Unit-1

Pharmacology-I

B.Pharma 4 Sem Notes

UNIT-I

General Pharmacology

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

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

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Introduction to Pharmacology-

Definition:

- "Pharmacology" can be defined as the study of interactions between drug and biological system.
- It can be defined as the science of drugs or study of drug. The word "pharmacology " derived from Greek word.

  Pharmacon – Drug Logos – studied
- Which means pharmacology is the study of drug and their action of living body. It includes the knowledge of history source, biochemistry and physiological effects, mechanism of action and therapeutic uses of drug.

"Branch of pharmacology"

1. Pharmacokinetics:–
- What body does to the drug. In this the study of the action of drugs on target organ. It deals with the study of absorption, distribution, metabolism, excretion of drugs.

2. Pharmacodynamics: –
- What drugs dose the body. It deals with the mechanism of action and pharmacological effect of drug.

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 plants and herbs as remidies.
- They discovered that extracts from plants, animals and minerals had medicinal had medicinal effects on body tissue.

1. **Francois Magendie (1783-1855):-** A French physiologist loid

down the dictres "Facts & Facts alone are the basis of science " Experimental procedures with animals are the testing grounds for determination of drug action.

2. **Claude Bernard (1813-1878):-** Investigated the plant extract curare and proposal a site of action for this agent.
3. **Rudolf Buchheim (1820- 1879):-** In 1847 Buchheim established the first laboratory for experimental pharmacology in the basement of his home and named Cradle of experimental pharmacology.
4. **Oswald Schmiedeberg (1838-1921):-** He is father of pharmacology and publish 1st journal of pharmacology. J.N. Longley (1852- 1925)- Herry dale (1875-1968):- Pioneered pharmacology in England taking physiological approach.

Scope of pharmacology

Nowadays, The term Pharmacology has been expanded and subdivided into various terms. These subdivisions are

- **Pathophysiology:** The science or the study of disease/disorder is defined as pathophysiology.
- **Pharmacodynamics:** That branch of pharmacology that considers the mode of action, and the effects of medicines.
- **Pharmacokinetic:**
  A-Absorption
  D- Distribution
  M- Metabolism
  E- Excretion

- **Clinical Pharmacology:** Study of drugs which includes both pharmacodynamics and pharmacokinetic parameters that are-(uses, contraindication, adverse effects etc).
- **Pharmacotherapeutics:** The use of drugs to treat the disease and to produce a therapeutic effect inside the body.
- **Toxicology:** It consists of two words- Toxin-which means poison & Logy- means to study. Hence, The branch of pharmacology that deals with the nature and effects and the treatment of poisons. Toxicology is one of the most important subdivisions of pharmacology as it is directly related to poisons and the other type of effects that are not desirable for us.
- **Pharmacovigilance:** The study of outcomes after the drug intake through case study and eradicate the problems.
- **Pre-Clinical Trials:** These trials are performed on the animals to

study the effects of the drug, by keeping the animal under regular observation.

- **Pharmacogenomics:** The branch of genetics that studies the genetically determined variations in responses to drugs in humans or laboratory organisms.

- **New Drug Development or Drug Discovery:** The development of a new drug molecule is a toilsome, time-consuming, and very expensive process. There are various tiers in New Drug Development.

Nature and source of drugs:

Nature of Drugs:

The nature of drugs depends on various factors such as physical properties, chemical properties , size, shape, etc.

1. Physical Properties: It reveals the state of the drug. Some of the examples are

- Solid- Aspirin, Paracetamol etc.
- Liquid- nicotine, ethanol etc.
- Gas- nitrous oxide.

2. Chemical Properties: Drugs can be organic or inorganic but the majority of the drugs are organic.

- Inorganic Drugs- These are the drugs relating or belonging to the class of compounds not having a carbon basis. For example ferrous sulfate, magnesium hydroxide etc.
- Organic Drugs- These are the drugs relating or belonging to the class of chemical compounds having a carbon basis. For example cocaine, penicillin, aspirin etc.

3. Drug Size: Most of the drugs come under the range of 100-1000 daltons. According to their size, drugs bind specifically to their binding site.
Molecules less than 100D don't generally have their unparalleled features such as shape, size, configuration, chirality etc.
Molecules having their MW of more than 1000D cannot readily diffuse within the cells/tissues of the body.
Few examples

- Lithium-7D
- Heparin-10-20D
- Gonadotropins-(>30D)

4. Drug Shape: Drug shape must be antonymous to the receptor site like that of lock & key so that they can bind easily and promote their actions accordingly. Most of the drugs show chirality.

Sources of the Drugs:

- The origin of drugs is versatile. It is obtained from many sources such as plants, animals, minerals, microbial, synthetic and biotechnologically.

A) Plant Source: It is the most plethoric source of drugs. Almost 90% of drugs are obtained from different parts of the plant. Drugs can be obtained from every part of the plant.

Examples

- Leaf – digitalis, tulsi, tobacco, neem.
- Flower- rose, vinca
- Fruit- senna, opium
- Root- rauwolfia serpentine, shatavari
- Seeds- coffee beans
- Bark- cinchona

B) Animal Source:

Drugs originated from the different parts of the animals (pancreas, stomach, liver, intestines etc.) Example

- Pancreas of cow- insulin
- Stomach of cow- pepsin
- Sheep- thyroid
- Cod liver oil
- Blood- vaccine
- Urine- hCG hormone
- Bone- gelatin, calcium

C) Minerals:

Drugs obtained from various minerals. Examples

- Chlorine – disinfectant
- Zinc- wound healing
- Silver- immunity booster
- Borax- antiseptic

D) Microbial Source:
Drugs which we get from microbes. Examples

- Penicillium notatum- penicillin
- Streptomycin- Streptomyces griseus
- Neomycin – Streptomyces fradiae
- Lactobacillus- lactic acid

E) Synthetic Source:
Drugs which are not of natural origin; prepared or made artificially. Examples

- Antihistamines
- Antipyretic
- Emetin
- Bismuth iodide
- Ampicillin

F) Biotechnological Source:

- Drugs that are prepared by combining the principles of biology & technology that are through recombinant technology are called biotech drugs. Examples
- Insulin is prepared in labs through biotechnology for humans by altering the DNA of Escherechia Coli bacteria.

Essential Drugs Concept And Routes Of Drug Administration:

WHO (World Health Organization) introduced the concept of essential medicines (drug) in 1977 (Included 208 medications)
Definition:
These are those drugs which satisfy the priority health care needs of the population.

Criteria:

- They are selected with due regard to:-
- Public health relevance
- Clinical evidence on efficacy and safety.
- Comparative cost effective (Individual and community can afford)
- Appropriate dosage form
- Available at all time in adequate amount.
- Assured quality and adequate information.

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" (includes 376 medicines).
The WHO updates the list in every two years.
It can be differ from country to country due to change their environment.

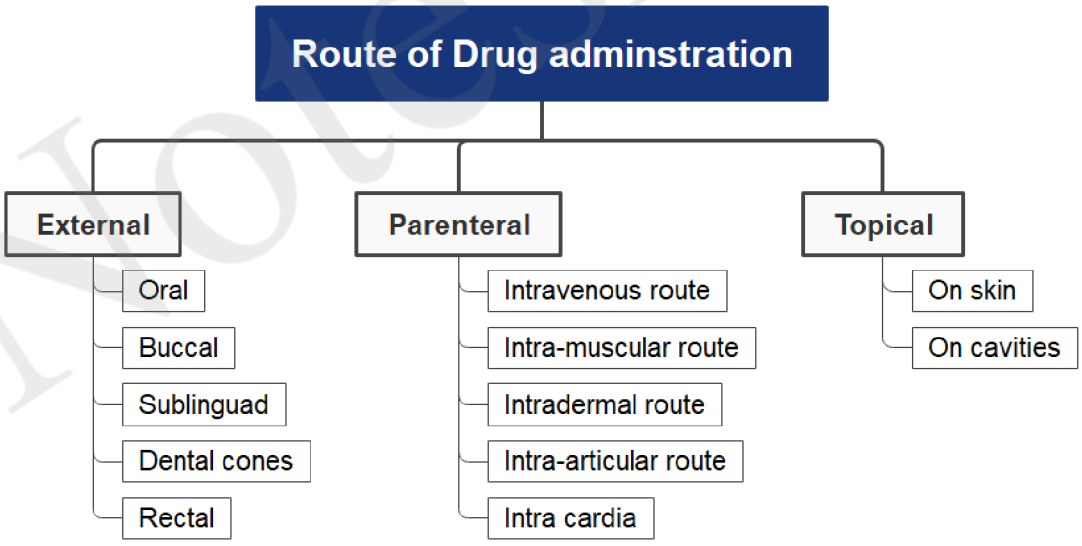
Eg:

- Acetylsalicylic Acid (Aspirin)
- Paracetamol
- Ibuprofen
- Morphine etc.

Routes of administration:

Introduction:-

- Routes of drug administration is the path by which the drug is introduced into thebody for treatment of disease. Drugs are available in various form like tablet, Capsule suspension, ointment, Cream, injection etc.



1. External administration:-

- This route is best for drug administration unless any specific advantageis desired associated with other delivery route.

a) **Oral :-** In this route of administration the drug either liquid or solid preparation is placed in mouthcavity is swallowed along with drinks such as water, milk etc.

Advantage:-

- Most of medicinal preparations are consumed orally.
- Economical chance of acute drug reaction.
- Very convenient for children and aged people.

Disadvantage:-

- Sometime inefficient for the patients.
- Irritation to gastric mucosa.
- Can cause Nausea& vomiting.

b) **Rectal: -** Suppositories/ Enema are drug that are placed in rectal route. Ex- Aspirin, Theophylline, Chlorpromazine.

Advantage:-

- Useful in the children/ adult.
- Use in the case of vomiting.
- Higher concentration of drug proparty achieved.

Disadvantage:-

- Irritation or inflammation of Rectal mucosa can occur.
- Absorption is slow of this route and Erratic.

c) **Sublingual/ Buccal route**

- **Sublingual:-** This dosage form is placed under the tongue and allow to dissolve in the mouth cavity. Thedrug is absorbed by sublingual mucosa.

- **Buccal route:-** In buccal route drug kept within the mouth around the cheeks or buccal cavity, where itdisintegrates and get absorbed.

Advantage:-

- Rapid absorption of the drug.
- Drugs do not undergo first- pass metabolism.
- Portal circulation is by passed.
- Maintained drug stability.
- No involvement of harsh GI environment.
- Less chance of infection.

Disadvantages:-

- Only small dose can take.
- Sometime complete drug is not absorbed.
- Not effective in emergencies.
- Drug couldn't be administered during emesis.
- Unpleasant teste of drugs.

2. Parenteral Administration:-

- The route of administration others than the enteral route comes under parenteral route.
- Parenteral Administration is injection or infusion by means of needle or catheterinserted in the body.

a. Intravenous (IV) Route

- IV is the route of drug administration in which the drugs are administered into the veins.
- Injection arepreferred for orally unabsorbed Drugs like Atracurium (neuromuscular blocker).
- IV route shows rapid effect the maintains level of drug in circulation.

Advantage:-

- 100% bioavailability.
- It this route shows rapid effect.
- This route is the best in the case of diarrhea and vomiting.
- Take medicine in large quantities.

Disadvantage:-

- This route is less safe than oral route.
- Technical and trained person required.
- Costly.
- Inconvenient and painful causing irritation, cellulitis and thrombophlebitis.

b. Intramuscular:-

- In this route the drug is administration into the muscles.

Advantage:-

- Rapid onset of action.
- No G.I.T. related factors.
- Mild irritants can be metabolism.
- The absorption is reasonably uniform.

Disadvantage:-

- Only 10ml of drug is given.
- Local pain cause, Abscess and infection.
- Can cause nervous damage.

c. **Subcutaneous Route (SC)**
- This route of administration the drug gives under the skin.

Example:-

- Hormonal Drug (Insulin Injection)

Advantage:-

- Can be easily self-administering by the patient.
- Complete but slow adsorption.
- Low risk of systematic infection.

Disadvantage:-
- Maximum 2ml of drug may be injected.
- Less painful then the IV /IM route.
- Irritatant drugs cause tissue damage.

d. **Intara-arterial:-**
- This route of drug administration the drugs are given into the arteries. Vasodilator, anticancer drugs aregiven by skin route.

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f. Intara-arterial:-

- This route of drug administration the drugs are given into the arteries. Vasodilator, anticancer drugs aregiven by skin route.

Advantage:-

- Bioavailability 100%.
- It is of great clinical value in administering anticancer drugs.

Disadvantage:-

- Only can used in cancer and vasodilator.
- Painful
- Risky

3. Inhalation :-

In case of inhalation route drugs are administered either as Aerosol system in form of vapors

Agonists, antagonists(competitive and non competitive), spare receptors, addiction, tolerance, dependence, tachyphylaxis, idiosyncrasy, allergy.

Agonists:

- These are those drug that binds to a receptor and cause the same pharmacological action as the substance that normally binds to the receptors.

It can be:-

- **Full agonists:** High efficacy, full response
- **Partial agonists:** lower efficacy, uses response
- **Inverse agonists:** Opposite response

Eg: Heroin, Methadone, morphine etc.

Terms:

Receptor:

- Those binding sites in which drug attach then activate it and give a pharmacological action.
- It is based on lock-key mechanism.

Antagonists:

- Those substance that acts against and blocks an action.
- Antagonist is the opposite of agonist.
- Agonists and antagonists are key players in the chemistry of the pharmacology in human body.

A. Competitive:

- Binds to the same site as the agonist but done not activate receptor.

B. Non competitive:

- Binds to the allosteric site (non-agonist sites) on the receptor to present activation of the receptor.

Spare Receptors:

- These are receptor that exist in excess of those required to produce of full effect.

Addiction:

- It is a condition in which a person is unable to stop using a substance in a behavior.

Tolerance:

- A is a decrease in response to a drug that is used repeatedly.

Dependence:

- The psychological or physical symptoms feel like they must continue taking a substance.

Tachyphylaxis:

- It is rapid development of tolerance when drug repeated in quick succession results in marked reduction in response.

Tachy = Fast
Phylaxis = protection

Idiosyncrasy:

- It is genetieally determined abnormal reactivity to a chemical.

Allergy:

- A is the abnormal reaction of immune system to a medication.

Or

- It is type of antigen that produces an abnormally immune response.

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

Pharmacokinetics

- Pharmacokinetics is the quantitative study of drugs movement in through and out of the body.

"What does body do to the drug"

- **It involves four processes. (ADME)**
  1) Absorption
  2) Distribution
  3) Metabolism
  4) Excretion

1) Absorption:-
Absorption is the process in which a pharmaceutical substance enters the blood circulation in the body. The pharmacokinetic parameters for absorption include:

- Absorption rate constant: absorption rate / amount of drug remaining to be absorbed
- Bioavailability: amount of drug absorbed / drug dose

2) Distribution:-
Distribution is the process in which a pharmaceutical substance is dispersed through the fluids and tissues in the body. The pharmacokinetic parameters for distribution include:

- Apparent volume of distribution: amount of drug in body / drug concentration in plasma
- Unbound fraction: unbound drug concentration in plasma / total drug concentration in plasma

3) Metabolism:-
Metabolism is the process in which a pharmaceutical substance is transformed into other substances, called metabolites, in the body. The pharmacokinetic parameters for metabolism include:

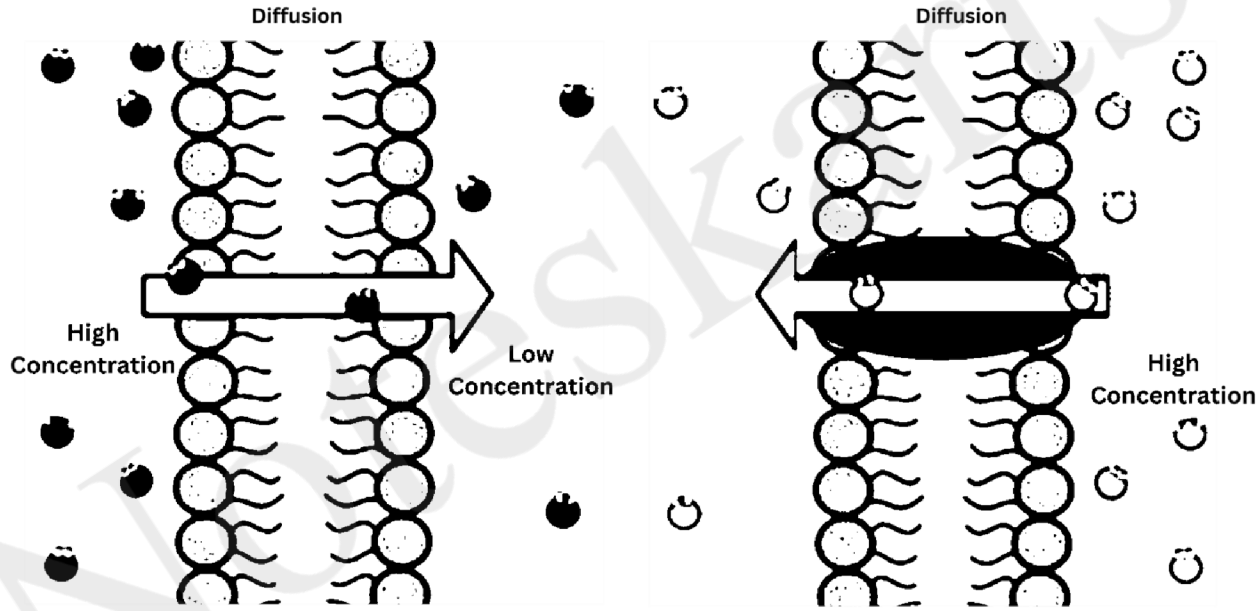
- Metabolic clearance: drug metabolism rate / drug concentration in plasma

Membrane transport:
When drugs reach in systemic circulation through membrane transport.
Which are following:-
1. Passive transport

2. Active transport
3. Facilitated transport
4. Endocytosis

1. Passive transport:

- Passive transport is the fundamental movement of ions and other molecular substances within the cells along the concentration gradient, without any external energy. It is also known as passive diffusion.
- It is the biological process of movements of the biochemical across the cell membranes and tissues.
- Passive transport is a natural phenomenon, which does not require any external energy.

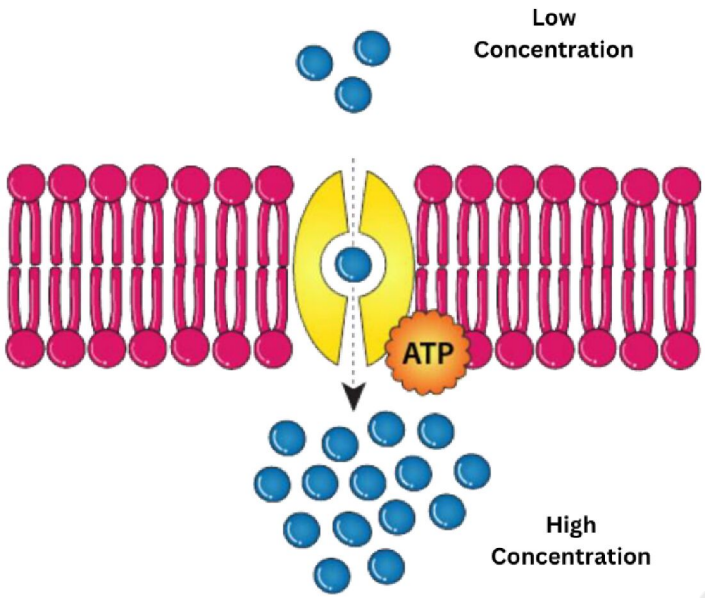


2. Active transport

In this transport drug molecules move against the concentration gradient (Low to High).

or

"Active Transport is defined as a process that involves the movement of molecules from a region of lower concentration to a region of higher concentration against a gradient or an obstacle with the use of external energy."

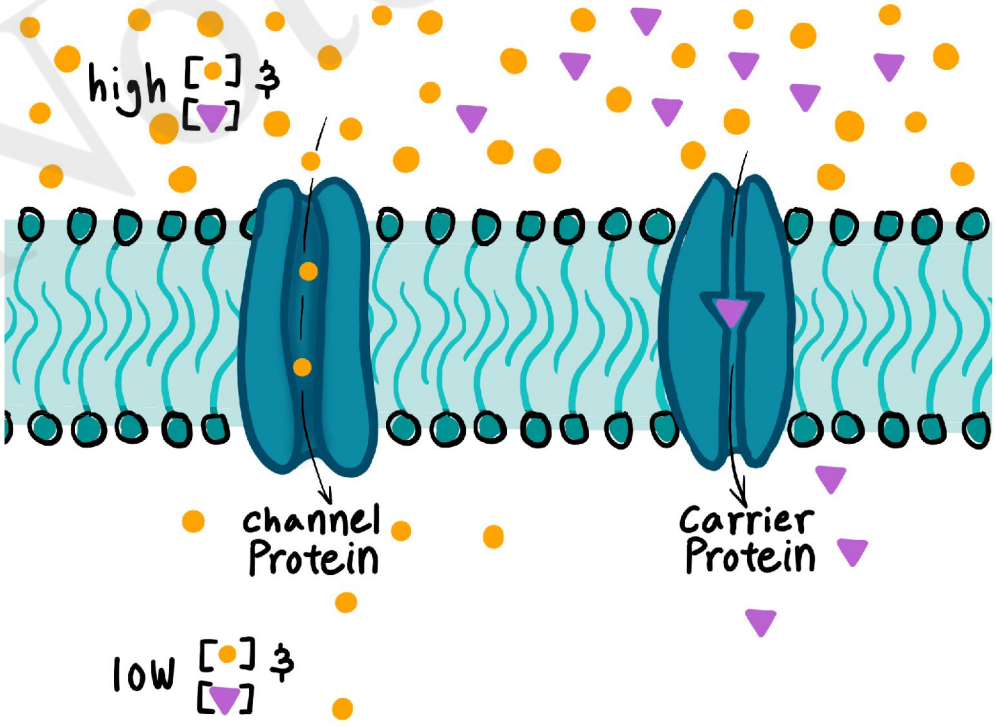


3. Facilitated Transport:

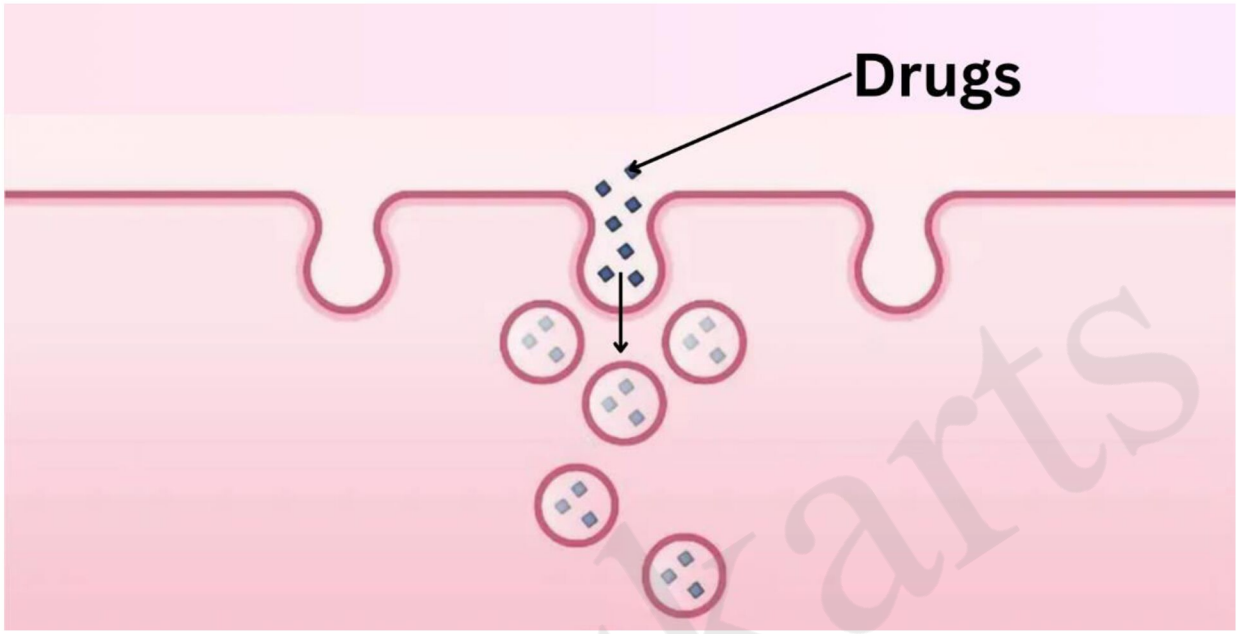
In this transport, drug molecules molecules move across the concentration gradient, but with the help of any carrier bodies.

Some large molecules or poorly duffusible 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 Transporter)



4. Endocytosis:-
In this transport, drugs of very large size get transport via engulfment by cell membrane.
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, depend on various factors.

4) Excretion:
Excretion is the process in which a pharmaceutical substance is removed from the body. In rare cases, some drugs may never be completely excreted from the body. They then irreversibly accumulate in the tissues.

Enzyme induction:

- Enzyme induction occurs when chemicals cause an increase in synthesis and activity of enzymes, thereby increasing the metabolism of drugs that are catalyzed by those enzymes.
- When one drug causes an increased rate of metabolism of another drug by inducing the Cytochrome P450 (CYP) enzyme involved in the biotransformation of that drug, there is a resultant effect on the drug's efficacy. The parent drug is metabolized at an accelerated rate, leading to low potency and reduced effect.

Enzyme inhibition:

- Inhibitors that do not contribute to the development of the product carry out the inhibition. The inhibitors can impact both the substrate and the enzyme. The stoppage of enzyme activity is referred to as enzyme inhibition.

- These enzyme inhibitors can attach to active areas and halt or inhibit further activity. This form of binding can be both reversible and irreversible.

Kinetics of elimination:

Clearance: The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in a unit time.

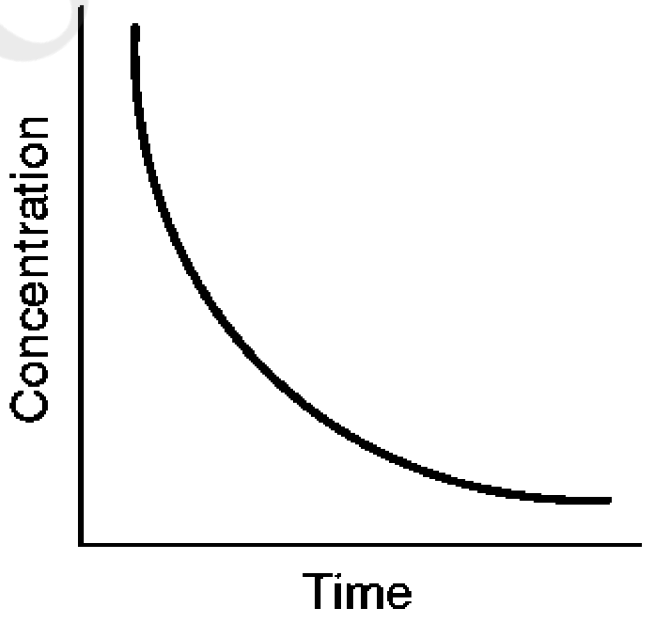
$$Cl = \frac{Rate\ of\ elimination}{Plasma\ concentration}$$

First-order kinetics:

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

$$Rate\ of\ elimination \times drug\ concentration$$

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

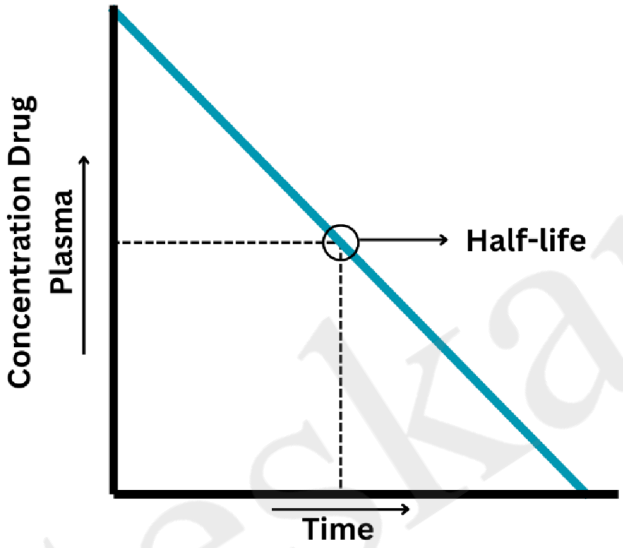


In this eg, drug eliminated at constant rate 15% but the amount of drug (mg) is changed.

Zero Order kinetics:

- The amount of drug eliminated is independent of drug concentration.

$$Rate\ of\ elimination = constant$$



Half Life: Time that is required to required to reduce drug concentration in plasma by half.