CHAPTER 3 Routes of administration of drugs

Routes of administration of drugs is the method by which the drug is introduced into the body.

CLASSIFICATION OF ROUTES OF ADMINISTRATION OF DRUGS. (Fig.3)

Enteral	**Parenteral (par=away, enteral = GIT, away from GIT)**	**Topical**
1.Oral 2.Sublingual 3.Rectal 4.Buccal	1.Injections i)subcutaneous ii)intramuscular iii)intravenous iv)intradermal v)interathecal/epidural vi)intraarticular vii)intraarterial 2.Inhalational administration 3.Transdermal administration	1.Drops i)nasal, eye and ear drops) 2.Vaginal, urethral tablets 3.Dermal – gel, ointment

For local action: The drug need not be absorbed. But for systemic action, the drug should be absorbed (absorption means, entry of the drug into the blood stream from the site of administration)

ORAL ROUTE: The drugs are administered by swallowing from the mouth. This route is meant for both local and systemic actions.

Dosage forms: tablet, capsule, powder, liquid preparations.

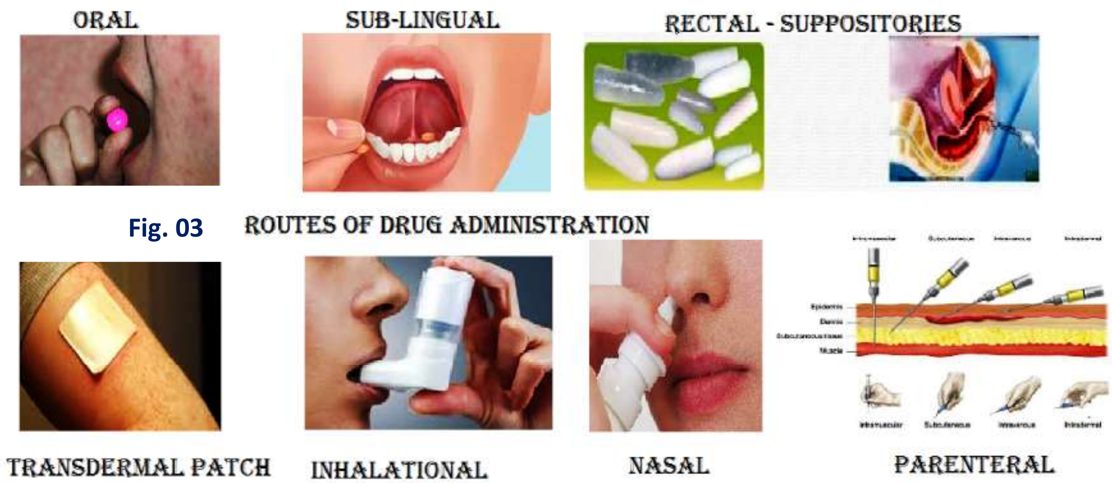


Fig. 03 ROUTES OF DRUG ADMINISTRATION

Advantages/merits of oral administration:

- Most common method.
- Very safe
- Self administration is possible.
- Non invasive
- Painless
- Economical, since sterilization and other procedure are not needed.

Disadvantages/demerits:

- Slow onset of action. Not suitable in emergency condition.
- Many drugs being polar are not absorbed (Gentamicin).
- The drugs which are destroyed by the gastric juice cannot be given by this route.
- The drugs which are having high first pass metabolism cannot be given by this route. (Example : GTN (Glyceryl Tri Nitrate)
- This route is not suitable in unconscious, noncooperative patients or in patients having severe vomiting.
- Unpalatable substances cannot be given by this route.

SUBLINGUAL ADMINISTRATION:

The drug is kept under the tongue mainly for systemic action. Example : Glyceryl Tri Nitrate (GTN)

Merits:

- This route is suitable for those drugs which have got high first pass metabolism, since this route bypasses liver (portal circulation) for the first time. The drug directly goes to the systemic circulation.
- Quick onset of action.

- Self administration is possible in case of emergency.
- The drug can be spit out as soon as action is over in order to avoid the side effects.

Demerits:

- Distasteful, irritant drugs cannot be given by this route.
- Higher molecular weight drugs like Insulin, Heparin cannot be given by this route, (otherwise it will be the best route for Insulin and Heparin).

RECTAL ADMINISTRATION for both local and systemic actions.

Drugs are administered through rectum. Dosage forms: suppository (conical shape) - Example : Dulcolax – (purgative in children). Liquids are administered with high pressure (enema). Example: Evacuant enema (soap water) is used to clear the GIT in case of emergency evacuation of bowel.

Merits:

- Useful in patients having severe nausea and vomiting.
- This route may be convenient in noncooperative children, (Diazepam suppository in febrile convulsion in children)
- It is alternate route for gastric irritant drugs.

Demerits:

- Inconvenient and embrassing to the patients.
- The drugs soil the clothes.
- Rectal inflammation is possible.
- Absorption is unreliable.

PARENTERAL ROUTES:

- Drugs are administered away from GIT (par= away, enteral=GIT) usually by injections or by inhalation.
- Injection → It is given by using needle and puncturing the skin. This route is preferred mainly for systemic action.
- Inhalation → The drug is administered through nose and mouth to the respiratory tract for local or systemic action.

INTRAMUSCULAR INJECTION:

Drugs are injected deep into the skeletal muscles.

Sites: Deltoid muscle, gluteal muscle of buttock (preferred for depot or long acting preparations of drugs).

Merits:

- Injections are suitable for those drugs which cannot be given by oral route. Injections are preferred, when quick action is required.
- Bioavailability is high (90 to 100%) after injection.
- Depot or long acting preparations are given by this route.

Demerits:

- Painful at the site of injection.
- Self administration is difficult.
- Expensive.
- Perfect aseptic conditions are required.
- Chances of abscesses or nerve damage at the site of injection is possible.
- Large volume cannot be given through this route.

SUBCUTANEOUS INJECTION:

The drugs are injected into the subcutaneous tissues of forearm, abdomen and thigh.

Merits:

- Self administration is possible.
- This is the best route for administering highly potent drug (among injections). Because of less blood supply, there will be slow absorption and hence less toxic. (Morphine, Insulin, Low molecular weight Heparin).
- Also depot preparation for prolonged action is given by this route (Example: Progesterone implant into the subcutaneous tissues for prolonged action as contraceptive).

Demerits:

- Only small volume can be given (maximum of 1 ml).
- Irritant drugs produce necrosis.
- Not suitable in shock as reduced blood circulation decreases the rate of absorption.

DERMOJET:

Subcutaneous administration of drugs with pressure (without needle). Useful for mass inoculation. No need for repeated sterilization.

INTRAVENOUS INJECTION (I.V.): (Slow administration of drugs into the vein is called as infusion)

Site: The drugs are injected into antecubital vein.

Merits:

- I.V. Injection is suitable for those drugs which cannot be given by oral route. I.V. injections preferred, when quick action is required.
- Bioavailability is 100%
- It is the best route in emergency.
- Large volume can be given (Example : IV infusion of Dextrose, Saline, Blood).
- For controlled dosage administration; (IV infusion of Oxytocin and IV General Anaesthetics).

Demerits:

- Painful at the site of injection.
- Self administration is difficult.
- Expensive.
- Perfect aseptic conditions are required.
- Chances of abscesses or nerve damage at the site of injection is possible.
- Necrosis and thrombophlebitis are common.
- Care should be taken that air should not enter into the vein (air embolism is fatal).
- Drugs of oily or suspension in nature (used for long action) cannot be given by this route.

INHALATIONAL ADMINISTRATION OF DRUGS:

The drugs are administered by inhalation through mouth and nose (through respiratory tract).

Example: Volatile general anaesthetics, Salbutamol in bronchial asthma, steroid (Beclomethasone) in bronchial asthma.

The drugs are administered and excreted through the same route.

Absorption is through alveoli (plenty of blood supply and also vast surface area). So the absorption is quick and there will be quick onset of action.

General anaesthetic dose is accurately monitored. (Fig.12)

TOPICAL ROUTES: Mainly for local action.

Example: Eye drops, Ear drops, Nasal drops, vaginal tablet, foam etc., Diclofenac sodium spray on skin is for systemic action (analgesic and anti-inflammatory actions).

In the modern days, the pharmacist is no longer required to prepare or to dispense the drugs for doctors' prescription. Drugs are now prepared and well packed by the pharmaceutical companies and supplied in various dosage forms and formulations for dispensing to the patients. The drugs are not administered as formulated Syrups, capsules, tablets or injections.

FORMULATION OF DRUGS

It is a recipe of drug preparation. It consists of active ingredients (the drug) and other substances like excipients, vehicles, flavouring agents and preservatives, with the quantity of each components.

DOSAGE FORM

It is the form (e.g., as tablet or capsule or injection or oral liquid) in which the above formulation of the drug can be administered to a patient.

EXCIPIENTS

Pharmacologically inert substances which are added to the pharmaceutical preparation either to add bulk of the tablet (active drug is extremely small in quantity) or to mask (or reduce) the unpalatable taste e.g., lactose, calcium lactate, starch etc.,

VEHICLES

These are the substances which are used to dissolve or suspend the drugs, in a pharmaceutical preparation, to make them suitable into usage form (as in ointments) or more palatable (as in liquids), e.g., sugar syrups, cherry syrup, gum acacia and petroleum jelly etc.,

CLASSIFICATION OF DOSAGE FORMS :

SOLID DOSAGE FORMS

POWDERS

These may be one drug or combination of drugs in a dried and finely powdered form intended for external use (e.g., dusting powders, boric acid) or for oral use (e.g., Aspirin powder).

EFFERVESCENT POWDERS

Drug powders are mixed with sodium bicarbonate, citric acid or tartaric acid. If dissolved in water, they effervesce with release of carbon dioxide (e.g., Eno Antacid powder) and thus make the mixture more palatable and tasty. In tablet form it is called dispersible tablet, e.g., Disprin (dispersible Aspirin tablet).

GRANULES

These are small units of powder bound together by a binding agent (e.g., starch or alcoholic spray), e.g., Vitamin D_3 granules. Some of these granules can be dissolved in a specific volume of water to make a suspension for immediate oral use in children, e.g., Amoxicillin or Ampicillin dry syrup.

TABLETS

Drugs which are powdered or granulated form are compressed under heavy pressure into a round or oval shaped making them suitable for swallowing.

i) Ordinary Tablets

These are uncoated compressed tablets, e.g., Paracetamol tablets.

ii) Sugar-coated Tablets

These tablets are coated with sugar to avoid bitter taste of ingredients, e.g., tab, Chloroquine, tab. Metronidazole.

iii) Film-coated Tablets

A transparent film coating is done by gelatin or cellulose derivatives just to mask the unpleasant taste. But the tablet size or weight remains the same. E.g., Cefuroxime film coated tablet, Diltiazem film coated tablet etc.,

iv) Enteric-coated Tablets

Coating of the tablet is made by cellulose acid phthalate, shellac or keratin which are resistant to gastric acid but dissolve at intestinal alkaline pH. The active drug is protected from destruction by acidic pH. Gastric irritation is reduced, e.g., Diclofenac enteric coated tab Enteric coated enzyme preparation), Enteric coated Aspirin tablets.

v) Long acting tablets (retard tablets-R, sustained release tablets-SR)

Each unit of drug particles have individual coating with different types of inert resins so that each type of coating dissolves at different time intervals. Such tablets provide a steady and sustained release of the drug over a period of 10-12 hr and hence have a lesser side effects, e.g., Pot.chloride retard tabs, Diclofenac sod.sustained release tablet. Nifedipine retard tab. Controlled release drugs are most suitable for drugs of short $t_{½}$. Therapeutic failure can occur for life saving drugs such as Nitro glycerine controlled release capsules.

vi) Pellets

Drugs which are in sterile spheres prepared by compression of drug powders such as hormonal preparations. Used for subcutaneous depot implantation of the drugs which will be slowly released for a long duration . e.g., Testosterone pellets.

vii) Lozenges

It is a tablet form of drug prepared with sugar and resin, and is meant for chewing to provide local effects in mouth or throat e.g., various cough lozenges, throat smoothening agents.

Capsules

These are inert gelatin coated shells of suitable size, incorporating powdered drug and excipients meant for swallowing, e.g., Doxycycline cap., Amoxicillin cap., etc., Thick gelatin capsules are used to incorporate powder form of drug (e.g., Amoxicillin) while soft, thin gelatin capsules are used to incorporate oily drug (e.g., Vit E). The gelatin coating quickly dissolves in gastric juice and release the drug in the GIT.

a) Spansules

These are longer acting capsules, similar to long acting tablets., e.g., Iron formulations, Isosorbide dinitrate Spansules, Nitroglycerine Spansules. These are visible coloured drug granules inside a transparent capsule. These beads are impregnated with various resins which will dissolve at different time intervals.

LIQUID DOSAGE FORMS OF DRUGS

AQUEOUS SOLUTIONS

These are subdivided into the following forms:

i) Syrups

Drug(s) present in concentrated solution. Sugar or Sugar free liquids plus flavouring agents and permitted colours, e.g., Commonly used cough syrups, vitamin syrups.

ii) Solutions (Liquor)

These are aqueous solutions of therapeutic agents e.g., hydrogen peroxide solution, liquor ammonia and iodine solution.

iii) Linctus

Viscous syrupy liquid formulations consist of the drug and demulcents, like menthol. Linctus provides soothing effect in sore throat, e.g., cough linctus.

iv) Injections

These are sterile solutions or suspensions of the drug in appropriate solvent and preservatives which are meant for parenteral use, e.g., Injection Diclofenac, Injection Lignocaine. Some drugs are supplied as dry powders which should be dissolved in aqueous vehicles like water for injection e.g. Cephalosporins, Amoxycillin etc.,

a) Depot injection

It is a longer acting injectable preparation similar to long acting Tablets or Spansules, but in injection form. The drug is suspended in sterile oily base from which it is slowly released for a prolonged duration, e.g., Testosterone depot inj. Fluphenazine depot inj.

AQUEOUS SUSPENSION

i) Mixtures

Solid drugs dispersed homogeneously in water by suitable suspending agent (agar agar), e.g.,Milk of magnesia etc.,

ii) Emulsions

They are prepared by mixing two or more immiscible liquid medicaments by means of a suitable suspending agent (Gum acacia). One liquid serves as continuous phase in which the other liquid is dispersed uniformly in fine droplet form, e.g., cod liver oil emulsion, liquid paraffin emulsion. This preparation helps for better absorption of the drugs.

ALCOHOLIC SOLUTIONS

i) Spirits

These are 10% v/v solution of volatile essential oils plus alcohol and are used as flavouring agents, masking agents and to some extent as preservatives, e.g., spirit chloroform, spirit ammonia aromaticus,

ii) Elixirs

These are pleasantly flavoured solutions of a drug in sugar syrup or glycerol along with higher proportions of alcohol,e.g., vitamin B – complex elixirs, cough elixirs; but these preparations are now on the decline. Alcohol is used in elixir as a solvent for drugs that are not suitable for water alone.

iii) Tinctures

These are alcoholic extracts of plant drugs (10-20 w/v), e.g., tinct. belladonna . Many tinctures are used as flavouring agents, e.g., tinct.cardamom . and tinct. Zingibaris (in such cases drug contents many range from 20% to 50%). Hydroalcoholic solutions of inorganic substances known as tinctures, e.g., Tinct.iodine which is used as an antiseptic.

Drops

Used mainly in paediatrics. These formulations contain small quantity of concentrated solutions of drug (s), e.g., vitamin drops and enzyme drops. Eye/ear drops are also included in this category. These are sterile, isotonic buffered solutions of the drug. These are usually supplied in a vial with a dropper, e.g., Ciprofloxacin eye/ear drops, gentamicin eye/ear drops etc.,

Enema

Medicated liquid preparations for rectal route of administration with high pressure and are used for emergency evacuvation of bowel e.g., soap and water enema

DOSAGE FORMS FOR EXTERNAL USE

Liniments

Liquid medicaments to be rubbed on skin with friction. It contains drug (s) in a liniment vehicle (fixed oil or soap) and water or alcohol. One ingredient is usually incorporated with another medium (Capsaicin, camphor which serve as counterirritant). These are mainly used as pain relievers or as rubefacient (making skin red), e.g., liniment capsaicin, and liniment turpentine.

Lotions

Liquid medicaments used for local application but without rubbing. They are generally used as antiseptics, soothing agents, astringents and antipruritic agents, e.g., Permethrin lotion, zinc calamine lotion, povidone iodine scrub lotion.

Ointments

These are soft, semi-solid substances containing the drug in a greasy base (paraffin or wool fat), e.g., Povidine Iodine skin ointment and Silver sulfadiazine ointment. Some ointments are in a water miscible base (vehicle). Ophthalmic ointments are sterile medicated ointments for eye ailments, e.g., Ciprofloxacin eye ointment, Atropine eye ointment.

Paste

It is like an ointment with some adhesive material (like starch) or a foaming agent (like carboxymethyl cellulose),e.g., zinc oxide paste, etc.,

Plaster

It consists of a drug mixed in a resinous base spread over a muslin cloth. Some plasters are coated with water repellent film also. The preparation remains hard at room temperature but becomes sticky at body temperature. These are used for protective, analgesic and antiseptic action, e.g., Flurbiprofen plaster, belladonna plaster and Band-Aid.

Gels/ Colloidal aqueous Suspensions

The drug is dissolved in a liquid and then dispersed in soft gelatin. These are usually transparent preparations, e.g., contraceptive gels. The colloidal aqueous suspensions of hydrated inorganic substances used as antacids, e.g., aluminium hydroxide gel.

Inhalants

Liquid preparations of a drug which is meant to be inhaled as vapour. e.g., Eucalyptol, Menthol, tincture benzoin inhalation. The contents may be poured into a jug of boiling water and inhaled to relieve nasal or chest congestion. Solid powdered inhalants, e.g., Salbutamol, Budesonide are inhaled with the use of rotahaler, turbo spin inhaler.

Aerosols

The drug is dissolved in a liquid form is kept inside a cylindrical container (canister) and is then filled with a propellant gas (air or oxygen) under pressure. A compression at the valve releases the microfine drug through a tiny nozzle in the form of mist which is inhaled. If one compression releases a measured dose of drug ,then these are called as “metered aerosols”, e.g., Salbutamol metered aerosol, Budesonide metered aerosol.

Suppositories (rectal), Pessaries (vaginal) and Bougies (urethral)

The drug is mixed with any one of the incredients e.g., glycerine, gelatine, soap, paraffin, cocoa butter. These remain solid at room temperature but become soft and melt at body temperature. Suppositories are bullet shaped, pessaries are conical, while bougies (for both male and female urethra) are pencil shaped. For example: Bisacodyl suppositories and Clotrimazole vaginal pessaries.

Transdermal drug delivery system - Transdermal patch

These are adhesive patches, the drug is incorporated into a polymer (usually polyisobutylene) which in turn is bonded to an adhesive plaster. The drug is delivered at the skin surface by diffusion, by percutaneous absorption it enters into circulation. These preparations are designed to provide steady and smooth plasma concentration of the drug for a period ranging from 1-3 days from the site of their application (usually chest, abdomen, upper arm or mastoid region). Examples are transdermal patches of Nitroglycerin patch, Nicotine patch and Estradiol patch.

TARGETED DRUG DELIVERY SYSTEMS

To improve the drug delivery at the site of action and to reduce the systemic adverse drug reactions special drug delivery systems have been developed recently which have an added advantage of reduced dosage with prolonged drug action. Examples of targeted drug delivery systems are:

Ocuserts

These are thin elliptical microunits of drug in a reservoir from which the drug is slowly released through a semipermeable membrane by diffusion at a steady rate. e.g., Pilocarpine ocusert used in glaucoma, which is placed under the lower eyelid to deliver pilocarpine for a period of 7 days, thus avoiding cumbersome frequent administration of eye drops every day.

Progestaserts

Intrauterine contraceptive device to deliver progesterone into uterus. It is inserted into uterus which delivers progesterone uniformily at a specified rate for a period of one year.

Liposomal drug encapsulation for Intravenous Infusion

Liposomes are minute spherical vesicles of phospholipids containing an aqueous suspension . They can be artificially filled with soluble drug particles, which may be delivered to target tissues. Amphotericin (an antifungal drug used to treat systemic mycoses) is available in a liposomal formulation for intravenous infusion; the preparation is less nephrotoxic and better tolerated. The cost is high due to the manufacturing.

Prodrugs

This is a form of inactive drug which will be converted in the body to an active drug. These are used to overcome the pharmacokinetic disadvantage of bioavailability of the therapeutically very useful drug. For example: Dopamine is very useful in treating parkinsonism, but it does not cross blood-brain barrier (Fig.56). Levodopa, its prodrug, can cross BBB, which is then converted to dopamine in the CNS. Prodrug may also be used to provide longer duration of drug action, e.g., esters of penicillins get slowly hydrolysed in the body to provide slow and sustained release of penicillins (e.g., Procaine Penicillin – G and Benzathine Penicillin –G).

Computerised Miniature Pumps (Fig.06)

These are Computer programmed pumps to release drugs at a definite rate, either continuously as in the case of insulin pumps or intermittently in pulses as in the case of GnRH (gonadotrophin-releasing hormone) pumps. These pumps may also be synchronized with glucose sensor devices which release the desired dose of insulin as per the blood glucose level.

Monocclonal Antibodies (MAbs) as Drug Carriers

These are antibodies which are produced by a single antigenic determinant (epitope) and directed against that particular antigen are called “monoclonal antibodies”.

Large scale production of monoclonal antibodies against any specific antigen is now done by using “hybridoma technology”. Hybridomas are somatic cell hybrids, obtained by fusing a specific B-lymphocyte (forming antibody against a specific antigen) with a mouse myeloma (tumour) cell. The resultant hybridoma, therefore, retains the antibody forming capacity of the B-lymphocyte with an ability of the myeloma tumour cell to proliferate endlessly.

To generate these antibodies, the mouse myeloma cells are first grown in a culture deficient in hypoxanthine phosphoribosyl transferase (HPRT) enzyme so as to inactivate antigen and to prevent the subsequent formation of immunoglobulins (because a tumour cell itself has a specific antigen on its surface). These myeloma cells are then fused with B-lymphocytes, obtained from the spleen of mouse immunised with the desired antigen, in polyethylene glycol. The fused cells (hybridomas) are then placed in HAT medium and cloned.In HAT medium, only the hybridomas can be maintained endlessly in this culture and can continue to produce monoclonal antibodies (MAbs) which can be eluted and purified for clinical use.

However, totally humanised MAbs are the least antigenic. These are obtained either by recombinant DNA technology (by replacing a part of mouse gene sequence with human gene sequence) or by grafting of “complimentarity determining regions (CDRs)” of murine MAbs on human immunoglobulins framework.

The name of any monoclonal antibody ends with a suffix “mab”. The letter before “mab” indicates the source of the antibody e.g., “o” for murine (omab), “xi” for chimeric (ximab) and “zu” for human (zumab). The letters appearing before these words denote their therapeutic use, e.g., “tu” for tumour, “vi” for virus and “ci” for circulation. If there is no prefix then such a “Mab” is generally an immunomodulatory.

For example, muromonab – CD3 is a murine anti – CD3 monoclonal antibody which is used to prevent transplant rejections. Rituximab is a chimeric monoclonal antibody used to treat non Hodgkin’s lymphoma (tumour). Palivizumab is a Mab that binds to fusion protein of respiratory syncytical virus (RSV) and thus prevents RS-viral infections in airways. Abciximab is a chimeric Mab which binds to GP IIb/IIIa receptors present on activated platelets to prevent their aggregations and very useful in preventing platelet aggregation in coronary angioplasty.

Mechanism of action of monoclonal antibodies: MAbs bind with specific antigens (virus, grafted tissues and neutralize (kills virus, prevent graft rejection) and also neutralize the specific antigens like non-self antigen and prevent the destruction of non-self tissues), prevent antigen antibody reaction on mast cell and prevent the release of chemical mediators from mast cells.

Clinical uses of monoclonal antibodies:

1. As antiviral : Palavizumab- it neutralizes RSV (Respiratory Syncytial Virus) and inhibits its fusion with human cell membrane. It is used to prevent lower respiratory tract infections due to RSV.
2. As anticancer: i) Rituximab : Used in B-cell lymphoma, chronic lymphocytic leukaemia. ii) Epratuzumab (humanized): Used in Non-Hodgkin's lymphoma. iii) Alemtuzumab- Used in B- cell chronic lymphoid leukaemia and T- cell lymphoma.
3. As antiasthmatic: Omalizumab: Used in allergic type of asthma. It inhibits the binding of IgE with mast cells and suppressses IgE mediated release of bronchoconstrictor chemical mediators (Histamine/LTs)
4. As immunosuppressive agents: Muromonab-CD-3 (anti CD3). It depletes cytotoxic T-cell (CD8+Tc) Hence it is useful to prevent graft rejection in organ transplantation. It is also useful in autoimmune diseases, since it inhibits the antigen and antibody reaction, which prevent the destruction of non-self tissues.

Fig.05 Insulin Delivery Devices

- Insulin syringes
- External Insulin Pumps
- Implantable Insulin Pumps
- Insulin Pens
- Insulin Injection Aids
- Insulin Jet Injectors
- Insulin Inhalers

(Fig.06)

Continuous subcutaneous insulin infusion (CSII) through pumps

-Most physiological method of insulin delivery

-Preferred in patients uncontrolled on multiple injections & those needing excellent control(pregnancy)

-Specially suitable for patients with risk of hypoglycemia, uncertain lifestyles,meal times.

- Consists of insulin reservoir, program chip, keypad& screen. Insulin infused through plastic tubings connected to s/c inserted infusion set .

INSULIN DELIVERY – short acting insulin analogues like Aspart(lispro) used.

- Provides constant basal infusion of insulin & patient can activate pre-meal boluses.
- Pumps can be discontinued for short periods for activities like exercise
- Pump can be pre-programmed to compensate for nocturnal & early morning glucose fluctuation.

Advantages

- Rate of insulin absorption more predictable than multiple injections
- Risk of hypoglycemia less

Drawbacks

-Pump failure -→ketoacidosis

-Injection site abscess

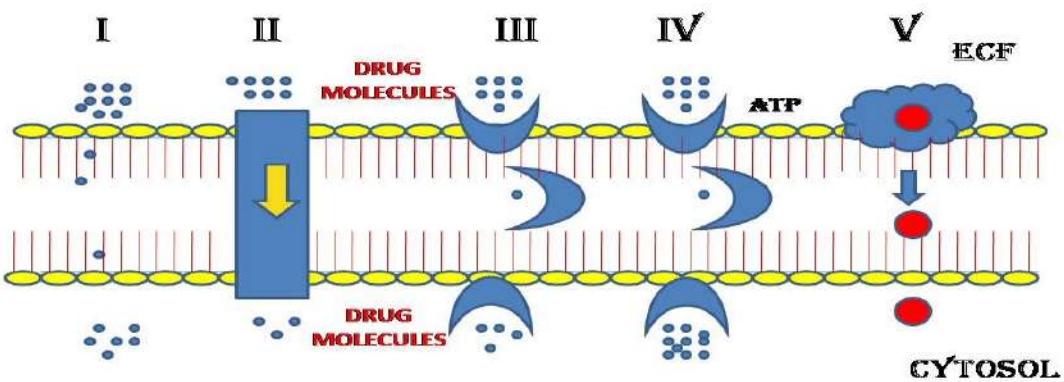
CHAPTER 5 Biological membrane and the mechanism by which the drugs cross (transported) the membrane

Before going to the pharmacokinetic properties of the drugs, it is better to know how the drugs cross the biological membrane or are transported across the membrane.

The drugs are carried all over the body mainly through blood stream. The drugs enter into blood stream and leave the blood to reach the site of action on the cell membrane or into the cell. Two membranes are involved for the drugs to cross and reach the site of action. One is capillary endothelium and another one is cell membrane. Biological membrane is present in all those places.

Structure of biological membrane (Fig.07)

It is made up of lipid bilayers. On the surface of the membrane, water filled pores are present. There are also carrier proteins present on the cell membrane. On the cell membranes, some specialised cells are also present to transport the big molecular sized drugs by engulfing.



I – PASSIVE DIFUSSION (LIPID SOLUBLE)
II – AQUEOUS PORE – FILTERATION (WATER SOLUBLE)
III - FACILITATED DIFFUSION
IV – ACTIVE TRANSPORT
V - PINOCYTOSIS

Fig.07 - STRUCTURE OF BIOLOGICAL MEMBRANE AND MECHANISM OF DRUG TRANSPORT

Mechanims of drug transport: (Fig.07)

1. Passive diffusion
2. Filtration
3. Carrier protein mediated transport:
   i) Facilitated diffusion
   ii) Active transport
4. Pinocytosis

1. Passive diffusion: It is the process by which the lipid soluble drugs dissolve in lipid layer of biological membrane and cross (move) from one end (from higher concentration of drugs) to the other end (lower concentration of drug) of the membrane till the concentration of the drug becomes equal on both sides. So in this process, the drugs move from higher concentration to lower concentration (along the concentration gradient).

- Only the lipid soluble drugs will cross by this process.
- No carrier protein or energy is needed for this transport
- Lipid soluble drugs are better absorbed, better penetrating BBB (Blood Brain Barrier) and better crossing all the cell membranes.
- This transport process depends on pH of the medium. i.e., pH dependent.
- All the drugs are either weak acids or weak bases
- Weak acidic drug in acidic medium→ unionized→ lipid soluble→ better diffusion→better absorbed/crossed. Example: Aspirin is a weak acidic drug and in the acidic medium of the stomach, it is unionized and better absorbed from stomach. Just opposite is for the weak basic drugs.

2. Filtration:

- Water soluble drugs will cross through aqueous pores present in the cell membrane.
- Drugs move from higher concentration to lower concentration like diffusion.
- No energy and no carrier protein is needed.
- It is not pH dependent. Filtration depends on the molecular size of the drug. If the molecular size of the drug is bigger than that of the pore, then the drugs will not cross. Only smaller molecular sized drugs are allowed to cross by filtration.
- The pore size of the capillary endothelium is 40 A^0. The pore size of renal capillary endothelium is the biggest. Hence, most of the drugs and metabolites except protein/protein bound drugs are filtered and excreted.

BBB (Blood Brain Barrier) and its CLINICAL SIGNIFICANCES: There is no pore in the endothelium of capillaries entering into CNS. So water soluble drugs will not cross BBB and reach CNS. Only lipid soluble drugs will cross BBB.

3. Carrier protein mediated transport

i) Facilitated Diffusion:

- Carrier protein is needed for the transport of drugs (the carrier protein combines with the drug and carries to the other end and leaves it there, comes back and takes another molecule of the drug and the process is repeated (ferry like transfer).
- Drugs move from higher concentration towards lower concentration like that of passive diffusion.
- Energy is not required.

ii) Active Transport:

- Carrier protein is needed for the transport of drugs.
- Drugs can also move from lower concentration to higher concentration (against concentration gradient).
- Energy is needed (obtained from ATP).

Example: Glucose transport to the peripheral tissues, Gentamicin enters into g^{-ve} bacteria by active transport only, α methyl dopa etc.,

4. Pinocytosis:

- Pino=I drink. Bigger molecules are engulfed.
- Cell engulfs bigger molecule in solution and transfers across the membrane. (Example :Insulin, which is a bigger molecular size is transported through BBB).

COMPARATIVE STATEMENTS OF EACH TRANSPORT:

Passive diffusion	Active transport
1. Drugs move from higher concentration to lower concentration (along concentration gradient, till the concentration become equal at both ends)	1. Drugs also move from lower concentration to higher concentration (against concentration gradient)
2. Energy is not required	2. Energy is required
3. Carrier protein is not required	3. Carrier protein is required
4. Lipid soluble drugs and all drugs acting on CNS will cross by this mechanism	4. Non lipid soluble and bigger water soluble drugs will cross by this mechanism
5. pH dependent	5. Not pH dependent

CHAPTER 6 Absorption of the drugs

Absorption of drugs means the entry of drugs into blood stream from the site of administration of drugs. It is possible by the drugs only after crossing the capillary endothelium. All the drugs cross the capillary endothelium and enter into venules (absorbed) and taken into the systemic circulation→to the heart→ reach all the body tissues through arterioles while cardiac out put. Remember, the capillaries (arterioles and venules) are important for absorption of drugs (through venules) and distribution of drugs (through arterioles) (Fig.08 and 09)

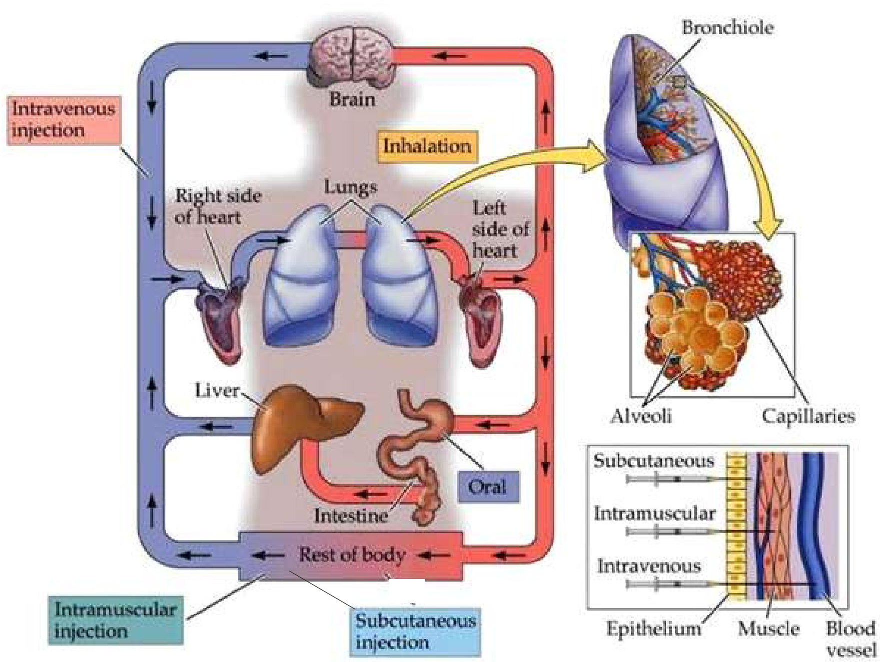
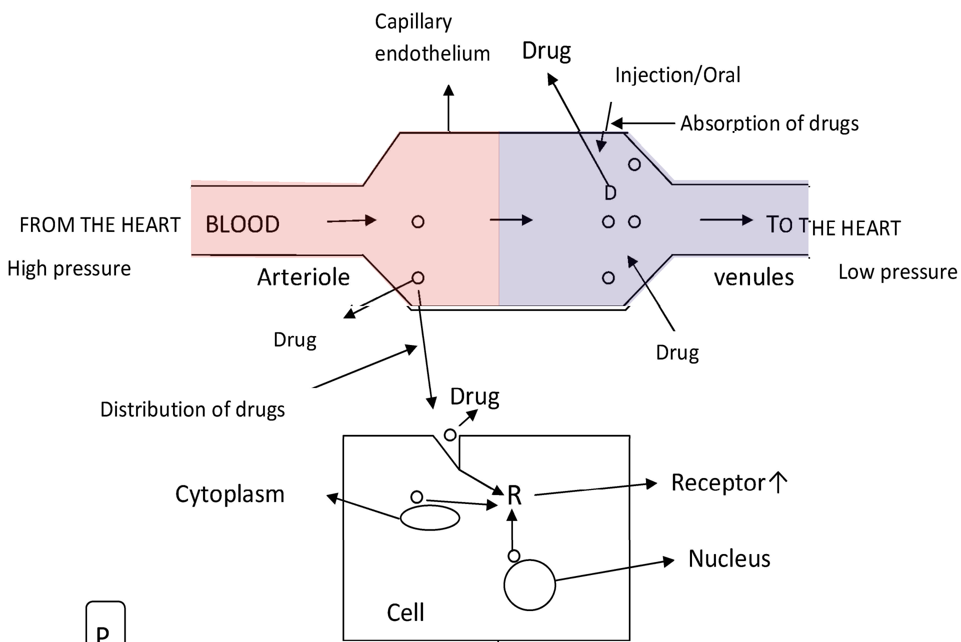


Fig. 08 Absorption of Drugs

Fig. 09 Absorption through capillary



PHARMACODYNAMIC

Therapeutic dose 5 → PHARMACOLOGICAL ACTIONS 1 → How it acts(MOA) 2 → (Mechanism of action of drugs)

- Wanted actions → Clinical uses 3
- Unwanted actions → Side effects(No drug is available without side effect, which is avoidable) 4

. Study of 1,2,3,4 & 5 is called pharmacodynamic properties of drugs.

Absorption after oral administration: (Fig.10)

First the drug has to cross intestinal epithelium
↓
and then it has to cross capillary endothelium (capillaries supplying the villi)
↓
the drug now is absorbed (entered into blood stream)
↓
enters portal vein
↓
liver
↓
then reaches the systemic circulation
↓
venacava
↓
reaches the heart
↓
from there the drug is pumped out (by cardiac output) to
↓
arteries
↓
arterioles
↓
reaches all over the body tissues.

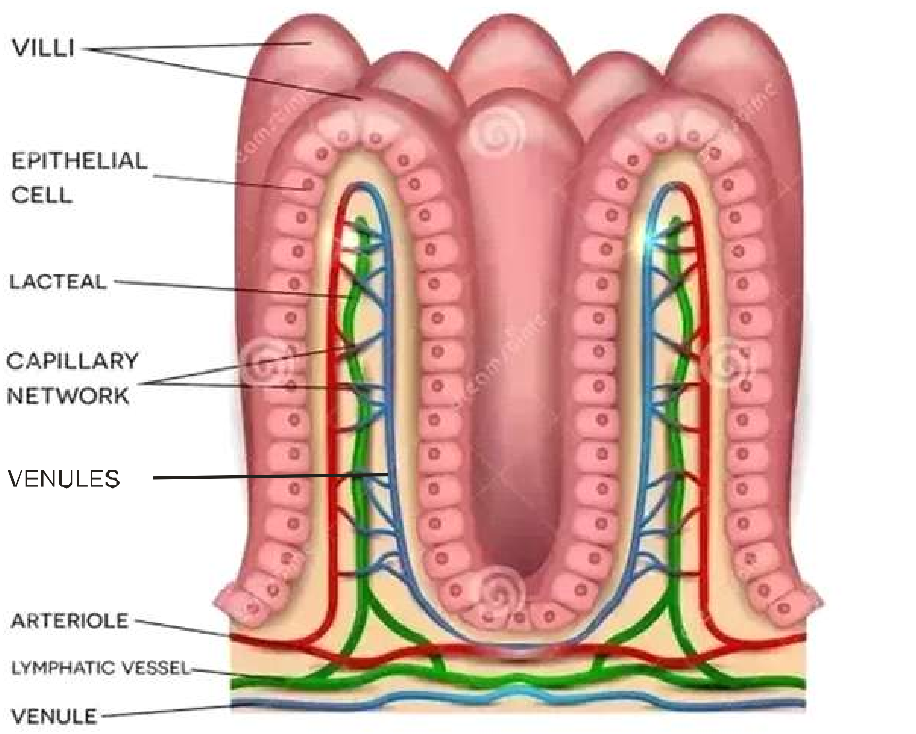


Fig. 10 Absorption of drugs after oral administration

The drugs are not absorbed or poorly absorbed after oral administration due to the following reasons:

1. If the drugs are in ionized form in the intestinal pH medium will become less lipid soluble and less or not capable of crossing the intestinal epithelium (villi) before reaching the capillaries, from where the drugs get absorbed and hence the drugs are poorly absorbed or not absorbed. (e.g., Gentamicin)
2. Certain drugs are degraded by gastric acid (Peniccilin - G) or by peptidase (Insulin), so they could not reach the intestine in sufficient concentration for absorption.
3. Some drugs form complexes and become bigger molecular size and not absorbed or poorly absorbed. Tetracyclines form complex with Ca++ (milk products) or antacids. Both the drugs are given two hours apart to prevent from forming complexes.
4. Certain drugs back diffuse into the intestinal lumen and hence poor absorption (Digoxin, Cyclosporine)

Absorption of drugs from sublingual

buccal mucosa
↓
buccal vein
↓
absorbed
↓
systemic circulation
↓
heart
↓
to all over body tissues through arterioles

parenteral injection
↓
cross the capillary endothelium
↓
absorbed
↓
systemic circulation
↓
heart
↓
to all over the body tissues through arterioles.

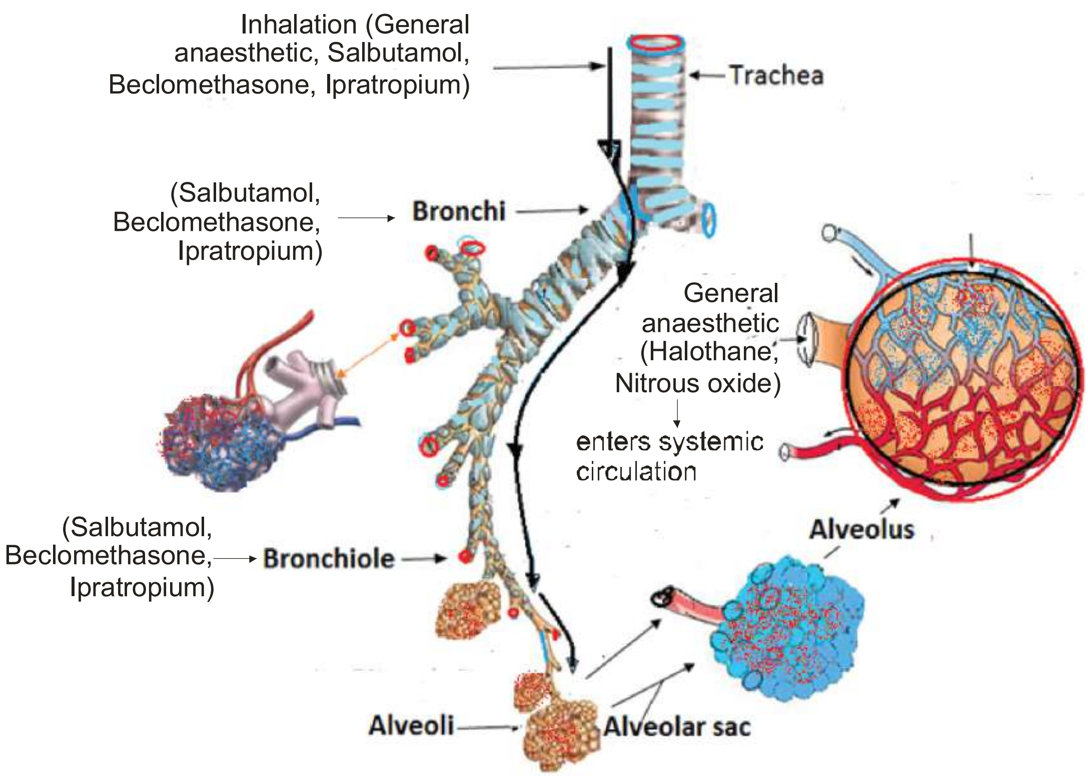
Absorption of drugs after injections:

The drugs which are not absorbed orally given by parenteral route for quick onset of action. The drug is injected (SC/IM) directly into the vicinity of capillaries. There is no need of crossing any other membrane except capillary endothelium, so there is quick onset of action. The drugs are also injected directly into the vein, hence there is no question of absorption and the onset of action is immediate.

Absorption after inhalation (via lungs): (Fig.11)

The lipid soluble drugs are administered in vaporized form (general anaesthetics), Salbutamol (aqueous solution spray) are absorbed (reach the blood stream) by crossing two membrane, first cross pulmonary epithelium/mucous membrane of trachea and lungs by simple diffusion and then capillary endothelium (now the drug enters into blood stream and hence absorbed). The absorption is rapid due to two reasons, 1. Vast surface area for absorption is available and 2. High vascularity for better absorption. As soon as the administration of the drug is discontinued, the drug back diffuses and is rapidly eliminated in the expired air. The control of the dose of general anesthetics accurately is possible.

Absorption of drugs after inhalation: (fig: 11A)



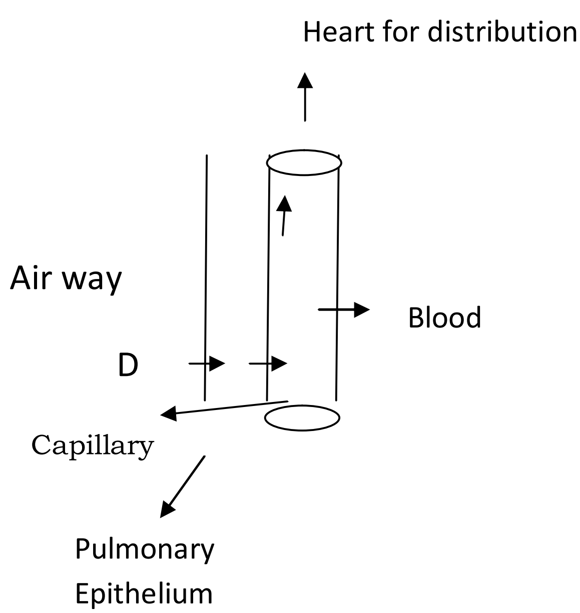
The drugs are administered through nose, mouth,respiratory tract. The drugs travel trachea→ bronchus → bronchioles→ alveoli→ capillaries → absorbed →systemic circulation.

For local action: (Fig.11A) Inhalation of Solbutamol, Iprotropium and Beclomethasone (all the drugs are used in bronchial asthma)→ reach the site of action directly only by crossing pulmonary epithelium (no need of absorption through capillaries). The action is quick.(hence systemic side effects are minimum). The inhalational Salbutamol produces less or no tremor, when compare to oral administration.

For systemic action: (Fig.11-B) The volatile General anaesthetics like Halothane will reach the alveoli quickly, crosses quickly and absorbed quickly through capillaries, which are plenty surrounding the alveoli, reach the site of action (CNS) through the systemic circulation quickly and produce the anaesthetic action quickly.

As soon as the drug administration is discontinued, the drug back diffuses from blood to pulmonary epithelium and crosses pulmonary epithelium and reaches airway and then exhaled (Rapidly eliminated in expired air).

The drugs are administered through inhaled air and excreted through exhaled air.



After Discontinuation:

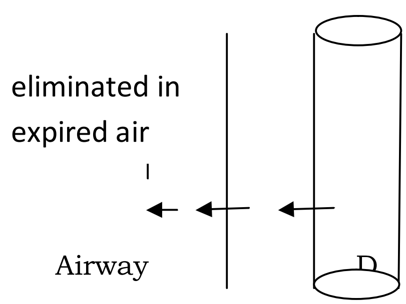


Fig. 11-B Absorption and elimination of drugs after inhalation

Note: The drug is absorbed through venules and distributed through arterioles.