



DSC Methods to Quantify Physical Aging and Mobility in Amorphous Systems: Assessing Molecular Mobility

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ABSTRACT

The specific heat capacity (C_p) of amorphous sucrose was determined by DSC after annealing at a particular temperature within the glass transition (T_g) region. The enthalpy recovery after physical aging was obtained from the C_p data through the T_g region after several aging times. This data was fitted to the empirical Williams-Watts equation to obtain values for the mean molecular relaxation time and a parameter for the distribution of relaxation times at the annealing temperature.

INTRODUCTION

Materials exist in a super-cooled liquid state if they have been melted and then cooled under conditions where they do not crystallize. They are termed amorphous since they are lacking in crystalline order. Their viscosity increases and molecular mobility and specific heat capacity decrease in a complex way as the material is cooled. Their data exhibit an S-shaped curve when measured against temperature and the inflection or midpoint of the S is often termed the glass transition temperature (T_g). The measured value of T_g and the value of these parameters through the T_g region depend on the thermal history of the material. Slow cooling through the T_g region allows adjacent molecules to find configurations of low enthalpy with less excess volume from inefficient packing. Rapid cooling through the T_g region leaves the material in a metastable state with more voids and less favorable intermolecular interactions. This is often illustrated by a diagram showing relative enthalpy (H) of the material as a function of temperature (T) as it is cooled at rapid or slow rates from the melt (Figure 1). Viewed in this way the T_g , as defined by the enthalpy data, decreases as the cooling rate decreases. This relative enthalpy diagram can be generated from DSC data by integrating the C_p or heat flow data.

When a material has been cooled rapidly from the melt and is thus in a higher enthalpy state, it will “relax” into a lower enthalpy state when it is held isothermally within the T_g region. This exothermic process is represented in Figure 1 as a vertical arrow at the annealing (or “physical aging”) temperature (T_{iso}). If the molecular mobility is sufficiently great at the selected temperature, this process can be

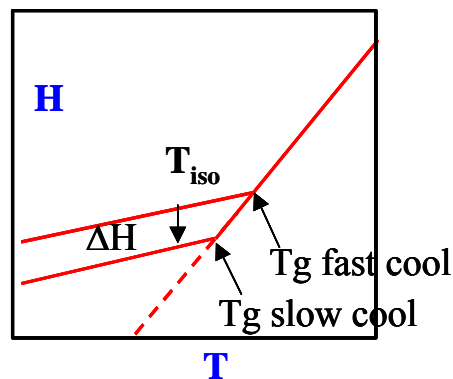


Figure 1. T_g Enthalpy Diagram of an amorphous material cooled at two rates

observed directly by isothermal DSC. This study is focused on aging well below T_g , where aging is too slow to observe directly.

The amount of physical aging (the length of the vertical arrow in Figure 1) depends on the time and temperature at which the material is held and the ability of the molecules to rearrange under these conditions. A material thus aged and then cooled to the DSC starting temperature will, when reheated, exhibit an endothermic peak in the T_g region. The difference in the area (enthalpy) between two DSC curves from samples having the same cooling history, but different aging times, is due to the “recovery” of the physical aging enthalpy. This method of assessing the mobility at the aging temperature calls for measuring the recovery of physical aging enthalpy after holding the sample for several aging periods. The extent of physical aging (the fraction of the total possible at that temperature) recovery is fitted to the Williams Watt equation to obtain the mobility parameters (*1*).

EXPERIMENTAL

A Q1000™ DSC from TA Instruments was used to obtain specific heat data on amorphous sucrose (*4*). Because it uses proprietary Advanced Tzero™ Technology, the instrument calibration provides an internal compensation for the effects of DSC cell asymmetry (*2,4*). The result is a baseline essentially at zero milliwatts and a displacement from that baseline that is due to the specific heat of the sample specimen itself. Hence, the DSC output from a single run can be accurately presented directly in Cp units.

The crystalline sucrose sample was heated above the melting point then removed and cooled in seconds to room temperature, thus trapping the sucrose in the amorphous state. The sample was reloaded in the DSC, equilibrated, and repeatedly heated over the temperature range to obtain Cp. Figure 2 shows the Cp data of several DSC runs in specific heat units after aging for different time periods. Alternatively, this procedure can be carried out using normalized heat flow data; however, it is essential that there be no instrumental curvature in the baseline.

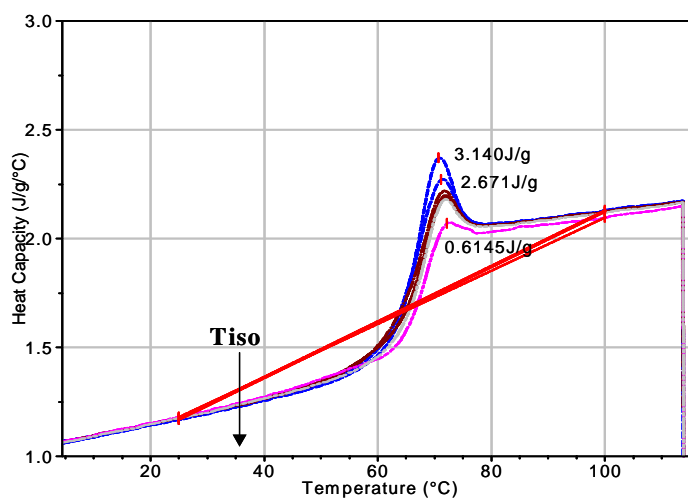


Figure 2. Specific heat capacity of amorphous sucrose after aging at T_{iso} for several periods. The ΔH differences reflect differences in physical aging (Individual areas have no physical significance).

CALCULATIONS

To determine the differences in physical aging from varying aging times, the data was integrated over an identical temperature range. The physical aging enthalpy was taken as the integral (the area between the curve and linear baseline) for a run after aging, less that for a DSC run where no aging occurred. The extent of physical aging was obtained by normalizing this value by the ΔH corresponding in Figure 1 to a vertical arrow between the un-aged run and the dashed line representing an extrapolation of the enthalpy data of the equilibrium liquid. In Figure 3, this is the ΔH_{∞} represented by the trapezoidal area defined by the heat capacity constructs for the Tg determination and the verticals representing a) the fictive temperature of the amorphous sample without physical aging, and b) the fictive temperature that has moved down to the temperature of physical aging, T_{iso} (3). The fictive temperature, which is an uncommonly used definition for Tg, is based on the intersection of pre- and post- transition lines on the enthalpy plot. It can also be obtained from DSC data as the temperature for which the area under the curve equals the area under the step function as indicated in Figure 3.

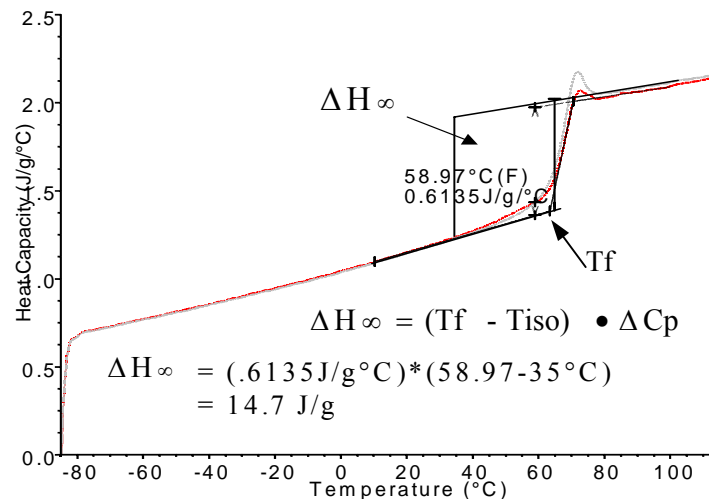


Figure 3. Determination of the total possible heat of aging ΔH_{∞} , at T_{iso}

The extent of physical aging (ϕ) after time t at T_{iso} is defined as:

$$\phi = 1 - \left(\frac{\Delta H_t}{\Delta H_{\infty}} \right) \quad \text{Equation 1}$$

Where:

ΔH_t is the physical aging enthalpy at T_{iso}

ΔH_{∞} is the total possible heat of aging at T_{iso} .

The Williams-Watt relationship (I) is:

$$\phi = \exp\left(-\frac{t^{\beta}}{\tau^{\beta}}\right) \quad \text{Equation 2}$$

Where:

t is the isothermal aging time at T_{iso}

τ is the mean molecular relaxation time

β a distribution figure for relaxation times

RESULTS

To determine τ , the (t, ϕ) data was fit by linear regression to the equation:

$$-\ln(\phi)^{-\beta} = \left(\frac{t}{\tau} \right) \quad \text{Equation 3}$$

The results of the fit are plotted in Figure 4. First, the value of β was obtained by trial and error to produce a linear fit. This produced a value of β of 0.3 ± 0.1 . Then the inverse slope was calculated to obtain a mean relaxation time (τ) of 11,000 hours or 1.25 years, a value in reasonable agreement with previous data (3).

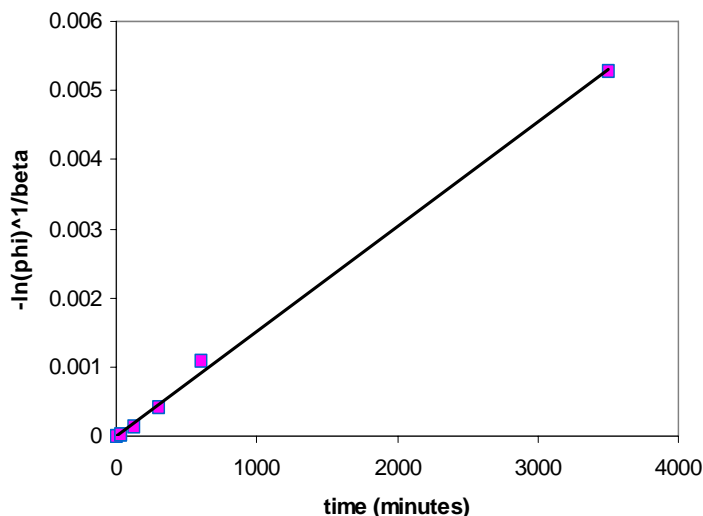


Figure 4. Plot of aging data to obtain τ and β

DISCUSSION

The use of the Williams-Watts equation implies a particular model of viscoelastic behavior. Other empirical relationships may be used to relate molecular mobility to viscoelastic or in this case, thermodynamic data. The significance of these mobility parameters is that the mean relaxation time is the half-life with respect to the relaxation process that builds enthalpy when an amorphous material is held within the Tg region. (In this case, the Tg region extends down to the neighborhood of the Kauzmann temperature where the extrapolated properties, specifically the entropy of the super-cooled liquid, equals that of the crystalline solid.) The process in question is that associated with the glass transition, which is primarily related to the freezing-out, or melting, of molecular translation. Hence, determining τ should correlate with the half-life with respect to the interaction of molecular species in an amorphous matrix. It has been reported that this parameter does correlate with the shelf life of unstable pharmaceuticals in freeze-dried (amorphous) formulations (3).

One consideration for this method is that obtaining usefully accurate values of τ requires carrying out physical aging experiments up to a few percent (at least) of the expected τ value. Thus, to predict the value of a shelf life of a year would require holding

the sample for several days (preferably weeks) at the proposed storage temperature. For this study, which was undertaken to promote this method, the aging was carried out in the DSC cell thus restricting the collection of long-duration aging. In this work, aging was performed at one temperature, but for unknown amorphous mixtures it would be preferable to carry out experiments at several aging temperatures. While the value of τ is different at each temperature, both τ and β should fall on a smooth curve with respect to temperature, and β would be expected to vary only slowly with temperature. In this study, the data was obtained on a single sample specimen, which was left in the DSC for the duration of data collection. It should be noted that where multiple samples are analyzed and aging is carried out in a separate, thermostatted device, care should be taken to prevent moisture uptake by the sample.

Finally, this analysis requires high sensitivity, accuracy and extremely reproducible instrumental baselines. The largest possible sample specimen should be used, and sample encapsulation and positioning in the DSC cell should be optimal and reproducible. The use of the Q1000 or Q100 with an autosampler is strongly recommended, especially if multiple samples are to be analyzed and the data combined.

REFERENCES

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3. B. C. Hancock, S. L. Shamblin and G. Zografi, "Molecular Mobility of Pharmaceutical Solids Below Their Glass Transition Temperatures" *Pharmaceutical Research*, 12, No. 6, (1995)
4. Tzero, Q1000 and Q100 are trademarks of TA Instruments

KEY WORDS

DSC, pharmaceuticals, molecular mobility, physical aging