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### **Stability in Glassy Pharmaceuticals: The Role of Glass Dynamics**

MICHAEL PIKAL, University of Connecticut

Many pharmaceutical products, particularly freeze dried therapeutic proteins, are often produced in the glassy state. Stability or resistance to degradation is often a serious problem, and we find stability differences between formulations of similar composition often differ by an order of magnitude or more. We seek a better understanding of those factors that determine physical and chemical stability so that more stable products may be efficiently developed. Our hypothesis is that differences in dynamics in the glassy state are at least partially responsible for formulation specific stability behavior of materials stored well below their  $T_g$ 's. Various measures of dynamics or "mobility" are compared with stability data obtained by chemical assay (HPLC) of samples stored at various temperatures and for various times. While the different measures of mobility are often well correlated, there exist several examples where a trend in dynamics with some variable depends greatly on the measure of dynamics being used for analysis. Experimental stability data suggest stability and calorimetric relaxation dynamics, an indicator of mobility on a large length scale and long time scale, or "global mobility", are well coupled in many cases. We review data for physical stability in small molecule amorphous systems, chemical stability in cephalosporin antibiotics, dimer formation in small molecule systems, and both chemical decomposition and aggregation in proteins. We also find evidence that stability may be improved by annealing, presumably as a result of the decrease in free volume (as determined by high precision density measurements) and the corresponding decrease in "global" mobility as determined by TAM experiments. We conclude that glass dynamics is an important factor in determining stability, both chemical and physical, of small molecules and proteins in the amorphous solid state. However, the correlations are far from perfect, and it appears that due recognition of "Fast Dynamics" may be critical for our understanding, particularly for stability well below  $T_g$ .