that is, A-A and B-B, dominate over interactions between unlike molecules, A-B, then ΔH_{mix} is very positive and may dominate the free energy change, and if so, from equation (4), $\Delta G_{mix} > 0$, and thus phase separation is thermodynamically favored. The model described is referred to as "the regular solution model" (40,41).

$$x_{AB} = \frac{z}{kT}\left(w_{AB} - \frac{w_{AA} + w_{BB}}{2}\right) \tag{3}$$

$$\Delta G_{mix} = RTX_A \ln X_A + RTX_B \ln X_B + RT\chi_{AB}X_A X_B \tag{4}$$

It should be obvious that entropy plays a significant role in phase separation. If mixing results in a very small entropic gain, as is the case with many polymer-polymer mixtures, a given positive change in enthalpy on mixing can more easily dominate, resulting in a positive free energy change on mixing and giving phase separation, at least for a system at equilibrium. Polymers behave differently than small molecules, and their size and structure are factors that impact the thermodynamics of mixing. Equation (5) describes ΔG_{mix} for a polymer mixture (40,42), where ϕ_A and ϕ_B represent volume fractions of A and B, respectively. n_A and n_B are degrees of polymerization for each polymer, A and B, respectively. The degree of polymerization is determined by calculating the number of repeat monomer units in the average polymer chain from the molecular weight of the polymer chain divided by the molecular weight of the monomer. χ_{AB} is the exchange parameter previously described, R is the ideal gas constant, and T is the temperature.

$$\frac{\Delta G_{mix}}{RT} = \frac{\phi_A}{n_A}\ln\phi_A + \frac{\phi_B}{n_B}\ln\phi_B + \chi_{AB}\phi_A\phi_B \tag{5}$$

Upon mixing of two polymers, A and B, the entropy and enthalpy are dependent on the volume fraction occupied by the polymers. Polymers are not able to fully utilize the available volume increase upon mixing because of their size and connectivity (43). Thus, large–molecular weight polymers experience a smaller entropic gain per unit weight than a "small molecule," and the thermodynamics of mixing are more easily dominated by a larger enthalpic contribution, resulting in phase separation. The above model is known as the Flory-Huggins theory.

Typically, a phase-separating system exists as a single phase at temperatures above or below a critical temperature and at specific concentrations. However, some solutions do have both an upper and lower critical solution temperature, although this is not typically the case for systems of pharmaceutical freeze-drying significance. Rather, formulations for freeze-drying typically have an upper critical solution temperature only, meaning that below that temperature phase separation is thermodynamically spontaneous. In Figure 1A, at temperature T_1, there exists two phases at two different compositions of components A and B, that is, compositions *a* and *b*. However, there exists only one phase above the upper critical temperature, T_{co}. A plot of the free energy of a system, which results in phase separation is given in Figure 1B. When ΔG_{mix} is greater than zero the system spontaneously phase separates into two phases. Thus, the presence of two free energy minima in Figure 1B means two stable compositions and therefore demands the formation of two phases to provide a thermodynamically stable system.