Pharmacology

"Pharmacology" word comes from two Greek words "Pharmacon" which means "Drug" and "logos" which means "study of", which means Pharmacology is the study of drugs. Or in other words, it deals with interaction of any administered chemical molecules with human body. Pharmacology covers all the aspects of drugs as well as their safe use for human well-being.

For thousands of years most drugs were crude natural products of unknown composition and limited efficacy. Pharmacology as an experimental science was uncovered by a German scientist Rudolf Buchheim who founded the first institute of pharmacology in 1847 in Germany. In the later part of the 19th century, Oswald Schmiedeberg, regarded as the 'father of pharmacology', together with his many pupils like J Langley, T Frazer, P Ehrlich, AJ Clark, JJ Abel propounded some of the fundamental concepts in pharmacology. Since then drugs have been purified, chemically characterized and a vast variety of highly potent and selective new drugs have been developed. The mechanism of action including molecular target of many drugs has been elucidated. This has been possible due to prolific growth of pharmacology which forms the backbone of rational therapeutics.

The two main divisions of pharmacology are: Pharmacodynamics and Pharmacokinetics.

- **Pharmacodynamics (**What the drug does to the body**)** is a combination of two greek words "pharmacon" which means "drug" and "dynamis" which means "power". It means the power of drug to affect our body. This includes physiological and biochemical effects of drugs and their mechanism of action at organ e.g.— Paracetamol helps to lower the body temperature, its targets in body, mechanism it follows to induce such effect everything this drug will do in body is studied under pharmacodynamics.

- **Pharmacokinetics** (What the body does to the drug) is a combination of two Greek words "Pharmacon" which means "drug" and "Kinesis" which means "movement". It means in what manners body is treating drug.
  This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion

of the drug, e.g. paracetamol is rapidly and almost completely absorbed orally attaining peak blood levels at 30–60 min; 25% bound to plasma proteins, widely and almost uniformly distributed in the body; extensively metabolized in the liver, primarily by glucuronide and sulfate conjugation into inactive metabolites which are excreted in urine; has a plasma half-life (t½) of 2–3 hours and a clearance value of 5 ml/kg/min.

Other than pharmacodynamics and pharmacokinetics there are few other branches of pharmacology are present which are:

- **Pharmacotherapeutics:** Pharmacotherapeutics is defined as "the study of the therapeutic uses and effects of drugs". It is the application of pharmacological information together with knowledge of the disease for its prevention, mitigation or cure. Selection of the most appropriate drug, dosage and duration of treatment taking into account the specific features of a patient are a part of pharmacotherapeutics.

- **Clinical pharmacology** It is the scientific study of drugs (both old and new). It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers and in patients for the evaluation of efficacy and safety of drugs and comparative trials with other forms of treatment, surveillance of patterns of drug use, adverse effects, etc. It has a broad scope, from the discovery of new target molecules, to the effects of drug usage in whole populations.

- **Toxicology** It is the study of poisonous effect of drugs and other chemicals. Posions are dangerous for human health. At certain dose even life-saving drug can act as poison. Toxicology is the branch of pharmacology which will explore the possible dose of drug which can act as a poison and give us idea about reducing the toxicity caused by these drugs. It also includes the study of adverse effects of drugs, since the same substance can be a drug or a poison, depending on the dose.

Drug

Word "Drug" comes from a French word "Drogue" which means "a dry herb". It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/ cure of a disease.

According to the WHO (1966) "Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

Sources of Drugs:

Natural Drugs: these are the drugs which comes from certain natural sources. They are further categorised as follows:

Minerals Drugs: These are the drugs which are of mineral origin. For example: Kaolin (it is used in diarrhoea), Charcoal (it is used in poisoning), magnesium sulphate (acts as Antacid), etc.

Animal Drugs: these are the drugs which comes from the animal origin. For example: insulin (used in diabetes), heparin (acts as anti-coagulant), adrenaline (increases hearts activity), etc.

Plant Drugs: these are drugs which comes from the plant origin, they are either whole plants or plant parts. For example: morphine (pain killer drug), digoxin (used in heart attack situations), quinine (anti-malarial drug) etc.

Microorganism Drugs: these are the drugs which are of microorganism origin, they can either contain whole microorganism or they can be extracted out from microorganisms. For example: penicillin (antibiotic drug), streptomycin (anti-biotic drug).

Semi synthetic Drugs: these are the natural drugs with slight modification. These drugs are isolated from the natural sources and afterwards they are modified. For example: coumarin is a natural drug which can be extracted from various plants, 7-hydroxy-4-methyl coumarin is its semi-synthetic derivative, which has better antioxidant property than simple ones.

Synthetic drugs: these are the drugs which can be synthesized by various chemical processes. For example: Paracetamol (anti-pyretic drug), cetirizine (anti-allergic drug), etc.

Essential Medicines

The WHO has defined *Essential Medicines (drugs)* as "those that satisfy the priority healthcare needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness.

It has been realized that only a handful of medicines out of the multitude available can meet the health care needs of majority of the people in any country, and that many well tested and cheaper medicines are equally (or more) efficacious and safe as their newer more expensive congeners. For optimum utilization of resources, governments (especially in developing countries) should concentrate on these medicines by identifying them as ***Essential medicines***.

The WHO has laid down criteria to guide selection of an essential medicine.

(a) Adequate data on its efficacy and safety should be available from clinical studies.

(b) It should be available in a form in which quality, including bioavailability, and stability on storage can be assured.

(c) Its choice should depend upon pattern of prevalent diseases; availability of facilities and trained personnel; financial resources; genetic, demographic and environmental factors.

(d) In case of two or more similar medicines, choice should be made on the basis of their relative efficacy, safety, quality, price and availability. Cost-benefit ratio should be a major consideration.

(e) Choice may also be influenced by comparative pharmacokinetic properties and local facilities for manufacture and storage.

(f) Most essential medicines should be single compounds. Fixed ratio combination products should be included only when dosage of each ingradient meets the requirements of a defined population group, and when the combination has a proven advantage in therapeutic effect, safety, adherence or in decreasing the emergence of drug resistance.

(g) Selection of essential medicines should be a continuous process which should take into account the changing priorities for public health action, epidemiological conditions as well as availability of better medicines/formulations and progress in pharmacological knowledge.

(h) Recently, it has been emphasized to select essential medicines based on rationally developed treatment guidelines.

India produced its *National Essential Drugs List* in 1996 and has revised it in 2011 with the title "*National List of Essential Medicines".* This includes 348 medicines.

Prescription and Non-Prescription Drugs

As per drug rules, majority of drugs including all antibiotics must be sold in retail only against a prescription issued to a patient by a registered medical practitioner. These are called 'prescription drugs'. In India they have been placed in the *schedule H* of the Drugs and Cosmetic Rules (1945).

However, few drugs like simple analgesics (paracetamol aspirin), antacids, laxatives (senna, lactulose), vitamins, ferrous salts, etc. are considered relatively harmless, and can be procured without a prescription. These are 'non-prescription' or 'over-the- counter' (OTC) drugs; can be sold even by grocery stores.

Orphan Drugs

These are drugs or biological products for diagnosis/treatment/ prevention of a rare disease or condition, or a more common disease (endemic only in resource poor countries) for which there is no reasonable expectation that the cost of developing and marketing it will be recovered from the sales of that drug. Examples are: sodium nitrite, fomepizole, liposomal amphotericin B, miltefosine, rifabutin, succimer, somatropin, digoxin immune Fab (digoxin antibody), liothyronine (T3) and many more.

Drug Compendia

These are compilations of information on drugs in the form of monographs; without going into the theoretical concepts, mechanisms of action and other aspects which help in understanding the subject. Following are the types of various compendia:

Pharmacopoeias*:* They contain description of chemical structure, molecular weight, physical and chemical characteristics, solubility, identification and assay methods, standards of purity, storage conditions and dosage forms of officially approved drugs in a country. They are useful to drug manufacturers and regulatory authorities, but not to doctors, most of whom never see a pharmacopoeia. Examples are Indian (IP), British (BP), European (Eur P), United States (USP) pharmacopoeias.

Formularies*:* Generally produced in easily carried booklet form, they list indications, dose, dosage forms, contraindications, precautions, adverse effects and storage of selected drugs that are available for medicinal use in a country. Drugs are categorized by their therapeutic class. Some rational fixed-dose drug combinations are included. A brief commentary on the drug class and clinical conditions in which they are used generally preceeds specifics of individual drugs. Brief guidelines for treatment of selected conditions are provided. While British National Formulary (BNF) also lists brand names with costs, the National Formulary of India (NFI) does not include these.

Martindale*:* Published every 2–3 years by the Royal Pharmaceutical Society of Great Britain, this non-official compendium is an exhaustive and updated compilation of unbiased information on medicines used/registered all over the world. It includes new launches and contains pharmaceutical, pharmacological as well as therapeutic information on drugs, which can serve as a reliable reference book.

Physicians Desk Reference (PDR) and Drug: Facts and Comparisons (both from USA), etc. are other useful non-official compendia.

Routes of drug administration:

Most drugs can be administered by a variety of routes. The choice of appropriate route in a given situation depends both on drug as well as patient related factors. Mostly common sense considerations, feasibility and convenience dictate the route to be used. Routes can be broadly divided into those for (a) Local action and (b) Systemic action.

a) **Local route:** when the site of desired effect is approachable.
b) **Systemic route**: when the site of desired effect is not approachable.

Factors affecting choice of route:

1. Physical properties of drug. If a drug molecule is in solid form then it will be administered locally or orally. For example: we take tableted and capsule orally, and we apply balms and oitments locally.
2. Chemical properties of drug. The solubility, stability, pH, etc, these chemical properties also affect the choice of route for drug administration. For example: if a drug molecule is not able to withstand acidic pH, then we cannot give it orally.
3. Desired site of action also affect the choice of route of drug administration. For example: if the desired site of action is approachable, then we will give drug locally, or otherwise if site is not approachable then we will give drug generally.
4. The rate and extent of absorption of drug from the site of action also affect the choice of route.
5. Effect of first pass metabolism also affect the choice of route, if a drug cannot pass first pas metabolism in liver then we cannot administer it orally.
6. Time taken by drug to give desired response also affect the choice of route. If we want a rapid response then we will administer drug via systemic routes instead of local routes.
7. Condition of patient also affect the choice of route. If a patient is unconscious then we will choose systemic route over local.

A) Local Routes:

These routes can only be used for accessible sites and for drugs whose escape by systemic absorption from these sites is minimal or absent. Thus, high concentrations can be attained at the desired site without involving the rest of the body. Because these drugs are present locally that's why the side effect on other parts of body will be absent or minimal. The local routes are mentioned as follows:

Topical route:

This route is suitable for those drugs which can be applied externally on various parts of body like skin, buccal mucosa, oral mucosa, canal of ear and other body cavities for localised action. Ointments, creams, powders, paint, sprays, lozenges, or suppositories are the examples of such dosage forms which can be administer locally.

B)Systemic Routes:

The drugs which are administered through systemic routes are intended to go directly into the blood stream and distributed all over, including the site of action, through circulation. Various systemic routes are given as following:

Oral:

Oral ingestion is the most common and convenient route of administration. Solid dosage forms like tablets, capsules, lozenges etc and liquid dosage forms like elixir, syrups, emulsions, suspensions, etc can be administered via oral route.

Advantages:

1. This method is the commonest of them all.
2. This method is easy, safe and does not need any assistance.
3. This method is painless.
4. In this method medication does not need to be sterilised.

Disadvantages:

1. Action of drug is slower.
2. Unpalatable drugs are difficult to administer.
3. Those drugs which are not able to withstand acidic pH are not suitable to administer via this route.
4. Administered drugs may cause nausea and vomiting.
5. The drugs will go through fist pass metabolism so the effectiveness of the drug may be lesser.
6. It is not possible to administer drug via oral route when patient is unconscious.

Sublingual:

The tablets containing drugs can be placed underneath the tongue or crushed in mouth so that it will spread over buccal mucosa. The drug will directly goes into the blood vessels present in the buccal mucosa and give a rapid effect. Glyceryltrinitrate (GTN) an antianginal drug can effect immediate effect.

Advantages:

1. It is also a convenient method.
2. The drug will directly goes into the blood circulation and hence it will by-pass the first pass metabolism.
3. The effect will be rapid.
4. Easy to administer.
5. Can even give to unconscious patients.

Disadvantages:

1. Only non-irritable and lipid soluble drugs can be administered.
2. Only a limited range of drugs can be administered via this route.
3. Difficult to administer bitter drugs.

Rectal:

Certain dosages like suppositories can be administer via this route. The dosages are directly inserted into the rectal cavity from where it can enter into the blood stream and induce effect. Drugs like diazepam, indomethacin, paracetamol, etc can sometime be given via this route.

Advantages:

1. The irritable, unpleasant drugs can be administer via this route.
2. The drugs can be given via this route to the patients having recurrent vomiting.
3. The drug can be given to unconscious patients.
4. The drugs will be absorbed from the rectum and directly goes into the blood and will by-pass first pass metabolism.

Disadvantages:

1. Absorption of drug is slower, irregular and unpredictable.
2. It can cause irritation in rectum.
3. Rectal inflammation is often seen.
4. This route of drug administration is embarrassing.

Cutaneous:

The drugs can be directly administer into the cutaneous layer of skin by applying the drug over skin. Ointments, creams can be administer via this route for localised action.

Advantages:

1. Effect will be prolonged.
2. Absorption can be enhanced by rubbing it over skin.
3. The drug will by-pass first pass metabolism.
4. Transdermal therapeutic system can be incorporated via this route.

Disadvantages:

1. Only lipid soluble drugs can be administer via this route.
2. Absorption of the drug will be slow.

Inhalation:

Certain volatile liquid as well as gases can be administer via this route. These drugs will be injected directly into the respiratory tract for systemic effect. Anti-asthmatic drugs and general anaesthetics can be administer via this route.

Advantages:

1. Absorption can be take place on a vast surface therefore, absorption will be rapid.
2. The drugs will by-pass first pass metabolism.

3. Mixture of gases and volatile liquid can be administer.

Disadvantages:

1. Irritable drugs cannot be administer via this route.
2. Drugs can cause inflammation of respiratory tract.
3. Drugs can increase respiratory tract secretions.

Nasal:

The drugs will be spread over the mucous membrane of nasal cavity with the help of nebuliser, from there the drug molecules will goes into the blood vessels present in the mucous membrane and further goes into the systemic circulation. Drugs like GnRH agonists and insulin can be administer via this route.

Advantages:

1. The absorption will be rapid.
2. First pass metabolism will be by-passed.

Disadvantages:

1. Irritable drugs cannot be administer via this route.
2. Drugs can cause nasal inflammation.

Parenteral:

With the help of this route we can inject the drug directly into the tissue fluid or in blood without having to cross the eternal mucosa. Drug action will be faster and definite. The gastric irritation and vomiting are avoidable. Drugs can be administer to unconscious patients. There are various parenteral routes:

a. Subcutaneous (*s.c.*): the drug is deposited in the loose sub-cutaneous tissue, it is highly supplied by nerves but less vascular. Small volume of drug can be administer via this route, self-injection is possible.
b. Intramuscular (*i.m.*): the drug via this route is administer into large skeletal muscles. The skeletal muscles are richly supplied by sensory nerves as well as are more vascular. This method is less ainfull but self-injection is not possible.

c. Intravenous (*i.v.*): the drug is injected as a bolus or infused slowly over hours in one of the superficial veins. The drug will directly reach in blood and the effect will be immediate. Even the irritable drugs can be administer via this route. This method is painfull.
d. Intradermal (*i.d.*): The drug is injected into the skin raising a bleb (e.g. BCG vaccine, sensitivity testing) or scarring/multiple puncture of the epidermis through a drop of the drug is done. This route is employed for specific purposes only.

Advantages of parenteral route:

1. The effect of the drug will be fast.
2. The gastric irritability will be avoidable.
3. The drugs can be administer to the patient with recurrent vomiting.
4. Drugs can be administered to the unconscious patients.
5. No chance of interference with gastro-intestinal juices.
6. First pass metabolism will be by-passed.

Disadvantages:

1. The preparations has to be sterilised, hence they are costlier.
2. The technique in invasive and painful.
3. Expert assistance is required.
4. Local tissue injuries are often seen in patients.

Pharmacokinetics

Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. The intensity of response is related to concentration of the drug at the site of action, which in turn is dependent on its pharmacokinetic properties. Pharmacokinetic considerations, therefore, determine the route(s) of administration, dose, latency of onset, time of peak action, duration of action and frequency of administration of a drug. All pharmacokinetic processes involve transport of the drug across biological membranes. So before discussing the absorption, distribution, metabolism and excretion of drug we have to go through the anatomy and physiology of biological membrane.

Biological membrane:

It is flexible, fragile and transparent barrier that contains all cell contents and separate them from surrounding environment. It is selective barrier that controls flow of material into and out of cell, maintains environment for cellular activities and plays role in communication among cells and between external environments.

Structure of the Biological Membrane:

The Lipid Bilayer The basic structural framework of the plasma membrane is the lipid bilayer, two tail-to-tail arranged layers of lipids. Lipid bilayer is made up of three types of lipid molecules—phospholipids, cholesterol, and glycolipids.

The bilayer arrangement occurs because the lipids are amphipathic, which means that they have both polar and nonpolar parts. In phospholipids, the polar part is the phosphate containing “head,” which is hydrophilic. The nonpolar parts are the two long fatty acid “tails,” which are hydrophobic. Because “like seeks like,” the phospholipid molecules orient themselves in the bilayer with their hydrophilic heads facing outward. The hydrophobic layer present inside plasma membrane makes it relatively impermeable to water soluble materials.

The plasma membrane also contains number of proteins present in it which are called Membrane proteins. Membrane proteins are of two types:

a. Integral proteins: These extend into or through the lipid bilayer among the fatty acid tails and are firmly embedded in it. Most integral proteins are Trans membrane proteins, which mean that they pass through entire lipid bilayer and protrude into both the cytosol and extracellular fluid.

b. Peripheral proteins: These are not as firmly embedded in the membrane and are associated loosely with the polar heads of membrane lipids or with integral proteins at the inner or outer surface of the membrane.

Transport across the plasma membrane:

Plasma membrane is a semipermeable membrane and transport across plasma membrane occurs by two methods:

1. **Passive Process:** In passive processes, a substance moves down its concentration or electrical gradient to cross the membrane using only its **own** kinetic energy (energy of motion). There is no input of energy from the cell. *E.g.* Simple diffusion.

2. **Active Process:** In active processes, cellular energy in the form of ATP (Adenosine Triphosphate) is used to move the substance "uphill" against its concentration or electrical gradient. *E.g.* Active transport.

1. Passive Processes:

A) **Diffusion:** It is a passive process in which random mixing of particles in a solution occurs because of particle"s kinetic energy. If a particular solute is present in higher concentration in one area and in low concentration in another area of a solution, then solute molecule will diffuse toward area of lower concentration *i.e.* they will move down their concentration gradient. Similarly a substance may diffuse through plasma membrane if there is concentration difference across plasma membrane. Diffusion is of 3 types:

a) Simple diffusion

b) Facilitated diffusion

- Channel mediated facilitated diffusion
- Carrier mediated facilitated diffusion

c) Osmosis

a) Simple diffusion: Simple diffusion is a passive process in which substances move freely through the lipid bilayer of the plasma membranes of cells without the help of membrane transport proteins. Nonpolar, hydrophobic molecules move across the lipid bilayer through the process of simple diffusion. *E.g.* oxygen, carbon dioxide, nitrogen gas, fatty acids, steroids and fat-soluble vitamins (A, D, E, and K). Small, uncharged polar molecules such as water, urea, and small alcohols also pass through the lipid bilayer by simple diffusion. Simple diffusion through the lipid bilayer is important in the movement of oxygen and carbon dioxide between blood and body cells, and between blood and air within the lungs during breathing. It also is the route for absorption of some nutrients and excretion of some wastes by body cells.

b) Facilitated diffusion: Solutes that are too polar or highly charged move through the plasma membrane by a passive process called facilitated diffusion. In this process, an integral membrane protein assists a specific substance across the membrane. Facilitated diffusion is of 2 types:

Channel mediated facilitated diffusion: In this process, the solute moves down its concentration gradient across plasma membrane through a membrane channel. The membrane channel allows passage of small inorganic ions that are too hydrophilic to pass through lipid bilayer. *E.g.* K+ ion channels, Cl- ion channels, Na+ ion channels and Ca2+ ion channels.

Carrier mediated facilitated diffusion: In this diffusion a carrier or transporter moves solute down its concentration gradient across plasma membrane. The solute binds to a specific carrier on one side of membrane and is released on the other side after carrier undergoes a change in the shape. Glucose, Fructose, Galactose and some vitamins move across plasma membrane by carrier mediated facilitated diffusion.

c) **Osmosis:** It is a type of diffusion in which there is net movement of solvent thorough selective permeable membrane. It is also a passive process. On living system is defined as movement of water from area of higher water concentration to area of lower water concentration through plasma membrane. During osmosis water molecule pass through plasma membrane either by simple diffusion or through an integral protein aquaporin which acts as water channel.

2. Active processes:

A) Active Transport: The charged or polar solutes that have to move against their concentration gradient cross the plasma membrane by a process called active transport. It is called so because energy is required to move solute against their concentration gradient. The energy required is provided by ATP. Solutes which are actively transported include Na+, Ca2+, H+, K+, I-, Cl-, amino acids and monosacchrides. Active transport is of 2 types:

a) Primary Active Transport

b) Secondary Active Transport

a) Primary Active Transport: In this type of transport, the energy required is provided by hydrolysis of ATP which changes the shape of carrier protein and thus the carrier protein pumps the substance across plasma membrane against its concentration gradient. *E.g.* Na+-K+ pump which expels Na+ out of cell and brings K+ ions inside the cell.

b) Secondary Active Transport: In this transport, the energy stored in Na+ or H+ ion concentration gradient is used to drive the substances across the membrane against their own concentration gradient. Because Na+ or H+ ion concentration gradient is maintained by primary active transport, so the secondary active transport indirectly uses the energy obtained from hydrolysis of ATP. In secondary active transport, a carrier protein simultaneously binds to Na+ and another substance and then changes its shape so that both substances cross the membrane at the same time. If these transporters move two substances in the same direction, they are called symporters (sym = same); and if transporter moves two substances in opposite direction, then they are called antiporters (anti = against). *E.g.* Na+/Ca2+ antiporters, Na+/glucose symporters.

B) Transport in vesicles: Vesicles are small spherical sacs which transport a variety of substances within cell. They also transport material to inside and outside the cell. The transport is done by Endocytosis and Exocytosis. Both endocytosis and exocytosis use energy supplied by ATP, so it is also an active process.

• **Endocytosis:** (Endo = within) In endocytosis, the material moves into cell by a vesicle formed from plasma membrane. Endocytosis is of 3 types:

➢ **Receptor mediated endocytosis** is a highly selective type of endocytosis in which cell takes up specific ligand. A vesicle is formed when a specific ligand binds to receptors on plasma membrane

➢ **Phagocytosis** (Phago = eat) is a form of endocytosis in which cell engulfs a large solid particles such as worn out cell, whole bacteria or virus.

➢ **Pinnocytosis** (Pinno = drink) is a type of endocytosis in which a tiny droplet of extracellular fluid is taken to form vesicles and all solutes dissolved in extracellular fluid are brought into the cell.

• **Exocytosis:** In exocytosis, vesicle move material out of the cell. It occurs generally in neurons and secretory cells. Neurons release neurotransmitter and secretory cells of digestive systems secrete enzymes. In some cases, waste products are also released by exocytosis.

• **Transcytosis:** In transcytosis, vesicles are used to move substance into, across and then out of the cell. In this vesicles undergo endocytosis on one side, move across the cell and undergo exocytosis on other side of the cell.

Absorption of drug

Absorption is movement of the drug from its site of administration into the circulation. Not only the fraction of the administered dose that gets absorbed, but also the rate of absorption is important. Except when given i.v., the drug has to cross biological membranes; absorption is governed by the above described principles.

Other factors affecting absorption are:

Aqueous solubility Drugs given in solid form must dissolve in the aqueous biophase solution before they are absorbed. For poorly water soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption. Obviously, a drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution

Concentration Passive diffusion depends on concentration gradient; drug given as concentrated solution is absorbed faster than from dilute solution.

Area of absorbing surface Larger is the surface area, faster is the absorption.

Vascularity of the absorbing surface Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface. Increased blood flow rushes drug absorption.

Route of administration route of administration of the drug highly affects the rate and extent of absorption. Like, if we are administering drug via oral route the rate of absorption will be slow because the drug has to cross the layers of the gastro-intestinal organs. But if we are administering drug via sublingual route the absorption will be faster than oral administration because the drug has to cross just the mucous membrane in buccal cavity to reach out to the blood circulation.

Bioavailability

Bioavailability refers to the rate and extent of absorption of a drug from a dosage form as determined by its concentration-time curve in blood or by its excretion in urine. If we are administering "X" concentration of drug, the fraction from the initial concentration which reach out in the systemic circulation, the measurement of that fraction is called bioavailability of that drug. The bioavailability of drug given via oral route will be less, and via *i.v.* route it will be the highest *i.e.* 100%.

Distribution

Once a drug has gained access to the blood stream, it gets distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues. The extent and pattern of distribution of a drug depends on its:

• lipid solubility
• ionization at physiological pH (a function of its pKa)
• extent of binding to plasma and tissue proteins
• presence of tissue-specific transporters
• differences in regional blood flow.

Movement of drug proceeds until an equilibrium is established between unbound drug in the plasma and the tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

Bio-Transformation (Metabolism)

Biotransformation means chemical alteration of the drug in the body. It is needed to render nonpolar (lipid soluble) compounds into polar (lipid-insoluble) compounds so that they are not reabsorbed from urine in the renal tubules and are excreted into the urine. Most hydrophilic drugs, e.g. streptomycin, neostigmine, pancuronium, etc. are little bio-transformed and are largely excreted unchanged. Mechanisms which metabolize drugs (essentially foreign substances) have also developed to protect the body from ingested toxins.

The primary site for drug metabolism is liver; others are—kidney, intestine, lungs and plasma.
Biotransformation of drugs may lead to the following.

1. Inactivation: most of the drugs and their active metabolites are converted to their inactive form after metabolism. For example paracetamol.
2. Active metabolite from an active drug: Many drugs have been found to be partially converted to one or more active metabolite; the effects observed are the sumtotal of that due to the parent drug and its active metabolite.
3. Activation of inactive drug: Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called a prodrug.

Biotransformation reactions can be classified into:
(a) Non-synthetic/Phase I/Functionalization reactions: a functional group is generated or exposed— metabolite may be active or inactive.
(b) Synthetic/Conjugation/ Phase II reactions: an endogenous radical is conjugated to the

drug— metabolite is mostly inactive; except few drugs, e.g. glucuronide conjugate of morphine and sulfate conjugate of minoxidil are active.

Excretion

Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

1. Urine The kidney is responsible for excreting all water soluble substances. The amount of drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion.

2. Faeces Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids, organic bases, other lipophilic drugs and steroids by distinct nonspecific active transport mechanisms. Relatively larger molecules are preferentially eliminated in the bile..

3. Exhaled air Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility. Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter that enters circulation.

4. Saliva and sweat These are of minor importance for drug excretion. Lithium, pot. iodide, rifampicin and heavy metals are present in these secretions in significant amounts. Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

5. Milk The excretion of drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. However, the total amount of drug reaching the infant through breast feeding is generally small and majority of drugs can be given to lactating mothers without ill effects on the infant.