Introduction to Pharmacokinetics

Drug absorption

The process by which the drug enters into the systemic circulation from the site of administration (except IV route) through the biological membrane is called absorption of drug.

In case of IV the drug is not absorbed and it enters into the circulation directly.

- **Process of absorption:**

A. Simple transport

- ✓ Passive transport→Simple diffusion
- ✓ Filtration

B. Specialized transport

1. Active transport
2. Facilitated transport
3. Endocytosis
   - ✓ Phagocytosis
   - ✓ Pinocytosis
4. Ion transport
5. Ion paired transport

Simple transport

❖ **Passive diffusion**

Movement of a solute through a biological barrier from the phase of higher concentration to phase of lower concentration. No need of energy. Highly lipid soluble drugs transport by this mechanism.

Examples- aspirin, barbiturates, sulfonamides, morphine, pethidine etc.

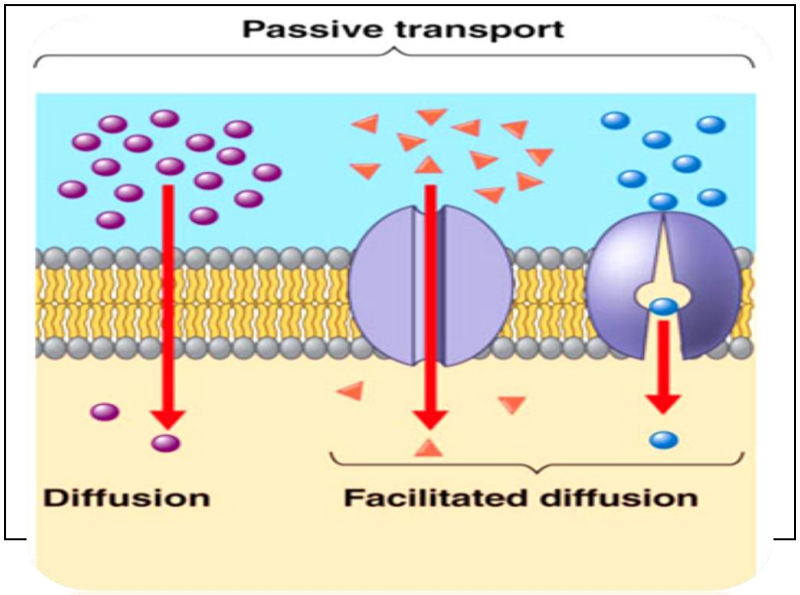
Simple diffusion is expressed by Fick's first law of diffusion -

"The drug molecules diffuse from a region of higher concentration to one of lower concentration until equilibrium is attained & the rate of diffusion is directly proportional to the concentration gradient across the membrane".

Characters

- Common
- Occurs along concentration gradient.
- Non selective
- Energy is not required
- No carrier is needed
- Depends on lipid solubility

- Depends on pka of drug and pH of medium.



❖ **Pore Transport or Filtration**

- Passage of drugs through aqueous pores in the membrane or through the paracellular spaces.
- Also known as convective (group of molecules within fluids) transport, bulk flow.
- Filtration is movement of water and solute molecules across the cell membrane due to hydrostatic pressure generated by the cardiovascular system.
- It is a kind of transport in which fluid is forced through a membrane because of a difference in pressure gradient on the two sides of a membrane
- Majority of cells (intestinal mucosa, RBC etc) have very small pore (4 A^o) and thus important in the absorption of low mol. Wt. (< 100).
- Low molecular size (smaller than the diameter of the pore) & generally water-soluble drugs.

  e.g. urea, water & sugars

  Rate of absorption via pore Transport depends on the number & size of the pores, & given as follows:

$$\frac{dc}{dt} = \frac{N.R^2.A.\Delta C}{(\eta)(h)}$$

Where,

$\frac{dc}{dt}$ = Rate of the absorption

N = Number of pores

R = Radius of pores

ΔC = Concentration gradient

η = Viscosity of fluid in the pores

h = Thickness of the membrane

Factors influencing the Rate of Net Diffusion of a Substance across a Membrane

Factor	Effect on Rate of Net Diffusion
↑Concentration gradient of substance	↑
↑Permeability of membrane to substance	↑
↑Surface area of membrane	↑
↑ Molecular weight of substance	↓
↑Distance (Thickness)	↓

Specialized transport

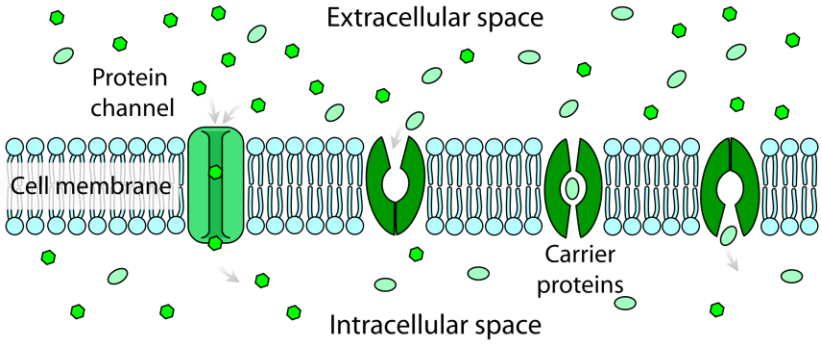
This can be carrier mediated or by pinocytosis.

1. **Carrier-mediated transport**

➔ Polar compounds like sugar and amino acids and certain drugs of therapeutic interest cannot penetrate through membrane by passive diffusion but are moved by a carrier system present on the membrane surface.

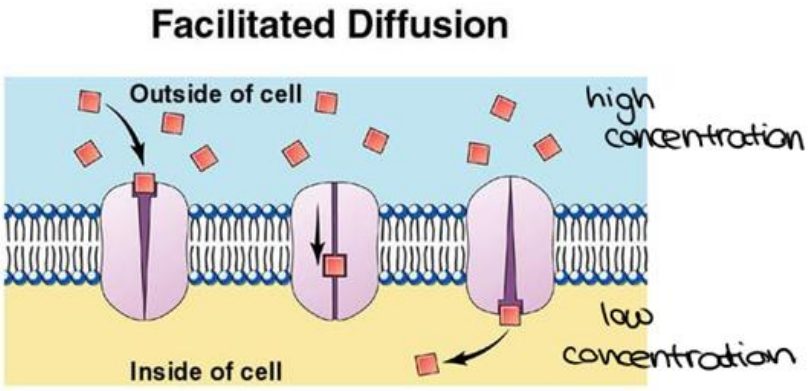
➔ Carrier molecules are usually proteins which combine with a drug substrate and form a complex.

➔ After the complex crosses the membrane; carrier dissociates from the drug and carrier returns to the original side of membrane for reuse.



2. **Facilitated diffusion**

Facilitated diffusion (also known as facilitated transport or passive-mediated transport) is the process of spontaneous passive transport of molecules or ions across a biological membrane via specific transmembrane integral proteins. Being passive, facilitated transport does not directly require chemical energy from ATP hydrolysis in the transport step itself; rather, molecules and ions move down their concentration gradient reflecting its diffusive nature. e.g. tetracycline, pyrimidine etc.



3. Active transport

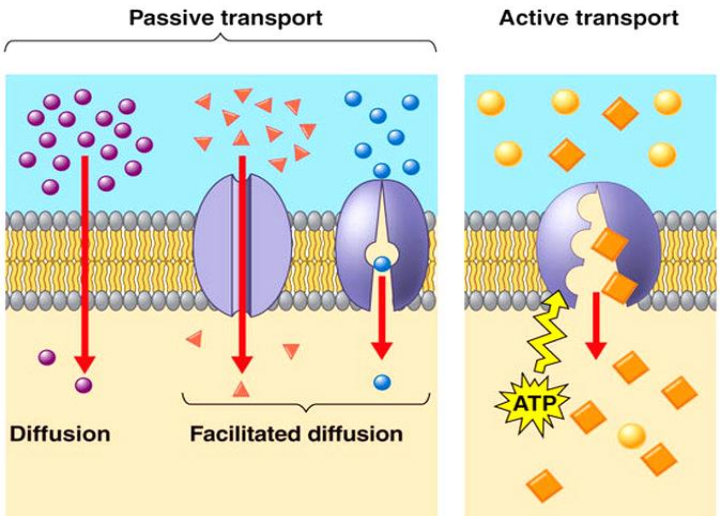
Active Transport is the mediated transport of biochemical and other atomic/molecular substances, across membranes that requires the expenditure of cellular energy to move molecules "uphill" against a gradient.

It also involves the use of a protein carrier to transfer a specific substance across the membrane, but against its concentration gradient (Low to high).

e.g. alpha methyl dopa, levodopa, 5-fluoro-uracil, 5 bromouracil.

Features:

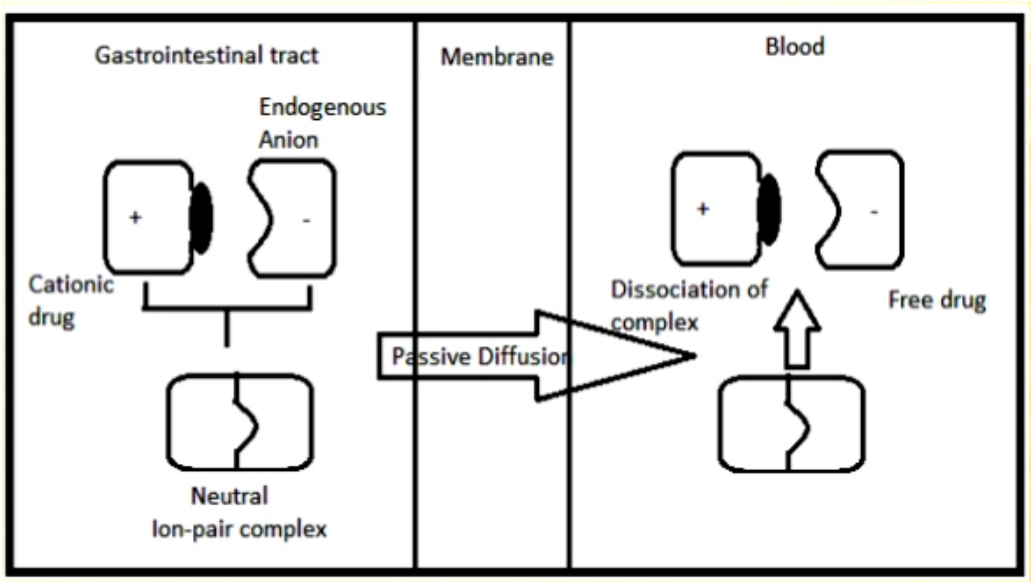
- ✓ Transport of drug is energy dependent
- ✓ Carrier mediated transport against a concentration gradient from lower to higher concentration
- ✓ Requires carrier and energy.
- ✓ Relatively unusual
- ✓ Specific



4. Ionic or Electrochemical diffusion

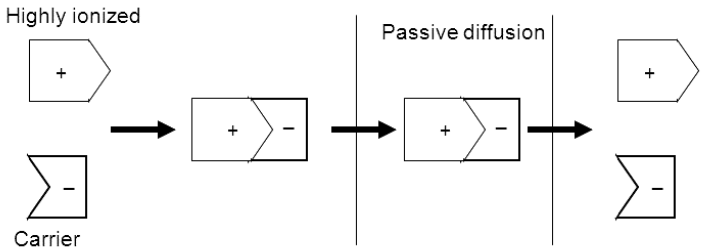
- ✓ Charge on membrane influences the permeation of drugs.
- ✓ Molecular forms of solutes are unaffected by the membrane charge & permeate faster than ionic forms.
- ✓ Once inside the membrane, the cations are attached to negatively charged intracellular membrane, thus giving rise to an electrical gradient.
- ✓ If the same drug is moving from a higher to lower concentration, i.e. moving down the electrical gradient , the phenomenon is known as electrochemical diffusion
- ✓ Thus, at a given pH, the rate of permeation may be as follows:

Unionized molecule > anions > cations



5. Ion pair transport

- ✓ It is another mechanism to explain the absorption of such drugs which ionize at all pH condition such as quaternary ammonium compounds, sulfonic acid
- ✓ Although they have low o/w partition coefficient values, they will penetrate the membrane by forming reversible neutral complexes with endogenous ions. e.g. mucin of GIT.
- ✓ Such neutral complexes have both the required lipophilicity as well as aqueous solubility for passive diffusion.
- ✓ This phenomenon is known as ion-pair transport.
- ✓ Fat soluble vitamins such as A, D, E, K and some anticancer drugs are absorbed by this way.

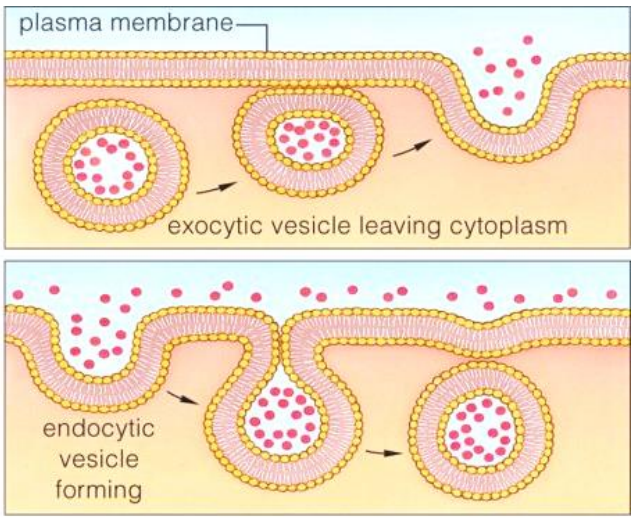


6. Vesicular Transport

Vesicular Transport is a mode of transport by which large particles are transported between the ECF and the ICF by being wrapped in a membrane-enclosed vesicle.

A substance transported out is by **exocytosis** and

A substance taken is by **endocytosis**.

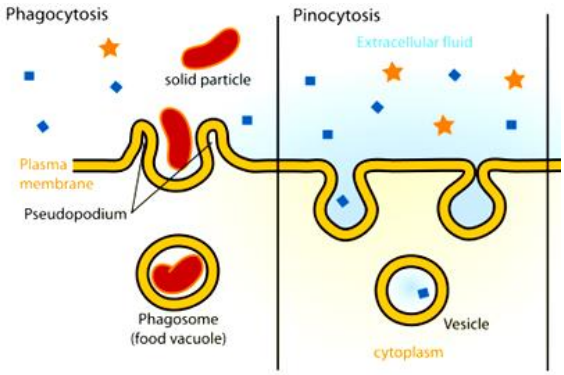


Endocytosis

- ✓ It involves engulfing extracellular materials within a segment of the cell membrane to form a vesicle which is then pinched off intracellularly
- ✓ It is used by all cells because most chemical substances important to them are large polar molecules that cannot pass through the hydrophobic portion of the cell membrane by passive means.
- ✓ Fats , starch , oil soluble vitamins, Insulin
- ✓ Absorbed into lymphatic circulation –bypassing first pass hepatic metabolism

In endocytosis, there are two process

1. Phagocytosis: if a large multimolecular substance is taken in it is called phagocytosis.
2. Pinocytosis: if a fluid is taken in it is called pinocytosis. This process is important in the absorption of oil soluble vitamins & in the uptake of nutrients.



- **Differences amongst different transport systems**

Characteristics	Passive diffusion	Facilitated diffusion	Active transport
Incidence	Commonest	Less common	Least common
Process	Slow	Quick	Very Quick
Movement	Along concentration gradient	Along concentration gradient	Against concentration gradient
Carrier	Not needed	Needed	Needed
Energy	Not required	Not required	Required

- **Factors affecting drug absorption**

❖ **Patient related factors**

- ❖ Physiological factor
- ❖ Clinical factor

❖ **Pharmaceutical factors**

- ✓ Physicochemical factors
- ✓ Formulation factors

❖ **Physicochemical factors**

1. Drug solubility and dissolution rate.
2. Particle size & effective surface area.
3. Polymorphism & amorphism.
4. Salt form of the drug
5. Drug pKa, lipophilicity & GI pH
6. Drug stability

1. Drug solubility & Dissolution rate

Rate determining process in the absorption of orally administered drugs are:-

1. Rate of dissolution
2. Rate of drug permeation through the biomembrane

2. Particle size & effective surface area

Particle size and surface area of a solid drugs are inversely related to each other.

Smaller particle size-> greater surface area->rapid dissolution

Micronization:

Hydrophilic drugs: grater surface area → rapid dissolution

E.g.: griseofulvin, spiranolactone

Hydrophobic drugs: decrease in effective surface area→ fall in dissolution rate

Causes

- Adsorption of air to surface
- Particle reaggregation

In that case add-surfactants –tween 80

E.g.: aspirin, phenacetin

3. Polymorphism and amorphism

Polymorphism: when substance exists in different crystalline forms, it is polymorphism.

Amorphism: these drugs can exist with no internal crystal structure.

Such drug represents the highest energy state and can be considered as super cooled liquids and thus have greater solubility. E.g. Novobiocin (antibiotic).

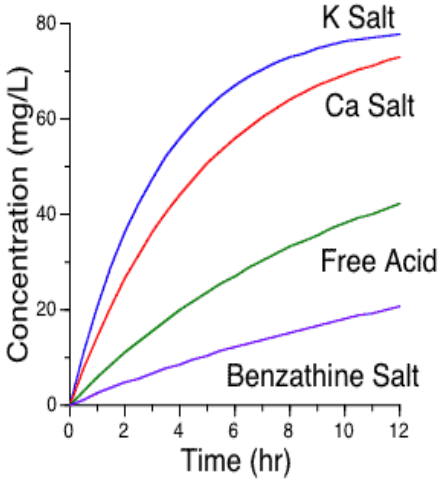
Thus, the order of Dissolution & hence Absorption for different solid dosage forms is

Amorphous > meta-stable > stable.

4. Salt form of the drug

Salt of weak acid and weak bases have much higher aqueous solubility than the free acid or base.

Therefore, if the drug can be given as a salt, the solubility can be increased and the dissolution thus can be improved.



Dissolution Profile of various salts

5. **Drug pKa, lipophilicity & GI pH**

Drug absorption by passive diffusion depend upon the following factor

- ✓ Dissociation constant of the drug i.e. pKa of the drug
- ✓ Lipid solubility of the unionized drug
- ✓ pH at the absorption site
- ✓ The amount of drug that exist in unionized form

pH partition Hypothesis

Simplest principle:

Unionized drug → High absorption

Ionized drug → Low absorption

High absorption → Weak Acid pKa>8 (Pentobarbital & aspirin)

Weak Base pKa<5 (Theophylline, caffeine)

Low absorption → Strong Acid (Disodium cromoglyate)

Strong Base (Guanethidine)

Lipophilicity

Only unionized drug having sufficient lipid solubility is absorbed into systemic circulation. So drug should have sufficient aqueous solubility to dissolve in the fluids at the absorption site and lipid solubility high enough to facilitate the partitioning of the drug in lipoidal membrane and into systemic circulation.

6. **Drug stability**

Two major stability problems are-

1. Degradation of the drug into inactive form

2. Interaction with one or more component either of the dosage form or those present in the GIT to form a complex that is poorly soluble

Drug distribution

Distribution in pharmacology is a branch of pharmacokinetics which describes the **reversible transfer of drug from one location to another within the body**.

Once a drug enters into systemic circulation by absorption or direct administration, it must be distributed into **interstitial and intracellular fluids**. Each organ or tissue can receive different doses of the drug and the drug can remain in the different organs or tissues for a varying amount of time.

The distribution of a drug between tissues is dependent on →

- ✓ Vascular permeability
- ✓ Regional blood flow
- ✓ Cardiac output and perfusion rate of the tissue
- ✓ Ability of the drug to bind with tissue and plasma proteins
- ✓ Lipid solubility of the drug
- ✓ Ionization at physiological pH
- ✓ Presence of tissue specific transporter

The drug is easily distributed in highly perfused organs such as the liver, heart and kidney. It is distributed in small quantities through less perfused tissues like muscle, fat and peripheral organs. The drug can be moved from the plasma to the tissue until the equilibrium is established.

- ❖ **Apparent volume of distribution (V):**

Presuming that the body behaves as a single homogenous compartment with volume V into which drug gets immediately and uniformly distributed.

V = dose administered i.v / plasma concentration

E.g. suppose total drug in the body is 1000mg and plasma drug concentration is 50mg/L. So apparent volume of distribution is 20L.

- ❖ **Plasma protein binding of drug:**

It means the **bonding between drug and plasma proteins** usually by **weak ionic bond**. This bonding takes place until the **conc. of plasma protein and drug conc. is saturated**. The rest drugs remain in free form. The **free form of drug produces actions, metabolized and excreted**.

Drugs extensively bound to plasma proteins are largely restricted to the vascular compartment and have low value. E.g. Diclofenac and warfarin (99% bound) 'V' = 0.15L.

Lipid insoluble drugs do not enter into cells. So 'V' approximates extracellular fluid volume.

E.g. Streptomycin (0.25L).

Drugs stored in other tissues may have 'V' much more than total body water or even body mass.

E.g. Propranolol (4L), digoxin (6L) because most of the drugs is present in other tissues and plasma conc. is low.

Most drugs possess physicochemical affinity for plasma proteins.

- ✓ **Acidic drugs** generally bind to **plasma albumin** (Barbiturates, Benzodiazepine)
- ✓ **Basic drugs** bind to **α_1 acid glycoprotein** (β-blocker, lidocaine)

- ✓ **Highly plasma protein binding drugs** are largely restricted to the **vascular compartment** because protein bound drugs do not cross membranes (except through large paracellular spaces, such as in capillary). They have **smaller volumes of distribution**.
- ✓ The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of free drug is reduced due to elimination. **Plasma protein binding acts as temporary storage of the drug**. (Penicillin)
- ✓ **High degree of protein binding** generally makes the drug **long acting**, because bound fraction is not available for metabolism or excretion.

- ❖ **Redistribution:**

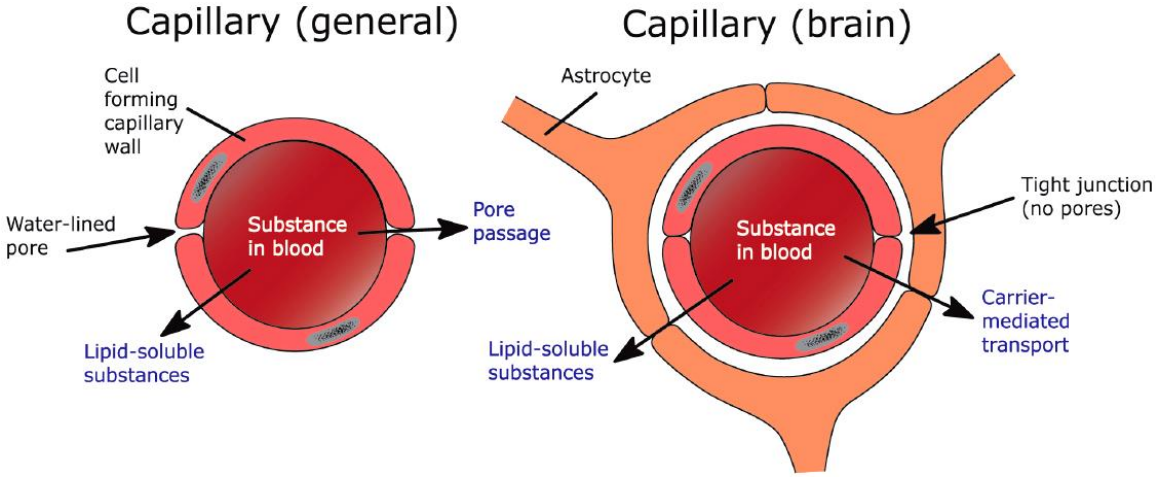
Highly lipid soluble drugs get initially distributed to **organs with high blood flow**, i.e. brain, kidney, heart etc. later, **less vascular** but more bulky tissues (muscle, fat) take the drug → plasma conc. falls and the drug is withdrawn from these site.

If the site of action of the drug is highly perfused organs, redistribution results in termination of drug action.

E.g. Anaesthetic action of thiopentone sodium inj. is terminated in few minutes due to redistribution.

- ❖ **Penetration into brain:**

Blood brain barrier (BBB): Endothelial cells are closely adherent to each other. A basement is present. A layer of astrocyte is present. This barrier is lipoidal and limit the entry of non-lipid drug. E.g. streptomycin. Exception- levodopa.



❖ **Passage into placenta:**

Placental membranes are lipoidal and allow free passage of lipophilic drugs, while restricting hydrophilic drugs. Placental **efflux P-gp** also serves to limit fetal exposure to maternally administered drugs. However, restricted amounts of **nonlipid soluble drugs**, when present in **high concentration** or for **long period in maternal circulation**, gain access to the fetus. **Some influx transporters** also operate at the placenta. Thus it is **incomplete barrier** and almost any drug taken by the mother can affect the fetus or the newborn (drug taken before delivery, e.g. morphine)

Metabolism / Biotransformation

Biotransformation means chemical alteration of the drug in the body.

It is needed to convert the nonpolar (lipid-soluble) compounds into polar (lipid insoluble) so that they are not reabsorbed in the renal tubules and are excreted.

Most hydrophilic drugs, e.g. streptomycin, neostigmine etc. are little biotransformed and are largely excreted unchanged.

The primary site for drug metabolism is liver. Others are kidney, lungs and plasma.

Biotransformation of the may lead to the following-

i. **Inactivation:**
   Most drugs and their active metabolites are rendered inactive or less active.
   E.g. Paracetamol, ibuprofen etc.

ii. **Active drugs are converted into active metabolites.**
   E.g. Morphine to morphine-6-glucuronide

iii. **Activation of inactive drug:**
   Few drugs are inactive and need conversion in the body to one or more active metabolites.
   Such drugs are called prodrugs.
   E.g. Levodopa → dopamine, Aspirin → salicylic acid

Biotransformation reactions can be classified into:

1. **Phase I / Non-synthetic / Functionalization reactions:**

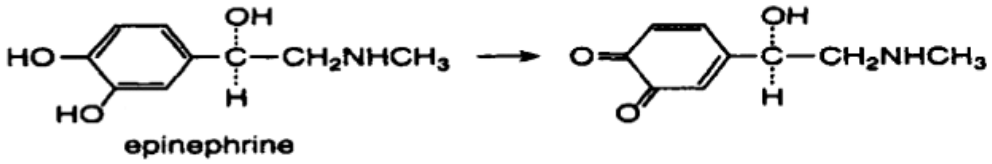
In phase I reaction, the drug is converted to a more polar metabolite by introducing a functional group (-OH, -NH_2, -SH etc.) following oxidation, reduction or hydrolysis reactions. If the phase I metabolite is sufficiently polar, it will be excreted in the urine.

Phase I reactions include:

- ✓ **Oxidation:**

  This reaction involves addition of oxygen / negatively charged radical or removal of hydrogen / positively charged radical. Oxidations are the most important drug metabolizing reactions. Various oxidation reactions are:

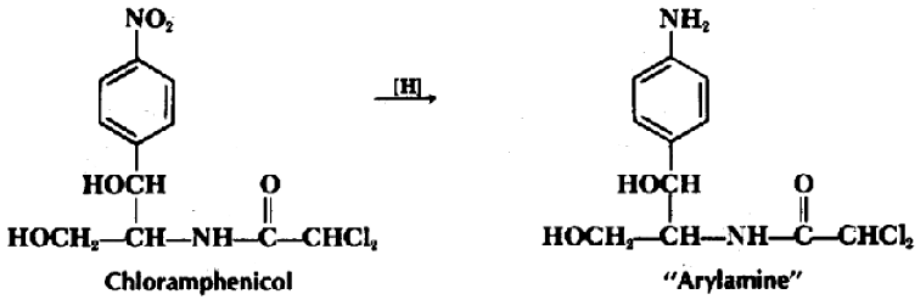
  Hydroxylation; oxygenation at C, N or S atoms; N or O-dealkylation; oxidative deaminatrion.



- ✓ **Reduction:**

  This is opposite reaction of oxidation. Alcohols, aldehydes, quinones are reduced.

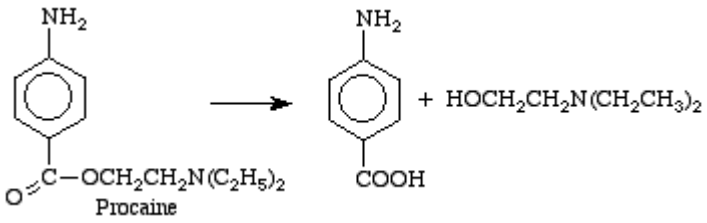
  Drugs primarily reduced are chloramphenicol, halothane, warfarin etc.



- ✓ **Hydrolysis:**

  The cleavage of drug molecule by taking up a molecule of water. Amides and peptides are hydrolyzed by amidase and peptidase. Hydrolysis occurs in liver, plasma and other tissue.

  Ester + Water → Acid + Alcohol



2. Phase II / Synthetic reactions:

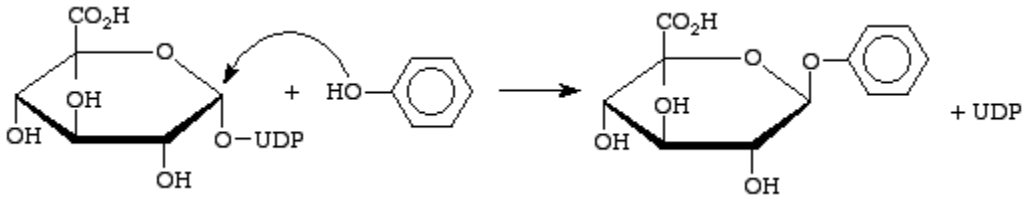
These involve conjugation of the drug or its phase I metabolite with an endogenous substrate (such as glucuronic acid, sulfuric acid, acetic acid, glycine etc.), generally derived from carbohydrate or amino acid, to form a polar highly ionized organic acid, which is easily excreted in urine or bile. Conjugation reactions have high energy requirement.

Phase II reaction includes-

- ✓ **Glucuronide conjugation:**

  Compounds with hydroxyl or carboxylic acid groups are easily conjugated with glucuronic acid which is derived from glucose.

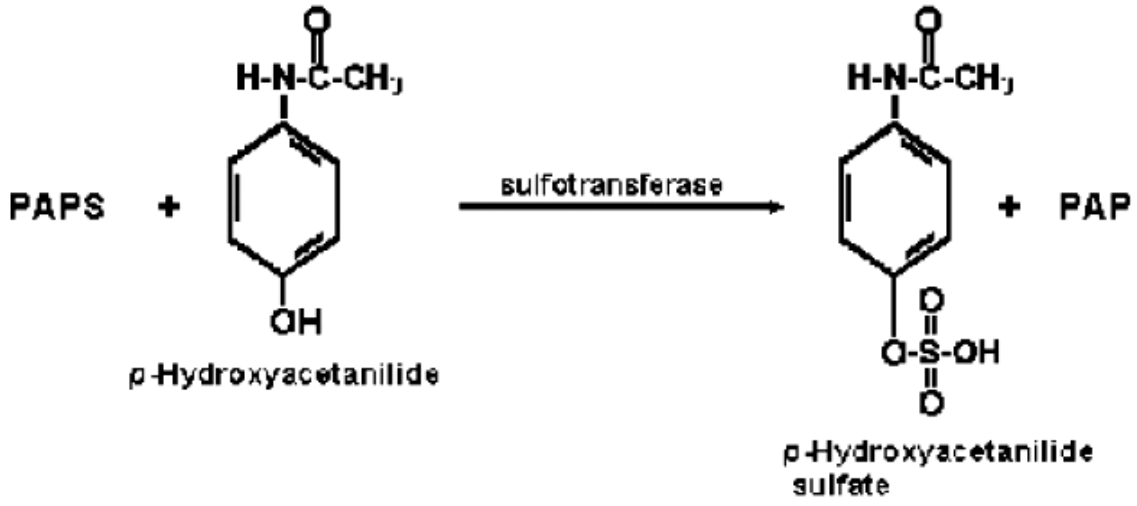
  E.g. Aspirin, chloramphenicol, paracetamol etc.



- ✓ **Sulfate conjugation:**

  The phenolic compounds and steroids are sulphated by sulphotranferase (SULT).

  E.g. chloramphenicol, methyldopa etc.



- ✓ **Methylation:**

  The amines and phenols can be methylated. Methionine and cysteine acting as methyl donors.

  E.g. adrenaline, histamine etc.

- ✓ **Acetylation:**

  Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A.

  E.g. sulfonamides, clonazepam etc.

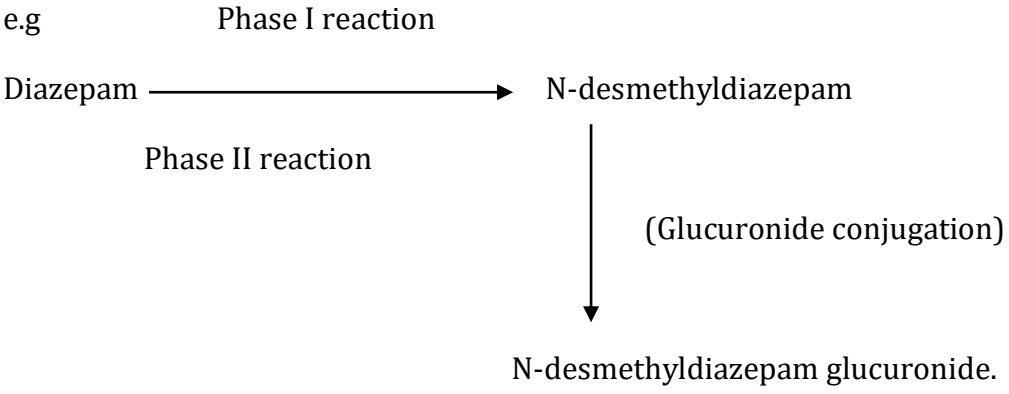
- ✓ **Glycine conjugation:**

  Salicylates and other drugs having carboxylic acid groups are conjugated with glycine.

- ✓ **Glutathione conjugation:**

  It inactivates highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs.

  E.g. paracetamol.



Excretion

The transportation of the drug and / or its metabolites out of the body is known as excretion.

Organs involved in excretion:

Kidney, liver, intestine, respiratory tract, sweat glands, lacrimal glands, vagina, seminiferous tubules, nails, hairs, mammary glands are involved in excretion of drugs.