cases of extreme silicone incompatibility. The main concern for compatibility of the formulation with the elastomer is leachable release from the elastomer. This can be controlled with fluoropolymer coating of the elastomer or optimization of the formulation. Finally, the formulator should attempt to maximize product concentration in the formulation to minimize cake height since this significantly impacts overall lyophilization time.

Product Characterization

It is crucial to understand the physicochemical characteristics of the formulation bulk solution that are critical in determining the optimal conditions for primary drying. Primary drying (ice sublimation) must be carried out by maintaining the product temperature below the glass transition temperature (T_g') or collapse temperature (T_c) for amorphous formulations or below the eutectic temperature for totally crystalline formulations. The glass transition temperature is a valuable guide, indicating the temperature at which the product viscosity reaches a point at which the solid matrix can begin to "flow." Differential scanning calorimetry (DSC) is typically used to measure the T_g' of the frozen drug product bulk solution. While it is a "critical" temperature for cycle design, most amorphous products will produce an acceptable cake structure at product temperatures slightly above the T_g'. It is only at the collapse temperature where a product will exhibit collapsed cakes. A more valuable tool in determining the optimum primary drying temperature is the T_c of the product. The T_c, as determined by one of several methods such as freeze-dry microscopy, is the temperature at which the frozen matrix physically collapses. Depending on the product, the T_c can be considerably higher than the T_g' (8). Collapse is a phenomenon common to frozen amorphous matrices. Collapse can occur when the product temperature during primary drying exceeds the T_g' to the extent that the frozen concentrate no longer possesses sufficient structural strength to support its own mass once the pure ice matrix is removed by sublimation. Eutectic melting, though a distinctly different physical phenomenon than collapse, is nevertheless dependent on the same process variables (shelf temperature, chamber pressure, and resultant product temperature) and results in similar catastrophic failure to the product. Although collapse and melting describe different phenomena, they are from a practical perspective similar and the corrective measures taken from a lyophilization cycle design standpoint are identical. The terms "collapse or melt-back" are regularly used to describe such a failure during primary drying.

FORMULATION DEVELOPMENT FOR THE DILUENT-CONTAINING CHAMBER

A key component of the dual chamber freeze-dried product is the selection of the appropriate diluent. The diluent chosen should enable rapid dissolution of the freeze-dried cake on transfer to the dry powder chamber, be compatible with the freeze-dried powder, and not negatively impact the chemical or physical stability of the reconstituted product. Typical diluents range from simple systems, such as water for injection, to tonicity modifying solutions, to water containing a preservative. Several of the dual chamber pen products have a preservative added to enable the reconstituted solution to be used in a