Freeze Drying of Pharmaceuticals : A Review of Critical Parameters

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Lyophilization, also called freeze-drying, is frequently the method of choice for the production of labile pharmaceuticals, including proteins. Yet, degradation during the process is common, and a freeze-dried product is not always perfectly stable during storage. This lecture provides an overview of the freeze drying process and formulation strategies with a focus on the impact of formulation on process design and product stability. Calorimetric methods for characterization of dynamics in glasses and the relationship between glass dynamics and product stability are also discussed.

Formulation and process are interdependent largely because of the variation of collapse temperature with formulation composition and the impact of freezing variations on solute crystallization, thereby producing large changes in collapse temperature. Process control is critical to minimize process time while maintaining product quality, and formulation details, particularly glass transition behavior, greatly impact both process design and ultimate product quality.

While the relationships between formulation and process are straightforward, the critical factors governing stability are very complex and only partially understood! Stability is extremely formulation sensitive, and formulation strategies are often based upon the concept of dispersing the unstable drug moiety in an inert glassy matrix of "stabilizer", such as sucrose or trehalose. The basic assumptions are: (a) the matrix allows the “native” and more stable protein structure to be maintained during drying, and (b) the non-reactive and structurally "rigid" glassy environment reduces the frequency and amplitude of motion needed for a chemical or physical reaction. Glass dynamics cannot be measured simply by the difference between the glass transition temperature and the storage temperature. The structural relaxation time, measurable by calorimetry, provides a measure of the dynamics in the glass which recent studies suggest may be a useful predictor of stability in that formulation. FTIR spectroscopy provides a useful measure of structure in the solid state, which also seems to correlate well with stability during storage.

Here, we describe a novel method for characterization of structural relaxation in glasses using isothermal microcalorimetry (i.e., the “TAM”), which measures directly the rate of heat release during the relaxation processes. The data demonstrate, as expected, that structural relaxation times of amorphous solids depend on a number of variables, including nature of material, temperature, moisture content, thermal history, etc. Isothermal microcalorimetry with the TAM provides a very fast and reliable way to characterize the dynamics of glassy materials, which in many respects is superior to the conventional DSC approach.