There are two stability issues in this case: (a) how stable is the lyophilized cake and (b) how stable is the solution after reconstruction?

10.2. Stability of Crystalline and Amorphous Lyophilates

It has been seen in Chapters 2 and 3 that a drug product in solution will possess an optimum pH. It is noted that this is accomplished by studying stability of the substance at different pH values, and that these latter are arrived at by the use of different buffers. If, for instance, the drug substance is a weak acid, then approximately speaking one may write

$$k_{obs} = k_0 + k_+[H^+] + k_-[OH^-] + k_{A^-}[A^-] + k_{HA}[HA] + k_{buffer}[HB] \tag{7.15}$$

where HB refers to buffer concentration and k_{HB} is the part of the rate constant attributable to the buffer. It is simplified, because k_{HB} is a combination of two terms, k_B and k_{HB}, but for this purpose it suffices to employ one (or at most two) terms. As discussed in Chapters 2 and 3, drugs mostly are protolytic and partly exist in ionized (A^-) and unionized (HA) form giving rise to the terms involving $k_{A^-}[A^-] + k_{HA}[HA]$, and k_0 is the part of the rate constant, which is neither acid nor base dependent. At lower pH, the term $k_-[OH^-]$ the term falls out, and $[A^-]$ and [HA] are dependent on the pH of the buffer used and of the $pK_{(a)}$ of the acid at the concentrations given. It is recalled that the $pK_{(a)}$ is also a function of ionic strength, the pK_a value being the value of $pK_{(a)}$ from which the ionic effect has been eliminated.

If such a substance in solution is allowed to cool down, then first water will freeze out as ice. The solution, hence, becomes more and more concentrated in both buffer and drug substance, and the pH changes as well. At the eutectic point (or the collapse temperature) all freezes out.

The stability of the substance as the concentrations change of course changes as well, because the buffer concentration changes, because the pH changes, and because the pK of the species in solution changes as well. Hence the optimum manufacturing pH is not the same as that of the corresponding solution. The experimental procedure to use is to make solutions of the desired concentrations of buffer and other excipients at several, say four, different pH values straddling the optimum solution pH, and then produce the lyophilized cake. The stability of this cake is then determined, and the optimum lyophilization pH determined in this manner.

10.3. The Labelling Dilemma of Parenteral Products

The FDA usually takes the strong positional stand that a different "salt form" constitutes a different drug substance and hence a new NDA is required. The drug on the label is the form of the drug in the dosage form. If for instance a product is made with a tetracycline base, then the label must state that this is the source of the antibiotic (as opposed to for instance the use of the addition salt, e.g., the hydrochloride).

But what about a lyophilized product? If one used tetracycline hydrochloride (RHCl) and buffered it at its pK value (at the given ionic strength), then, first