



Solution-Pharmacy

Pharmacodynamic and Pharmacokinetics

Note- This is a point wise, image rich explanation. It's beyond our capacity to cover all point.

<http://watcut.uwaterloo.ca/webnotes/Pharmacology/DrugMetabolism.html>

<https://www.msdmanuals.com>

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Pharmacology

Pharmacodynamic & Pharmacokinetic ADME

(Absorption-Distribution-Metabolism- Elimination)

Pharmacology- Pharmacology is made-up of two main words- 'Pharma' + 'Logy' in some books there is Pharmakon in the place of Pharma, but to make you better understand we have made little changes. **Pharma is related with drug or medicine and logy means- to study.** So if we merge these two words together, this will become- **PHARMACOLOGY**.

“To study the complete life cycle of drugs as per pharmacodynamic and pharmacokinetic profile is known as Pharmacology” now again we have got two new words- Pharmacodynamic and pharmacokinetic. Let's understand them also.

Pharmacodynamic- **Pharmacodynamic is a study of drug's effect on body, so we can say it's a study of- what does DRUG do to the BODY.** Let's illustrate it in a very easy language.

Explanation- When you will ask a question from yourself- why we take medicine then you will get a simple answer and that is- just to get relief from the problem which we are facing. So once we took medicine we will start being healthy and our associated problem will slowly disappear. This is actually what we expect from medicine, but is this real story or something else is hidden. Yes there is another part which is in the dark side. It is not always possible to achieve only desired or therapeutic action from any drug we have taken, drug may produce desirable or undesirable effect, which include- side effect, toxic effect, adverse effect, Teratogenic effects etc.

Tips- If you want to memorize this and clear the doubt between pharmacodynamic and kinetic then use one tip-

Pharmacodynamic- What does **DRUG**¹ do to the **BODY**². Means is Drug is in the first line. (**D** of Dynamic and **D** of Drug is in continues mode)

Every drug has a special mechanism of action to produce that effect for which it is used for. So now its turn to understand mechanism of action-

Mechanism of action- The simplest explanation for MOA is- How any drug gives its effect, and again the answer is in the question itself, we take any of drugs when there is some abnormality due to any of reason so drug will try to normalize that factor and try to maintain homeostatic condition.

Example- In case of diabetes there is two main reasons- first the **Beta cell is not able to make enough Insulin** and second- **Beta cells are completely destroyed and not able to make any of insulin.** In both case there is deficiency of insulin, so our aim of treatment is to make insulin available to the body and for that we have to take such medicine which will either increase the production of insulin by stimulating beta cells or in case of second condition we should take insulin from external sources. These two are the mechanism of action (Replacement) of Insulin in management of diabetes. (Somewhere- Principle)

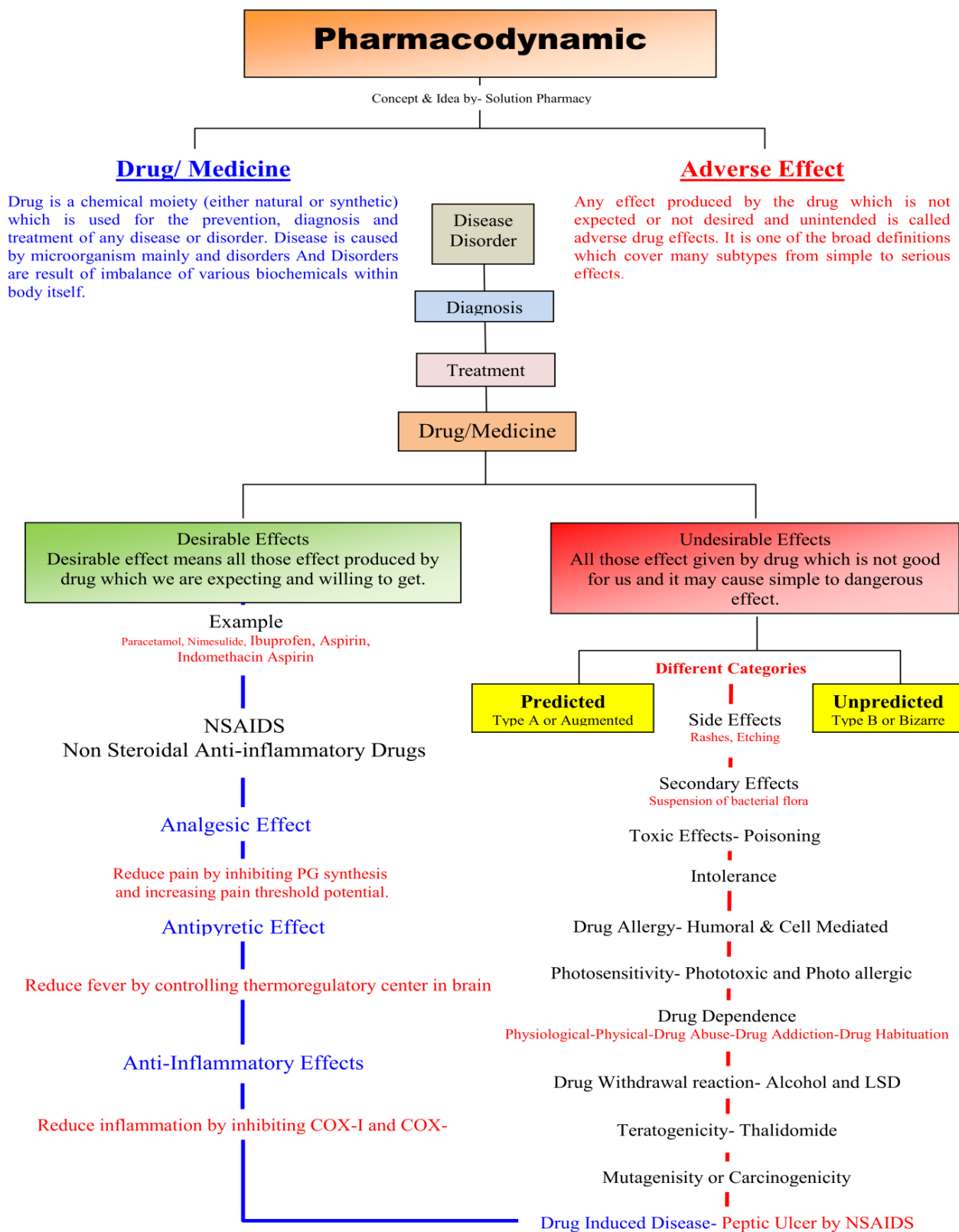


Figure 01- Effect of drugs in body (Pharmacodynamic)

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Principle of Drug Action

Irritation

Example- Counter Irritant
like- drugs for constipation

Irritation- There is few drugs which irritate the site of action and produce there effect. Example- Senna and some other drug used in constipation irritate the intestine and increase defecation. Other balm in case of headache will irritate the forehead tissue and gives relief from pain for short duration.

Stimulation

Example- Adrenaline. Stimulates heart, pilocarpine stimulates salivary glands.

Stimulation- Stimulation means to increase the function of any specialized organ, which will result in extra work, like in case of fear or fight adrenaline is get secreted and heart rate increase which give FFF response.

Depression

Example- Barbiturate depresses CNS, Quinidine depresses heart, and Omeprazole depress gastric acid secretion.

Depression- The simple meaning of depression is the reduction of specialized activity. For example- Barbiturate and benzodiazepine depress the CNS and give depression action. As same Omeprazole reduce gastric acid secretion.

Replacement

Example- Levodopa in Parkinson's, Insulin in diabetes and Iron in Anemia.

Replacement- When any hormone or biochemical substance is in inadequate quantity and there recovery is not possible then there is one option of replacement. The replacement is done for insulin in case of insulin dependent diabetes; here insulin is given by injection to maintain the requirement

Cytotoxic

Selective Cytotoxic action on invading parasite or cancer cell without affecting host cell.
Example- Penicillin, Chloroquine, Zidovudine, cyclophosphamide.

Cytotoxic- When there is entry of any parasite, or there is no other option to control the growth of own body cell then Cytotoxic drugs are used. They kill the microorganism or kill the uncontrolled and excessive growing cells.

**ACTION
COMPLETE**

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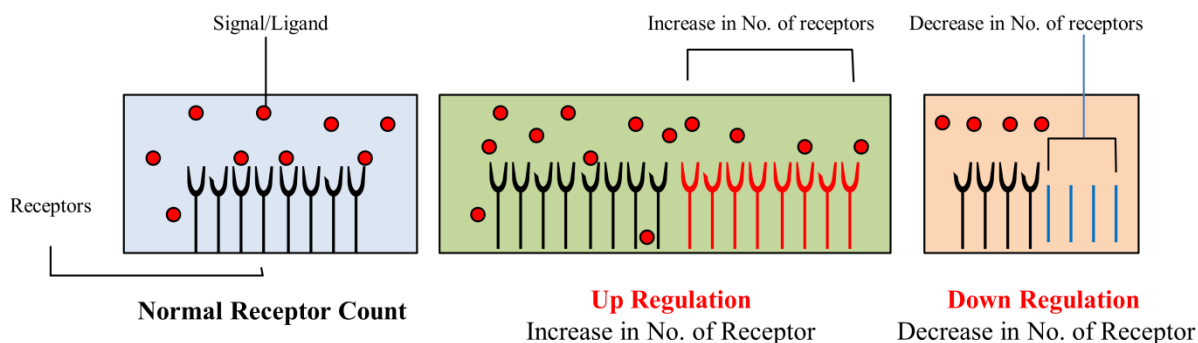


Some Important Diagrammatic Representation of Pharmacodynamic

Receptors Upregulation and Downregulation

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Downregulation- An example of downregulation is the cellular decrease in the number of receptors to a molecule, such as a hormone or neurotransmitter which reduces the cell's sensitivity to the molecule. This is an example of a locally acting (negative feedback) mechanism



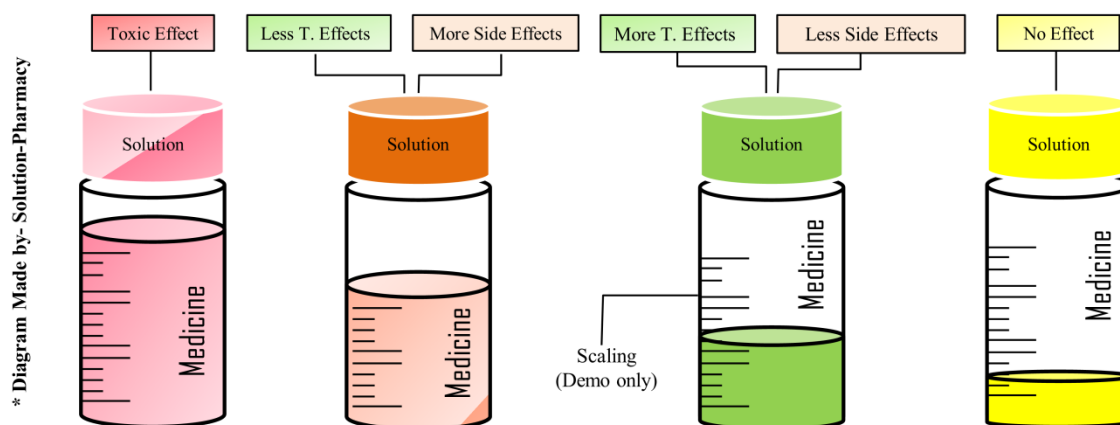
Upregulation- An example of upregulation is the response of liver cells exposed to such xenobiotic molecules as dioxin. In this situation, the cells increase their production of cytochrome P450 enzymes which in turn increases their degradation of these molecules

*** Diagrams and Explanations by- Solution-Pharmacy**

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DOSE TITRATION

Titration is the process of determining the medication dose that **reduces symptoms** to the **greatest possible degree** while **avoiding possible side effects**. If the dose is too small than that will not be able to produce desired effect and if the dose is too high it may or may not give desired effect but more than that it will give side effects. The titration method involve finding of that suitable dose which will give effect which we want without any side effects (Ideal, but generally give very few) www.facebook.com/pharmavideo/

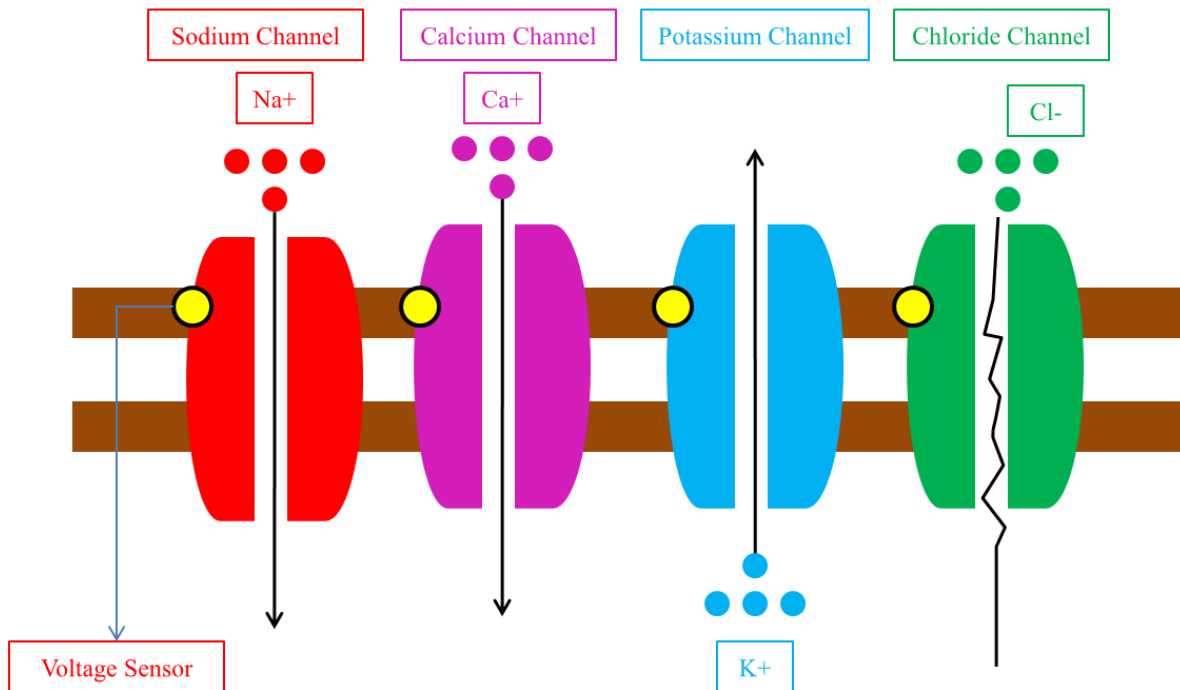


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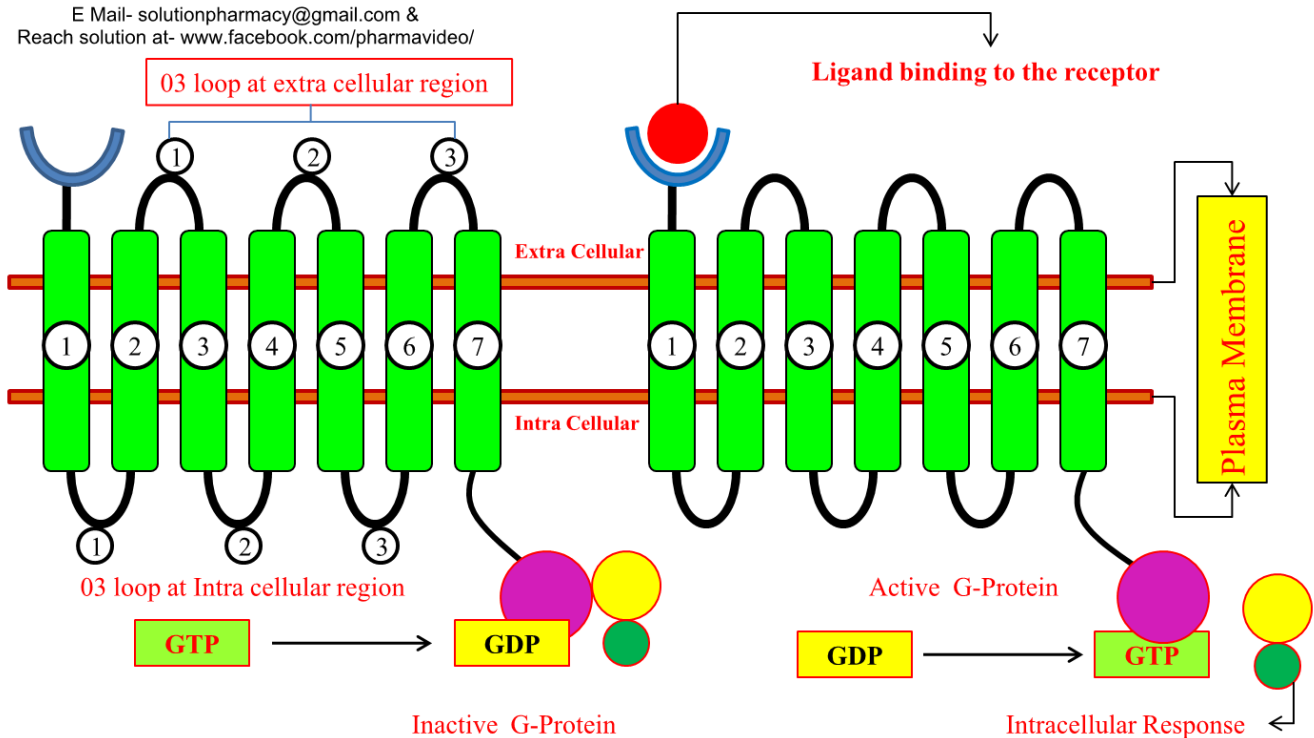
Types of voltage gated ion channels



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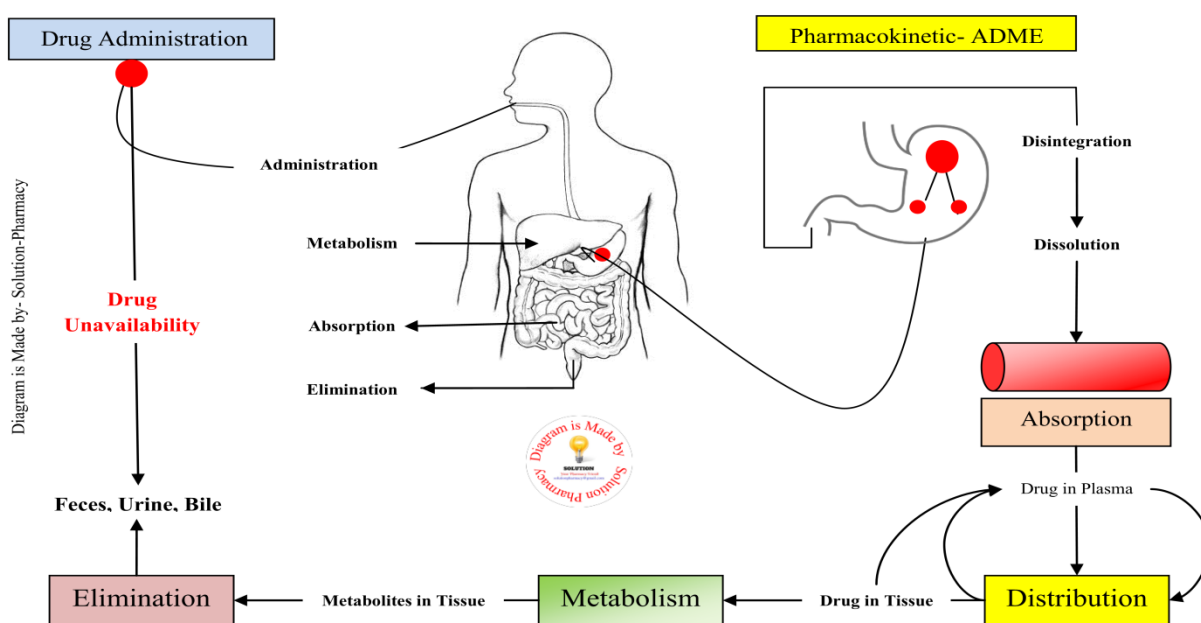
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Pharmacokinetic

Pharmacokinetic- “What does **BODY**¹ do to the **DRUG**²” we have simple interchanged the BODY and DRUG to make a definition. And as per the definition our body responds to any drug by giving **ADME** effects.

1. **A** stands for - Absorption
2. **D** stand for - Distribution
3. **M** stand for - Metabolism
4. **E** stands for - Elimination or Excretion



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Absorption- Absorption means reaching of drug into blood vessels for further distribution. Until drug is absorbed it will not be able to produce its effect so absorption of drug is important and it is obviously done by body. Absorption has several phases and this includes-administration of drug by any of the available dosage form, here in above diagram we have taken oral route of drug administration. Once the drug reach into stomach it get disintegrated into small partials than it is get dissolved by the fluid available in stomach. Then these drug moves towards a small intestine from where they usually get absorbed into circulation. Drug given by other than oral route directly reach the systemic circulation and they don't need to get disintegrated because they are already in liquid form.



Transport Process Across Cell Membrane

Transport of drug from small intestine to the systemic circulation takes place by many methods like-

1. **Passive Diffusion**- Does not need energy for the movement till equilibrium achieved. Drugs diffuse across a cell membrane from a region of high concentration (GI fluids) to one of low concentration (blood). Diffusion rate is directly proportional to the gradient but also depends on the molecule's **lipid solubility, size, degree of ionization, and the area of absorptive surface**. Because the cell membrane is lipid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones.

2. **Active Transport**- Need energy. Active transport is selective, requires energy expenditure, and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances like- **ions, vitamins, sugars, amino acids**. These drugs are usually absorbed from specific sites in the small intestine.

3. **Endocytosis and Exocytosis**- Process of engulfing either Pinocytosis or Phagocytosis. In Pinocytosis, fluid or particles are engulfed by a cell. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. Energy expenditure is required. Pinocytosis probably plays a small role in drug transport, **except for protein drugs**.

4. **Carrier mediated transport** – Need some molecule which will carry and drop the substance. Certain molecules with low lipid solubility penetrate membranes more rapidly than expected. One theory is facilitated passive diffusion: A carrier molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. In such cases, the membrane transports only substrates with a relatively specific molecular configuration, and the availability of carriers limits the process. The process does not require energy expenditure, and transport against a concentration gradient cannot occur.



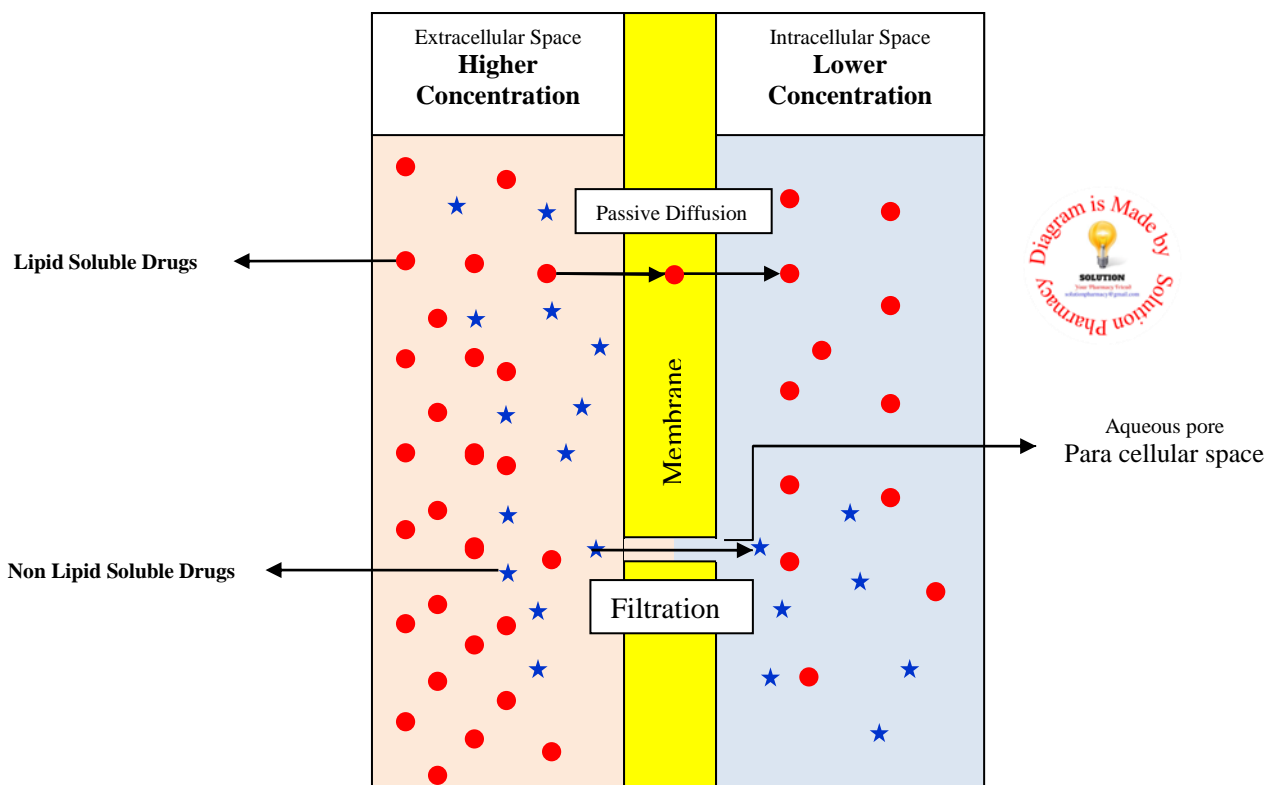


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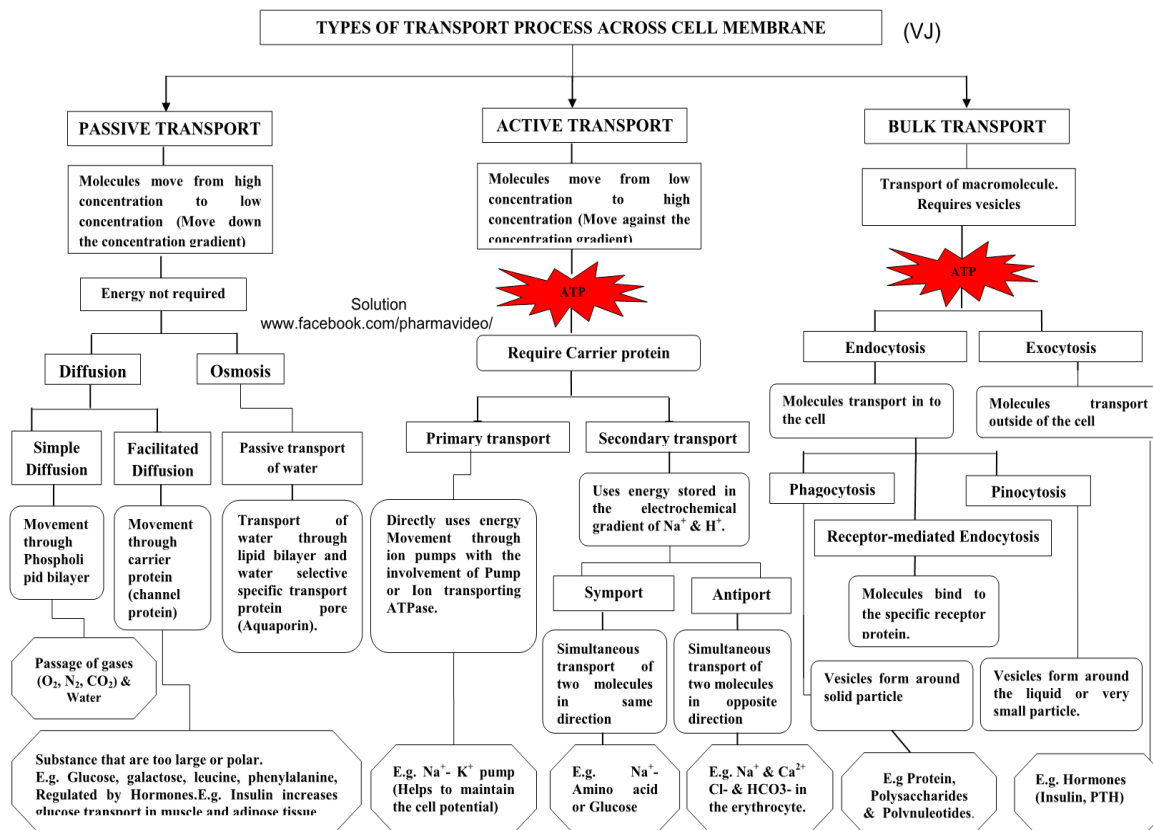
Diagram made by Solution Pharmacy. Idea- KD Tripathi

Passive diffusion and filtration across the lipid biological membrane.

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Bioavailability

Bioavailability means- “The rate and extent of absorption of drug from its dosage form”

Bioavailability is very important for any drug for its action point of view. The more bioavailability will be more drug action and less bioavailability means less availability of drug thus less action. Bioavailability of drug given by oral route is never 100% but the drug given by Systemic route is considered to be 100%.

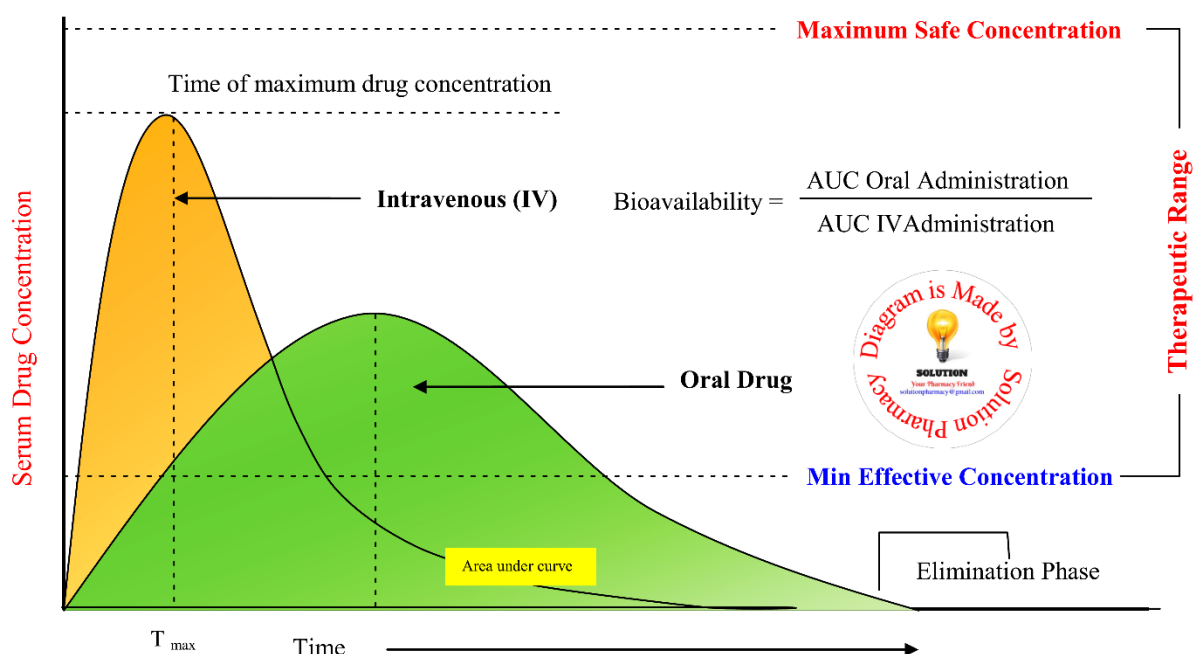


Image- Bioavailability- Plasma drug concentration Vs Time Graph, along with various indications

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Factor affecting Bioavailability-

S.N.	Pharmaceutical Factors	Pharmacological Factors
01	Partial Size	Gastric emptying and gastric motility
02	Salt form	Gastrointestinal disease
03	Crystal forms	Food and other substances
04	Water of hydration	First pass effects
05	Nature of Excipients	Drug-drug interaction
06	Degree of Ionization	Pharmacogenetic Factors
07	Formulation Factors	Emotional Factor (Psychological Factors)

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Factors affecting Bioavailability

Pharmaceutical factors

Partial Size

Smaller the partial size the greater will be surface area and greater surface area will have more dissolution, and more dissolution will result in more bioavailability

Salt Form

Salt of weakly acidic drug are more water soluble. Free acidic drug is precipitated from this salt in a micro crystalline form so they show enhanced bioavailability

Crystal Form

Amorphous form of drug is more water soluble and hence having more bioavailability than of crystalline form. **Example- Chlourmphenicol palmitate**

Water of Hydration

Anhydrous form of caffeine, theophylline and Ampicillin has faster dissolution rate and better bioavailability than hydrous form of the drug.

Nature of Excipients

There are so many additive used in the production of tablet, capsule and many other formulation. The strength and concentration of binding agent used in tablet preparation affect its disintegration and dissolution rate, and as we have already seen that dissolution rate affect the bioavailability. More dissolution means more bioavailability. So more binding agent are of poor bioavailability

Pharmacological factors

Gastric Emptying

Factor that accelerate gastric emptying permit drug to reach the large absorptive surface of small intestine sooner and increase the bioavailability

GIT Disease

In gastroenteritis there is decreased absorption of drug given orally. There is much other condition which will affect the absorption of drug and hence decrease the bioavailability, like- diarrhea

Food and other substance

In general gastrointestinal absorption of drug is favored by the empty stomach and reduced in the presence of other food materials. Absorption of tetracycline is getting reduced in the presence of milk in the stomach. Absorption of certain antifungal drug is get rapidly absorbed in the presence of fatty food.

First Pass Effect

All drug taken orally shows first pass metabolism and it means their degradation is possible thus as compare to parental administration their bioavailability is low.

Drug- Drug Interaction

Drug- drug interaction is one of the most important factors which affect bioavailability. **Example- liquid paraffin decrease the absorption of vitamin A**

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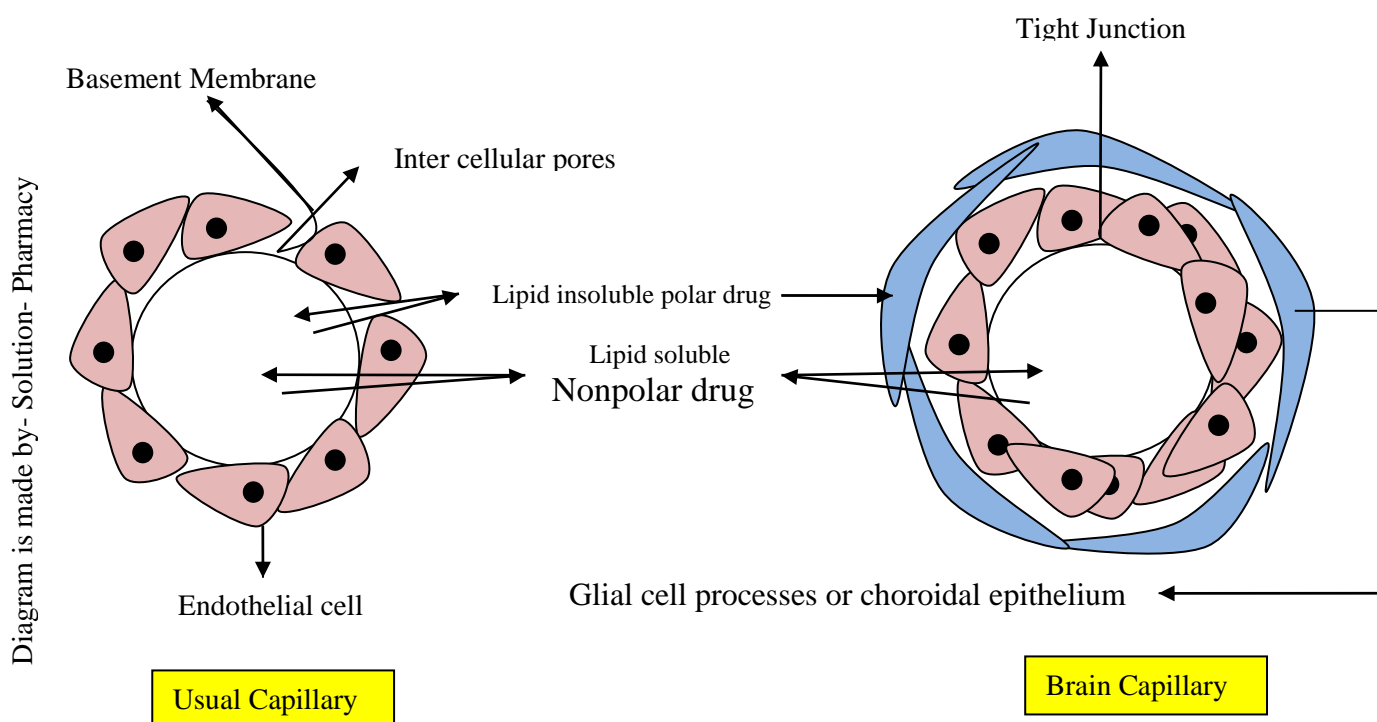
Distribution

Distribution is very important to achieve the homeostasis between all body compartments. When drug is administered into body and it reached into blood vessels, its distribution starts as per the concentration gradient. The extent of drug distribution is depends on **lipid solubility, ionization and physiological pH**. Movement of drug proceeds till the equilibrium is achieved between unbound drug in plasma and tissue fluid.

Drug distribution can be defined as the movement of drug between blood and extra vascular tissues. As drug absorption occurs, drug transfers to the blood, resulting in a concentration gradient across the capillaries, allowing filtration of drug into the interstitial fluid. The accumulated drug in the interstitial fluid drives its passive diffusion into tissues and organs.

The apparent volume of distribution (VD) is the volume of fluid in which the total drug dose would theoretically have to be diluted to produce the observed drug concentration in the blood plasma. It can be calculated as follows:

$$\text{Apparent volume of distribution} = \frac{\text{amount of drug in body}}{\text{drug concentration in plasma}}$$



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The drug distribution is usually varied, and depends on several factors such as- blood perfusion, tissue binding, regional pH, cell membrane permeability. Additionally, the rate at which a drug enters into a tissue depends on- the flow of blood to the tissue, the mass of tissue, and the barrier existing between blood and tissues.

Redistribution – Highly lipid soluble drugs get distributed to that organ which has high blood flow like- **brain, heart kidney** etc. later, less vascular but more bulky tissue like- **muscle, Fat** take up the drug, plasma concentration fall and drug is withdrawn from these site. If the site of action of drug was one of the highly perfused organs redistribution results in termination. Greater the lipid solubility of drug faster is the redistribution.

Binding- The distribution of a drug in the body also depends on the extent to which the drug binds to proteins and tissues in the body. **Only drugs that are unbound to proteins and other components in the blood are free to diffuse across the cell membranes into the tissues of the body.** The most important proteins in the blood that can affect the distribution of a drug include the plasma protein albumin, the alpha-1 acid glycoprotein, and lipoproteins. It is observed that **albumin binds acidic drugs**, in general, while more **basic drugs bind to the lipoproteins and acid glycoprotein.** Although proteins are the most common binding sites in the blood, there are other molecules in the blood to which a drug molecule may bind.

As only the unbound drug can be utilized in extra vascular and tissue sites, it is important to establish or estimate the unbound drug fraction in the blood. The following equation is used for this:

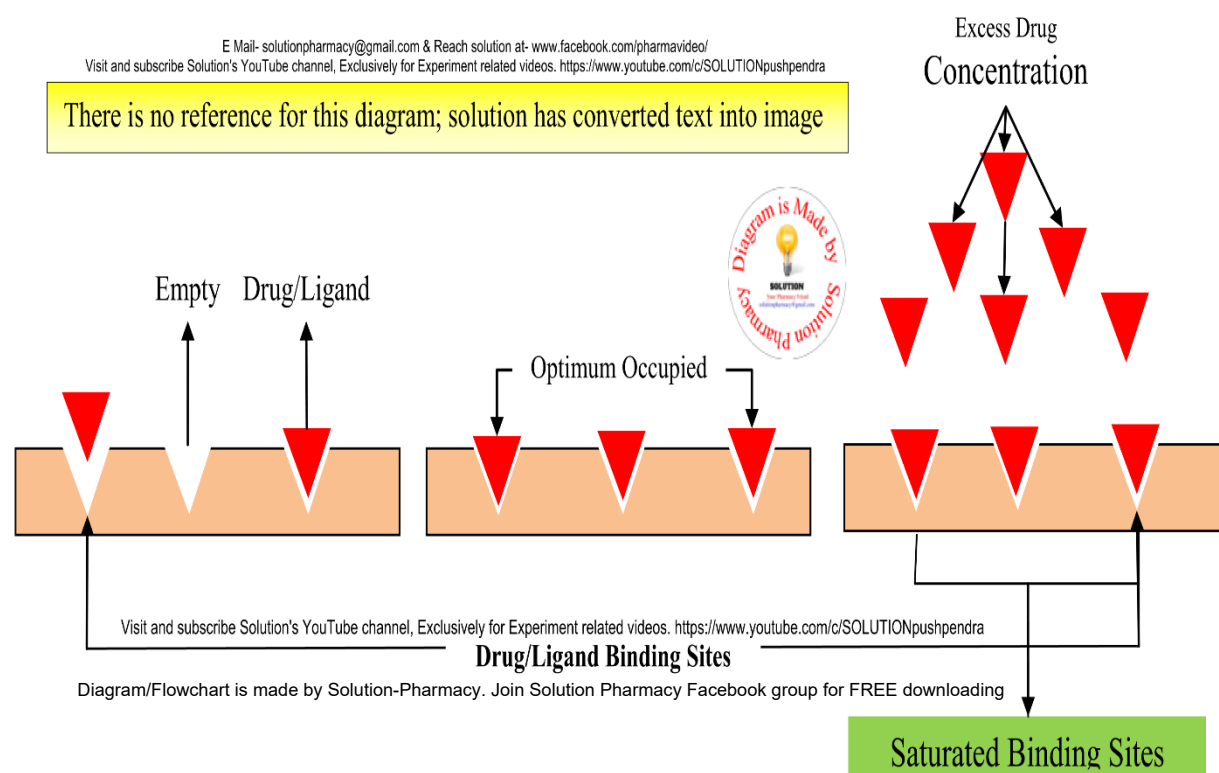
$$\text{Unbound fraction} = \frac{\text{unbound drug concentration in plasma}}{\text{total drug concentration in plasma}}$$

Plasma protein binding- There is some important plasma protein binding of drug-

1. Acidic drugs generally bind to plasma albumin
2. Basic drugs bind to Alpha₁ acid glycoprotein
3. Extent of binding of drug to the plasma protein is not on general basis, and there are no such classes. Example- (KDT) **Flurazepam- 10%, Alprazolam- 70%, Lorazepam- 90%, Diazepam- 99%**
4. Increasing the concentration of the drug may ultimately saturate the binding site. Saturation means the available binding site of receptor will be all most full and there will be no available free space for further binding, so no new drug molecule or Ligand can bind over the same receptor.

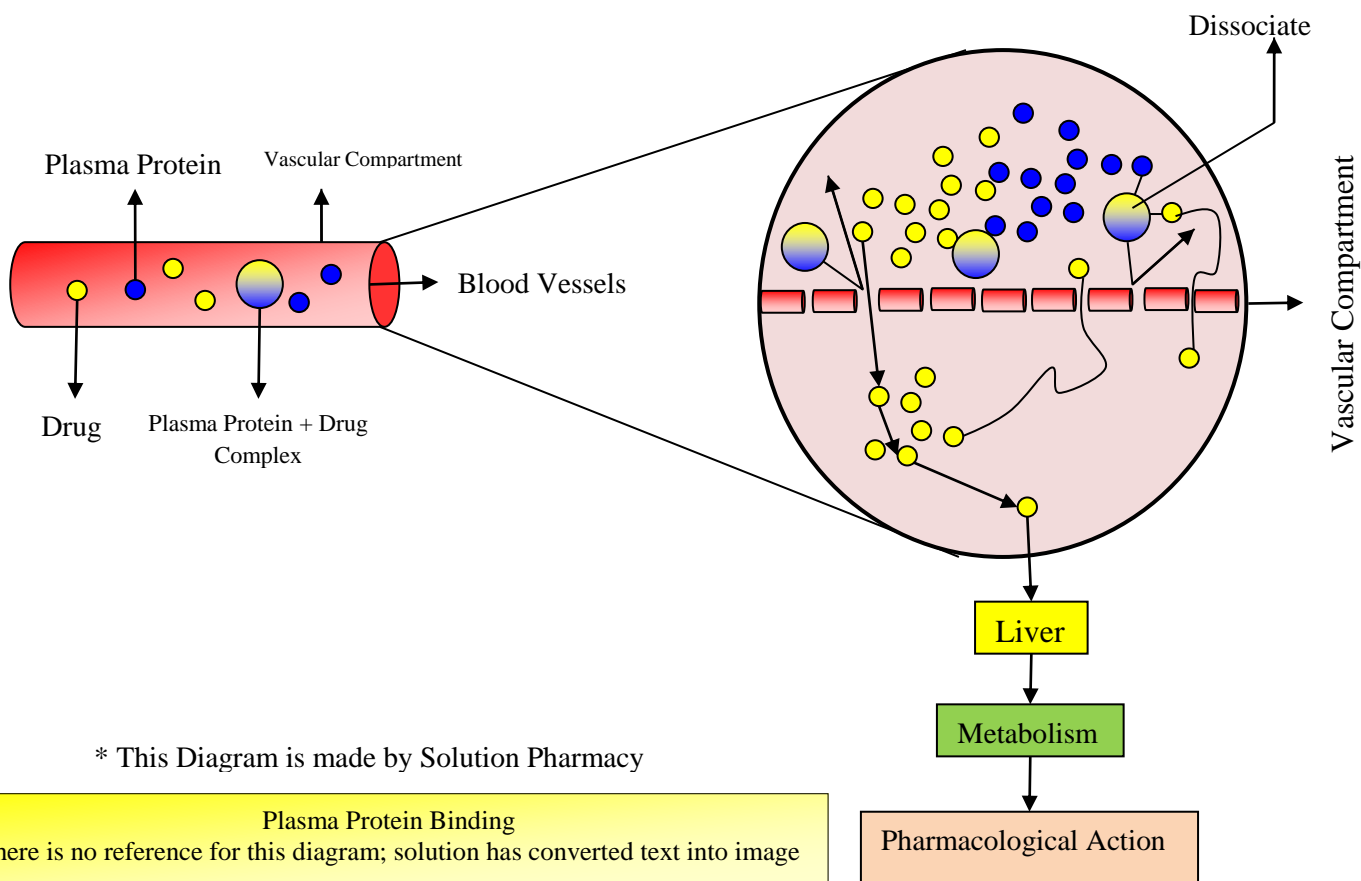


5. **Highly plasma protein bound drugs are mostly restricted by vascular compartment**, because protein bound drug does not cross membrane, because these protein bound drug got increase in their size and the size of pores of membrane is not that much large to allow protein bound drug. This is the reason behind their low volume of distribution.
6. The bound fraction drug is not available for the action.
7. **High degree of protein binding generally makes the drug long acting**, because bound fraction is not available for metabolism or excretion, unless it's actively extracted by liver of kidney tubules.



Drug Concentrated in tissues	
Skeletal muscle, Heart	Digoxin, Emetine (bound to muscle proteins)
Liver	Chloroquine, Tetracycline, Emetine, Digoxin
Kidney	Digoxin, Chloroquine, Emetine
Thyroid	Iodine
Brain	Chlorpromazine, Acetazolamide, Isoniazide
Retina	Chloroquine
Iris	Ephedrine, Atropine
Bone and Teeth	Tetracycline, Heavy Metals
Adipose Tissue	Thiopropionate, Ether, Minocycline, DDT,

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Metabolism or Biotransformation

Biotransformation is made up of two common terms- **Bio-** in living organism and **transformation-** conversion of anything *here drug from one form to another form, which is required by the body. The liver is the principal site of drug metabolism. Although metabolism typically inactivates drugs, some drug metabolites are pharmacologically active—sometimes even more so than the parent compound. An inactive or weakly active substance that has an active metabolite is called a prodrug, especially if designed to deliver the active moiety more effectively.

Drugs can be metabolized by **oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or Isomerization**; whatever the process, the goal is to make the drug easier to excrete. The enzymes involved in metabolism are present in many tissues but generally are more concentrated in the liver. Drug metabolism rates vary among patients. Some patients metabolize a drug so rapidly that therapeutically effective blood and tissue concentrations are not reached; in others, metabolism may be so slow that usual doses have toxic effects.

Individual drug metabolism rates are influenced by genetic factors, coexisting disorders (particularly chronic liver disorders and advanced heart failure), and drug interactions (especially those involving induction or inhibition of metabolism).

The primary site for drug metabolism is- liver, other are- kidney, intestine, lungs and plasma.

Biotransformation of drug many give any of this activity-

- 1- Inactivation of drugs
2. Active metabolites from active drugs
3. Activation of inactive drugs

S.No.	Phase I Metabolism
01	Oxidation (via cytochrome P450), reduction, and hydrolysis reactions
02	Phase I reactions convert a parent drug to more polar (water soluble) active metabolites by unmasking or inserting a polar functional group (-OH, -SH, -NH ₂)
03	Geriatric patients have decreased phase I metabolism
04	Drugs metabolized via phase I reactions have longer half-lives
05	Geriatric patients metabolism drugs by phase II reactions

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S.No.	Phase II Metabolism
01	Glucuronidation, acetylating, and sulfation reactions "conjugation reactions" that increase water solubility of drug with a polar moiety
02	Glucuronate, acetate, and sulfate, respectively
03	Phase ii reactions convert a parent drug to more polar (water soluble) inactive metabolites by conjugation of subgroups to -oh, -sh, -nh ₂ functional groups on drug
04	Drugs metabolized via phase ii reactions are really excreted
05	Patients deficient in acetylating capacity (slow acetylators) may have prolonged or toxic responses to normal doses of certain drugs because of decreased rates of metabolism

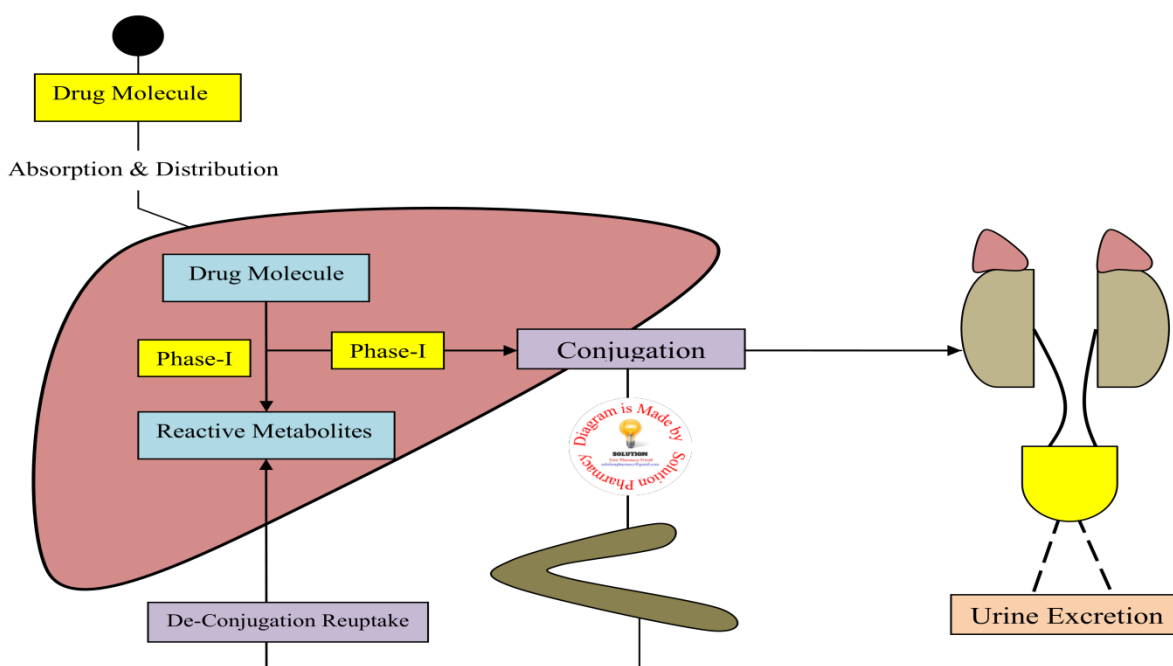


Holfman Elimination- Holfman inhibition means inactivation of the drugs in the body fluids by the spontaneous molecular rearrangement without the agency of any enzyme like- **atracurium**

Microtonal enzyme- these are located on a smooth endoplasmic reticulum, primarily in liver, also in kidney, intestinal mucosa, and lungs. **Example-monooxygenase, cytochrome P450, glucronyl transferase** are common one.

Nonmicrosomal enzymes- these are present in the cytoplasm and mitochondria of hepatic cells as in other tissue including plasma.

Inhibition of drug metabolism- one drug can competitively inhibit the metabolism of another dug molecule taken at the same time or later if both drugs utilize the same enzyme or cofactors. Metabolism of drug with high hepatic extraction is dependent on liver blood flow. Propranolol reduce rate of iodine metabolism by decreasing hepatic blood flow. Some other drugs whose rate of metabolism is limited by hepatic blood flow are- morphine, propranolol, Verapamil and imipramine.



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Image- Phase I and Phase II metabolism



Biotransformation Reaction

Non Synthetic Phase-I/ Functionalization Reaction



Synthetic Phase-II/Conjugation Reaction

Reduction

Converse of oxidation and involve cytochrome P-450 enzyme working in the opposite direction. Alcohols, Aldehydes, quinines, are reduced.

Exa- Chloral hydrate,
Chloramphenicol, Halothane,
Warfarin.

Hydrolysis

This is cleavage of drug molecule by taking up water molecule.

$\text{Ester} + \text{H}_2\text{O} \rightarrow \text{Acid} + \text{Alcohol}$

Crystallization

This is a formation of ring structure from a straight chain compound,
Like- Proguanil.

Decyclization

This is opening of ring structure of cyclic drug molecule, Like- Barbiturate, Phenytoin.

Glucuronide conjugation

Most imp synthetic reaction carried out by group of- UDP. Example- Chloramphenicol, Aspirin, paracetamol, Lorazepam, morphine, Metronidazole.

Acetylation

Compound having amino or hydrazine, residue are conjugated with the help of acetyl co enzyme A. Exa- Sulfonamide, Isoniazide, PAS, Hydrazine etc

Methylation

The amine and phenols can be methylated. Methionine and cysteine act as a methyl donor. Exa- Adrenaline, Histamine, Nicotinic acid, methyl dopa, Captopril.

Sulphate Conjugation

The phenolic compound and steroids are sulfated by sulfotransferases. Exa- Chloramphenicol, Methyl dopa, adrenal and sex steroids.

Glycine Conjugation

Alicylates and other drugs having carbonic acid group are conjugated with Glycine, but this is not a major pathway of metabolism.

Ribonucleotide/nucleotide synthesis

Glutathione Conjugation

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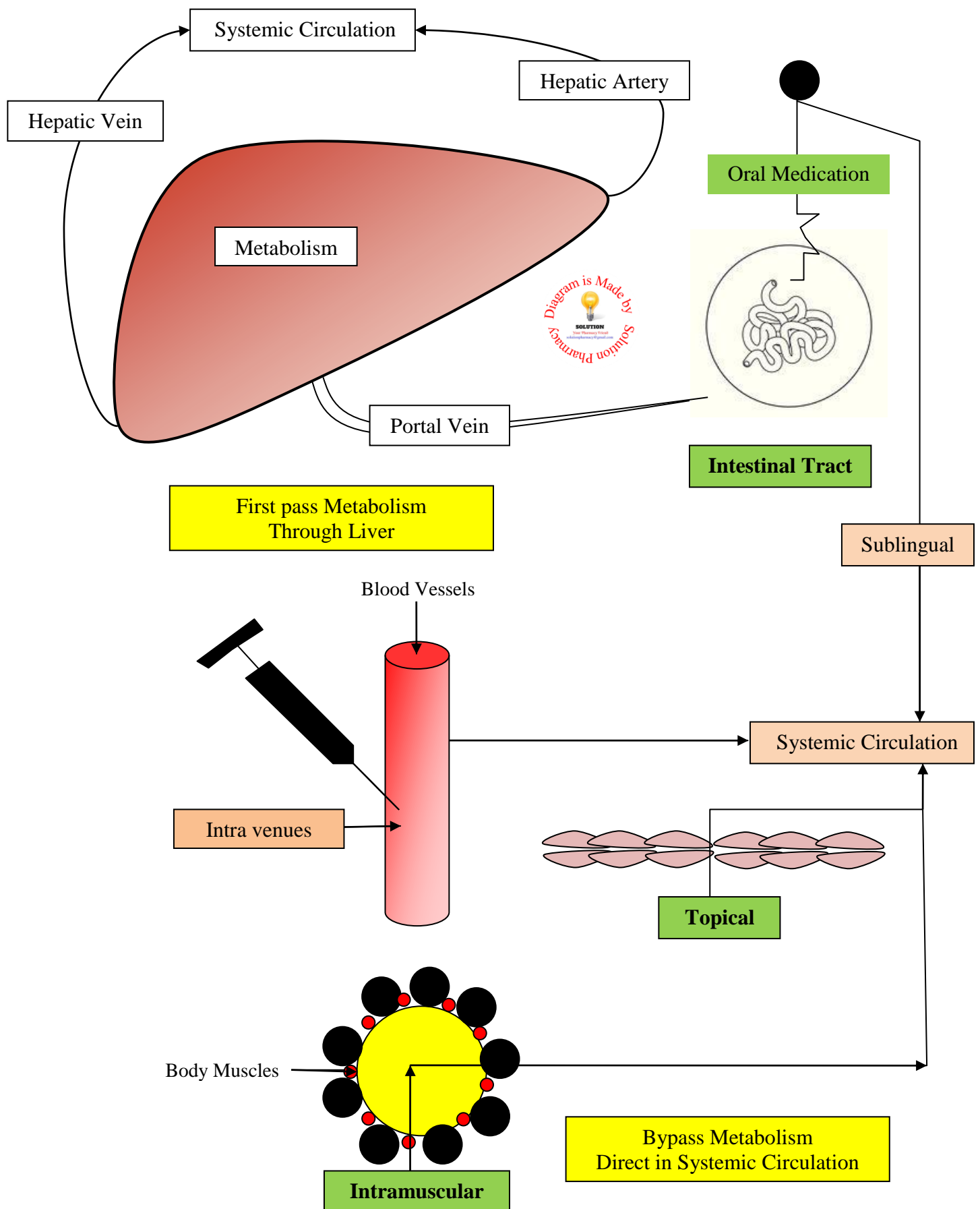


Image- Diagram showing first passes and bypass metabolism through liver

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Excretion or Elimination

Excretion- Drug excretion is the process of eliminating a drug from the body. A drug, which is either biologically active itself or a prodrug, may be excreted in its original chemical state. Alternatively, all or a portion of a drug may undergo chemical modification and be eliminated as biologically active, or inactive, metabolites. There are several routes for drug elimination from the body, the majority of drugs are eliminated by pathways that involve the kidneys or the liver. Renal excretion plays an important role in eliminating unchanged drugs or their metabolites into urine.

The kidneys are the principal organs for excreting water-soluble substances. The biliary system contributes to excretion to the degree that drug is not reabsorbed from the GI tract. Generally, the contribution of intestine, saliva, sweat, breast milk, and lungs to excretion is small, except for exhalation of volatile anesthetics. Excretion via breast milk may affect the breastfeeding infant

Renal excretion

Renal filtration accounts for most drug excretion. About one fifth of the plasma reaching the glomerulus is filtered through pores in the glomerular endothelium; nearly all water and most electrolytes are passively and actively reabsorbed from the renal tubules back into the circulation. However, polar compounds, which account for most drug metabolites, cannot diffuse back into the circulation and are excreted unless a specific transport mechanism exists for their reabsorption. **Example- glucose, ascorbic acid, and B vitamins**

Biliary excretion

Some drugs and their metabolites are extensively excreted in bile. Because they are transported across the biliary epithelium against a concentration gradient, active secretory transport is required. When plasma drug concentrations are high, secretory transport may approach an upper limit (transport maximum). Substances with similar physicochemical properties may compete for excretion.

Drugs with a molecular weight of > 300 g/mol and with both polar and lipophilic groups are more likely to be excreted in bile; smaller molecules are generally excreted only in negligible amounts. Conjugation, particularly with glucuronic acid, facilitates biliary excretion.



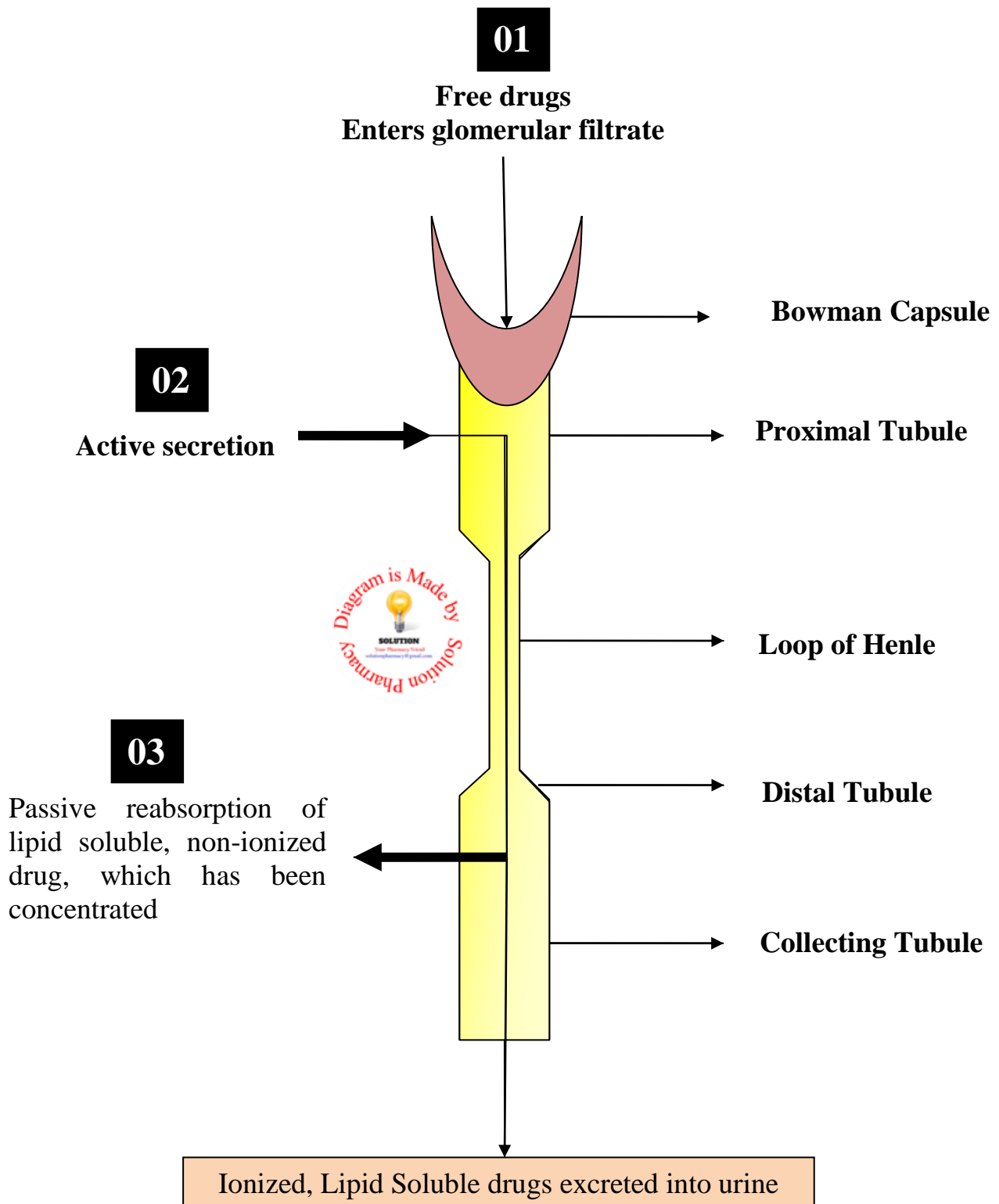


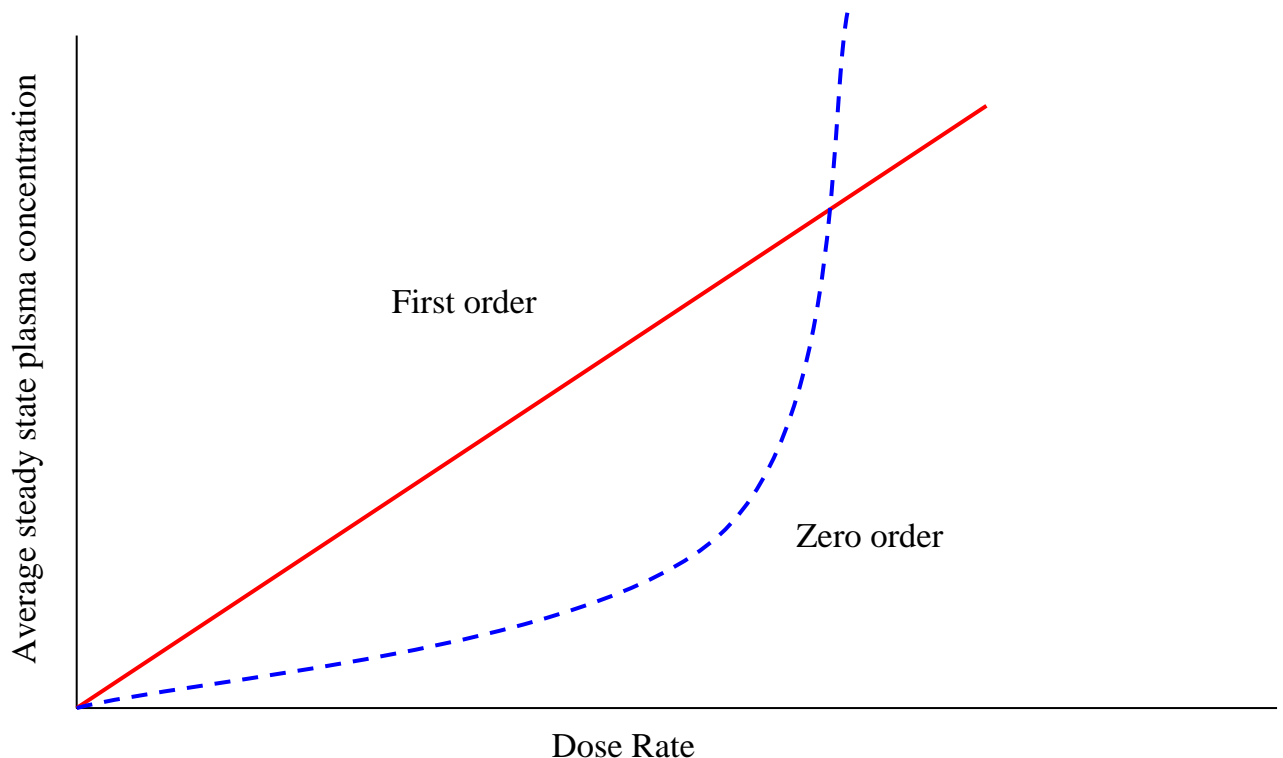
Image (Made by Solution) - Drug Elimination by the Kidney * Idea- Lippincott

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Important terms and definition

1. **Clearance-** Drugs are removed from the body by various elimination processes. *Drug elimination* refers to the irreversible removal of drug from the body by all routes of elimination.
2. **First order kinetics-** the rate of elimination of drug is directly proportional to the drug concentration, clearance remain constant or a constant fraction of drug present in the body is eliminated in unit time.
3. **Zero order kinetics-** the rate of elimination is constant irrespective of drug concentration, or a constant amount of drug is eliminated in unit time.
4. **Plasma half life-** This is the period of time required for the concentration or amount of drug in the body to be reduced by one-half. We usually consider the half life of a drug in relation to the amount of the drug in plasma. A drug's plasma half-life depends on how quickly the drug is eliminated from the plasma.



**Relationship between dose rate and average
Steady state plasma concentration of drug eliminated by first order and zero order kinetics.**

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