

Buffers in Pharmaceutical and Biologic Systems

In Vivo Biologic Buffer Systems

Blood is maintained at a pH of about 7.4. The plasma contains carbonic acid/bicarbonate and acid/alkali sodium salts of phosphoric acid as buffers. Plasma proteins, which behave as acids in blood, can combine with bases and so act as buffers. In the erythrocytes, the two buffer systems consist of hemoglobin/oxyhemoglobin and acid/alkali potassium salts of phosphoric acid.

The dissociation exponent pK_1 for the first ionization stage of carbonic acid in the plasma at body temperature and an ionic strength of 0.16 is about 6.1. The buffer equation for the carbonic acid/bicarbonate buffer of the blood is

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} \quad (8-34)$$

where $[\text{H}_2\text{CO}_3]$ represents the concentration of CO_2 present as H_2CO_3 dissolved in the blood. At a pH of 7.4, the ratio of bicarbonate to carbonic acid in normal blood plasma is

$$\log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} = 7.4 - 6.1 = 1.3$$

Or

$$[\text{HCO}_3^-]/[\text{H}_2\text{CO}_3] = 20/1 \quad (8-35)$$

Lacrimal fluid, or tears, have been found to have a great degree of buffer capacity, allowing a dilution of 1:15 with neutral distilled water. The pH of tears is about 7.4, with a range of 7 to 8 or slightly higher. It is generally thought that eye drops within a pH range of 4 to 10 will not harm the cornea. However, discomfort and a flow of tears will occur below pH 6.6 and above pH 9.0.

Urine

The 24-hr urine collection of a normal adult has a pH averaging about 6.0 units; it may be as low as 4.5 or as high as 7.8. When the pH of the urine is below normal values, hydrogen ions are excreted by the kidneys. Conversely, when the urine is above pH 7.4, hydrogen ions are retained by action of the kidneys in order to return the pH to its normal range of values.

Pharmaceutical Buffers

Buffer solutions are used frequently in pharmaceutical practice, particularly in the formulation of ophthalmic solutions.

Many buffers are available today. One of the most common biological buffers is phosphate buffered saline (PBS). Phosphate buffered saline contains sodium chloride (NaCl) and dibasic sodium phosphate (Na_2PO_4). It may also contain potassium chloride (KCl), monobasic potassium phosphate (KH_2PO_4), calcium chloride (CaCl_2), and magnesium sulfate (MgSO_4).

General Procedures for Preparing Pharmaceutical Buffer Solutions

The following steps should be helpful in the development of a new buffer.

- a- Select a weak acid having a $\text{p}K_a$ approximately equal to the pH at which the buffer is to be used.
- b- from the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired pH. The buffer equation is satisfactory for approximate calculations within the pH range of 4 to 10.
- c- Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity.

A *concentration* of 0.05 to 0.5 M is usually sufficient, and a *buffer capacity* of 0.01 to 0.1 is generally adequate.

- d- Other factors of some importance in the choice of a pharmaceutical buffer include availability of chemicals, sterility of the final solution, stability of the drug and buffer on aging, cost of materials, and freedom from toxicity. For example, a borate buffer, because of its toxic effects, certainly cannot be used to stabilize a solution to be administered orally or parenterally.
- e- Finally, determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter. In some cases, sufficient accuracy is obtained by the use of pH papers. Particularly when the electrolyte concentration is high, it may be found that the pH calculated by use of the buffer equation is somewhat different from the experimental value. This is to be expected when activity coefficients are not taken into account, and it emphasizes the necessity for carrying out the actual determination.

Stability versus Optimum Therapeutic Response

The undissociated form of a weakly acidic or basic drug often has a higher therapeutic activity than that of the dissociated salt form. This is because the former is lipid soluble and can penetrate body membranes readily, whereas the ionic form, not being lipid soluble, can penetrate membranes only with greater difficulty. It is observed an increase in therapeutic response of weakly basic alkaloids (used as ophthalmic drugs) as the pH of the solution, and hence concentration of the undissociated base, was increased. At a pH of about 4, these drugs are predominantly in the ionic form, and penetration is slow or insignificant. When the tears bring the pH to about 7.4, the drugs may exist to a significant degree in the form of the free base, depending on the dissociation constant of the drug.

when the solution is instilled in the eye, the tears participate in the gradual neutralization of the solution; conversion of the drug occurs from the physiologically inactive form to the undissociated base. The base can then readily penetrate the lipoidal membrane. As the base is absorbed at the pH of the eye, more of the salt is converted into base to preserve the constancy of pK_b ; hence, the alkaloidal drug is gradually absorbed.

pH and Solubility

At a low pH, a base is predominantly in the ionic form, which is usually very soluble in aqueous media.

As the pH is raised, more undissociated base is formed. When the amount of base exceeds the limited water solubility of this form, free base precipitates from solution.

Therefore, the solution should be buffered at a sufficiently low pH so that the concentration of alkaloidal base in equilibrium with its salt is calculated to be less than the solubility of the free base at the storage temperature.