

Drug permeation: the influence of pH on solubility in water and lipid

- Whether you are polar or nonpolar in a solution depends on the acidity of the solution.
- This ratio of polar to non-polar is described by the Henderson-Hasselbalch equation

HENDERSON HASSELBALCH EQUATION

$$\text{Log} \frac{[\text{Concentration of the ionized form of the substance}]}{[\text{Concentration of the non-ionised form of the substance}]} = \text{pK}_a - \text{pH}$$

- The pKa is the pH at which concentration of ionized and non-ionised forms is equal.

Seeing as many drugs are either weak acids or weak bases, they will either be charged or uncharged in solutions with different pH.

- A weak acid will be neutral until it dissociates into a negatively charged ion (anion) and a proton.
 - o While it hangs onto its proton, it is still neutral and thus lipid-soluble.
 - o In an alkaline environment, there are few protons, and the acid will tend to donate them.
THUS: IN AN ALKALINE ENVIRONMENT, WEAK ACIDS ARE IONISED AND WATER-SOLUBLE
- A weak base will become positively charged (cation) if it ever accepts a proton
 - o While it is still proton-free, the weak base will also be neutral and lipid-soluble.
 - o In an acidic environment, there are tons of free protons and the base will tend to grab them.
THUS: IN ACIDIC ENVIRONMENTS, WEAK BASES ARE IONISED AND WATER-SOLUBLE

IN SHORT

A substance will become more lipid soluble in a solution with a pH similar to its own pH.

- **A weak acid is more lipid-soluble in an acidic solution**
- **A weak base is more lipid-soluble in an alkaline solution.**
- **A weak acid is more WATER-soluble in an alkaline solution**
- **A weak base is more WATER-soluble in an acidic solution.**

The higher the pKa, the more this is affected.

A base with high pKa will clear faster into acidic urine than a base with low pKa

Why is this important?

- The VAST majority of drugs are filtered out by the glomerulus
- If the drug is in a neutral lipid-soluble form, like a weak acid in acidic urine, it will be REABSORBED
- If the drug is in a polar form, like a weak acid in alkaline urine, it will be water-soluble; and water-soluble drugs will BE TRAPPED IN THE URINE.
- If you are trying to prevent reabsorption, MAKE THE URINE pH OPPOSITE to the drugs acidity.

Its not just urine. Native body fluid pH of vaginal/prostatic secretions, stomach juice and breast milk can all cause a trapping effect, concentrating drug molecules. Also, acidic environments of abscesses can interfere with polarity of local anaesthetics, making them less lipid soluble and thus less effective.