Structured Notes According to

PHARMACOLOGY

Revision friendly **Fully Colored Book/Structured Notes**

For Best results, watch the video lectures along with reading note

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(Author)

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1 INTRODUCTION TO GENERAL PHARMACOLOGY

Pharmacokinetics
- Deals with the movement of the drug inside the body.
- The drug gets absorbed, circulates in the body, and then excreted.
- Pharmacokinetics is "what the body does to the drug"

Pharmacodynamics
- Deals with the effect produced by the drug.
- A drug moving inside the body goes to the organ and binds to its target or receptor, through this it produces its effect.
- Pharmacodynamics is "what a drug does to the body"

General pharmacology

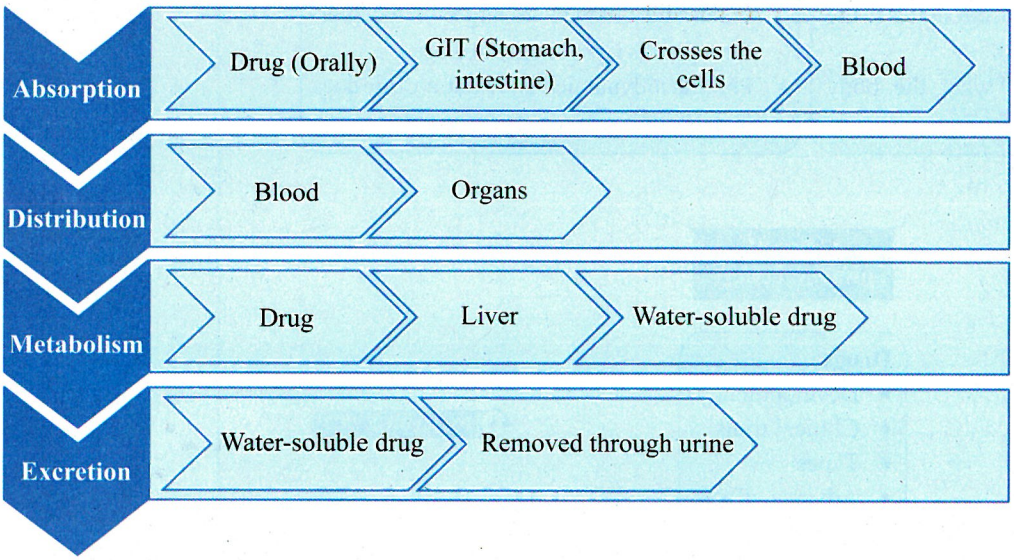
Drugs
- Development
- Clinical trials
- Types
- Adverse effects

PYQ: FMGE 2022

2 PHARMACOKINETICS: ABSORPTION PART -1

Pharmacokinetics

- Pharma: Drug
- Kinetics: Movement of the drug inside the body
- Also known as the ADME study



- The drug is a foreign material, our body tries to remove drugs from the body through body secretions like Urine, sweat, saliva (as these are water-based water soluble drugs are excreted)

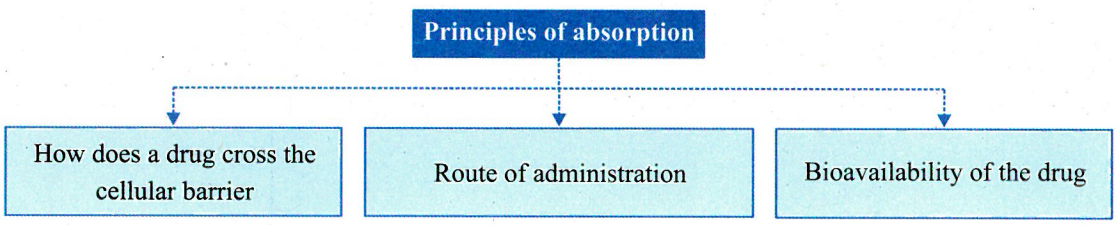
Primary Pharmacokinetic parameters	Secondary Pharmacokinetic parameters

• Absorption
  ○ Bioavailability (BA) of the drug- Amount of drug coming into the blood
• Distribution
  ○ The volume of distribution (Vd)
• Metabolism, Excretion
  ○ Clearance capacity (CI) – Power of the body to excrete drug
	• Half-life (t1/2)
	• Loading dose
	• Maintenance dose

Absorption of a drug

00:05:15

- Absorption is the cellular barrier, a drug has to cross to reach systemic circulation (blood veins)

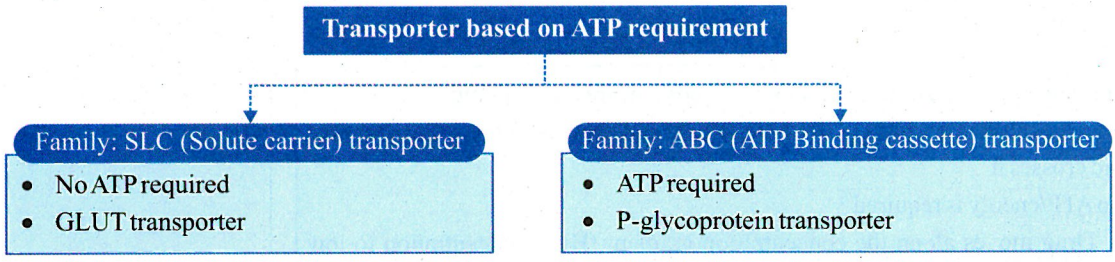


How does a drug cross the cellular barrier 00:07:15

Simple/ Passive diffusion	• The cell membrane is made of phospholipids that are fatty/lipophilic. • Like dissolves like- Only a lipid-soluble drug dissolves in the cell membrane and crosses it • No ATP/energy is required ○ Drug moves along the concentration gradient (High concentration to low concentration) • Most drugs cross by simple or passive diffusion	
Aqueous diffusion	• Hydrophilic (Water soluble) drug crosses the cell membrane • Aquaporins are present on the cell membrane, for carrying water-soluble drugs • No ATP required • Commonly seen in kidney/nephron: ADH (Antidiuretic Hormone) increases the synthesis of Aquaporins • Drugs absorbed by aquaporins: Lithium	
Filtration	• Drugs cross the space between two cells known as Paracellular spaces • No ATP required • In the kidney, from Glomerular capillaries, blood gets filtered into nephrons • Injection of insulin is given into the subcutaneous fat ○ Between subcutaneous fat, endothelial cells of capillaries are present, through which insulin gets absorbed into blood by Filtration	

Endocytosis	• Also known as Pinocytosis
	• The cell changes its cell membrane, through a specific receptor and the drug enters the cell membrane
	• Large proteins can be absorbed
	  ○ Botulinum toxin (food poisoning)
	  ○ Vitamin B12	

Transport/ Carrier mediated absorption	**Facilitated diffusion**	**Active transport**
	• Pump: Specialized transporter • The drug enters the cell with the aid of a pump	• Pump: Specialized transporter • The drug enters the cell with the aid of a pump
	• No ATPase enzyme	• ATPase enzyme present
	• It does not require energy (ATP)	• Requires energy (ATP)
	• Drug moves along the concentration gradient (High to Low concentration)	• Drug moves against the concentration gradient (Low to High concentration gradient)
	E.g. • GLUT transporter	E.g. • Na^+K^+ ATPase transporter • P-glycoprotein transporter
	• 5 Fluorouracil gets absorbed through GIT	• Levodopa and methyldopa get absorbed through GIT by Dopamine transporters

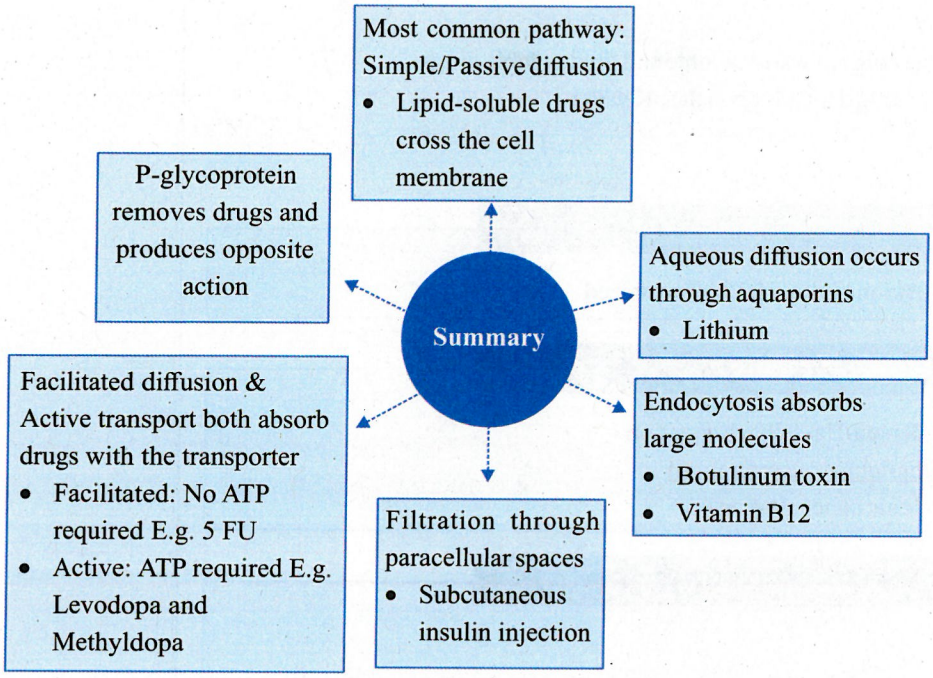


P-glycoprotein transporter 00:22:58

- **Also known as**
  - MDR (Multidrug Resistance) transporter
  - MRP (Multidrug Resistance Protein) transporter
- **Functions**
  - P-glycoprotein is an efflux transporter containing the ATPase enzyme
  - Its main function is to throw an already-absorbed drug from the cell
  - This inhibits absorption of the drug reducing its levels and effect.
  - P-glycoprotein is an enemy of the drug
- Location
  - GIT: Decreases absorption of the drug
  - Kidney: Increases urinary excretion of the drug
  - Liver: Increases bile excretion of the drug
  - BBB/placenta: Decreases entry of the drug
    → Protection
- Substrate of p-glycoprotein transporter
  - Any drug identified by p-glycoprotein is a substrate of p-glycoprotein transporter
  - E.g. Digoxin (heart failure treatment)

	P-glycoprotein inducer	P-glycoprotein inhibitor
Activity on p-glycoprotein	Increase activity of p-glycoprotein	Decrease activity of p-glycoprotein
Drugs	Rifampicin: anti-TB	Mnemonic: QVACKER • Quinidine • Verapamil • Amiodarone • Clarithromycin • Ketoconazole • Erythromycin • Ritonavir
Combined with Substrate of p-glycoprotein (Digoxin)	**Increases activity of p-glycoprotein** • Increase urinary excretion • Digoxin is excreted	**Reduces activity of p-glycoprotein** • Reduced urinary excretion • Increased plasma concentration of the drug • Toxicity of digoxin-Arrhythmias

Q. Which of the following drug inhibit ATP Binding cassette (INICET)
Ans. Verapamil



Simple/Passive diffusion 00:33:55

- Rate/Speed of diffusion is governed by Fick's law = CAP/T

  Fick's law = $\frac{CAP}{T}$
  - C: Concentration of drug
  - A: Area of cell membrane
  - P: Permeability coefficient
  - T: Thickness of cell membrane
- The rate of diffusion is directly proportional to the concentration of the drug and the Area
  - The higher the concentration of the drug, the more the drug enters the cell
  - The intestine has a large surface area, due to the presence of the brush border cells
- The rate of diffusion is inversely proportional to the thickness of the cell membrane

Simple diffusion depends on lipid solubility 00:37:35

Lipid soluble drugs	Water soluble drugs
Also known as Non-polar or Non-ionic drugs	Also known as Polar or Strong ionic drugs
If a drug is 100% lipid soluble, it crosses the cell membrane easily by simple/passive diffusion	If a drug is 100% lipid soluble, it does not cross the cell membrane easily by simple/passive diffusion
	• Oral Heparin ○ Anticoagulant (blood thinner) ○ Highly acidic ○ Not absorbed Orally • Aminoglycosides ○ Streptomycin, Gentamicin ○ Highly polar ○ Water soluble ○ Strong ionic ○ Not absorbed orally

- Weak ionic drugs
  - These drugs lie in between the range of water-soluble and lipid-soluble drugs
  - The solubility of a weak ionic drug depends upon the pK value

pK value 00:41:30

Definition

The pH at which the drug becomes 50% ionized and 50% non-ionized

Calculation of pK value

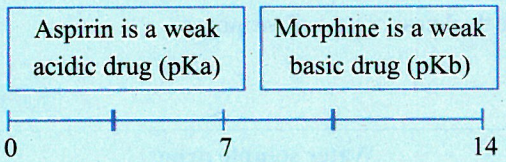
- pK value is calculated by the Henderson-Hasselbach equation
- pK (drug) = pH (media) + Log (Non-ionic concerntration) / (Ionic concentration)

Drugs with pK values

- Aspirin: 3.5
- Morphine: 8.5
- pK value may change based on the pH of the media
  - Stomach: pH is highly acidic (HCI): 0-1
  - Intestine: pH is highly basic (HCO3-): 8-9

pH scale

- Acidic: 0-<7
- Neutral: 7
- Basic: >7-15



- **In the same media, the drug becomes lipid-soluble**
  - If a weak acidic drug is kept in more acidic pH media, it becomes highly non-ionic or lipid soluble
  - If as weak basic drug is kept in more basic pH media, it becomes highly non-ionic or lipid soluble
- **In the opposite media, the drug becomes water-soluble**
  - If a weak acidic drug is kept in more basic pH media, it becomes highly ionic or water-soluble
  - If a weak basic drug is kept in more acidic pH media, it becomes highly ionic or water-soluble

Important Information

- Strong acidic or basic drugs are not influenced by the pH of the media
- Always remain Ionic

Importance of pK value clinically 00:50:35

- **Example: Aspirin (pKa: 3.5)**

In Stomach (pH: 0-1)	• Aspirin behaves as lipid soluble or non ionic drug • Cross cell membrane barrier • Enter stomach cells
Inside stomach cells	• pH similar of blood pH (7.2-7.4) • Ionised, water soluble • Does not cross cell membrane and does not enter circulation
Trapped inside stomach cells	Ion trapping
Destroy stomach cells	Gastric ulcers

Ionization and non-ionization of the drug based on pH of the media 00:53:55

- The change in pH of media by 1 changes ionization by 10% (log10)
- **Example: Aspirin (pKa: 3.5)**

Media pH	Lipid solubility/ non ionized	Water soluble/ ionized
3.5	50%	50%
2.5	90%	10%
1.5	99%	1%
0.5	99.9%	0.1%

- Basic drugs are absorbed from small intestine (Duodenum) >>> stomach
- Acidic drugs are absorbed from small intestine (Duodenum) > stomach
- Drug absorption mainly depends on area of cell membrane than pH
  - Intestine has brush border cells
  - All drugs are absorbed from small intestine due to the greater surface area
- Acidic drugs are absorbed in greater proportion from the stomach

Q. Antacids mainly reduce the absorption of?

A. Acidic drugs

B. Basic drugs

Ans. Acidic drugs

- Antacids are basic drugs
- Neutralise HCl in stomach neutralising the pH
- More acidic drugs are absorbed from stomach
  - Antiepileptics
    → Phenytoin
    → Valproate
  - NSAIDs
    → Aspirin

3 PHARMACOKINETICS: ABSORPTION PART -2

Routes of drug administration

Local route

- The drugs act locally and are not absorbed into systemic veins

Types of local route

Topical

- Applying a drug on some surface like skin, or mucous membrane (buccal mucosa, rectal mucosa, vaginal mucosa)

Into a closed cavity

Intra arterial

- The drug is administered into an artery.
- By blocking the artery above the site of injection produces, it produces a local effect.
- E.g. In the case of limb cancer, intra-arterial injection is used to avoid the side effects of anti-cancer drug

Intra-articular

- Administered into a synovial space
- To control inflammation corticosteroids are given in conditions like osteoarthritis, rheumatoid arthritis

Intravesical

- Administered into the bladder
- Anti-cancer drugs like Mitomycin and BCG vaccine are given for superficial bladder cancer (initial stage)

Intrathecal

- Administered into CSF
- Like methotrexate for brain cancer are given through intra thecal route

Intravitreal

- Administered into vitreous humor
- Vitreous humor is produced once in a lifetime and the drug comes in direct contact with retina when administered through this route.
- **E.g.** Ganciclovir used to treat CMV retinitis (CMV-cytomegalovirus)

Systemic route

00:06:20

- Drugs are absorbed into systemic veins
- the drug enters the venous circulation and is distributed to the rest of the body by the heart

Types of systemic route

Enteral route

- Through the GIT
- Oral route (drug absorbed from stomach and small intestine)
- Sublingual (Keeping a drug below the tongue)
- Rectal route

Parenteral route

- Routes outside the GIT

Injectable route

- IV (intravenous)
- IM (intramuscular)
- IO (intraosseous)
- ID (intradermal)
- SC (subcutaneous)

Non-injectable route

- Transdermal (through skin)
  - In topical route the drug will remain on the skin, in transdermal the drug absorbed into the skin
- Inhalational

Systemic route

Enteral route

00:09:14

1. **Oral route**

- The drug gets absorbed through the small intestine and stomach (more through the small intestine due to its greater surface area)

Advantages	Disadvantages
• Safest route ○ If harmful molecule gets absorbed, the liver and intestinal enzymes removes these toxins • Cheapest route • Preferred route	• Cannot be given in an unconscious patient • Cannot be given in an emergency • Unpredictable Bioavailability

- Drugs given through the oral route undergo First pass metabolism

First-pass metabolism

00:11:45

Drug administered through oral route

↓

Absorbed from stomach and small intestine

↓

Drains first into portal vein

↓

Drug enters the Liver through portal vein → If the liver identifies the drug before it reaches the heart, then the liver degrades the drug. This is known as first-pass metabolism

↓

Reaches the heart through IVC from liver

↓

Drug is distributed to all other organs from the heart

E.g. If given 100 mg of the drug is given through oral route, only 40 mg of the drug is reaching the heart. So, 60 mg of the drug undergoes first-pass metabolism in the liver

- The final amount of the drug reaching the heart is known as Bioavailability
- Other areas where first-pass metabolism occurs include walls of the stomach and small intestine
- First-pass metabolism of the drug reduces the bioavailability of a drug

Hepatic clearance-calculating fist-pass metabolism

00:15:40

- First-pass metabolism of the liver also known as Hepatic clearance

$$\text{Hepatic clearance} = \frac{CA - CV}{CA} \times \text{Hepatic blood flow}$$

  - CA= Drug in the portal vein
  - CV= Drug in the IVC

- Hepatic blood flow = When the drug is taken orally, it is continuously supplied to the liver by portal vein

- Amount of blood degraded by the liver is called the extraction ratio i.e., $\frac{CA-CV}{CA}$

- E.g. if 100 mg of the drug is given through oral route and 40 mg of the drug enters the IVC. The extraction ratio is,

  $= \frac{CA-CV}{CA}$

  $= \frac{100-40}{100}$

  $= 0.6$ or 60%

  = Hence the liver degrades 60% of the drug.

Q. If a drug has a very high first-pass metabolism in the liver. Is this given orally or not?
Ans. Either they are not given orally or they are given in very high oral doses.

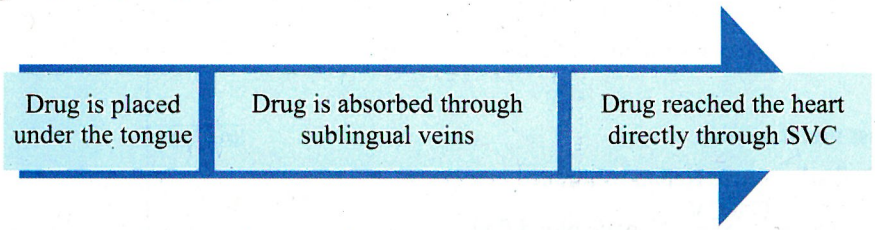
Drugs having high first-pass metabolism

Drugs not given orally	High oral dose drug
• Lignocaine	• Propranolol
• Fentanyl	• Morphine
• Natural steroids	• Verapamil
• Estrogen	• Pethidine
• Progesterone	• Salbutamol (Salbutamol is also given by syrups or tablets)
• Testosterone	• Nitrates
• Hydrocortisone	
• Aldosterone	

- Natural estrogen is not used in oral contraceptive pills because it has a very high first-pass metabolism
- Only synthetic estrogen known as ethenyl estradiol is given orally

Q. How to avoid (bypass) first-pass metabolism of the liver:
- By giving a drug by all other systemic routes except oral.
- Sublingual, rectal, and all parenteral routes

2. Sublingual or Buccal route



- Bypasses the first pass metabolism of liver
  - Example is sublingual nitrates
    - → Glyceryl trinitrate
    - → Isosorbide dinitrate
    - → It is the only drug for acute attack of angina
    - → All other anginal drugs for the prevention of angina

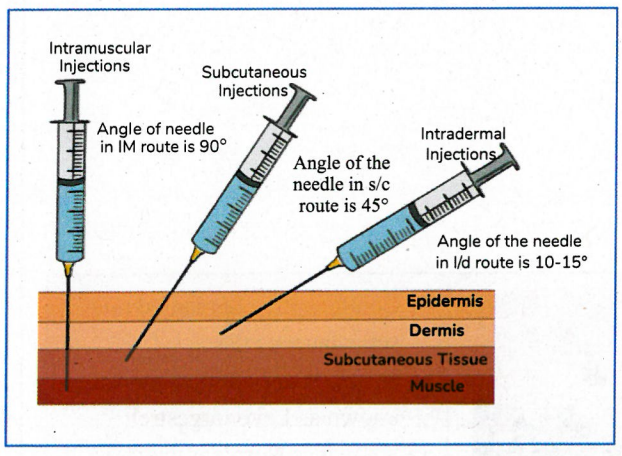
3. **Rectal route**
   - A drug given into the rectum is absorbed into a vein called an External hemorrhoidal vein
     - External hemorrhoidal vein is a tributary of IVC, hence the drug drains directly into the heart bypassing first-pass metabolism.
   - But, deeper in the rectum, the Internal hemorrhoidal vein is the tributary of the portal vein, thus the drug undergoes first-pass metabolism.
   - Example of rectal route: Rectal diazepam
     - It is the drug of choice for febrile seizures in children

Parenteral routes 00:30:30

- Injectable route

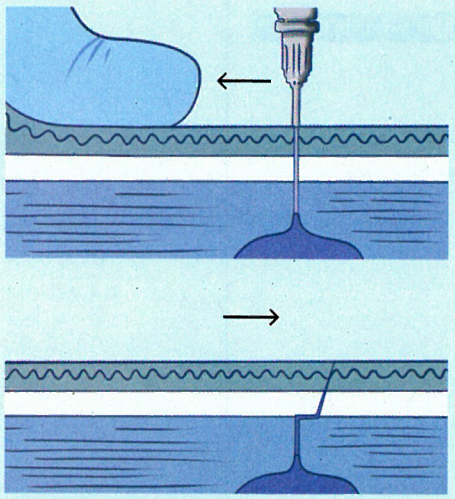
1. **Intravenous (IV)**
   - The drug is administered into a peripheral vein, and the vein directly goes to the heart
   - In the intravenous route there is no cellular barrier
   - IV route has 100 % bioavailability because there is no cellular barrier PYQ: INICET 2022
   - Dose titration of a drug is possible
     - It means, changing the dose slightly according to the effect of a drug , example:
     - Insulin produces hypoglycemia- reduce the dose
     - Insulin produces hyperglycemia- increase the dose
   - Dose titration done by two routes
     - Intravenous
     - Inhalational route (general anesthetics)
   - Intravenous is the route of choice in the emergencies, during surgeries
     → As intravenous route has predictable bioavailability

2. **IO (intraosseous)**
   - The drug is administered into a bone
   - The most common bone is the Tibia as it is a long bone, not covered by muscle, directly attached to the skin
   - IO route is preferred when IV route is not possible (during shock veins collapse)



3. **Intramuscular (IM)** 00:39:20
   - The drug is administered into the muscle
   - Water soluble drugs are rapidly absorbed due to the presence of a lot of blood vessels

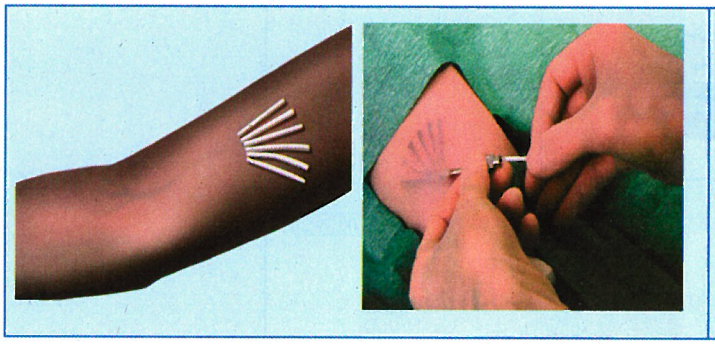
- DEPOT preparations
  - A rapidly absorbed drug can be converted into a slowly absorbed drug or a short-acting can be converted into a long-acting drug. by making a water-soluble drug into a lipid-soluble drug by attaching a lipid moiety
  - Example:
    - → Haloperidol (an antipsychotic drug) is a water-soluble drug, Fast onset of action.
    - → Attach one lipid moiety (undecanoate) to form an oily preparation thus making the drug longer acting
    - → This type of preparation is known as haloperidol decanoate
- Staining of subcutaneous fat
  - When IM injection is given, the fascia is punctured, and if the drug leaks back from this puncture site, it can lead to staining of subcutaneous fat.
  - E.g. Iron
  - Z (zigzag) technique



- When IM drug is administered, the skin is first pulled downwards, so that the fascia of the neighboring muscle is under the injection site.
- After administering, the skin is pushed back, and the fascia will be back to the normal position.
- This prevents the drug to be leaked from the puncture site avoiding staining of subcutaneous fat
- This technique is known as the zigzag technique
- Commonly used drugs
  - Iron dextran injection
  - Antipsychotic drugs

4. **Subcutaneous route (SC)**
   - The drug is administered by injection or a vacuum known as Dermoget.
   - Drug enters into subcutaneous fat, then absorbed into dermal blood vessels
   - Example:
     - Insulin
     - Low molecular weight Heparin

5. **Intradermal (ID)**
   - Given for allergic testing
   - Used in BCG vaccine



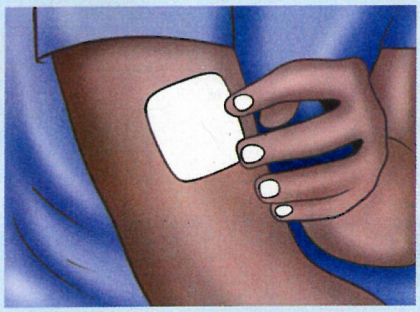
- Contraceptive implanted into subcutaneous tissue
- 6 rods of one contraceptive known as Levonorgestrel
- Known as Norplant which is implemented into subcutaneous fat

Transdermal route

00:48:30

Non injectable parenteral route

- Drug absorbed into the skin from a patch
- Through
  - Simple/passive diffusion
  - Absorption into dermal blood vessels



Dose of drug

- Depends on area of the patch and not on it's thickness
  - cm^2 or mm^2

Advantage

- Delivers constant amount of drug continuously around the clock
- Provides non fluctuating/constant drug level in the blood

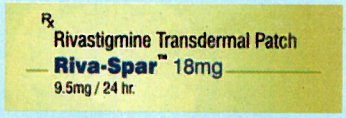
Site of maximum absorption

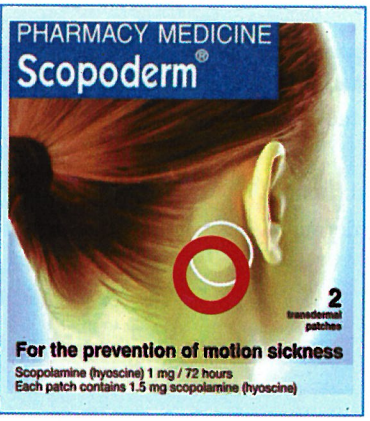
- Posterior auricular area- on mastoid process behind the pinna
- Scrotum
- Face and neck
- Posterior auricular area > scrotum > face and neck

Site of least absorption

- Hyperkeratinized areas (skin is thick)
- Palms and soles

Transdermal patch	Indication
Nicotine patch	Smoking cessation
Nitrate patch	Long-term treatment of chronic angina
Hyoscine (scopolamine, anticholinergic drug)	Motion sickness
Diphenhydramine (antihistaminic drug)	Motion sickness
Selegiline	Depression
Rivastigmine patch	Alzheimer's disease
Rotigotine patch	Parkinson's disease
Clonidine	Long-term treatment of hypertension
Natural estrogen/progesterone	In Postmenopausal women as hormone replacement therapy





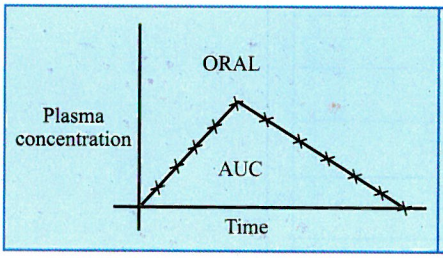
Inhalation 00:56:45

- Inhalational route can be local or systemic depending on the disease
- Example:
  - Bronchodilators given in asthma due to their local action on constricted bronchus
  - Anesthetic gases have systemic action as they are small molecules that enter the blood through alveoli and then cross the blood-brain barrier.
- Depending upon the particle size the drug enters the alveoli or remains in the bronchus
- To produce local action
  - Drug should have large particle size
  - 2-5 micron in diameter
- To produce systemic action
  - Drug should have a smaller particle size
  - < 2 micron in diameter

Bioavailability [F] 00:59:07

- Bioavailability is the fraction of the drug that reaches systemic circulation (veins)
- The unchanged form of drug reaching blood with time is Bioavailability
  - If drug is taken orally, it undergoes first pass metabolism
  - The drug that is not metabolized is unchanged form of drug
  - Drug takes certain time to reach blood after administration
- Bioavailability of intravenous route : 100%
  - IV route is taken as standard
    - → In calculating the bioavailability of other routes
- In remaining routes, bioavailability is < 100%
    - → Due to cellular barriers

Calculation of bioavailability- Concentration time graph



- If a drug taken orally,
  - The concentration of drug in blood increases slowly with respect to time and then it decreases
- In concentration time graph of that drug,
  - Area under the curve (AUC) – the total amount of blood that entered into circulation with time PYQ: INICET 2022