A preliminary investigation of pH-solubility profile with different counterions provides an indication of the counterion best suited to maximize solubility (or optimize for pH based on stability and/or tolerability). Multiple counterions added in predetermined amounts so as not to exceed the solubility product K_{sp} of any salt, provided significantly higher solubility than any single counterion. The relevance of pHmax to solution formulations with acceptable pH for intravenous administration has been reported (Stahl and Wermuth, 2002).

However, salt formation is not feasible for compounds without ionizable groups. In addition, the formed salts may also converse to respective acid or base forms in the bloodstream or gastrointestinal tract (GIT). Since blood is a very efficient buffer (pH 7.4), this can result in potential precipitation of the drug at the injection site, leading to issues such as hemolysis, phlebitis, thromboembolism, and potential changes in drug distribution (Yalkowsky et al., 1998). The risk of precipitation is reduced by the efficiency of the compound to bind to blood proteins, by slow administration, by reducing the drug concentration in the vehicle, and by the relative buffering capacity if a buffer is used (Alvarez-Nunez and Yalkowsky, 1999). The propensity for precipitation has been evaluated using *in vitro* methods (Portmann and Simmons, 1995; Johnson et al., 2003). Similar issues are expected with water-insoluble acid drugs formulated as solutions with pH adjustment. When administered orally, the formulation is dispersed in the stomach's acidic environment. A potential problem is that the acid drug may precipitate out from the solution. Because the precipitation kinetics are highly dependent on local conditions and may require nucleation of the particle, they occur with high variability and, hence, may affect oral absorption in a variable manner, and result in poor bioavailability.

Drugs in solution formulations may be more susceptible to chemical reactions leading to degradation. The most common reactions are hydrolysis and oxidation. Usually, the reaction rate or type is influenced by pH. For example, the hydrolysis of acetylsalicylic acid (aspirin) is pH dependent, and its pH-rate profile shows a large and complex variation of k_{obs} due to four distinct mechanistic patterns (Alibrandi et al., 2001). Therefore, it is essential to monitor and understand the chemical stability of the drug in pH-adjusted formulations.

Cosolvents

A common practice in solubilizing water-insoluble compounds is to use water-miscible solvents. The use of cosolvents can enhance the solubility of nonpolar solutes by several orders of magnitude. Following the principle of *like dissolves like*, the polarity of water should be reduced by mixing with other less-polar hydrophilic substances and thus increasing the solubility of nonpolar, water-insoluble substances. For molecules without any ionizable group(s), which cannot be solubilized by pH adjustment, a cosolvent approach is often used. Solubility of a cosolvent system typically increases logarithmically with the linear increase in the fraction of organic solvent(s) (Rubino and Yalkowsky, 1987).

Assuming that the total free energy of the system is equal to the sum of the free energy of the individual components (Trivedi and Wells, 2000), the solubility of a compound in a binary mixture of water and an organic solvent can be described as

$$\log S_t = \log S_w + f(\log S_c - \log S_w)$$

where S_t is the total solubility in the cosolvent mixture, S_c is the solubility in pure organic solvent, S_w is the solubility in water, and f is the fraction of organic solvent in the cosolvent mixture.

If the cosolvent mixture contains more than two organic solvents (i.e., a ternary or higher cosolvent mixture), the total drug solubility can be approximated by a summation of solubilization potentials as

$$\log S_t = \log S_w + \Sigma(f_i(\log S_{ci} - \log S_{wi}))$$