

INTRODUCTION

Pharmacology is the science of drugs¹; it tells us the life story of the drug starting from the **sources** from which the drug is obtained, passing with the **dosage forms** prepared from these sources, the **routes of administration** of these dosage forms, ending with elimination of these drugs from the body.

During the life period of the drug, it is given many types of names; first a **chemical name** that describes its formula, then it is given a code name during screening & initial evaluation. The promising drug is given a unique **generic name**. After delivering it for use, the company that sells it may give it another trade or **brand name**

e.g. Acetylsalicylic acid (chemical)

Aspirin (generic)

Aspro, Rivo or Aspeol (trade).

Aspirin



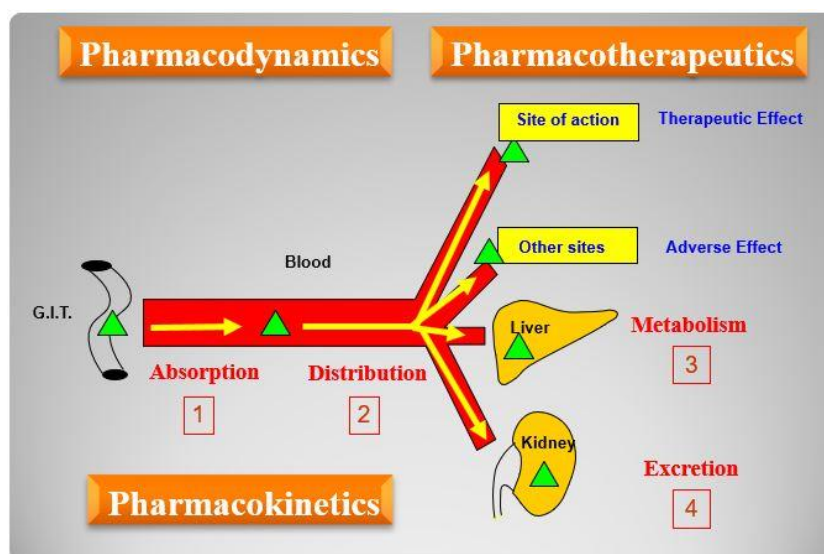
The science of pharmacology is divided into:

A) **Basic pharmacology** which deals with 2 major topics:

Pharmacokinetics (PK) which is the effect of the organism on the drug (i.e. absorption, distribution, metabolism and excretion; or simply **ADME**).

Pharmacodynamics (PD); which is the biological effect of the drug on the organism (i.e. the therapeutic effects & adverse effects together with the mechanism of each effect).

B) **Clinical pharmacology** which deals mainly with **Pharmacotherapeutics** (PT). PT includes all the factors related to the use of the drug in therapy of disease e.g. the indications of the drug (together with the dosage forms, the doses, the routes of administrations in each indication & the precautions during its use), the contraindications that prevents the use of the drug, and the drug interactions that might occur from the use of more than one drug.

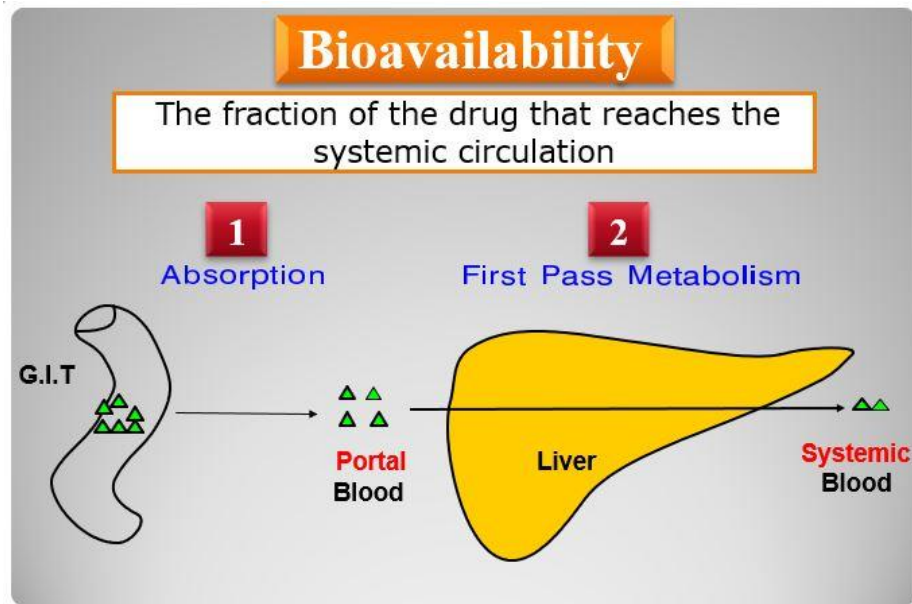


¹ The drug is any chemical substance that can be used for diagnosis, prevention or treatment of a disease and is recognized in pharmacopoeia. The pharmacopoeia is an official book containing a list of approved drugs with the available information about them e.g. British pharmacopoeia (B.P.), United state pharmacopoeia (U.S.P.), Egyptian P.

PHARMACOKINETICS

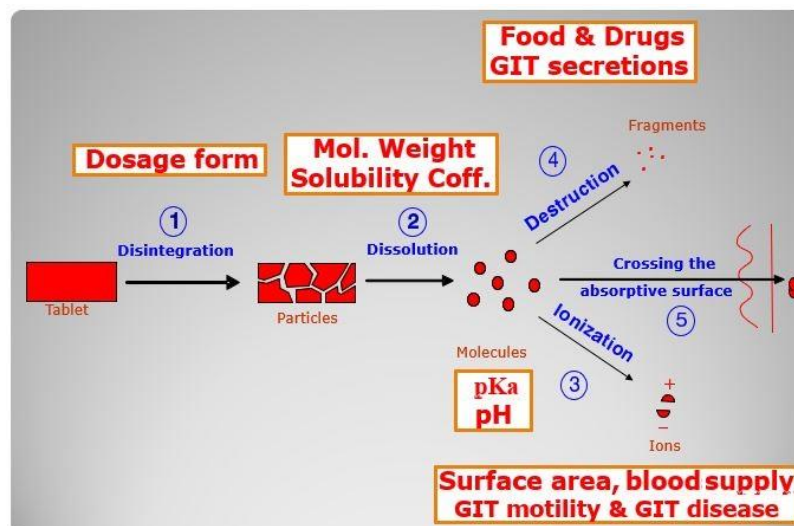
A) ABSORPTION

During its transport from the site of administration to the systemic circulation, the drug crosses many cell membranes (**absorption**); part of the drug may be metabolized before reaching the systemic circulation (**first pass metabolism**) & is eventually lost. The remaining fraction which succeeds to reach the systemic circulation is called the **bioavailability**.

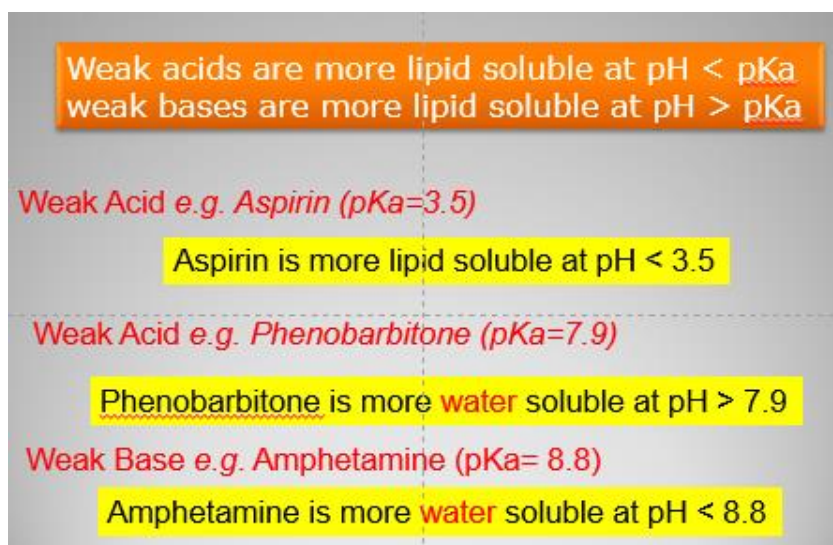


Factors which affect absorption of drugs:

1. **Factor related to the dosage form** e.g. synthesis techniques & excipients added during preparation can affect the **disintegration** of the dosage form into particles.
2. **Factor related to the drug** e.g. the molecular weight, & solubility coefficient of the drug can affect the **dissolution** of the drug particles into molecules.
3. **Factor affecting the stability of the drug in gut contents** e.g. GIT secretions; food & other drugs taken concomitantly can affect the **destruction** of the molecules.



4. The **pH of gut**, in relation to the **pKa of the drug** affects the **Ionization** of the molecules into ions².



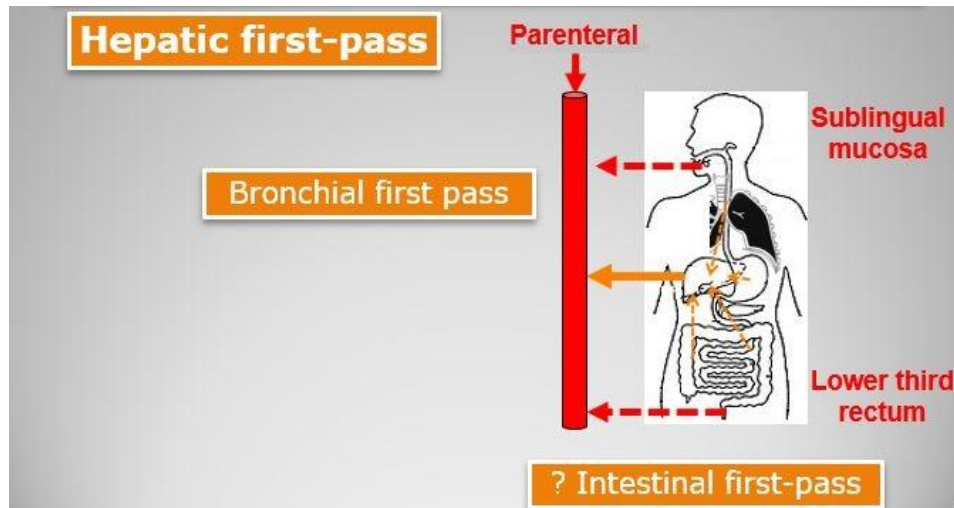
5. **Factor related to the absorptive system** e.g. the rate of gastric emptying, surface area available for absorption³, blood flow that carries the drug, any GIT disease that modifies the rate of **crossing of the absorptive surface**.

Factors affecting first-pass metabolism of drugs:

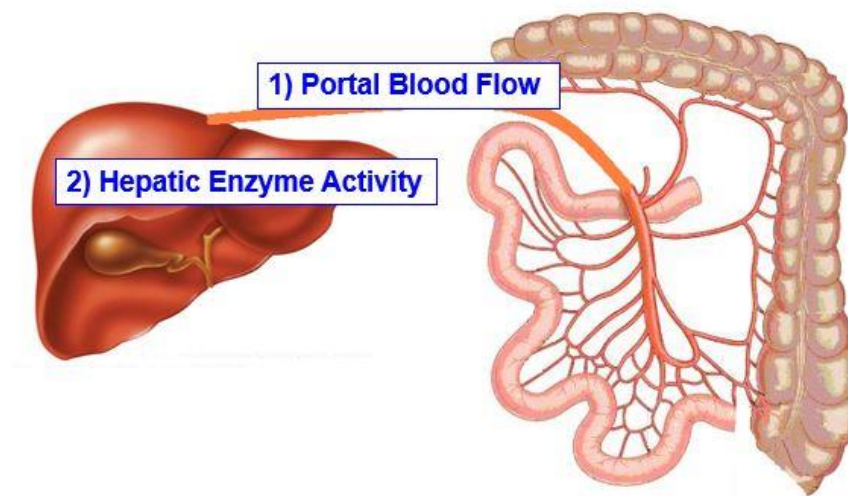
1. **The route of administration of the drug:** the hepatic first-pass effect can be completely avoided by parenteral administration (e.g. **verapamil**) or sublingual administration (e.g. **nitroglycerin**). Rectal administration, however, did not completely eliminate the hepatic first pass effect since the blood supply of the upper third of the rectum passes to the liver through the mesenteric circulation
2. **The nature of the drug:**
 - a. **Hepatic first-metabolism** occurs for drugs whose liver metabolism is very active e.g. **propranolol**, **nitroglycerin**, **morphine**
 - b. **Intestinal mucosal first pass metabolism** occurs for **estrogens**.
 - c. **Pulmonary first pass** metabolism occurs for **nicotine**.

² Absorption of drugs is mostly through simple diffusion through the lipid membranes. Ionized form of the drug is water soluble & can pass only through the water filled pores which are too narrow to allow the passage of large drug molecules. Non-ionized form of the drug is lipophilic & can pass easily through lipid membranes. When the pH of the medium = pKa of the drug; 50% of the drug molecules exist in the ionized form & 50% in the non-ionized form. Ionization of weak acids increases at pH > pKa while ionization of weak bases increases at pH < pKa e.g. aspirin (pKa= 3.5) exists mainly in the non-ionized (lipid soluble) form at gastric pH (1.5-2.5).

³ The intestine is the largest absorptive surface (200 m²); the lung come next (70 m²).



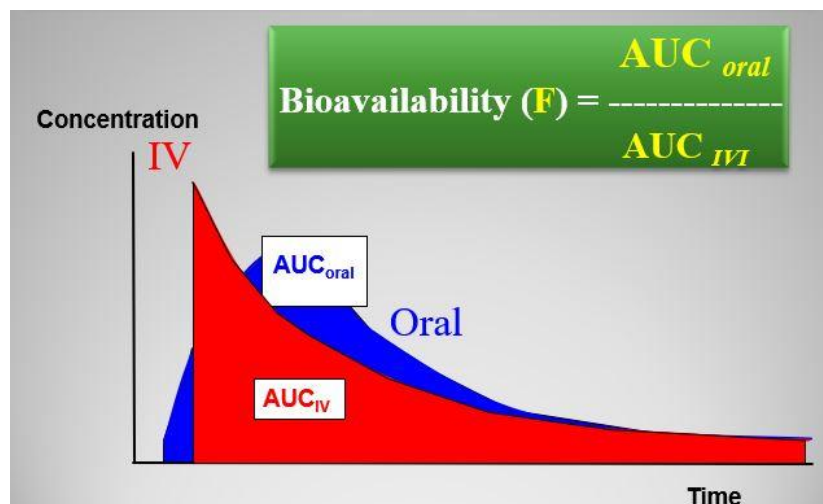
3. **Hepatic first pass metabolism** is largely reduced in situations associated with:



Decrease of the **portal blood flow** (e.g. portal hypertension, treatment with β -blockers e.g. propranolol)

Inhibition of the **hepatic enzyme activity** (e.g. liver failure, treatment with enzyme inhibitors e.g. chloramphenicol)

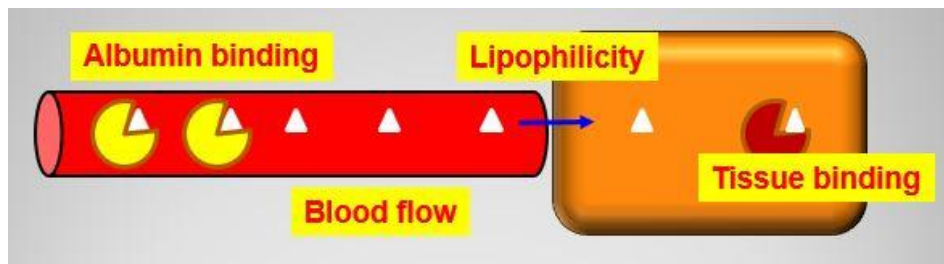
Calculation of bioavailability:



$$\text{Bioavailability (F)} = \frac{\text{AUC after administration by certain route}}{\text{AUC after IVI}}$$

B) DISTRIBUTION

After absorption; the drug is carried by the blood to various body organs. The amount of the drug delivered to each organ depends on the rate of **blood flow** to that organ. The drug may be in the free state (non-ionized lipophilic or ionized hydrophilic) or bound state (**albumin-bound**). The bound form cannot enter the organ due to the large size of the drug-albumin complex. The free non-ionized form is allowed to enter the organ freely because of its **lipophilicity** while the entrance of the free ionized form is limited as they are forced to enter through the narrow water-filled pores in the surrounding. After entrance into the tissue, **tissue binding** can attract more of the free drug molecules to enter the cell. **Capillary permeability** is not a limiting factor except in the brain.



Factors affecting Drug distribution & Vd:

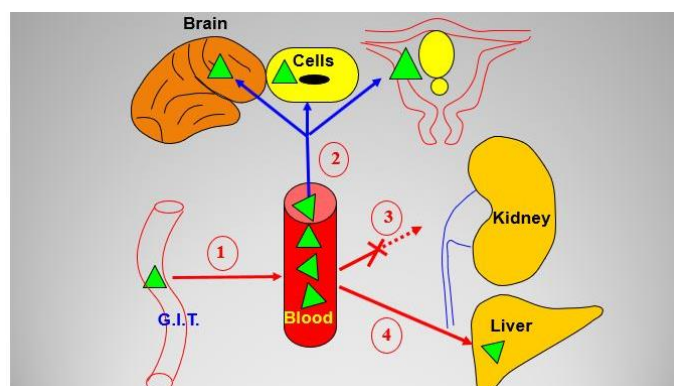
1. Blood flow (perfusion):



2. Lipophilicity:

The most important rule in PK is
“**Membrane penetration \propto lipophilicity**”

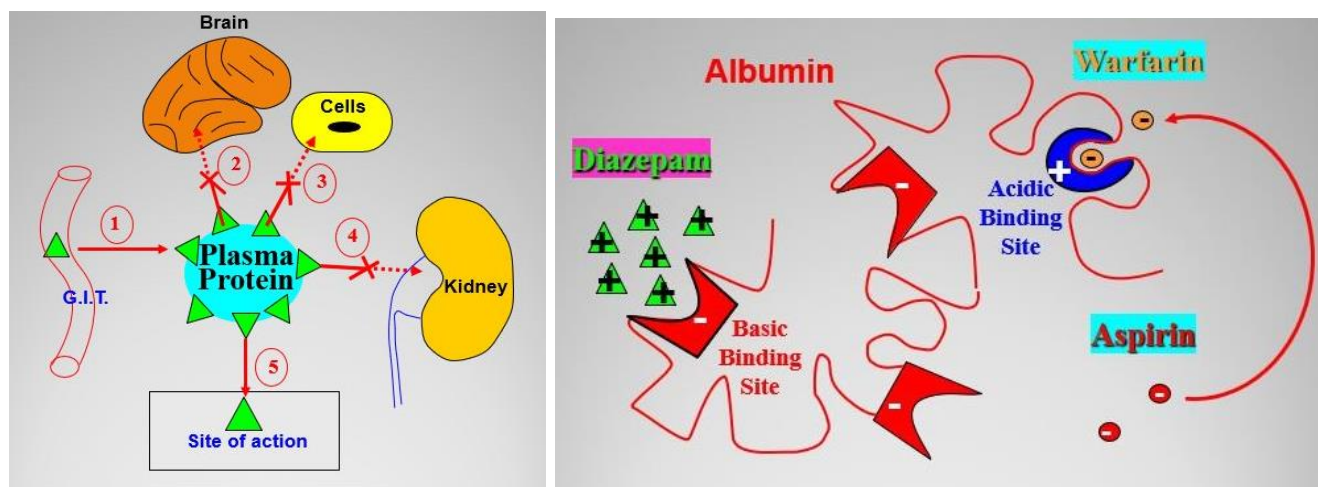
- Lipophilicity facilitates drug absorption
- Lipophilicity increases V_d , (lipophilic drugs can penetrate most tissues).
- Lipophilicity enhances hepatic elimination (lipophilic drugs enter the liver)
- Lipophilicity reduces renal excretion (due to enhanced tubular re-absorption)



Lipophilicity markedly modifies PK

3. Plasma Proteins Binding:

Albumin is the main protein that binds drugs. It has **basic binding sites** with high binding capacity (but low affinity) e.g. for diazepam, propranolol & **acidic binding sites** with high affinity (but low capacity) e.g. for warfarin, NSAIDs,



- Binding to plasma proteins may facilitate drug absorption
- Binding to plasma proteins decreases Vd, (bound drug cannot penetrate into tissues).
- Binding to plasma proteins protects the drug from renal excretion (bound drug cannot be filtered) & probably from hepatic metabolism as well⁴
- The bound drug (inactive) provides a reservoir that releases the free part (active).
- Drugs interaction occurs between highly protein-bound drugs that bound to the acidic binding site of albumin e.g. between aspirin and warfarin. The interaction is serious if one of the involved drugs is highly toxic e.g. warfarin.

Binding to albumin modifies not only PK but also PD

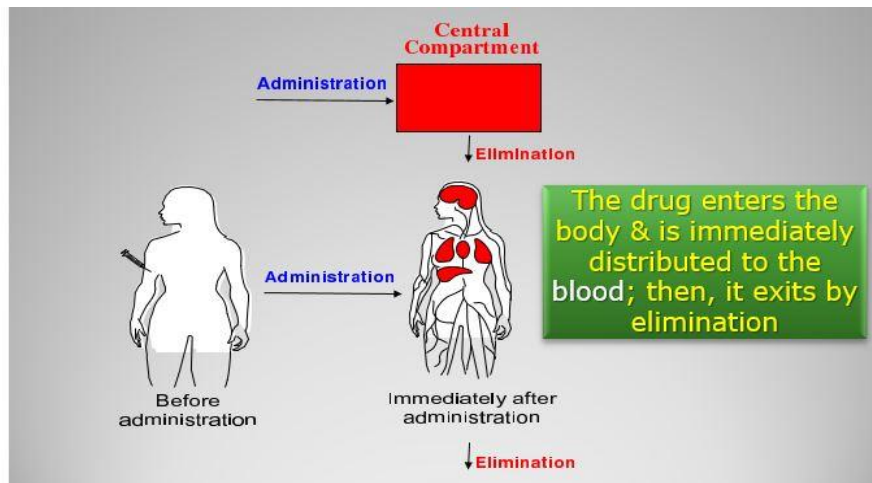
4. **Tissue Binding:** some drugs are highly bound in certain tissues e.g.
 - **Chloroquine** is highly bound to hepatic nucleic acids⁵.
 - **Tetracyclines** deposit in bone and teeth as they chelate calcium⁶.
5. **Capillary permeability:** is usually not limiting factor in distribution except in the blood brain barrier (BBB) where the capillary permeability is low:
 - **Non-ionized molecules** as 2^{ry} or 3^{ry} amines can cross BBB e.g. general anesthetics, L-DOPA, while ionized molecules as 4^{ry} ammonium compounds cannot cross e.g. neostigmine
 - **Some hydrophilic antibiotics** can cross BBB **in case of meningitis** e.g. penicillin G, as meningeal permeability is increased in this particular case.

⁴ However, albumin binding does not protect drugs with very active hepatic metabolism e.g. propranolol; in fact, binding in such case increases delivery of the drug for metabolism

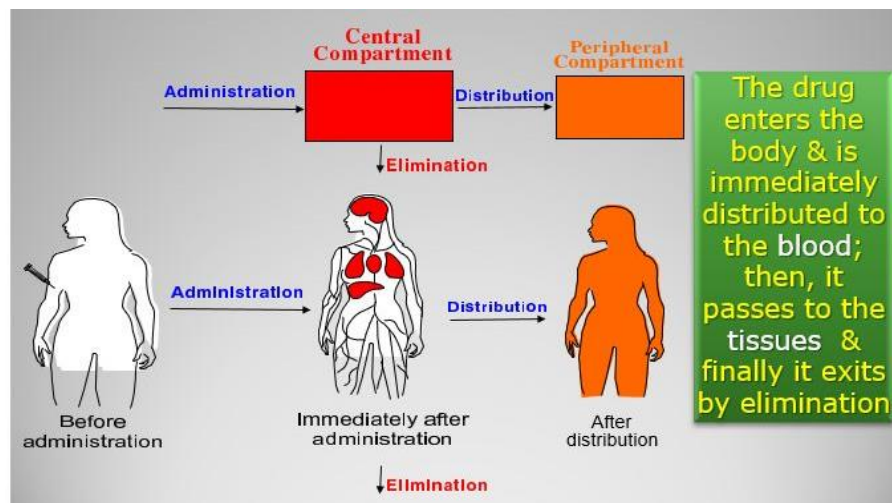
⁵ This explains its effectiveness in hepatic amoebiasis

⁶ This explains bone deformities & enamel hypoplasia in children

The drugs which do not leave the blood to enter the tissues are said to follow single compartment model of distribution.

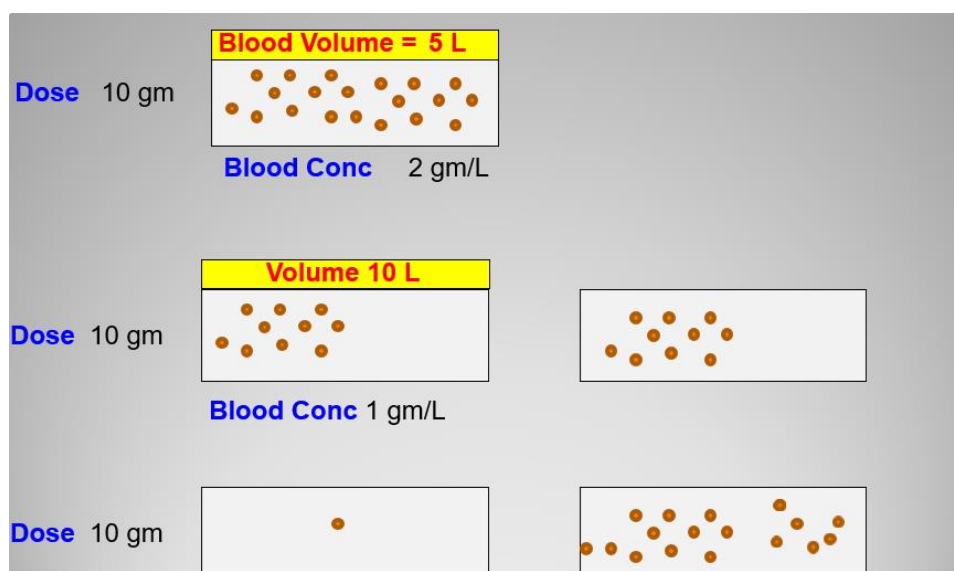


While the drugs which can enter the tissues are said to follow two compartment model of distribution,



Distribution may be roughly described by a global parameter called apparent volume of distribution (V_d).

Volume of distribution



Definition:

V_d = amount of the drug in the body / plasma or blood concentration of the drug

Importance:

1. Estimation of the tissue uptake of drugs. High V_d indicates extensive uptake
2. Estimate dializability (Drugs with high V_d are not amenable to dialysis).
3. Estimation of the loading dose (LD). (See later: $LD = V_d * C_{ss} / F$)

Passage of Drugs to the Fetus

A. Teratogenic drugs

1. Chloramphenicol → grey baby syndrome
2. Tetracyclines → enamel hypoplasia
3. Warfarin → hemorrhage/ teratogenicity.
4. Methimazole → goiter hypothyroidism.

B. CNS drugs

Narcotics, Alcohol, Nicotine → Addiction

C. Others

Laxatives e.g. senna → diarrhea

Corticosteroids → growth retardation



Chloramphenicol



Tetracycline



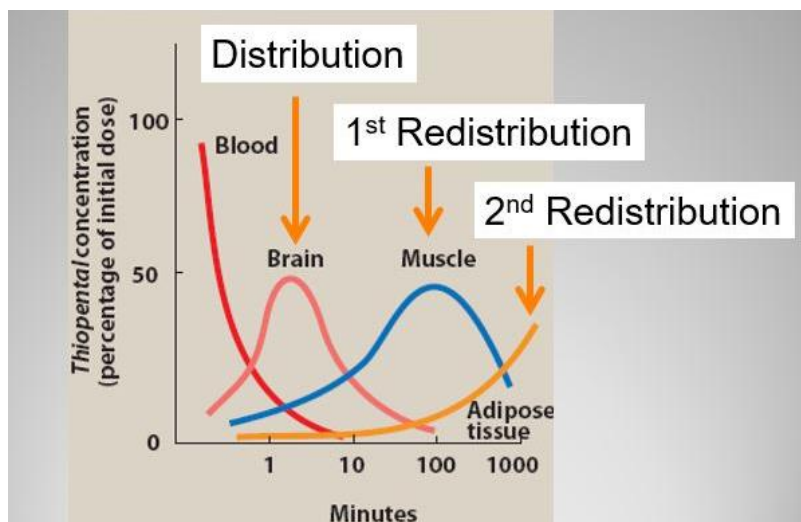
Warfarin



Methimazole

Thiopental (an IV general anesthetic) distribution is a classic example to demonstrate the importance of understanding drug distribution for clinical practice:

- **Immediately after injection** it is distributed to the brain (because of good blood flow & lipid nature of the CNS) → anesthesia
- **After about 10 minutes**, it leaves the brain to the muscles (because of the good blood flow) → Recovery from anesthesia.
- **Finally**, it leaves the muscle to stored in adipose tissue (because of high lipid content despite poor blood flow).

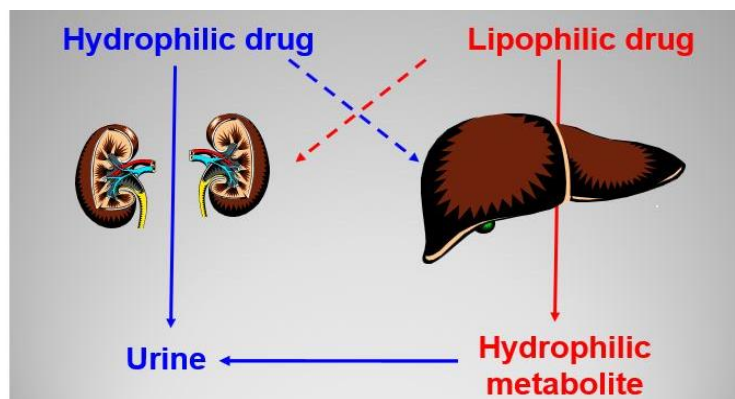


C. ELIMINATION

Lipid soluble drugs are eliminated mainly by hepatic metabolism while water soluble drugs are eliminated mainly by renal excretion⁷.

METABOLISM

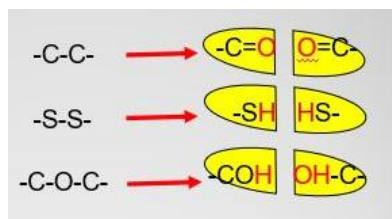
The aim of drug metabolism is to convert lipid soluble drugs into water-soluble metabolites that can be easily excreted. Although, the activity of the drug is usually lost, sometimes metabolism leads to activation of prodrugs or formation of a toxic metabolite.



Types of metabolic reactions:

1. Non-synthetic, (Phase I): usually converts the drug to a more polar metabolite:

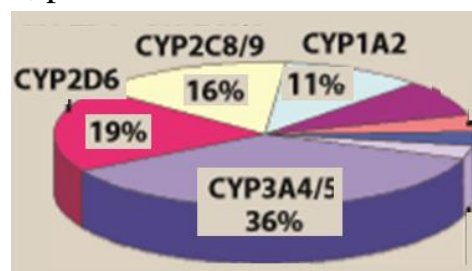
- ❑ Oxydation, e.g. adrénaline
- ❑ Reduction, e.g. nitrates
- ❑ Hydrolysis, e.g. ACh,



2. Synthetic, (Phase II):

if phase I is not efficient enough for elimination, phase II is resorted to. It includes conjugation e.g.

- ❑ Sulphation e.g. estrogens
- ❑ Acétylation, e.g. isoniazide
- ❑ Glucuronidation e.g. chloramphenicol



Sites of metabolizing enzyme:

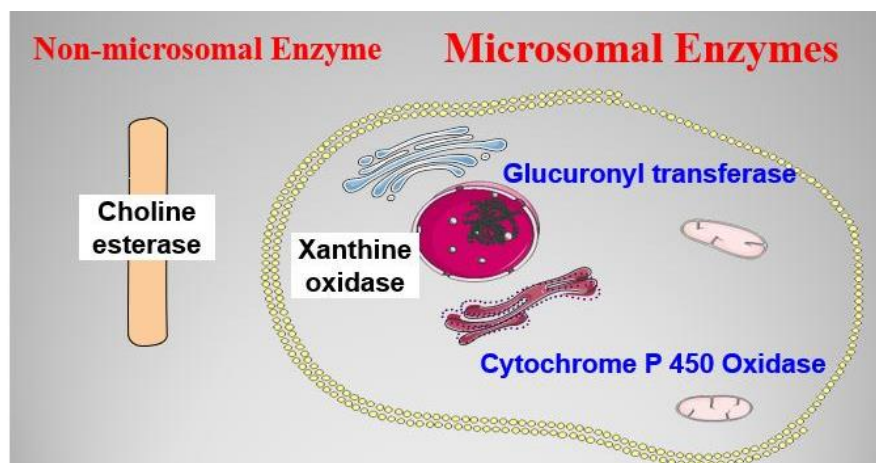
1. Microsomal enzymes e.g. **cytochrome P450 oxidases** or simply “CYP”. CYP is the most important metabolizing enzyme system. This enzyme system is further classified by family, subfamily & gene into many isozymes. The name of each one is designated by the term CYP followed by 3 characters e.g. CYP 2C9:

- 1) The first Arabic numeral represents the family,
- 2) The alphabetic letter represents the subfamily &
- 3) The second Arabic numeral represents its gene.

⁷ Renal elimination of lipophilic drugs is limited since the renal tubules will reabsorb any lipophilic molecules filtered from the glomeruli.

Hepatic elimination of hydrophilic molecules is also limited since hydrophilic molecules cannot penetrate the hepatocyte membrane

2. Non-microsomal enzymes e.g. dehydrogenase & esterases



Factors affecting drug metabolism:

1. Physiological changes in metabolizing activity due to age & sex. Or Pathological factors which affect hepatic activity e.g. liver cell failure
2. **Pharmacogenetic variations** (see idiosyncrasy later).
3. **Enzyme induction & enzyme inhibition** (see drug interactions later).

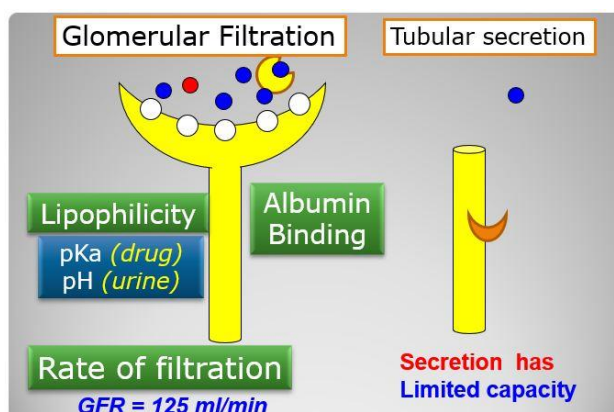
EXCRETION

Routes of Excretion:

1. The **kidney** is the most important route of elimination. Elimination occurs through:
 - **Glomerular filtration** for water-soluble molecules whose size are < the glomerular pores
 - **Active tubular secretion** either through acid carrier e.g. for penicillin, probenecid, salicylic acid, or basic carrier e.g. for amphetamine, quinine.
2. Other sites for excretion e.g. **Lungs** e.g. volatile anesthetics, **Saliva**: e.g. iodides, **Milk**: in lactating mothers e.g. basic & lipophilic drugs, **Bile**: e.g. rifampicin

Factors affecting renal excretion:

- **Glomerular filtration rate** (GFR)
- **Plasma protein binding** (PPB) → prevents filtration
- Drug **Lipophilicity** (i.e. **pH** of urine & **pKa** of the drug) → enhances reabsorption



ELIMINATION PARAMETERS

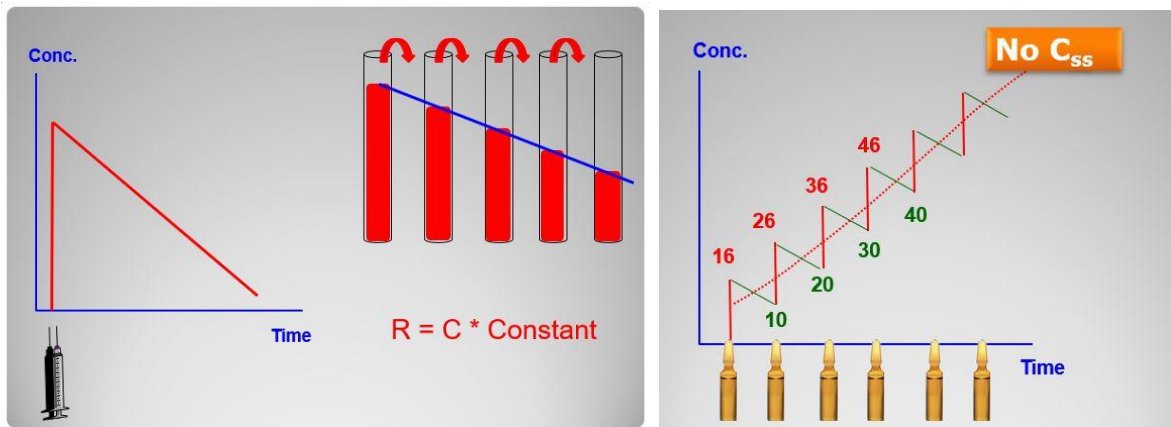
These are numerical values commonly used in measuring and describing the extent of elimination. These include the Kinetic orders, Half-life, Clearance, and Extraction Ratio.

1. Kinetic orders

Zero order Kinetics ($R = C^0 * \text{constant}$)

The rate of elimination is constant i.e.

*a constant **amount** of drug is eliminated per unit time*

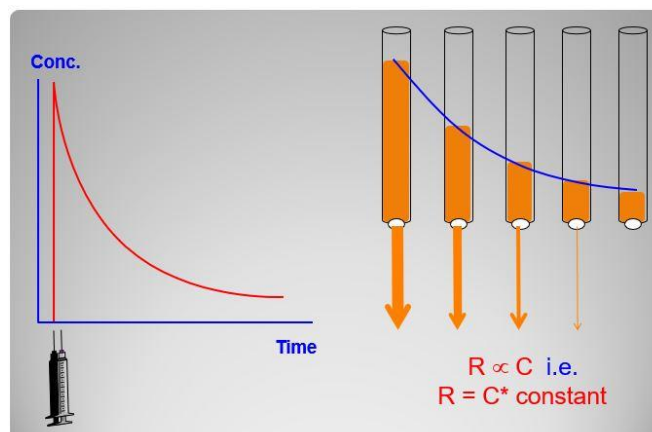


1. The concentration-time curve is linear
2. No constant half life
3. No C_{ss} is reached; repeated dosing \rightarrow overshoot conc.
4. Modest changes in dose or bioavailability can \rightarrow toxicity.
5. Examples: ethanol

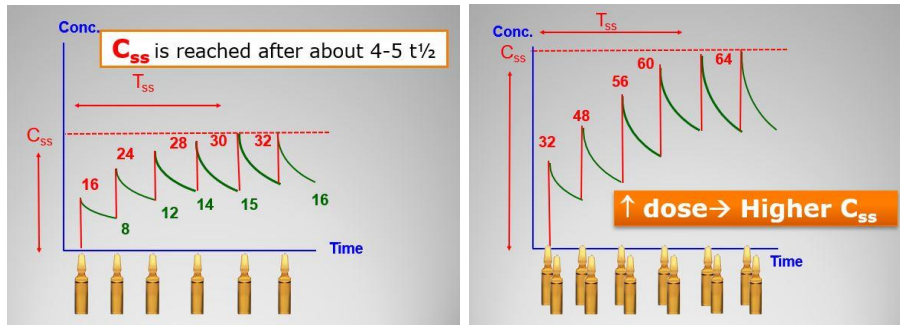
First order kinetics ($R=C * \text{constant}$)

The rate of elimination is proportional to the concentration i.e.

*a constant **fraction** of drug is eliminated per unit time*



1. The concentration-time curve is exponential
2. It can be adequately described by a constant $t_{1/2}$.
3. On repeated dosing; a steady state concentration (C_{ss}) is reached; $C_{ss} \propto \text{dose}$; Time to reach the steady state concentration (T_{ss}) is approximately 4-5 $t_{1/2}$.



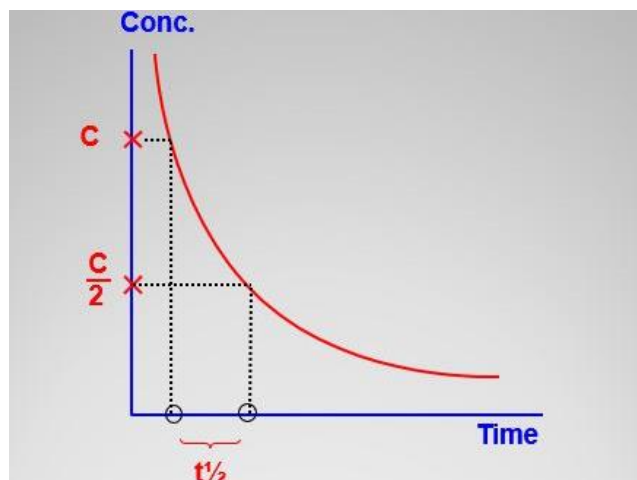
4. Modest changes in dose or bioavailability are safe
5. Examples: Most drugs are eliminated by this method

Saturation kinetics

The drug follows first order kinetics if it is eliminated by very active or non-restricted mechanism e.g. glomerular filtration or metabolism with very active enzyme. If the elimination mechanism is a lazy one; the drug follows zero order kinetics. Sometimes the elimination mechanism is in between; in such case the drug follows first order kinetics at small dose & zero order kinetics at big doses (e.g. phenytoin, theophylline & salicylates). The elimination mechanism is said to be saturated.

2. Elimination half-life ($t_{1/2}$)

It is the time required to reduce the plasma concentration of drug to half the initial concentration⁸.



Value of elimination $t_{1/2}$:

1. Deciding on the dosage interval:

- If dosage interval = $t_{1/2} \rightarrow$ body stores twice the dose⁹
- If dosage interval < $t_{1/2} \rightarrow$ more drug accumulation.
- If dosage interval > $t_{1/2} \rightarrow$ marked fluctuations in conc between doses.

2. Estimate the time to attain steady state concentration (T_{ss}): $\approx 4-5 t_{1/2}$

⁸ Elimination half-life = $\ln 2 /$ elimination rate constant = $0.693 /$ elimination rate constant.

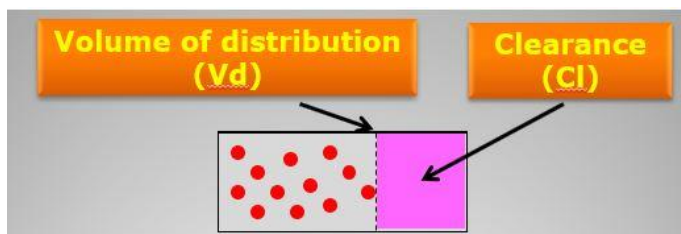
⁹ This is an accepted choice. For drugs with too short $t_{1/2}$; we may resort to IV infusion or slow release (SR) oral preparations.

Factors affecting elimination $t_{1/2}$:

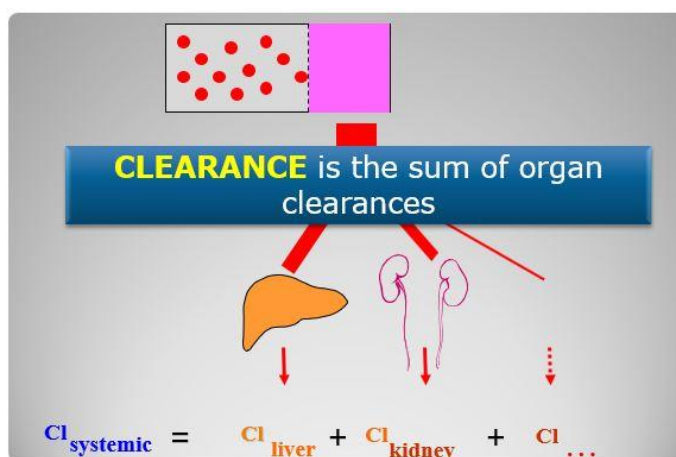
1. Function of eliminating organs i.e. liver & kidney functions
2. Delivery of the drug to the eliminating organs e.g. albumin binding limits renal filtration; also drugs with very high V_d may escape from elimination in the tissues.

3. Systemic clearance (CL)

Definition: It is the volume of a fluid cleared from the drug per unit time.



It is equal to the sum of individual organs clearance i.e. renal and non-renal clearances.



Factors affecting drug clearance: same as those affecting the half-life,

Significance of systemic Clearance

1. Calculation of elimination rate constant & half-life: $t_{1/2} = 0.693 * V_d / Cl$
2. Calculation of maintenance dose (MD): $MD = Cl * C_{ss}$

Hepatic clearance (Cl_{liver}) is the volume of blood cleared by the liver per unit time:

$$Cl_{liver} = E * Q \quad \text{where } E \text{ is the extraction ratio \& } Q = \text{hepatic blood flow}$$

Extraction ratio (E) is the fraction of the drug eliminated by the liver.

- When E is $> 0.6 \rightarrow$ clearance is nearly *flow-dependent*, e.g. propranolol.
- When E is $< 0.2 \rightarrow$ clearance is nearly *enzyme-dependent*, e.g. warfarin

