

Passage of unchanged drug through a membrane

- A drug passes through membranes more readily if it is unchanged as either weak acids or weak bases
- The effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms
- The ratio between the two forms is determined by the pH at the site of absorption and by its pK_a value

Determination of how much drug will be found on either side of a membrane

Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_a + \log \frac{[\text{non-protonated species}]}{[\text{protonated species}]}$$

$$\text{For acids: } \text{pH} = \text{pK}_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

$$\text{For bases: } \text{pH} = \text{pK}_a + \log \frac{[\text{B}]}{[\text{BH}^+]}$$

- The equation is useful in determining how much drug will be found on either side of a membrane that separates two compartments that differ in pH

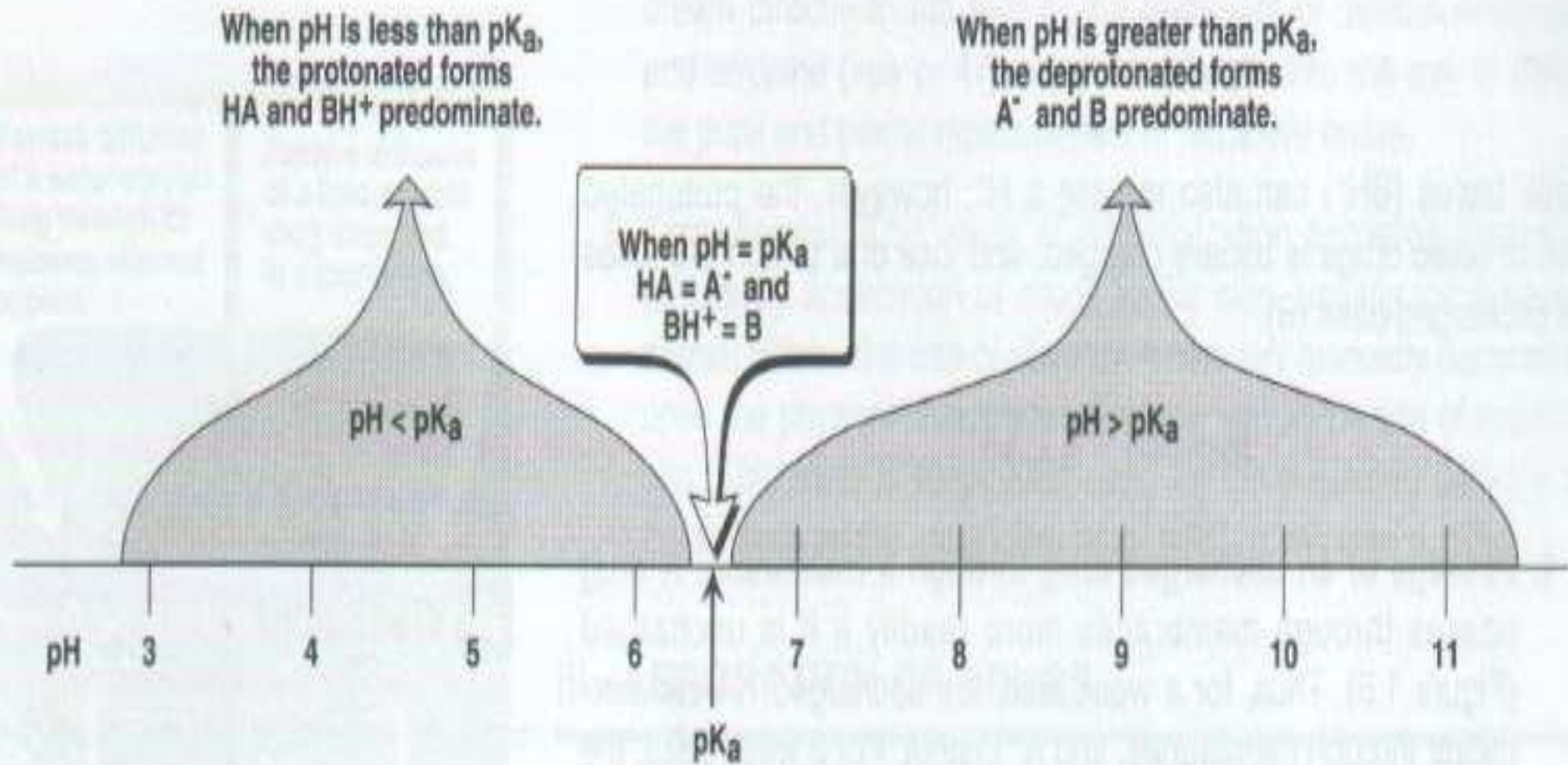


Figure 1.6

The distribution of a drug between its ionized and un-ionized form depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

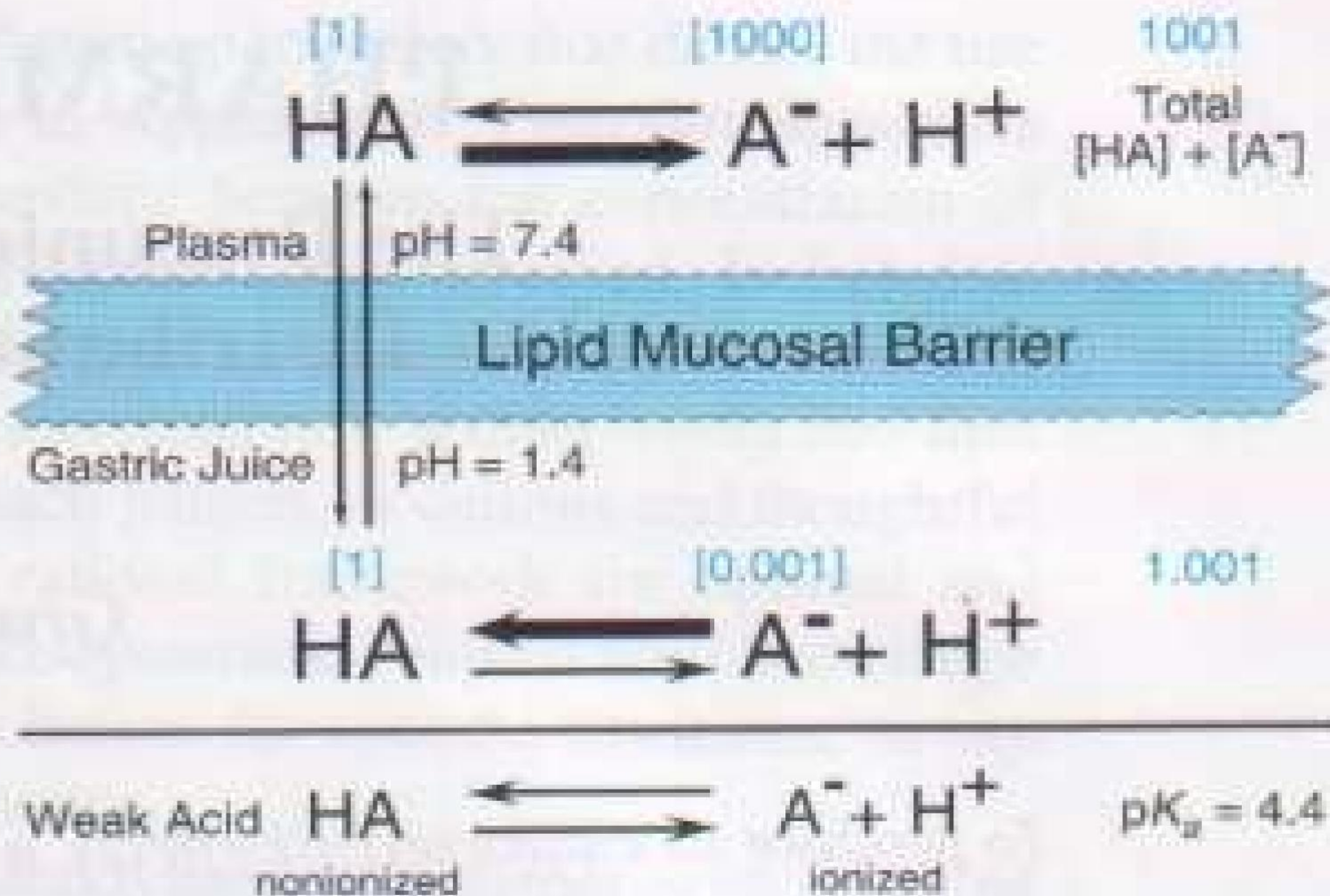


Figure 1-2. Influence of pH on the distribution of a weak acid between plasma and gastric juice, separated by a lipid barrier.

Ion Trapping

At steady state:

- An acidic drug will accumulate on the more basic side of the membrane.
- A basic drug will accumulate on the more acid side of the membrane.
- The phenomenon has obvious implications for the absorption and excretion of drugs

Table 1-2. Ionization constants of some common drugs.

Drug	pK _a ¹	Drug	pK _a ¹	Drug	pK _a ¹
Weak acids		Weak bases (cont'd)		Weak bases (cont'd)	
Acetaminophen	9.5	Amiloride	8.7	Methamphetamine	10.0
Acetazolamide	7.2	Amiodarone	6.56	Methyldopa	10.6
Ampicillin	2.5	Amphetamine	9.8	Metoprolol	9.8
Aspirin	3.5	Atropine	9.7	Morphine	7.9
Chlorothiazide	6.8, 9.4 ²	Bupivacaine	8.1	Nicotine	7.9, 3.1 ²
Chlorpropamide	5.0	Chlordiazepoxide	4.6	Norepinephrine	8.6
Ciprofloxacin	6.09, 8.74 ²	Chloroquine	10.8, 8.4 ²	Pentazocine	7.9
Cromolyn	2.0	Chlorpheniramine	9.2	Phenylephrine	9.8
Ethacrynic acid	2.5	Chlorpromazine	9.3	Physostigmine	7.9, 1.8 ²
Furosemide	3.9	Clonidine	8.3	Pilocarpine	6.9, 1.4 ²
Ibuprofen	4.4, 5.2 ²	Cocaine	8.5	Pindolol	8.6
Levodopa	2.3	Codeine	8.2	Procainamide	9.2
Methotrexate	4.8	Cyclizine	8.2	Procaine	9.0
Methyldopa	2.2, 9.2 ²	Desipramine	10.2	Promazine	9.4
Penicillamine	1.8	Diazepam	3	Promethazine	9.1
Pentobarbital	8.1	Dihydrocodeine	3	Propranolol	9.4
Phenobarbital	7.4	Diphenhydramine	8.8	Pseudoephedrine	9.8
Phenytoin	8.3	Diphenoxylate	7.1	Pyrimethamine	7.0
Propylthiouracil	8.3	Ephedrine	9.6	Quinidine	8.5, 4.4 ²
Salicylic acid	3.0	Epinephrine	8.7	Scopolamine	8.1
Sulfadiazine	6.5	Ergotamine	6.3	Strychnine	8.0, 2.3 ²
Sulfapyridine	8.4	Fluphenazine	8.0, 3.9 ²	Terbutaline	10.1
Theophylline	8.8	Guanethidine	11.4, 8.3 ²	Thioridazine	9.5
Tolbutamide	5.3	Hydralazine	7.1	Tolazoline	10.6
Warfarin	5.0	Imipramine	9.5		
Weak bases		Isoproterenol	8.6		
Albuterol	9.3	Kanamycin	7.2		
(salbutamol)		Lidocaine	7.9		
Allopurinol	9.4, 12.3	Metaraminol	8.6		
Alprenolol	9.6	Methadone	8.4		

¹The pK_a is that pH at which the concentrations of the ionized and un-ionized forms are equal.²More than one ionizable group.

