ADME 1_Absorption

- **Drug Absorption**: Absorption is the process by which a drug enters the blood circulation. Of course, if a drug is delivered intravenously or into an artery, then there is no absorption involved because the drug is already in circulation. But for most other routes of administration, there is an absorption step involved before a drug can reach the systemic circulation. Examples of such routes include oral, parenteral (which would include subcutaneous and intramuscular injections), inhalation, rectal, nasal, etc.

- **Barriers**: If we are using a drug for a local effect (such as eye drops or skin ointment) then we don't need to worry about absorption too much. But for most targets within the body, the drug needs to first enter the systemic circulation in order to have an effect on its target organ or tissue. This presents a challenge because there are barriers, such as GI tract, liver, skin, muscles and lungs, which need to be overcome in order for a drug to enter the plasma (Figure 1).

![Figure 1](image1.png)

**Figure 1.** Barriers to absorption through different routes of administration.

- **Epithelial and Endothelial Barriers**: At the cellular level, drugs often have to cross multiple barriers before they can reach systemic circulation (Figure 2). For example, an oral drug would need to cross the epithelial barrier first. The epithelial barrier consists of a layer of cells that are tightly connected to each other, so the only way for a drug to cross this barrier is to pass through the cells. First, it has to enter an epithelial cell and then it has to exit the cell on the other side to reach the...
inner layer of the gastric mucosa. Once the drug has passed the epithelial barrier, then it is transported to the systemic circulation through the capillary beds. However, this represents the second barrier that the drug would have to overcome because the capillaries are made up of endothelial cells. Vascular endothelium is different from the epithelial barrier. Depending on the organ where this vasculature is involved, the endothelial layer may be discontinuous and the gaps between the cells may allow a drug to go through and enter the capillary circulation. In some organs, such as the brain, the endothelium is more prohibitive and selective in what goes through, so the drug would have to enter and then exit the endothelial cells themselves. In any case, invariably a drug would have to cross lipid membranes at least twice in order to enter circulation.

- **Cellular Entry of Drugs:** There are **four possible ways** in which a drug can enter a cell (See **Figure 3**). First, a drug might simply cross the lipid bilayer through **simple diffusion**. However, that would require a drug to have certain **lipophilicity** or fat solubility. The second possibility is to enter through small aqueous pores known as **aqua porins**. However, this is very rare because these channels are very small and usually allow very small molecules such as gases to go through. The third possibility is that a drug might enter through a **transporter** or a **carrier**. We will look at this in detail later on. Finally, a drug might bind to a **specific receptor that is**
internalized into the cell through endocytosis, so the drug essentially goes in with the receptor.

- **Simple Diffusion**: Two factors play a critical role in determining whether a drug can traverse the cell through simple diffusion. First, the drug has to have a degree of **lipophilicity**. Polar drugs have limited capacity to diffuse across the lipid bilayer and would have to find another way to get inside. In addition to lipophilicity, a drug would also need to have a **favorable pKa**. Drugs that are weak acids or weak bases exist in both the unionized and ionized form in ratios that depend on the drug pKa and the physiological pH. So the ionized form will not be able to cross the lipid bilayer.

- **Ion Trapping**: When it comes to the **gastric mucosa**, some weak organic acid drugs can be trapped within the mucosal epithelial cells due to ion trapping. Because of the low gastric pH (pH 2-3), 99.9% of a drug is actually in the unionized form within the stomach. Since it is unionized, it will be able to cross the cell membrane and enter the epithelial cells. However, the intracellular pH is close to 7.5, so once the drug is inside the cells, it will become ionized and only 0.1% will exist in the unionized form. Since the drug is ionized now, it will not be able to cross the cell membrane again very easily, so it is trapped inside the epithelial layer. One example is **acetylsalicylic acid or aspirin**. Aspirin gets trapped within the epithelial layer through this ion trapping mechanism and can actually cause local damage within the gastric mucosa as a result.

- **Carrier-mediated entry**: Unlike lipophilic drugs which can simply diffuse across the lipid bilayer, most polar molecules enter a cell through carriers or transporters. There are two types of solute carriers. First, there may be an **ATP-**
driven transport that actively imports the drug. Another type of carrier involves facilitated diffusion, where there is no energy needed. In both cases, the carriers and transporters may be there for the cell to important nutrients and other biochemical, but the drugs basically exploit them to enter the cell.

- **Barriers to Oral Absorption**: The most common route of administration is oral, but this route also presents the most challenges and barriers. We already mentioned how ionization of weak acids and bases could inhibit absorption across the gastric mucosa. Additional barriers include potential drug decomposition by saliva, gastric acid and enzymes. However, by far the most important barrier is the metabolic degradation by enzymes present within the GI tract and the liver. This is refer to as the **first pass effect**.

- **First Pass Effect**: See **Figure 4**. Everything that is absorbed in the GI tract has to go through the liver before entering the systemic circulation. This includes the nutrients as well as drugs. So if a drug manages to remain intact after a passage through the stomach then it is absorbed into the enterocytes that line up the small intestine. After crossing these cells, the drug would enter the liver through the hepatic portal vein and then finally reach the circulation. There are detoxifying metabolic enzymes within the GI tract as well as the liver that can effectively inactivate most of the drug before it can enter the systemic circulation. This is called the first pass effect.

**Figure 4. First Pass Effect.**
Drugs absorbed from the small intestine enter the liver through the hepatic portal vein. Metabolic enzymes in the GI tract and the liver may inactivate some drugs completely.
Bioavailability: Bioavailability is the fraction of a drug that reaches the systemic circulation unchanged. Anything that alters the drug in anyway or interferes with its absorption will decrease its bioavailability. Since the intravenously introduced drug does not have to overcome any barriers, 100% of the drug is bioavailable. We denote bioavailability with \( f \), so intravenous bioavailability is 100% or if we use the fractional then it will be 1.

- **Bioavailability calculation**: Bioavailability (\( f \)) is oral AUC divided by intravenous AUC. If the two AUCs are the same then we have bioavailability of 1 or 100%, but usually it’s less than that.

- **Factors that affect bioavailability**: There may be a great deal of variability in oral bioavailability because of many factors. For example, the metabolic enzymes involved in the first pass effect can be inhibited or activated by other drugs that one may be taking. Diet may also play an important role. For example, grapefruit juice inhibits some of the enzymes involved in first pass effect, so it can actually increase bioavailability. Bioavailability can also be affected by diseases, for example liver disease or inflammation within the GI tract. For some drugs, oral bioavailability is so erratic and unpredictable, that it preferable to use alternate routes.