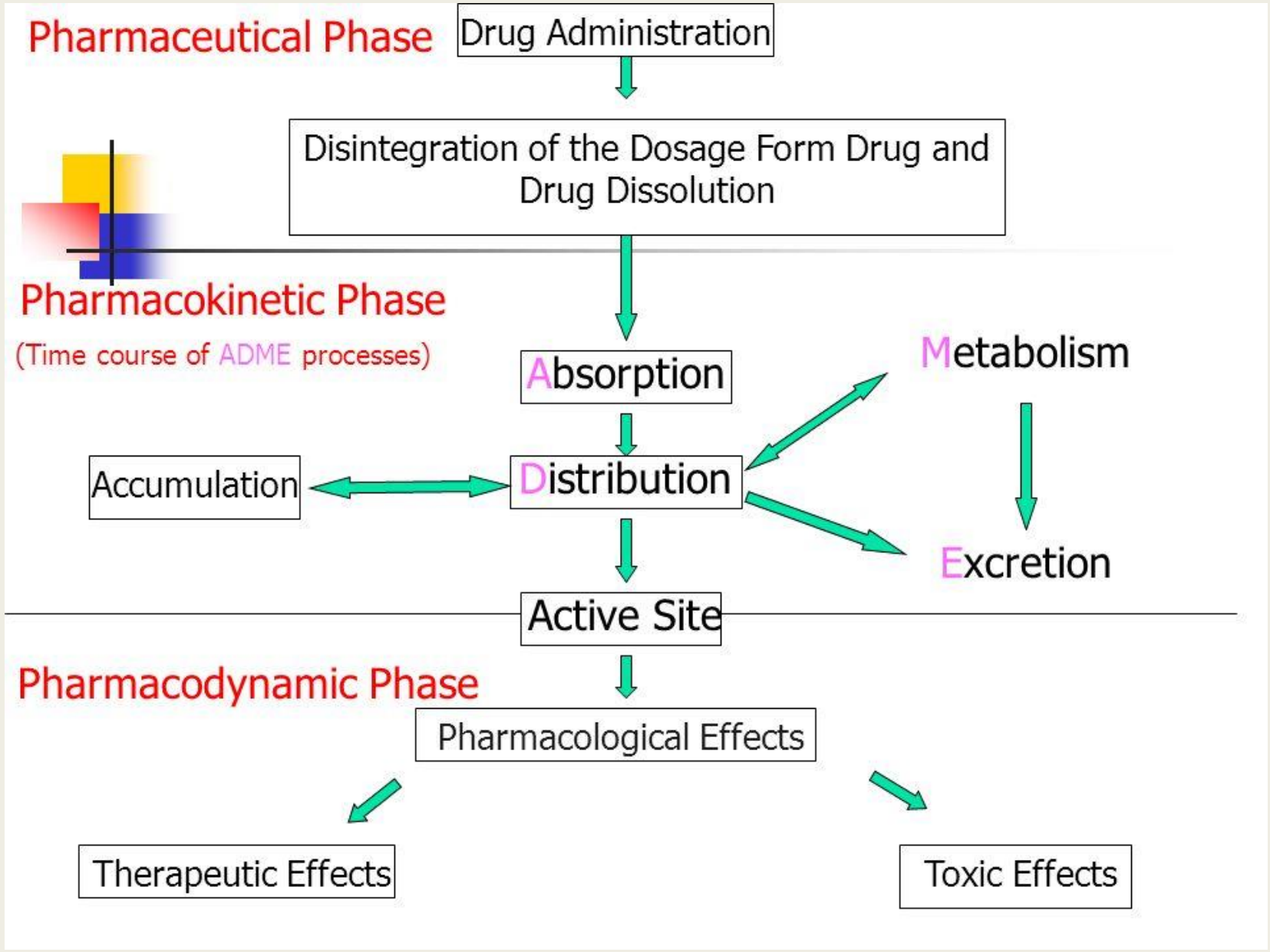
PHARMACOKINETIC, ABSORPTION AND *IONISATION* OF DRUGS

Prof Dr Sibel Süzen

DRUG ACTIVITY



Drug Activity

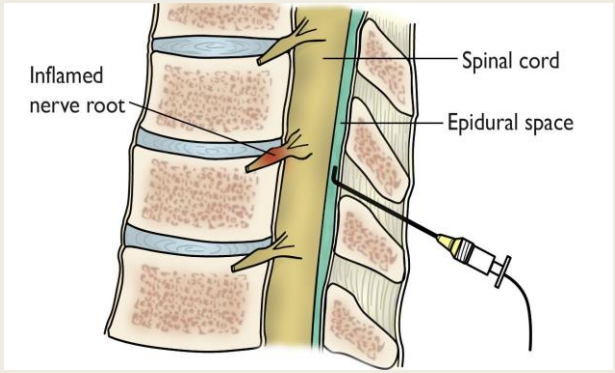
1- Pharmaceutical Phase: Drug Administration

There are four major routes of drug administration which are,

- Topical route
- Pulmonary or inhalation route
- Enteral route
- Parenteral route

- **Topical route**
  - *Dermal – cream, ointment (local action)*
  - *Transdermal- absorption of drug through skin (i.e systemic action)*
- **Pulmonary or inhalation route**
  - *Vaporization – drug is changed from a liquid or solid to a gas or vapor by the use of heat (e.g. steam inhalation)*
  - *Gas inhalation – restricted to anesthesia*
  - *Inhalation – drug is converted into a fine spray by the use of composed gas*
- **Enteral route**
  - *Oral route*
  - *Sub-lingual route (*allows a drug to diffuse into the capillary network and therefore, to enter the systemic circulation directly)
  - *Rectal and vaginal*

- Parenteral route
  - *Intra muscular (into the skeletal muscle) – injected to buttock, thighs and deltoid*
  - *Intra venous (into a vein) – injected as bolus or infused slowly over hours into cubital, basilic and cephalic veins*
  - *Intra arterial (into an artery) – effect of a drug can be localized in a particular organ or tissue by choosing the appropriate artery*
  - *Subcutaneous route (Hypodermic) – Injected under skin, e.g. Insulin*
  - *Intra cardiac – injected directly into the heart muscles*
  - *Intra thecal – injected into the spinal canal*
  - *Intra pleural – injected within the pleura or the pleural cavity.*
  - *Intraosseous- injected into bone marrow*
  - *Intraperitoneal – injected into the peritoneum*
  - *Intra-articular – injected into the joint activity*
  - *Intradermal (Intracutaneous) – within skin layers (dermis)*



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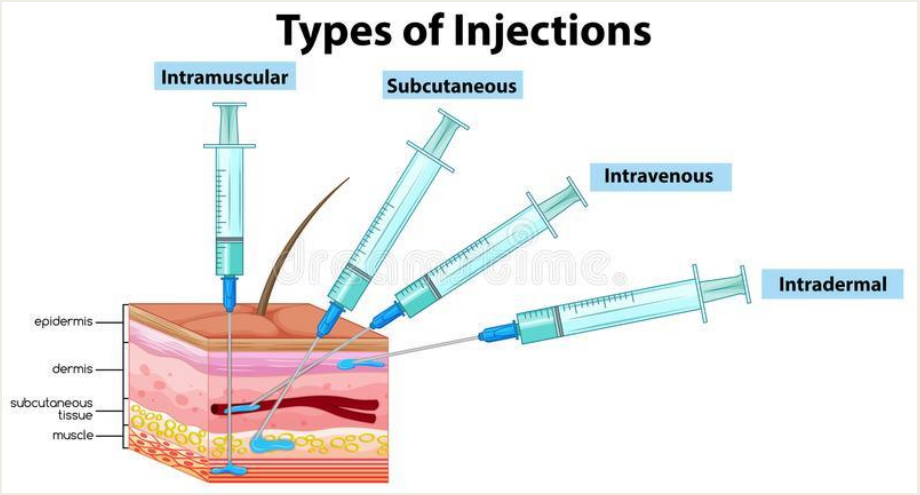

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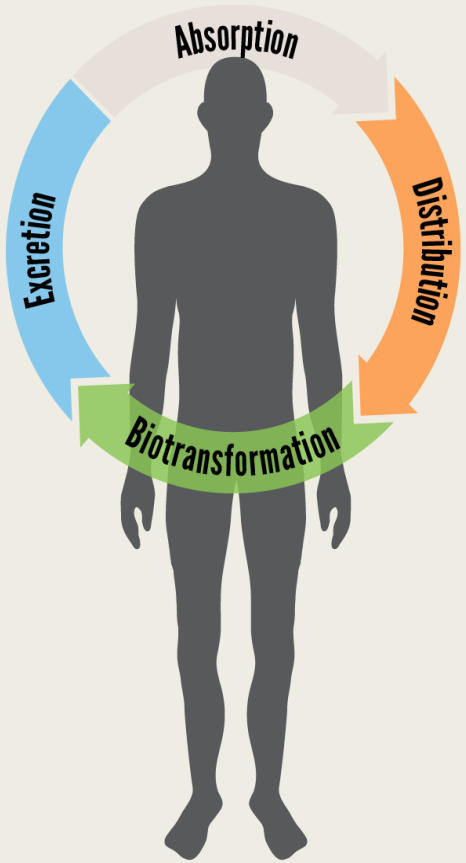
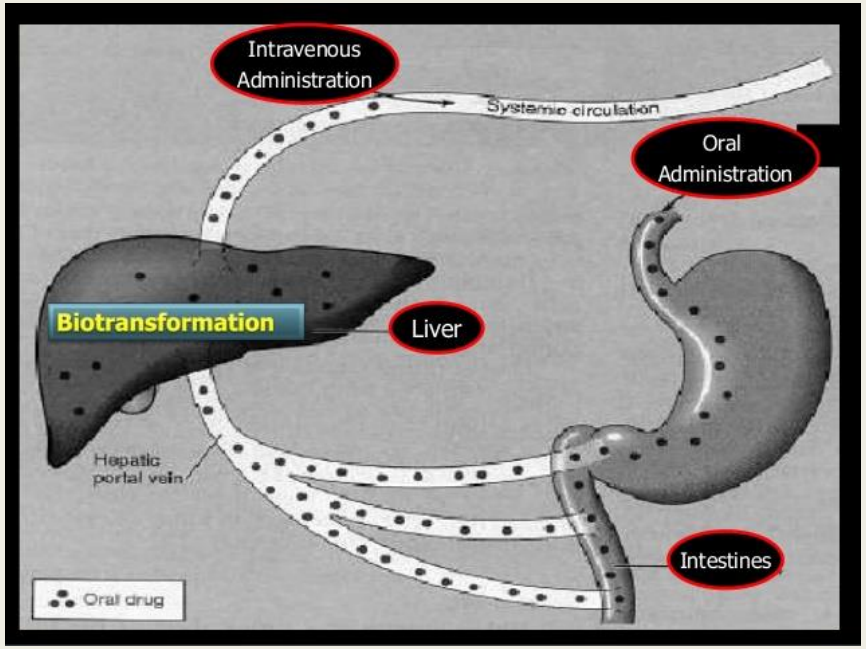
Drug Activity:
2- Pharmacokinetic Phase



- Pharmacokinetics is the study of drug disposition in the body.
- What the body does to the drug?
- It describes, both qualitatively and quantitatively, the pharmacokinetic processes of absorption, distribution, metabolism, and excretion and their relationship to the pharmacological, therapeutic or toxic response in animals and man.

What is ADME?

- ADME is the abbreviation for
  - *Absorption*
  - *Distribution,*
  - *Metabolism*
  - *Excretion*



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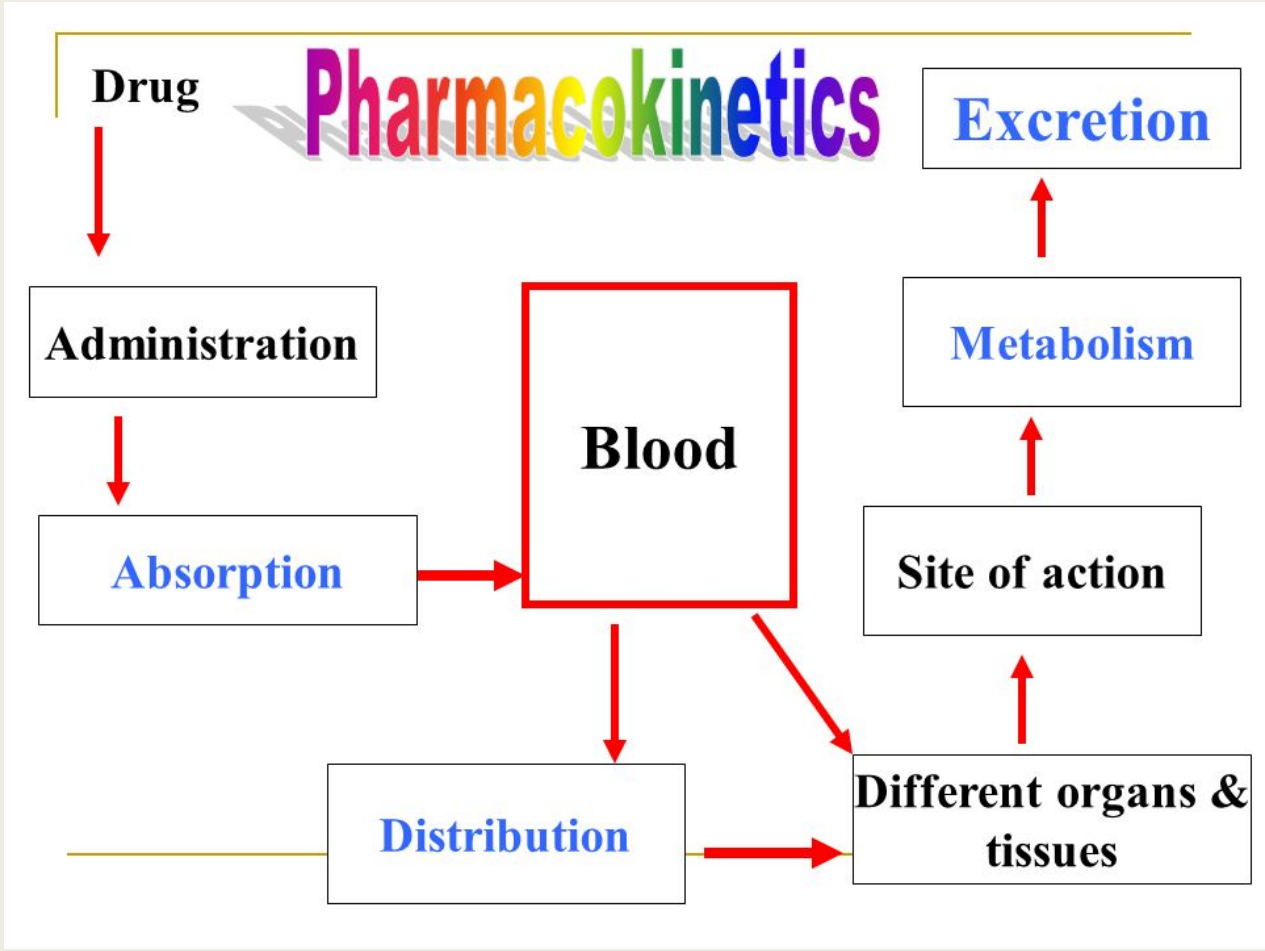
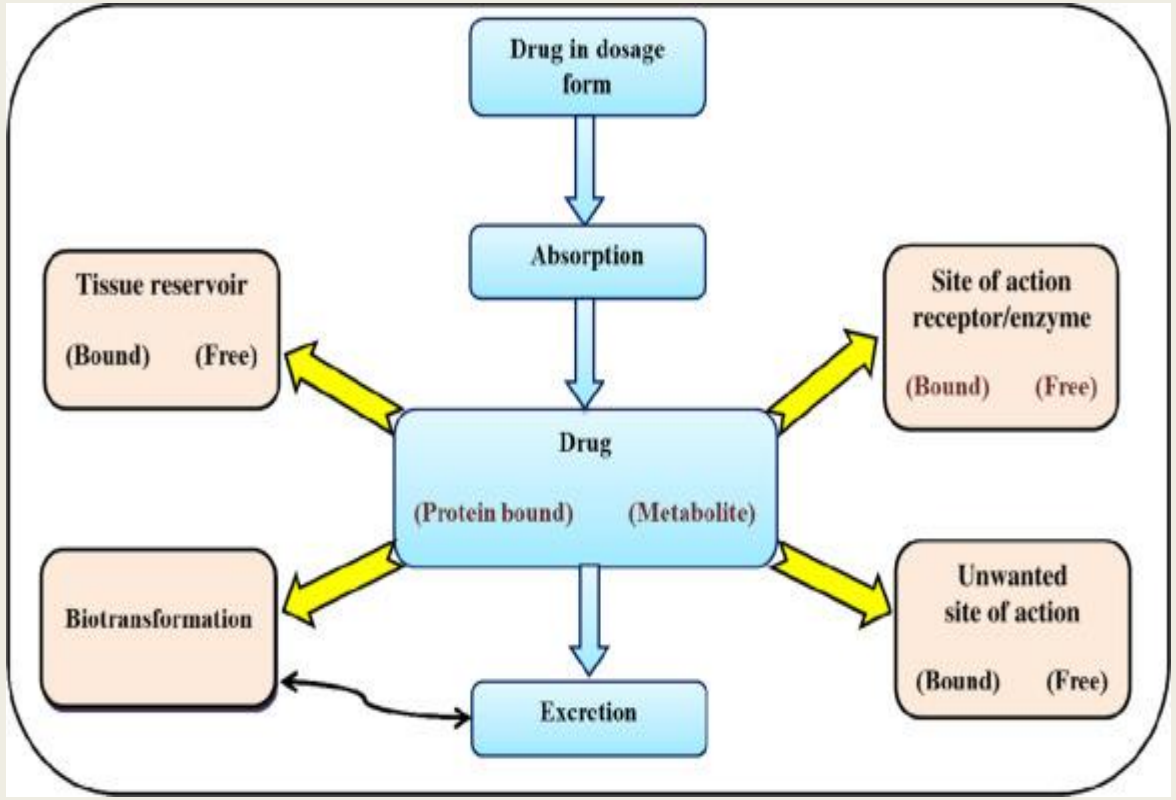


ADME:
Absorption

- Absorption describes how a chemical enters the body. Absorption relates to the movement of a chemical from the administration site to the bloodstream.
- Only injected compounds enter directly into the systemic circulation.



There are 4 ways through which a chemical can cross a membrane and enter the bloodstream.

Passive diffusion: When a molecule moves from an area of high concentration to an area of low concentration. This is the most common way a drug is absorbed.

Facilitated diffusion: When a molecule moves from an area of high concentration to one of low concentration with the help of carrier proteins in the membrane.

Active diffusion: An energy-dependent process during which a molecule requires energy in the form of ATP to cross a membrane.

Endocytosis: Cells take in substances from outside of the cell by engulfing them in a vesicle.

FACTORS AFFECTING DRUG ABSORPTION

A. Physicochemical factors

1) Drug solubility & dissolution rate
2) Particle size & effective surface area
3) Polymorphism & amorphism
4) Pseudoploymorphism (hydrates/solvates)
5) Salt form of the drug
6) Lipophilicity of the drug pH- Partition
7) pKa of drug & gastrointestinal pH hypothesis
8) Drug stability

B. Pharmaceutical factors

1) Disintegration time (tablets/capsules)
2) Dissolution time
3) Manufacturing variables
4) Pharmaceutical ingredients (excipients/adjuvants)
5) Nature & type of dosage form
6) Product age & storage condition

C. Patient related factors

1) Route of administration
2) Membrane physiology
   a) Nature of cell membrane
   b) Transport processes
3) Age
4) Gastric emptying time
5) Intestinal transit time
6) Gastrointestinal pH
7) Disease states
8) Blood flow through the GIT
9) Gastrointestinal contents and presystemic metabolism by enzymes

ADME:
Distribution

- Distribution is the process by which the drug reversibly leaves the site of administration and is distributed through out the tissues of the body.

- Volume of distribution= Amount of drug in the body
  Conc. in plasma

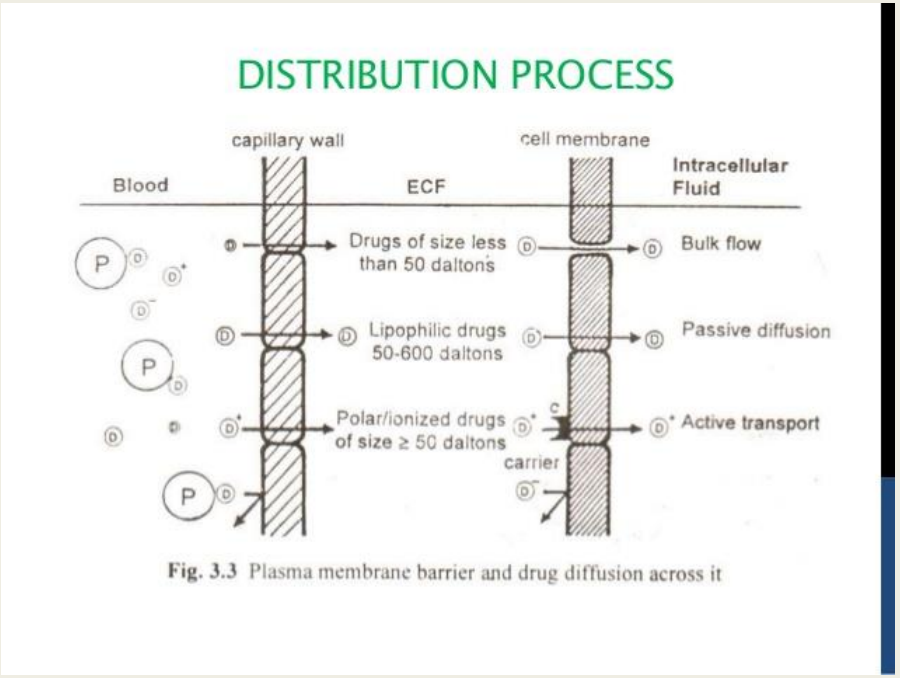


Fig. 3.3 Plasma membrane barrier and drug diffusion across it

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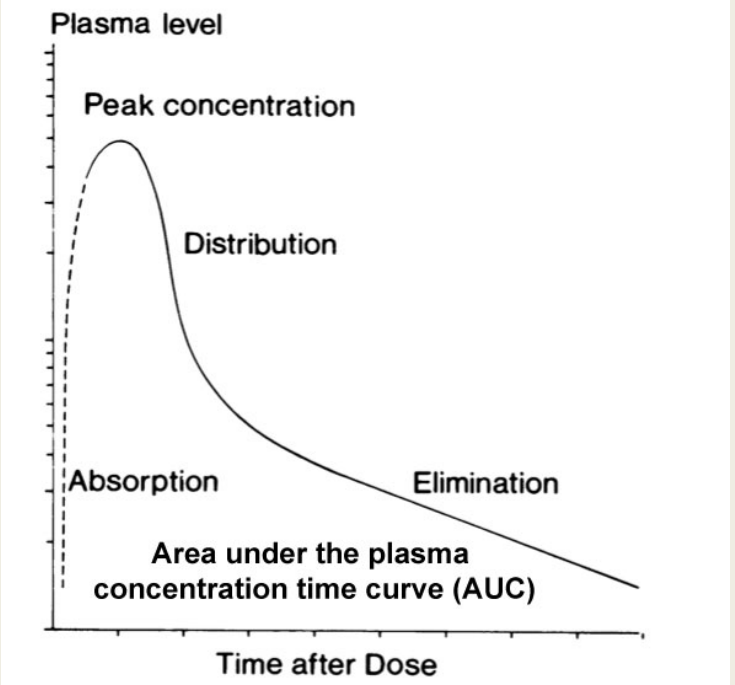


■ MECHANISM OF PROTEIN DRUG BINDING:

Binding of drugs to protein is generally *reversible* which is suggests that it generally involves weak chemical bonds such as:

Hydrogen bonds, Hydrophobic bonds, Ionic bonds, Vander wall's forces

Binding of drugs falls into 2 classes:

1. Binding of drug to blood components

Plasma proteins

Blood cells

2. Binding of drugs to extra vascular tissue protein, fats, bones, etc.

■ BINDING OF DRUGS TO BLOOD COMPONENTS

The main interaction of drug in the blood compartment is with the plasma protein which are present in abundant amounts and in large variety.

The binding of drugs to plasma proteins is reversible.

The extent or order of binding of drugs to various plasma protein is:

Albumin > α 1- Acid Glycoprotein > Lipoprotein > Globulins.

- **HUMAN SERUM ALBUMIN :**

- The therapeutic doses of most drugs are relatively much smaller and their plasma concentration do not normally reach equimolar concentration with HSA. Four different sites on HSA have been identified for drug-binding.

- **BINDING OF DRUGS TO GLOBULINS :-**

- Several plasma globulins have been identified and are labelled as α 1-, α 2-, β 1-, β 2 and γ - globulins.

- α 1-globulin: also called as transcortin or CBG, it binds a number of steroidal drugs such as cortisone and prednisone. It also binds to thyroxin and cyanocobalamine

- α 2-globulin: also called as ceruloplasmin, it binds vitamins A, D, E and K cupric ions

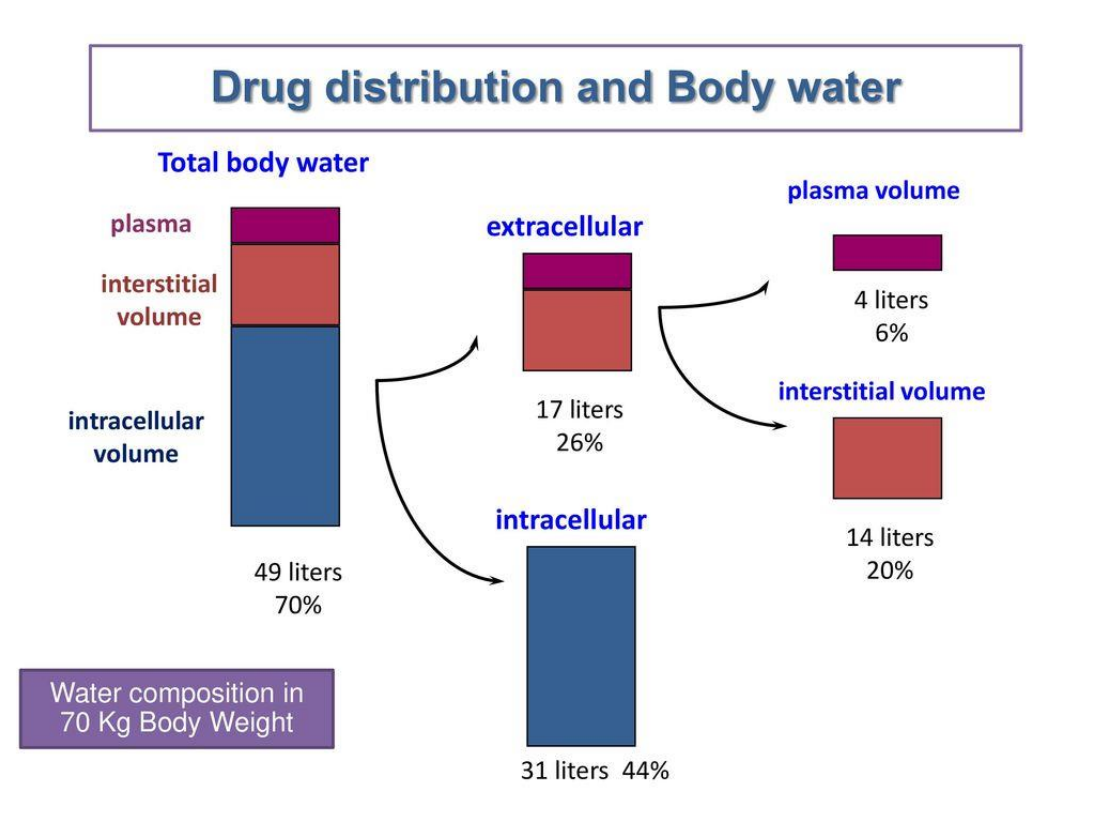
- β 1-globulin: also called as transferring, it binds to ferrous ions.

- β 2-globulin: binds to corticosteroids

- γ - globulin: binds specifically to antigens

Distribution

- The body is a container in which a drug is distributed by blood (different flow to different organs) - but the body is not homogeneous.



a- Plasma Compartment
If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment (6%)

b- Extracellular Fluid
(Plasma + Interstitial Fluid)If a drug has a low molecular weight but is hydrophilic, it can move through the endothelial slit junctions of the capillaries into the interstitial fluid. However, it cannot move across the lipid membranes of cells to enter the water phase inside the cell (6%-20%)

c- Total Body water
(Extra cellular + Intracellular)If a drug has a low molecular weight and is hydrophobic, not only can it move into the interstitial fluid, but it can also move through the cell membranes into the intracellular fluid (6% - 20% - 44%)

Factors Related to the Drug:

1. Lipid Solubility
   - *Greater the lipid solubility, more is the distribution.*
2. Molecular size
   - *Larger the size, less is the distribution. Smaller sized drugs are more extensively distributed.*
3. Degree of Ionization
   - *Drugs exist as weak acids or weak bases when being distributed. Drugs are trapped when present in the ionized form, depending upon the pH of the medium. This fact can be used to make the drug concentrated in specific compartments.*
4. Cellular binding
   - *Drugs may exist in free or bound form. Bound form of drugs exists as reservoirs. The free and bound forms co-exist in equilibrium. Cellular binding depends on the plasma binding proteins.*

   Tissue binding:
   - *Different drugs have different affinity for different cells. All cells do not bind the same drugs.*
5. Duration of Action
   - *The duration of action of drugs is prolonged by the presence of bound form while the free form is released. This leads to a longer half life and duration of action of drugs.*
6. Therapeutic Effects:
   - *Bisphosphonate compounds bind with the bone matrix cells and strengthen them. They are used in the treatment of osteoporosis.*
7. Toxic Effects:
   - *Tetracycline can bind the bone material. It may also get bound to the enamel of the teeth.*

Factors Related to the Body:

1. Vascularity
   - *Most of the blood passes through the highly profused organs (75%) while the remaining (25%) passes through the less profused areas. Therefore, most of the drugs go first to the highly profused areas. They may get bound to these organs. They are then redistributed to the less profused areas like the skin and the skeletal muscles. This phenomenon is common among the lipid soluble drugs.*
   - *Example includes thiopentone sodium which is used as general anesthetic. When given, it goes to the brain producing its effects. It is then redistributed to the less profused organs. Because of high lipid solubility, it is accumulated in the fatty tissue for longer duration. Thus the clearance of the drugs is slow, producing prolonged period of drowsiness (up to 24 hours).*

2. Transport Mechanism
   - *Different drugs are taken up by different compartments of the body differently. Lipid soluble drug move by passive transport which is non specific. Active transport occurs only where carrier proteins are present.*

3. Blood Barriers
   - *Different blood barriers exist. Blood brain barrier is present because of the delicacy of nervous tissue to avoid chemical insult to the brain.*
   - ***Structure:*** *Endothelial cells and pericytes and glial cells form the barrier through which drugs cannot pass easily. Only selective passage takes place.*
   - ***Transporters:*** *Certain efflux pumps or transporters exist through which drugs can be effluxed as well. Example includes p-glycoprotein.*
   - ***Disruption:****Disruption of barrier may occur, e.g. by inflamed meningitis. Drugs may pass which might be toxic as well as beneficial i.e. during meningitis penicillin can pass which has beneficial effects.*

4. Placental Barriers
   - *Trophoblastic tissue separates maternal blood from fetal blood. Different transporters are present. Efflux transporters cause efflux back of the drugs from the fetus to the mother.*

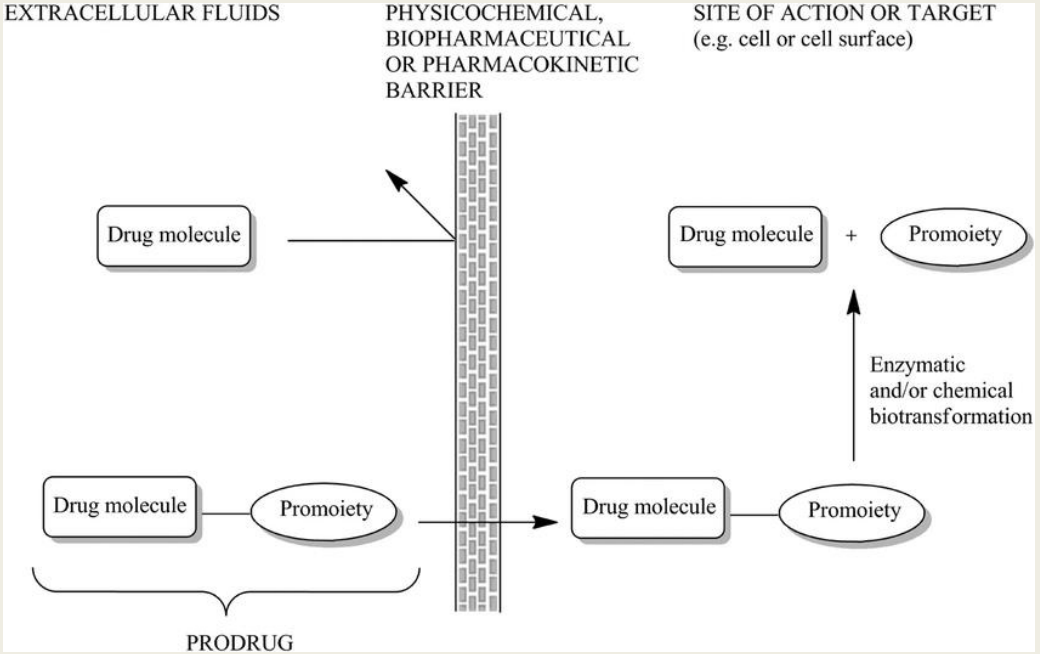
5. Plasma Binding Proteins

Therapeutic Index

- *Therapeutic index is the safety margin, the range in which the drug is safe. If drug has a large therapeutic index, then large concentrations of the drug are safe. If it has a small therapeutic index, it may move out of the safe range and cause toxic effects. Thus the drug displacement phenomenon is significant in low therapeutic index drugs.*

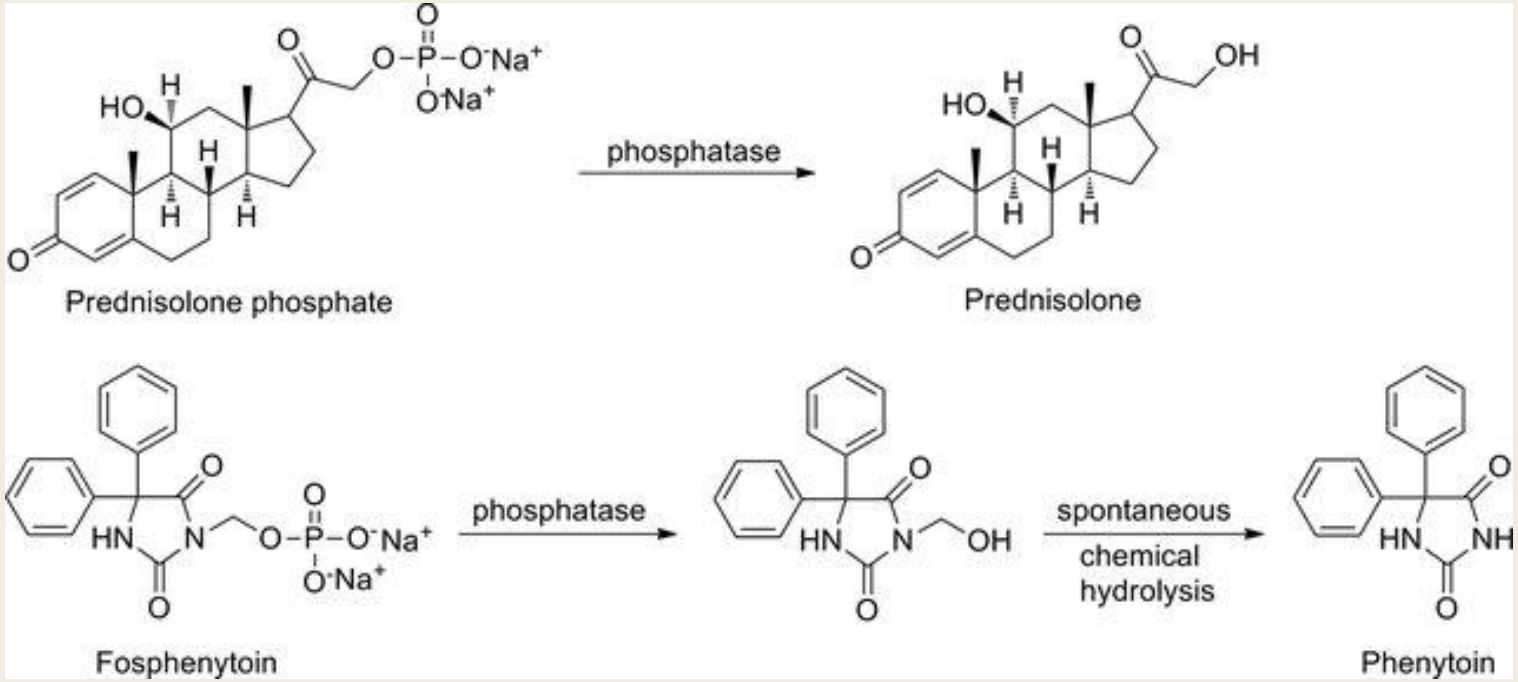
Pro-Drug

- *Produgs are derivatives of therapeutic agents designed to improve the pharmacokinetics profile of the drug. Within a prodrug, pharmacological activity of the drug is masked and is recovered within the human body upon bioconversion of the prodrug, a process that is typically mediated by enzymes.*



PHARMACOLOGICALREVIEWS, Vol. 63, No. 3:750–771, 2011 (15) (PDF) Prodrugs--from Serendipity to Rational Design. Available from: https://www.researchgate.net/publication/51475317_Prodrugs--from_Serendipity_to_Rational_Design [accessed Mar 08 2021].

Pro-Drugs



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ADME: Metabolism

- Metabolism (Biotransformation) Process of converting a drug into product or inert substances after or before reaching at the site of action.
- Metabolism is an essential pharmacokinetic process, which render lipid soluble and non polar compounds to water soluble and polar compounds so that they are excreted by various process from the body.
- Biotransformation: It is a specific term used for the chemical transformation of xenobiotics (drugs) in the living organisms.
- Xenobiotics: These are all chemical substances that are not nutrient for the body (foreign body) and which enter the body through ingestion, inhalation or dermal exposure
- Most organic compounds entering the body are relatively lipid soluble (lipophilic).
- To be absorbed, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract.
- Then, once in the bloodstream, these molecules can diffuse passively through other membranes and be distributed effectively to reach various target organs to exert their pharmacological actions.
- Because of reabsorption in the renal tubules, lipophilic compounds are not excreted to any substantial extent in the urine.

Consequences of biotransformation

- Active drug → Inactive metabolite
- Active drug → Active metabolite
- Inactive drug (Prodrug) → active metabolite

Phases of Metabolism

Phase I

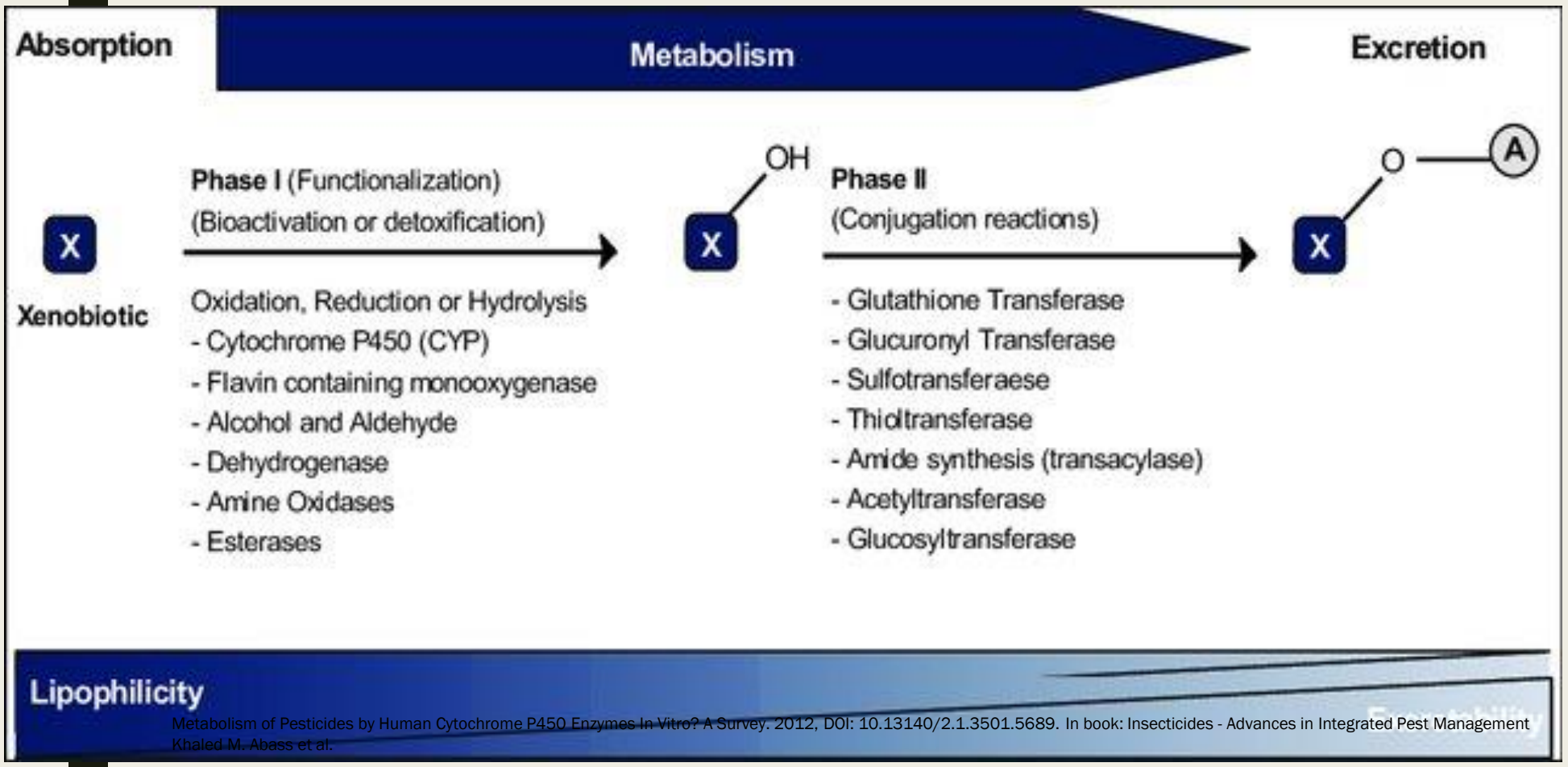
- Functionalization reactions: Converts the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH2, -SH).

Basically oxidation, hydrolysis, reduction happen in Phase I

Phase II

- Conjugation reactions: Subsequent reaction in which a covalent linkage is formed between a functional group on the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid

Basically conjugation, methylation and acethylation happen in Phase II



Metabolism of Pesticides by Human Cytochrome P450 Enzymes In Vitro? A Survey. 2012, DOI: 10.13140/2.1.3501.5689. In book: Insecticides - Advances in Integrated Pest Management
Khaled M. Abass et al.

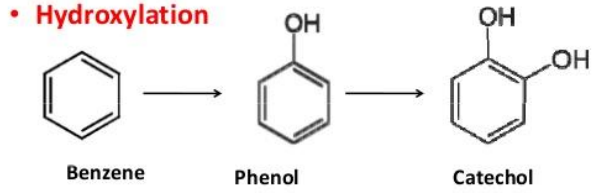
Schematic description of the two main phases of drug metabolism. In general, a parent compound is converted into an intermediate metabolite which is then conjugated, but metabolism may involve only one of these reactions. Some metabolites are more toxic than the parent compound

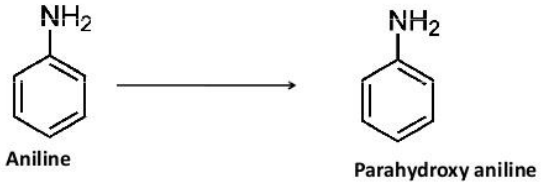
Site/Organs of drug metabolism

- The major site of drug metabolism: is the *liver* (microsomal enzyme systems of hepatocytes)
- Secondary organs of biotransformation: kidney (proximal tubule), lungs, testes (Sertoli cells), skin (epithelial cells); plasma, nervous tissue (brain); intestines

Examples of phase I reactions

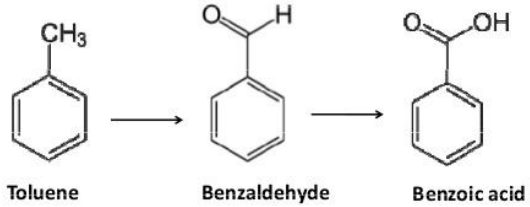
- **Hydroxylation**



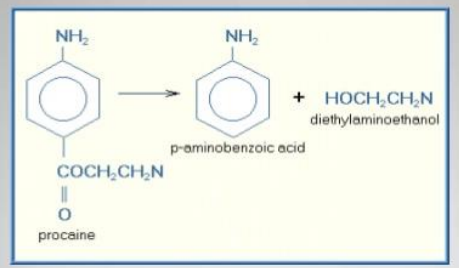


Examples of phase I reactions

- **Oxidation**



C)Hydrolysis



A) Oxidation

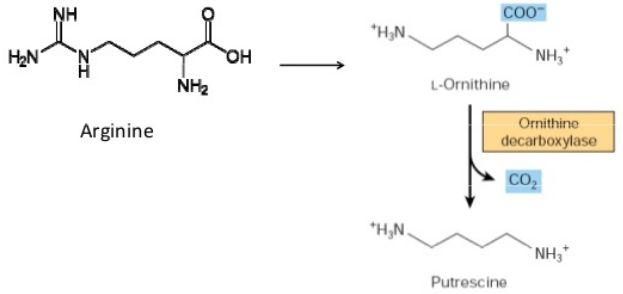
- **Oxidation of Aromatic Hydrocarbons**

Aromatic hydrocarbons are oxidized to phenolic compounds, which can further be conjugated with Glucuronic acid or Sulfuric acid in phase 2 reactions so as to be excreted through urine.

https://www.slideshare.net/namarta28/xenobiotics?next_slideshow=1

Examples of phase I reactions

- **Deamination**



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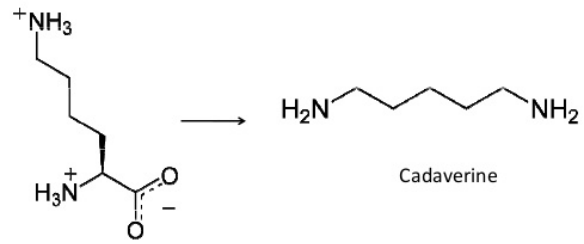
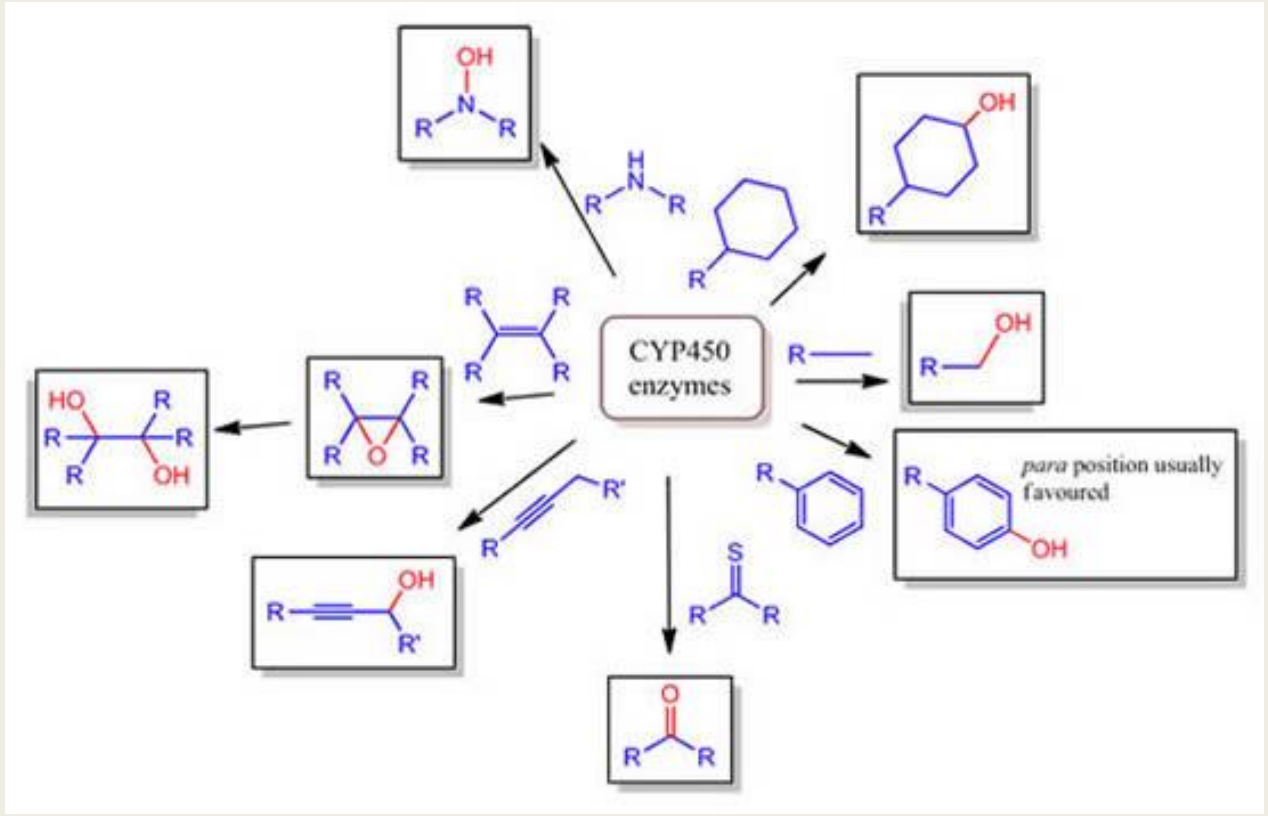
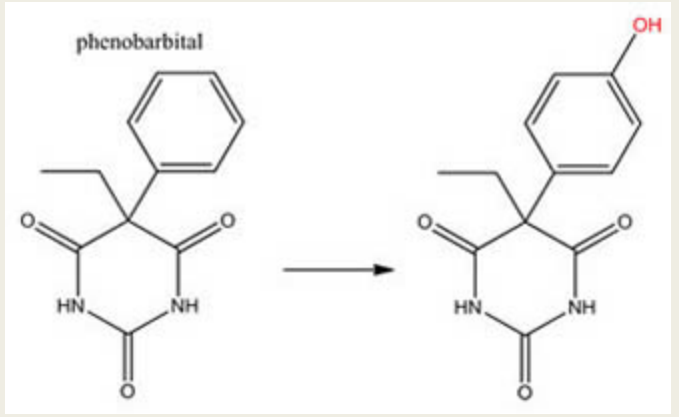
Examples of phase I reactions

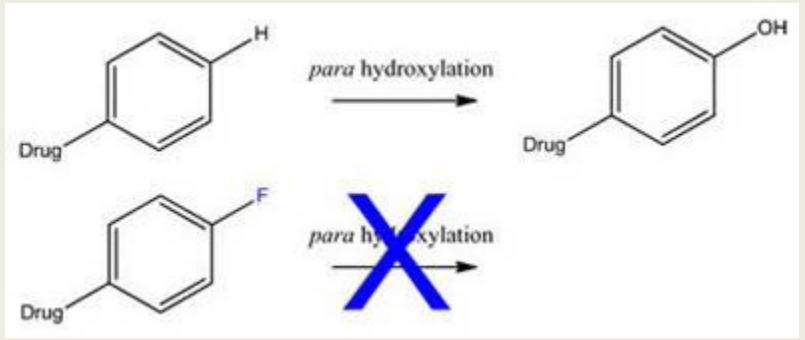
- **Decarboxylation**

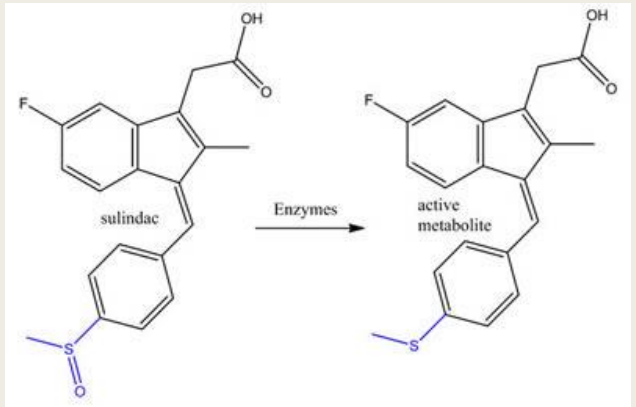


Phase I examples





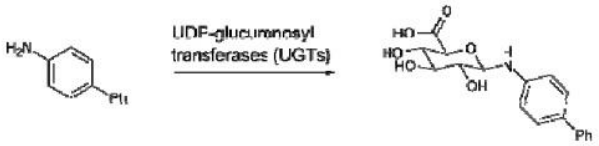




https://pharmafactz.com/medicinal-chemistry-understanding-drug-metabolism/

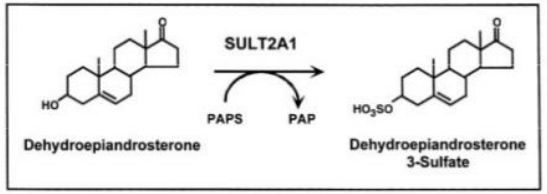
Phase II reactions

- **Glucuronidation**
- Uses UDP-Glucuronate
  - Enzyme gucuronyl transferase
  - Substrates include: benzoic acid, aniline, meprobamate, phenol, steroids.



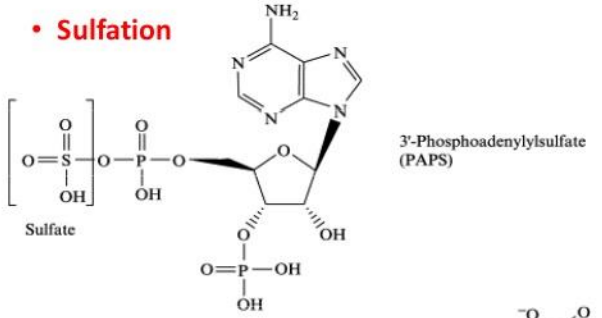
Phase II reactions

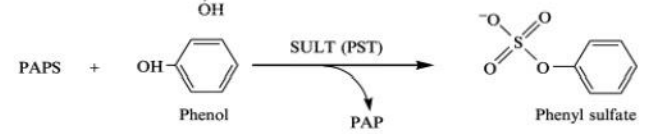
- **Sulfation**
  - Uses adenosine-3-phospho-5-pyrophosphate (PAPS) as sulfate donor
  - Substrates include: alcohols, arylamides, steroids, phenols.



Phase II reactions

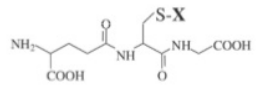
- **Sulfation**





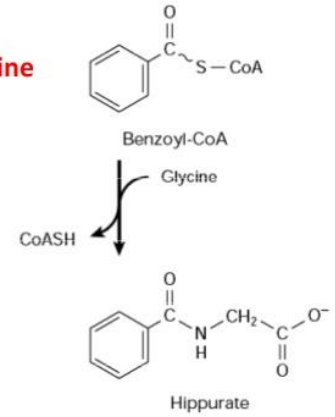
Phase II reactions

- **Conjugation with glutathione (GSH)**



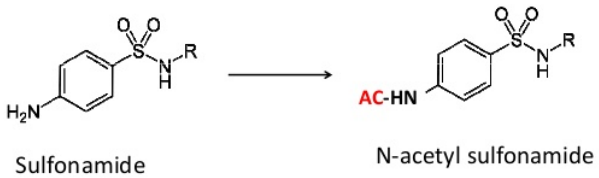
Phase II reactions

- **Conjugation with glycine**



Phase II reactions

- **Acetylation**



https://www.slideshare.net/namarta28/xenobiotics?next_slideshow=1

Factors affecting Biotransformation of drugs

- **Prior administration** of the drug or Co administration of other drugs
- **Diet**
- **Hormonal status**
- **Genetics**
- **Disease** (e.g., decreased in cardiac and pulmonary disease)
- **Age** and **developmental status**
- **Functional status** of Liver and Kidney

ADME: Elimination

Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine.

Other routes include :
the bile,
intestine,
lung, or
milk in nursing mothers.

First-Pass Effect

The first pass effect (also known as first-pass metabolism) is a phenomenon in which a drug gets metabolized at a specific location in the body that results in a reduced concentration of the active drug upon reaching its site of action or the systemic circulation.

The first pass effect is often associated with the liver, as this is a major site of drug metabolism. However, the first pass effect can also occur in the lungs, vasculature, gastrointestinal tract, and other metabolically active tissues in the body.

The greater the first pass effect, the lesser the amounts of the drug that reach the systemic circulation.

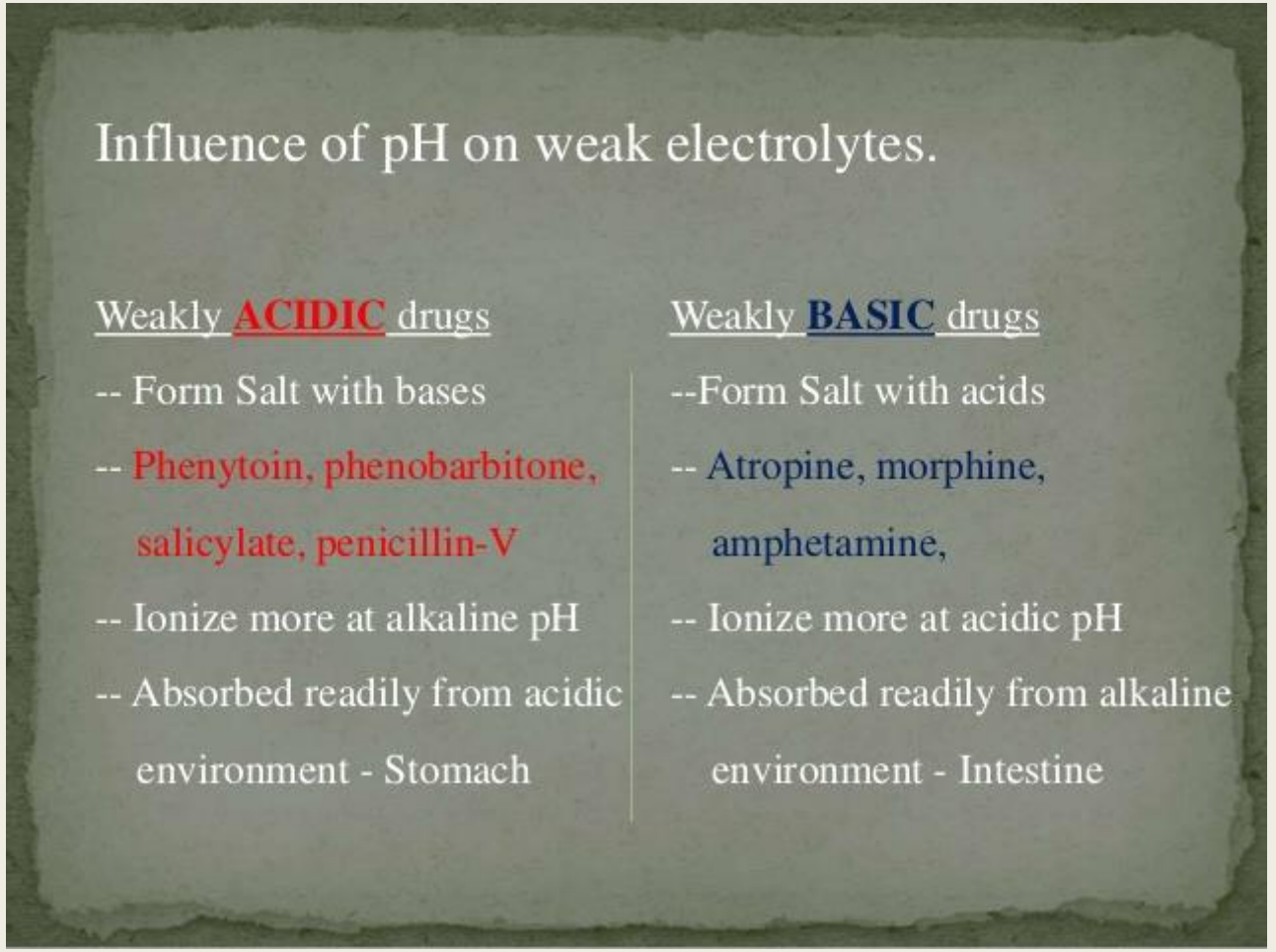
Drug Absorption Mechanisms

1. Passive Diffusion

2. Carrier mediated Transport
   - i) Facilitated Diffusion
   - ii) Active Transport

3. Endocytosis
   - i) Phagocytosis
   - ii) Pinocytosis

4. Filtration



https://www.slideshare.net/SalmanRizvi8/drug-transport-across-cell-membrane-113509419

A relationship that exists between *degree of ionization* of a weak electrolyte and *the pH of surrounding medium* is given by **Henderson-Hasselbalch equation.**

$$pK_b = pH + \log \left| \frac{\text{charged}}{\text{uncharged}} \right| \quad \text{for bases}$$

$$pK_a = pH + \log \left| \frac{\text{uncharged}}{\text{charged}} \right| \quad \text{for acids}$$

Implications of this equation :

1. Stronger acids/ weak bases have a lower pKa value.
2. Weakly acidic drugs – stomach
   Weakly basic drugs – intestine
   Net absorption from intestine usually exceeds that from stomach (short transit time and limited surface area).

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

3. At **pH = pKa**, the drug is **50%** ionized and **50%** unionized.
4. For each **unit change in pH**, there is **10 fold change** in ratio of log **[ionized form/ unionized form] of a drug**.
5. Strongly acidic/ basic drugs and quaternary ammonium compounds remain **predominantly ionized** and **are poorly absorbed.**
6. **Basic** drugs attain higher concentration **intracellularly**. (pH 7.0)

Effect of pH on Drug Absorption

- Acidic drug better absorbed in acidic media.
- Basic drug better absorbed in basic media.

- Acidic drugs (Aspirin) are better absorbed in stomach (in acidic media)

and

- Basic drugs (Diazepum) are better absorbed in intestine (in alkaline media)

Basic drugs increasingly ionized

Bases	pH	Acids
Weak		***Strong***
	2	Penicillin G (pK_a 2.8)
Diazepam (pK_a 3.3)	3	Probenecid (pK_a 3.4)
		Aspirin (pK_a 3.5)
Chlordiazepoxide (pK_a 4.8)	4	Furosemide (pK_a 4.7)
	5	Warfarin (pK_a 5.1)
		Sulfamethoxazole (pK_a 5.8)
Triamterene (pK_a 6.2)	6	Cimetidine (pK_a 6.8)
Trimethoprim (pK_a 7.2)		
Ergometrine (pK_a 7.3)		
Physiological pH	7.4	**Physiological pH**
Etidocaine (pK_a 7.7)		Thiopental (pK_a 7.5)
Lidocaine (pK_a 7.9)		Phenobarbital (pK_a 7.5)
Morphine (pK_a 8.0)	8	Phenytoin (pK_a 8.3)
Cocaine (pK_a 8.4)		
Propranolol (pK_a 9.5)	9	Chlorthalidone (pK_a 9.4)
Atropine (pK_a 9.7)		
Amphetamine (pK_a 9.8)		
Amantadine (pK_a 10.8)	10	
Lorazepam (pK_a 11.5)	11	Ascorbic acid (pK_a 11.6)
Neostigmine (pK_a 12)	12	
Strong		***Weak***

Acidic drug increasingly ionized

Absorption, permeability and bioavailability

In the mouth, the pH is neutral (or close to neutral).
In the stomach, the pH is acidic at arround 2.
In the small intestine, pH is basic at arround 8.
Finally, it reaches 7 as it reaches the end (anus).

The effect of ionisation state on rates of absorption of drugs from the small intestine is important.

Acids with pK_a values below 3 and bases with pK_a values above 8 are poorly absorbed in small intestine.

The transport of molecules across membranes is more rapid for the uncharged species.

Due to the nature of membranes and their lipophilic character, the generalisations of non-ionised states and permeability are fully understandable.

Neutral molecules are more readily able to traverse non-polar lipidic membrane environments, unlike charged compounds, where this process is energetically disfavoured.

Acid/base character and pK_a values are important determinants for absorption and permeation, however other factors need to be taken into account such as: lipophilicity, size, metabolic lability, efflux mechanisms and hydrophilicity.

In general, drugs need a suitable degree of lipophilicity to:

(a) reach the site of action, commencing with absorption from the GI tract, and

(b) interact with the appropriate receptor.

Hence, aqueous solubility is often compromised to some extent by the desired lipophilicity. The acid/base character of a drug plays an important role in determining the solubility, but this is often extensively modulated by the pH of a solution formulation causing variable polarity in aqueous solution.

Solubility

- "Solubility" is defined as the amount of a given substance that can be dissolved in a certain amount of solvent.
- Salts are ionic compounds. Recall that ionic compounds are composed of a metal and a nonmetal. Metals form cations, and nonmetals form anions.
- "Salt" is another name for an ionic compound. Salts can be soluble, sparingly soluble, and insoluble, depending on the identity of the cation and anion.