UNIT-1

General Pharmacology

Pharmacology is basically the study of effects of drugs on the body and body's response to drugs.

Drug → It is the active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/cure of a disease. A drug alters or modifies the physiological systems or pathological states of the body.

History and scope

→ Oswald Schmiedeberg, regarded as the 'father of pharmacology', together with his pupils propounded some of the fundamental concepts in pharmacology. Since then, drugs have been purified, chemically characterised, and a vast variety of new drugs have been developed.

→ Hippocrates (father of medicines), who said that disease is the normal reaction of the body.

→ Paul Ehrlich, the father of chemotherapy found a cure for syphilis in 1909.

Nature and Sources of Drugs

Nature of drugs may be based on physical and chemical properties

(1) Physical Properties: It reveals the state of drug.

solid- Aspirin, paracetamol
liquid - nicotine, ethanol
gas - nitrous oxide

(2) Chemical properties :- Drugs can be organic or inorganic but the majority of drugs are organic.

inorganic drugs - ferrous sulfate, magnesium hydroxide.
organic drugs - cocaine, penicillin, aspirin, etc.

Sources

(1) **Animal Drugs** → Drugs obtained from different parts of animals such as pancreas, stomach, liver, intestine.
Example- Insulin, heparin, thyroid, vaccine, etc.

(2) **Plant Source** → Almost 90% of drugs are obtained from different parts of plant.
Example- Leaf (digitalis, tulsi, neem); flower (rose, vinca); Fruit (senna, opium); Root (Rauvolfia, shatavari); seeds (coffee beans).

(3) **Mineral sources** → Drugs obtained from minerals.
Examples- Kaolin, charcoal, $MgSO_4$, $NaHCO_3$

(4) **Microbial source** → obtained from microbes
Example- penicillin, streptomycin, neomycin

(5) **Synthetic Source** → drugs prepared artificially.
Examples- antihistamines, antipyretic, emetin, bismuth iodide, ampicillin.

(6) **Biotechnological source** → drugs prepared through recombinant tech.
Example- insulin is prepared by altering the DNA of Escherechia coli bacteria.

Essential Drugs Concept

WHO has defined essential medicines as "those drugs that satisfy the priority healthcare needs of the population.
Essential medicines should be available:
- at all times and in adequate amounts.
- in appropriate dosage forms
- with assured quality and adequate informa^n
- at low cost
- safe and effective

countries have its own list of essential medicines due to differing climatic conditions.
There are total 384 drugs in India's latest updated "National List of Essential Medicines (NLEM)".

Routes of Drug Administration

Drugs can be administered into the body through different routes. The choice of route depends upon nature of drug and patient-related factors:

(1) Physical and chemical properties of the drug: eg. solid, liquid, gas, pH, solubility, stability.
(2) Tissue or organ to be treated
(3) Rate and extent of absorption of drugs
(4) Effects of digestive juices and first pass metabolism of drug.
(5) Urgency of situation
(6) Patient condition :- unconciousness, vomitting

First-pass metabolism → a process in which a drug administered by mouth is absorbed from GI tract and directly transported to the lives via the hepatic portal vein, where it is metabolized (degraded). As a result, only a small portion of drug reaches the systemic circulation (blood) and the target tissue.

Classification

- **Systemic**
  - **Enteral**
    - Oral
    - Sublingual
    - Rectal
  - **Parenteral**
    - Injections
      - Intravenous
      - Intramuscular
      - Subcutaneous
      - Intraarterial
      - Intrarticular
      - Intrathecal
      - Intradermal
- **Local**
  - Topical
  - Nasal
  - Ocular
  - Mucosal
  - Inhalational
  - Transdermal

Systemic Routes → The drugs administered through systemic routes are intended to enter directly in blood circulation and distribute to the body and target site.
Examples- oral tablet, capsules, suspensions, injection

Local Routes → drugs act locally to the applied areas.
Example- topical ointment, lotion, cream, spray, drops, etc.

Oral or Enteral Route

→ Drugs are administered through the alimentary tract (enteron) known as oral route (mouth).

→ most common route

e.g. tablets, capsules, solution, syrups, powders

Advantages

- safest route
- economical
- systemic distribution
- no sterility required
- easy self-medication

Disadvantages

- onset of drug action is slow.
- irritant and unpalatable drugs cannot be administer
- not a useful route in presence of vomitting and diarrhoea.
- Drugs likely to be destroyed by digestive juices cannot be administered. e.g. insulin
- oral route is not useful in unconcious and uncooperative patients.

Sublingual route

The tablet or pellet containing the drug is placed under the tounge.

Example- GTN, buprinorphine

Advantages

- Rapid onset of action
- No first pass metabolism
- systemic effects

Disadvantages

- Inconvenient
- chances of spitting of drug

Rectal Route → drugs are placed into rectum for systemic effects.

Ex- suppositories, enema. This route can be used when patient is unconcious, vomitting.

Parenteral Route

Routes other than alimentary tract.

This route eliminates the factor of absorption because the drug is directly injected into the circulation.

Advantages of parenteral Route

- Drug can be administered to unconcious or uncoopestive patients.
- Drugs having low or slow absorption are administered parenterally.
- avoid drug modification by the alimentary juices and liver enzymes.
- Rapid action and accuracy of dose are ensured
- No first pass metabolism (FPM)

Disadvantages

- less safe and more expensive
- Inconvenient for use, self-medication is difficult
- may cause infection if proper care is not done.
- likely to injure important structures such as nerves and arteries.
- Drugs must be in acqueous solution
- once injected, drug cannot be removed.

Injections → with the help of a fine, hollow needle.

(1) **subcutaneous** → drug is generally injected into subcutaneous tissue of the forearm, upperarm, thigh, or abdomen.

(2) **Intramuscular (IM)** → into the skeletal muscles at the deltoid, triceps, gluteus maximus, rectus femoris or lumbar muscles.

(3) **Intravenous (IV)** → directly injected into the vein.

(4) **Intra-dermal ID** → administered into the skin layers (usually no hairs).

(5) **Intrathecal** → administration into the subarachnoid space of spinal cord.

(6) **Intraarticular** → into the joint cavity directly for the treatment of inflammatory joint condition.

Inhalational → drug quickly absorbed and produce rapid action.

Topical → applying medication to the skin or mucous membranes.

Nasal → drugs are insufflated through the nose.

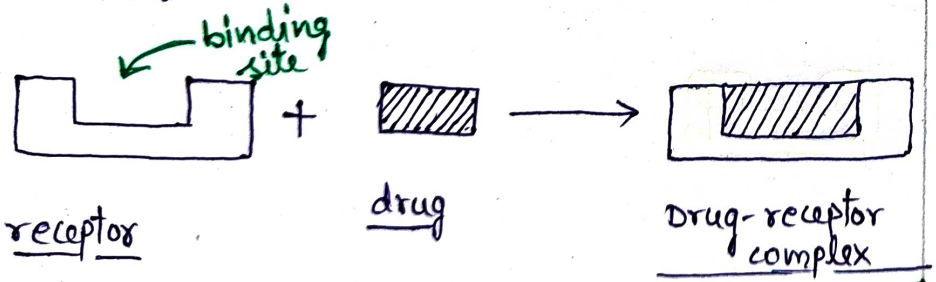
ocular → applied on anterior surface of the eye.

Transdermal → applying a drug formulation onto intact and healthy skin.

Agonists

A drug produces its effect on the body by first binding the receptors present on the surfaces of cells.

Drug forms the complex with the receptor to do that.



Generally, there are various hormones or neurotransmitters which bind to the receptors to produce their pharmacological effects endogenously.

An agonist is any drug substance that provides the same pharmacological action/effect as the hormones or neurotransmitters (endogenous drugs).

Agonists may be of following kinds:

(1) Endogenous agonists → a compound naturally produced in the body that binds and activates a particular receptor.

(2) Full agonists → bind to and activate a receptor with maximum response and high efficacy.

(3) Partial agonists → with partial efficacy and low response.

(4) Inverse agonists → produces an opposite effect as that of an another agonist.

(5) A co-agonist → works with another agonist to produce the desired effect together.

(6) A selective agonist → is selective for a specific type of receptor.

Antagonists

Antagonists are drugs that bind to the receptors and blocks them and inhibit the endogenous agonists to bind with the receptor.

→ Antagonists are similar in structure with agonists.

→ Antagonists do not give any pharmacological action.

Antagonists basically inhibit or prevent an agonist to produce a response by blocking their binding with the receptors.

Based on the interaction of antagonist with the receptor, antagonists are classified as competitive and non-competitive.

(1) Competitive Antagonist

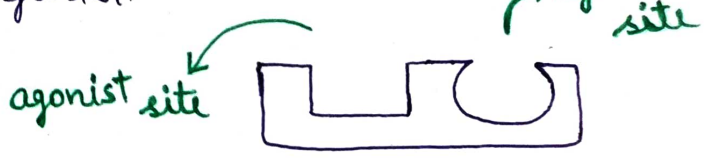
Competitive antagonism works on the principle that an agonist and an antagonist may have similar structure and they can bind to same binding site on the receptor, then, they compete for such sites.

→ An antagonist activity can be overcome by increasing the concentration of agonist.

example- naloxone is a competitive antagonist at all opioid receptors.

(2) Non-competitive

These antagonists bind to the receptor at a site closely associated to the site where the agonist will bind. They make the receptor inactive for agonist.



Spare Receptors

Spare receptors are those which are left unoccupied even after the maximum response of an agonist at a particular concentration. But if the concentration of agonist is increased, spare receptors may also be occupied.

Addiction

Addiction is the physical and psychological inability to stop consuming a drug despite all the adverse consequences.
It generally occurs when a drug is used for a long duration of time repeatedly.
e.g. heroine or cocaine.

Tolerance

Drug tolerance is the reduced pharmacological effect of a drug due to its repeated use for a long time. Dose of the drug is increased to bring back the normal pharmacological effect.
For example, when morphine or alcohol is used for a long time, larger and larger doses must be taken to produce the same effect.

Dependence

Drug dependence refers to someone feeling like they cannot function normally without the use of the particular substance or drug.
It may be physical or psychological dependence.
ex- nicotine, morphine, heroin, cocaine

Tachyphylaxis

It is the rapid decrease in response to a given dose of drug due to repetitive administration of the drug at short intervals of time.
Increasing the dose may be able to restore the original response.
ex- depression medications and eye drops that relieve redness or irritation.

Idiosyncrasy

Idiosyncracy refers to an strange reaction, which is an adverse reaction of a drug, which does not occur in most patients who have used the same drug.

The response of drug may be abnormally exaggerated or may be an abnormal lack of response.

example- liver injury

Allergy

An unusual response of the immune system towards a drug is called drug allergy.

Immune system does its job by attacking anything it thinks could put your body in danger.

ex- allergy to ibuprofen

Pharmacokinetics

Pharmacokinetics is the quantitative study of drug movement in, through and out of the body.

It is basically the study of what happens to the drug within the body.

Pharmacokinetics involves the following processes:

1) Absorption
2) Distribution
3) Metabolism
4) Excretion

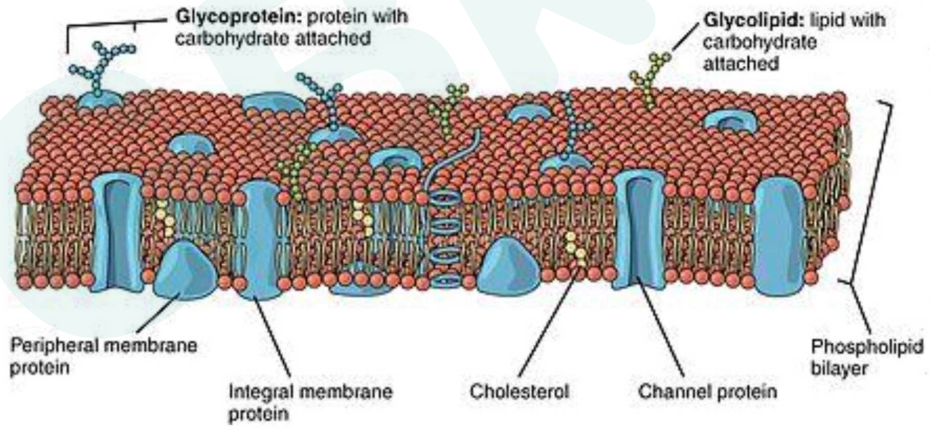
But before discussing all these processes, we will go through the anatomy and physiology of biological membrane.

Biological Membrane → It is flexible, fragile and transport barrier that contains all the cell contents and separate them from surrounding environment. It has selective permeability that controls flow of materials into and out of the cell.

Biological membrane (or cell membrane) plays a role in communication among cells and between cells internal and external environment.

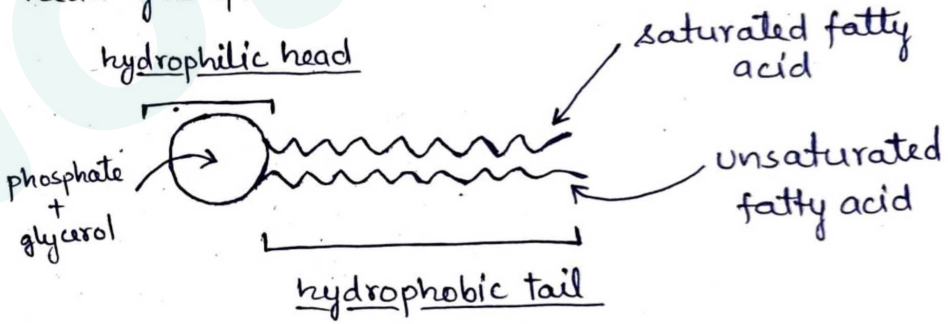
structure of biological Membrane

The currently accepted model of structure of plasma membrane is fluid mosaic model which was given by Singer & Nicholson in 1972.



The principal components of the plasma membrane are phospholipids, proteins and carbohydrate groups.

→ A phospholipid is a lipid made of glycerol, two fatty acids tails and a phosphate-linked head group.



Biological membranes usually involve two layers of phospholipids with their tails pointing inwards. This arrangement is called phospholipid bilayer.

→ The proteins may be embedded partly into the membrane, cross it entirely or loosely attached to its inside or outside face.

→ Carbohydrate groups are present only on the outer surface of the plasma membrane and are attached to proteins, forming glycoproteins or attached to lipids, forming glycolipids.

For a typical human cell, proteins account for about 50% of the total composition by mass, lipids – 40% and remaining 10% – carbohydrates

Membrane Transport

Transport across plasma membrane occurs by two methods:

1) Passive Transport → a substance moves down its concentration, across the concentration gradient. No energy required during the entire process.

(2) Active Transport → substance moves uphill against the concentration gradient. Energy in the form of ATP required.

Passive Processes of Transport

Diffusion → The movement of particles due to their kinetic energy from the region of their higher concentration to the region of lower concentration.

This may be of following types:

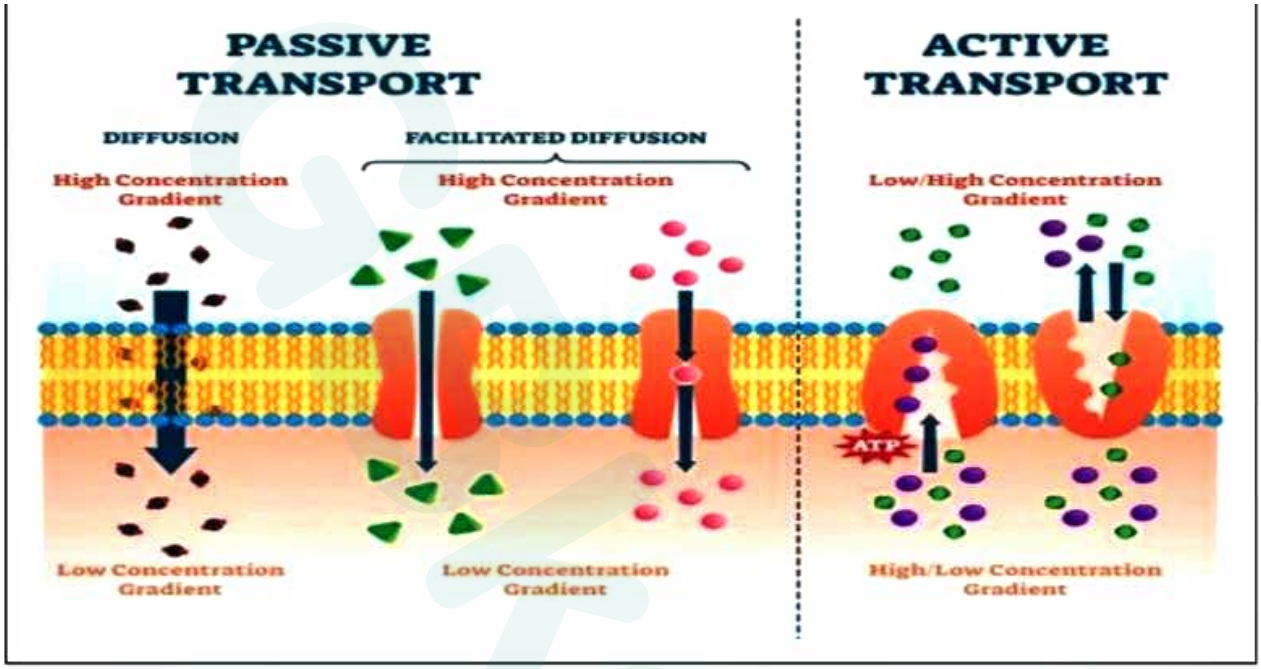
(1) simple diffusion → the particles move freely through the lipid bilayer.

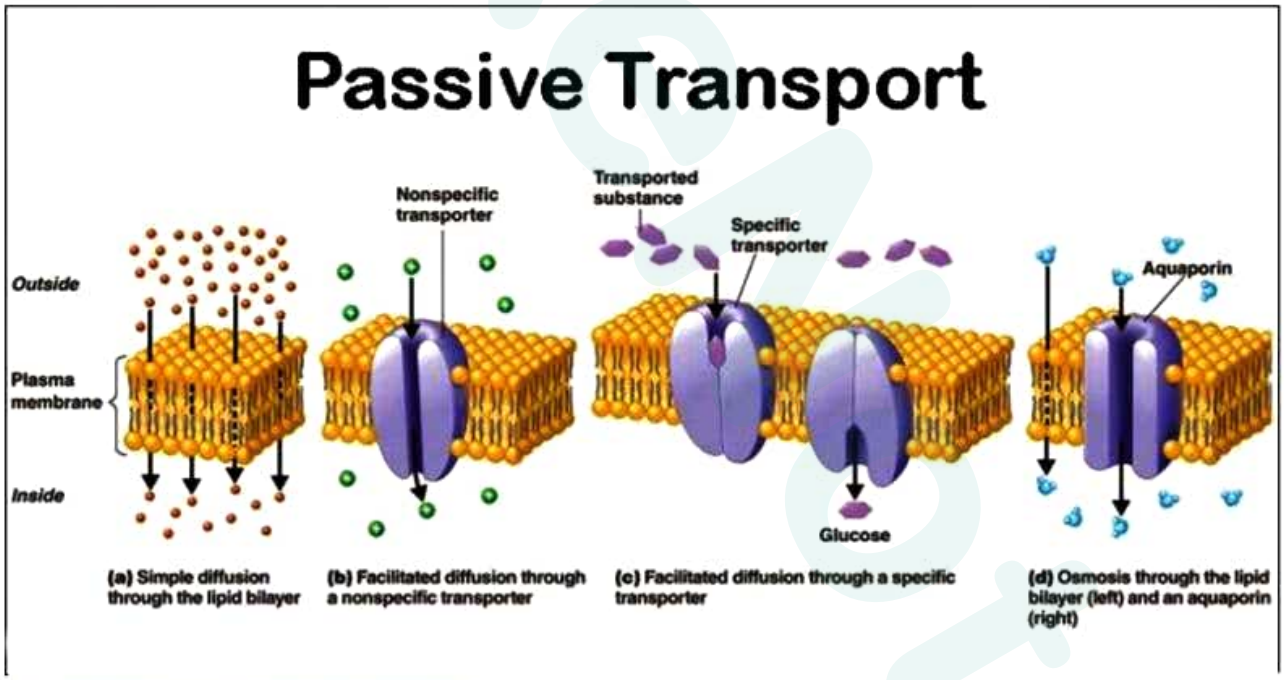
(2) Facilitated → membrane proteins or protein channels assist a substance in crossing the plasma membrane.

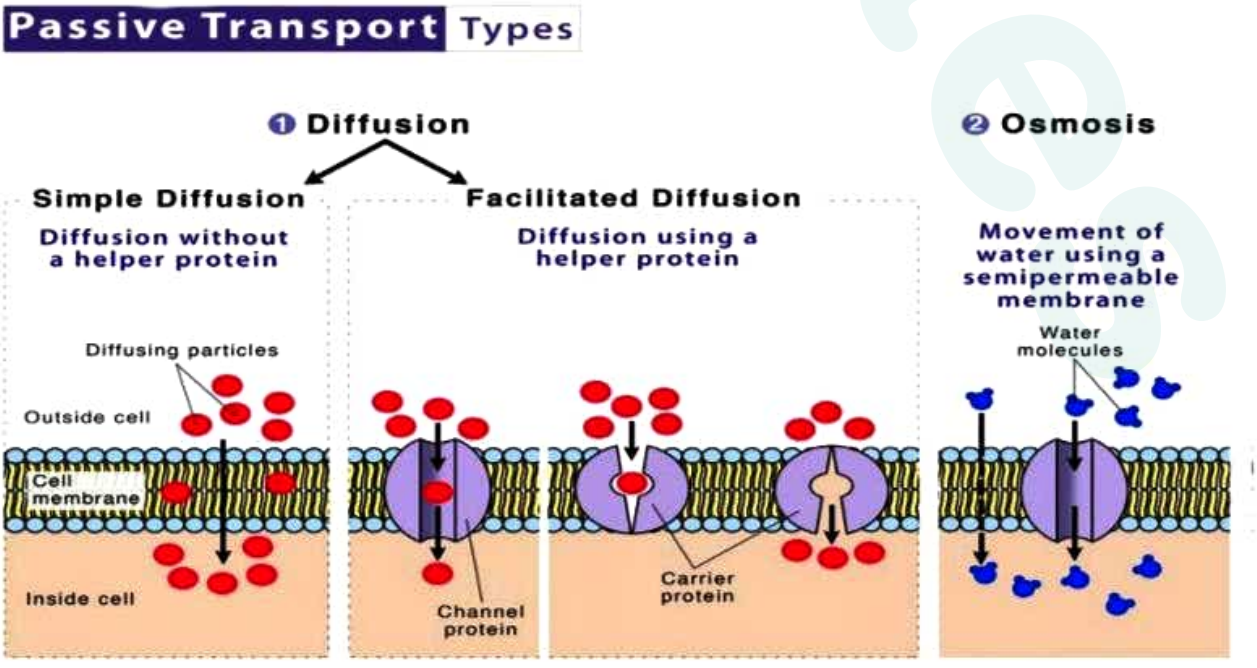
(3) osmosis → it is a special type of diffusion in which the movement of a solvent occurs through the cell membrane.

Active processes of Transport

Endocytosis → the material moves into the cell within a vesicle formed from plasma membrane.



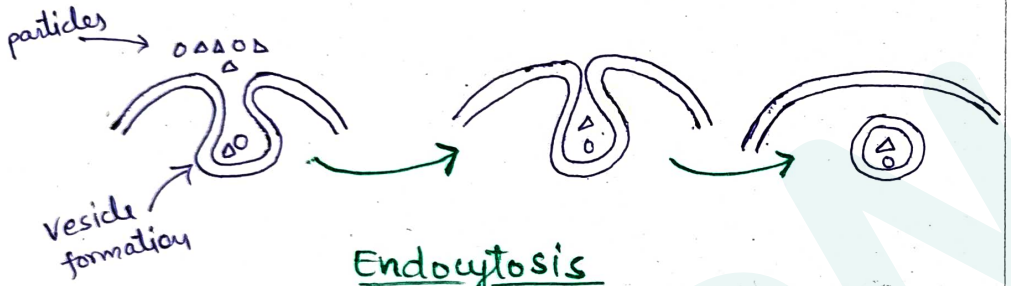




Endocytosis of 2 types:

(1) Phagocytosis → cell engulfs a large solid particles.

(2) Pinocytosis → vesicle contain a tiny droplet of fluid taken up by the cell.



Endocytosis

Now, we will discuss the pharmacokinetic processes.

Absorption of Drug

Absorption is movement of the drug from its site of administration into the blood circulation. Not only the quantity of drug absorbed is important but also the rate of absorption is important.

Absorption occurs through the biological membranes, so above mentioned methods apply.

Factors affecting absorption

(1) Aqueous solubility → a drug given as watery solution is absorbed faster than given in solid form or as oily solution.

(2) Concentration → drug given as concentrated solution is absorbed faster than from dilute solution.

(3) Surface area → Larger the surface area of absorption, faster it is.

(4) Vascularity of absorbing surface

More blood vessels (means more blood flow) at the site of absorption increases drug absorption.

(5) Route of administration → Route highly affects the rate and extent of absorption. Like, a drug administered via oral route will have slow rate of absorption than the sublingual route because in the former route, the drug has to cross various

layers of gastro-intenstinal organs while in the sublingual route, the drug has to cross just the mucous membrane in buccal cavity, to reach out to the blood circulation.

(6) Particle size of drug → smaller the particle size, greater the absorption.

(7) Ionisation → During absorption, the drug should be in unionised form.

(8) pH → pH of drug will decide where a drug will be absorbed.

- an acidic drug will be absorbed in stomach. e.g. aspirin.
- a basic drug will be absorbed in intestine. e.g. morphine

(9) Lipid solubility → Since the biological membranes have phospholipids, a lipopilic drug will diffuse more easily through it. Hydrophilic drugs have slower absorption.

Bioavailability

Bioavailability is the measure of how much of the administered drug becomes available at the site of action.

Also, bioavailability is the amount of a drug that arrives in bloodstream after its absorption.

Therefore, the drugs that are directly administered into the bloostream through intravenous means show 100% bioavailability. This is called absolute bioavailabity.

Relative bioavailability is the amount of drug that reaches the bloodstream by any other route than intravenous.

Relative bioavailability is always lesser than absolute bioavailability.

other routes may be:

- oral and sublingual
- Topical
- Nasal, etc.

Substances administered via routes other than I.V. have a much more complex journey. The drug has to cross various membranes, and bioavailability can be decreased in variety of ways.

Distribution

After absorption, drugs travel from the absorption site to various tissues around the body like fat, muscle and brain.

The path of drug distribution :

And this path is followed throughout the body

Drug is distributed by passive diffusion non-uniformly throughout the body.

It is a reversible process.

During drug distribution, transfer of drugs occur between one compartment (blood) to another (extravascular tissue or interstitial fluid).

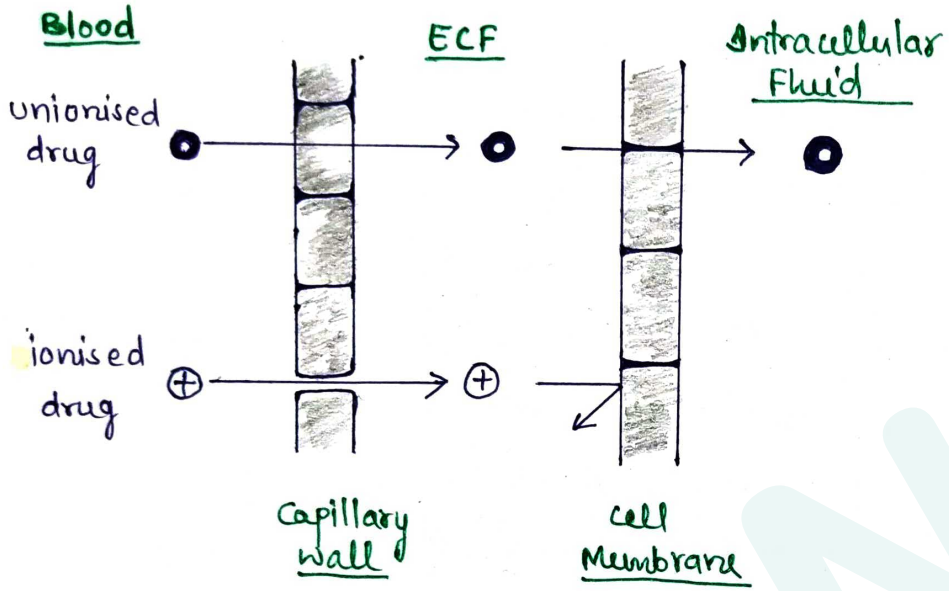
The presence of concentration of drug in extracellular fluid (ECF) will decide effect of drug.

Factors Affecting Distribution of Drugs

(1) Molecular size → Almost all drugs having molecular weight less than 500-600 Daltons easily cross the capillary membrane and enter the plasma or ECF. But only molecules of size below 50 Dalton enter the cell.

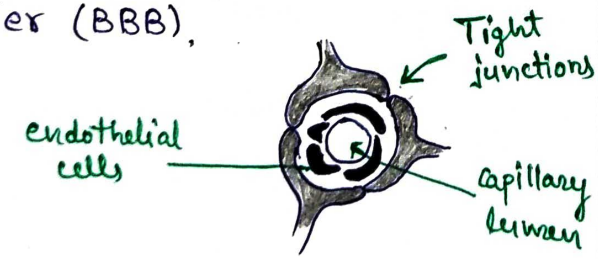
(2) Degree of ionisation

As we know that an unionised drug (lipophilic) easily pass the cell membrane. So, if the drug remains unionised at the pH of ECF, then it can permeate the cells relatively more rapidly.



3) Blood Brain Barrier

The capillaries that are found in brain are highly specialized and much less permeable to water-soluble drugs.
The brain capillaries consist of endothelial cells which are joined to one another by continuous tight intercellular junctions which is called blood brain barrier (BBB).



BBB is lipoidal in nature, so only lipophilic drugs are distributed (cross barrier).

✱ Blood-Cerebrospinal Fluid Barrier (BCSFB).

This is similar to BBB but BCSFB can also be crossed by highly lipid-soluble drugs.

✱ Blood-Placenta Barrier (BPB)

BPB restrict the effects of drugs from going to foetus during pregnancy.
BPB is also lipoidal and allows lipophilic drugs to enter plasma.

(4) Protein Binding of Drug

→ In the bloodstream, drug occurs in an equillibrium of partly bound to blood components and partly free (unbound).
→ The blood components may be plasma proteins, or blood cells and the drug bind to them reversibly.

→ The most important plasma proteins are albumin, α-1 acid glycoprotein and lipoproteins.

→ Only unbound drug is available for passive diffusion to extracellular fluid or tissue sites where the pharmacologic effects of the drug occur. Therefore, the concentration of unbound drug concentration in systemic circulation (i.e. blood) determines drug conc. at the active site.

→ The bound drug to proteins cannot cross the capillary due to larger size. Only unbound drug is available for this purpose.

(5) Volume of Distribution

Volume of distribution (Vd) is the ratio of amount of drug in the body and concentration of drug in plasma.

$$Vd = \frac{\text{Amount of drug in body (mg)}}{\text{Plasma concentration of drug}}$$

→ A drug with a high Vd has a tendency to leave the plasma and enter other compartments of the body. So, a higher dose of drug is required to achieve a given plasma concentrⁿ.
High Vd → more distribution to other tissue.

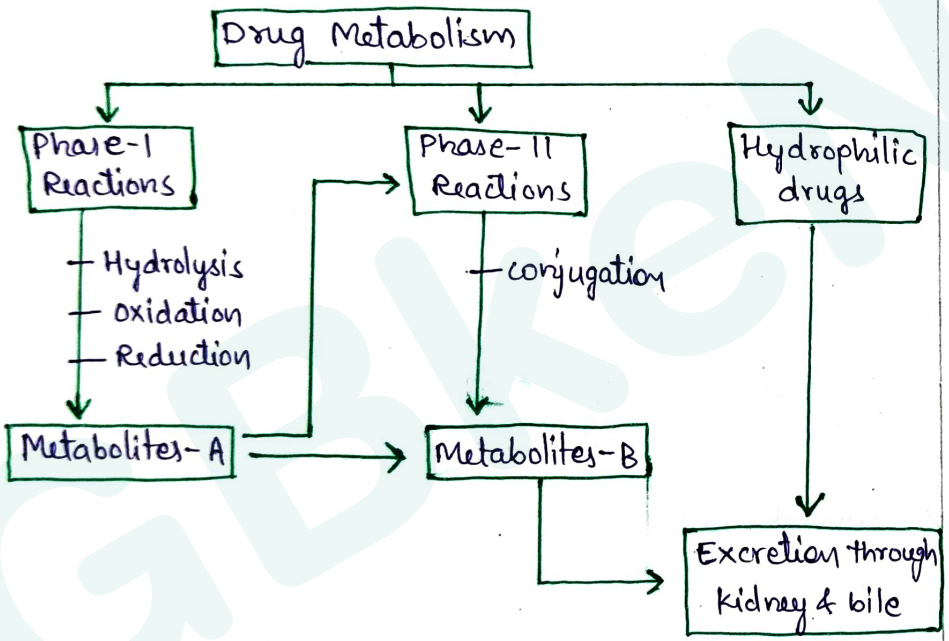
→ A drug with low Vd has a tendency to remain in the plasma (ECF) and will not leave to other tissues. So, a lower dose is required to achieve a given plasma conc.
Low Vd → Less distribution to other tissue.

Biotransformation

It involves the processes of metabolism.
The drug needs to be excreted out of the body after it has shown its pharmacological effects. otherwise, the drug will cause toxicity.
For this, the active form of drug is first converted to inactive form (biotransformation) before its excretion.

→ During metabolism, a lipid soluble drug is converted to water-soluble drug so that it does not get avoid during reabsorption and excreted out.

→ But an already hydrophilic drugs are excreted unchanged.



→ The primary site for drug metabolism is liver. There are some other tissues/organs also for metabolism — kidney, intestine, lungs, and plasma.

→ There are certain enzyme systems which catalyse the biotransformation processes in both phase-I and phase-II reactions.

→ These enzymes are microsomal enzymes such as cytochrome P_{450} oxidase, glucuronyl transferase.

Phase-I Reactions → Drug is metabolized by the processes like hydrolysis, oxidation, and reduction which increases the drug's polarity so that the drugs can easily be excreted out through kidney.

Phase-II Reactions → Faster than phase-I. Those drugs which are not metabolized in phase-I are also metabolized in phase-II.

Metabolites → These are the products formed during the reactions of phase-I and phase-II. These are inactive.

Factors affecting Drug Metabolism

Types of factors:

(1) Chemical factors
- enzyme induction
- enzyme inhibition

(2) Altered physiological factors
- Pregnancy
- Hormonal Imbalance
- Diseased states

(3) Route of drug administration

① **Enzyme Induction** → It is a process in which a drug induces or enhances the expression of an enzyme.

For example, Rifampicin, if taken by female patients who are already taking contraceptives, causes the decreased therapeutic effect of contraceptives, leading to pregnancy.

② **Enzyme Inhibition** → it is the decrease in the drug metabolizing ability of enzymes. Competition between the inhibitor and drugs occur for the active sites. When enzyme inhibitor attaches, less metabolism occurs.

Examples,
- Sulphonamides decrease the metabolism of phenytoin so that its blood levels become toxic.
- oral contraceptives inhibit metabolism of antipyrine.

③ **Pregnancy** → During pregnancy, metabolism of some drugs is increased while that of others is decreased due to the presence of steroid hormones.

Example-
- phenytoin metabolism ↑
- phenobarbitone metabolism ↓
- Pethidine ↓

④ Hormonal Imbalance → Higher levels of one hormone may inhibit the activity of few enzymes while inducing that of others. Examples-

Hypothyroidism increases drug metabolising capacity while hyperthyroidism decreases it.

⑤ Disease state → Liver disease such as hepatic carcinoma, cirrhosis, hepatitis, etc. reduce the drug-metabolizing ability of liver.

→ CVS diseases, although have no direct effect, decrease the blood flow, which may slow down biotransformation of drugs like isoniazid, morphine and propranolol.

⑥ Route of administration → oral route can be responsible for potentially high hepatic metabolism of some drugs due to first pass metabolism.

Ex- Lignocaine is almost completely metabolised if taken orally, therefore the preferable route for it is topical.

Excretion

Excretion is the process of removing a drug and its metabolites from the body. This usually happens in the kidneys via urine produced in them.

→ other routes are bile, saliva, sweat, tears and faeces.

→ Most drugs are polar (water-soluble) which are excreted directly. Those which are not polar are first metabolized become polar and then excreted.

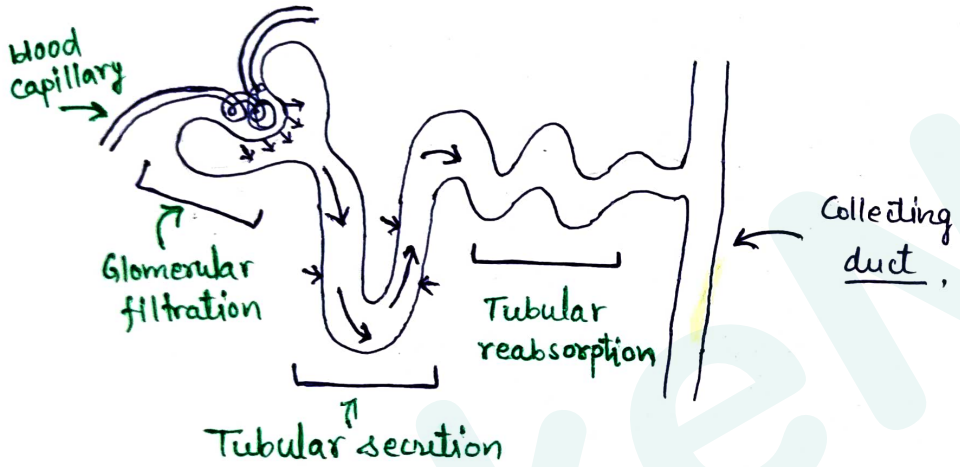
Excretory System

The excretory system is made up from two kidneys, ureters, bladder, urethra together with the branches of the two renal arteries and veins.

Nephron is the structural unit of kidney. It is a tubule of kidney. Drugs are eliminated from the nephron by the three processes:

(1) Glomerular filtration
(2) Tubular secretion
(3) Tubular reabsorption

- Glomerular filtration → small drug particles and metabolites and those not bound to plasma protein are filtered from the blood. Blood capillary contains drug.



Structure of Nephron

- Tubular secretion → most drugs enter the kidney tubule (nephron) from the interstitial fluid by leaking into the tubule and not by glomerular filtration. The process involves active transport.

Example of drugs- dopamine, histamine, penicillin,

- Tubule reabsorption → some drugs and metabolites are absorbed back into the bloodstream. This does not require energy. It is passive transport.

Clearance

Clearance is the rate at which a drug is eliminated from the blood. Drugs have different clearance rates. It is important to know the clearance, in order to determine the correct doses to be given.

→ Higher doses of drugs are required if it has a high clearance because the drugs are removed from the body rapidly.

→ Drugs with low clearance rates means that lower doses can be given to maintain the required concentration of drug in bloodstream.

$$\text{clearance} = \frac{\text{Rate of elimination}}{\text{plasma drug conc.}}$$

Kinetics of excretion

Generally, excretion is a first order kinetic process. It means that, the rate at which a drug is excreted is directly proportional to its concentration in blood plasma.

When administering a drug, if the times between doses are such that the drug is being replaced as quickly as it is being excreted, a constant drug concentration is maintained and a steady state is reached.

The equation for first order excretion is;

$$\text{rate of excretion} = K[D]$$

where,

[D] = drug concentration in blood plasma

K = rate constant

graph of concentration, [D] and time.