stachyose, and trehalose are formulated in a 1:1 weight ratio of excipient:hGH, whereas the dextran formulation is 6:1 dextran:hGH. While the concept that an excipient system must remain at least partially amorphous to improve protein stability is not in question, it is clear that remaining amorphous is not a sufficient condition for stability. Apparent aggregation in the dextran formulation is greater than in the pure protein. HES shows a slight improvement in stability over the pure protein, but is not nearly as effective as the glycine:mannitol formulation, and increasing the level of HES to 3:1 HES:hGH does not improve stability (38). Conversely, both stachyose and trehalose provide better stability than the glycine:mannitol system, with trehalose superior to stachyose. All systems are glasses at the storage temperature of 40°C, and for those formulations where glass transition temperatures are available, it is clear that storage is well below the T_g, and there is no simple relationship between T_g and stability. While one might speculate that a glass is more "solid," and therefore more stable, the higher the difference between T_g and the storage temperature, the data are not consistent with this speculation. Comparing the stachyose and trehalose formulations, which are both 1:1 formulations with hGH, the T_g of the stachyose formulation is nearly 20°C higher than the trehalose formulation, but trehalose offers slightly better stability than does stachyose. These observations and other similar results (38) suggest that while it is necessary for the formulation to have a T_g well above the highest anticipated storage temperature for both elegance and stability reasons, T_g is not a relevant stability variable for systems stored well below their glass transition temperatures.

STRUCTURE AND DYNAMICS IN AMORPHOUS PROTEIN FORMULATIONS

Protein Formulations as Amorphous Solids

Freeze-dried protein formulations are amorphous systems, at least in part, and the physical and chemical behavior of such products depends on the characteristics of amorphous systems, perhaps as much as their behavior depends on the unique behavior of proteins. Amorphous materials below their glass transition temperatures are termed glasses, and in many respects are solids in the same sense as are crystalline solids. That is, while the long-range order characteristic of crystalline solids is absent, short-range order does exist, and the dynamics in glasses more closely resembles crystalline solids than liquids above their equilibrium fusion temperatures. Glasses differ from liquids in another important respect. The short-range order or structure in liquids represents an equilibrium between possible configurations that responds essentially immediately to changes in temperature. The short-range order in glasses does not represent an equilibrium distribution of configurations. Rather, as a first approximation, the short-range order or configurations characteristic of the liquid at T_g are "frozen in" by cooling quickly through the glass transition, and the resulting glass is in a metastable state. With aging, transitions to lower energy states or enthalpy relaxations occur (39). In short, sufficient mobility exists even well below the glass transition temperature to allow changes in configuration. These relaxations are typically nonexponential in time due to contributions from a number of substates in the glass (39). Dynamics is important in amorphous materials since nearly any degradation reaction will require some degree of motion, or molecular mobility, for the reaction to proceed at a significant rate. The glass transition temperature, T_g, marks the division