General Pharmacology

Pharmacology ↗ Pharmacon ⇒ drug
↘ logos ⇒ to study or knowledge

- Pharmacology is the branch of science that deals with the study of drugs and their interaction with living system.
- It is detail study of two divisions –
  → Pharmacodynamics
  → Pharmacokinetics
- Pharmacology as an experimental science was started (ushered) by Rudolf Buchheim who founded the first institute of pharmacology in 1847 in Germany.
- In 19th century, Schmiedeberg, regarded as the father of pharmacology.

⇒ Pharmacodynamics :– (dynamis – power)

– What the drug does to the body.

This includes physiological and biochemical effects of drug and their mechanism of action at organ system or site of action.

⇒ Pharmacokinetics :–(Kinesis - movement)

– What the body does to the drug.

- It is the effect of body on the drug. i.e. movement of the drug in, through and out of the body. It is also called ADME, study as it deals with Absorption, Distribution, Metabolism and Excretion of a drug.

Some other important aspects of pharmacology are: (2)

⇒ **Pharmacotherapeutics** –

It is the applications of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure.

⇒ **Clinical Pharmacology** :– Study of drugs with their clinical & uses.

It includes the evaluation of efficacy and safety of drug and comparative trials with other forms of treatment; surveillance of patterns of drug use, adverse effects, etc, are also part of clinical pharmacology.

⇒ **Chemotherapy** :–

It is the treatment of systemic infection with specific drugs that have selective toxicity for the infecting organism with no or minimal effects on the host cells.

⇒ **Toxicology** :–

It is the study of poisonous effect of drugs and other chemicals with emphasis on detection, prevention and treatment of poisonings. And also includes the study of adverse effects.

⇒ **Bioavailability** :–

It is the fraction or amount or concentraction of drug that reaches the systemic circulation in the unchanged form.

eg By. I.V. route it is 100%.

Historical Landmarks

The knowledge of drugs and their uses for disease are old as history of mankind.

- Primitive man (Ancient) gather the knowledge of healing and medicines by observing the nature, noticing the animals while ill and personal experience after consuming plant and herbs as remedies.

→ they discovered that extracts from plants, animals and minerals had medicinal effects on body tissue

Landmarks :-

- Hippocrates (460-375 BC) — A Greek Physician consider "Father of Medicines."

He was the first person who recognize disease as abnormal reaction of body. He introduce use of metallic salts for the treatment of disease.

- Paracelsus (1493-1541) - Grand father of pharmacology.

He introduces the use of chemicals for treatment of disease.

Modern Pharmacology :-

- Oswald Schmiedeberg (1838-1921) —
  ↳ Father of Pharmacology

→ He established pharmacology as an independent discipline.

→ Estimation of Chloroform in blood.

⇒ John Jacob Abel (1857-1938)-

→ Isolation of histamin from pituitary
↳ start allergic response (vasodilation etc)

→ Preparation of pure crystalline insuline

⇒ Paul Ehrlich (1854-1915) -

Paul Ehrlich was Nobel-prize-Winner.
↳ Father of Chemotherapy.

- Find a cure for syphilis in 1909.

⇒ Alexandar Flemming (1881-1955) -
↳ Scottish physician.

- He discovered world's first broadly effective antibiotic substances which he named Penicillin.

⇒ Ramnath Chopra (1882-1973) -

He was an Indian Medical Service Officer (IMS)

→ Father of Indian Pharmacology.

→ Systemetic study of Indian medicinal plant.

⇒ Scope of Pharmacology

- study about drug and their actions.

⇒ Study about disease or disorder which is comes under pathophysiology.

⇒ Study about pharmacodynamics, what it is effect of drug to the body in which study

about both desirable and undesirable effect of drug.

⇒ Study about pharmacokinetics.

⇒ In present time their are many ~~#~~ scope in Pharmacology such as Research, Industries and Academic

⇒ Study of clinical pharmacology, in which we study contraindication of drugs, their bioavailability. and also about posology.

⇒ Study of toxicology.

⇒ Study of forensic science (investigating).

⇒ Their are also great scope of pharmacology in ~~reach~~ research such as, drug development, drug discovery and clinical trials.

Nature and Source of Drugs

⇒ **Nature of drugs** - All drugs are chemical entities with simple or complex molecules.

⇒ Some drugs are inorganic nature.
eg- Ferrous sulfate, lithium carbonate, magnesium hydroxide etc.

⇒ ~~So~~ Majority of drugs are organic compounds.
it may be -
→ weakly acidic ⇒ Aspirin, penicillin, or
→ weakly basic ⇒ morphine or
→ non-electrolytes ⇒ Alcohols.

- Mostly drugs are normaly solids.
eg- Paracetamol, ampicillin etc.

but some such as ethanal, glyceral etc. are liquid and few like nitrous oxide is gaseous.

- the molecular weight of majority of drugs in the range of 100 - 1000 D.

⇒ According to their action -

(i) Preventive - Those drugs which used to prevent the cause of the disease.

(ii) Symptomatic - Those drugs which used to treat the symptoms of that disease.

(iii) Diagnostic - Those drugs which helps to determine the treatment or cause of disease.

(iv) Curative - Those drug which used in treatment of any disease.

(v) Health maintainance - Those drugs which help to maintain our health.

Source of Drugs

1. Plants
2. Animals
3. Microbes
4. Minerals
5. Synthetic
6. Biotechnology

① **Plants**:- Many plants contain biologically active active substances and are the oldest source of drugs.

eg- Alkaloids, Glycosides, Oils
- ↳ morphine
- ↳ Ephedrine
- ↳ Atropine
- ↳ digoxin,
- ↳ gentamicin
- ↳ Castor oil

② **Animals**:- Through animal parts have been used as cured since early times.
- used for making vaccines (blood).
- used of insulin for control diabetes.

eg- Thyroxine, insulin, liver extracts (Vit. B_{12}).

③ **Microbes**: Most antibiotics are obtained from fungi, ~~antibiotics~~ actinomycetes and bacteria,

e.g penicillin, gentamicin, actinomycin D (anticancer) etc.

⇒ Some times vaccines are also produced by the use of microbes.

④ **Minerals**: Few minerals, eg. iron salts, calcium salt, lithium carbonate, magnesium/aluminium hydroxide, iodine are used as medicinal substances.

⑤ **Synthetic**: It is largest source of medicines. It has the advantages of purity and uniformity of product, they can be manufactured as per need.

eg- Fluroquinalones, Bismuth iodine etc.

or some families - Benzodiazepines, thiazides etc.

⑤ Biotechnology :-

In which, Combined biological organism with technology and generate new drugs.

eg. Peptides & proteins are now produced by recombined DNA technology.

- Human growth hormones
- Human Insulin etc.

⑥ Essential Drugs Concept

WHO (World Health Organization) introduced the concept of essential medicines/drug in 1977.

[included 208 medications].

According to WHO, "Those that satisfy the priority healthcare needs of the population."

Criteria :-

They are selected with due regard to -

⇒ Public health relevance.

⇒ Clinical evidence on efficacy and safety.

⇒ Comparative cost effectiveness

⇒ Available at all time in adequate amount.

⇒ Appropriate dosage form.

⇒ With assured quality and adequate information and at a price the individual and the community can afford.

⇒ India proposed its first list in 1996, and has revised it in 2011, and now in April 2015 with the title name "National List of

Essential Medicines" [include 376 medicines].

→ the WHO updates the list in every two years. It can be differ from country to country due to change their environment.

eg - · Acetysalicylic acid (Aspirin)
· Paracetamal
· Ibuprofen
· Morphine etc.
for pain and palliative cure
↳ retieving pain

· Activated charcoal used as a antidote (used in poisonings)

Route of Drug Administration

- Local
  - Topical (on skin)
  - Inhalation (Nasal)
  - Rectal / Vaginal
  - Auricular (Ear).
- Systemic
  - Enteral
    - Oral
  - Parenteral
    - Sublingual
    - Buccal
    - Inhalation / Nasal
    - Subcutaneous
    - Rectal
    - Injection
      - Intravenous
      - Intramuscular
      - Intradermal
      - Intracardiac
      - Intraarterial.

A route of administration in pharmacology is the path by which a drug / medicine or any other substance is taken into the body.

- ~~Inter~~ .

(A) Local Routes of drug Administration

It is the simplest route in which drug is applied only an particular area or directly on ~~at~~ a site of action.

(i) Topical route - Drug is applied to the skin or mucous membrane at various sites for local action.

Advantages -

→ Apply for local action ✓

→ Painless, safe, cheap and useful ~~for~~ child.

Disadvantages -

→ Slow action ✓

→ Some drugs cause irritation. ✓

eg - Ointment, lotion, cream, powder, spray etc,

(ii) Inhalation / Nasal

It ~~is~~ also a part of systemic circulation. in which drug is inhaled through mouth / nose and give their action on particular area and also some drug is absorbed in blood capillaries present in mucous / muscles (Rapid absorption & effects)

eg Asthma used as a bronchodilators.

(iii) Rectal/Vaginal -

In which, special types of drug preparation is injected into rectum and vagina to give their local action on it.

Also some part is absorbed in systemic circulation, so it is also include in systemic route.

eg:- Suppositories or Enema etc.

advantages -

- gives to unconscious patients
- Ideal if drug cause vomiting.

disadvantages

- Cause irritation
- not a well accepted route.

(iv) Auricular/ear -

In this, drug is introduced into body cavity like ear, eye, and produced a local effect in it.

eg- drops, ointment and some times suspensions.

(B) Systemic Routes

In which, the drug administered through systemic routes means absorbed into the blood stream and distributed all over, including the site of action.

(1) Enteral: It means through intestinal (GIT) In which drug pass through intestine then reach into blood. It show first pass metabolism.

- First pass metabolism

In which drug directly goes into liver after intestine through portal vein, in which drug metabolise and their ~~distribution~~ bio availability will be decrease

① Oral route -

It is the oldest and simplest method (route) for drug administration. In which drug is directly take through mouth and it reach in systemic ct by passing GIT.

→ Both solid dosage form (powder, tablet, capsules etc) and liquid dosage form (elixirs, syrups, emulsion etc) can be ~~&~~ given orally.

advantage -

- Safe, more convenient, does not need assistance.
- painless, cheap and cost effective
- Easily available.

disadvantage -

⇒ Slow response due to first pass metabolism.
⇒ not suitable for emergencies.

② Parenteral :- (par - Beyond, enteral - intestinal)

It this drug is reaches into blood stream other than intestinal routes.

⇒ It follow Bypass - metabolism.

Bypass metabolism :- In which drug directly reaches into blood then reach at site of action through circulation without

passing intestine and liver.

(i) Sublingual / Buccal route – It may be in the part of enteral.

The tablet or pellet containing the drug in placed under the tongue / crushed in the mouth and spread over the mucosa, which further absorbed into the blood.

- only lipid soluble drug can be administrated also it is non-irritating.

advantage –

→ rapid action.
→ it follow bypass metabolism

(ii) Subcutaneous – (45°)

Drug is deposited into loose subcutaneous tissue, which is richly supplied by nerves.

• action of drug are uniform.

→ ~~set~~

(iii) Intravenous (IV) :-

In this, drug is directly injected into veins through injection, which absorb directly in to blood stream.

⇒ Injection inject at a angle of 25°.
→ 100% Bioavailibility, also for unconsious patients.

(iv) Intramuscular (IM). - (90°)

The drug is injected into muscles, then drug reach into blood circulation.

⇒ Rapid response.

(v) Intradermal - The drug is injected into the skin raising a bleb (a small blister of the skin).

→ injected into epidermis/dermis
→ rarely used (only for specific purpose)
eg. BCG Vaccine.

(vi) Intra cardiac:-

Drug is directly injected into muscles of heart.

- It is only used in an emergency situation.
- Need an expert for this.

(vii) Intra arterial:-

Drug administrate into artery.
(Blood vessels that ~~can~~ carries blood from the heart to the tissue & organs).
- Anti-cancer drug can be injected through it.

∴ Agonists ∴

These are those drug/substance ~~which has similar structure like ago~~ that bind to a receptor and cause the same pharmacological action as the substance that normally binds to the receptor.
It can be -
⇒ Full agonist - high efficacy, full response.
⇒ partial agonist - lower efficacy, less response

⇒ Inverse agonist – opposite response.
eg- Heroin, methadone, morphine (are full ex.) etc

Receptor – These are the binding sites of the drug on which drug attach, then activate it and give a pharmacological action.

- Two important terms related to the receptors are affinity and intrinsic activity(IA) or potency.

⇒ Affinity or Efficacy – ability of a drug to combine with the receptor.

⇒ Intrinsic Activity/Potency – After binding receptors, the ability to activate the receptor is called its intrinsic activity.

⇒ Antagonists – bind to the receptor but produces no effect. But now agonist is not able to the bind to the receptor because these are already occupied by the antagonist. Thus, it decreases the action of the agonist but itself has no effect.

⇒ It is of two types –
(i) Competitive Antagonist.
(ii) non-competitive Antagonist.

⇒ (i) Competitive – these are those antagonist which have similar structure like agonist.

⇒ It have affinity (100%) but no intrinsic activity (IA = 0).

⇒ There are a competition b/w antagonist and agonist, by increasing the concentration of agonist

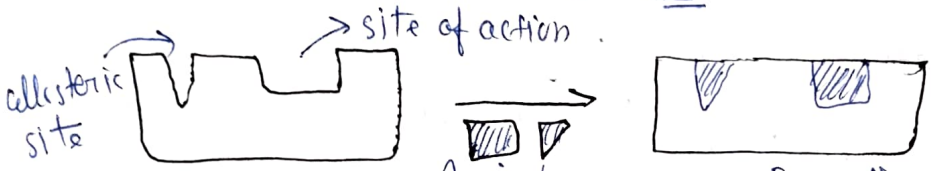
can overcome competitive antagonist activity.

eg- Morphine → Naloxone,
→ propranalol, atropine, etc.

(ii) Non-competitive antagonist – These are those antagonist which bind to an allosteric (non-agonist) site on the receptor to prevent activation of the receptor.

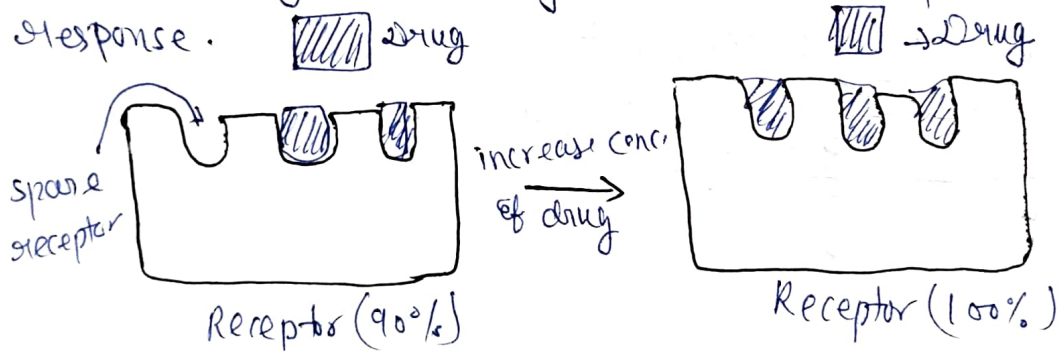
⇒ They have different structure than agonist.

eg- Diazepam → Bicuculline.



⇒ Spare receptor :-

These are those receptor which are not occupied by the drug molecules to produce 100% response.



eg. β_1-receptor (occupied only 90% drug)
of heart ↓ emergency situation (such as heart feilure)
occupied 100% receptor and give more pharmacological action.

⇒ **Addiction-**

"Specific side/adverse effect of drugs caused by prolonged use" means—

- When we take any drug/substance for a long duration, then it show some unusual response in our body.
- It is a psychological & physical inability to stop consuming drug even drug cause harm.

⇒ It is considered as brain disorder.

eg. Heroin, Cocain, Alcohol etc.

⇒ **Tolerance-**

It is the diminished effect (response) of any drug, when drug give repeatedly for long duration in the same dose.

- It happens when a person no longer responds to a drug in the way they did it first. So it takes a higher dose of the drug to achieve the same effect as when the person first used it.

eg- excess use of paracetamol etc..

⇒ **Dependence-** When a person take any drug/substance for a long duration for any reason/to cure, then our body become dependent on that drug and behave normal with that drug.

- If body not receive that drug, then it

may cause unusual effect such as Headache, & nausea, discomfort etc.

Body's with drug → Normal

Body without drug → Abnormal

eg. excess use of Analgesics drug
Used to releive pain (painkillers)

⇒ **Tachyphylaxis** :-

"Rapid decrease in the response of drug upon repeated administration of some dose in short intervals."

- also known as acute tolerance.

eg. Ephedrine, Nicotine etc.

⇒ **Idiosyncrasy** :-

It is the condition in which a side effect of any drug is seen only in very less population (or a particular people).

These effects known as idiosyncrasy effect.

eg. Barbiturates - (CNS depressant), but it cause some side effect such as mental confusion & excitment in some people.

⇒ **Allergy** → Some drugs/substance cause the unwanted side effect or adverse effect to our body.

"An abnormal reaction of the immune system to a medication/drug."

eg. Ibuprofen, Aspirin etc.
- Most common form of allergic reaction are skin reaction such as rashes, itching etc.

Pharmacokinetics

⇒ It is the quantitative study of drugs movement in, through and out of the body.
"What does body do to the drug."
- It invalves four procels - [ADME]

① Absorption
② Distribution
③ Metabalism
④ Excretion

1. Absorption

It is defined as the movement of drug molecules from its sites of administration to the systemic circulation.

⇒ When we take any drug through oral ~~route~~ route it goes into stomach in which disintegrate and dissolution take place, then drug reach into intestine.
- Now, after dissolution drug absorb into blood from intestine/stomach through membrane.

⇒ only lipid soluble drugs can cross the biological membranes.

So, if a drug is administrated by 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.

⇒ If a drug is a weak electrolyte, it is the unionized form which is lipid soluble and the ionized form is water soluble.

Membrane:- It is a biological membrane, which made up with phospholipid and cholesteral and other groups (Bilayer).

- It act as a semi-permeable membrane.

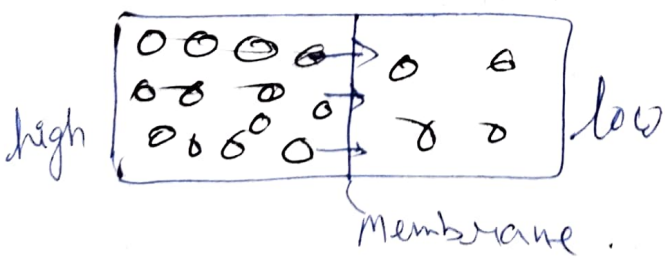
Now,

Drug reaches into systemic circulation through membrane transport - which are following -

(i) Passive transport ✓
(ii) Active transport ✓
(iii) Facilitated transport ✓
(iv) Endocytosis.

Concentration gradient.

When any drug / substance move from high concentration to low concentration



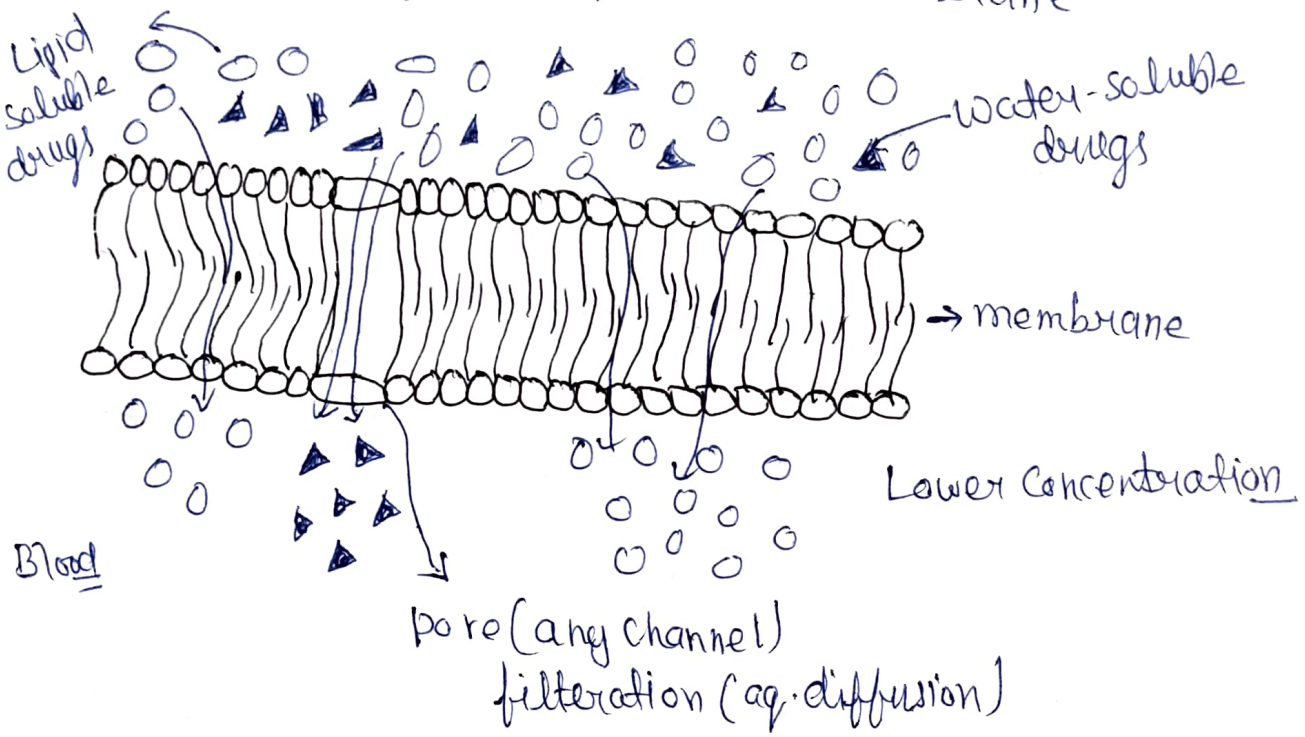
① Passive transport –

– also known as passive diffusion.

In this transport, drug move across the concentration (high to low).

- most of the drug absorb by passive diffusion.

diffusion ⇒ across the cell membrane
osmosis ⇒ through semi-permeable membrane.

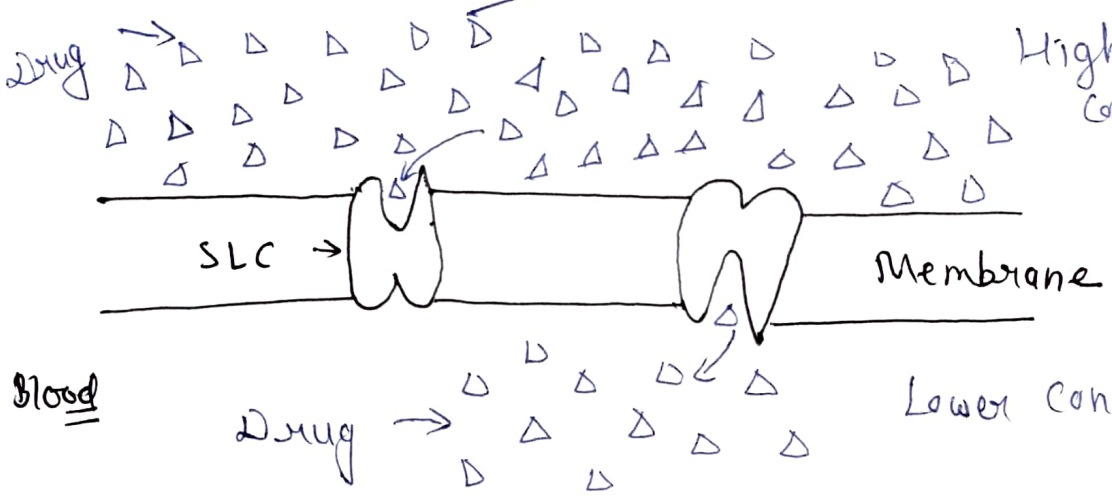


② Facilitated diffusion :-

In this transport, drug molecules move across the concentration gradient, but with the help of any carrier bodies.

- Some ~~layer~~ large molecules or powrly diffusible substance does not passes through passive transport, so they required help of any carrier body to cross the membrane.

- Carrier such as SLC (Solute-carrier transport)

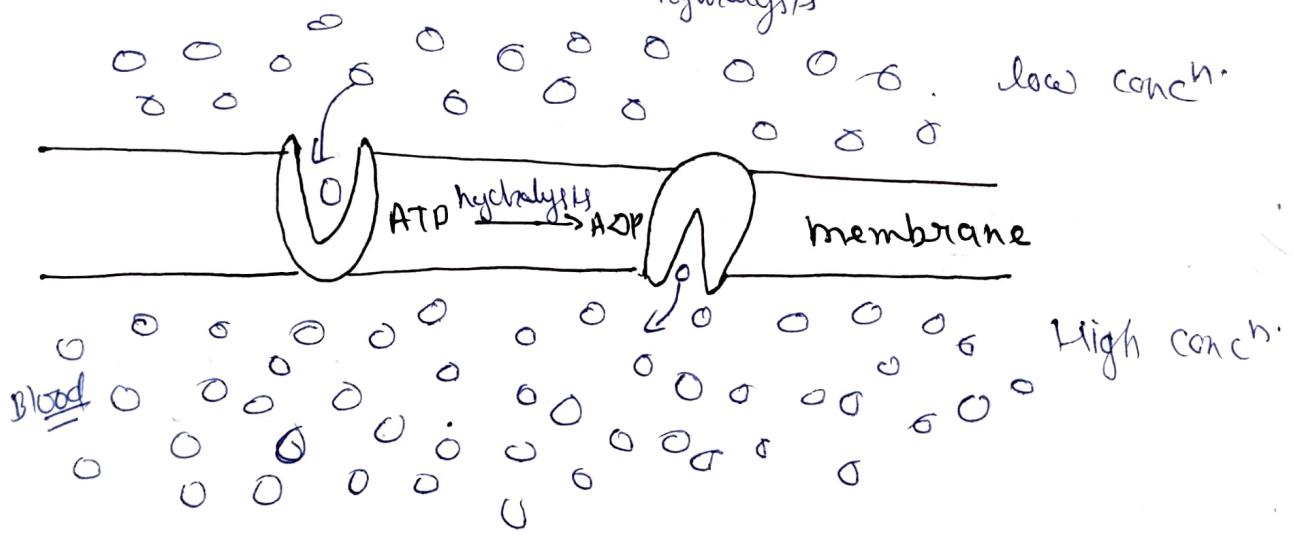


(iii) Active transport–

In this transport, drug molecules move against the conc^n gradient (low → High).

→ It required energy due to movement of drugs against the conc^n gradient.

- ATP is used ATP $\xrightarrow{\text{hydrolysis}}$ ADP



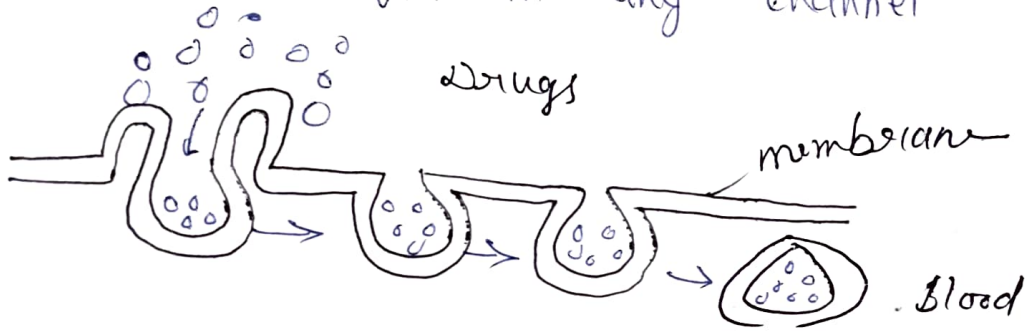
type

→ primary - through energy (ATP) | eg Na-K pump etc.

→ secondary - antiporter & symporter pump

(iv) Endocytosis :- In this transport, drugs of very large size get transport via engulfment by cell membrane. (23)

⇒ Due to large size, they do not cross membrane and also not fit in any channel.



• Absorption is not exactly straight forward (simple), it is a variable process; depends on various factors -

⇒ Ⓓ Factor affecting drug Absorption -

① Physio-chemical properties -
   (i) Particle size (drug molecules)
   (ii) Formulation (dosage form)
   (iii) Ionisation
   (iv) pH
   (v) Lipid solubility & Concentration.

② Biological factor.
   (i) surface area
   (ii) Membrane transport
   (iii) Gastric emptying time
   (iv) Blood flow (circulation)
   (v) Food

③ Routes of administration [Bioavailability & first pass metabolism]

① Physio-chemical

(i) Particle size -

It is inversely proportional to the absorption.

$$\text{Particle size} \propto \frac{1}{\text{Absorption}}.$$

- The smaller the particle size, the greater will be its absorption - because small size drug particles dissolve easily.

(ii) **Formulation** - In solid, liquid, parenteral (injection)

Parenteral > liquid dosage form > Solid

← Absorption.

(iii) **Ionisation** - We all know that, both form (ionized & unionized) are important for pharmacological response of drugs. But, for absorption drug must be in unionized formed.

(iv) **pH** - It tell about nature of drug (Acidic & Basic).

- Acidic drug must absorbed in stomach → Aspirin.
- Basic drug must absorbed in intestine → Morphine.

(v) **Lipid Solubility** - Lipophilic nature's drug has slightly higher absorption than hydrophilic. because in

membrane transport lipid soluble drug cross membrane easily.

(2) Biological Factor –

(i) **Surface area** – Area of absorbing surface.

It is directly proportional to the absorption.

Surface Area ∝ Absorption.

(ii) **Membrane transport** –

- Most of the drug absorb through passive diffusion, because it does not require energy or anything and also follow conc. gradient.

Passive transport > Facilitated transport > Active transport

Absorption.

(iii) **Gastric emptying time** –

- Those drugs whose gastric emptying time is more (fast), their rate of absorption is high.
- But time is not too fast, otherwise drug is excrete without absorption. So it is at optimum time.

(iv) **Blood flow (circulation)** – directly proportional the more blood flow in body, the greater will be absorption of drug.

⑤ Food- It will also affect the absorption of drug.

- If the food is present inside the stomach, then it dilute the drug and absorption will be decreased.
- So, take medicine after some time of meal.

③ Route of Administration-

This affects drug absorption, because each route has its own peculiarties (Characteristics).

Orally ①

② I.V

GIT → liver → vein → heart → Inhalation

Absorption

Excrete out ← Artery ← Heart ← lungs

⇒ Route of administration affect the bioavailability of drugs.

⇒ Bioavailability is the amount of drug, which reach into the systemic circulation.

⇒ Parenteral routes has maximum bioavailability.

⇒ In I.V., drug directly release into blood, so their absorption & bioavailability is 100%.

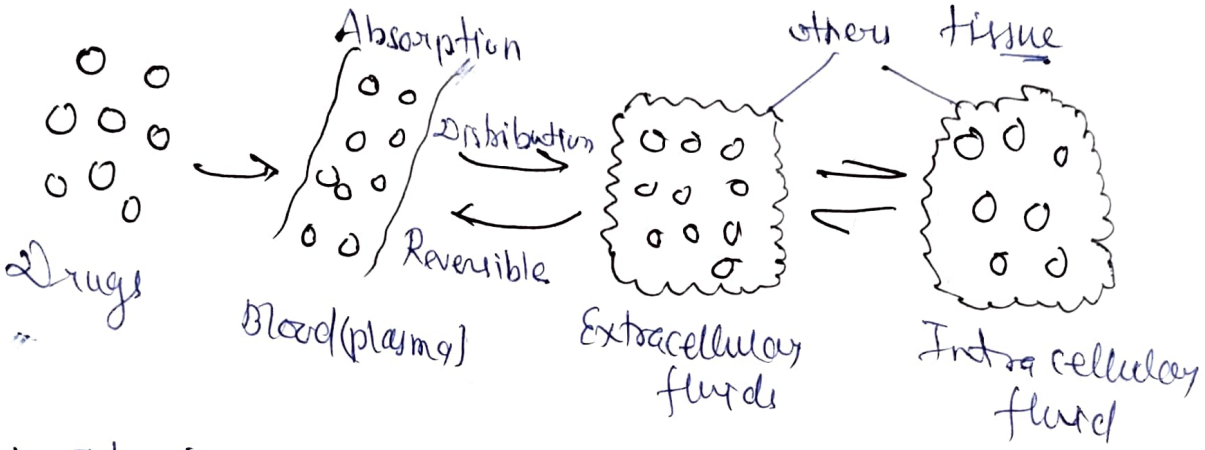
⇒ In subcutaneous / intramuscular, drug injected near the capillaries also have great absorption and bioavailability.

- Enteral (oral) has less absorption because it follow first pass metabolism

drug passes through liver which decrease the absorption.

2. Distribution

The movement of drug from systemic circulation to interstitial fluid (extracellular fluid) and various other part of body.



⇒ It is a passive diffusion process.
⇒ Drug distribute non-uniform throughout the body.
⇒ It is reversible process

- **Factor affecting drug distribution:-**

Distribution is very important step of pharmacokinetics, because in which drug reach to site of action then bind with receptor and give pharmacological action.

- It is also depend on many factor.

(i) Blood flow
(ii) Lipophilicity
(iii) Capillary permeability.
(iv) Plasma protein binding
(v) Some other factors.

(i) Blood flow – where will be more blood flow, there will be more distribution.

Blood → high blood flow → Brain, heart, kidney, liver etc.. [Distribution ↑]

Blood → Low blood flow → skeletal muscle, Adipose tissue etc [Distribution ↓]

(ii) Lipophilicity –

Greater the lipid solubility of the drugs, faster is its distribution.

- Because membrane is lipophilic, so drug can easily cross.

Lipophilicity ↑ = Distribution ↑.

(iii) Capillary permeability –

The higher the permeability of a capillary, the greater will be the distribution of drugs.

→ It is depends upon –

⇒ Barriers → (physiological barriers:)

(1) BBB (Blood brain barrier) –

The capillary endothetial cells in brain have tight junction & lack space, and investment of neural tissue cover the capillary.

Both forms BBB (eg liver ↑, Brain ↓ distribution)

⇒ These barrier are lipoidal, so only lipophilic drug distributed.

(ii) BCSFB → Blood-CSF-barrier, same as BBB.

(iii) Blood Placenta Barrier (BPB) -

It is seen in prengency, which protect to etus.

- It is also lipoidal and allow lipophilic drugs, and restrict hydrophilic.
- But sometimes it not work or drug taken by mother can affect the foetus/ new born.

⇒ Nature - Lipid soluble drug ⇒ has great permeability so high distribution.

(iv) Plasma protein binding -

When drug reach into systematic circulation then their are two form of drug.

- Free drug & Bound drug (those drug which bind with plasma protein)
- Most of the drug bind with albumin.

eg. Acacia drug generally bind to albumin.
Baic drug generally bind to α_1 acid glycoprotein.

⇒ Bound drug (plasma protein ~~to~~ bound drug) has less distribution, because their size increase so they can not cross easily membrane.

⇒ Free drug has good distribution.

~~eg~~.
- Barbiturates bound with albumin.
- Methadone bound with α-acid-glycoprotein.

⓿ Others-

- Age- also effect distribution, due to different in total body weight, fat. content etc.-
- obesity, high adipose tissue can take up large fraction of lipophilic drugs.
- Redistribution; distributed drug again distributed.

drug → Brain/heart/kidney/liver → distributed such as muscle/fat etc.

Volume of distribution-

- apparently volume of distribution.

$$aV_d \text{ or } V_d = \frac{\text{amount of drug in body (given)}}{\text{plasma concentration}}$$

- It help to know the distribution of drug in ~~our~~ body fluids. throughout the body.

3. Metabolism

→ Biotransformation.

⇒ To convert lipid soluble (non-polar) drug into water soluble (polar) drug to avoid reabsorption in renal tubules and help in excretion (remove the drug from body).

- Lipophilic → hydrophilic (increase polarity)
- Active drug (which gives pharmacological response) → Inactive form of drug (does not give any pharmacological response)

eg- Morphine → Morphine-6-glucuronide
Digitoxin → Digoxin

⇒ Primary site for drug metabolism is liver, others are – kidney, intestine, lungs and plasma.

⇒ There are different kinds of enzymes system present in the liver (highest) which biotranform the drug molecules.

⇒ Enzymes located in smooth endoplasmic reticulum of liver and also in other organs such as kidney, lungs etc. but in smaller concentration.

⇒ Mostly biotransformation are done by microsomal enzymes such as → Cytochrome, P-450, oxidas, glucuronyl tranferase.

- Biotransformation reactions can be classified into –

(a) Phase I / Non-synthetic / Functionalization reaction.

(b) Phase II / Synthetic / Conjugation Reaction.

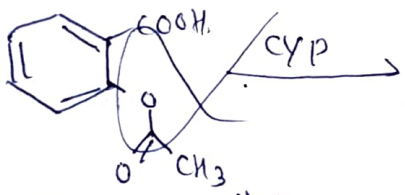
(a) Phase I reaction :-

In this, the drug can be metabolized by oxidation, reduction, hydrolysis and increase polarity of drugs. So drug can easily excrete from kidney.

- These are non-synthetic reaction.

Eg Oxidation –

This reaction involves addition of oxygen or negatively charged radical or removal of hydrogen



- Mostly in this reaction carried out by a group of monooxygenases in the liver.

- **Reduction –** This reaction is the converse of oxidation and involves cytochrome P-450 enzymes working in the opposite direction.
- Alcohols, aldehyde and quinones are reduced.

- **Hydrolysis –**

This is cleavage of drug molecule by taking up a molecule of water.

Ester + H_2O $\xrightarrow{\text{esterase}}$ Acid + Alcohol.

Similarly, amides and polypeptides are hydrolysed by amidases and peptidases.

⑤ Phase II -

It is faster than phase-I and also those drug not excreted after phase-I can excreted through phase-II.

⇒ It invalve the conjugation of with an endogenous substance such as glucuronic acid, sulfate, glycine.

⇒ these reaction are more polar, so drug can easily excreted by the kidney and liver (bile).

(i) Glucuronide conjugation -

This is the most important synthetic reaction carriedout by a group of UDP-glucuronosyl transferases.

Compound with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose.

eg- Chloramphenical, aspirin, paracetamol, diazepam etc.

(ii) Sulfate conjugation -

The phenolic compounds and steroids are sulfated by sulfotransferases (SULTs).

eg. → chloramphenicol, methyl dopa, adrenal and sex steroids.

(iii) Methylation -

The amines and phenols can be methylated by methyl transferase (MT);

eg- Adrenaline, histamine.

4. Excretion or Elimination

It is the removal of systemically absorbed drug from our body.

- It is the last stage of pharmacokinetics.

Routes of elimination-

1- Urine - Most of the drug excreted through the kidney by the process of urination.

- Water soluble drug excreted out through this.

2- Faeces-

Some of the drug in liver is absorbed in bile (which is secreted in liver) which further excreted through faeces.

- Mostly lipid soluble drug excreted through this.

eg- Erythromycine etc..

3. ~~Ext~~ Exhaled air-

Some drug is excreted in the form of gases or volatile liquid are eliminated by exhalation by lungs.

eg- general anaesthetics, alcohal etc.

4. Saliva & Sweat -

Some of drug is excreted b in the form of sweat ~~an~~ from skin.

- Some drug excreted through sputum which is mix with saliva, but most drug which along with saliva go into oral route.

eg. ↑ Lithium, heavy metal etc.
- Minor excretion.

5- Milk - In pregnant or new mother women's, Some drugs enter breast milk by passive diffusion and the excreted through mother's milk.
- mostly lipid soluble & less protein bound drug excreted through this -
eg - Alcohal, Lithium etc..

Enzyme induction

The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals known as enzymes. induction & agents called as enzyme inducers.
- It is due to -
  - increase in both liver size & liver blood flow.
  - increase Stability of cytochrome P-450 enzymes.

eg: Oral Contraceptic Steroids $\xrightarrow{CYP3A4}$ Inactive, Eliminated
↑ Induction

Rifampicine → enzyme inducers.
EI.
→ ethanol → Carbamazepine.
→ Phenobarbital → Warfarin.

Enzyme inhibition -

A decrease in the drug metabolizing ability of an enzyme is called as enzymes inhibiton.

- Azole antifungal drugs, macrolide antibiotics and some other drugs bind to the heme iron in CYP-450 and inhibit the metabolism of many drugs ~~and~~ as well as some endogenous substance like steroids, ~~bibib~~ bilirubin.

- direct → interaction at the enzyme site and change enzyme activity (comp. & non-comp.)
- Indirect → due to fall in rate of enzyme synthesis (repression) or due to nutritional deficiency or hormonal imbalance (altered physiology)

eg - Terfenadine → Active antihistamine

↑ → Inhibition

Erythromycin Ketoconazole

⇒ Kinetics of Elimination -

The knowledge of kinetics of elimination of a drug provides the basis for, as well as serves to devise rational dosage regimens and to modify them according to individual needs

⇒ These are three fundamental pharmacokinetics parameters, viz - bioavailability, volume of distribution and Clearance which must be understood.

→ bioavailability
→ volume of distribution } - discussed
→ Clearance (CL).

⇒ **Clearance (CL)** - The clearance of a drug is, "the theoretical volume of plasma from which the drug is completely removed in a unit time."

$$CL = \frac{\text{Rate of elimination}}{\text{plasma concentration (C)}}$$

→ **First order kinetics** -

The amount of drug eliminated over time is directly proportional to the concentration of drug in body

Rate of elimination ∝ drug concentration.

- Most of the drug is eliminated through first order kinetics.

eg - 1000 mg
- 150 mg ↓ -15 %
750 mg
- 188 mg ↓ -15 %
562 mg

- In this, eg. drug eliminated of constant rate 15% but the amount of drug ~~conch, so. Aspirine~~ (mg) is changed.

- **Zero ~~ed~~ order kinetics–**

The amount of drug eliminated is independent of drug conc^{n}. So, Aspirine.

Rate of elimination = Constant

eg- 1000 mg

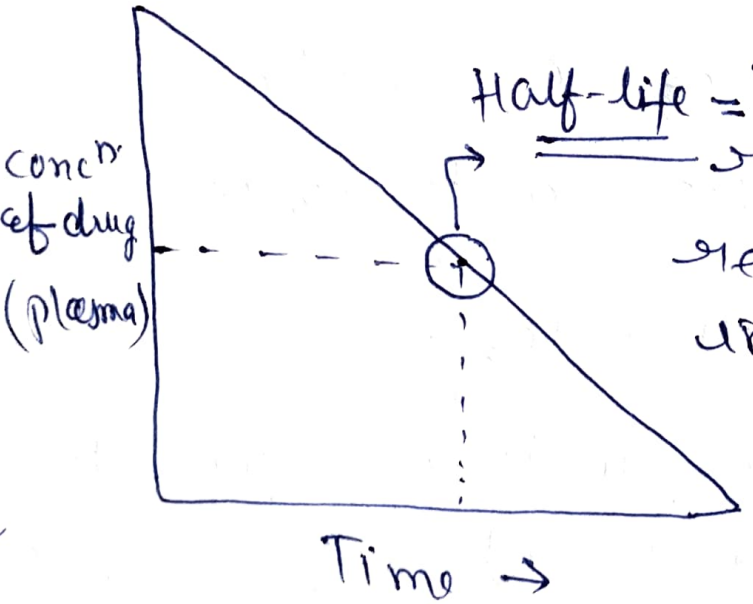
-11% | -100 mg

900 mg

-11% | -100 mg

800 mg

-12.5 % | -100 mg



Half-life = Time that is required to reduce drug conc^{n}. in plasma by half.