to execute dissolution for the formulations of a poorly water-soluble drug. In the 1% SLS-sink condition, the drug release from all the formulations was complete. However, the best bio-relevant dissolution condition was with 0.25% SLS, in which drug from all formulations could not release completely.

## IONIZATION CONSTANT, p$K_a$

### Importance of p$K_a$

Knowledge of the aqueous ionization constant, p$K_a$, of an ionizable drug candidate is very important because it can be used to predict solubility, lipophilicity, and permeability at different pH; therefore, help to improve drug adsorption by selecting suitable pH. Drugs in solution are distributed between their neutral and charged forms based on the pH and p$K_a$. Depending on whether drugs are acidic or basic compounds, pH lower or higher, respectively, than their p$K_a$ will create more ionization, and make the drugs more soluble but less permeable.

If the p$K_a$ of a drug substance is known in the early stage of the drug development process, the analytical assay method development, solubility and stability estimation as a function of pH can be accomplished with a minimum number of experiments, and it can guide formulation development for IV formulations.

### Temperature Effect on p$K_a$

The effect of temperature on ionization constants is related to the entropy change of the ionization process through the following equation (Perrin et al. 1981):

$$\frac{-d(pK_a)}{dT} = \frac{(pK_a + 0.052\Delta S^0)}{T} \tag{4.26}$$

Because the entropy change associated with ionization is different for different acids or bases, it is obvious that the effect of temperature on the ionization constants is highly structure dependent.

The p$K_a$ values of common carboxylic acids vary only slightly with ambient temperature. For the ionization of organic bases little entropy change is involved because the number of ions and their charges do not change ($\Delta S^0$ lies in the range of −17 Jdeg$^{-1}$mol$^{-1}$). Therefore the effect of temperature on the p$K_a$ values of organic bases is given with acceptable accuracy by the following equations:

For monocations:

$$\frac{-d(pK_a)}{dT} = \frac{(pK_a - 0.09)}{T} \tag{4.27}$$

For dications:

$$\frac{-d(pK_a)}{dT} = \frac{(pK_a)}{T} \tag{4.28}$$

for temperatures near 25°C where $T$ is in Kelvin.

For example, for a weak base with a p$K_a$ of 7.0, every 10-degree increase in temperature will lower the p$K_a$ by about 0.2 units.

When developing IV formulations for very insoluble weak bases, it is important to consider the temperature effect on the p$K_a$. If the pH values of these formulations are not low enough, the compound may precipitate out as the free base upon autoclaving. At elevated temperature, the p$K_a$ of the compound may be shifted to such an extent that the solubility of the free base becomes limiting at the solution pH. The precipitated free base may take a very long time to redissolve due to its low solubility and slow dissolution rate, resulting in product failure (Tong et al. 1994).