Lecture 1: Physicochemical Properties of Drugs and Drug Disposition

Key objectives:
1. Be able to explain the benefits of oral versus IV drug administration
2. Be able to explain the factors involved in drug absorption
3. Be able to state if a drug possesses a charge at a given pH value
4. Be able to explain the effect of lipophilicity on drug absorption

Drug administration

Oral and topical administration can be very convenient routes of administration. However, oral administration can be hindered by (a) poor absorption of the drug or by (b) extensive metabolism by the liver and/or intestines. And topical administration can also be limited by drug penetration through the skin such that only small amounts enter the body. This can limit topical administration to treating only skin conditions, or some special systemic conditions provided that the drug is very potent.

Figure 1. Oral and topical drug administration

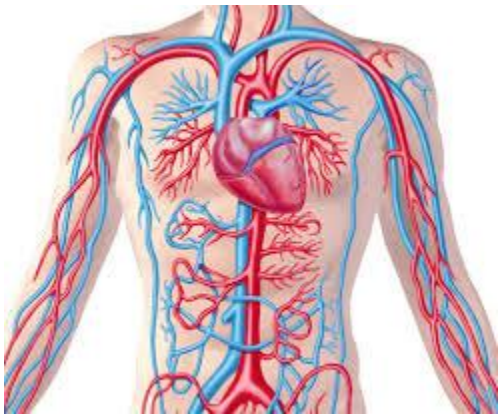


Figure 2a. Heart, arteries, and veins

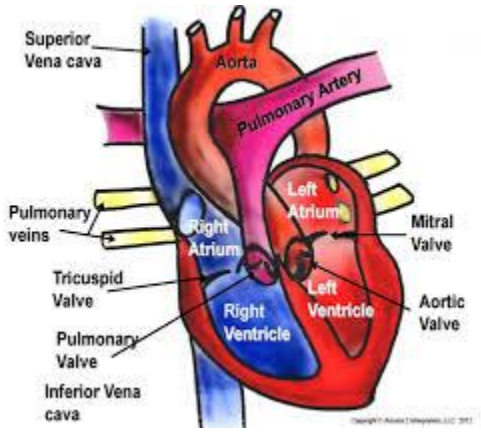


Figure 2b. Heart components

Sometimes the best way to introduce drugs into the human body is by direct injection into veins (Figure 2a). Many accessible veins exist in the hands, arms, and feet. This approach achieves high concentrations of drugs in the systemic blood immediately. This approach requires no drug absorption. It also avoids initial chemical breakdown and/or metabolism of the drug(s) by the stomach, liver and intestines.

For some medical purposes, direct injection (infusion typically) of drugs into a vein (e.g. superior vena cava) near the heart is done (Figure 2b). This approach is very common in cancer treatments for the delivery of several oncology agents because of the direct toxicity of the agents, or to avoid first pass metabolism by the liver. The heart chambers handle large volumes of blood every minute, and this can help with rapid dilution of the drugs. This can reduce the local toxic effects of certain drugs. Special ports are attached to patients for this purpose.

Examined on a lower level, many drugs must still pass through several cell membranes to reach their targets. These membranes are lipid bilayers (Figure 3) which must be crossed in order for drugs to reach their targets and achieve their therapeutic effects. Over time when a drug encounters a cell membrane it will slowly pass through the membrane to reach the interior (cytoplasm) of the cell. Some drugs target sites within the cell nucleus and in these cases, the drugs must pass through two membrane barriers (cytoplasmic and nuclear).

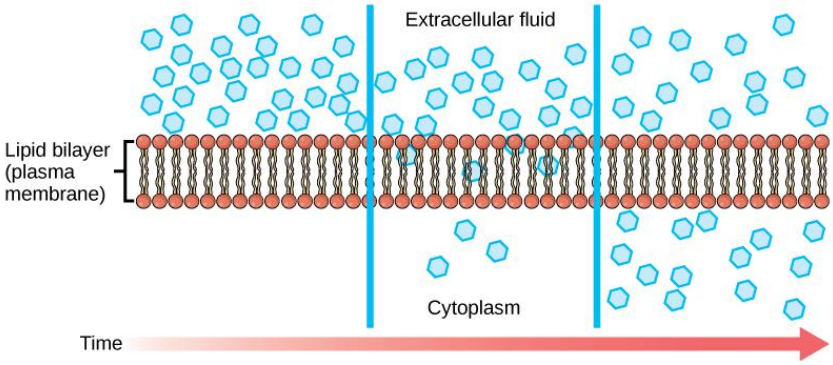


Figure 3. Cell membrane (lipid bilayer) with solutes (in blue) in the extracellular and cytoplasmic compartments

Fortunately, we can use our knowledge of molecular charge, lipophilicity, and molecular size to understand and approximate the absorption of drugs across cell membranes into the cytoplasm of the cells. (Note: the approximation of drug absorption can be quite inaccurate if drug transporters are involved.)

Drugs (all molecules in fact) can be classified in terms of their membrane permeability coefficient which is a function of lipophilicity and molecular charge (Figure 4). Coefficients that are very small (highly negative exponents) indicate poor permeability, while coefficients that are high (slightly negative exponents) indicate good permeability.

As we move forward to discuss the attributes (charge, polarity, lipophilicity) of drugs, remember that all these factors also influence how drugs bind to receptors, enzymes, etc. when they are inside cells. So these factors go beyond drug absorption.

In the figure below, membrane permeability coefficients are simplistic estimates of how fast different molecules move through membranes. Notice how polarity and charge slow down or reduce the permeability.

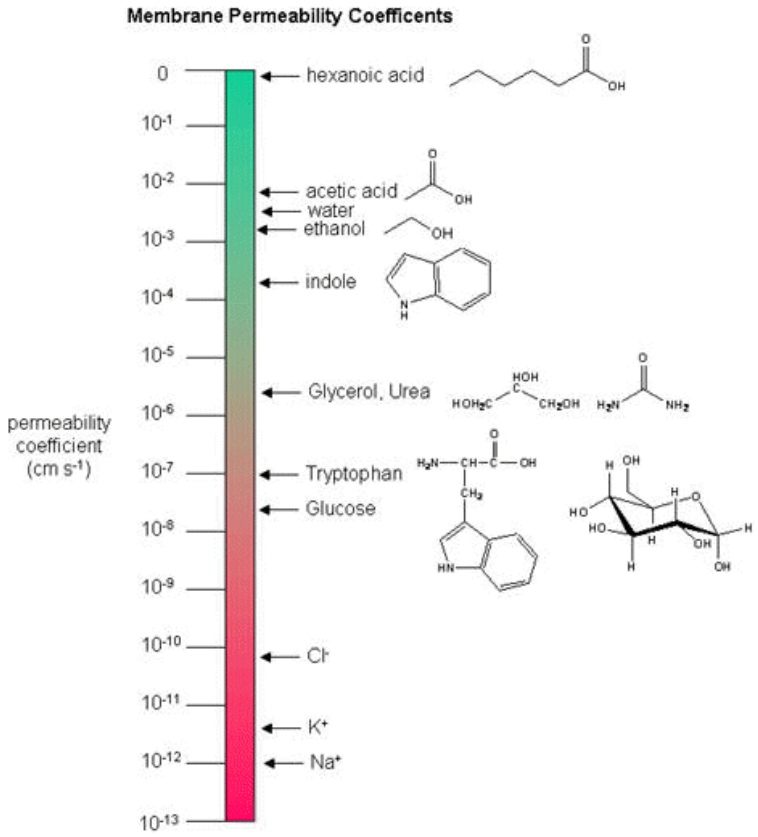


Figure 4. Membrane permeability coefficients of a few molecules

Drugs can pass through cell membranes by several mechanisms: passive diffusion, facilitated diffusion, and active transport; the latter mode requiring energy in the form of ATP (Figure 5).

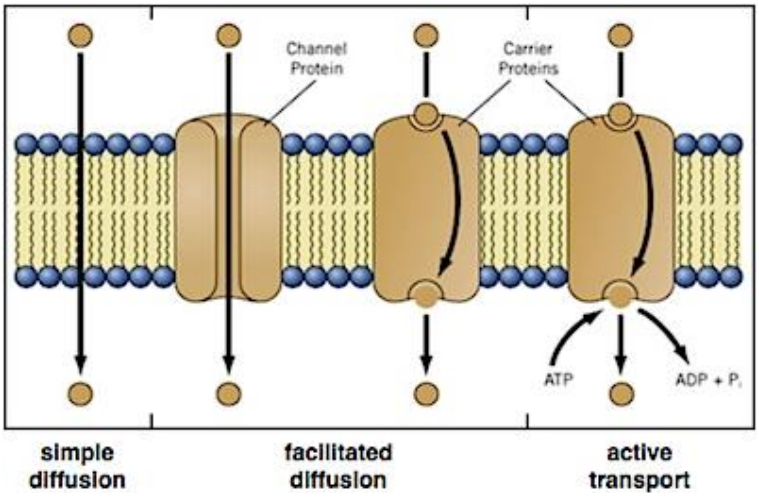


Figure 5. Different modes of movement through a membrane

Drug solubility, permeability and charge

Solubility: Drugs that are charged (either positive or negative) and/or are very polar can dissolve relatively well in water. We define such drugs as “soluble” but we explicilty mean they are “water soluble” as we are lazy and just say “soluble”. Gastric fluids and the plasma of blood are largely

composed of water. Being water soluble (soluble) is beneficial for oral dosing, because the very first step that must happen is for the drug molecules to dissolve and become solvated by water molecules. Drug molecules pass through membranes individually, not as groups or clumps.

For intravenous (IV) dosing, water soluble (soluble) drugs are easier to formulate. Drugs that are not water soluble (drugs that are lipophilic and don't possess any ionizable groups) require unusual formulating techniques and components. Oftentimes, the components of these unusual formulations cause undesirable effects. There will be more discussion of this in later lectures because many oncology drugs are not very water soluble.

Permeability: Drugs that are highly charged (either positive or negative) and/or are very polar do NOT pass through membranes very well. They are not very permeable. Approximately 80% of drugs will possess a charge, depending on the pH of the medium and the pKa of the functional group(s) on the drug.
Here below are the approximate pH values for various fluids (or locations) in the human body:

Blood and intracellular fluid pH = 7.4
CSF = 7.3
Urine = 5-8 (normal is ~7)
GI tract = 1-7; the pH gradually rises through the intestine toward the colon
-stomach ~1
-duodenum ~ 5
-ileum ~ 7
-colon ~8-10

The transition from low pH to high pH in the GI tract is important as it influences where absorption will occur for a given drug.

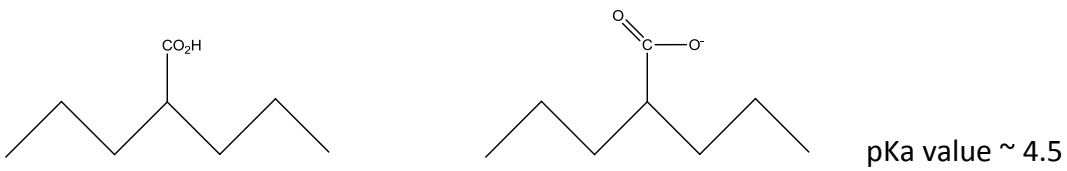
The equation that explains the charge that can exist on a molecule (or drug) is called the **Henderson-Hasselbach equation**:

$$pKa = pH - \log \frac{[\text{conjugate base}]}{[\text{conjugate acid}]}$$

We can rearrange the equation to make it more user-friendly as follows:

$$\frac{[\text{conjugate base}]}{[\text{conjugate acid}]} = 10^{(pH - pKa)}$$

An example can be the drug valproic acid (VPA; an anticonvulsant drug) shown below in Figure 6 in both its conjugate acid and conjugate base forms.



pKa value ~ 4.5

Conjugate acid form Conjugate base form

Figure 6. The two forms of VPA

Note the following: If the pH value = pKa value, then 10 to the zero power = 1. In this case, the concentration of the conjugate base must equal the concentration of the conjugate acid form.

$$\frac{[\text{conjugate base}]}{[\text{conjugate acid}]} = 10^{(pH - pKa)} = 10^{0} = 1$$

We are primarily interested in the **ratio of unionized drug to ionized drug**. We also need to know whether the conjugate base is charged (carboxylic acid type) or the conjugate acid is charged (amine type).

It is important to differentiate between the two types of ionized drugs, the amine type and carboxylic acid type (Figure 7).

Carboxylic acid type **AH** ⟷ **A- + H+** the base form is charged (-)

Amine type **BH+** ⟷ **B + H+** the acid form is charged (+)

Figure 7. The two types of charged drugs

Carboxylic acid (benzoic acid) example:

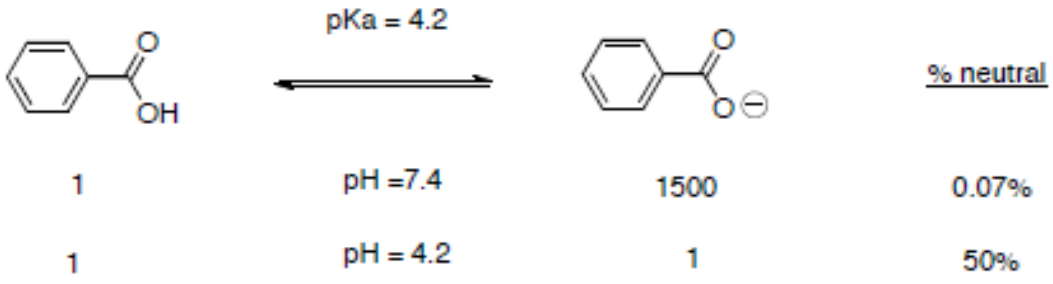


Figure 8. The acid base equilibrium of benzoic acid

Aliphatic amine (amphetamine) example:

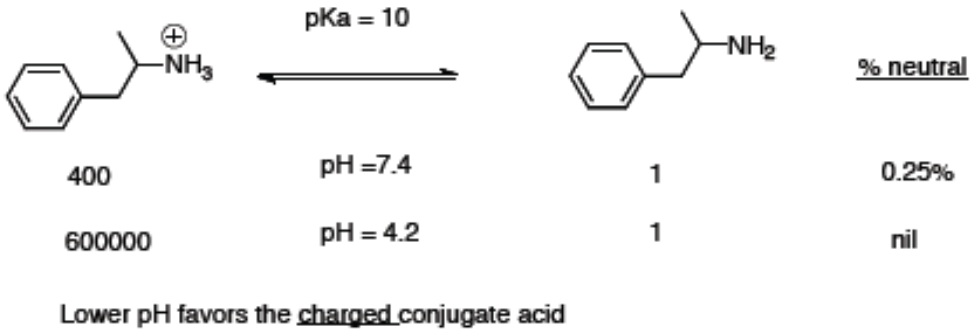


Figure 9. The acid base equilibrium of amphetamine

The pKa value of amphetamine is 10; thus the charged conjugate acid predominates at most physiological pH values. The neutral conjugate bases of amine drugs are generally highly lipid soluble and most simple amines are absorbed in the distal GI where the pH value is higher.

Again, always remember:
1. First determine if the functional group is the amine type or the carboxylic acid type.
2. Then compare the pH value to the pKa value.

Let's return to the Henderson-Hasselbach equation one final time.

$$pKa = pH - \log \frac{[\text{conjugate base}]}{[\text{conjugate acid}]}$$ This is the traditional way it is written.

If it is rearranged, it looks like this:

$$\frac{[\text{conjugate base}]}{[\text{conjugate acid}]} = 10^{(pH - pKa)}$$

If the pH = pKa value, then 10 raised to the zero power = 1, and the [conjugate base] must equal the [conjugate acid].
If the pH > than pKa value, then the [conjugate base] form must be > [conjugate acid] form.
If the pH < than pKa value, then the [conjugate base] form must be < [conjugate acid] form.

Always remember whether the acid form or the base form is charged!

Finally, some drugs possess multiple functional groups. For example, the antibiotic drug ciprofloxacin (Figure 10) has three different types of functional groups. It has an aliphatic amine (pka ~ 9-10), an aromatic amine (pka ~ 4-5), and a carboxylic acid (pka ~ 4-5).

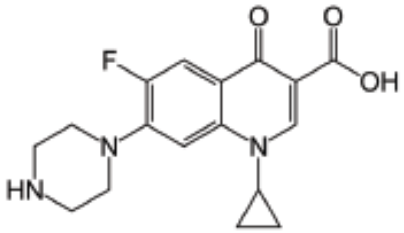


Figure 10. Structure of ciprofloxacin

Molecules or drugs that can possess both positive and negative charges are called zwitterionic. Ciprofloxacin has zwitterionic character, as it can possess both positive and negative charges at the same time. As a consequence, the drug passes through membranes poorly by passive diffusion. If not for active transport, this drug would have very poor absorption.

So always remember that overall drug availability (bioavailability) is dependent on drug physiochemical properties, potential drug metabolism, and potential drug transporters.

And understand that the drug's physiochemical properties (e.g. polarity, lipophilicity, pKa value) will also influence its behavior in the systemic circulation (i.e. the blood or within cells).