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Pharmacology

Pharmacology is the Science of drug (Greek)
Pharmacon = drugs
Logos = disposing

In the sense it deals with interaction of endogenosly administrated chemical molecule with living system not any single chemical substance which can produces the biological response is a drug it encomposes all aspect of knowledge about drug but mostly important those that are relevant to effectiveness rate of safe medicinal purpose.

Pharmacodynamic - Greek word dymomis = power what the drug does the body.
This include physiological and biochemical effect of drug and their mechanism of action.
The two main division of Pharmacology are Pharmacodynamic / Pharmacokinetic and organ System Sub cellular micromoleeul level.

Pharmacokinetics - Pharmacokinetics (Greek) kinesis movement what the body does to the drug.
This refers to the movement of drug in to alteration of the drug by the body (ADME) Absorbtion, distribution metabolism and excretion.

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Scope of Pharmacology

- **Drug** – It is the single active chemical entity present in the medicine that is use for diagonosis, prevention treatment or cure of disease.

- Pharmacokinetics → previous
- Pharmacodynamics →

- **Clinical pharmacology** – The branch of pharmacology these with the study of drug on human being. (Both involuntary patients)

- **Pharmacotherapeutics** – It is the application of pharmacology information together with the knowledge of the disease for if prevention or cure it consist of rational pharmacotherapeutics and inpirical pharmacotherapeutics.

Rational Pharmacotherapeutics –

It include the rational use of drugs for example –

- Adrenaline is use in bronchial Asthma

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Impirical Pharmacotherapeutics

It include the use of drugs in particular disease but its machanism action is unknown.

e.g- Colchicines was at one time use in treatment of gout: but how it act was unknown.

- **Therapeutics** — It deals with the use of drugs in the prevention or treatment of the disease.
- **Pharmacoeconomics** — It deal with the cost is the economic expect of drug use therapatically.
- **Pharmacogenomic** — It is branch of pharmaco-genetics which deals with the use of genetics information in a selected drugs for a person
- **Pharmacoepidemiology** — It is the study of both the useful and adverse effect of drug and large number of people.
- **Pharmacovigilance** — It is a branch of pharmaco-epidemiology which deal with the epidemiology study of adverse drugs effects.

Malignancies - A term for disease in which abnormal cells devide without contural and can invade nearby tissues

- **Toxicology** - A deal with the adverse effect of drug or also the study of poisions like detection prevention and treatment of poisioning.
- **Chemotherapy** - It is use of chemicals for the treatment of infections the term now also include the use of chemical compounds to treatment of malignancies.
- **Pharmacopoeia** - In a Greek word
  pharmacon = Drugs
  poeia = To make
  is the official publication containing a list of drugs and medicinal.

Source of drugs are following

Minerals - Charcoal, bentonide, Mg, sulphate.
Animals - Insulin, thyroid extract, heparin.
Plant - Morphine, cinchona, atropin

- **Semi synthetic drug** - S.D. are affected by slightly modifing the naturally occuring drugs.

e.g. Homatropin is obtained from naturally occuring atropin by chemical process.

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Synthetic – These drugs are synthesise by chemical process.
e.g- Aspirin is synthesise by acetylene acetylating the salicylic acid.

Note- Majority of drugs currently practice ar synthesis.

Various route of drug administration

- A route of admistration is the path by which a drug fluid poision ar other substance is brought in to contact with the body.
- Most drugs can be administrated by a variety of route the choice of appropiate route in a given situation depends both on drugs well as patients related factors.

Route of administration can broadly be divided in to following —

Tropical Drugs are applied tropically to the skin ar mucosa membrane (mainly for local action.)

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Oral - Oral drug use for systemic effect..... given via the digestive tract (Non local)

Parentral - A drug administrated parently and injected via a hold needle in to the body at various site on to varing depth.

Rectal - Drug given through rectum by suppositories or anema.

Inhalation - The lungs provide and exellent surface for absorbtion when the drug is delivered in gasies, aerosal or ultrafine solid particle form.

Nasal - The mucosal membrane of the nose can raidly absorbe mainly drugs.

Tropical route -

Skin - Drug can be efficiently delivered to lacalisations on skin.

ⓐ **Dermal** - Local action (Cream Ointment)

ⓑ **Transdermal** - absobtion of drug through skin (Systemic action)

- **Systemic action** - Stable blood level

CRDDS (control drug delivery system)

- No first pass metabolism
- Drug must be potent as patch become to large.

Mucosal membrane —

- Eye drops (On to the conjuctive eye drops)
- Intranasal route (in to the nose)

Oral route —

- By Swallowing
- It is intended for systemic effect resulting from drug absorbtion through the various epithelia & mucosa of G.I.T tract.

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Various route of drug administration.

Defination - A route of admistration is the path by which a drug, fluid, poison or other substance is brought into contact with the body. It is known as route of drug admistration.

Classification

- Systemic route
  - Enteral
    - Oral
    - Sublingual
    - Rectal
  - Parentral
    - Inhalational
    - Injections
      - Intravenous
      - Intramuscular
      - Subcutaneous
      - Intra arterial
      - Intra articular
      - Intrathecal
      - Intradermal
      - Transdermal
- Local route
  - Skin / Topical
  - Intranasal
  - ocular drops
  - mucosal throat
  - Inhalation
  - Transdermal

Systemitic route In Systemic route the drug reaches to the Systemic circulation so that it is called Systemic route.

Systemic route is again classify into two classes

Enteral - In this route the drug is placed in the gastrointestinal tract (G.I.T) and then it absorb to the blood.
This route is further classified in to three classes —

Oral route — In this route the drug is placed in the mouth and swallowed.
It is also called per oral - (P.O)
e.g. P.C.M (paracetamol) Diclofenac and aspirin etc

Advantage —	Disadvantage.
• Convenient • absorbtion • cheap	• Sometimes insufficient only part of drug may be absorb.

• 1st pass effect drug are orally are initialy transported to the liver.

Sublingual - In this route of administration the drug is placed under the tounge and it is taken without the use of water.
when it is placed under the tongue then in it digested then absorbtion occur in mouth
e.g Nitroglycerine tablet / vitamic C

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Parentral route The drug is introduced in the body with the help of a syringe and needles to produced certain pharmacological action.

- This route of administration the drug does not pass through the G.I.T.
- It directly reaches to the blood.

It can further be classify in to two classes are as follows —

① With injection
② without injection

① **With injection** — In this class the drug are administered with the use of injections.

e.g.-
- Intravenous I.V.
- Intramuscular I.M
- Subcutaneous

② **without injection**- In this class the drug are administered without the use of injection.

e.g- Inhalation

- **Inhalation** — Drug administered by inhalation through the mouth must be atomized in to smaller droplets then those administered by the nasal route so that the drug can passes through the wind pipe (trachea) in to the lungs.

e.g. General anaesthatics
chloroforms

Injection — An injection is the act of administrating a liquid specially a drug in to the person body using a needle of syringe.

- **Intravenous / Intravascular** — (IV)
In this route of administration the drug is directly taken in to the blood with the help of injection.
- Absoption phase is bypassed

e.g. Antibiotics
Antifungal drugs

- **Intramuscular** — In this route of administration the drug is given in to the muscles with the help of injections.

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advantages

- Rapid absorbtion
- Drug Stability
- Avoid first pass effect.

Disadvantages

- Inconvenient
- Small dosages
- Unplesant test of some drugs.

Rectal - Many drugs that are admisterd orally can also be admisterd rectaly as a Suppositories.
In this form a drugs mixed with a waxy substances dissolve as liquify after it is inceard in to the rectum because the rectum wall is thin and its blood supply will rich then the drug readly absorb.

e.g Suppositories

Advantages

- Unconsious patient and children
- Of patient haveing nausea or vomiting
- may cause irritation
- absorbtion may be variable.

Disadvantages

Drug once reaches to the muscles absorbed in to the blood.

e.g- Tetanus injection

- **Subcutaneous** –

In this route of administration the drug is given in to the subcutaneous layer with help of injection.

The drug once reaches to the subcutaneous layer crosses the membrane and absorbe in to the blood.

e.g- Insulin
Opioids

- **Intra arterial** –

Sometimes a drug is injected in to an artery to localise its effect in a particular tissue or organs.
However the therapeutical value of such pratice is doubtful.

e.g- This method is used for chemotherapy in cause malignant tumors.

And angiography (Test of blood vessels)

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Intra articular – Injections of antibiotics and corticosteroids are administer in inflamade joints. cavities by experts.

e.g – Hydrocorticortisone in rheumatoid arthritis.

Intrathecal – In this route of administration for drug via an injection into the spinal canal / canal into the subarchanoids space so that it reachs cerebro spinal fluid. Anesthesiologist inject.

e.g – Help control pain after surgery. (opioids)

Intradermal – The drug in small quantity is introduced in the upper layer of the skin with the help of needle and syringe.

e.g – B.C.G (Bacillus Calmette. Guerin) vaccine. Small pox.

Advantages or merits of injection –

- There is very rapid response of drugs.
- The drug go directly into the blood, so no absorption is required.
- This route can be used in case of a unconcious patients.

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Disadvantage -

- This is appearing when needle is insert.
- This route can be used by the traind person only like doctor, pharmacist & nurses. who required the presence of a skilled or trained person for administration of drug.
- The needle and syringe are required to be properly sterilized.

Transdermal - In this delivers medications through the skin via patches or other delivery system.

e.g - Testoron.

- local route The local route is the simplest mode of administration of a drug at the site where the desired action is required.

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Advantages -

- large surface area.
- high blood flow.

Disadvantages.

Nose addictive route of administration because it hits the brain so quickly.

Transdermal - Transdermal drug delivery is a painless method of delivery drug systemically by applying a drug formulation on to intact and healthy skin.

Eg - Nicotine patches, opoids patches nitroglycerine patches.

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Drug absorption

Drug- Drug absorption is the movement of drug in to the blood stream.

- It is determine by the drugs physiochemical properties, formulation and route of administration.
- Dosage form (Tablets, Capsules, Solution) consisting of the drug plus other ingredient are formulated to be given by various route.

e.g- (Oral, Sublingual, rectal, parentral topical and Inhalation)

- Regardless of the route of administration drug must be in solution to be absorb.
- Thus, Solids forms (Tablets) must be able to disintigrate and diagregates.

Definition of drug absorption —

- Absorption is the process by which a drug enters the blood stream without being chemically altered etc.
- The movement of drug from it site of application in to the blood or lymphatic system.

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- Intranasal

Intranasal delivery of drug allow the drug enter the brain by bypassing the B.B.B. (Blood Brain Barrier) and avoid exhaustive hepatic and intestinal metabolism.

e.g- Antiasthma / antiasmatic medication such as Salbutamol

- Ocular drop -

This medication is use to relief itching eyes cause by seasonal allergy.

e.g- Ketorolac / Iodoxamine etc

- Mucosal throat -

- Inhalation -

Use for gasious agent volatile agent and aerosols.

- Solid and liquid are excluded in larger than 20 (11) micron the particals impact in the mouth and throat.

Smaller than 0.5 (11) micron.

e.g. Vicks Inhaller

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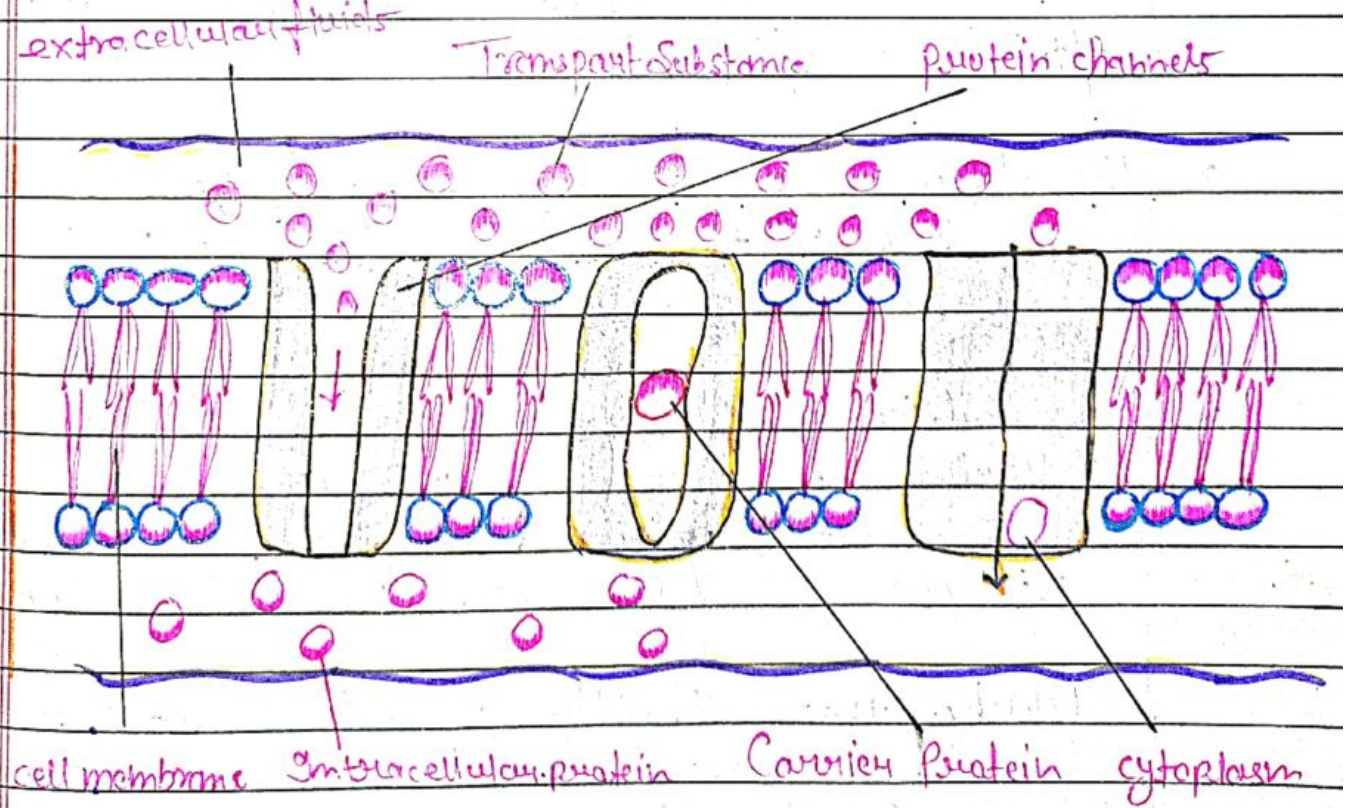
Types of Drug absorption – There are various types of drug absorption are as follows –

① Passive diffusion/Transport
② Pore transport
③ Carrier - mediated transport
   • Facilitated Diffusion
   • Active transport
④ Ionic or electrochemical diffusion
⑤ Ion pair transport
⑥ Endocytosis

① Passive diffusion/Transport – Passive transport is a type of membrane transport that does not require energy to move Substance ~~across~~ across cell membrane.



(Passive diffusion/Transport)

- Diffusion rate is directly perposnal to the gradient but also depponds on the molecules lipid solubility, size degree of ionization and the area of absorb surface (absorbtive substance).

- Because the cell membrane is lipid soluble Drug diffuse most rapidly small molecules tends to painitrate membrane more rapidly.

Small molecules tends to painitrate membrane more rapidly then larger once.

(2) Pore transport - It is called as connective transport, bulk flow or filtration.

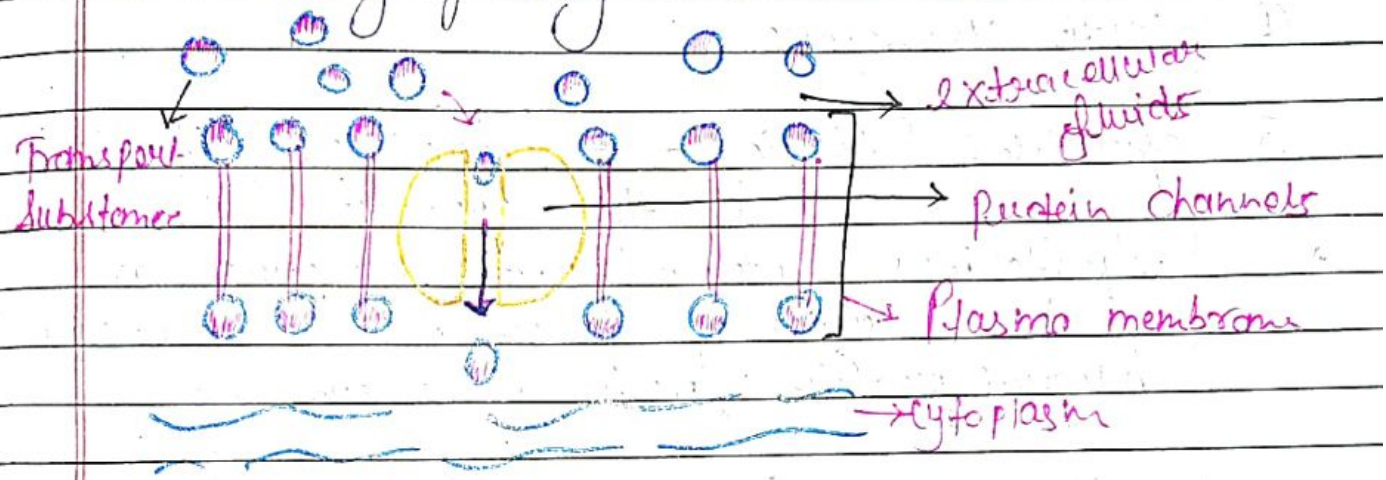
- The deriving force for the passage of the drug is the hydrostatic or the osmotic pressure.

- Absorption of low molecule weight, low molecular size and generally water soluble drugs ——— eg field channels or pore in the membrane structure

Machanism - Through the protein channel present in the cell membrane

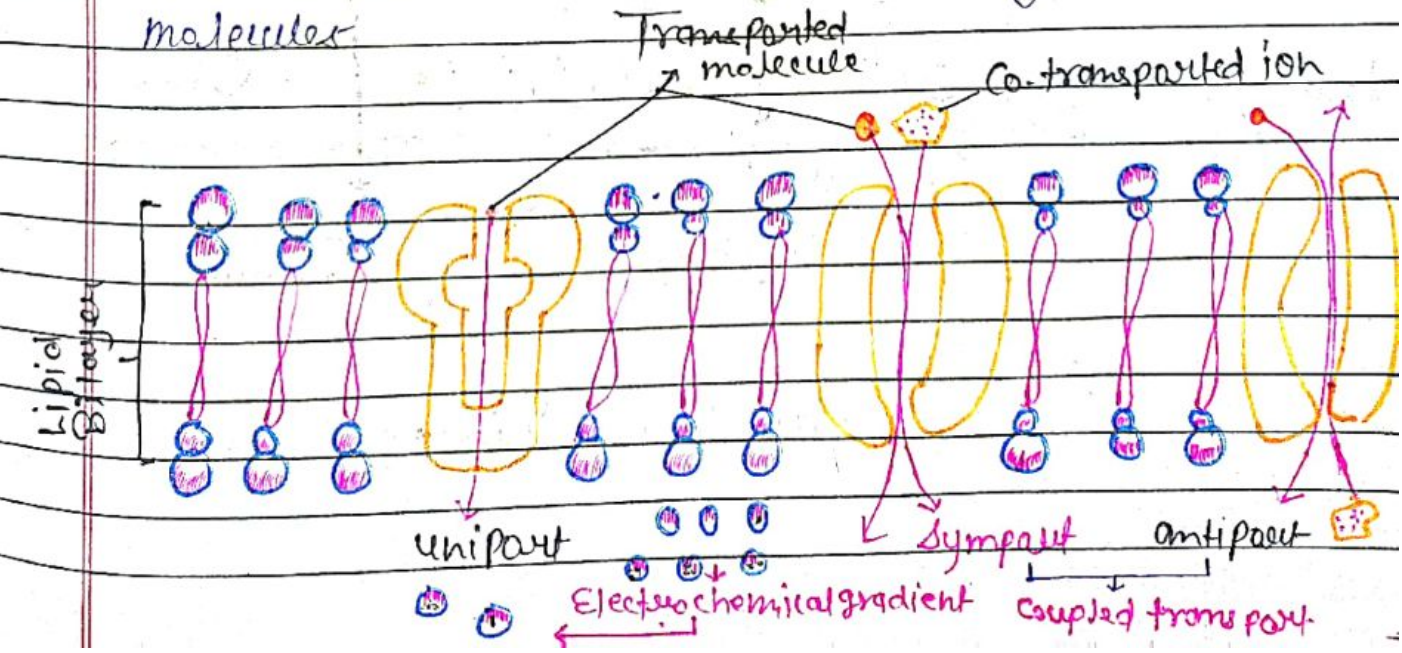
- drug permiation through pore transport —

Renal secretion, removable of drug from C.S.F (Cerebro Spinal fluids) and entry of drug in to the liver



Pore transport

③ Carrier mediated transport — it involves a carrier which bind reversively with solute molecule to be transported to yield the carrier solute substance complex which transverses across the membrane to other side where it dissociate to yield the solute molecules



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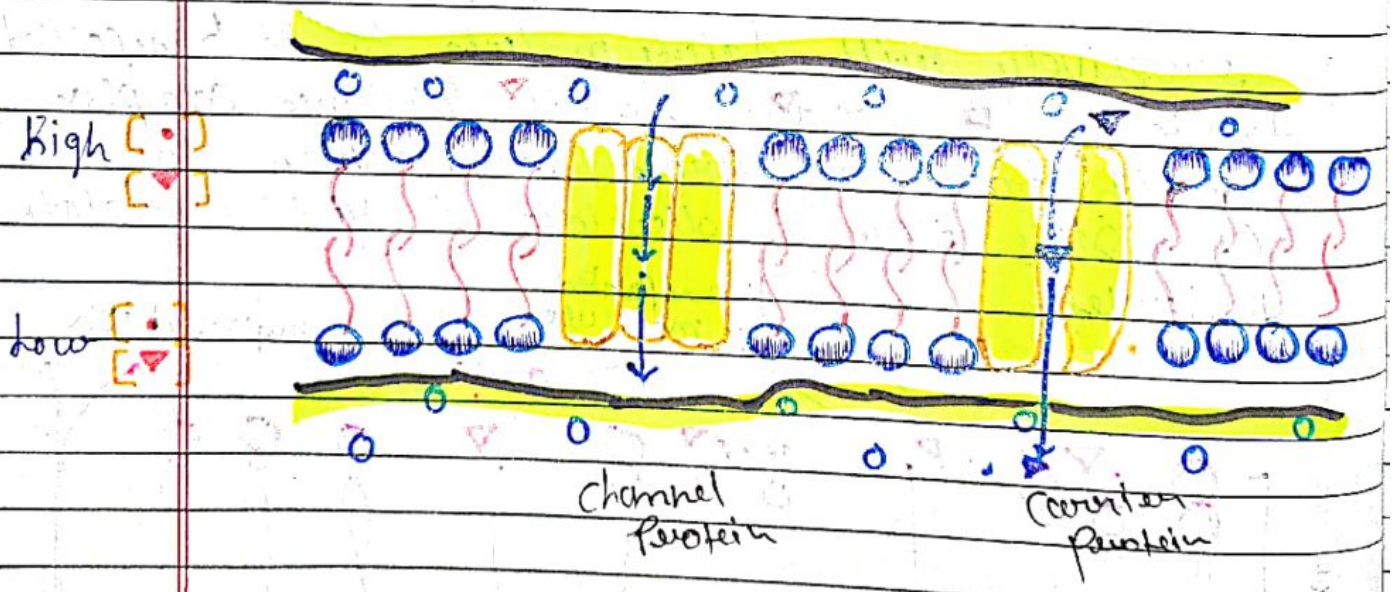
- There are two types of carrier mediated transport
  - (a) Facilitated Diffusion
  - (b) Active Transport

(a) Facilitated Diffusion —— facilitated diffusion is the process of spontaneous passive trasport molecules or ion across a biological membrane via integeral protein specific transmembrane

d . . . . from active transport in that the drug food along a concentration gradient. Therefore, this system does not require energy input.

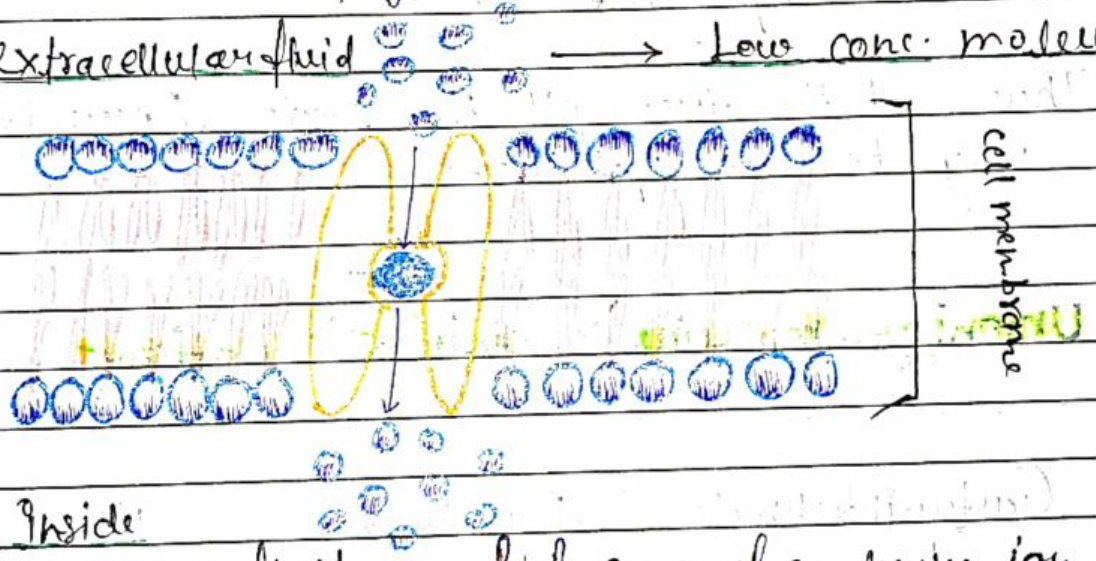


Facilitated Diffusion

(b) Activ Transport — Molecules move against the concentration gradient from area of low concentration of molecules to area of high concentration of molecules impails both a carrier molecules and energy.

- Good for accumulation of drug with in a part of the body

Extracellular fluid ⟶ Low conc. molecules ions



Inside
Intracellular fluid ⟶ High conc. of molecules ion.

ATP → ADP + Pi

(Active transport)

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④ Ionic or electrochemical diffusion.

This charge influences the permiation of drugs.
molecules form of drugs are unaffected by the membrane charge and permiate faster then ionic form.

- The permiation of ion and cation is also influence by pH.
- Thus at the given pH the rate of permiation may be as follows -

Unionized molecules > Anions > Cations

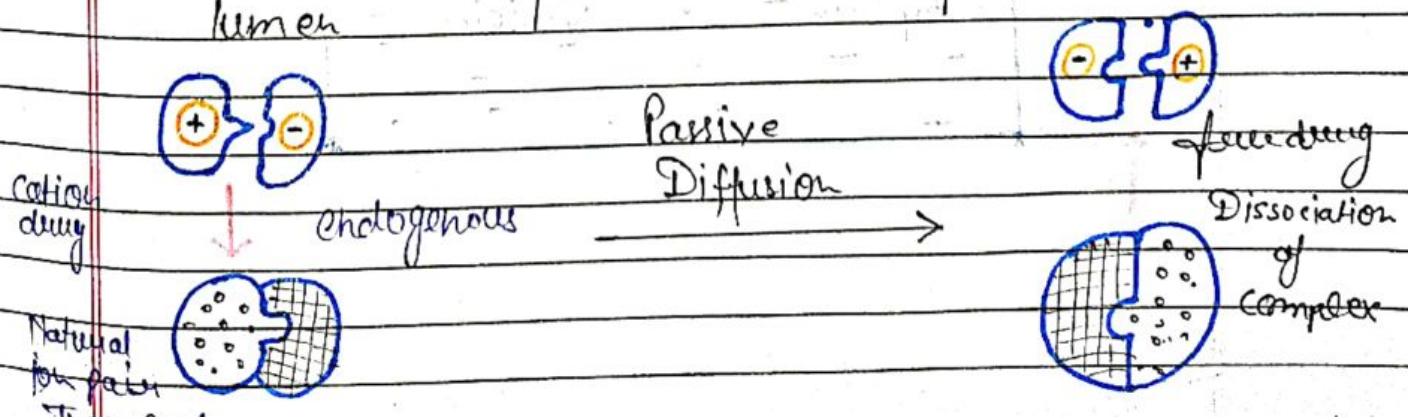
Gastrointestinal lumen	Membrane	Blood
○ Unionized form	Rapid absorption	○
⊖ Anions	Moderate	⊖
⊕ Cations with high kinetic energy (K.E)	Slowly absorbed	⊕

Charge - The charge on membrane influence the permiation of drugs

(5) Ion pair transport
absorption of drug like quaterny ammonium compound.
eg- Benzaalkonium chloride.
benzethonium and Sulphonic acid (Sulfonic a-)

- which ionize under all PH condition is ionic transport.
- Dipolar either low o/w partition Cofficient value, Such agent painitrate the membrane by forming reversible nutral complexes with endogeneous ion of G.I.T like mucin.
- Such nutral complexes have both the required lipophilic city as well as aqueous Solubility for passive diffusion Such as Fenamine is called as ion pair transport

Gastro intestinal lumen	Membrane	Blood



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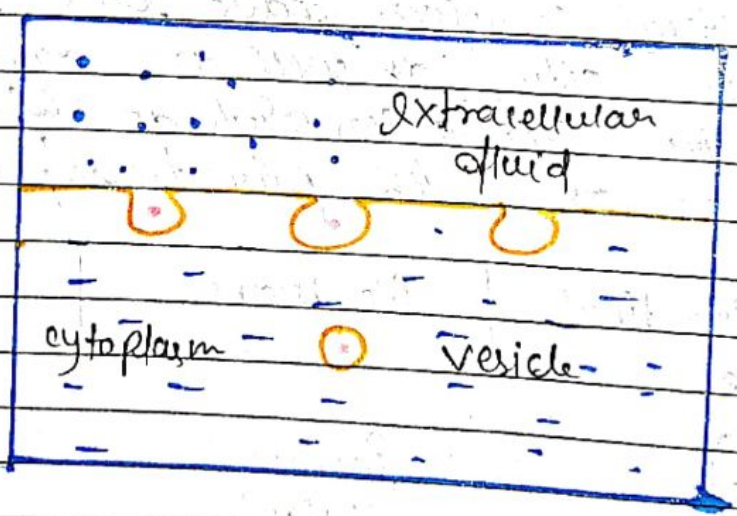
⑥ Endocytosis — This type of drug delivery transport drugs of exceptionally large size across cell membrane.

° Involves engulfen engulf of a drug molecule by the cell membrane and transport in to the cell endocytosis involve 2 types of process.

① Phegocytosis
② Pinocytosis

① phegocytosis — It is a bulk uptake of solid material.

② phinocytosis — It is a bulk uptake of liquid material.



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factor affecting of drug absorption —

Pharmceutical factors

Physicochemical factor affecting drug absorption

- Drug solubility and dissolution rate
- particle size and effective surface area.
- polymorphism and amorphism.
- Salt form of drug
- Ionization State
- Drug Pka and Lipophilicity hypothesis.

Dosage form characteristic

- Disintegration time
- Manufacturing variable
  - Method of granulation
  - Compression forces
- Nature and type of dosage forms
- pharmaceutical ingredient
- product Storage Condition

Patient Related factors

membrane Physiology

- Nature of cell membrane
- Transport processes

Gastrointestinal motality

- Gastric empty rate
- Intestinal motality
- Drug stability in G.I.T
- PH of G.I.T
- Surface area of G.I.T
- Intestinal transit
- Blood flow to G.I.T
- effect of food

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Drug Solubility and dissolution rate

The rate determining steps in absorption of orally administered drugs are -

Rate of dissolution
Rate of permiation through the biomembrane

- Dissolution is the rate determining step for hydrophobic (water hating) and poorly aquous soluble drug.
- permiation is the rate determining step for hydrophilic (water loving) and poorly aquous soluble drug.
- Partical size and effective surface area.
- partical size and surface area are inversilly related to each other at the partical size decrease, surface area increase which is don turn increase the solubility and dissolution.
- There are two types of surface area.
- Absolute surface area - which is the total surface area of any particle.

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effective surface area — which is the area of solid surface exposed to the dissolution medium.

- Polymorphism and amorphism —

↓

A substance exists in more than one crystaline form, the different form are design as polymorps and phenomenon is called as polymorphism.

Amorphism — In addition to different polymorphism form a drug may exists it a amorphous form which is a non crystaline are poorly crystalise form it is known as amorphism.

Solvates and Hydrate — (Pseudopolymorphism)

Solvates Crystaline Solvates Solid adict containing Solvate molecule with the crystal Structure give like molecule with the unique difference in physical and pharmaceutical properties.

Hydrate — Crystaline Solid crystaline adict containing water molecule with is the Crystaline Structure.

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Salt form of drug

Salt formation is one of the simplest chemical reaction, involving either a proton transfer or a neutralization reaction between an acid and a base.

The salt form of drug is usually more soluble than parent drug.

Ionization State -

Ionized or (charged) drug are not absorb as efficiently as un ionized drug.

This means that taken orally, a drug that is weak acid will be absorb primarily in the acidic environment where is a drugs that is weak base in basic alkaline in the stomach.

Drug PKa & lipophilicity hypothesis -
(G.I. PH partition hypothesis) -

The PH partition thoroughly explained in simple term the process of drug absorption from the G.I.T and its distribution across all biological membrain.

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The theory states that for drug compound of molecular weight greater than 100 which are primarily transmitted across the biomembrain by passive diffuse the process by absorption governed by -

- The dissociation constant (Pka)
- The lipid solubility of the unionized drugs.
- The pH at the absorption site.

Note- Enteric dosage - Coated with a material that permits and transmit through the stomach to the G.I before the medication relief.

Dosage forms characteristic

① Disintegration time.

The disintegration of some dosage from pH sensitive with enteric coated formulation. the coat dissolve only in the intestine followed by disintegration for table.

② Manufacture Variable

Several manufacturing process influence drug dissolution are -

ⓐ Method of granulation -

- The wet granulation process is most conventional in the manufacturing process.

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- The method of direct compression has been utilized to yield tablet that dissolve at faster rate

(b) Compression process forces —

- The compression forces en . . . in tableting process influence density porosity hardness disintegration time, dissolution of tab.

(3) Nature and types of dosages forms

- A part from the selection of the drug clinical support to the greater than extend or the proper of the dosage form of the drug.
- for a given drug a 2-5 folds perhaps more difference could be absorb in the oral bioavailability of a drug depending upon the nature and the type of dosage form.

(4) Pharmaceutical ingredients

More the number of exipient in the dosage form more complix it is on greater the potential and bioavailability problems. Commonly used ex. in various dosages formes.

① Vehicle ② lubricant
③ Suspending agent ④ Surfactant etc.

(5) Product and Storage condition

A number of changes specially physiochemical properties of drug in dosage form can result due to ageing in a storage condition which adversily bioavailability.

eg- Precipitation of drug in solution and hardening of tablet.
Change in partial size of suspension

Patient related factors -

Membrane physiology -

(a) Nature of cell membrane -

The ~~cell~~ membrane is the various that separates ~~out side~~ the inside of the cell from the out side.

Cell membrane is made of of phospholipid protein and other micro molecule.

- The phospholipid make up of the bilayer because its contain hydrophobic molecules.

(b) Transport process - Molecule can be transported by following process -

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① Passive diffusion of lipid solid molecules
② Passive diffusion of water soluble molecules
③ Carrier mediated transport by carrier protein.

Active transport
facilitated diffusion

④ Pinocytosic (indocytosis / Exocytosic)
⑤ Passive filtration.

Gastrointestinal Motality.

ⓐ Gastric emptying rate — Gastric empty is the first order process.

Several parameters are used to quantity gastric empty.

Gastric empty rate is the speed at which the stomach contain empty into the intestine.

ⓑ Gastric emptying time — This time requires for the gastric contain to empty into the small intestine longer the gastric empty time. lesser the gastric E. rate.

ⓒ Gastric empty — t/2 is the time taken for half the stomach contain to empty —.

(b) Intestinal motality – A drug may take about 4-8 hrs to pass through the Stomach and Small intestine during fasting stage.

The drug must have sufficient time (residence time) at absorption site for optimum absorption.

In the case of high motality in the Intestinal track as diarrhoea. the drug have very brief residence time and less opertunity for adiquate (as per needed) absorption.

(c) Drug Stability in G.I.T –

- A drug for Oral use may destabilized either during its Self life or in the G.I.T.
- A measure stability problems resulting in poor bio availability of an orally administered drug are digradation of the drug in to in active form, and intraction with one or more different compound are those present in the G.I.T, to form a complex that is poorly soluble or in unabsorable

(d) PH of G.I.T

Gastric empty is retarded at low Stomach pH & promoted at higher for alkaline pH.

Chemical that affect G.I.T. pH also alter Gastric empty decrease with increase in molecular weight and in the following order

HCl > acetic > lactic > tartaric > citric

⑥ Surface area of G.I.T

Area of absorptive surface affect oral as well as other route greater absorption occur.
intestinal resection decrease the surface area leading to a decrease absorption
Similarly when the topically action drug are applied. On a surface area they are betterly absorbe.

⑦ Intestinal Transit

Since small intestine is the measure site for absorption of most drug long intestine transit time is desirable for complete drug absorption

Transit time for content from Different regions of intestine —

Duodenum — 5 min
Jejunum — 2 hr
ileum — 3 to 6 hr
Caecum — 0.5 to 1 hr
Colon — 6 to 12 hr

(g) Blood flow in G.I.T

- Its play a measure role in absorption by continuosely maintain the concentration gradient across the epithelial membrane
- The G.I.T is extensively supplied by blood capillary
- blood flow is important for actively absorption of drug
- absorption of polar molecule dosing depend on the blood flow but lipid soluble molecule highly depend on the Blood flow

(h) Effect of food

- food may increase, decrease or not affect drug absorption.
- In most cases food alter the rate of absorption but does it affect the extend.

- In some case food may substancelly alter the extend of absorption on rate of absorption.

Bioavailability and their factor affecting bioavailability -

* Bioavailability —
  Bioavailability is the fraction of administered drug bioavailability that reaches the systemic circulation

- Bioavailability is extressed as the fraction of administered drug that gains acess to the systemic circulation in a chemically uncharged form.

eg- If 100 mg of a drug are administered orally and 70 mg of this drug and absorb unchanged the bio availability is 0.7 or 70 %.

- Parentral route has maxium bioavailability drug absorb maxium.

- In I.V drug directly release in to blood so their absorption and bioavailability

is 100 %.

- In Subcutaneous / I.M, drug inject near the capillaries also have great absorption and bioavailability. Enteral / Oral
- Enteral, Oral has less bioavailability and absorption because it follows 1st pass metabolism drug passes thoroughly liver which decrease the absorption.

Types of Bioavailability —

There are two type of bioavailability —

1. absolute bioavailability
2. Relative / Comparative Bioavailability

(1) Absolute Bio availability — (F) when the systemic Bioavailability of drug administered orally is determine in comparision to its I.V administration is called as absolute bioavailability.

It is denoted by Symbol (F).

(2) Relative / comparative bio availability — (Fr)

when the systemic availability of drug after oral administration —

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Q. Compare with relative and comparative bioavailability.

- It is dehated by symbol (Fr)

factor affecting bioavailability -

There are meany factors influencing bioavailability are as follows -

① Pharmaceutical or physical factor
② Biological factor

① pharmaceutical or physical factor

② physical State of drug -

Solution > Suspension > Capsule > tablet > Coated tablet

[→ Low ← high]

(b) partical size -

- partical plays a measure role in drug absorption.
- This case is important when the drug is poorly soluble

- particle size reduction has been used to increase ↑ the absorption of large no. of poorly soluble drug.

[Particle size (P.S) ∝ ——— absorption]

(c) PH of the fluid :—

- weak acidic drug → like aspirin, barbiturate → Stomach.
- weakly basic drug — like pethitine, ephedrine → Small intestine.
- Strong acidic / basic drug highly ionized poorly absorb.

(d) Solubility of drug — very hydrophilic drug poorly absorb because of their inability to cross the lipid rich cell membrane

[↑ hydrophilic drug ∝ absorption ↓]

Very lipophilic drug are highly absorb because easy cross cell membrane.

[↑ lipophilic drug ∝ absorption ↑]

(d) Intraction with drug / food -

The content of food present in the G.I.T may cause delayed decrease / increase the absorption of drug.

- Delyed absorption like Aspirin . P.C.M.
- Some drug decrease bio. availability penicillin , erythromicine , tetracycline

(2) Biological factor -

(a) Effect of 1st pass metabolism -

- Drug with extensive 1st pass liver metabolism and poor bioavailability after oral administration.
  that is ↓
  eg. Glyceryl trinitrate ↓
  use in treatment of angina.

(b) Disease State -

- Several disease State can also influences the bioavailability of drug.
- Mearue disease affect the bioavailability of drug.
  like - G.I.T disease / Cardiovascular disease / Hepatic disease.

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e.g- Cardiovascular —

Decrease the flow through G.I.T

↓

Decrease the absorption

↓

Bioavailability

P.T.O →

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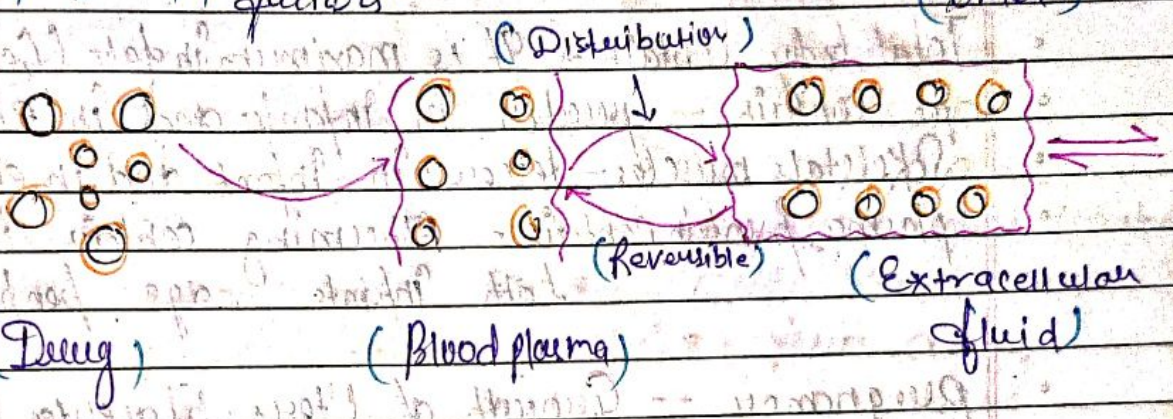
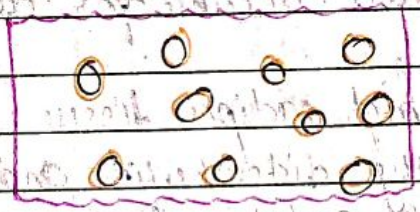
- full body fluid = 42 litter
- I.C.F = 28 litter
- E.C.F = 14 factors





(intracellular fluid)

factor affecting distribution — several factors influence drug distribution to various tissue of the body

- Age
- pregnancy
- Obesity
- diet
- disease State
- drug intraction
- Blood flow
- lipophilic city
- plasma protein binding

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- Age - Age is also affect distribution due to different in body weight, fat contain.
- Total body contain - It is maximum in fats (General).
- fat contain - greater in Infants and in elders.
- Skeletals muscles - lesser in infant and in elders.
- plasma protein contain - Albuming contain in low in both infants age people.
- Pregnancy - Growth of Uters, placenta on fetus rises volume for drug distribution pregnancy.
- Obesity - high adipose tissue contain result to low drug distribution and perfusion.
  high fatty acid contains Salter the binding the properties of acidic drugs.
- Diet - Eat reach diet ring free fatty acid conc. in the blood and affect the binding of acidic drugs.
  example - NSAID, Albuming etc
- Disease State -
  Drug distribution is several affected in disease condition.
  Such as -

(i) Alfration in Albuming and there drug perotein conc.
(ii) Reduce or after perfusion to ranges and tissue

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Drug distribution

The distribution refered to the reversible transfer a drug b/w the blood and extra vasicullar fluid and tissue of the body.

or

It use to pointed the distribution of drug b/w plasma and the rest of the body after oral or parentral dosing.

Elimination -

which involves reversible loss of drug from the body. It's compoise by biotransformation and excretion.

Distribution - which involves reversible transfer of drug b/w compartment.

Volume of distribution - also known as apparent volume and distribution is used to qualified the dictribution of drug b/w plasma and the rest of the body after or parentral dosing.

Apparent volume -

All parts of body equilibrated with the drug and do not have equal conc.

$$\text{Apparent volume of distribution} = \frac{\text{amount of drug in the body}}{\text{Plasma drug conc.}}$$

Alteration in tissue pH

So -

Drug distribution is in ∝ to the disease condition

↑ing disease condition ∝ drug distribution.

Drug interaction —

Two or more drug administrated together competite for binding site and hence to replace each other and a free drug many cause local effect.

Blood flow — where blood flow (Brain, heart, kidney liver etc) will be more ∝ flow there we more distribution.

Blood
- High blood flow (Brain, heart, kidney liver etc) ∝ drug distribution ↑ng.
- low blood flow (Skeletal muscles adipose tissue etc) ↓ ∝ drug distribution ↓

lipophilicity — Greater the lipid solubility of the drug faster is its distribution.

Plasma protein conc. — plasma protein binding may decrease in renal disease due to "Uremia" "hypoalbumilemia" or due to drug intraction.

- ↓ Plasma proteins binding leads to an ↑ing free plasma fraction causing an ↑ing in ∝ volume of distribution.

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Biotransformation
or
Also known drug metabolism —

Biotransformation of drug is defined as the chemical conversion of one form to another.

The term is vary synonymously with metabolism

Aim of biotransformation

To convert lipid Soluble drug to water Soluble drug to avoid reabsorption in renal tubules and help in excretion

Drug metabolising Organs.

- liver is the heart of metabolism.
- Because of its relative richness of enzymes in large amount.
- Systemic charge of metabolising organs

liver > lungs > kidney > intestine > placenta > skin > Brain > testis muscle > Spleen

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Types of biotransformation of reaction-

There are two types of Biotransformation reaction are as follows :-

(1) Phase one reaction / Non Synthetic reaction
(a) Oxidation
(b) Reduction reaction
(c) Hydrolysis.

(2) phase 2 reaction

(a) Sulphate conjugation
(b) Glucuronide conjugation
(c) Glutathione Conjugation
(d) Amino acid Conjugation

(1) Phase One / Non-Synthetic reaction

- In this reaction the drug can be metabolized by oxidation, reduction, hydrolysis and increase polarity of drug.
- So can drug easly excret from kidney

(a) Oxidation - addition of oxidation Or / -charge radical or removel of hydrogen / +charge radical.
- Oxidation is the main process of metabolism.

produce unstable intermediate epoxidise. Superoxidise.

(b) Reduction reaction - addition of hydrogen atom and removal of O_2 from a drug molecules.

- Nitroreduction ⇒ chloramphenical → arylamine

  Ketoreduction ⇒ Cortisone → hydrocortisone

(c) Hydrolysis — (add water to) ester and amides and there isosteres the OH form water ends on the carboxylic acid and the 'H' is the Hydroxy amine

(2) Phase 2 reaction

The reaction is faster than phase one reaction and also Non excreted after phase one reaction and excretion through phase 2 reaction.

- It's involve conjugation with and endogenous substances such as Glucuronic acid Sulphate.

- These reactions are more polar so the drug can easy excret by the kidney and liver.

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eg- Salicylic acid $\xrightarrow{\text{Glucuronic acid}}$ excretion

(a) Sulphate Conjugation- are a heterogenous classes of polar, anionic organosulphate compounds containing and ester of Sulphuric acid.

(b) Glucuronide Conjugation- The conjugation of compands with Glucuronic acid result is production of strongly acid derivative that is more soluble and physiologic pH then the parent compound.

(c) Glutathione Conjugation- Is a tripeptide found is most of the tissue specially in high concentration in the liver and play and ~~also~~ essentially imp. role in protecting hepatocytes, erythrocyte and other cells against toxic injury.

(d) Amino acid Conjugation- drug phase 2 Conjugates metabolised of the previous phase are directly converted into hydrophilic compounds by conjugating which sugar or amino acid ~~and~~

Factors affecting drug metabolism

There are many factors that affect the drug metabolism here as follow

- Age
- Sex
- Body temperature
- Stimulators
- Inhibitors
- diet
- physio chemical property of drug

- Age - Metabolising enzyme glucuronide conjugation are not fully develop at birth so infant and young child need to take small dosages then adults to avoids toxic effect.
- Sex - Metabolic differences F/M have been observed for certain compounds.
- Metabolism of diazepam, caffiene and P.C.M. is faster in female than in males
- Why oxidative metabolism of lidocaine are faster in male than female.
- Body temperature - Temp. of body is directly proportional to drug metabolism.

↑ body temperature ∝ metabolism ↑

- Diet - The enzyme content and activity is affected by a directly compound.

eg - low protein diet — Slow metabolism

- high protein diet — fast metabolism

  ↑ protein diet ∝ metabolism ↑

- Stimulator — Certain drugs like phenobarbitone and rifampicin can increase the activity of enzymes that metabolise a drug.
- hence it proves advantages when drugs like ~~that~~ phenytoin and warfarin are administered as it increase their metabolism.
- Inhibitor - Certain drug like Omeprazole, Ciprofloxacin Cimetidine can inhibit enzyme that metabolise a drug.

physiochemical property of drug

(already written in absorption)

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Excretion of drug

Excretion is defined as the process where by drug or metabolites are irreversibly transferred from internal to external environmental through renal or non-renal route.

- Excretion of unchanged or intact drug is needed in termination of its pharmacological action.
- The principle organ of excretion are kidney.

Routes of drug excretions.

There are two route of drug excretion are as follows -

Major routes of excretion
- Renal excretion
- Biliary excretion

Minor routes of excretion
- Pulmonary excretion
- Salivary excretion
- Mammary excretion milk
- Skin / dermal excretion via sweat

Major routes of excretion

(a) Renal excretion - The renal excretion of drug is the route of different mechanism. glomerular filtration, passive back diffusion tubular secretion and tubular reabsorption

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(b) Biliary excretion - Biliary excretion involves active secretion of drug molecules of their metabolites from hepatocytes in to the bile

Minar routes excretion

(a) pulmonary excretion -

pulmonary excretion is a primary route for the elimination of gases & some volatile compounds.

(b) Salivary excretion -

Salivary excretion is an imp. pathway for the body to excrete small molecule with digestive enzyme.

(c) Mammary excretion -

The excretion of drug in human breast milk is reviewed with regard to milk production, composition, feeding period and mechanism of drug transfer into milk.

(d) Skin / dermal excretion -

- The skin release sweat through sweat gland present in the body.
- The sweat evaporates and helps to keep the body cool when it is warm outside.
- Skin assist in the process of excretion through sweating by eliminating water, salt and urea.

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General mechanism of drug action and factors modifying drug action.

Most of the drugs produce their action by interacting with a target biomolecules like protein etc.

How any drug produces their action is known as mechanism of drug action.

The general mechanism of action of drugs can be classified into the following four classes—

- Transport process
- Enzyme
- ion chemical
- Receptors

(1) Transport Process — Several substance are move across membrane by binding to specific transporter (through facilitate diffusion)

(2) Enzyme — Enzyme catalyse almost all biological reaction thus enzyme are important as target for action of a drug.

So when drug interact with enzyme it can either increase or decrease the rate of enzyme activity ~~and~~.

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③ Ion channels – Their are many ion channels in our body which helps transmembrane signaling and regulate intracellular ionic composition.
- Drug can also act ion channels
- Drug can also affect ion movement.

④ Receptor-
Receptors are protein or binding site which present on surface and inside the cell.

factor modifying drug effect
- Age
- Body weight
- Sex
- Time of administration
- Route of administration
- Drug interaction
- Tolerance
- Nutritional Status
- Therapeutic index
- presence of disease

Age –
pharmacokinetics of many drug changes with age.
Newborn liver and renal function less developed.
Elderly hepatic and renal function decline.
Blood Brain barrier more permeable in infants and many cause accumulation.

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Body weight
- It influence the ions of drug attained at the site of action.
- The average adult dose refers to individuals of medium built.

Sex
- females have smaller body size and so require doses of the drug on the lower side of the dose range.
- They should not be given quinine during pregnancy and sedative during lactation.

Time of administration -
- Aim to administer with 60 minutes of the scheduled time.
- for medicines administered within 2 hrs. The actual timing used in practice is influenced by a number of vaariable.

Route of drug administration
Route governs the speed and intensity of drug response.
I.V route dose smaller than oral route
A drug may have entirely different uses through different route.

Magnesium Sulphate
- Orally purgative
- Perenterally sedative
- Locally reduces inflammation

Tolerance –

Requirement of higher dose of ar a drug to produce a given response refractoriness → Seen in neurons. In type 2 diabetes and beta 2 agonists in bronchial asthma. adeptive biological phenomenon

Nutritional Status – Is the current body Status of a person ar a population group related to their state of nourishment.

Therapeutics Index –

A ratio that compare the blood concent which a drug Causes a therapeutic effect to the ammount that causes death ar toxicity.

Presence of disease –

Presence of disease because so many factors affect drug response doctors must chose a drug appropriate.

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Respiratory tract –

propanolol increase bronchial resistance by blocking β_2-receptor. the effect is hardly discernible in normal individuals because sympathetic bronchodilator tone is minimal

C.N.S

No central effect are produced by propanolol. However behavior changes forgetfulness, increase dreaming at nightmares have been reported

local anaesthatic.

propanolol is a potent a local anaesthatic has lidocaine but is not clinically used for this purpose because of its irritant property.

Metabolic –

Propanolol blocker adrenergically adrenes induced lipolysis and consequent increase in plasma free fatty acid level. plasma triglyceride level and LDL/HDL ratio is increased during propanolol therapy.

Skeletal muscle propanolol inhibit adrenergically provoked tremmers.