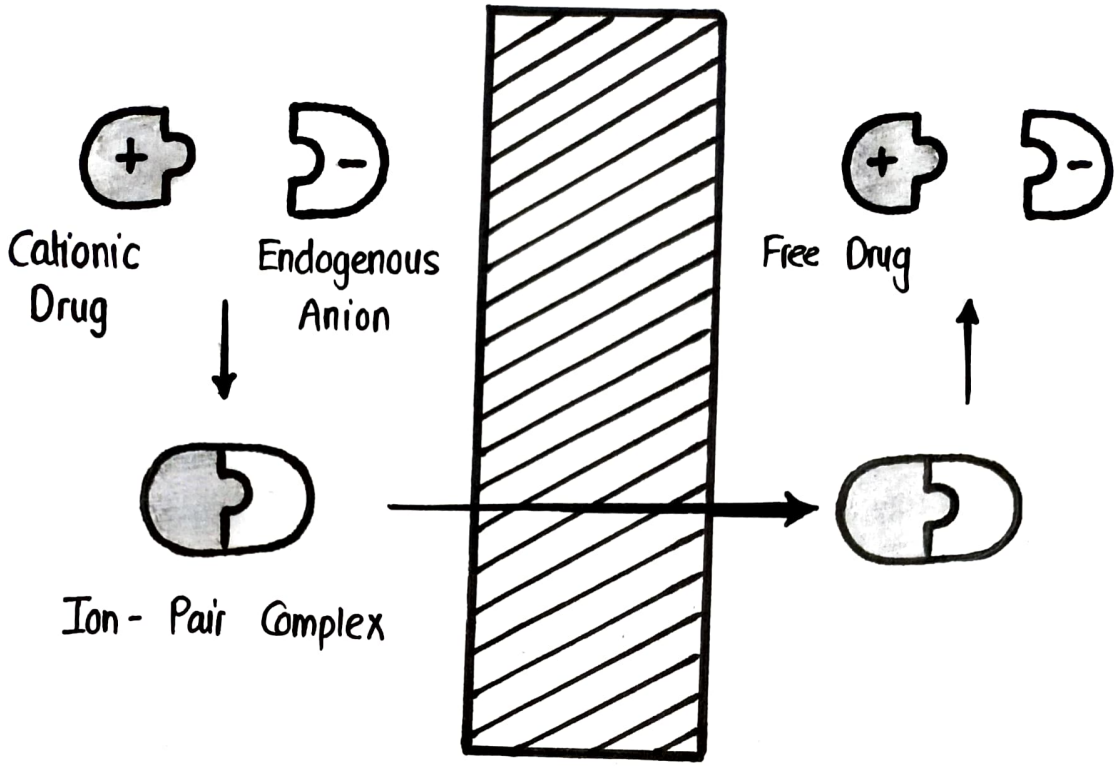


④ ACTIVE TRANSPORT

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

⑤ ION PAIR TRANSPORT

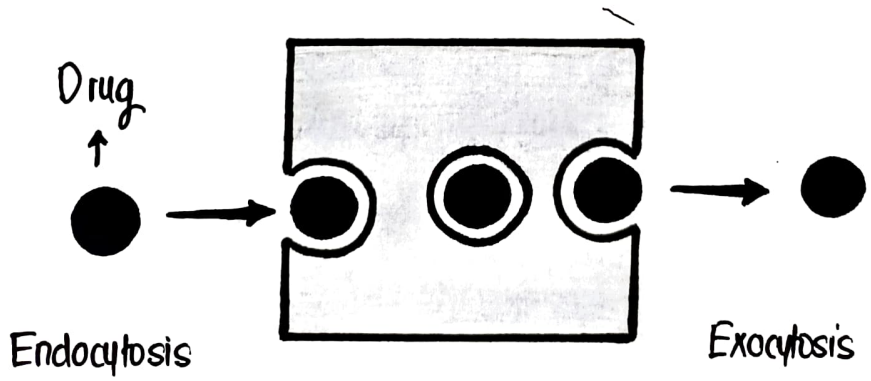
- Ion pair transport is a mechanism of drug transport in which drugs are transported across cell membrane as part of a paired complex with an ~~ion~~ endogenous ion.
- It particularly relevant for drugs that are poorly soluble and have low membrane permeability.



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)



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 :

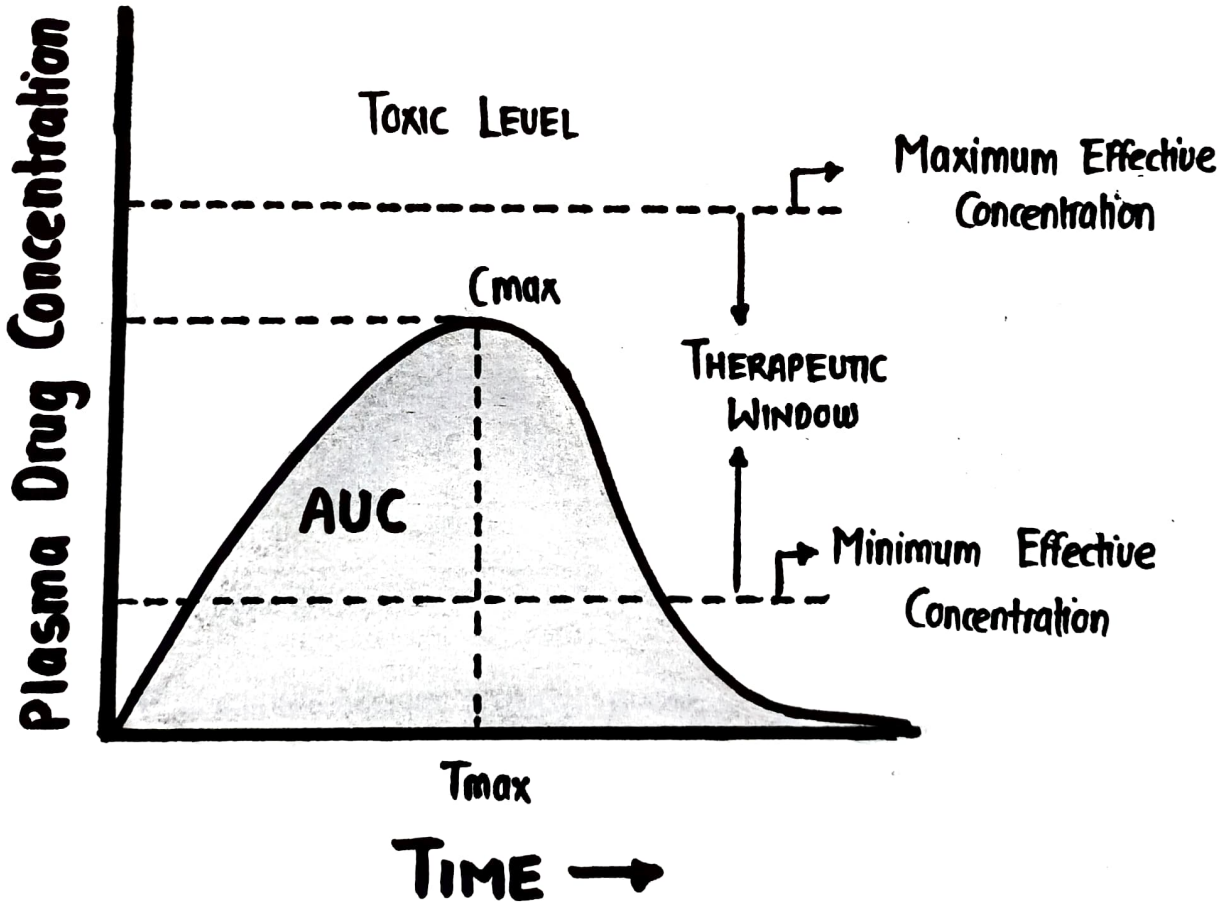
① Weak Acids
② Weak Bases

- 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)

BIOAVAILIBILITY

- Bioavailibility is defined as fraction of administered drug that reaches the systemic circulation in the unchanged form.
- It is expressed in percentage
- For Example: If 100 mg of a drug is taken orally and 50 mg reaches circulation, the bioavailibility is 50%..
- By IV route, bioavailibility is always 100%.
- Bioavailibility of Oral drugs can be calculated by comparing the Area under curve (AUC) of oral & iv route

$$\text{BIOAVAILIBILITY} = \frac{AUC_{oral}}{AUC_{IV}}$$



Here, Cmax = Peak Plasma Concentration Tmax = Time to reach Cmax

First Pass Metabolism

First Pass Metabolism is the process in which a drug is partially metabolized before reaching systemic circulation when administered orally.

How It Works

- When you take a drug (orally) by mouth, it first goes to the stomach and small intestine, where it is absorbed.
- From there, the absorbed drug enters the liver through the portal vein.
- The liver metabolizes (breakdown) a portion of drug before it can reach the bloodstream.
- Because of this breakdown, only a smaller amount of drug enters the bloodstream and reaches the target organs.

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 ~~ee~~ also affect absorption efficiency.

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.

Plasma Protein Binding

- Plasma Protein binding refers to the reversible interaction between a drug and proteins in the blood, primarily albumin, α_1-acid glycoprotein and lipoproteins.
- This binding affects the drug's distribution, metabolism, elimination and pharmacological properties.

Key Aspects

① Bound Vs Free Drug

- Bound Drug : Inactive, cannot cross membranes.
- Free Drug : Active form that can interact with receptors.
- Only free drug exerts pharmacological effect.

② Types Of Plasma Protein Involved

- Albumin : Binds acidic drugs like Warfarin, Phenytoin.
- α_1- Acid Glycoprotein : Binds basic drugs like propranolol, lidocaine.
- Lipoproteins : Bind lipophilic drugs like cyclosporine

③ Extent Of Binding

- Highly Protein-bound drugs : Longer Duration
- Weakly Protein-bound drugs : Shorten action

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.

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

METABOLISM

- It is also known as 'Biotransformation'.
- It is a process by which body transforms a drug into more readily excretable forms.
- The primary site for metabolism is Liver.
- Other sites include kidney, intestines, lungs and plasma
- Metabolism usually involves enzymatic reactions in the liver that alter (changes) the chemical structure of drug.
- These reactions makes the drug more water soluble and thus drugs becomes easier to be eliminated from the body via urine or bile.
- The metabolism of a drug usually converts:
  - Lipid Soluble → Water Soluble
  - Unionised → Ionized
- Metabolism is crucial for drug's duration and intensity of action, as well as for its overall safety profile.

DRUG METABOLISM

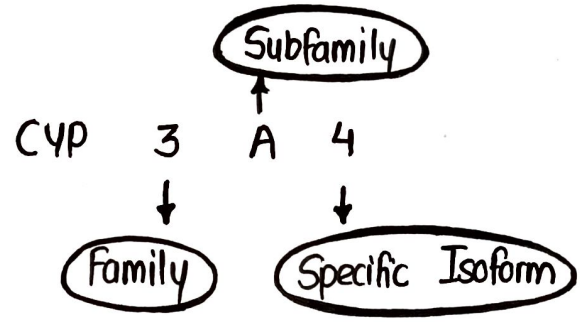
Metabolism usually leads to conversion of:

- Active Drug → Active Metabolite
- Active Drug → Inactive Metabolite
- Inactive Drug → Active Metabolite

Cytochrome P450 Enzymes

- Cytochrome P450 enzymes are group of proteins in the body that help breakdown drugs, toxins and other substances
- In Cytochrome P450, P stands for pigment that has maximum light absorption at wavelength 450 nm.
- Several families of CYP enzymes are involved in metabolism of drugs.
- These are named as CYP followed by a number (denotes family), then alphabet (subfamily) and again a number (specific isoform of the enzyme)

Example :



- CYP 3A4 forms the maximum hepatic content (26%) of CYP enzymes and is involved in metabolism of maximum percentage of drugs (33%).

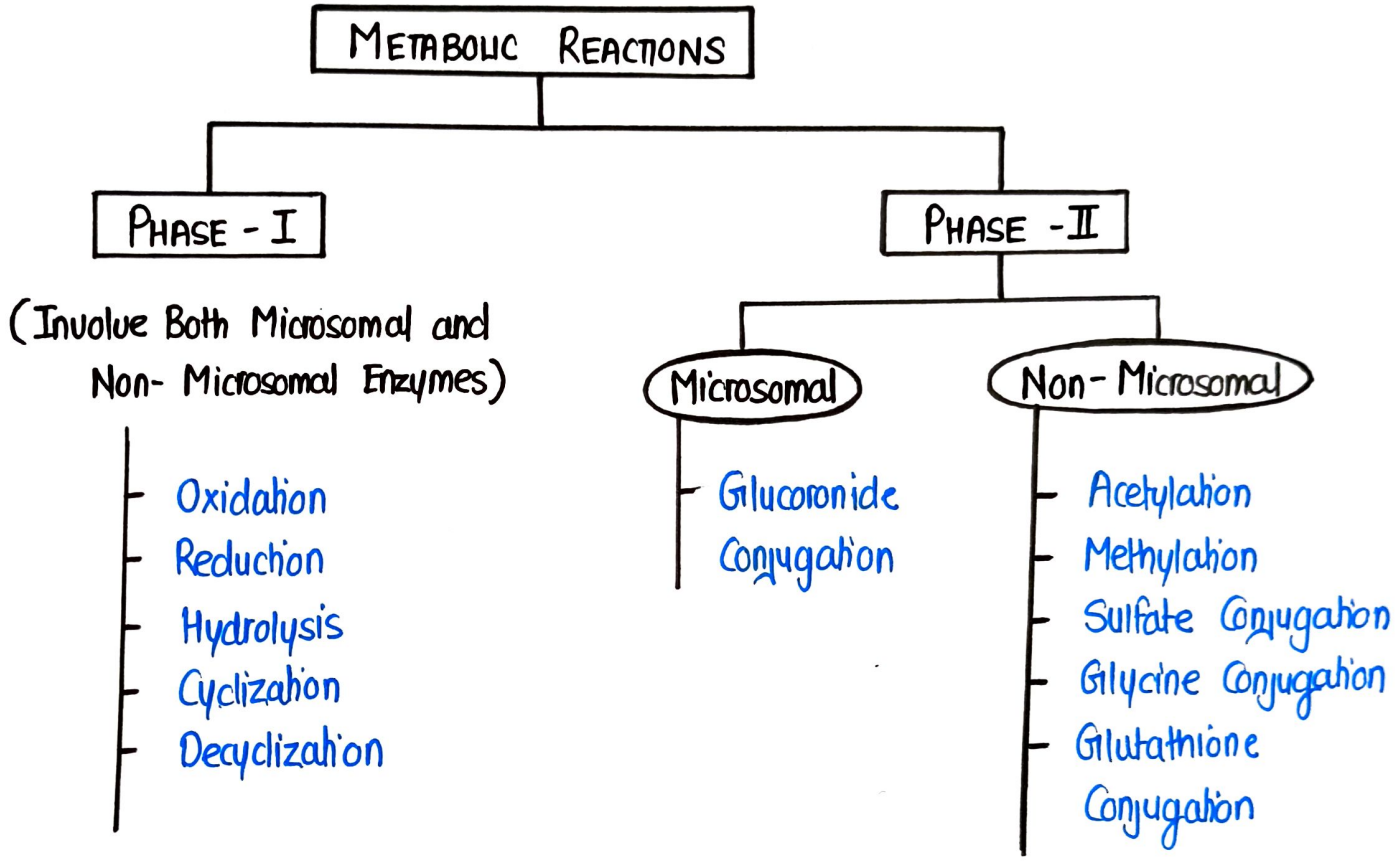
Example Of CYP Enzymes

- CYP3A4
- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2

Types Of Metabolism Reaction

There are mainly two types of Biotransformation reactions :

- Phase I Reaction
- Phase II Reaction



① Phase - I Reactions

These reactions introduce functional groups in the drug e includes :

- Oxidation
- Reduction
- Hydrolysis
- Cyclization
- Decyclization

ⓐ Oxidation

- Oxidation is the process of addition of oxygen to a drug molecule or removal of hydrogen from a drug molecule.
- Oxidation is primarily mediated by enzymes like CYP450s and results in the formation of more polar metabolites, which can be easily excreted from the body.
- Example : Phenytoin, Phenobarbitone, Propranolol

ⓑ Reduction

- Reduction is the process of addition of Hydrogen or removal of Oxygen from a drug molecule.
- It is less common than Oxidation.
- Example : Chloramphenicol, Warfarin etc.

ⓒ Hydrolysis

- Breakdown of drug molecule by addition of water is known as Hydrolysis.
- This is common among esters and amides.
- It is mediated by enzymes such as esterase, amidases & pephidases.

ⓓ Cyclization

- In this, straight chain compound converted into ring structure.
- example : Cycloguanil from Proguanil

ⓔ Decyclization

- It involves opening up of ring structure of cyclic drug molecule.
- Example : Barbiturates.

② PHASE II REACTIONS

- Phase II Reactions are also known as Conjugation Reactions
- These reactions attach polar groups (e.g. glucaronic acid, sulfate, acetyl, methyl) to the drug making it highly water soluble.
- These reactions include :

ⓐ Glucuronide Conjugation
ⓑ Acetylation
ⓒ Methylation
ⓓ Sulfate Conjugation
ⓔ Glycine Conjugation
ⓕ Glutathione Conjugation

ⓐ Glucuronide Conjugation

- It is the process of addition of Glucuronic Acid.
- It is mediated by UDP - glucuronosyl transferases (UGTs)
- Examples : Chloramphenicol, aspirin, paracetamol etc.

ⓑ Acetylation

- It is the process of addition of Acetyl Group.
- It is mediated by N- Acetyltransferases.
- Example : Sulfonamides, isoniazid.

ⓒ Methylation

- It is the process of addition of Methyl Group.
- It is mediated by Methyltransferases.
- Example : Methyldopa, Mercaptopurine.

ⓓ Sulfate Conjugation

- It is the process of addition of Sulfate Group.
- It is mediated by Sulfotransferases.
- Example: Chloramphenicol, Methyldopa etc.

ⓔ Glycine Conjugation

- It is process of addition of Glycine to the drugs.
- It is mediated by Glycine- N- Acetyltransferases.
- Example: Salicylates, Nicotinic Acid etc.

ⓕ Glutathione Conjugation

- It is the process of addition of Glutathione.
- It is mediated by Glutathione - S- Transferases.
- Example: Paracetamol

Factors Affecting Drug Metabolism

There are various factors affecting drug metabolism as follows:

- Age
- Genetics
- Liver Health
- Gender
- Diet and Lifestyle
- Drug Interactions

① Age

- Newborn babies shows slow metabolism as their liver is not fully developed.
- Liver functions decline with age, hence eldely people also shows slow metabolism.

② Genetics

- Some people naturally break down drugs faster or slower due to differences in their genes.

③ Liver Health

- If the liver is damaged (due to any liver disease), it cannot process drugs properly.

④ Gender

- Some drugs speed up or slow down metabolism when take together.

⑤ Diet and Lifestyle

- Grapefruit Juice slows metabolism of some drugs, leading to higher drug levels.
- Smoking & Alcohol increase metabolism, making some drugs work less effectively.

⑥ Gender

- Men and women process some drugs differently due to hormones.

Enzyme Inoduction

- It is the process by which a drug increases the prooduction (expression) or activity of metabolic enzymes.
- This leads to faster metabolism of drugs.
- As a result, drug levels in the bloodstream may decrease, potentially reducing therapeutic effect.
- Example: Rifampin induces CYP3A4 leading to increased metabolism of oral contraceptives, reducing their effectiveness.

Enzyme Inhibition

- It is the process by which a drug decreases the activity of metabolic enzymes.
- This leads to slower metabolism, causing increased drug levels in the bloodstream, which may lead to toxicity.
- Example: Ketaconazole inhibits CYP3A4, leading to increased levels of drugs like statins, increasing the risk of side effect

EXCRETION

- Excretion is the process by which drugs and their metabolites are eliminated from the body, primarily through the kidneys (renal excretion) but also via other routes such as liver, lungs, sweat, saliva and breast milk.
- It is a key factor in determining drug's half life, clearance and overall duration of action.

ROUTES OF DRUG EXCRETION

① RENAL EXCRETION : MAJOR ROUTE

Renal excretion is the major route of drug excretion and involves following steps:

- Glomerular Filtration : Drug molecules (specially unbound / free drug) are filtered through the glomerulus into the renal tubule.
- Tubular Secretion :
  - It is active transport of drugs from blood into the renal tubule.
  - Example : Penicillin is actively secreted in urine.
- Tubular Reabsorption :
  - Some drugs may be reabsorbed back into the bloodstream reducing excretion
  - Example : Weak acids like aspirin are reabsorbed in acidic urine.

② Hepatic Excretion

- In this, Drugs and their metabolites are excreted into bile and eliminated in feces.
- Example : Digoxin and steroids are excreted via bile.

③ Pulmonary Excretion

- Volatile gases and drugs are eliminated through exhalation.
- Example : Anesthetic gases are excreted via the lungs.

④ Sweat And Saliva Excretion

- Some drugs can be excreted in sweat or saliva, but this is usually a minor route.
- Example : Heavy metals and alcohol may be excreted in sweat.

⑤ Breast Milk Excretion

- Some drugs may excreted via breast milk in lactating mothers.
- Example: Tetracylines & Opoids.

KINETICS OF ELIMINATION

① CLEARANCE

The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time.
It can be calculated as

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

② ORDER OF KINETICS

The rate at which a drug is eliminated follows specific kinetic principles, primary first order or zero-order kinetics:

ⓐ First Order kinetics

- In this rate of elimination is directly proportional to the drug concentration.
- A constant fraction of the drug is eliminated per unit time
- As drug concentration decreases, elimination rate also decreases.
- Most drugs follow first order kinetics.

ⓑ Zero Order kinetics

- The rate of elimination is constant and does not depend on drug concentration.
- A constant amount of drug is eliminated per unit time.
- Very few drugs follow zero order kinetics

③ PLASMA HALF LIFE

The half life ($t_{1/2}$) of a drug is the time required for its plasma concentration to reduce by 50%..

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

Here, $t_{1/2}$ = Half life
0.693 = Constant (logarithm of 2)
Vd = Volume of Distribution
Cl = Clearance

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