methods of detection of phase separation using technology developed in other fields of science. We do not focus on systems which result in crystalline phases. Detection of crystalline phases is relatively straightforward and general formulation knowledge, if used correctly, can lead the formulator away from formulations that will likely give crystallization problems. Additionally, we highlight possible solutions to the problem of phase separation in pharmaceutically relevant freeze-dried systems through formulation and process design related changes.

THERMODYNAMICS OF PHASE SEPARATION DURING FREEZING

The classical representation of phase separation can be best approached from the basic thermodynamics of mixing of a simple two-component ideal solution (39). Consider a system of component A and component B. The free energy of mixing, ΔG_{mix}, is given by equation (1), whereas the entropy of mixing, ΔS_{mix}, is represented by equation (2). The thermodynamics of mixing in an ideal solution is controlled by the entropy contribution. That is, since in an ideal solution, $\Delta H_{\mathrm{mix}} = 0$, the free energy change is completely determined by the entropy change.

$$\Delta G_{\mathrm{mix}} = \Delta H_{\mathrm{mix}} - T\Delta S_{\mathrm{mix}} \qquad (1)$$

$$\Delta S_{\mathrm{mix}} = -\mathrm{n}R(x_{\mathrm{A}} \ln x_{\mathrm{a}} + x_{\mathrm{B}} \ln x_{\mathrm{B}}) \qquad (2)$$

However, we rarely encounter ideal solutions in real practice. Thus, interactions are typically present and the solution deviates, at least moderately, from ideal solution behavior. A regular solution is the next level of complexity and is a useful model for many real solutions, even if only for qualitative understanding. In many cases ΔH_{mix} is positive and opposes mixing to at least some extent. Therefore, it is the competition between enthalpy and entropy that ultimately dictates the phase separation process. In a regular solution a dimensionless quantity referred to as the exchange (or interaction) parameter (χ_{AB}) is defined (40). The exchange parameter describes the energetic cost of starting with pure A and B and transferring one molecule of B into a medium of pure A and one molecule of A into a medium of pure B. The equation defining χ_{AB} is shown in equation (3) (40), where w_{AB} is a measure of the energy of interaction between A and B molecules, w_{AA} and w_{BB} represent the energy of interaction between like molecules A or B, z describes the number of nearest neighbors (or coordination number), k is Boltzman's constant, and T is temperature. Therefore, if A-B interactions dominate over A-A and B-B interactions there will be a preference for A molecules to be next to B molecules, that is, mixing will tend to be spontaneous. On the other hand, if like molecule interactions dominate there will be a preference for phase separation, but whether phase separation actually occurs will depend on the magnitude of the entropy of mixing. An expression for the ΔG_{mix} in a regular solution can be described by equation (4) (40), where X_{A} and X_{B} are mole fractions of A and B, respectively. The first two terms of equation (4) describe the entropic term of the equation and the last term describes the enthalpic contribution, ΔH_{mix}. We note that, in a regular solution, the entropy of mixing is the same as for an ideal solution, which for any real solution is only an approximation. If the interactions between like molecules,