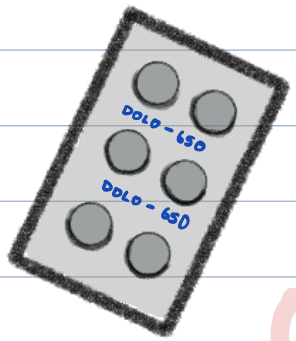
Drug: any substance or product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient

Non-Prescription Drugs (OTC)

→ sold over-the-counter
→ without prescription
- vitamins
- antacids
- paracetamol



Prescription Drugs

→ drugs used under medical supervision
→ dispensed by an order of a registered medical practitioner
- antibiotics
- antidepressants
- antihypertensives.

Drug Nomenclature:

Chemical Name

→ given acc. to chemical constitution of the drug
→ complex
→ sometimes a code name may be given by the manufacturer for convenience.

Non-Proprietary / Generic

→ assigned by USAN / BAN Council only when the drug has been found to be of potential therapeutic usefulness.
→ uniform names all over the world by an international agreement through the WHO
→ when included in pharmacopoeia, non-proprietary name becomes official name
→ names could vary acc. to USAN & BAN

Proprietary / Trade / Brand

→ trade name selected by the pharmaceutical company to market the drug
→ small & easy to recall & thus, most widely used by the medical practitioner
→ multiple trade names from diff. companies

Non-proprietary / official Name:

USA	UK
epinephrine, norepinephrine	adrenaline, noradrenaline
furosemide	frusemide
cromolyn sodium	sodium cromoglycate

Allotment of Generic Names has some elements of drug classification:

olol	β-adrenergic receptor blockers	Propranolol, atenolol (anti-HTN) (except: Stanozolol ⇒ anabolic steroid)
caine	local anaesthetics	• Lignocaine • Prilocaine
dipine	Ca^{2+} channel blockers (anti-HTN)	• Nifedipine • Amlodipine
prazole	proton pump inhibitor (used to decrease gastric acid secretion)	• Omeprazole • Lansoprazole
cycline	tetracycline group of antibiotics	• Doxycycline • Amoxycycline
pril	ACE inhibitors (used to treat hypertension & heart failure)	• Lisinopril • Enalapril • Ramipril
sartan	angiotensin receptor antagonists (used to treat HTN)	• Losartan • Telmisartan • Candisartan
gli	oral hypoglycemic agents (anti-diabetic drugs)	• Glipizide • Sitagliptin • Gliclazide
statin	anti-hyperlipidemic agents	• Atorvastatin • Rosuvastatin
floxacin	fluoroquinolone group of antibiotics	• Ciprofloxacin • Ofloxacin

Chemical Name	Non-proprietary Name	Proprietary Name
Acetyl salicylic acid	Aspirin	• Ecosprin • Dispirin • Mejoral • Lopsin-DS
p-acetamido-phenol	Paracetamol	• Crocine • Calpol
Aminobenzyl penicillin	Ampicillin	• Biocillin • Synthocillin • Roscillin • Albercillin

Subdivisions of Pharmacology:

Pharmacokinetics: ADME studies [Absorption, Distribution, Metabolism, Excretion]
→ what the body does to the drug

Pharmacodynamics:
→ Study of – biological effects produced by the drug
– site at which and the mechanism by which it acts
– relationship of plasma concentration of the drug with its response & duration of action
→ what the drug does to the body.

Pharmacotherapeutics: clinical application of the pharmacodynamic & pharmacokinetic info. in the prevention, treatment, diagnosis of a disease.

Toxicology: toxicity of drugs & poisonous effects of various chemicals in use
→ symptoms & treatment of poisoning
→ **harm** is the endpoint in toxicology
benefit is the endpoint in pharmacotherapeutics.

Chemotherapy:
→ treatment of systemic infections or malignancy with drugs that have selective toxicity for the infecting organism (living / multiplying) or malignant cells with minimal toxicity to host cells.

Pharmacogenetics:
→ study of inherited (single-gene mediated) differences in drug metabolism or drug response in humans.

Pharmacogenomics:
→ makes use of the genome of an individual so as to choose a particular drug therapy for the responders only & to avoid giving such drugs to non-responders

Ex: anticancer drug gefitinib: highly effective in curing lung cancer but only in those patients who have mutations in the tyrosine kinase receptor [10% of the cases]

Pharmacoepidemiology:
→ study of use & effects of a drug in large population after its approval for clinical use.
→ risk: benefit ratio of the drug can be ascertained.

Pharmacovigilance:

→ adverse drug reaction of any old / new drug should be shared with global health care community

→ continuous monitoring for unwanted effects & other safety related aspects of marketed drugs

→ Detection
Assessment
Understanding
Prevention
} DAUP of adverse effects.

Pharmacognosy:

→ study of the sources & identification of drugs from various sources

Biopharmaceutics:

→ study of effects of drug formulation on the therapeutic response

Sources of Drug Information:

→ pharmacopoeias + formulary → official
Drug Compendia → non-official

Pharmacopoeias: info. on drug substances & dosage forms

Formulary: info. on drug substances & dosage forms + pharmaceutical ingredients

Official Compendia: acc. to non-proprietary names of drugs

→ compilation of legally approved drugs for use in that country with their legal standards of purity

eg: Pharmacopoeias, formularies

Non-Official Compendia: secondary source of drug info.

→ both by trade name & generic name

→ info. is generalised & not restricted to a particular country's legally approved drugs.

Ex: Martindale Extra Pharmacopoeia
AMA Drug Evaluations

Nature & Sources of Drugs:

① Synthetic Source:

→ advantages – quality can be better controlled
– process is easier & cheaper
– chemical structure of the prototype drug can be modified in search of better, more potent & safer drug.

Eg: – aspirin – chlorpromazine
– paracetamol – amphetamine
– phenytoin – chloroquine – sulfa drugs

② Vegetable / Plant Source:

(i) Alkaloids: alkali-like

→ nitrogenous heterocyclic bases

→ insoluble in water

→ form salts with acids which are water soluble.

Eg: – Atropine from Atropa belladonna
– Quinine from Cinchona bark
– Morphine from Papaverum somniferum
– Reserpine from Rawolfia serpentina
– Nicotine from tobacco leaves

→ Names of alkaloids end with 'ne'.

(ii) Glycosides: sugar moiety joined to a non-sugar moiety (aglycon) with an ether linkage

→ Sugar portion governs the pharmacokinetic characteristics of the glycoside.

Eg: – cardiac glycosides used in Tx of congestive heart failure:
- digoxin } Digitalis purpurea
- digitoxin }
- ouabain ⇒ Strophanthus gratus

(iii) Oils: → essential / volatile oils
→ fixed oils

Essential / Volatile Oils:

→ obtained from leaves or flower petals by steam distillation

→ volatile, aromatic, no calorific / food value

eg: - eucalyptus oil
- peppermint oil
- clove oil

→ some are solid at room temperature & sublimate on heating - menthol
- camphor

Fixed Oils:

→ non-volatile, have calorific / food value

→ obtained by solvent extraction of crushed seeds

eg: - groundnut oil
- coconut oil
- olive oil
- castor oil (purgative)
- arachis oil (demulcent)

(iv) **Gums**: colloidal exudates of plants

→ used as emulsifying or suspending agents

eg: - gum acacia
- gum tragacanth

(v) **Tannins**: non-nitrogenous phenolic derivatives

→ soluble in water

→ mainly used as astringents (shrink or constrict body tissues by drawing water out of cells)

eg: - tincture catechu
- tincture rhubarb.

(vi) **Resins**: polymers of volatile oil

→ insoluble in water

eg: - benzoin [used as inhalation in common cold]
- tincture benzoin [as antiseptic protective sealing over bruises]

- colophony (used as an ingredient in various plasters)
- shellac (from Lucifera lacca ⇒ used for enteric coating of tablets)
- Tolu balsam (used as an expectorant in cough mixtures)

③ **Animal Source**: hormones, vitamins, vaccines, sera

eg:
- insulin
- Vit. B12
- thyroxine
- BCG
- small pox
- polio
- antirabies vaccine
- antidiptheria serum
- antitetanus serum

④ **Microbiological Source**:

eg:
- Penicillin ⇒ Penicilium notatum
- Chloramphenicol ⇒ Streptomyces venezuelae
- Griseofulvin ⇒ Penicilium griseofulvum
- Streptomycin ⇒ Streptomyces griseus
- Neomycin ⇒ Streptomyces fradiae.

⑤ **Mineral Source**:
- solid / powder & liquid preparations
- mineral preparations

(i) **Solid / Powder & Liquid Preparations**:

eg:
- ferrous sulphate (anemia)
- magnesium sulphate (purgative)
- aluminium hydroxide, calcium carbonate, sodium bicarbonate } (antacids)
- tincture iodine, povidone iodine } (antiseptics)
- ^{131}I (diagnosis & treatment of thyrotoxicosis & thyroid malignancy)
- Kaolin / aluminium silicate (adsorbent in antidiarrhoeal preparations)

(ii) Mineral Preparations: mostly petroleum products obtained by dry distillation of wood

→ no calorific / food value

→ do not become rancid

→ mainly used as vehicles for:

eg: — hard & soft paraffin → preparation of ointments

— liquid paraffin ⇒ purgative - laxative.

⑥ Genetically Engineered / Biotechnology Based Drugs:

→ desired gene is inserted into a very fast multiplying non-pathogenic strain of some bacteria, eg: E. coli - K12

→ host cell now produces large amounts of gene-directed proteins which are required

eg: — humulin (human insulin)

— Recombivax HB (Hep B vaccine)

— Human erythropoietin (hormone that stimulates RBC production)

Dosage Forms:

Formulation: recipe by which a drug is prepared

→ list of active ingredients & other substances like excipients, vehicles, flavouring agents & preservatives

Dosage Form: form in which the above formulation can be administered to the patient

Excipients: pharmacologically inert substances which are added to the pharmaceutical preparation either to add bulk to the active drug or to mask the unpleasant taste

e.g: lactose, calcium lactate, starch, etc.

Vehicles: substances which are used to dissolve or suspend drugs in a pharmaceutical preparation to make them better applicable / more palatable

e.g: sugar syrups, cherry syrup, gum acacia, petroleum jelly.

SOLID DOSAGE FORMS

- Powders
- Effervescent Powders
- Granules
- Tablets
  - Ordinary
  - Sugar-coated
  - Film-coated
  - Enteric-coated
  - Long tablets (retard / sustained release)
  - Pellets
  - Lozenges
- Capsules
- Spansules

Powders:
- simple: contain one drug
- mixture: contain ≥ 2 drugs

↳ dried & finely pulverised form

- aspirin powder
- sodium bicarbonate powder
- dusting powder

Effervescent Powders: powdered drug + sodium bicarbonate / citric acid / tartaric acid

↳ when dissolved in water, they effervesce with evolution of CO_2 bubbles which makes it more palatable & tasty • Eno salt

→ same formulation in tablet form ⇒ dispersible tablet

- Dispirin (dispersible aspirin tablet)

Granules: small aggregates of powder held together by a binding agent (starch / alcoholic spray)

- vit. D_3 granules
- Amoxycillin or ampicillin dry syrup – to be dissolved in a specified volume of water just before oral use

Tablets: powdered / granulated form of drug compressed under heavy pressure into round / disc-like shaped structures.

① **Ordinary Tablets:** uncoated, compressed
- aspirin
- paracetamol

② **Sugar-coated Tablets:** tablets coated by sugar to make them more palatable
- chloroquine
- metronidazole

③ **Film-coated Tablets:** transparent film-coating by gelatin or cellulose derivatives so that tablet size/weight remain unaffected, but unpleasant taste is masked
- Ceftum (cefuroxime)
- Dilzad (diltiazem)

④ Enteric-coated Tablets: coating made of cellulose / acid phthalate / shellac / Keratin

→ this coating is resistant to gastric acid but dissolves at intestinal alkaline pH

∴ incidence of gastric irritation is reduced

- Diclofenac - EC
- Enzar forte
- Ecosprin - 75 (enteric coated aspirin)

⑤ Long Tablets (Retard Tablets, Sustained Release): aggregated drug particles have individual coating with different types of inert resins so that each type of coating dissolves at different time intervals to provide a uniform, sustained release of the drug over a period of 10-12 hrs ∴ these have a low incidence of side effects.

- K Gard (KCl)
- Diclofenac - SR
- Depin Retard (nifedepine)

⑥ Pellets: sterile spheres which are implanted subcutaneously, from which the drug is slowly released for a long duration of time

- testosterone pellets

⑦ Lozenges: drug tablet containing sugar & a gum

↳ meant for chewing / sucking to provide local effects in mouth / throat

- various cough Lozenges like Strepsils

Capsules: tasteless gelatin containers (meant for swallowing)

- Hard gelatin capsules: enclose powdered drug • amoxycillin
- Soft gelatin capsules: enclose oily drug • vit. E

→ the gelatin shell dissolves in GIT fluid to release the drug for absorption into circulation.

Spansules: longer acting capsules

↳ coloured beads of drug granules inside a capsule

→ these beads are coated with different resins which dissolve at different time intervals

- iron formulations like Fefol
- Isomack Retard (isosorbide dinitrate)
- Angispan - TR

LIQUID DOSAGE FORMS

1) Aqueous solutions *
2) Depot injection
3) Aqueous suspensions < mixtures, emulsions
4) Alcoholic solutions < spirits, elexirs
5) Drops
6) Enema
7) Liniments
8) Lotions
9) Tincture & solutions
10) Ointment
11) Cream
12) Gel
13) Paste
14) Plaster

* < Syrups, Liquors, Linctus, Injections

D²OC L²E G TA³P²

Aqueous Solutions:

① **Syrup:** drug in concentrated solution of sugar + flavouring agent + permitted colours

- various cough syrups
- vitamin syrups

② **Liquor:** aqueous solution of medicinal substances which are gases / volatile / sublimate

- H_2O_2 soln.
- Liquor ammonia
- Iodine soln.

③ **Linctus**: viscous syrupy liquids containing drug + demulcent (eg: menthol)
→ to be sipped without dilution to provide soothing effect in sore throat locally
- cough linctus

④ **Injections**: sterile solutions + preservatives ⇒ meant for parenteral use
- digoxin inj. - xylocaine inj.

→ some injections are supplied as dry solids in sterile vials ⇒ use water/Ringer soln. etc. before use - procaine penicillin inj. - chloramphenicol inj.

Depot Injection: longer acting injectable preparation (practically same as Long Tablets, Spansules)
→ drug is dissolved in a sterile oily base from which it is slowly released for a prolonged duration
- Testovirон depot (testosterone)
- Anatensol (fluphenazine)

Aqueous Suspensions:

① **Mixtures**: solid drugs dispersed homogeneously in water
- antidiarrhoeal mixtures
- milk of magnesia

② **Emulsions**: two or more immiscible liquid medicaments are dispersed together
- cod liver oil emulsion - castor oil emulsion
- liquid paraffin emulsion - milk (naturally occurring emulsion)

Alcoholic Solutions:

① **Spirits**: 10% v/v solution of volatile essential oils + alcohol
- spirit chloroform - spirit ammonia aromaticus - peppermint spirit

② **Elixirs**: pleasantly flavoured solutions of a drug in sugar syrup / glycerol along with higher proportions of alcohol. - vit. B complex elixir
- cough elixir - Lanoxin elixir (digoxin) - theophylline elixir

③ **Tinctures**: alcoholic extracts of plant drugs - tinct. belladona
- tinct. digitalis - tinct. iodine - tinct. zingiberis

Drops: pediatric formulations which contain small amounts of highly concentrated solutions of drugs • vitamin drops • enzyme drops

- **Eye / Ear Drops:** – sterile
  – Isotonic buffered solutions of the drug
  – usually supplied in a vial with a dropper
  – sulfacetamide eye drops
  – gentamicin ear drops.

Enema: medicated liquid preparations for rectal administration & are used for evacuation of colon • soap water enema • procalys enema

Liniments: liquid medicaments to be rubbed on the skin with friction
→ contain camphor which serves as a counterirritant
→ used as pain relievers or as rubefacient (making skin red)
• liniment camphor • liniment turpentine

Lotions: liquid medicaments for local application but without rubbing
↳ used as antiseptics / for soothing / astringents / antipruritic
• zinc calamine lotion • providone iodine scrub lotion

Tinctures & Solutions: hydroalcoholic solutions of inorganic substances
Tincture • tinct. iodine • tinct. benzoin
Solutions • povidone iodine solution (used as antiseptic to sterilize the skin surfaces before surgery or to wash wounds)

Ointments: soft, semi-solid masses containing the drug in a greasy base
• soframycin • chloramphenicol eye ointment
• silver sulfadiazine • atropine " "

Cream: emulsion, semi-solid
→ contains > 20% water & volatile oil &/or < 50% hydrocarbons, waxes, polyols as vehicle
→ for external application to skin or mucous membrane

Gels: active drug dissolved in a liquid & then dispersed in some gelling agent (soft gelatin)
↳ usually transparent

- contraceptive gels
- aluminium hydroxide gel

Paste: does not have a greasy base like ointment
→ prepared with some adhesive material (starch) or foaming agent (carbo methyl cellulose)

- zinc oxide paste
- toothpaste

Plaster: contains the drug mixed in a resinous base spread over a muslin cloth
→ preparation remains hard at room temperature but becomes sticky at body temperature

- zinc oxide plaster
- belladona plaster
- Band-Aid

SPECIAL & NOVEL DOSAGE FORMS: SITA

Inhalants: liquid preparations containing a drug to be inhaled as vapour
→ contents may be poured into a jug of boiling water & inhaled
→ solid inhalants like Fintal (sod. cromoglycate) are inhaled by turbo spin inhalers.

- tinct. benzoin inhalation
- Karvol inhalant

Aerosols: devices in which therapeutically active ingredients dissolved in a liquid is put inside a cylindrical container (nebulizer) & is then filled with a propellant gas (air/oxygen) under pressure
→ if one push releases a measured dose of drug ⇒ Metered aerosol.

- salbutamol metered aerosol
- terbutaline metered aerosol

→ **Spinhaler**: aerosol device in which therapeutically active ingredients are packed in the form of a powder & released upon activation of an appropriate valve system in the form of micronised powder mist

- tiotropium metered spinhaler.

Suppositories (Rectal), Pessaries (Vaginal), Bougies (urethral):

→ drug + glycerine / gelatin / hard soap / coca butter

→ solid at room temperature ; melt at body temperature

- Suppositories: bullet shaped
- Pessaries: conical
- Bougies: pencil shaped

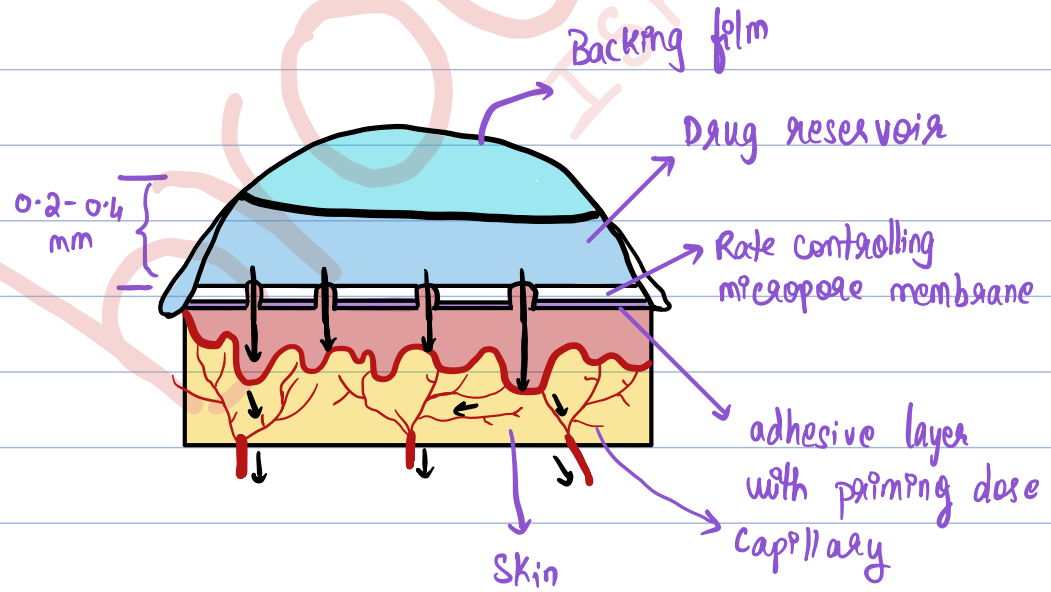
- Dulcolax suppositories
- Candizole - T pessaries

Transdermal Adhesive Patch: drug is incorporated into a polymer which is in turn bonded to an adhesive plaster.

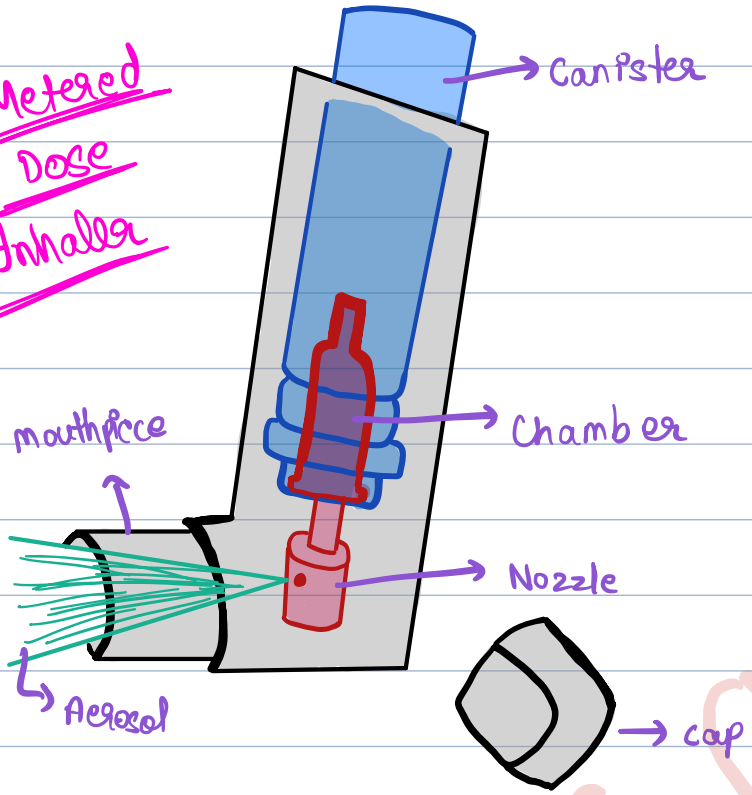
→ drug is delivered at the skin surface by diffusion (for percutaneous absorption into circulation)

→ provide steady & smooth plasma concentration of drug for 1-3 days

- Nitroderm - TTS (nitroglycerin)
- Estraderm - TTS (estradiol)
- Nicotinell - TTS (nicotine)



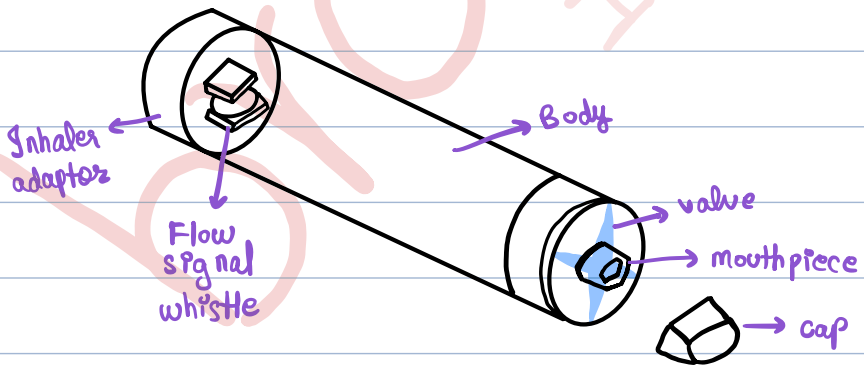
Metered Dose Inhaler

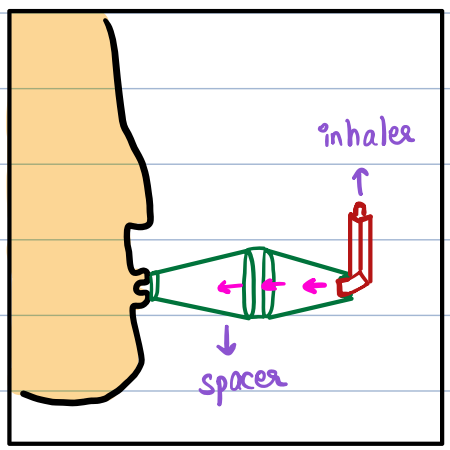


Spacer Device: infants & young children often have difficulty in coordinating the use of inhaler.

∴ spacer can be attached to an inhaler

(a face mask may be attached to the spacer if necessary.)





Vacutainer Tubes:

Colour	Anticoagulant	Use
Red	No anticoagulant	Serological examination in biochemistry
White	Sodium fluoride	Glucose estimation
Purple	EDTA	Haematological examination like complete hemogram, ESR
Blue	3.2% sodium citrate	Coagulation studies like PT, APTT
Green	Heparin	Bone marrow studies
Yellow	Citrate	Blood culture
Pink	(K2) EDTA	Blood bank tests, Blood typing, ABO grouping, etc.

Aspiration From a Vial :

- Wash your hands
- Disinfect the top of the vial
- Use a syringe with volume of twice the required amount of drug/soln. & add the needle
- Suck up as much air as the amount of solution needed to aspirate
- Insert needle into the top of the vial & turn upside down
- Pump air into the vial [creating pressure]
- Aspirate the required amount of solution & 0.1 mL extra. Make sure that the tip of the needle is below the fluid's free surface
- Pull out the needle
- Remove possible air from the syringe
- Clean up, dispose of waste safely, wash your hands.

Eye Drops :

- Wash your hands
- Do not touch the dropper opening
- Ask patient to look upwards
- Pull the lower eyelid down to make a gutter.
- Bring the dropper as close to the gutter as possible without touching it or the eye
- Apply the prescribed amount of drops in the gutter
- Close the eye for about 2 min. Do not shut the eye too light
- Excess fluid can be removed with a tissue.
- If more than one kind of eye drop is used, wait atleast 5 minutes before applying the next.

When giving eye drops to children:

- Let the child lie back with head straight
- The child's eyes should be closed
- Drip the amount of drops prescribed into the corner of the eye.
- Keep the head straight
- Remove excess fluid.

Nasal Drops:

- Blow the nose
- Ask the subject to sit down & tilt head backwards strongly or lie down with a pillow under the shoulders (head must be straight)
- Insert the dropper 1cm into the nostril
- Apply the amount of drops prescribed
- Immediately, tilt the head forwards strongly (head between knees)
- sit up after a few seconds, the drops will then drip into the phaynx
- Repeat the procedure for the other nostril if necessary
- Rinse the dropper with boiled water

Nasal Spray:

- blow the nose
- sit with head tilted slightly forward
- Shake the spray
- Insert the tip in one nostril
- Close the other nostril & mouth
- Spray by squeezing the vial & ask the subject to sniff slowly
- Remove the tip from the nose & bend the head forwards strongly (head between knees)

- Sit up after a few seconds; the spray will drip down the pharynx
- Breathe through the mouth
- Rinse the tip with boiled water.

Suppository:

- Wash your hands
- Remove the covering (unless too soft)
- If the suppository is too soft, let it harden first by cooling it (fridge / under cool water) & then remove the covering
- Remove possible sharp rims by warming in the hand
- Moisten the suppository with cold water
- Ask subject to lie on the side & pull up the knees
- Gently insert suppository, rounded end first, into the back passage.
- Remain lying down for several minutes
- Wash your hands
- Try not to have a bowel movement during the first hour.

Transdermal Patch:

→ do not apply over bruised or damaged skin

→ do not wear over skin folds or under tight clothing

→ change site of application regularly

- Apply with clean, dry hands
- Clean & dry the area of application completely
- Remove the patch from the packet; do not touch the drug side.
- Place on skin & press firmly; rub the edges to seal

Ear Drops:

- Warm the ear drops by keeping them in the hand / armpit for a few mins. (Do not use hot tap water)
- Tilt head sideways or lie on one side with the ear upward
- Gently pull the lobe to expose the ear canal.
- Apply the amount of drops prescribed
- wait for five minutes before turning to the other side
- Use cotton wool to close the ear canal after applying the drops only if the manufacturer has explicitly recommended this.
- Ear drops should not burn or sting longer than a few minutes.

Metered Dose Inhaler:

1. Remove the dust cap from the mouthpiece & shake the inhaler vigorously.
2. Hold the inhaler vertically. Breathe out slowly & gently until the lungs are comfortably empty. Tilt the head back. Close the lips tightly around the mouthpiece.
3. Start breathing slowly & press the metal canister down firmly.
4. Continue breathing in slowly & steadily until the lungs are full.
5. Remove the inhaler from the mouth while holding the breath as long as possible ; wait for atleast one minute before puffing the next dose.

Routes of Drug Administration:

Enteral
- oral
- sublingual
- rectal

Parenteral
(i) Injections
- intravenous
- intramuscular
- intraperitoneal
- intrathecal
- intramedullary
- intra-arterial
- intra-articular
- subcutaneous
- Intracardiac
- epidural

(ii) Inhalation

(iii) Transdermal

Topical
- Conjunctival, nasal, auditory mucosal
- vaginal & urethral
- Junction & dermal

Enteral: placement of a drug directly into any part of the gastrointestinal tract.

① **Oral:** most commonly used

Adv: – safe, convenient, painless
– economical as sterilization of drug is not essential

Disadv: – slower onset of action (due to slow & erratic absorption)
– highly polar drugs (aminoglycoside group of Antibiotics – Streptomycin) & quaternary salts (d-tubocurarine) are not absorbed
– drugs that are destroyed by digestive juices cannot be given orally (insulin, penicillin-G, oxytocin, testosterone)
– drugs having first pass effect (those destroyed in liver before reaching systemic circulation) are not preferred (nitroglycerine morphine, isoprenaline)
– palatability of drug is essential
– oral route cannot be used in unconscious & uncooperative patient or a patient having nausea, vomiting, diarrhoea.

② **Sublingual / Buccal:** drug is placed beneath the tongue or crushed in mouth & spread over the buccal mucosa

Adv: – quick onset of action (because of rapid absorption taking place through buccal or sublingual mucosal membrane)
– after absorption, drug passes directly into systemic circulation (bypasses portal circulation ∴ avoids first-pass degradation)
– drug can be spitted out if side effects are observed.

Disadv: – distasteful, irritant drugs cannot be given.
– drugs of high molecular weights are not well absorbed.

Ex: – isosorbide dinitrate & nitroglycerin tablets (for angina)

③ Rectal:

Adv: – useful for patients having nausea & vomiting
– first-pass degradation is relatively less (as major portion of the drug is absorbed from external haemorrhoidal veins)
– useful for gastric irritant drugs also

Disadv: – chances of rectal inflammation
– absorption is unreliable
– inconvenient & embarassing to the patient

eg: – aminophylline (bronchodilator)
– Indomethacin (ant-inflammatory agent).

Parenteral Routes: routes other than enteral routes

① Injections: provide fast systemic effects by passing first-pass inactivation

• Intravenous (I.V) Administration: through lumen of veins

Adv: – drug enters the systemic circulation directly, by-passing first pass degradation [100% bioavailability]
– quicker onset of action; lesser dose is required to achieve the desired plasma concentration
– can be used even in unconscious / uncooperative patients or patients with nausea, vomiting, diarrhoea.
– hypertonic solutions & GIT irritant drugs can also be infused by this route
– Large volume of fluids can be infused at a uniform rate
– amount of drug can be controlled with an accuracy not possible by other routes.

Disadv: – strict aseptic conditions needed
– patient has to depend on a medical proffesional for giving the injection
– painful
– risky (because once the drug is injected, it cannot be recalled)

- Introduction of any particulate matter or air can produce embolism which may prove fatal.
- drugs in suspension / oily drugs cannot be given I.V. (no depot injections)
- Venous thrombosis, thrombophlebitis, necrosis around the site of injection can result if extravasation occurs.

eg: - Glucose Normal Saline [GNS]
- dopamine & norepinephrine
- barbiturate anaesthetics
- diazepam
- heparin.

- Intramuscular (I.M.): in deltoid / gluteus maximus / vastus

Adv: - absorption is more predictable & rapid, less variable
- depot injections can also be given

Disadv: - perfect aseptic conditions are needed.
- chances of abscess at the site of injection.
- chances of nerve damage leading to paresis of muscle supplied by it
- large volumes cannot be given [maximum = 5 mL]

eg: - antibiotics, antiemetics
- depot injects of testosterone
- depot injects of neuroleptics (haloperidol & peaphanazine)

• **Intraperitoneal:** into the peritoneal space

Adv: — rapid absorption due to larger surface area

Disadv: — painful
— risky due to chances of adhesions & infections in peritoneal cavity (peritonitis)
— aseptic conditions are needed

eg: — dialysing fluids for peritoneal dialysis (in poisoning & renal failure).

• **Intrathechal / Intraspinal:** into subarachnoid space

Adv: — drug diffuses from lumbar sac ⟶ subarachnoid space ⟶ BBB & blood CSF Barrier are bypassed
∴ significant CSF levels are provided which is not possible by any other route [drug directly acts on meninges & spinal cord]

Disadv: — strict aseptic conditions
— great expertise is required for such injections to be given
— painful & risky.

eg: — radiopaque contrast media for myelography
— xylocaine injection (for spinal anaesthesia)

• **Intramedullary:** into tibial or sternal bone marrow

Adv: — fast onset of action (as vascular spaces of bone marrow communicate directly with large veins).

Disadv: — risky, painful, strict aseptic conditions are needed
— skill is also needed.

eg: — Bone marrow transplantation
— Sometimes, blood is also transfused by this route (especially in children) if veins are not available.

- **Intra-arterial:** into the lumen of the desired artery

Adv: – greater concentration of the drug can be delivered at the desired site of action

Disadv: – great expertise required

– aseptic conditions needed

eg: – radiopaque contrast media for coronary angiography & cerebral angiography

– anticancer drugs

- **Intra-articular:** injection into joint space

Adv: – ensures high concentration of drug in a localised area

Disadv: – strict aseptic conditions needed

– repeated administration into the joint space may further damage the joint

– painful

eg: – hydrocortisone or gold chloride injection for Tx of rheumatoid arthritis.

- **Subcutaneous:** into subcutaneous tissue under the skin

Adv: – smooth but slower absorption for a longer period

– depot injections or implants can also be made

Disadv: – suitable only for small volume of drugs [maximum = 1 mL]

– irritant drugs cannot be administered as sloughing & necrosis may result.

– not suitable in the states of shock (since reduced peripheral circulation decreases the rate of absorption)

eg: – local anaesthetics

– insulin

– vaccines [so that the active protein reaches the lymphatics directly & is not destroyed by enzymes elsewhere in the body].

Other related (cutaneous) routes :

- **Intradermal / Intracutaneous:** drug is injected into outer layers of skin

  eg: – BCG vaccine
  – allergic sensitization testing in patients

- **Deamojet Injections:** subcutaneous needleless injection of a drug by means of a high-velocity jet projected through a micrafined orifice

  → painless
  – useful for mass inoculation

- **Pellet & Biodegradable Implants:** drug as a solid pellet or packed into biodegradable tubes is implanted under the skin

  → provides a uniform but slow release of the drug lasting over months.

  eg: – testosterone
  – contraceptives

- **Epidural Injection:** drug is injected through a vertebral interspace between dura of spinal cord & lining of spinal canal.

  eg: – lidocaine injection to provide epidural nerve block

- **Intracardiac Injection:** injection is given by a long needle into the heart muscle through the left 4th intercoastal space close to the sternum.

  eg: – injection of adrenaline to restart the heart in cases of sudden cardiac arrest.

② Inhalation: through nose or mouth

Adv: – faster absorption, quick onset of action (due to larger surface area of alveoli)
– self-administration is possible

Disadv: – bronchial irritation leading to increased bronchial & salivary secretions

Eg: – oxygen & general anaesthetics
– metered aerosol preparations of salbutamol & isoprenaline for Tx of bronchial asthma
– inhalation of sodium cromoglycate through spin inhaler as prophylaxis for bronchial asthma

③ Transdermal Administration: topical application of patches (for systemic effects)
→ can be applied to chest, upper abdomen, mastoid region.

Adv: – slow but sustained release of the drug for several days
– bypasses first-pass hepatic inactivation

Disadv: – NIL
– if irritation results ⇒ site of application can be changed

Eg: – nitroglycerin (for angina)
– scopolamine (for motion sickness)
– nicotine (for smoking cessation)

Topical Routes:

① **Conjunctival, Nasal, Auditory Mucosal:** ointments or isotonic aqueous solutions

eg:
- sulfacetamide
- chloramphenicol
- gentamicin
- ciprofloxacin

} applied or instilled onto the conjunctiva

→ nasal drops, nasal sprays, ear drops.

② **Vaginal & Urethral:**

eg:
- sulfa drugs
- antifungal agents
- metronidazole

③ **Inunction & Dermal:**

Inunction – rubbing the drug preparation onto the skin

Dermal – dusted or sprayed over the surface of the skin.

Adv: – safe & convenient

Disadv: – difficult to ascertain the amount of drug absorbed
– systemic absorption may take place if the skin has abrasions.

eg:
- antibiotic - antifungal ointments
- lotions, liniments, creams, ointment ⇒ antiseptic / antipruritic / analgesic effects

ISHITA KANODIA

Biotransportation of Drugs:

- Passive diffusion (non-ionic / simple)
- Carrier Mediated
  - Facilitated Diffusion
  - Active Transport
- Pinocytosis, Phagocytosis } ENDOCYTOSIS
- Filtration

↳ transportation of drug molecules across biological membranes / barriers.

Passive Diffusion: transport of drug molecules from a region of their higher concentration to region of their lower concentration.

→ along the concentration gradient / Down-hill

→ no expenditure of energy

→ non-electrolytes (non-ionised drugs) can diffuse passively at a rate proportional to their lipid : water partition coefficient

- highly lipid-soluble drugs diffuse rapidly
- less lipid-soluble drugs diffuse more slowly

→ For weak electrolytes (partly ionised drugs), diffusion depends on:

- degree of ionisation of drug
- pH of environment
- lipid: water partition coefficient of undissociated form of drug.

Henderson-Hasselbalch Equation:

$$pH = pKa + \log \frac{[salt]}{[acid/base]}$$

(OR)

$$pH = pKa + \log \frac{[ionised\ form]}{[unionised\ form]}$$

Implications of HH Equation:

→ stronger the acid ⇒ lower pka
stronger the base ⇒ higher pka

→ weakly acidic drugs [Aspirin, Phenytoin, Barbiturates] remain predominantly unionised in acidic media & are better absorbed from stomach
weakly basic drugs [Morphine, Diazepam, Amphetamine] remain predominantly unionised at alkaline pH & are better absorbed from intestine

→ If pka of drug = pH of medium ⇒ drug is 50% ionised & 50% unionised.

→ strongly acidic/basic drugs & quaternary ammonium compounds remain predominantly ionized at all pH & are poorly absorbed.

→ conditions which favour the neutral/unionised form of drug will enhance drug absorption
conditions that favour ionisation will restrict the absorption of a drug.

⇒ Ion Trapping

eg: Nonionised form of weakly acidic drug (Aspirin: pka = 3.5) which crosses the gastric mucosa (pH = 2), reverts to the ionised form within the cell (pH = 7) & hence slowly passes to extracellular fluid [This ion trapping possibly contributes to gastric mucosal cell damage caused by Aspirin].

Carrier - Mediated Transport : for transport of polar compounds like sugars, amino acids

→ carrier molecules are mostly proteins

→ drug - carrier complex permeability > permeability of the drug alone.

- **Facilitated Diffusion (FD):** transport along the concentration gradient (Down - hill)

→ no energy utilised

→ Capacity - limited process : rate of diffusion depends upon the binding ability of the drug to its carrier & is limited by the availability of the carrier

[eventually, absorption rate becomes constant regardless of the dose due to saturation of carrier molecules]

→ Two drugs having similar physico - chemical characteristics can compete for the same transfer mechanism & thus, interfere with each other's absorption.

FD: - amino acids in brain
- antimetabolit - anticancer drugs
- riboflavin, thiamine, B12.
- antiviral drugs
- adenosine - like drugs

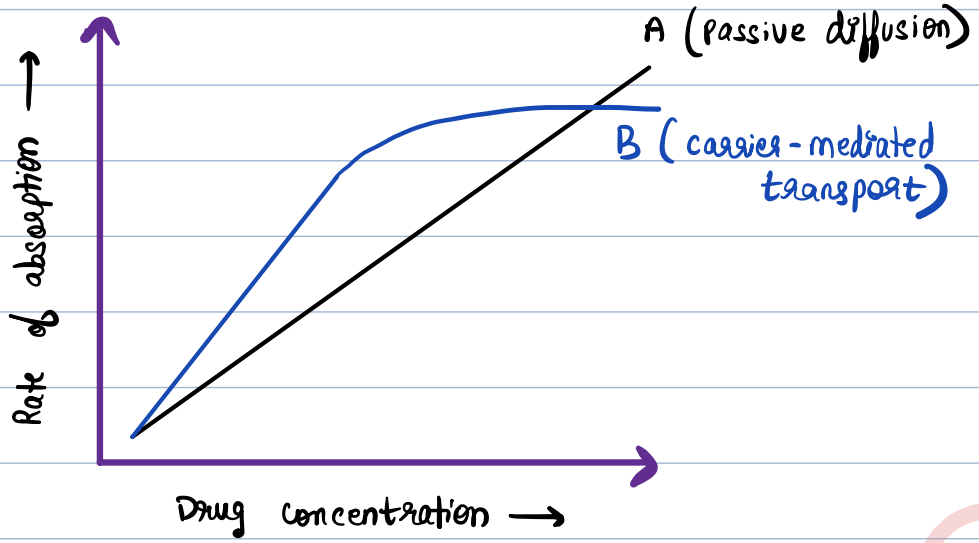
- **Active Transport (AT):** energy - dependent carrier - mediated Up - hill transport

→ energy needed for active transport is generated by membrane ATPase.

→ process of active transport can be blocked by inhibiting cell metabolism or by reducing ATP levels by using : sodium cyanide, sodium fluoride, 2,4 - dinitrophenol.

→ Two drugs having similar physico - chemical characteristics can compete for the same transfer mechanism & thus, interfere with each other's absorption.

→ Capacil - limited process



AT:
- 5-fluorouracil by intestine
- nitrogen mustard by lymphocytes
- digitalis glycosides by liver
- sympathomimetic amines by neural tissue
- choline by cholinergic neuron

ACTIVE TRANSPORT

Primary AT

→ transportation of drugs is directly coupled with ATP hydrolysis for deriving energy

→ usually carried by ABC group of biotransporters

eg:
- antibiotics
- digoxin
- anticancer drugs
- HIV protease inhibitors
- anticonvulsants

Secondary AT

→ one ion (X) supplies the energy for transport of another ion (Y)

Symporter: transports X & Y in the same direction

eg: $Na^+ / K^+ / 2Cl^-$ symporter

Antiporter: transports X & Y in opposite directions

eg: Na^+ / K^+ ATPase pump

ABC Superfamily of Transporters	SLC group of Transporters
ATP Binding Cassette	Solute - Linked Carrier
→ involved in primary AT & are coupled to ATP hydrolysis	→ involved in facilitated diffusion & secondary AT
→ 7 subclasses [ABC-A to ABC-G]	→ 43 SLC families
→ encoded by 49 genes	

Endocytosis: cellular uptake of exogenous molecules inside plasma membrane derived vesicles.

→ requires expenditure of energy ; no carrier required.

- **Pinocytosis [Cell Drinking]**: cell engulfs a fluid or a drug in solution

Steps: macromolecular solutes are trapped in the microscopic cavities formed by invagination of membrane

↓

membrane fuses around & completely encloses the fluid to form a vesicle

↓

vesicle is pinched off into cytoplasm, passing some fluid & the solute into the interior of the cell

eg:
- most polypeptides
- insulin which crosses the blood-brain barrier
- antitumor drugs (entrapped into lysosomes)
- receptor mediated absorption of LDL in liver

- **Phagocytosis [Cell Eating]:** transfer of particulate matter by local invagination of cell membrane

→ rare process

eg: – poisoning by botulinum toxin
– allergic reactions occurring after ingestion of antigen/allergen.

Filtration: free/unbound drugs of smaller molecular size can pass through the pores/spaces between the cells

→ purely physical process

→ rate of filtration is proportional to pressure gradient

eg: – urea
– alcohol
– glucose

Drug Absorption:

Absorption = movement of drug into blood stream from its site of administration

Distribution = movement of drug molecules from blood into target tissues.

① Absorption via GIT: mainly by passive diffusion (uptake of sugar & other nutrients is by active transport)

- From mouth: saliva pH is slightly acidic ; but pH of stimulated saliva (as with sublingual drugs) reaches 7.4 (alkaline)

→ ∴ lipid-soluble (unionised) basic or neutral drugs can be absorbed from this site

- From Stomach: acidic pH

→ lipid-soluble (unionised) acidic or neutral drugs are absorbed

→ after absorption ⇒ hepatic portal circulation ⇒ systemic circulation

[∵ chances of first-pass effect are high]

- From Intestine / Colon: pH alkaline

→ lipid-soluble (unionised) basic or neutral drugs can be absorbed from this site

→ from external haemorrhoidal vein ⇒ systemic circulation

[∵ minimal first pass effect]

Rate of absorption: sublingual > rectal > oral.

② Absorption via Parenteral Sites:

IV: complete & rapid absorption (as they reach blood stream directly without crossing any membrane)

IM & SC: passive diffusion from site of injection to plasma / lymph

Absorption: IM > SC (due to high vascularity of muscle compared to SC tissue)

IV > IM > SC

→ IM & SC absorption is reduced in patients with circulatory failure (eg: shock) due to decreased tissue perfusion.

③ Absorption Via Lungs:

Lipid-soluble drugs when given in a vapourised form (generalised anaesthetics) or as aqueous solution spray (salbutamol) or spray of suspended micronised particles (disodium cromoglycate) are absorbed by simple diffusion from pulmonary epithelium & mucous membrane of trachea & lungs.

→ absorption is rapid (due to large surface area & high vascularity)

→ first-pass effect is avoided.

④ Absorption Via Topical Sites:

absorption through intact skin is poor (since, keratinized epidermis behaves like a barrier to permeability)

Methods for Delaying Absorption:

① **Using an Appropriate Dosage Form:** slow release dosage forms (retard tablets / spansules / depot injections / subcutaneous implants)

→ slow but sustained absorption of drugs

② **Changing the Physical Characteristics of the Drug:**

- depending on the pH of the reaction, insulin can form:
  - fine amorphous zinc suspension (semilente) ⟹ relatively rapidly absorbed.
  - cloudy zinc suspension (ultralente) ⟹ slowly absorbed.

- procaine penicillin-G is such a salt of penicillin which is only slightly water soluble; when injected as an aqueous suspension it is slowly absorbed & exerts a prolonged action.

③ **Adding a Vasoconstrictor Drug / Applying a Tourniquet:**

→ addition of a vasoconstrictor drug (eg:- noradrenaline or adrenaline to a solution of local anaesthetic - xylocaine) reduces the absorption of the local anaesthetic into general circulation

→ usefully prolongs the local anaesthetic effect.

→ application of a tourniquet to arrest the blood flow, followed by IV injection of local anaesthetic below the tourniquet delays the systemic absorption but prolongs the local anaesthetic effect.

→ decreased peripheral blood flow in shock, significantly reduces the rate of absorption of injected drugs.

Methods to Facilitate Absorption:

→ Rate limiting factors in absorption from the injection site are:

- diffusion through the tissue
- removal by local blood flow

eg: – adding hyaluronidase (enzyme which breaks down the intercellular matrix) to the injection fluid, increases rate of diffusion through interstitial spaces & greatly speeds up drug absorption

– applying hot fomentation or doing massage increases the local blood flow ∴ increasing the absorption.

Bioavailability: rate at which & extent to which the active concentration of the drug is available at the desired site of action.

→ If two or more similar dosage forms of the same drug reach the blood circulation at the same relative rate & to the same relative extent, these are called ⟹ Bioequivalent preparations.

→ Bioavailability of any drug after IV administration = 100%
(this is sometimes assumed to be close with IM or SC route also)

→ Phenytoin, Digoxin, diazepam, chlordiazepoxide partly get precipitated at the site of injection & hence, the bioavailability gets reduced if given by SC or IM route.

→ Bioavailability assumes a much greater concern with drugs that:
(i) show a steep dose-response relationship (drugs that obey zero-order or mixed-order elimination kinetics) eg: warfarin, phenytoin, digoxin
(ii) have a narrow margin of safety eg: theophylline, cyclosporine, antiarrhythmics, antidiabetics.

- In such cases, the patient should be stabilised with one brand formulation only & that brand should never be changed
- If a patient who is stabilized on one brand product is switched over to another brand of the same drug, there could be either a therapeutic failure (due to decreased bioavailability) or drug intoxication (due to increased bioavailability)

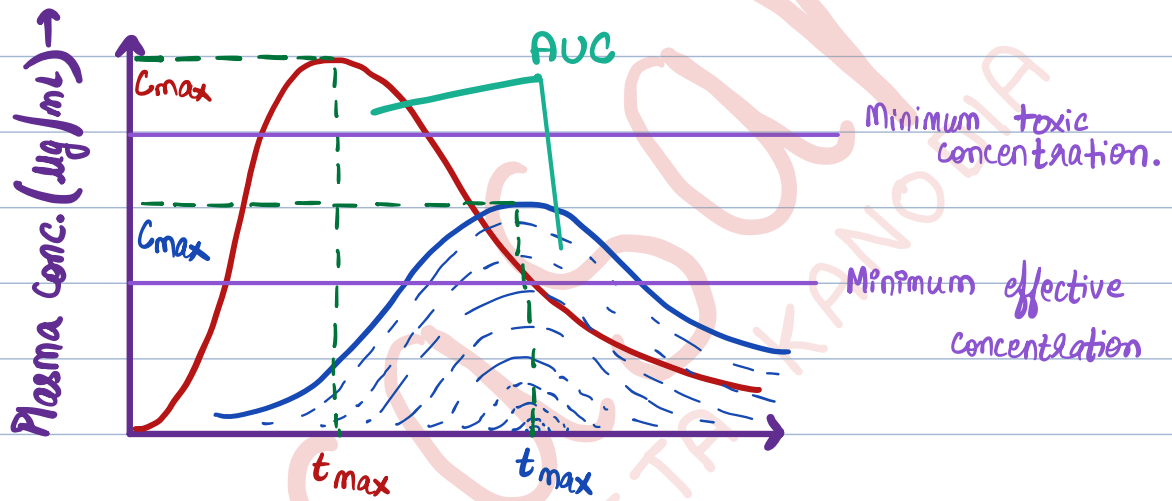
→ If two or more dosage forms of the same drug contain the same labeled quantities of the drug as specified in pharmacopoeia: Chemical Equivalence

→ Two brand products of one drug can be considered as Therapeutic Equivalence, if they provide an identical in vivo pharmacological response.

Dilantin, Eptoin } chemical equivalents & therapeutic equivalents

Measurement of Bioavailability: from plasma concentration - time curves

- peak plasma concentration [C_{max}] } indicators of rate of absorption
- time to attain peak plasma concentration [t_{max}] } indicators of rate of absorption
- area under the curve (AUC) of plasma concentration versus time curve (till plasma concentration has fallen to 10% of peak value) ⇒ indicates extent of absorption



→ Measurement of AUC for bioavailability is a better index of bioavailability for drugs to be given for a longer period because here, the total drug absorbed becomes more crucial than the peak concentration achieved or the time required to achieve the peak concentration

$$\text{Drug (F) Bioavailability (\%)} = \frac{\text{AUC after oral administration}}{\text{AUC after IV "}} \times 100$$

Factors Affecting Bioavailability :

Pharmaceutical

- formulation of drug
- particle size
- salt form
- crystal form
- water of hydration
- Nature of excipients & adjuvants
- Degree of ionisation

Pharmacological

- Gastric emptying, GI motility
- GI diseases
- Food & other substances
- First - pass effect
- Drug - drug interactions
- Pharmacogenetics
- Miscellaneous factors

- **Formulation of Drug :**

  Solution > suspension > capsule > tablet > coated tablet

- **Particle Size :** drug usually dissolves more rapidly when its surface area is increased by decreasing its particle size

- **Salt Form :** salts of weakly acidic drugs are highly water soluble
  → free acidic drug is precipitated from these salts in a microcrystalline form which has faster dissolution rate
  ∴ increased bioavailability

  eg:- tolbutamide sodium & phenytoin sodium have better bioavailability than tolbutamide & phenytoin

- **Crystal Form:**

eg: — amorphous chloramphenicol palmitate & amorphous novobiocin have faster dissolution.

- **Water of Hydration:** drugs can associate with water to produce crystalline forms called the hydrates.

eg: — anhydrous forms of caffeine, theophylline & ampicillin have faster dissolution rate & better bioavailability than their hydrous forms

- **Nature of Excipients & Adjuvants:** → pharmacologically inert substances added to the drug formulation as a filling material / binding agent / bulking agent.

→ some excipients are wetting agents (lactose, polysorbate-80) ⇒ enhance solvent penetration in drug particles & also minimise aggregation of the particles ⇒ faster dissolution ⇒ quicker absorption

- **Degree of Ionisation:** unionised lipid-soluble drugs are better absorbed than strongly acidic / basic or highly ionised drugs

eg: — streptomycin — Ach & its analogues
— neostigmine — d-tubocurarine

- **Gastric Emptying, GI Motility:**

→ factors that accelerate gastric emptying permit drugs to reach the large absorptive surface area of small intestine faster ⇒ increase in bioavailability

- fasting
- anxiety
- lying on right side
- hyperthyroidism
- with gastrokinetic drugs like metoclopramide.

→ factors retarding gastric emptying:
- fatty diet
- endogenous depression
- lying on left side
- pyloric stenosis
- hypothyroidism.

- **GI Disease:**

→ coeliac disease (malabsorption of fats)

- Amoxycillin, pivampicillin ⟹ decreased absorption
- cephalexin : increased absorption
- Ampicillin : No change

→ Crohn's Disease: shows disproportionate absorption of individual components from tablets of Cotrimoxazole – Trimethoprim : decreased
– Sulfamethoxazole : increased.

→ Gastroenteritis : decreased absorption of drugs if given orally.

- **Food & Other Substances:**

→ GI absorption is favoured by empty stomach ; reduced after ingestion of food

→ Absorption of tetracyclines is markedly reduced with milk / milk products

→ vit. C keeps Iron in ferrous form ⟹ increased bioavailability

- **First-Pass Effect:** all drugs that are taken orally

⇓

portal system

⇓

systemic circulation

∴ drug degradation occurring before the drug enters systemic circulation

⇓

decreased bioavailability

eg:- bioavailability of l-dopa, morphine, nitroglycerin, isosorbide dinitrate & propranolol / labetalol & less if given orally

- Drug-Drug Interactions:

eg:- liquid paraffin decreases the bioavailability of fat soluble vitamins (since it emulsifies fats & ∴ causes deficiency of fat-soluble vitamins A, D, E, K)

- antacids containing aluminium, calcium & magnesium & haematinics containing iron cause reduced bioavailability of tetracyclines (because the resultant chelated complex is poorly absorbed)
- barbiturates reduce bioavailability of several drugs due to enzymatic induction
- probenecid blocks penicillin excretion & thus, enhances its bioavailability.

- Pharmacogenetics:

- Slow acetylators of isoniazid show increased bioavailability
  ∴ more subject to isoniazid-induced neurotoxicity (American whites, Israelis)
- fast acetylators (Eskimos, Japanese, Chinese) show reduced bioavailability

- some people have atypical plasma pseudo-chE (which has very low hydrolysing capacity for succinylcholine)
  ∴ even $\frac{1}{6}$th dose of succinylcholine provides the same effect as the normal therapeutic dose.

- **Miscellaneous:**

→ route of administration

→ area of absorbing surface

→ state of circulation at the site of absorption

[Drug Disposition = drug distribution + metabolism + excretion]

Barriers to Drug Distribution:

① **Blood-Brain Barrier:** endothelial cells of brain capillaries differ from peripheral capillaries of the body (∵ they are very tightly joined & lack intercellular pores)

→ brain capillaries are also enveloped by less permeable cells called glial cells.

→ Anatomically, there exists a dual barrier in CNS:

- blood-brain barrier
- blood-CSF barrier.

Functions:

(i) protects the brain tissue from toxic substances in circulating blood & from neurotransmitters (like epinephrine, norepinephrine, dopamine) which have peripheral effects but could bind to CNS receptors to cause adverse effects.

→ only lipid soluble non-ionised form of drugs penetrate more easily eg: – volatile anaesthetics like ether & chloroform
– ultra short acting barbiturates like thiopental
– narcotic analgesics like morphine & heroin

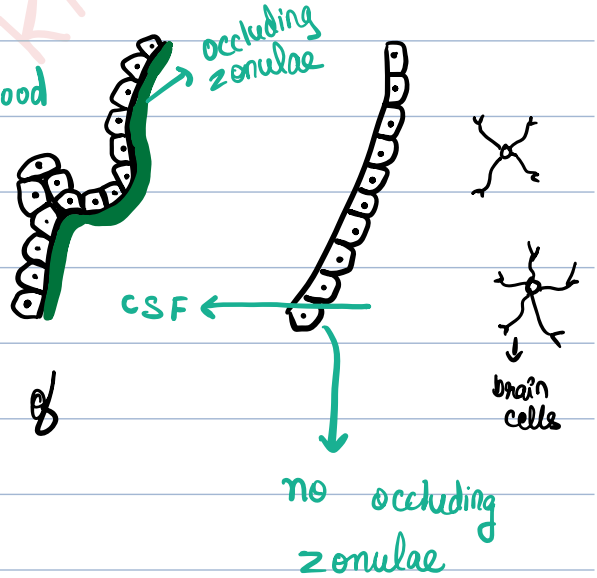
- dopamine precursors like L-dopa
- sympathomimetics like amphetamine & ephedrine
- diazepam, propranolol

→ polar compounds fail to penetrate BBB
- dopamine
- serotonin
- streptomycin
- quaternary substances like d-tubocurarine, neostigmine, acetylcholine

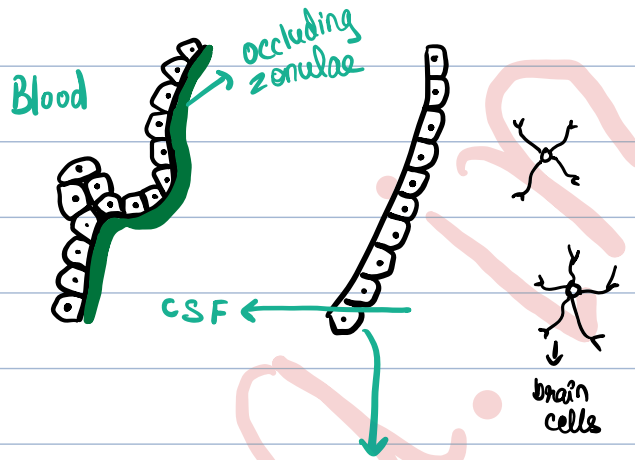
→ inflammatory conditions (as in cerebral meningitis, viral infections of brain or heat stress) usually increase the permeability of BBB (penicillins & chloramphenicol which otherwise have a poor penetration through BBB, can penetrate)

→ 5 regions of the brain which are relatively more permeable or leaky (because of no occluding zonulae) & thus, are devoid of BBB :-

(i) pituitary gland
(ii) pineal body
(iii) medial eminence
(iv) choroid plexus capillaries
(v) area postrema (near the floor of 4th ventricle which includes chemoreceptor trigger zone & vomiting centre)



② Blood-CSF & CSF-Brain Barrier :



→ CSF - brain barrier is extremely permeable due to absence of occluding zonulae

Clinical Advantage:

- proper distribution of drugs like penicillin into brain [penicillin being less lipid-soluble has poor penetration to BBB but if given by intrathecal route it can cross CSF-brain barrier & reach the brain in sufficient concentration to treat conditions like brain abscess]

③ Placental Barrier:

readily allows transfer of non-polar lipid-soluble substances (mainly by passive diffusion)

eg: - hypnotics
- narcotics
- certain antibiotics.
- general anaesthetics
- alcohol
- cardiac glycosides
- neuroleptics

→ polar substances cannot cross the placental barrier

eg: - quaternary ammonium compounds like d-tubocurarine
- substances with high molecular weight (dextran, insulin)

→ Some degree of foetal exposure is likely to occur with virtually all drugs

First trimester
- thalidomide
- phenytoin
- trimethadione
- Streptomycin
- Methotrexate

} may lead to congenital abnormalities in the fetus (teratogenic effects)

Last trimester – morphine (during labour) ⇒ asphyxia
– antithyroid drugs (carbimazole) ⇒ neonatal goitre

→ fetal plasma is slightly more acidic (7) than the mother (7.4)
∴ ion trapping of basic drugs (like morphine) occurs in fetal plasma.
→ hypoxia increases permeability of drugs through placental barrier.

Special Compartments of Drug Distribution (Sanctuary Compartments):

→ usually the sites where drugs get accumulated are not those where they exert their pharmacological effects

① Cellular Reservoir: occurs if the tissue has higher affinity for the drug than plasma proteins.

→ affinity could be due to binding to tissue proteins or nucleoproteins.

eg: – digoxin & emetine in heart, liver, kidney (bound to muscle protein)
– iodine in thyroid
– cadmium, lead & mercury (muscle protein, metallothioncin)
– chloroquine – in liver tissue (tissue proteins)
– in retina (nucleoproteins)
– chlorpromazine in eye (affinity to retinal pigment melanin)

② Fat as Reservoir:

→ highly lipid-soluble drugs get accumulated in fat & adipose tissue (thiopentone, DDT)

→ fat is a sluggish reservoir due to lesser blood flow

→ if the body starts depleting (as occurs during starvation), the stored drug may be mobilised & toxicity may ensue.

③ Transcellular Reservoir:

- aqueous humour (chloramphenicol & prednisolone)
- CSF (aminosugars, sucrose)
- endolymph, joint fluid (ampicillin)
- pleural sac (imipramine, methadone)

④ Bones & Connective Tissue:

- tetracyclines
- cisplatin
- lead
- arsenic
- fluorides

} form a complex with bone salts & get deposited in nails, bones, teeth

- antifungal drug griseofulvin ⇒ affinity for keratin precursor cells

⑤ Plasma Protein: serves as a circulating drug reservoir

Free drug + Protein ⟺ Drug - Protein complex

→ only free fraction of drug ⇒ pharmacologically active ⇒ can diffuse through capillary wall, be metabolised & excreted

→ protein bound drug component ⇒ inert

→ As the free/unbound drug gets eliminated from the body, more drug dissociates from the drug-plasma protein complex to replace the free drug that was lost

∴ extensive protein binding does not prevent the drug from reaching its site of action, but only prolongs drug availability & duration of action.

Plasma Protein	Drugs
Albumin	Acidic drugs – warfarin – penicillins – sulfonamides – tolbutamide – salicylic acid
α_1- Acid Glycoproteins	Lipophilic basic drugs – quinidine – imipramine – lidocaine – chlorpromazine – propranolol – spiroperidol
Tissue proteins & Nucleoproteins	Drugs with high apparent Volume of Distribution – digoxin – emetine – chloroquine
Transcortin	– steroids
α- globulins	– thyroxine
γ- globulins	– antigens

→ highly plasma protein bound drugs remain largely restricted to vascular compartment & tend to have lower aVd.

→ highly plasma protein bound drugs are difficult to be removed by dialysis (& need special techniques for treatment of their poisoning)

→ Binding of drugs to plasma proteins is a capacity-limited & saturable process

→ In liver diseases, uremia, hypoalbunemic states ⇒ even the therapeutic dose of the drug can lead to toxicity

→ In physiological stress, MI, Crohn's disease, inflammation, plasma conc. of acute phase reactant proteins increase ⇒ binding of same basic drugs like propranolol, quinidine increases.

→ More than one drug can bind to the same site of albumin ⇒ displacement interactions wherein a drug bound with a higher affinity will displace the one having lower affinity.

Important Displacement reactions:

1. - phenylbutazone
   - salicylates
   - some sulfonamides

   } displace → tolbutamide ⇒ hypoglycemia

2. - Salicylates
   - Indomethacin
   - Phenytoin
   - Tolbutamide

   } displace → warfarin ⇒ haemorrhage

3. - sulfonamides
   - vitamin K

   } displace → endogenous ligands (like bilirubin) ⇒ Kernicterus in neonates

4. Salicylates → displace → methotrexates.

Apparent Volume of Distribution (aVd):

→ volume of distribution does not represent a real volume but must be regarded as the size of the pool of the body or fluids (available space) that would be theoretically required if the drug was distributed equally throughout all portions of the body.

Intracellular volume	= 28L
Interstial volume	= 10L
plasma volume	= 4L
Total	= 42L

Def: total space which should apparently be available in the body to contain the known amount of drug.

$$aVd = \frac{\text{Total amount of drug in the body (mg/kg)}}{\text{conc. of the drug in plasma (mg/L)}}$$

Generalisations:

① if the drug does not cross capillary walls & is given IV ⟹
aVd = plasma water = 3L.

② drugs highly bound to plasma proteins have a low aVd
(tolbutamide, furosemide, warfarin)

- lesser the plasma protein binding ⟹ greater aVd (chloroquine, metoprolol)

③ aVd for many drugs > actual body volume
⇒ such drugs are widely distributed in the body
⇒ such drugs are difficult to be removed by haemodialysis in toxicity.

④ aVd < 5L ⟹ drug is retained within vascular compartment
aVd ≈ 15L ⟹ drug is restricted to extracellular fluid
aVd > 20L ⟹ drug is distributed throughout total body water.

Redistribution of Drugs: observed typically with highly lipid-soluble drugs

→ drug action is terminated after its withdrawal because of redistribution (into viscera, muscles, lean tissue, fat)

→ these drugs, being highly lipid-soluble, enter the brain rapidly, causing general anaesthesia

→ they also diffuse out of the brain & are redistributed in muscles, lean tissue, fat

eg: – single dose of ultrashort-acting barbiturate is very short-acting.

Biotransformation:

→ enzyme catalised biochemical transformation of drugs within living organisms

→ metabolites thus formed are much less lipid soluble ∴ not reabsorbed from renal tubules & are excreted.

→ occurs mainly in liver (also in kidney, intestine, adrenal cortex, lungs, placenta, skin)

3 consequences of Biotransformation:

① Active Metabolite —forms→ Inactive metabolite:

- phenobarbitone ⟶ hydroxyphenobarbitone

② Inactive metabolite (prodrug) —forms→ Active Metabolite:

- L-dopa ⟶ Dopamine
- Parathion ⟶ Paraxon
- Talampicillin ⟶ Ampicillin

③ Active Metabolite —forms→ Another Active Metabolite:

- Diazepam ⟶ Oxazepam
- Amitriptylline ⟶ Nortriptylline
- Imipramine ⟶ Des-imipramine
- Codeine ⟶ Morphine

First-Pass Effect / Metabolism [Pre-systemic Metabolism]:

→ drug metabolism occurring before the drug enters systemic circulation

→ Result : – decreased bioavailability
– decreased therapeutic response

→ First-pass effect may be bypassed if the drug is administered parenterally or sublingually

(In liver diseases ⇒ oral bioavailability of drug increases)

Liver	Intestinal Mucosa	Bronchial Mucosa
– Isosorbide dinitrate	– L-dopa	– nicotine
– Morphine	– α-methyldopa	– Isoprenaline
– Xylocaine	– testosterone	
– Pethidine	– progesterone	
– Propranolol		

Phase I Reactions (Degenerative Reactions)	Phase II Reactions (Synthetic / Conjugation Reactions)
→ drug is diminished to a smaller polar / non-polar metabolite by introduction of a new group	→ microsomal / mitochondrial / cytoplasmic
→ mainly microsomal reactions	→ metabolite formed is usually:
→ • Oxidation • Reduction • Hydrolysis	• polar • water soluble • mostly inactive
→ metabolite formed may be active / inactive	

- **Microsomal Enzymes**: the drug-metabolising enzymes are located primarily on the smooth endoplasmic reticulum of liver (also present in intestinal mucosa, lungs, kidney)

→ principal enzymes are Mixed Function Oxidases (MFOs) or Cytochrome P-450 (eg:- glucoronyl transferase)

→ microsomal enzymes: — non-specific in action
— can be induced or activated — can metabolize only lipid-soluble drugs

→ Classification of CYP-450 on the basis of amino acid sequence & cDNA cloning studies:
* family & subfamily
eg: CYP 2 D 6 → specific isoenzyme
*

→ these exhibit genetic polymorphism.

Enzyme	Drugs metabolised	Inducers	Inhibiters
CYP3A4, CYP3A5.	50% of xenobiotics	- Barbiturates - Carbamazepine - Phenytoin - Rifampicin	- erythromycin, clarithromycin - ketoconazole, fluconazole - verapamil, diltiazem - ritonavir
CYP2D6	25-30% commonly used drugs	- X	- quinidine - fluoxetine
CYP2C8, CYP2C9	15-18% commonly used drugs	- Barbiturates - Rifampicin	- Fluconazole - Fluvastatin
CYP1A1, CYP1A2	few drugs - theophylline, warfarin, clomipramine, paracetamol	Inducers: - barbiturates, rifampicin, Carbamazepine, smoking	
CYP2E1	very few drugs - general anaesthetics, alcohol, paracetamol	Inducer: chronic consumption of alcohol Inhibitor: disulfiram	

- **Non-Microsomal Enzymes**: present in cytoplasm, mitochondria of hepatic cells & in plasma

Eg: – monoamine oxidase – amidases – conjugases
– esterases – transferases

→ catalize all phase II reactions [except glucoronide conjugase], certain phase I reactions
→ non-inducible
→ can be inhibited.

Reactions	Drugs
Phase I Reactions	
• **Microsomal Oxidation**	
① Aromatic Hydroxylations	• phenobarbitone → p-hydroxy phenobarbitone
② Aliphatic Hydroxylations	• digitoxin • ibuprofen
③ Dealkylation (N-, O-, S-)	• phenacetin → paracetamol • mephobarbitone → phenobarbitone • codeine → Morphine
④ N-, S- Oxidation	• Trimethylamine → Trimethylamine N-oxide • Cimetidine → Cimetidine sulfoxide
⑤ Deamination	• Amphetamine → phenylacetone derivative
⑥ Desulfurisation	• Parathion → Paraoxon
• **Non Microsomal oxidation**	
① Mitochondrial oxⁿ	• Epinephrine —(monoamine oxidase)→ Vinyl-mandelic acid
② Cytoplasmic oxⁿ	• ethyl alcohol —(alcohol dehydrogenase)→ acetaldehyde
③ Plasma oxⁿ	• histamine → imidazole acetic acid • xanthine → uric acid

Reactions	Drugs
• Microsomal Reductions	
① Nitro Reduction	• chloramphenicol ⟶ arylamine metabolite
② Azo Reduction	• prontosil ⟶ sulfanilamide
③ Keto Reduction	• cortisone ⟶ hydroxycortisone • methadone • nalaxone
• Non Microsomal Reduction	• chloral hydrate ⟶ trichloroethanol
• Microsomal Hydrolysis	• pethidine ⟶ pethidinic acid • hydrolysis of lidocaine by hepatic membrane-bound esterase
• Non-Microsomal Hydrolysis	• Procaine ⟶ PABA • Atropine ⟶ tropic acid
Phase II Reactions	
• Microsomal Conjugations	
① Glucoronide Conjugation	Drug + UDGPA —(microsomal glucoronyl transferase)→ Drug Glucoronide + UDP • Morphine • Aspirin • Endogenous substances like bilirubin • Paracetamol • Chloramphenicol
• Non-microsomal Conjugations	
① N-Acetyl Conjugation	• isoniazid • dapsone • procainamide • histamine
② Sulphate Conjugation	• Aspirin • Paracetamol • Methyldopa • Chloramphenicol
③ Amino acid Conjugation	• Aspirin • Nicotinic acid • Benzoic acid • Deoxycholic acid

Reactions	Drugs
④ Glutathione Conjugation	• ethacrynic acid • sulfobromophthalein
⑤ Ribosides & Riboside Phosphates	• purines & pyrimidines

Non-Enzymatic Biotransformation (Hofmann Elimination):

- atracurium (skelet muscle relaxant)

→ drug is metabolized in the plasma spontaneously through molecular rearrangement

→ without involvement of any enzyme action

Enzyme Induction:

→ several drugs, on repeated administration, stimulate or induce the growth of smooth endoplasmic reticulum (reversible)

↓

enhanced microsomal activity → accelerated metabolism

↓

decreased pharmacological response of inducer & co-administered drugs utilizing same enzymatic pathway

→ most prominent in liver (also seen in lung, placenta, kidney)

Clinical Relevance:

① → decreased plasma levels & decreased therapeutic effect of co-administered drug

→ decreased drug effect if its metabolite is inactive

→ increased drug effect if its metabolite is active.

- unwanted pregnancy can result (even after using oral contraceptives) if potent enzyme inducers (phenytoin, rifampicin) are used concomitantly
- patients on enzyme-inducing drugs (like barbiturates), would need higher doses of oral anticoagulants (like warfarin)
- Enzyme inducers (phenytoin) accelerate metabolism of vitamin D_3 leading to osteomalacia
- Enzyme inducers (barbiturates) usually enhance their own metabolism leading to development of pharmacokinetic tolerance.

② Enzyme induction may lead to drug toxicity:

- ethanol drinkers have more probability of developing hepatotoxicity from paracetamol overdose / therapeutic dose due to increased production of N-acetyl-P-benzo-quinoneimine

③ Knowledge of enzyme induction can be used for therapeutic benefits:

- to treat neonatal jaundice: phenobarbitone can be given to the pregnant mother 7-14 days prior to labour or to the infant soon after birth to induce fetal hepatic glucoronyl transferase which catalyzes conjugation of bilirubin to glucuronic acid.

Enzyme Inhibition:

→ One drug may inhibit the metabolism of another drug with results in:
- slowly metabolism of drug
- increase in the circulating levels of the drug
- prolongation / potentiation of its pharmacologic effects.

→ usually reversible ; rapid process

→ could be irreversible as in case of secobarbital overdose

Clinical Relevance: [− ⇒ harmful effects ; + ⇒ beneficial effects]

− → unexpected nausea / vomiting & tremors due to theophylline with concamitantly admistered chloramphenicol or erythromycin

− → enhanced bleeding tendency with dicumarol when administered with cimetidine

− → severe respiratory depression with morphine when given with MAOIs

− → Severe ataxia & drowsiness with phenytoin in combination with dicumarol or chloramphenicol

− → Precipitation of cardiac arrhythmias with terfenadine when given with chloramphenicol or Ketoconazole

+ → Increased accessibility of L-dopa in brain when given with carbidopa [carbidopa prevents peripheral decarboxylation of L-dopa]

+ → aversion to alcohol after prior administration of disulfiram (aldehyde dehydrogenase inhibitor) ∴ further conversion of acetaldehyde to acetic acid is prevented

+ → reversal of skeletal muscle paralysis due to d-tubocurarine by neostigmine

Inhibitor	Enzyme Inhibited	Drug whose metabolism is inhibited
Cimetidine	Hepatic Microsomal MFOs	• Phenytoin • Theophylline • Warfarin • Testosterone
Sod. Valproate	Hepatic Microsomal MFOs	• Phenytoin • Primidone • Phenobarbital
Erythromycin	Hepatic Microsomal MFOs	• Theophylline • Carbamazepin • Warfarine • Cyclosporine
Ciprofloxacin group (except ofloxacin)	Hepatic Microsomal MFOs	• Theophylline
Chloramphenicol	Hepatic Microsomal MFOs	• Phenytoin • Tolbutamide • Terfenadine
Verapamil, Diltiazem	Hepatic Microsomal MFOs	• Theophylline • Cyclosporine • Carbamazepine
Allopurinol	Xanthine oxidase	• 6-mercaptopurine • Azathioprine
MAOIs	Monoamine oxidase	• Morphine • Pethidine
Disulfiram, Metronidazole	Aldehyde dehydrogenase	• Alcohol • Phenytoin
Echothiophate	Acetylcholine esterase	• Suxamethonium • Propanidid
Captopril, enalapril	Angiotensin-converting enzyme	• Angiotensin I
Carbidopa	L-aromatic amino acid decarboxylase	• L-dopa

Factors Affecting Drug Metabolism:

- Age
- Disease
- Sex
- Genetic Variation
- Species
- Nutrition & Diet
- Race
- Drug-drug interactions

① Age:

→ Neonates: low microsomal enzyme & glucoronyl transferase enzyme activity

→ Elderly Persons: reduced hepatic blood flow ⇒ slow metabolism
⇒ increased incidence of toxicity.

② Sex: seldom important in human beings
(Male rats sleep for a short duration than females, after receiving hexobarbital)

③ Species: Rabbits metabolize atropine faster than humans

④ Race:

→ Chinese: high alcohol dehydrogenase but low aldehyde dehydrogenase activity ∴ they exhibit higher plasma concentration of aldehyde after consuming alcohol (∴ headache, palpitation, etc.)

④ Genetic Polymorphism:

Genetic Defect	Drug	Therapeutic Use	Clinical Consequences
• Atypical pseudocholinesterase (autosomal recessive trait)	Succinyl choline	Neuromuscular blocker	prolonged apnea due to retarded metabolism
• Slow N-acetylation Rapid N-acetylation (autosomal recessive trait)	- Isoniazid - Isoniazid	- Antitubercular - Antitubercular	- peripheral neuropathy - hepatotoxicity
• Faulty expression of CYP2D6 (autosomal recessive trait)	Codeine	Opioid analgesic	Reduced analgesia

⑤ **Nutrition & Diet:** diet rich in protein & low in carbohydrate enhances the rate of drug metabolism

⑥ **Disease:** activity of hepatic cytochrome P-450 enzymes are impaired (viral hepatitis, active/inactive liver cirrhosis, alcoholic hepatitis, hepatocellular carcinoma)

→ **Hypothyroidism:** decreases metabolism of drugs

→ **Hyperthyroidism:** increases metabolism of drugs.

⑦ **Drug - Drug Interactions:** enzyme induction / enzyme inhibition.

Drug Elimination: drugs are eliminated either unchanged or as water-soluble metabolites

Renal Excretion: most important for elimination of free drugs

eg: – frusemide – gentamicin – d-tubocurarine
– digoxin

→ Renal excretion of drugs is determined by
- Glomerular filtration
- Active tubular secretion
- Passive tubular reabsorption.

Glomerular Filtration:

Factors influencing glomerular secretion:

- Molecular size: > 20,000 not filtered
- Plasma Protein Binding: only free drugs can be filtered
- Renal Blood Flow: greater the glomerular perfusion ⇒ faster is the drug removal from plasma.

Tubular Secretion:

→ It is an energy-requiring carrier-mediated active transport
∴ protein-binding (which interferes with glomerular filtration) does not affect tubular secretion

→ Two Indepent Carries systems:

① For Acidic Drugs
- Penicillins
- Salicylic acid
- Thiazide diuretics
- Probenecid
- Indomethacin
- Methotrexate
- Sulfonamides
- glucoronide metabolites

② For Basic Drugs
- Morphine
- quinidine
- procaine
- quinine
- neostigmine
- quaternary ammonium Compounds (dopamine, histamine, choline, serotonin)

→ drugs having similar physico-chemical characteristics compete for the same carrier systems (due to nonselectivity of the two systems)

→ Probenecid (weak acid) competitively inhibits tubular secretion of penicillins & amoxycillins

∴ increase in plasma half-life & effectiveness of penicillins in the treatment of certain infectious diseases

Tubular Reabsorption: renal tubule ≈ typical lipid barrier

∴ reabsorption of drugs is predominantly by passive diffusion.

→ Dependent upon: — lipid solubility of drug
— ionisation constant (pKa)
— pH of urine

→ since, the pH of urine is acidic, all acidic drugs (salicylates, barbiturates, sulfonamides) remain predominantly non-ionised & have more chances of reabsorption than excretion.

→ ∴ alkalisation of urine is a part of therapeutic regimen in the case of salicylate or barbiturate poisoning.

→ strongly acidic / basic drugs remain ionised at all pH ranges & ∴ not reabsorbed

→ Quaternary ammonium compounds, Aminoglycoside antibiotics } highly polar drugs ⇒ ∴ not reabsorbed

→ Amount of drug excreted = Total amount of drug filtered − amount of drug reabsorbed.

Biliary Excretion & Enterohepatic Circulation:

- quinine
- d-tubocurarine
- erythromycin
- colchicine
- corticosteroids

} biliary excretion & subsequent elimination through faeces

→ some drugs are secreted through bile, but after being delivered to intestine, are reabsorbed back & the cycle is repeated [enterohepatic circulation]

eg: – digitoxin – Vit. D_3
– indomethacin

→ certain drug metabolites are excreted through bile & delivered to the intestine where these metabolites are deconjugated / hydrolysed releasing the parent active drug again.

– the free drug is then reabsorbed & the cycle is repeated [enterohepatic circulation]

eg: – thyroxine – chloramphenicol
– morphine – tetracycline
– phenolphthalein – ethinyl estradiol

→ net result of enterohepatic circulation is prolongation of action of drug (as the drug serves as a small circulating reservoir)

Faeces Elimination: for

(i) orally ingested drugs that are not absorbed through gut

eg: – magnesium sulphate – neomycin
– streptomycin – bacitracin
– cholestyramine – certain purgatives

(ii) certain drugs which are excreted through bile but are not reabsorbed from intestine

eg: – erythromycin
– corticosteroids.

Alveolar Excretion: for gases & volatile liquids

eg: – general anaesthetics – ether
– nitrous oxide – alcohol

→ eliminated irrespective of their lipid solubility
→ excretion through alveoli depends on partial pressure of the drug in blood.

Excretion Through Breast Milk:

→ drugs are transferred to breast milk according to the pH partion principle.
- basic drugs (being predominantly nonionised at plasma alkaline pH) can diffuse through mammary epithelium & get accumulated in milk

↓

once diffused into milk, these drugs cannot be reabsorbed back to plasma (due to relatively acidic pH of milk which causes the drug to ionize)

[Ion trapping of basic drugs]

→ Basic drugs (excreted more through milk) eg: – chloramphenicol – immunosuppressive / cytotoxic drugs
– tetracyclines – bromocriptine
– ergotamine – estrogen / progesterone
– morphine – Oral contraceptives
– diazepam – antihistamines
– senna alkaloids (purgatives)

→ certain acidic drugs (though less secreted) can cause serious side effects in infants

- Sulfonamides (Kernicterus, allergy)
- Penicillins (allergy)
- Ampicillin (diarrhoea)
- Dapsone (hemolytic anaemia)
- Phenindione (bleeding)
- Phenobarbitone (drowsiness)
- Phenytoin (methaemoglobinemia)
- Theophylline (restlessness)

Drugs Contraindicated in Breast-Feeding Mothers:

- chloramphenicol
- chloroquine
- primaquine
- quinine
- quinidine
- procainamide
- nitrofurantion
- nalidixic acid
- dapsone
- isoniazid
- probenecid
- sulfonamides

Excretion Through Skin, Hair, Sweat, Saliva:

- griseofulvin ⇒ through keratin precursor cells
- arsenic, mercury salts, iodides ⇒ hair follicles
- iodine, potassium iodide, lithium, phenytoin ⇒ saliva
- certain amines & urea derivatives ⇒ sweat

Kinetics of Drug Elimination:

Plasma Half-Life ($t_{½}$): time duration in which plasma concentration of the drug falls to 50% of earlier value

→ reflects on the drug's elimination/clearance kinetics

Biological effect Half-Life: time duration in which the principal pharmacological effect of the drug declines by half.

FIRST-ORDER KINETICS: shown by majority of drugs

→ a constant fraction of drug is eliminated at a constant interval of time

→ rate of drug elimination ∝ plasma concentration of drug

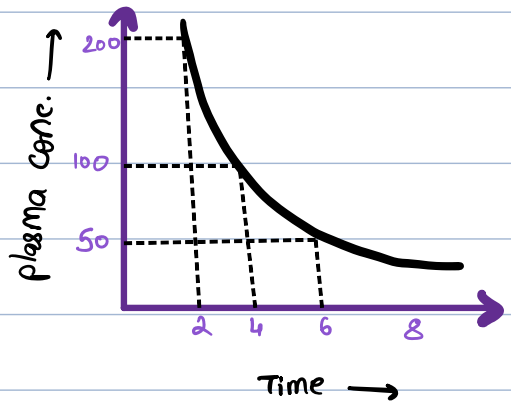
→ $t_{½}$ remains constant (irrespective of the dose).

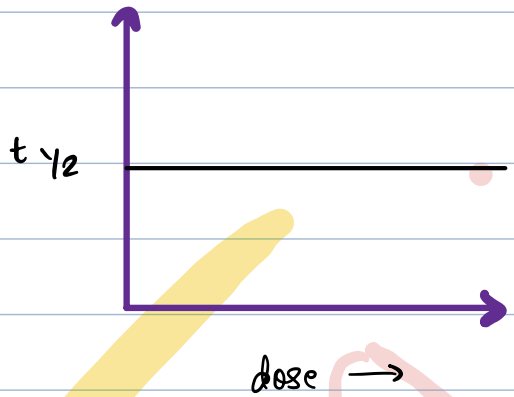
→ Plasma fall-out curve (fall in plasma concentration is plotted against time) ⇒ Curvilinear

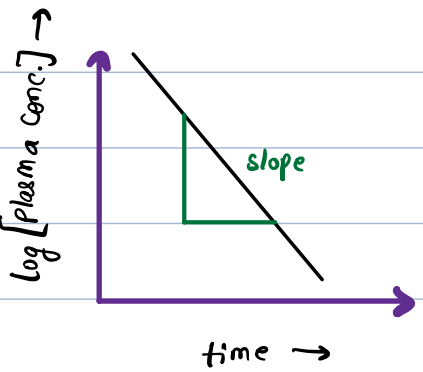
→ After a single dose, about 97% of the drug gets eliminated after 5 half-lives

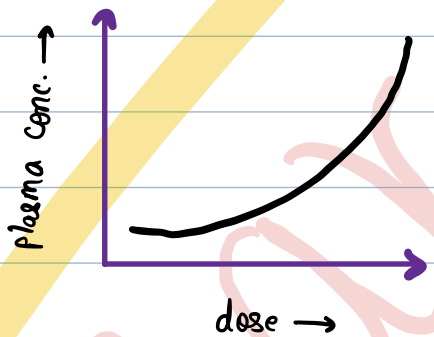
→ If the dose of the drug is doubled, duration of action is prolonged for 1 more $t_{½}$.

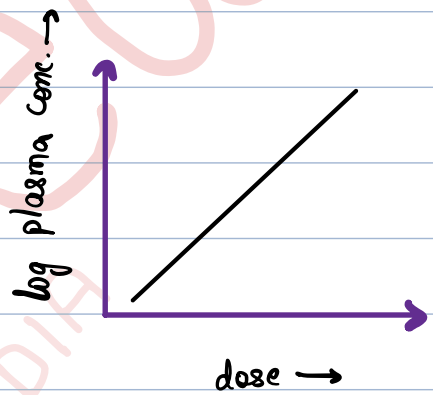
[if dose is made = dose × 2^n ⇒ duration of action is prolonged by n half-lives]











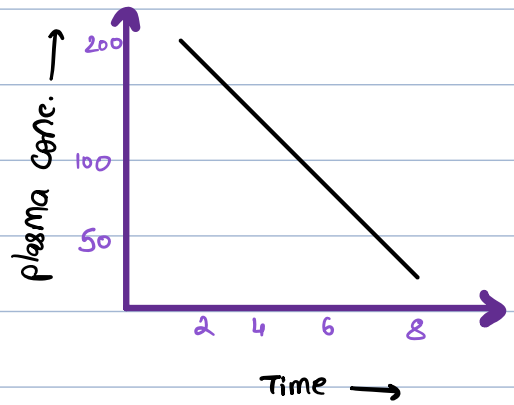
- Slope = $-\frac{K}{2.303}$ K (elimination rate constant)
- $t_{1/2} = \frac{0.693}{K}$.

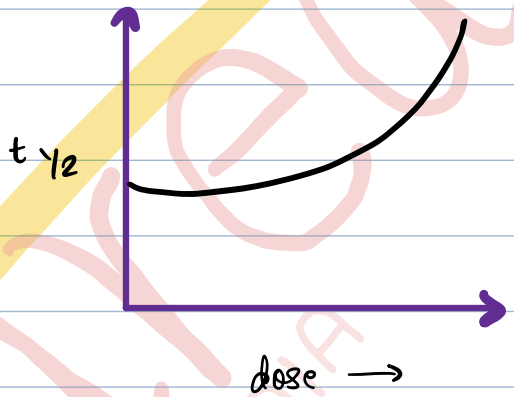
ZERO - ORDER KINETICS: Hardly a few drugs (eg: ethyl alcohol)

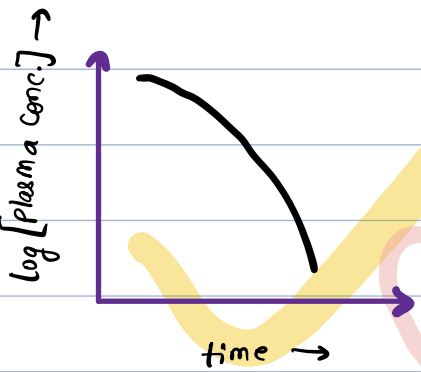
→ a constant/fixed quantity of drug is eliminated per unit time.

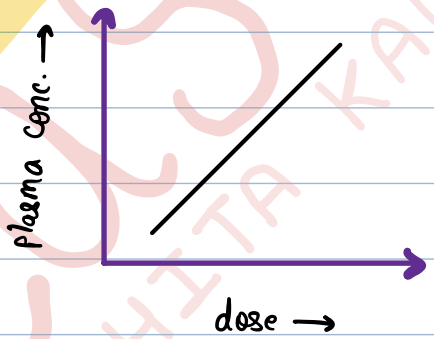
→ rate of elimination is independent of plasma concentration of drug.

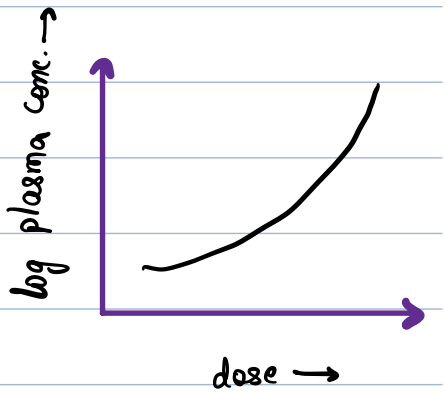
→ $t_{1/2}$ is never constant.









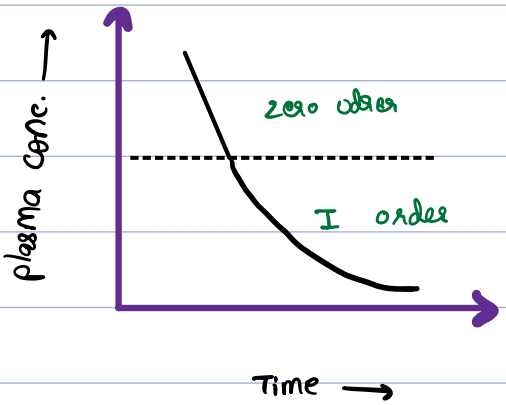


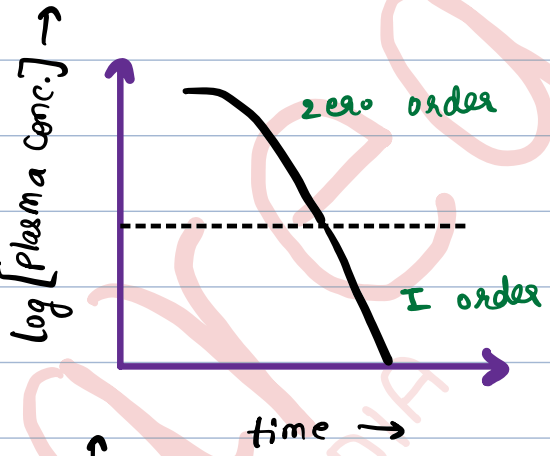
MICHAELIS - MENTEN / MIXED - ORDER KINETICS: Dose - dependent Kinetics

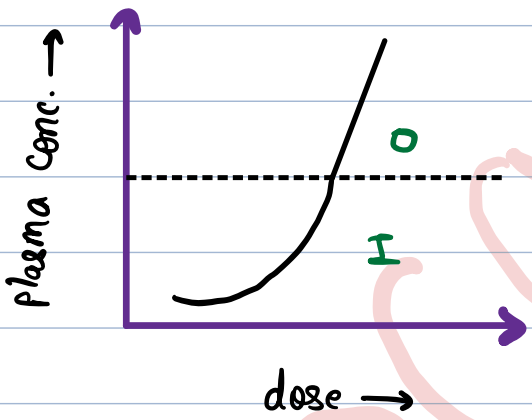
- phenytoin
- Warfarin
- Tolbutamide
- digoxin
- Dicumarol
- Aspirin

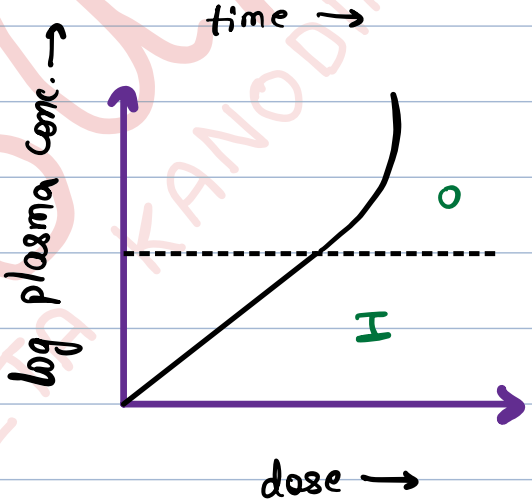
→ **Smaller Doses:** handled by first - order kinetics

Increased Plasma Conc: zero - order kinetics









Dosing Schedules:

Type of Drug	Dosing
• very short half life (few minutes)	- epinephrine - dopamine - dobutamine - oxytocin ⇒ constant IV infusion (to maintain their steady state plasma conc.)
• short $t_{1/2}$ (30 min – 2 hrs)	- cephalexin - benzylpenicillin - paracetamol dose can be so increased that the drug can be administered at every 6-8 hours interval
• $t_{1/2}$ between 4 to 12 hrs	administered at every half-life interval.
• medium $t_{1/2}$ (12-24 hrs)	- usually given at 12 hourly interval - drugs having $t_{1/2}$ of 24 hrs ⇒ half of the therapeutic dose is given at every half life.
• longer $t_{1/2}$ (> 24 hrs)	- digoxin - desipramine - diazepam - digitoxin - chloroquine • initial loading dose / priming dose is given to reduce the time needed to reach steady plasma conc. • this is followed by a maintenance dose to maintain the already attained steady plasma conc.

- **Loading Dose** = Desired plasma conc. (mg/L) × a Vd (L/kg body weight)

- **In case of Renal Disease:** (reduced drug clearance)

$$\text{Corrected dose} = \text{Normal dose} \times \frac{\text{Patient's creatinine clearance}}{\text{Normal creatinine clearance (100 ml/min)}}$$

Fixed Dose Combinations [FDCs]:

→ combination of two different drugs in a single pharmaceutical formulation

→ Rational FDCs can be advantageous ; but illogical/inappropriate combinations could be dangerous.

→ if 2 drugs are to be combined in a single formulation, these drugs must have approximately equal $t_{1/2}$.

- Cotrimaxazole = sulfamethoxazole + trimethoprim (antibacterial)
- sulfadoxin + pyrimethamine = anti-malarial
- clavulanic acid + ampicillin/amoxycillin = for treatment of infections
- Carbidopa + levodopa = treatment of parkinsonism.
- amoxicillin 500 mg + clavulanic acid 125 mg

Advantages of FDCs:

(i) Convenience in dose schedule & better patient compliance

(ii) Enhanced effect of the combinations

eg: trimethoprim ⟹ bacteriostatic
+ sulfamethoxazole ⟹ bacteriostatic
cotrimoxazole ⇒ bactericidal

(iii) Minimisation of side effects

eg: combining carbidopa with levodopa help:
- reduce the dose required for levodopa
- minimises the peripheral side effect due to dopamine by preventing the degradation of l-dopa to dopamine peripherally by l-amino acid decarboxylase enzyme.

Disadvantages of FDCs:

(i) dose of any component drug cannot be adjusted independently if required.

(ii) if pharmacokinetic characteristics of the two drugs do not match, there would be unacceptable range of fluctuations in plasma conc. of the component drugs at steady state.

(iii) It becomes difficult to identify one particular drug which is causing harmful / beneficial effects.

FDCs should not be prescribed unless:

- there is a good reason to believe that the patient needs all the drugs in the formulation
- pharmacokinetic parameters of the component drugs match with each other.