Advances in Instrumental Analysis Applied to the Development of Lyophilization Cycles

William J. Kessler, Puneet Sharma and Mircea Mujat

Key Phase Transitions During the Lyophilization Process

The lyophilization process is commonly used to formulate compounds that are unstable in aqueous solution. In order to develop a successful lyophilization process, a comprehensive understanding of the physical and chemical characteristics of formulations in the frozen and freeze-dried form is essential.

The three crucial steps in the lyophilization process are: freezing, primary drying, and secondary drying. The freezing process involves transformation of a liquid formulation to a frozen state. During this transformation, the key transition events are ice nucleation, crystallization of water, and simultaneous increase in solute concentration. Once the formulation is frozen, crystalline components crystallize out. Most disaccharides and proteins tend to remain in an amorphous phase and at the end of the freezing step may contain up to ~20 % of supercooled water. These transitions during the freezing process can be illustrated using a state diagram of a binary solution of sucrose and water (Fig. 1) [1]. Point A shows the initial temperature and composition of the liquid formulation. As the solution is cooled, ice nuclei form in the solution (point B). This event typically occurs below the thermodynamic equilibrium freezing point of the formulation. Ice nucleation is an exothermic event that leads to an increase in the solution temperature (point C). As the solution is further cooled, the solutes (such as buffer salts) may crystallize out (point D) at the eutectic temperature (T_{eu}). For a binary system, W_e represents the weight of crystalline solute at T_e. If the solutes remain amorphous (example sucrose), a glass transition event is observed (point E) at the glass transition temperature of the maximally freeze-con-

W. J. Kessler (✉) · M. Mujat
Physical Sciences Inc., 20 New England Business Center, Andover, MA 01810-1077, USA
e-mail: kessler@psicorp.com

P. Sharma
Genentech Inc., 500 Forbes Boulevard, South San Francisco, CA 94080, USA

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