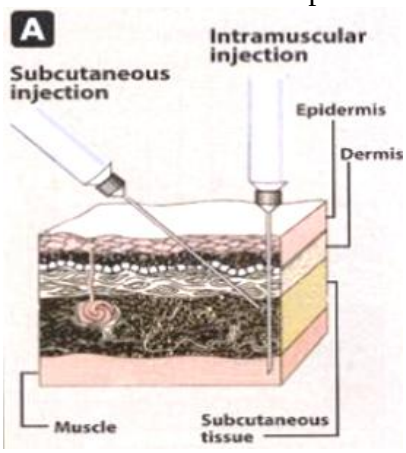
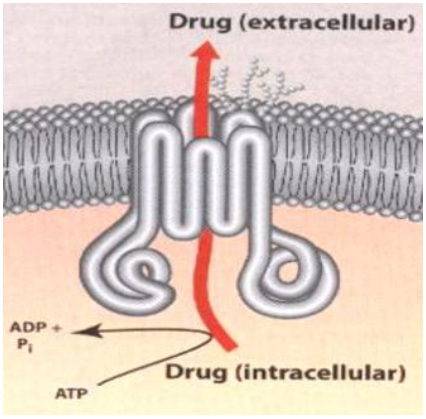
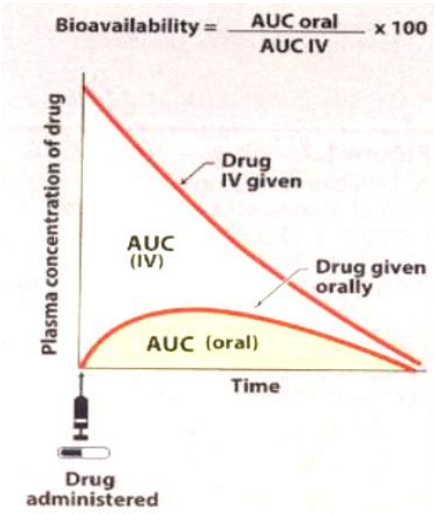
- Remember that a balanced state is always defined as a balance between input and output (input = output). This is known as a one-compartment model.
- Two-compartment model: input going to compartment 1 → transported to compartment 2 → output.
- Three-compartment model: input going to compartment 1 → then it will be transported either to compartment 2 or directly to compartment 3 → output.
- **Pharmacokinetics**: it is represented by actions of the body on drugs, including the principles of drug absorption, distribution, biotransformation (which is also known as metabolism) and excretion.
- **Major routes of drug administration:**
  - **Alimentary (enteral – معوي): this could be**
    - ✓ Oral: commonest route.
    - ✓ Buccal: between gum and cheeks.
    - ✓ Sublingual: under the tongue (bypassing hepatic first-pass metabolism).
    - ✓ Rectal (suppository – تحميلة): approximately 50% of drug absorbed from the rectum will bypass the liver.
  - **Parenteral (بالحقن): this could be:**
    - ✓ Intravenous: 100% of drug enters the circulation.
    - ✓ Intramuscular: minimizes hazards of intravascular injection.
    - ✓ Subcutaneous.
    - ✓ Intrathecal: in cases of acute CNS infection or spinal anesthesia.



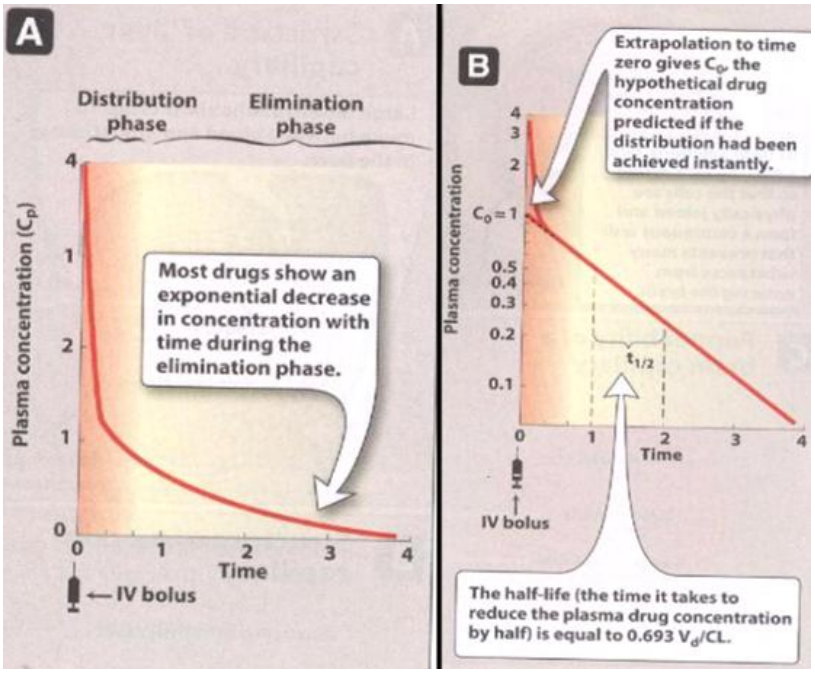
  - **Inhalation**: pulmonary agents such as sprays used for asthma.
  - **Topical**: usually for treatment of localized disease (e.g. psoriasis الصدفية, acne and eye infections).
  - **Transdermal.**
  - **Subcutaneous.**
- **How does a drug pass across the cell membrane?**
  - **Passive diffusion:**
    - ✓ A water-soluble drug will pass through an aqueous channel or pore.
    - ✓ A lipid-soluble drug will dissolve in the membrane.
  - **Facilitated diffusion**: a drug will be transported across the cell membrane through a carrier protein without the need for energy (ATP).
  - **Active transport**: a drug will be transported across the cell membrane through a carrier protein with the need for energy (ATP).
  - **Endocytosis**: especially when the drug molecule is large.
- **How does an intracellular drug moved to extracellular fluid?**
  - The six-membrane spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.



- **Bioavailability:**
  - **Definition**: the fraction of administered drug that gains access to its site of action or a biological fluid that allows access to the site of action.
  - The bioavailability of an intravenously injected drug is 100% (it will not pass through the liver and will not be metabolized). Other drugs which are not intravenously injected will have bioavailability less than 100%.
  - **Factors which affect bioavailability include the following:**
    - ✓ First-pass metabolism: biotransformation that occurs before the drug reaches its site of action. It most commonly occurs in the liver.
    - ✓ All of the factors that affect absorption of the drug (e.g. pH, blood flow, drug solubility, drug-drug interactions and route of administration).



  - **Bioavailability** = $\frac{Area\ Under\ Curve\ (for\ an\ orally\ administered\ drug)}{Area\ Under\ Curve\ (for\ intravenously\ administered\ drug)}\ x\ 100$
- **Structures of capillaries in liver and brain:**
  - **Liver capillary**: it has large fenestration which allow drugs to move between blood and interstitium in the liver.
  - **Brain capillary**: blood-brain barrier is composed of tight junctions which only allow lipid-soluble drugs to enter the brain.



- The movement of drugs from one compartment to the other involves transport across the biological membranes that is determined by physicochemical properties of drugs (e.g. molecular weight, lipid solubility, plasma protein binding and pKa) and different membrane transport mechanisms.
- Kinetics of drugs can be modeled using one-compartment, two-compartment, three-compartment and sometimes multi-compartment models. The physicochemical properties of drugs will determine which model is appropriate to study the distribution of drugs in body fluid compartments.
- The input is determined by the route of drug administration. the output (clearance) is determined by biotansformation and elimination of drugs from the body.

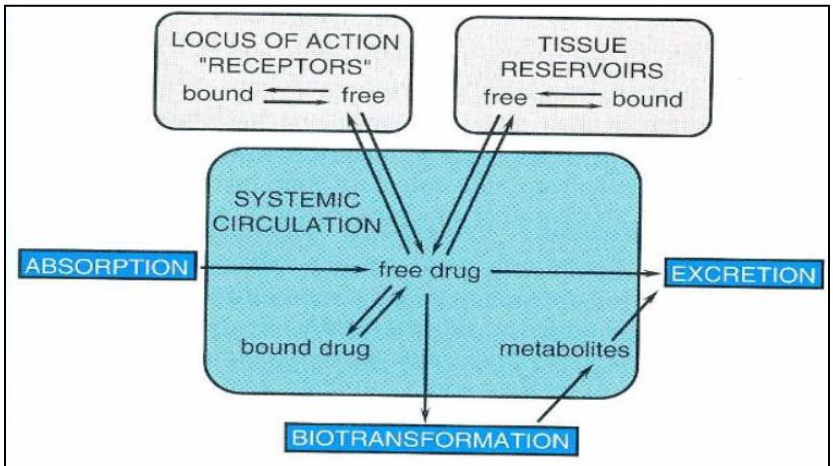
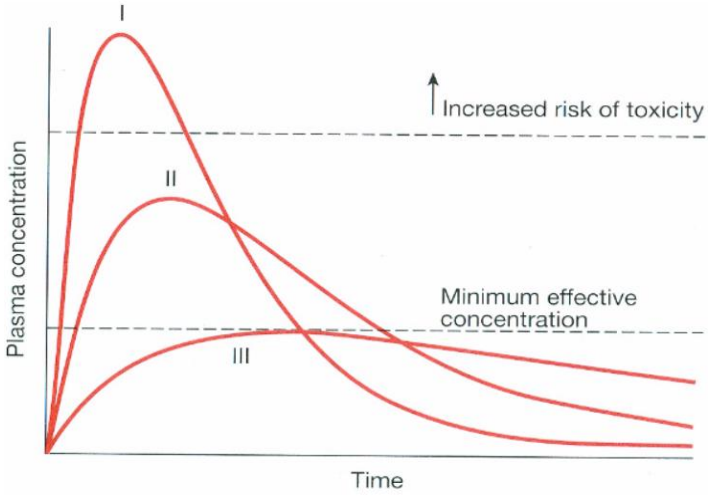
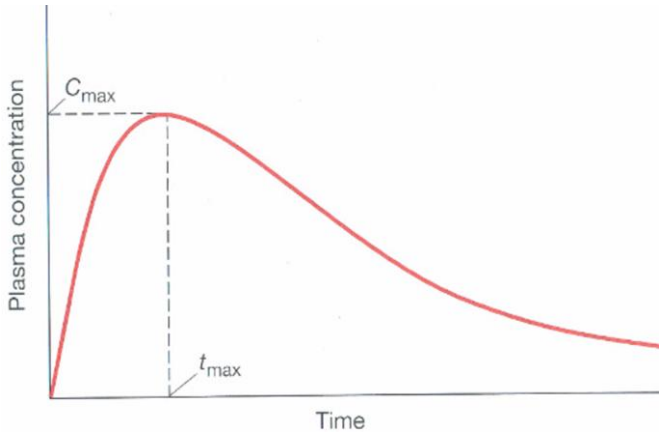


Figure 1–1. Schematic representation of the interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its locus of action.

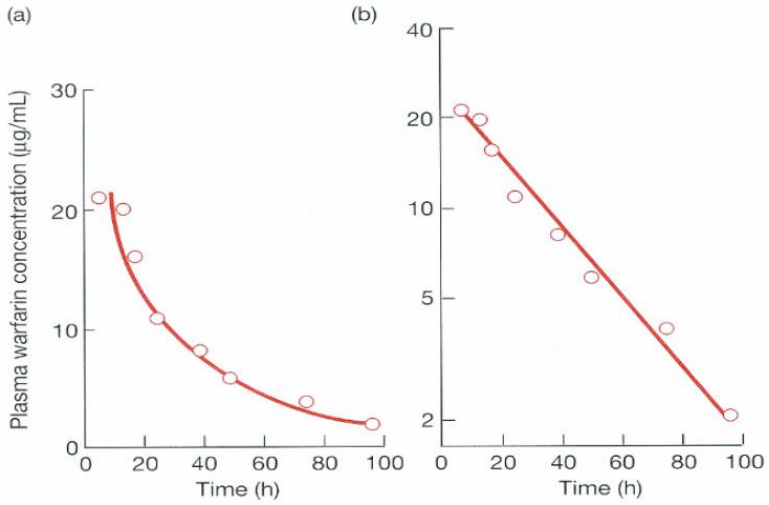
- **Absorption**: the rate at and extent to which a drug moves from its site of administration. Factors which affect absorption were mentioned previously.
- **Distribution**: the process by which a drug leaves the bloodstream and enters the interstitium or the cells of the tissues.
- **Biotransformation**: the lipophilic properties of drugs that allow them to pass through cell membranes hinder their elimination. Therefore, drugs are modified to become more polar, so that elimination can occur more quickly. In some cases, however, drugs are activated from their prodrug state through biotransformation.
  - **First-order kinetics**: the higher the concentration of the drug, the greater the absolute amount of drug biotransformed or excreted per unit of time.
  - **Zero-order kinetics**: the process by which a constant amount og drug is metabolized per unit of time regardless of the drug concentration.
- **Excretion**: the process by which a drug or metabolite is removed from the body. major routes of excretion are:
  - Renal.
  - Fecal.
  - Respiration.
  - Breast milk.
  - Skin.
- **Theraputic window**: is the effective concentration of a drug which is between the minimum effective concentration (under which there is not effect) and maximum tolerated dose (above which there is increased risk of toxicity).



- **The graph below shows time-concentration of a drug after oral administration. C_{max}: Maximal (peak) plasma concentration, T_{max}: Time to peak plasma concentration.**



- **Graphs below show plasma concentration of drug versus time: arithmetic (left side) and log scale (right side) plots.**



- **Volume of distribution (V_d) = $\frac{Dose}{C^0 P}$ L/kg**
  - **If volume of distribution exceeds actual physiologic volumes, it suggests that drug is bound to tissues. Hence it is called apparent volume of distribution.**