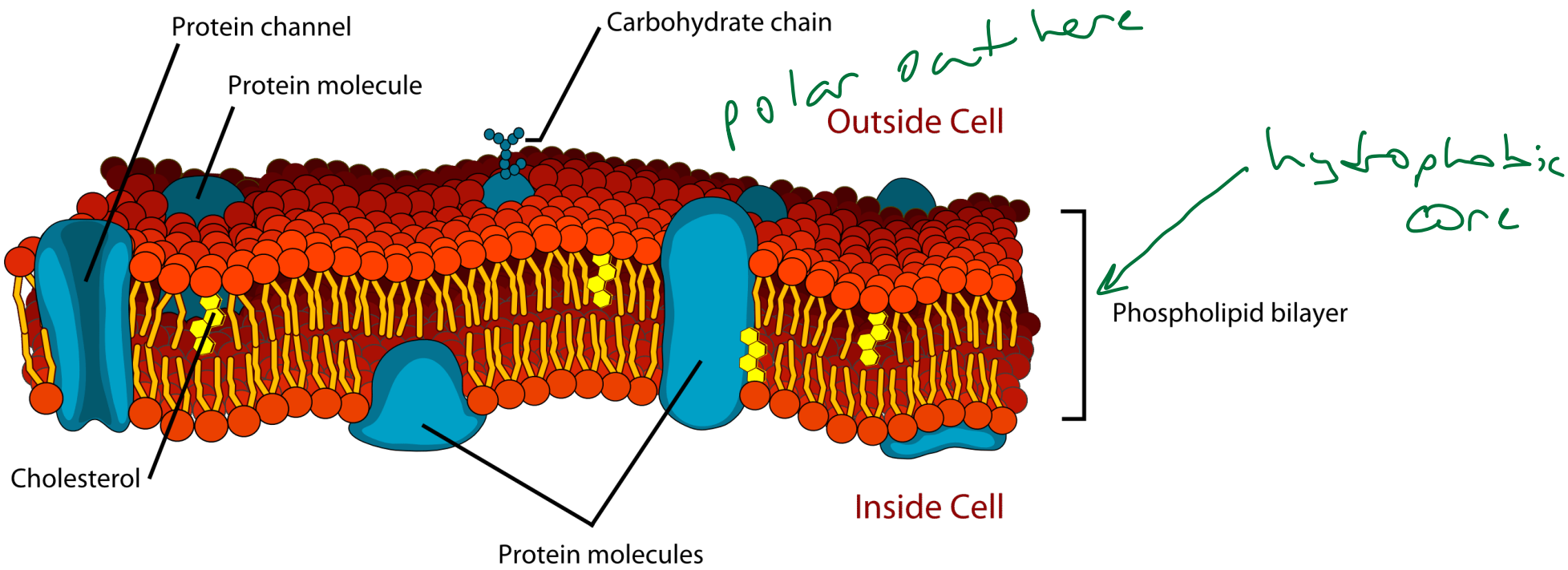
pH Partition Theory

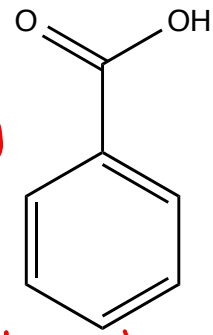
Membrane Solubility

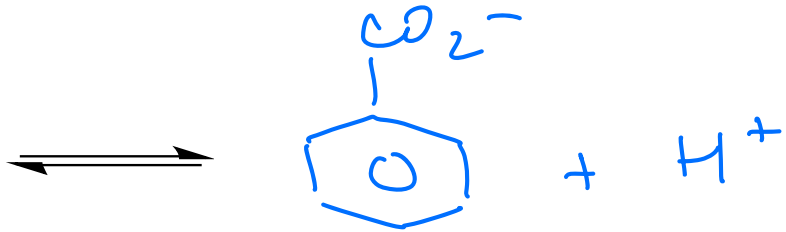


Drugs need to be soluble in the lipid core to get across

Two common fx groups RCO_2H

pKa = 4.2



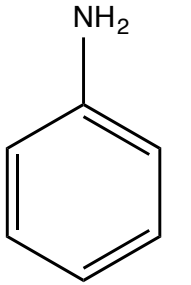


lipid soluble

water soluble

pH < 4.2

pKb = 9.4



lipid soluble

water soluble

pH > 9.4

Drug Administration

Enteral

enteric

GI tract

drugs need to be stable to conditions of stomach

not enteral

Parenteral

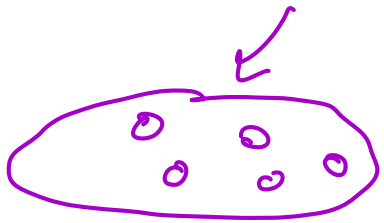
Injections
- Intravenous
- Intramuscular
- Subcutaneous

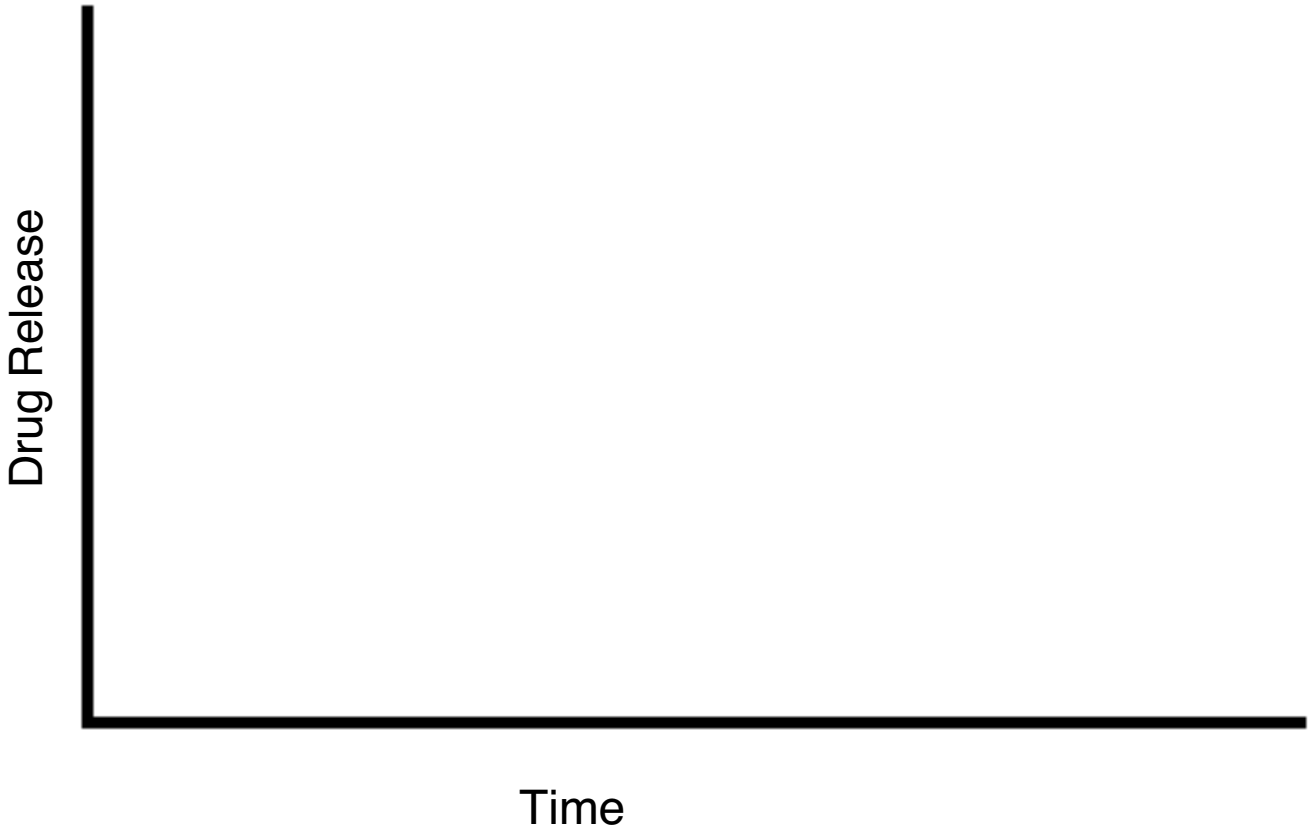
Transdermal

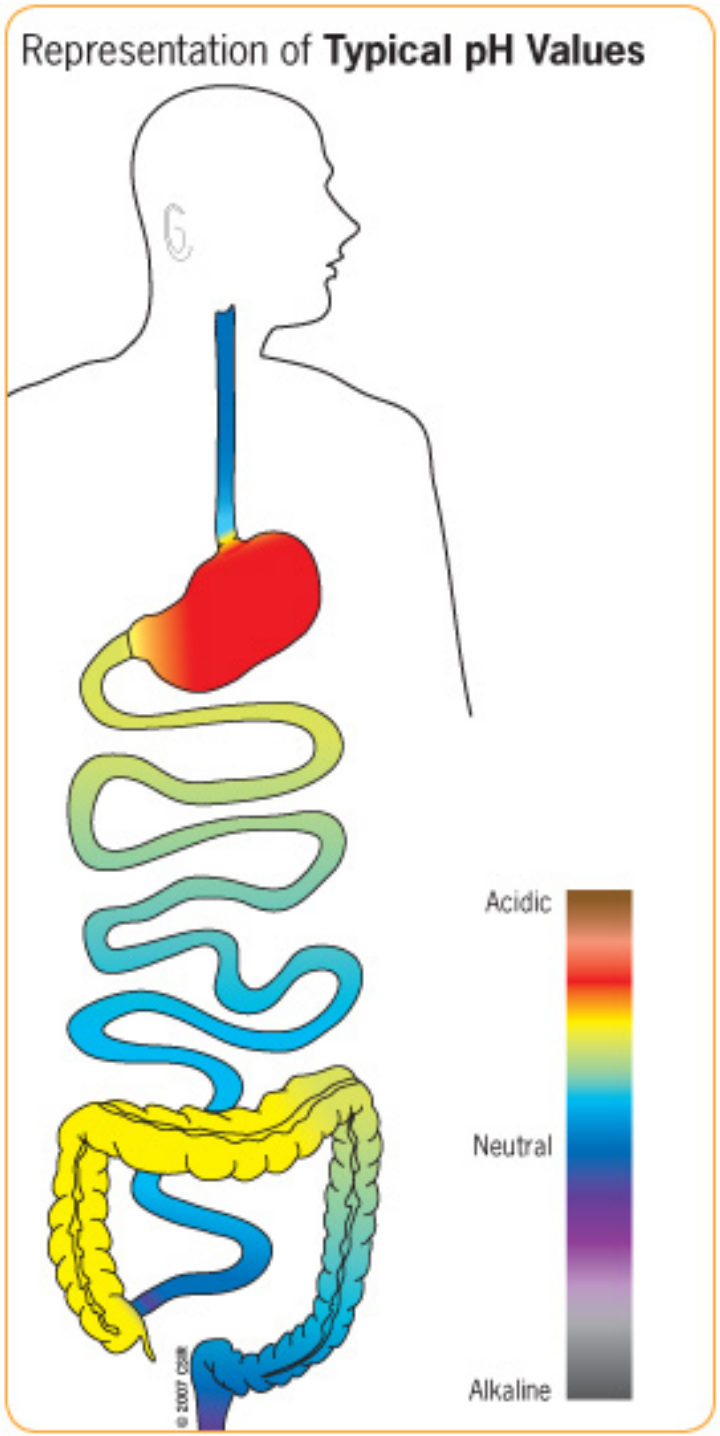
nasal inhalants

Mucous Membranes

Considerations for oral drugs…….







GI tract

Part I stomach

pH 1 to 2.5 ish

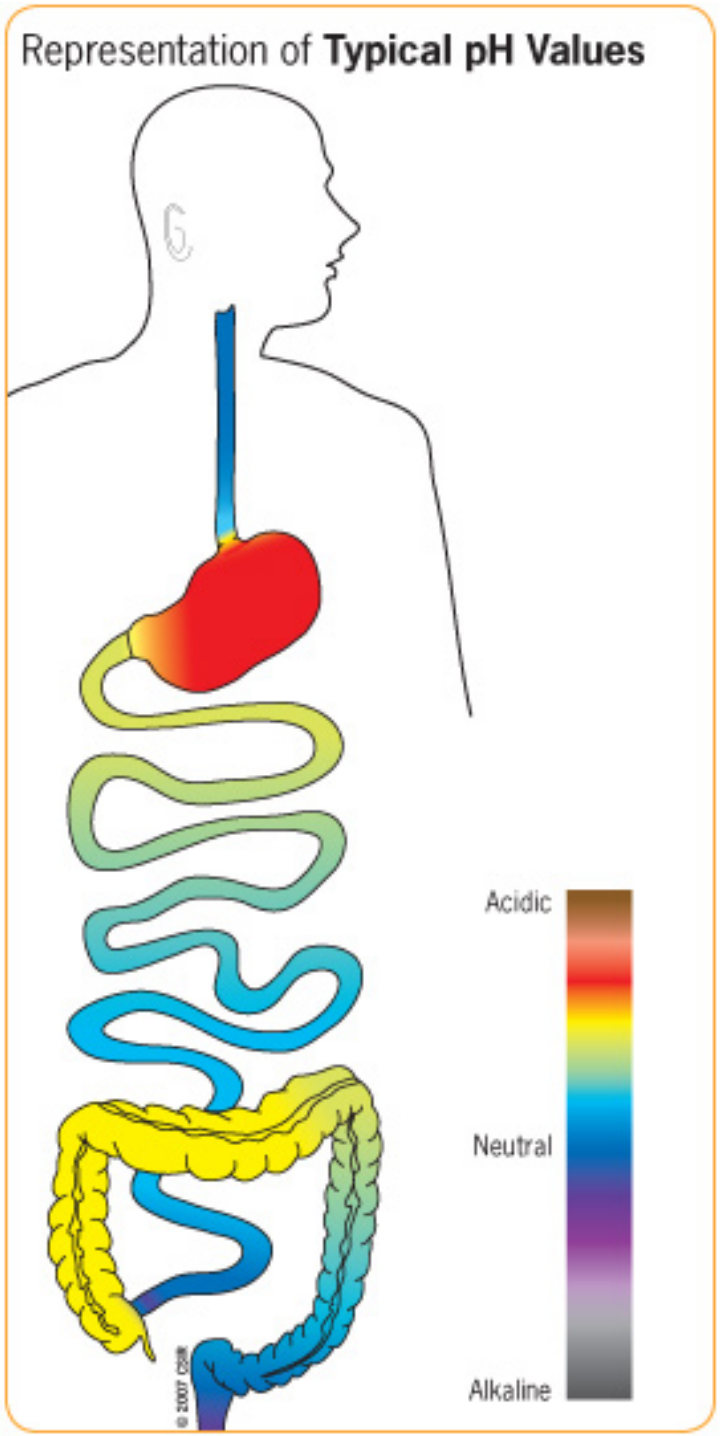
pepsin

HCl

Pills disaggregate + dissolve

Amines are very soluble

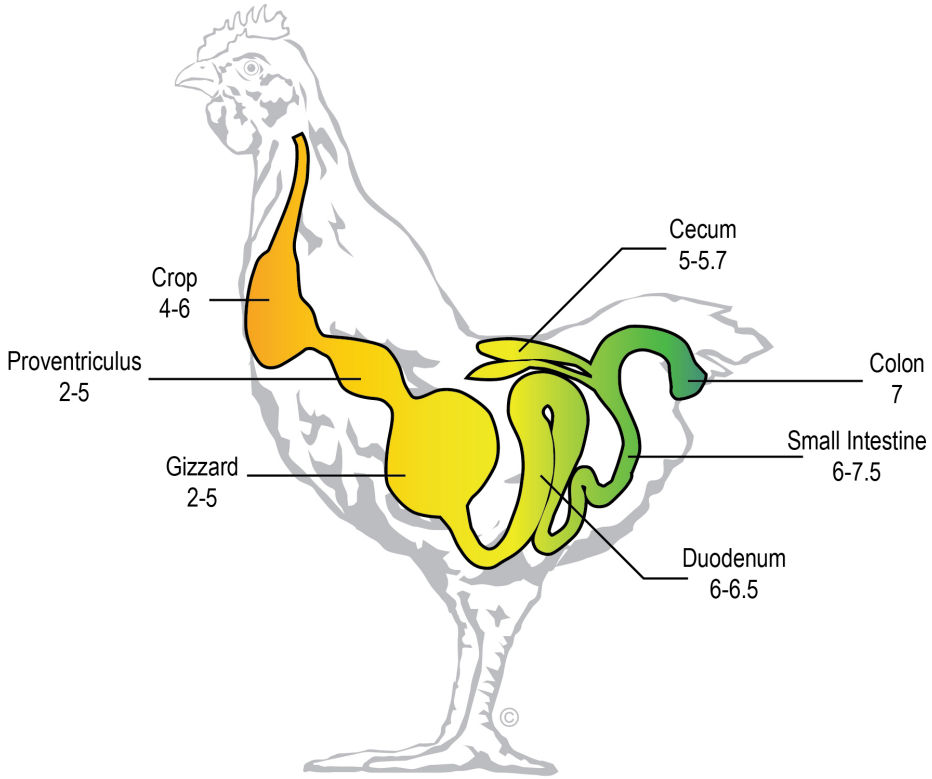
Carboxylic acids can get absorbed here

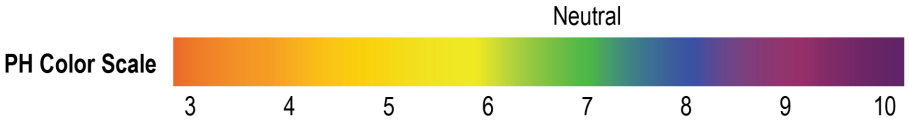


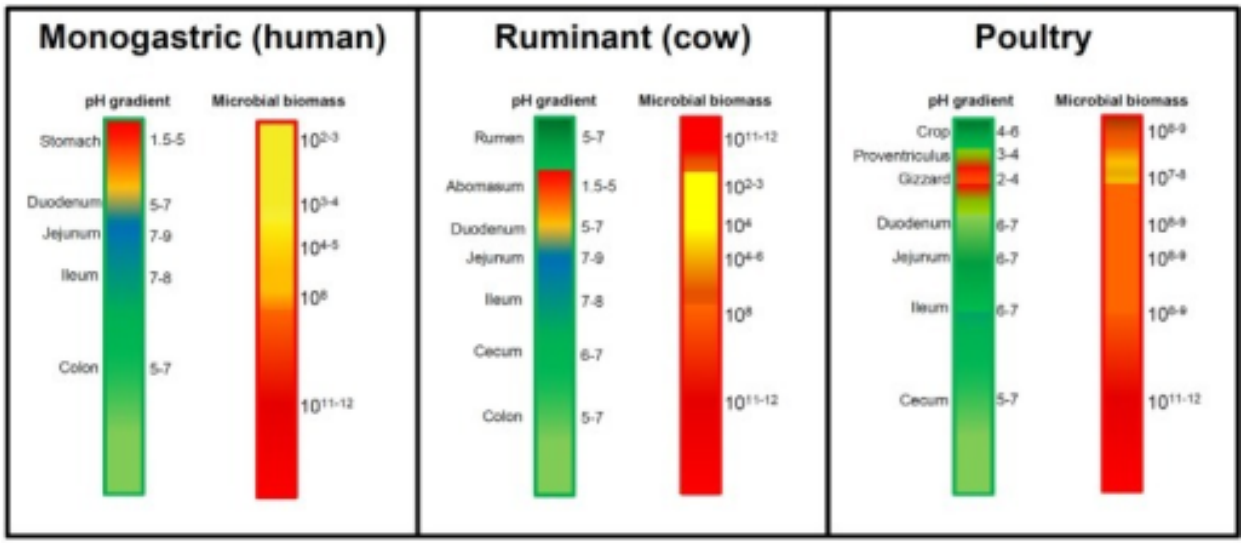
Part II intestines
higher pH

Amines lose protons
become uncharged
get absorbed here

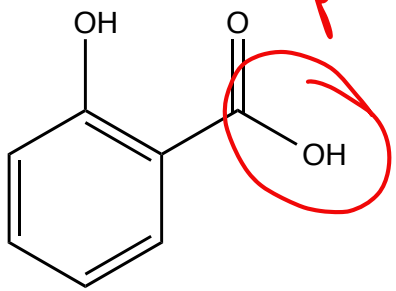
pH partition theory
most drugs are
absorbed by passive
diffusion of the
unionized form


Crop
4-6
Proventriculus
2-5
Gizzard
2-5
Cecum
5-5.7
Colon
7
Small Intestine
6-7.5
Duodenum
6-6.5

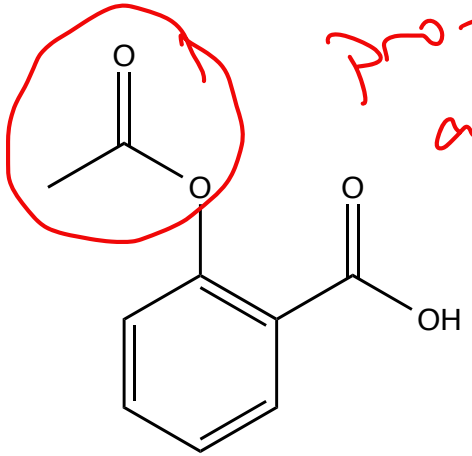

Neutral
PH Color Scale
3
4
5
6
7
8
9
10


Monogastric (human)
pH gradient
Microbial biomass
Stomach
1.5-5
Duodenum
5-7
Jejunum
7-9
Ileum
7-8
Colon
5-7
10^{2-3}
10^{3-4}
10^{4-5}
10^{8}
10^{11-12}
Ruminant (cow)
pH gradient
Microbial biomass
Rumen
5-7
Abomasum
1.5-5
Duodenum
5-7
Jejunum
7-9
Ileum
7-8
Cecum
6-7
Colon
5-7
10^{11-12}
10^{2-3}
10^{4}
10^{4-6}
10^{8}
10^{11-12}
Poultry
pH gradient
Microbial biomass
Crop
4-6
Proventriculus
3-4
Gizzard
2-4
Duodenum
6-7
Jejunum
6-7
Ileum
6-7
Cecum
5-7
10^{8-9}
10^{7-8}
10^{8-9}
10^{8-9}
10^{8-9}
10^{11-12}

Salicylates



pKa = 2.97

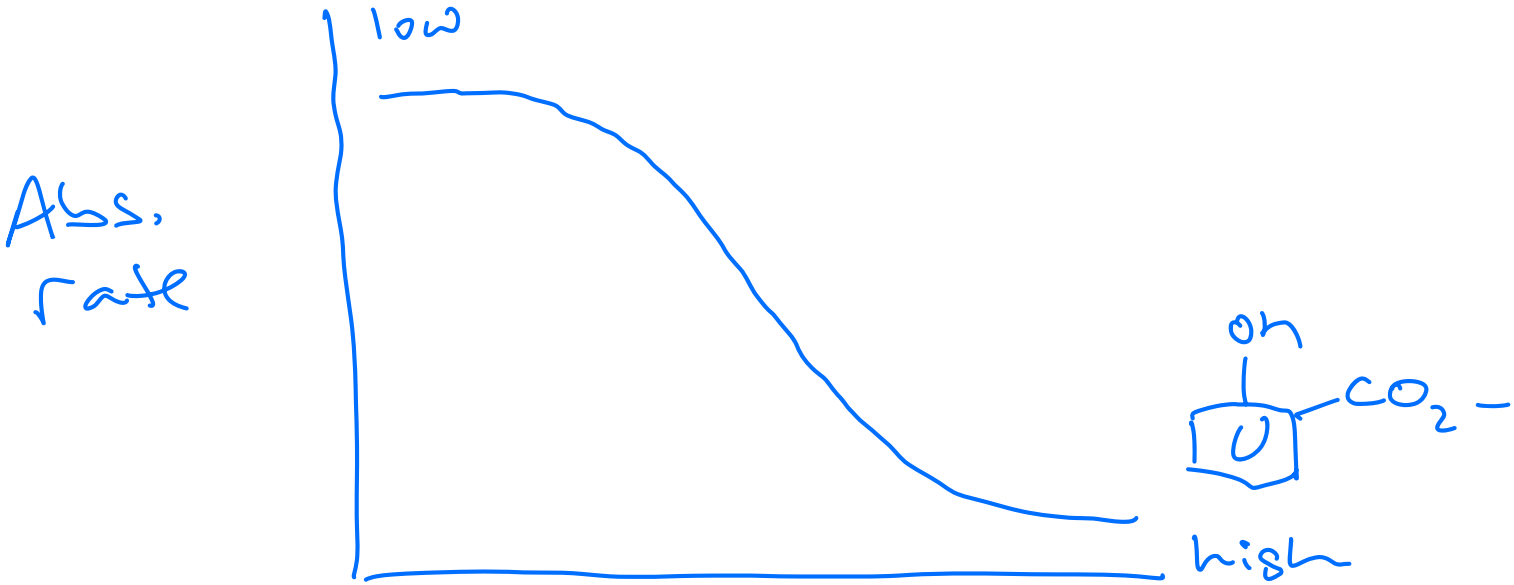


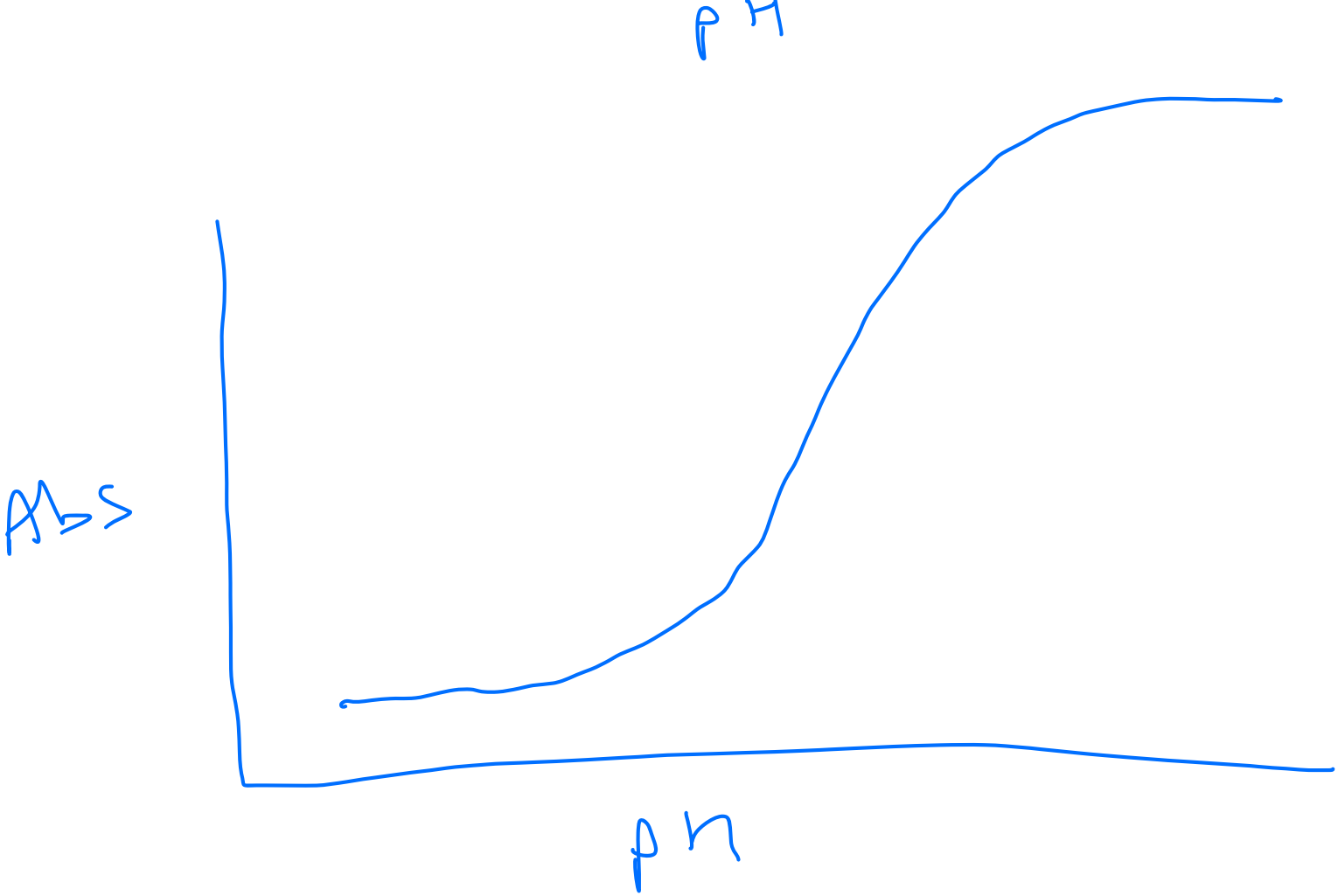
pro-drug
acetylsalicylic acid
aspirin

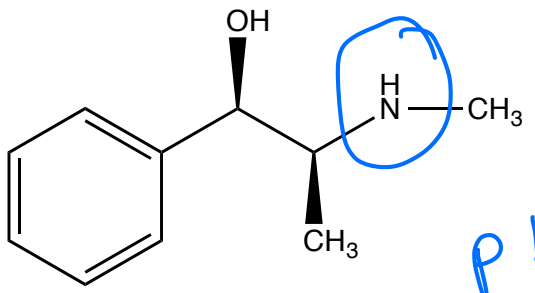
pKa 3.5

Salicylic acid
(willow bark)

can cause gastric bleeding



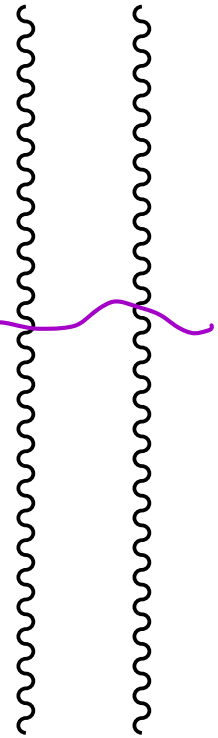




ephedrine

pKa = 9.65

We can calculate the amt of drug crossing a membrane



$pK_a = 4.4$

At steady state acidic drugs accumulate on the basic side

$HA \rightleftharpoons A^- + H^+$

$HA \rightleftharpoons A^- + H^+$

$10^{pH-pK_a} = \frac{[A^-]}{[HA]}$

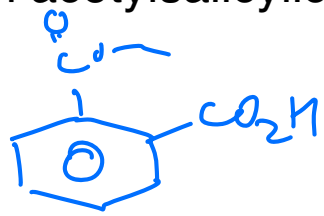
$10^{7.4-4.4} = \frac{A^-}{HA}$

$\frac{A^-}{HA} = 10^3$

$10^{1.4-4.4} = \frac{A}{HA}$

$10^{-3} = \frac{A}{HA}$

If the stomach has a pH of 1.3, what percentage of acetylsalicylic acid is ionized in the stomach? The pKa for ASA is 3.49.



$$10^{pH-pK_a} = \frac{A^-}{HA}$$

$$10^{1.3-3.49} = \frac{A^-}{HA}$$

$$6.457 \times 10^{-3} = \frac{A^-}{HA}$$

$$6.457 \times 10^{-3} HA = A^-$$

$$A + HA = 100$$

$$6.457 \times 10^{-3} HA + HA = 100$$

$$1.006457\ HA = 100$$

$$HA = 99.4\%$$

$$A^- = 0.6\%$$

pH Partition Theory

1. Gastrointestinal and other biological membranes act like lipid barriers
2. The unionized form of the drug is preferentially absorbed
3. Most drugs are absorbed by passive diffusion
4. Weakly acidic or neutral drugs may be absorbed in the stomach. Basic ones aren't
5. The rate and amount of drug absorbed is related to its oil/H_2O partition coefficient