Before conducting a mixture study, some preliminary experimentation must be done to narrow down and select the cosolvents or other excipients to be used in the design. After selecting the appropriate excipients, the ranges to be studied must be determined. In doing so, one will usually want to stay within the ranges that have been previously used for marketed products. Another item for consideration is if a buffer will be used, and if so, what concentration and what pH or apparent pH will be used. In deciding the pH, one must select a pH or pH range that will ensure that the solid-state form of the compound does not change throughout the samples studied. Although this cannot be prevented with complete certainty, as simply changing cosolvent concentrations can induce such changes, selecting an apparent pH should help ensure against a change from the ionized to the unionized state for ionizable compounds.

STABILITY CONSIDERATIONS

Influence of Dielectric Constant on Reaction Rates

There are theoretical expressions for the effect of the solvent on the reaction rate using dielectric constant ($\in$) and viscosity parameters. Grissom et al. (1993) have reported the increase in photostability of Vitamin B-12 by addition of viscogens, such as glycerol and Ficoll. However, in this section the focus will be on the influence of the dielectric constant of the solvent.

The degradation rate of a drug can change with the $\in$ of the medium. As a general rule, for reactions leading to products that are less polar than the starting material, a less polar media may accelerate the reaction. On the other hand, reactions leading to products that are more polar than the starting material can proceed more rapidly in polar media.

From the Debye–Huckel theory for the potential (Ψ) in the vicinity of an ion, Scatchard (1932) derived an expression for the effect of dielectric constant of the solvent:

$$\psi = \frac{Z_i \varepsilon}{\mathrm{D}r} \frac{\exp^{[\chi(a_i - r)]}}{1 + \chi a_i} \tag{9.14}$$

In Equation 9.14, Z_i is the valance of the ith ion, ε is the electron charge, D is the dielectric constant of the solvent medium, a_i is the distance of the closest approach to the ith ion, r is the distance from the ion at where the potential is Ψ, and χ is the Debye kappa. The Debye χ is

$$\chi = \sqrt{\frac{4\pi\varepsilon^2}{\mathrm{Dk}T}} \sqrt{\sum n_i Z_i^2} \tag{9.15}$$

where k is the Boltzmann's gas constant, T is the absolute temperature, n_i is the number of the ith ion.

The activity coefficient f_i of the ith ion is

$$\ln f_i = \frac{1}{\mathrm{k}T \int_0^{Z_i \varepsilon} \psi \, d(Z_i \varepsilon)} \tag{9.16}$$

Substituting the value of Ψ from Equation 9.14 into Equation 9.16:

$$\ln f_i = \frac{Z_i^2 \varepsilon^2}{2\mathrm{Dk}T(1 + \chi a_i) r} \exp^{[\chi(a_i - r)]} \tag{9.17}$$

For the simple reaction

$$A + B \Leftrightarrow [G] \rightarrow \text{Products} \tag{9.18}$$