

## Amorphous and Activated Systems

### Amorphous mixtures

There is one aspect of amorphous mixtures that I find troublesome. From Kauzmann's now classic entropy paradox, we know that entropy plays a critical role in glass formation. However, if we look at the equations available for estimating the glass transition temperature of amorphous mixtures, we see that a term to account for the effect of the entropy of mixing is conspicuously missing in every case. The typical argument is that entropy of mixing in polymer mixtures is small, so it gets ignored. But being small is not the same as being absent. The polymer argument gets extended to amorphous mixtures of low molecular weight compounds and the effect of the entropy of mixing is still absent. My position (*Entropy* 2008, **10**, 207-223) is that the entropy of mixing must play a role on the glass transition temperature of amorphous mixtures and that to a first approximation, the effect of entropy of mixing has the form:

$$T_g'' = T_g \exp\left(-\frac{\Delta S_{mix}^c}{\Delta C_p}\right)$$

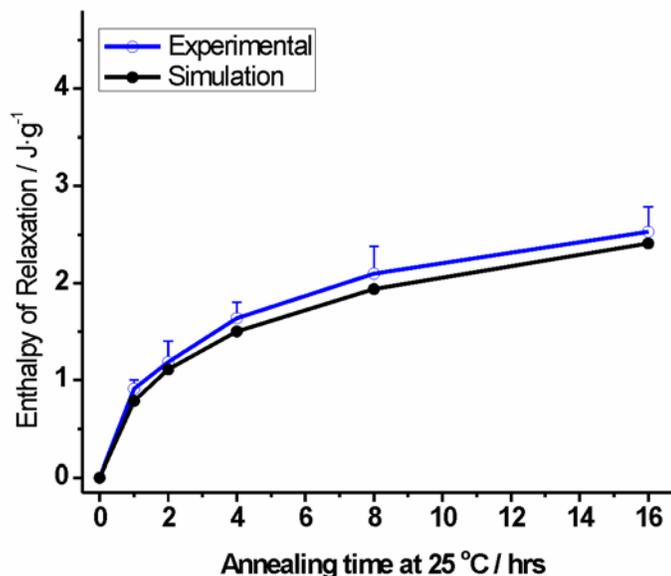
where  $T_g''$  is the glass transition temperature as influenced by the entropy of mixing, and  $T_g$  is the value for the case where the entropy of mixing has no effect on glass formation,  $\Delta S_{mix}^c$  is the configurational entropy of mixing and  $\Delta C_p$  is the difference in heat capacity between the liquid and the glass.

### Modeling Molecular Mobility

*Time and temperature dependence of the structural relaxation time*

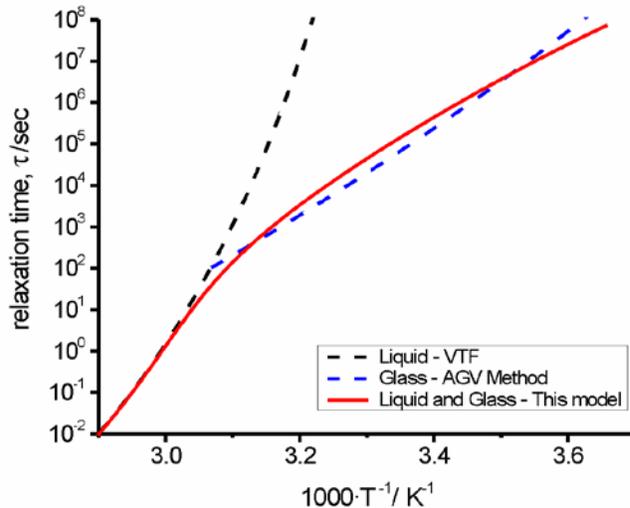
The stability of amorphous formulations is of particular importance given that these systems are by nature metastable. One way or another, as the product changes from the metastable to the stable form, the change involves molecular rearrangement. The structural relaxation time is a quantitative indicator of the degree of molecular mobility in amorphous systems. The relaxation time changes drastically with temperature, and this aspect has been the subject of numerous studies in the past. However, the relaxation time is also strongly dependent on time. This aspect has not received nearly the same degree of attention. Stability at constant temperature is a very important question and my group studies the time- and temperature-dependence of the structural relaxation time.

It is possible to model the relaxation time from a small set of carefully conducted heat capacity measurements. In this approach, the experimental values are fitted to the model. From the initial fitting to the glass transition using the freshly prepared glass as reference, the glass forming parameters of the material are "extracted". The extracted values can then be used again in the model to predict the behavior of the same material when exposed



to different temperatures for different lengths of time, heating, cooling, and combinations of such steps. One important point is that this model has no adjustable parameters - all parameters that are “extracted” can be measured separately. For example, Moynihan’s activation enthalpy (the change in the glass transition temperature as a function of heating rate) is one of the extractable parameters. The extracted parameters in the model can be put to work to predict time consuming experiments. For example, the DSC profiles of relaxation enthalpy measurements after various annealing times can be estimated by the model.

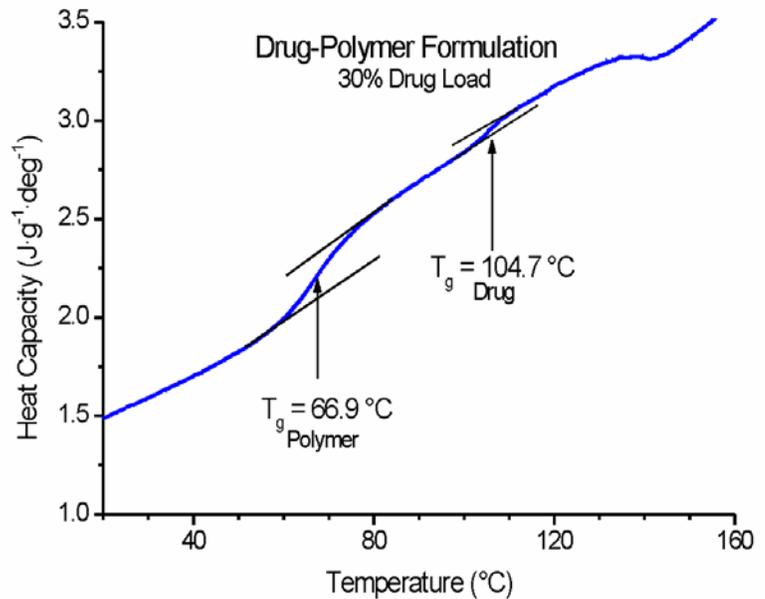
Crossover Liquid-to-Glass

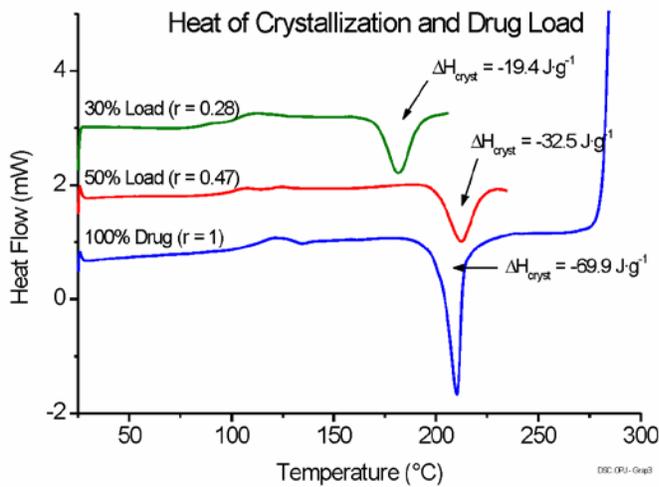


An important conceptual aspect of the model is the smooth cross-over between the liquid and the glass. This is an important point because the Arrhenius behavior of the glass and the super-Arrhenius (VTF) behavior of the liquid give place to a kink when they meet, giving place to sharp glass transition temperature instead of to a more realistic glass transition region. In this model, the expressions gradually evolve over a glass transition region from the Arrhenius (glass) to super-Arrhenius (liquid) profile.

*Why do we want amorphous formulations?*

When the crystal structure of the solute is so strong that the molecules simply do not get dislodged from the crystal to go into solution and be subsequently absorbed, then we need to explore the possibility of a non-crystalline formulation. We apply energy (by different possible means) so that we obtain a solid without the ordered structure that makes crystals stable. This high energy form is more soluble, but also less stable. At present, amorphous dispersions of drugs in polymers is a subject that generates intense interest. I am particularly interested in exploiting the properties of two-phase amorphous dispersions. These are dispersions where the amorphous drug and the polymer are not miscible.



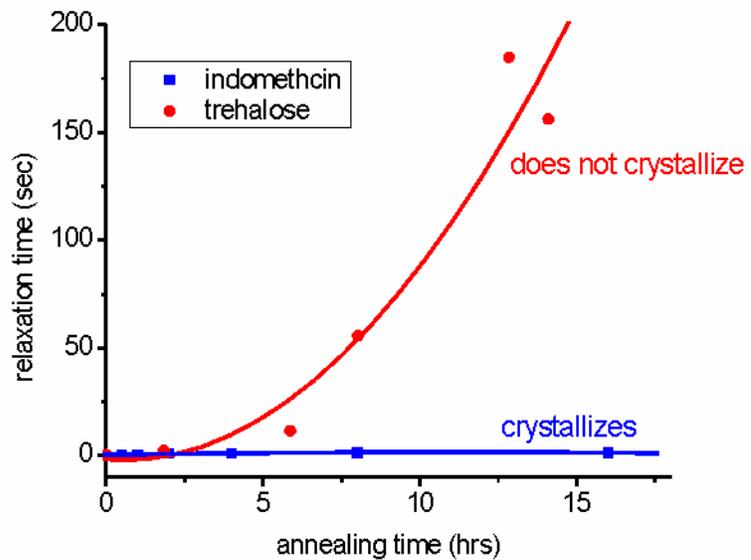


Having the amorphous drug in a separate phase offers some important advantages. In a very practical sense, the stability of the formulation will be to a good extent independent of drug concentration. This way, the characterization work can focus primarily on the properties of the amorphous drug, and the properties of the mixture itself, although still important, can be treated separately.

### Understanding the Amorphous State

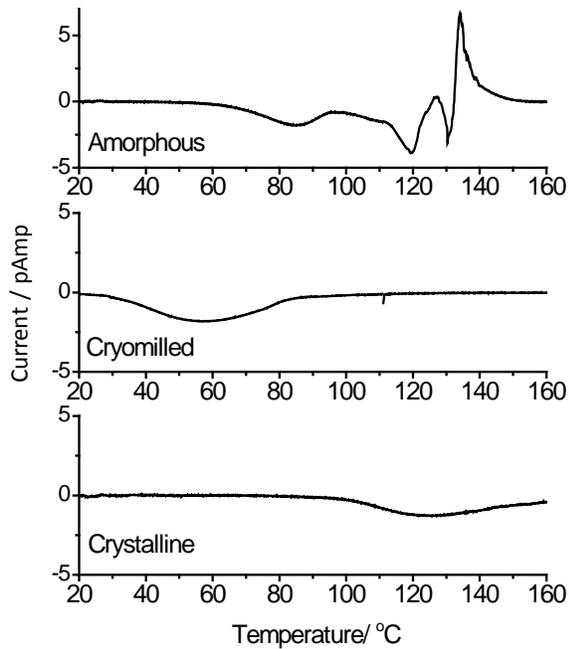
With all their potential advantages, amorphous formulations present some significant challenges. The same properties that make them so attractive for enhancing the dissolution of insoluble drugs also make them unstable. It is critical to be able to have a very good handle on the molecular mobility of amorphous substances. Molecular mobility will determine the feasibility for a compound to be developed as an amorphous formulation. It will also determine the changes in reactivity and physical stability over the shelf-life of the product.

### Time-dependence of Mobility vs. Crystallization



### Activation through Milling

Powders subjected to milling undergo what has been termed powder activation. A portion of the mechanical energy applied by the milling process gets stored into the milled material. The internal structure of the material is changed by the process to a structure of higher energy. That is how the energy is stored.



Milling crystalline compounds has the effect of reducing crystallinity and there is currently an active debate as to what is the structural character of the material with reduced crystallinity. The creation of the amorphous phase is the first to come to mind. Some materials become amorphous when milled. But amorphization takes some milling time for some compounds. The signal of TSC (thermally stimulated current) measurements is the manifestation of molecular mobility. Specifically, current is generated with the motion of molecular dipoles subjected to an electric field. The figure to the left shows the TSC profiles of griseofulvin. The profile of the amorphous form is distinctly different from that of the cryomilled material, which resembles more the starting crystalline material. The main difference between the cryomilled and original crystals is that the mobility hump in

the milled crystals is shifted to lower temperatures (below the glass transition temperature). Amorphization by milling does not necessarily take place immediately upon the onset of milling. Some milled materials get activated by developing dislocations (structural defects) in the crystal, before the accumulation of such imperfections evolves into amorphization.