ADME_2: Distribution

- **Drug Distribution**: While absorption is the entry of a drug from the site of administration into the systemic circulation (vascular compartment), distribution is the process by which a drug partitions into extravascular compartments (i.e. other organs & tissues).

- **Drug Distribution Phase in concentration curve**: See Figure 1. After an IV bolus of a drug, the plasma concentration of a drug slowly declines over time. However, this concentration curve exhibits a biphasic nature. The initial decline is much faster and then it changes to a slower rate of decline. The reason is that the initial phase of decline in plasma drug concentration includes the distribution phase, where the drug is leaving plasma and moving into different organs and tissues. The second phase is due to only elimination of the drug from the body.

![Figure 1. Distribution & Elimination phases of a drug concentration curve.](image)

- **Body fluids**: See Figure 2. So how is a drug distributed throughout the body? How does it move from one place to another? Well, obviously a drug would be moved around the body from one place to another by the fluids in the body. On average about 60% of the body weight is due to body water. So a 70 kg man has about 42 liters of water in the body. About two thirds or 26L will be intracellular while the remaining will be extracellular. The extracellular is further broken down into plasma, interstitial, and transcellular fluids. Interstitial fluid is the fluid surrounding individual cells. The transcellular fluids include cerebrospinal fluid, saliva, tears,
digestive juices, and synovial fluids. So a drug can potentially distribute into all these fluids, but that is going to depend on the physiochemical properties of a given drug and we will see examples of a drug that might be present in only a few of these fluid compartments. Physiochemical variables that play a role are drug size, its pKa, its lipid solubility, its ability to bind to plasma proteins, and its affinity for a specific cell or tissue type.

- **Apparent Volume of Distribution (V_d)**: describes the partitioning of a drug between plasma and extravascular compartments. If a drug has a very low volume of distribution, then that means the drug pretty much stays in the plasma. On the other hand, if a drug has a very large volume of distribution, then that indicates that the drug can penetrate most extravascular compartments. Of course, volume of distribution will depend on the physiochemical properties of a drug, such as lipid solubility, pKa, protein binding, etc.

$$V_d = \frac{\text{Dose (mg)}}{C_0 \text{(mg/L)}}$$

- We can calculate apparent volume of distribution using the above equation. Keep in mind that Vd is not a real volume but rather an apparent volume. Vd is the volume that would be required for a given dose to reach the same concentration as in plasma. Vd is determined by dividing the dose with initial concentration $C_0$. How do we get $C_0$?
Obtaining $C_0$: We can estimate $C_0$ from the curve shown in Figure 3. Remember that this is a biphasic curve. The first or initial phase is a sharper decline in plasma drug concentration because of drug distribution. The second phase of the curve represents the rate at which the drug is eliminated. We can extrapolate this second phase all the way to time zero to estimate the initial concentration before any elimination has taken place. That's our $C_0$.

Examples:
- Chloroquine has a Vd of 9000L because it penetrates most tissues and is sequestered in fatty tissues.
- Azithromycin has a Vd of 2000L because it accumulates in white blood cells and then is slowly released back into plasma over several days.
- Warfarin is highly bound to plasma proteins and is pretty much confined to plasma, so it has a very low Vd of 10L.

Plasma Protein Binding (PPB): There are numerous proteins in plasma that can bind to drugs, but the most abundant protein is albumin. PPB affects Vd because only the free drug can move to extravascular compartments, so drugs with high plasma protein binding have low apparent volume of distribution.

PPB & Drug Interactions: Plasma protein binding can be a source of drug-drug interactions. For example, if a patient takes two drugs that bind to plasma proteins, the two drugs will compete for PPB. As a result, the free drug...
concentrations for each will be different when the drugs are taken together compared to when taken individually. In addition to drugs, many hormones as well as bilirubin tend to exhibit high degree of plasma protein binding, so a drug that binds to plasma proteins can also compete with and alter the concentrations of free hormones or bilirubin resulting in increased effects of such hormones in presence of that drug.

- **Blood Brain Barrier**: the blood brain barrier is a selective permeability barrier that keeps many drugs out of the brain. The major component of this barrier is the capillaries within the brain that consist of endothelial cells that are kept very close together through tight junction. These tight junctions exclude most substances out. Lipophilic molecules would enter the brain by passing through the lipid bilayer of the endothelial cells. Polar nutrients and chemicals would be imported into the brain through specialized transporter proteins. When it comes to drugs, if they are not lipophilic enough to pass the endothelial cell membrane, then they will be kept out of the brain. In addition to the endothelial tight junction, the barrier is also created through efflux of chemicals and drugs by efflux pumps such as the p-glycoprotein. This pump actively pumps drugs out of the brain and back into circulation so significant concentration of a drug is not achieved.