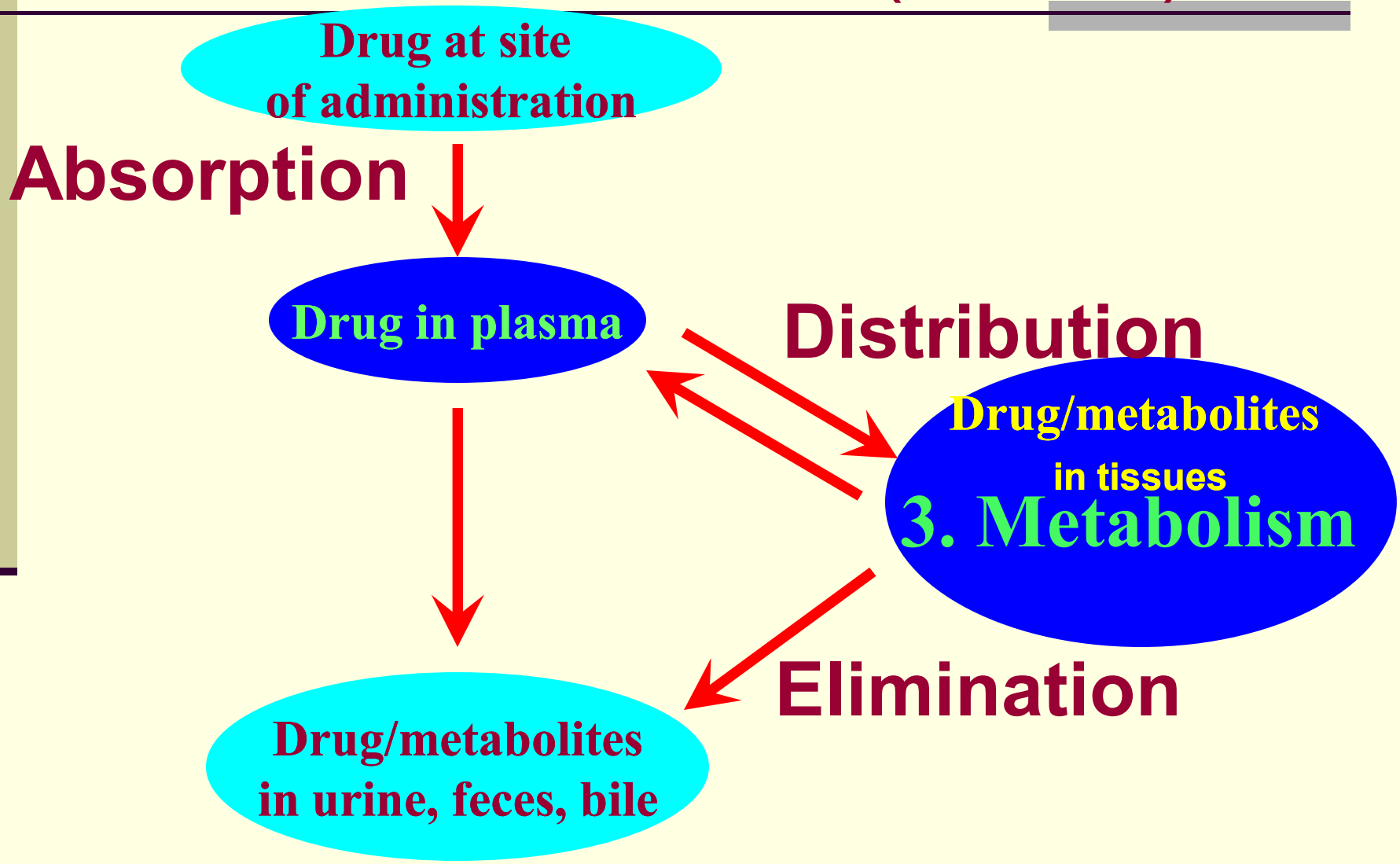
Introduction to Pharmacology
II- Pharmacokinetics

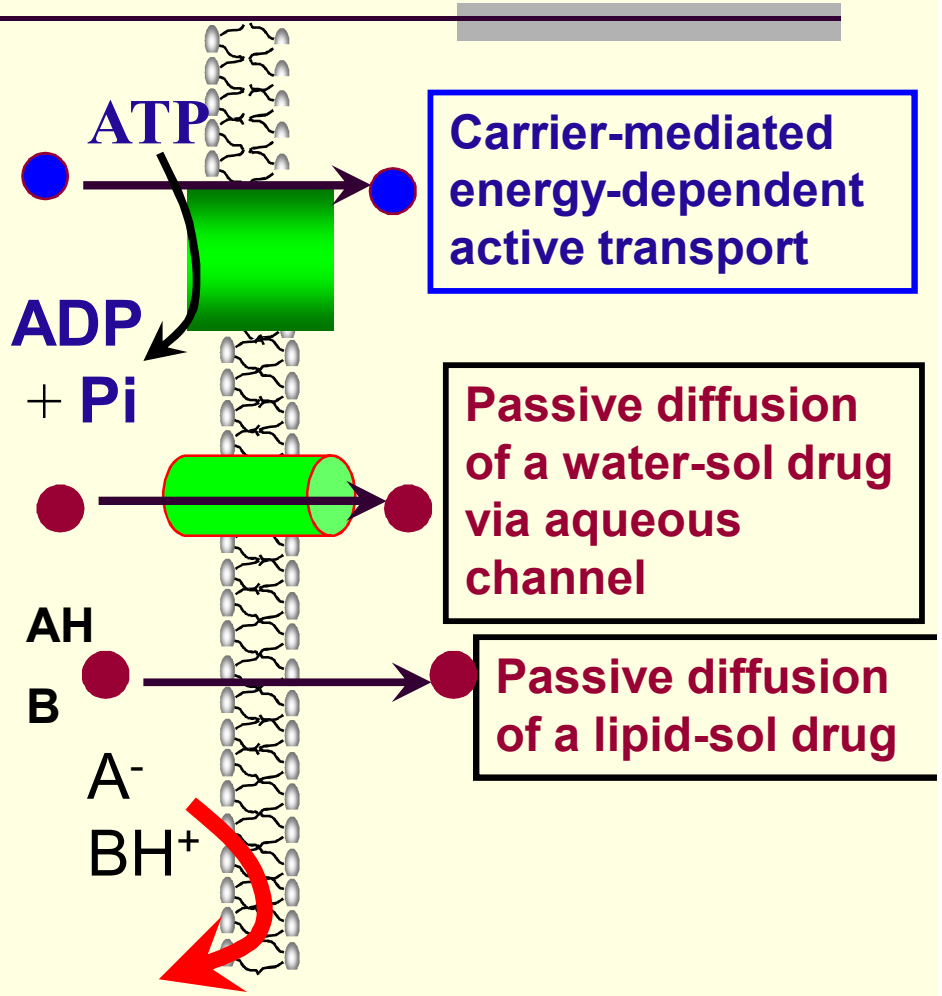
PROF DR MAHMOUD KHATTAB

Aspects of Drug Pharmacokinetics (ADME)



Drug Absorption
Active vs. Passive

- **Active transport:**
  - Carrier-mediated
  - Energy-dependent
  - Against conc gradient
  - Shows carrier saturation kinetics
- **Passive transport**
  - Energy-independent
  - No carrier involved
  - Along conc gradient
  - No saturation kinetics



Drug Absorption

- **Facilitated Diffusion**
  - Protein carrier-mediated transport
  - Saturable, selective
  - Energy-independent
  - Transport from higher to lower concentration, i.e., concentration gradient is the driving force
- **Endocytosis:**
  - Phagocytotic uptake of membrane-bound particles
  - Pinoctosis of particles into the cells as vesicles that undergo lysosomal digestion or fusion

Drug Absorption
Factors Affecting Absorption

- Effect of pH
- Only non-ionized fraction of drugs (acids or bases is absorped
- Non-ionised/ionised fraction is determined by the pH of absorption site & drug pK_a according to Henderson-Hasselbalch:

$pH = pK_a + \log \frac{\text{non-protonated}}{\text{protonated}}$

- If $pH < pK_a \rightarrow$protonated forms predominate
- If $pH > pK_a \rightarrow$non-protonated forms predominate

Absorption of basic/acidic drugs in GIT??

Factors Affecting GIT Absorption

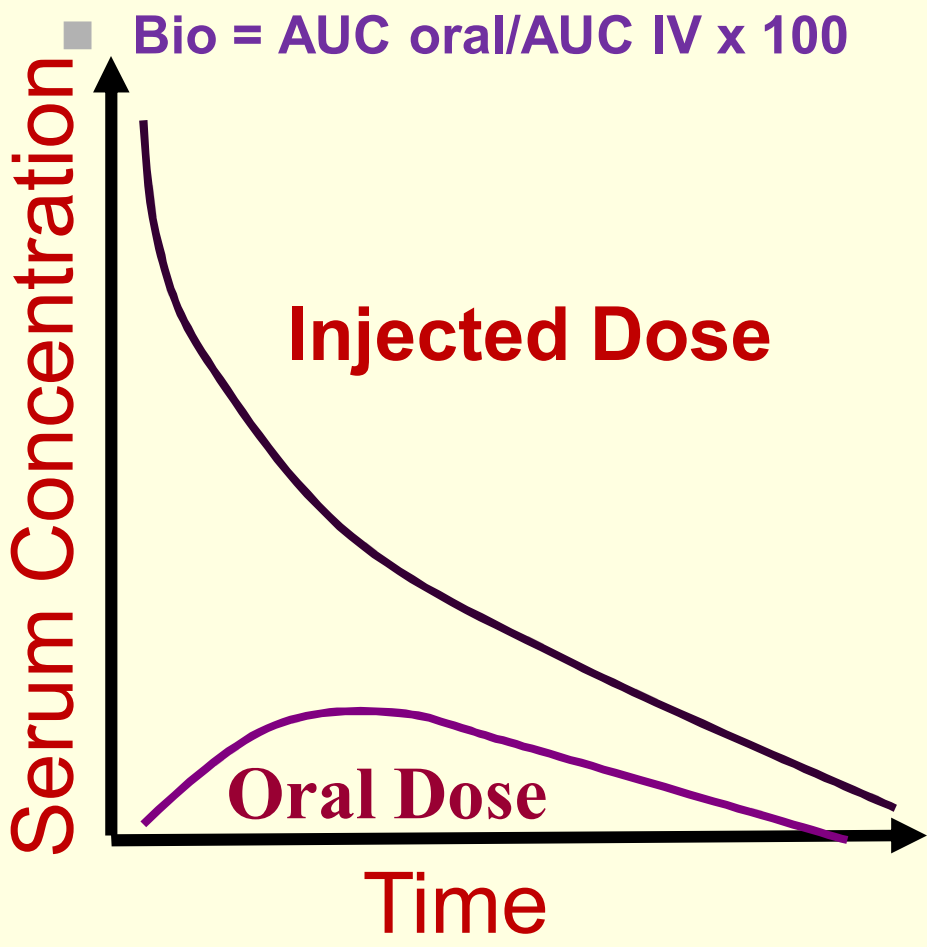
- Blood Flow To Absorptive Site:
  - Greater blood flow raises absorption
  - Intestine has greater BF than stomach
- Total Surface Area of Absorptive Site:
  - Intestinal microvilli increases surface area to 1000-fold that of the stomach favoring intestinal absorbion
- Contact Time at Absorptive Site:
  - Diarrhea reduces absorption
  - Accelerated *gastric emptying*→ faster delivery to intestinal large surface → increased absorption

Factors Affecting GIT Absorption

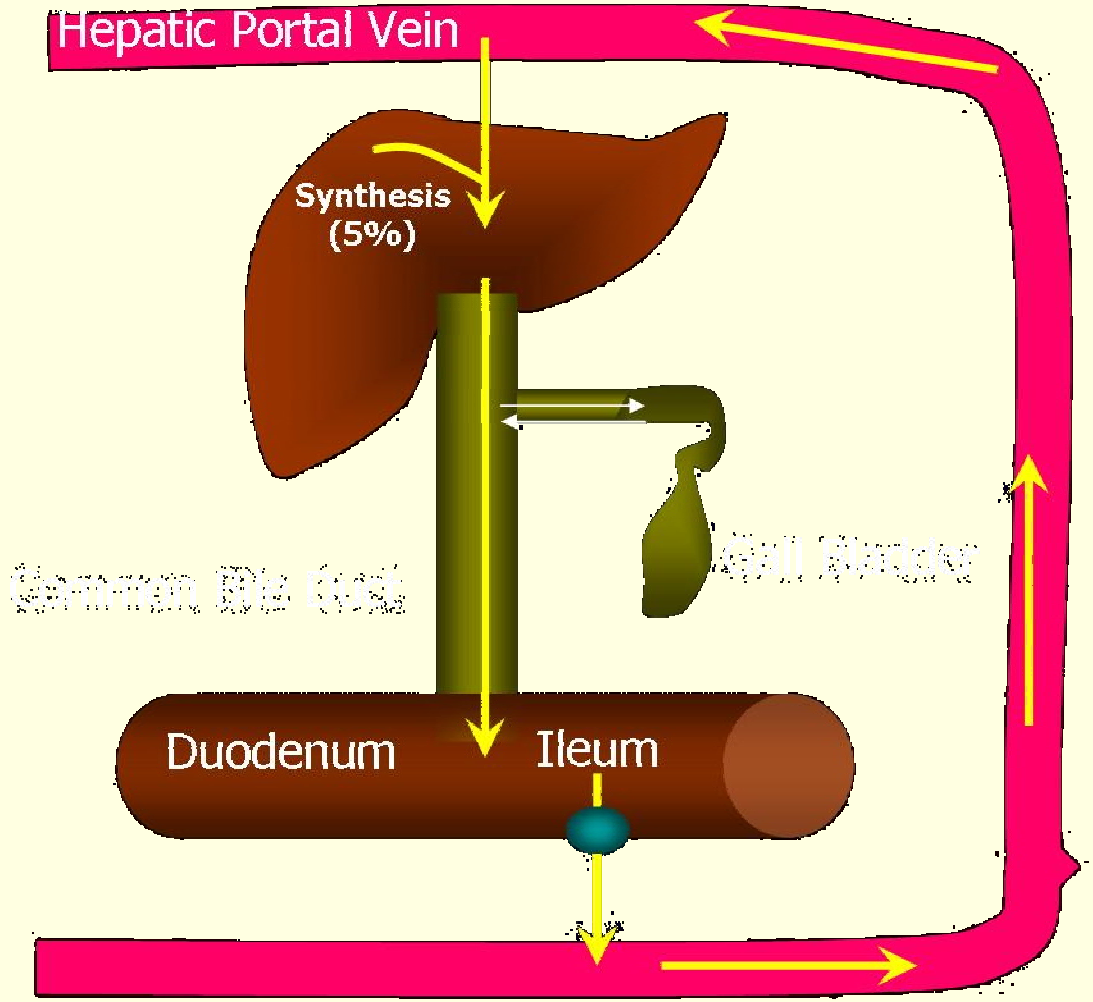
- Food: Presence of food in the gut reduces/delays drug absorption from GIT
  - Increased splanchnic blood flow during eating increases drug absorption
  - Ionized drugs as tetracycline can form insol complexes with Ca^{2+} in food/milk
- Formulation Factors:
  - Solid dosage forms dissolution & sol are essential
  - Aqueous solutions are absorbed more quickly than tablets or suspensions

BIOAVAILABIITY

- Fraction of a drug reaching systemic circulation after a particular route
- First pass metabolism, i.e., rapid hepatic metabolism, reduces bioav. (lidocaine, propranolol, nitrates)
- Drug solubility
- Chemical instability in gastric pH (penicillin G, insulin)
- Drug formulation: Standard & SR formulations



First Pass Metabolism & Enterohepatic Circulation

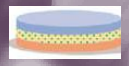


Routes of Drug Delivery

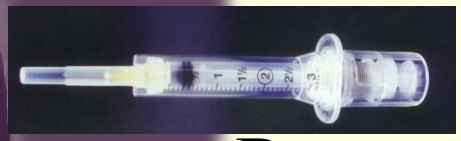
Parenteral (IV)

Inhaled

Oral



Transdermal



Parenteral (SC, IM)

Topical

Rectal

Routes of Administration

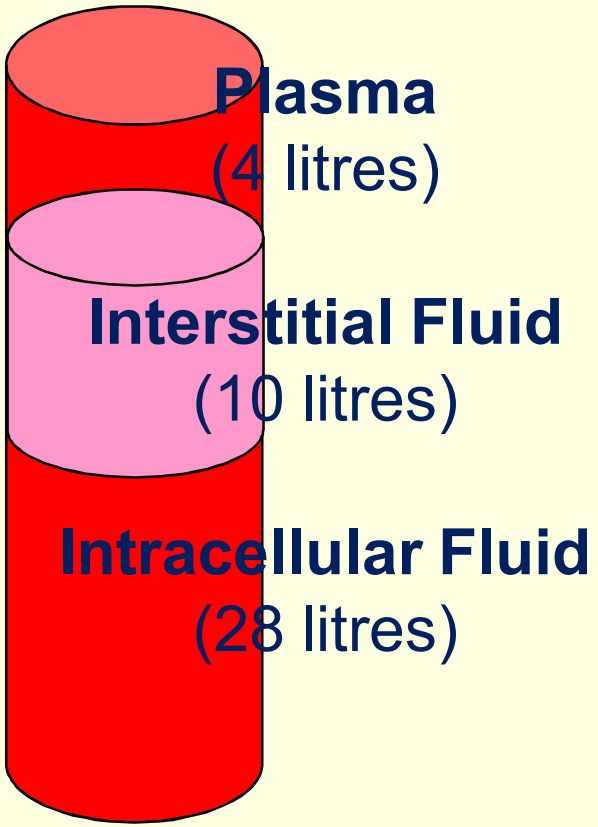
Route	Advantages	Disadvantages
Enteral	Simple, no pain, convenient	Labile to 1st pass metabolism & gastric acid, slow effect
Parenteral	Fast effect, high bioavailability, NOT labile to 1st pass metabolism & gastric acid	Infection, pain, fear, need for skill, irreversible, rapid reactions
Mucous membrane	Fast effect, NOT labile to 1st pass metabolism & gastric acid, minor systemic effect Simple, no pain, convenient	Applicable to only few drugs
Transdermal	Fast effect, NOT labile to 1st pass metabolism & gastric acid Good for prolonged regimen	Only highly lipophilic drugs, slow effect, may be irritant

Routes of Administration

- Other Routes include:
- Intranasal Route for systemic administration of drugs as clacitonin as an alternative for parenteral route
- Rectal route using suppository has the advantage of administering to drugs to unco-operative patients like children
  - Rectal route has only ~ 50% first-pass metabolism

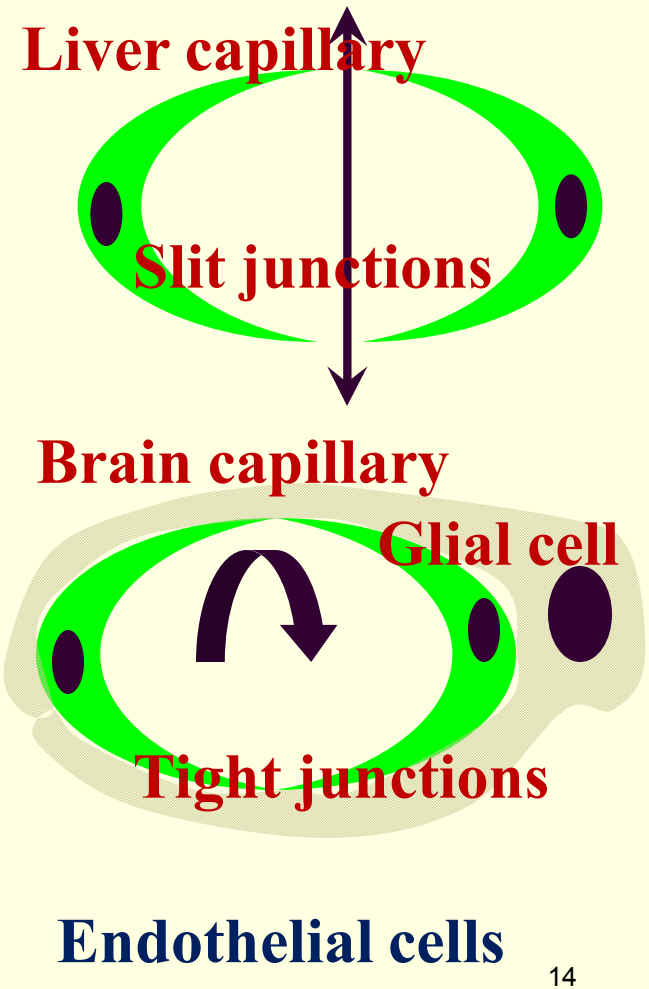
Volume of Drug Distribution
Water Body Compartments

- Drugs may distribute into
- **Plasma (Vascular) Compartment:**
  - Too large mol wt
  - Extensive plasma protein binding
  - Heparin is an example
- **Extracellular Fluid**
  - ✓ Low mol wt drugs able to move via endothelial slits to interstitial water
  - ✓ Hydrophilic drugs cannot cross cell membrane to the intracellular water
- **Total Body Water;** Low mol wt hydrophobic drugs distribute from interstitial water to intracellular



Factors Affecting Distribution

- ***Capillary permeability***
  - Endothelial cells of capillaries in tissues other than brain have wide slit junctions allowing easy movement of drugs
  - Brain capillaries have no slits between endoehelial cells, i.ee., tight junction or blood brain barrier
  - Only carrier-mediated transport or highly lipophilic drugs enter CNS
  - Ionised or hydrophilic drugs can't get into the brain



Barriers to Drug Distribution

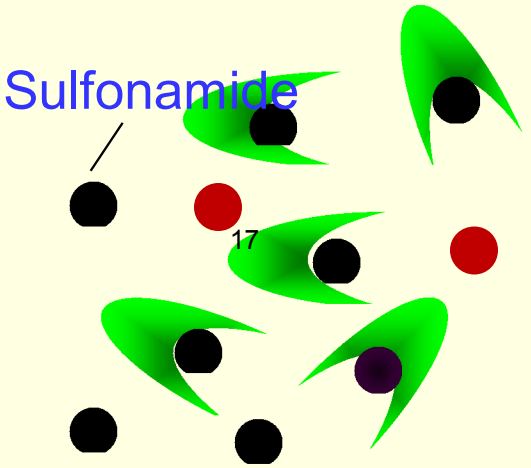
- Blood-Brain barrier:
  - ✓ Inflammation during meningitis or encephalitis may increase permeability into the BBB of ionised & lipid-insol drugs
- Placental Barrier:
  - ✓ Drugs that cross this barrier reaches fetal circulation
  - ✓ Placental barrier is similar to BBB where only lipophilic drugs can cross placental barrier

Factors Affecting Distribution

- **Blood Flow (Tissue Perfusion):**
  - The greater the blood flow to a tissue, the faster and more distribution occurs from the plasma to the interstitial fluid
  - Thus, Drugs will be distributed more rapidly to liver, brain & kidney more than muscles, skin, or fat depot (more cardiac output)
- **Plasma Protein Binding:**
  - Many drugs bind reversibly to plasma proteins especially albumin **D + Albumin↔ D-Albumin (Inactive) + Free D**
  - Only free drug can distribute, binds to receptors, metabolized and excreted

Clinical Significance of Albumin Biding

- **Class I**: dose < available albumin binding sites (most drugs)
- **Class II**: dose > albumin binding sites (e.g., sulfonamide)
- Drugs of class II displace Class I drug molecules from binding sites→ more therapeutic/toxic effect
- In some disease states → change of plasma protein binding
- In uremic patients, plasma protein binding o acidic drugs is reduced
- Plasma protein binding prolongs duration



Displacement of Class-I Drug

Selective Distribution of Drugs

- Kidney: Metallothionin leads to accumulation of metals like lead, cadmium & mercury
- Eye: Retinal malanin has affinity for drugs like chlorpromazine (& phenothaizines) & chloroquione leadig to their accumulation
- Fat: Highly lipid-sol drugs tend to accumulate in body fat
- Bone can accumulate agents like tetracycline, lead, and cisplatin
- Lungs (the whole cardiac output)
  - Basic amine lipophilic drugs with pKa > 8 tend to accumulate in the lungs
  - Herbicides like paraquat tend to deposit in lung as well

Apparent Volume of Distribution

Volume of Distribution V_D

V_D = Dose/Plasma Concentration

- The volume (non-real) required to contain the total amount of absorbed drug in the body at a uniform concentration equivalent to that in plasma at steady state
- Units: L and L/Kg
- Drugs retained in the intravascular space have the lowest V_D values
- An extensively distributed drug like amiodarone has V_D of 60 L/Kg (4200 L/70 Kg)
- In general, larger V_D leads to prolonged duration ($t_{1/2}$)

Drug Elimination
Renal Excretion

- **Glomerular filtration depends on:**
  - Renal blood flow & GFR; direct relationship
  - Plasma protein binding; only free unbound drugs are filtered
- **Tubular Secretion** in the proximal renal tubule mediates raising drug concentration in PCT lumen
  - ✓ Organic anionic & cationic transporters (OAT & OCT) mediate active secretion of anionic & cationic drugs
  - ✓ Passive diffusion of uncharged drugs
  - ✓ Facilitated diffusion of charged & uncharged drugs
  - ✓ Plasma protein binding has ONLY slight effect because of the fast removal of unbound drug from peritubular capillaries
  - ✓ Penicillin is an example of actively secreted drugs

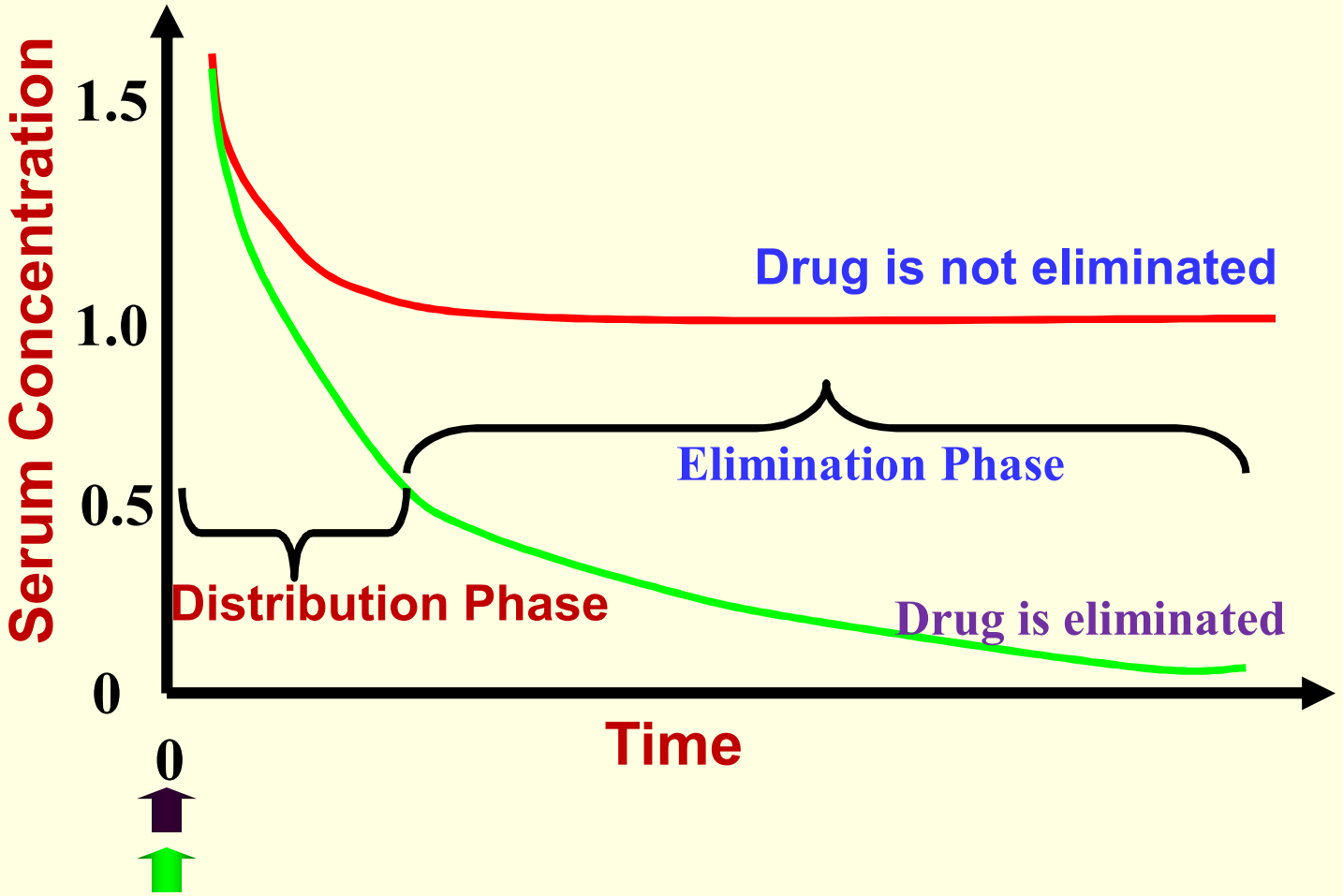
Drug Elimination
Renal Excretion

- **Tubular re-absorption in DCT:**
- **Because of water re-absorption, urinary D concentration increases towards DCT favoring passive diffusion of un-ionized lipophillic drugs**
- **It leads to lowering urinary drug concentration**
  - **Urinary pH trapping:**
  - **Chemical adjustment of urinary pH can inhibit or enhance tubular drug reabsorption**
  - **For example, aspirin overdose can be treated by urine alkalinization with Na Bicarbonate (ion trapping) and increasing urine flow rate (dilution of tubular drug concentration)**
  - **Ammonium chloride can be used as urine acidifier for basic drug overdose treatment**

Drug Elimination

- **Pulmonary excretion of drugs into expired air:**
  - Gases & volatile substances are excreted by this route
  - No specialized transporters are involved
  - Simple diffusion across cell membrane predominates
  - It depends on:
  - ✓ *Drug solubility in blood*: more sol gases are slowly excreted
  - ✓ *Cardiac output* rise enhances removal of gaseous drugs
  - ✓ *Respiratory rate* is of importance for gases of high blood solubility
- **Biliary excretion** of few drugs into feces
  - Such drugs are secreted from the liver into the bile by active transporters, and then into duodenum
  - Examples: digoxin, steroid hormones, some anticancer agents
  - Some drugs undergo enterohepatic circulation back into systemic circulation

Drug Distribution and Clearance



Clearance

- Clearance (CL) is *the volume* of blood/fluid cleared of drug per unit time
- It is ability of kidney, liver and other organs to eliminate drug from the bloodstream
- Units are in L/hr or L/hr/kg
- Used in determination of maintenance doses
- Drug metabolism and excretion are often referred to collectively as clearance
- The endpoint is reduction of drug plasma level
- *Clearance (total) = renal clearance + Hepatic clearance + others*
- Hepatic, renal and cardiac failure can each reduce drug clearance and hence increase elimination $T_{1/2}$ of the drug
- **$CL = kV_D$**, k: elimination rate constant

Metabolism & Excretion Kinetics

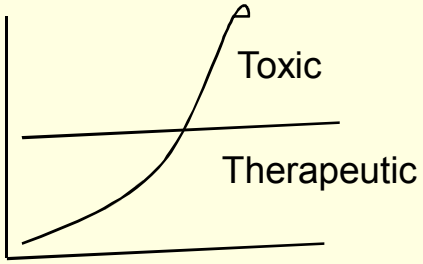
- Elimination (metabolism + excretion) of most drugs follow *first-order kinetics* at therapeutic dose level
- Amount of drug cleared in a given unit of time is directly proportional to the concentration of the drug according to *Michaelis-Menten (linear) kinetics:*

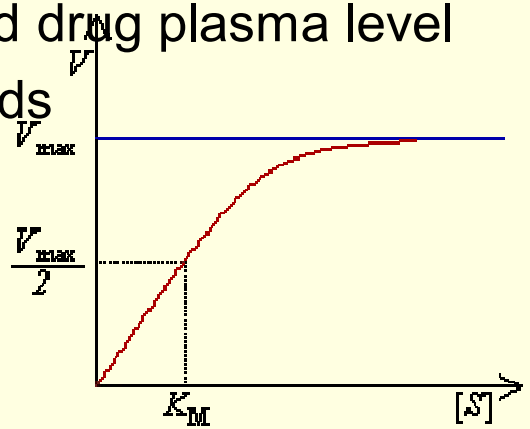
$$E = \frac{V_{max} \times C}{k_m + C}$$

- Only few drugs (e.g., phenytoin, alcohol) show

saturation clearance (Zero-order, non-linear) kinetics

- Clearance mechanisms become saturated at therapeutic level, and clearance remain constant even with increased drug plasma level
- SLOW ELIMINATION at therapeutic levels leads to toxic reactions





Loading Dose

- Loading Dose = Target Plasma C x VD
- What Is the is the loading dose required fro drug A if:
  - target concentration is 10 mg/L
  - VD is 0.75 L/kg, patients weight is 75 kg

Answer

- VD = 0.75 L/kg x 75 kg = 56.25 L
- Target Conc. = 10 mg/L
- Dose = 10 mg/L x 56.25 L = 565 mg

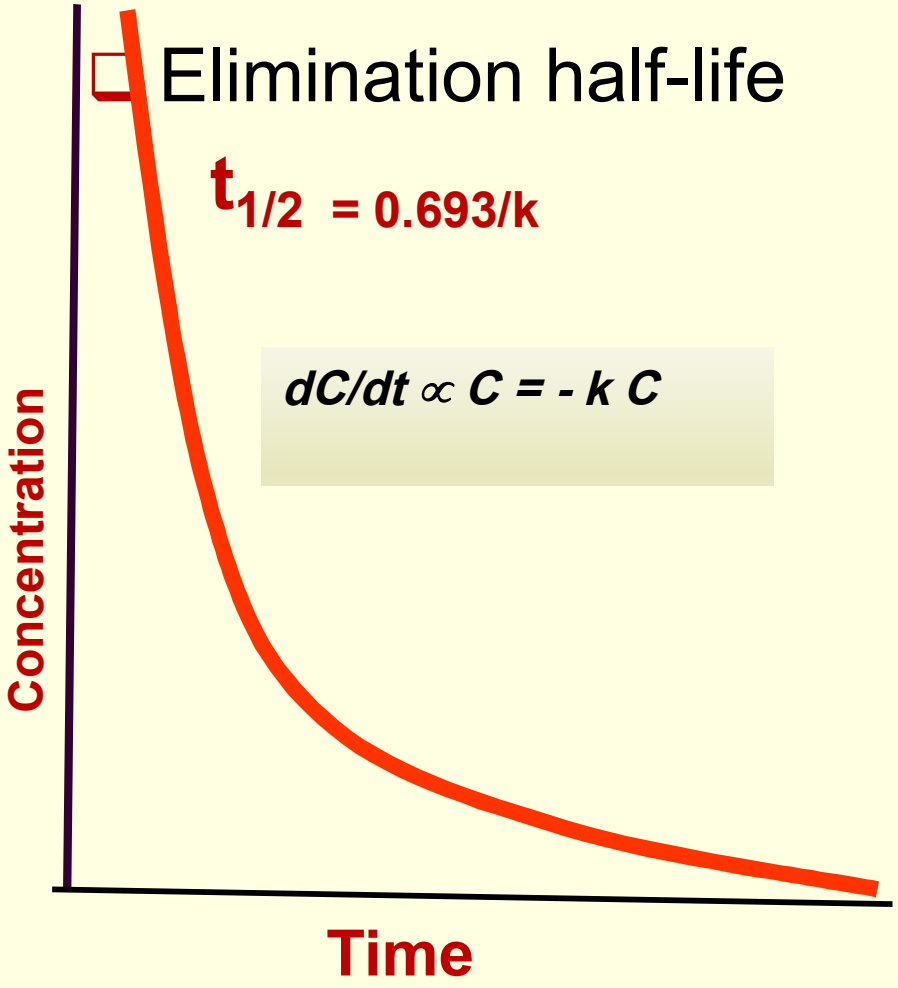
Maintenance Dose

- **Maintenance Dose**

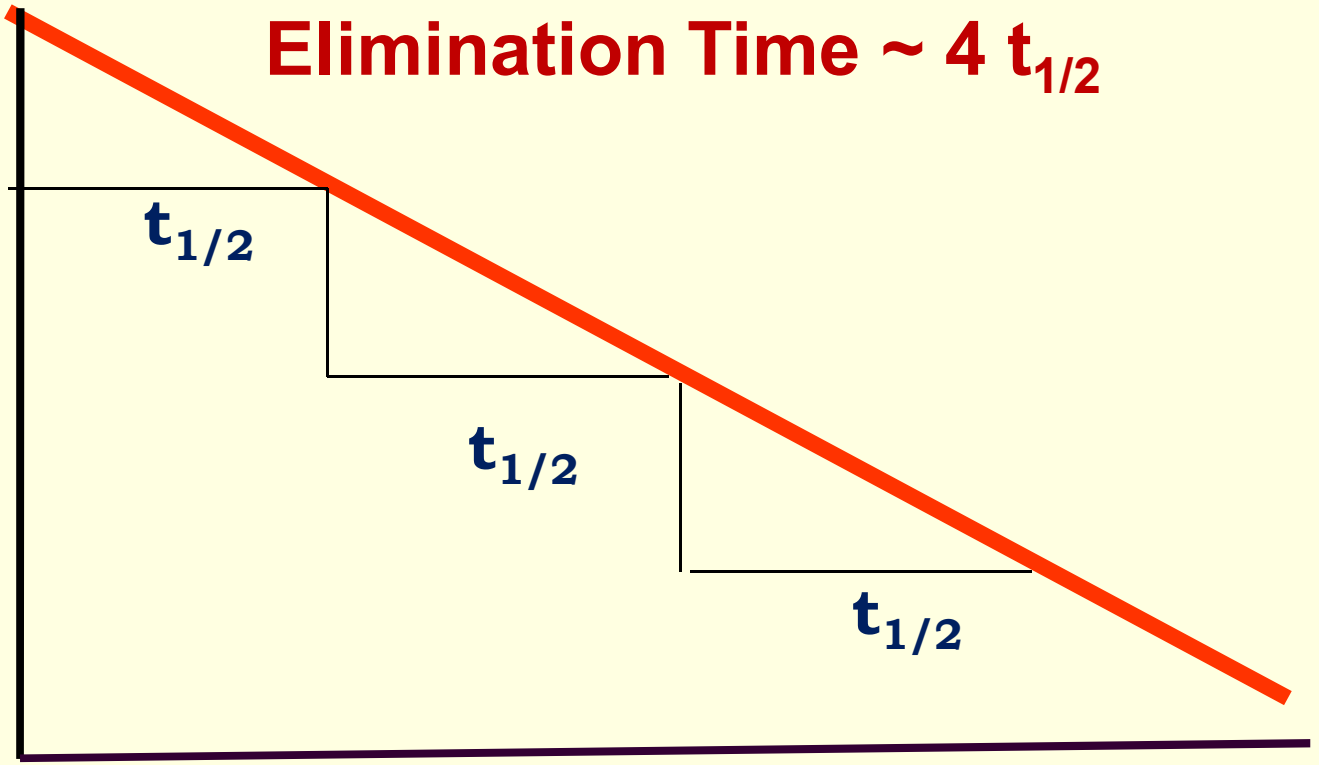
  = CL x target steady state drug concentration
- The units of CL are in L/hr or L/hr/kg
- Maintenance dose will be in mg/hr
- Total daily maintenance dose = multiplying by 24

Half-Life and Elimination Rate Constant (k)

- Half-life is the time taken for the drug concentration to fall to half its original value
- The elimination rate constant (k) is the fraction of drug removed per unit time

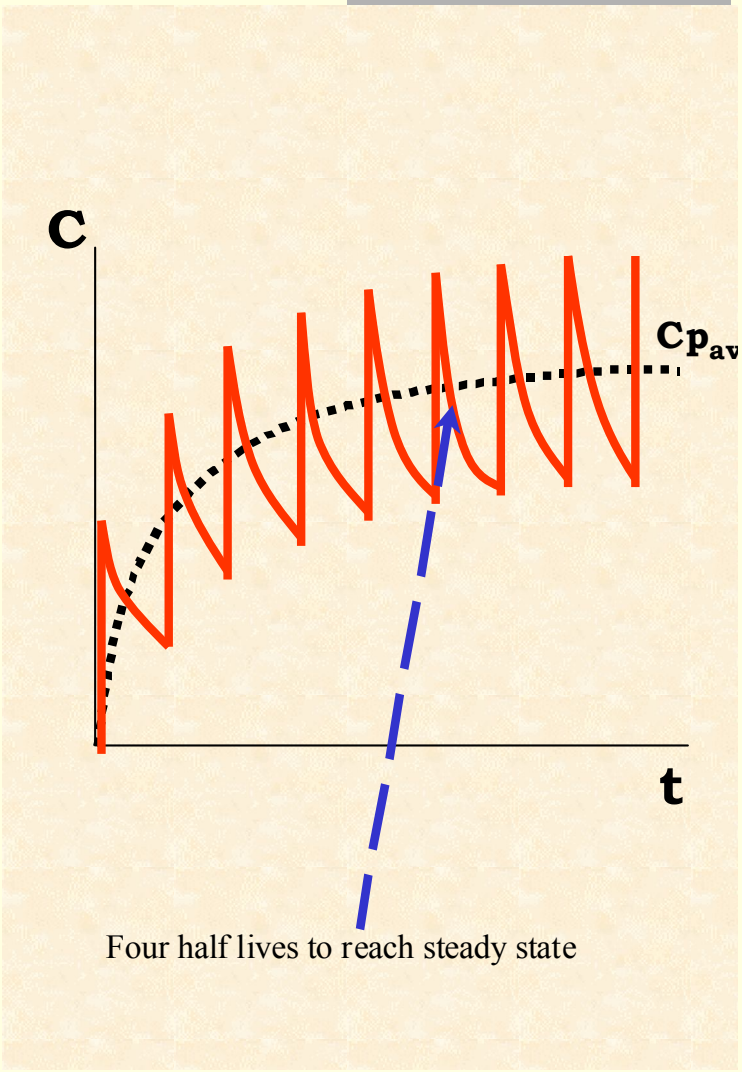


Elimination Time ~ 4 $t_{1/2}$



Steady-State

- Steady-state occurs after a drug has been given for approximately 4-5 $t_{1/2}$
- At steady-state the rate of drug administration equals the rate of elimination
- Plasma concentration after each dose is approximately the same



Importance of Steady State (SS)

- At SS Rate in = Rate Out
- Steady state is reached usually within 4 – 5 half-lives at linear kinetics
- It is important for drug concentrations interpretation in:
  - Therapeutic Drug Monitoring (TDM)
  - Evaluation of clinical response