Physical Aging and Fragility of Amorphous Sucrose by DSC

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ABSTRACT

A method for quantifying physical aging and fragility by DSC is discussed and exemplified. Amorphous sucrose is analyzed through the glass transition region with the glass transition temperature being determined for several cooling rates, and for subsequent heating. The results are analyzed using TA Instruments' Thermal Advantage Software and associated spreadsheet. Improved DSC performance using Tzero™ Technology is described.

INTRODUCTION

Amorphous materials undergo order-of-magnitude changes in viscoelastic properties when they are heated or cooled through the glass transition region (*1*). DSC has long been used to determine the glass transition temperature (Tg) as part of the characterization of materials. However, unlike the melting point of a crystalline material that marks a change in structure and is associated with a single temperature, the glass transition takes place over a temperature range. Moreover, the properties of the material below the glass transition region are dependent on the thermal history of the material as it was cooled from the liquid state. In particular, the rate of cooling from the melt, or the amount of annealing at temperatures in or near the glass transition region effect the molar volume, enthalpy and viscoelastic properties of the material in the glassy state. Since the classic work of Tool (*2*) quantifying glass transition behavior, there have been numerous efforts to model the glass transition process to rationalize the physical properties.

Interest in this topic surfaces from time to time in connection with "unexpected" changes in material properties when an amorphous material is stored for some period within a few tens of Celsius degrees below the glass transition. At this temperature, the material appears solid and in a fixed state. In fact, if it is close enough to Tg, it undergoes slow changes in thermodynamic and viscoelastic properties. This is referred to as physical aging. As a result of these changes the increased molecular mobility may allow crystallization or reaction to occur.

While some degree of physical aging occurs with all amorphous materials, the level to which it occurs varies by an order of magnitude depending on the material (*3*). Predicting this for a particular material, quantifying it, and looking for ways to modify it are reasons for carrying out the analyses described here.

The term used to describe the sensitivity of a material to physical aging is "fragility". Fragility may be measured by DSC. The enthalpic fragility parameter is defined as (*3*):

$$m_{\Delta h} = - (d \log \beta_c)/(d(T_{f,ref}/T_f)) \qquad \text{(eq. 1)}$$

where

$m_{\Delta h}$	is the fragility parameter,
β_c	is the prior cooling rate,
T_f	is the fictive temperature measured in heating, and
$T_{f,ref}$	is the reference fictive temperature

The glass transition temperature is a temperature taken to represent the range over which the glass transition takes place. The glass transition temperature depends upon the practical needs at hand, the physical property being measured and the experimental conditions used. It is a somewhat arbitrary value assigned to a measurable point within the glass transition region as defined by a specific procedure. In general, the value of Tg depends on the analytical technique, for example, calorimetry, volumetric analysis, or rheology. It also depends on the time scale of the measurement, *e.g.,* the heating rate, or Modulated DSC® or Dynamic Mechanical Analysis frequency. And it depends on the previous thermal (and mechanical) history of the sample.

One measurement of Tg that has particular utility for determining fragility is the fictive temperature (T_f) (*1*). The fictive temperature is defined as the extrapolated intersection of the pre-transition and post-transition DSC baselines in enthalpy units. To obtain enthalpy, the DSC heat flow curves are integrated. There is also an equivalent graphical method of obtaining T_f directly from the DSC trace (*4*). Figure 1 shows the T_f on a DSC heat capacity trace and its integral.

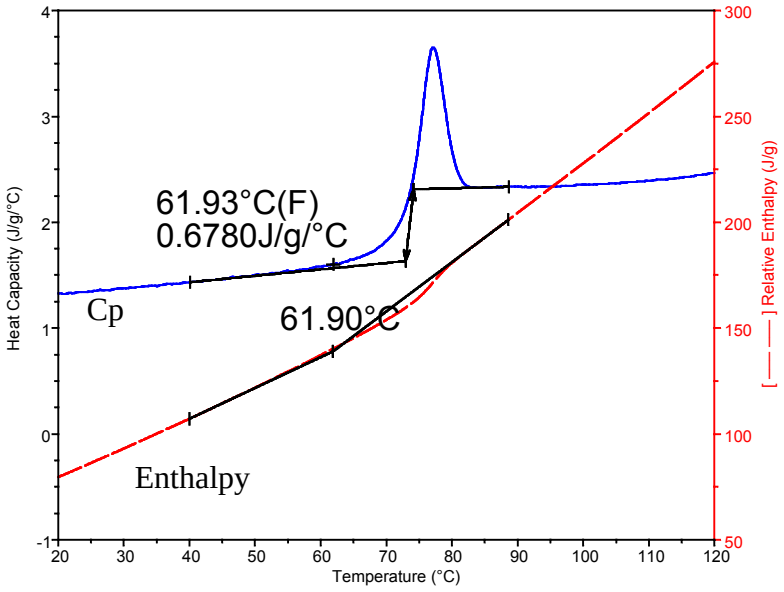

Figure 1 - Heat Capacity and Enthalpy Curve of Sucrose Showing Fictive Tg Constructs

The unique property of the fictive temperature is it's independent of the DSC heating rate used to measure it. Hence, it gives a value for Tg that depends only on the previous cooling rate through the glass transition region, determining the enthalpy state of the material below Tg.

EXPERIMENTAL

A Q1000 DSC with Advanced Tzero™ Technology is used for this analysis. This new DSC and sensor technology are described in a number of publications (*5*). The capabilities of this technology are particularly useful for this method. After calibration, the indicated temperature scale is essentially the temperature of the DSC pan holding the sample. Hence, for a sample that is well coupled to the pan, all thermal lag is addressed in the abscissa data. This allows data to be compared at different heating and cooling rates with confidence that the DSC is calibrated for all these conditions (*6*).

The really critical feature for this analysis is the absolute stability and linearity of the baseline. Because determining the fictive temperature requires an extrapolation across the glass transition interval, it is essential that the baseline be devoid of slope or curvature. The design of the Q Series™ DSC cell and sensor makes this capability possible. Rapid equilibration and fast cooling rates are also necessary, and both of these characteristics are with available the Q Series DSCs.

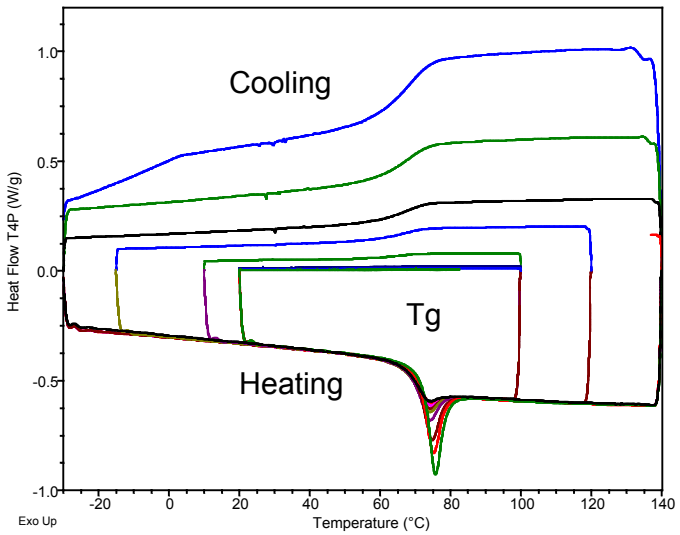

Figure 2 - Raw Data for Determining Sucrose Fragility

A third advantage of the Advanced Tzero™ Technology is that the DSC heat flow signal may be fully normalized into units of specific heat capacity, the fundamental thermodynamic property of the material being measured. Figure 2 shows much of the raw data for this analysis, from both heating and cooling steps, and Figure 1 shows the analysis of one of the heating steps.

The collection of data for this analysis is accomplished with a single, overnight, multiple-step program that alternately conditions the sample through the glass transition region at successive cooling rates and alternately heats at a fixed rate, here 15 °C/min. (The experimental method is reproduced in the appendix.)

Sucrose is selected to demonstrate the method because of its use, along with others sugars, as a pharmaceutical excipient. The encapsulated 20 mg crystalline sucrose sample was heated to 210 °C in nitrogen in the DSC to melt it. The sample is then removed and placed on a conductive surface at room temperature. This "quench" cooling prevented crystallization of the sample, thus "trapping" it in the amorphous state.

RESULTS AND DISCUSSION

The Tg results of the DSC analysis on sucrose are presented in Table 1 and Figure 2. The glass transition was measured at the indicated cooling rates using the half heat capacity glass transition assignment protocol (*7*). The Tg is measured in the subsequent heating step using both the fictive temperature method used for the fragility calculation and the half heat capacity (1/2 Cp) method. Table 1 shows that the Tg is depressed both when measured in cooling and when using the fictive protocol. This is consistent with the changes in other physical properties that accompany physical aging, namely, increased mobility at lower temperatures. This slow change in mobility that attends physical aging leads to stability problems for long term storage of amorphous formulations.

Table 1 - Glass Transition of Sucrose After Various Cooling Rates

Rate (°C/min)	Fictive Heat (°C)	_ Cp Heat (°C)	_ Cp Cool (°C)
25	66.35	68.62	67.93
15	66.08	68.85	67.13
8	65.21	68.57	66.04
5	63.7	68.25	65.49
2	62.69	68.16	64.2
0.5	61.36	68.3	62.84
0.25	60.71	69.04	62.18
0.1	57.3	69.52	60.4

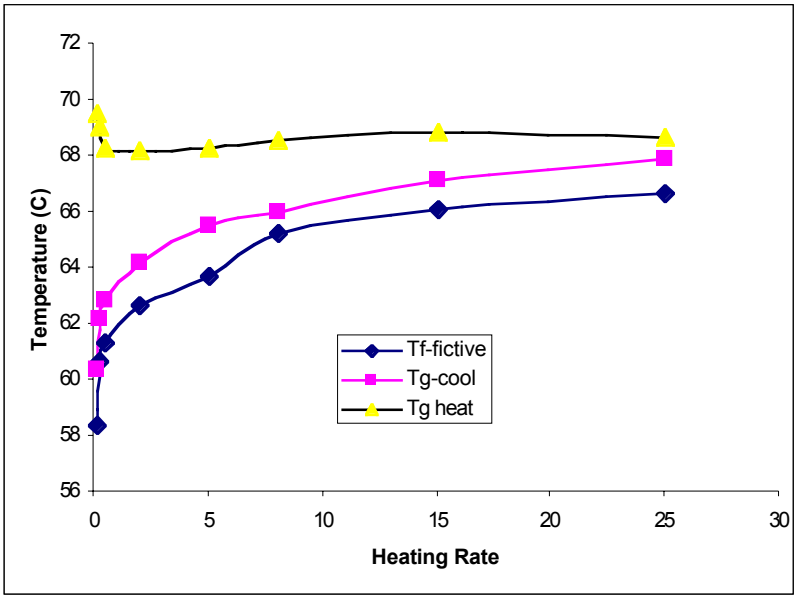

Figure 3 - Glass Transition of Sucrose after Cooling at Several Rates and Subsequent Heating

In contrast to the fictive and cooling data, the standard Tg method does not show this trend at 15 °C/min because of kinetic delay. Heating at a very slow rate gives Tg data approaching that of T_f . One of the advantages of the half heat capacity change method for determining Tg is that it is *less* sensitive to physical aging changes and therefore more likely to give a material-dependent measure of the Tg region midpoint.

Using Equation 1 and the fictive data in Table 1, the fragility parameter, $m_{\Delta h}$, for sucrose was calculated using least squares fit, to be 100 ± 5. Using equation 1, the physical aging for three weeks (a cooling rate through Tg of 0.001 ºC/min) would predict a Tg of 53 ºC. Storage above this temperature would be expected to provide the mobility for crystallization or reaction.

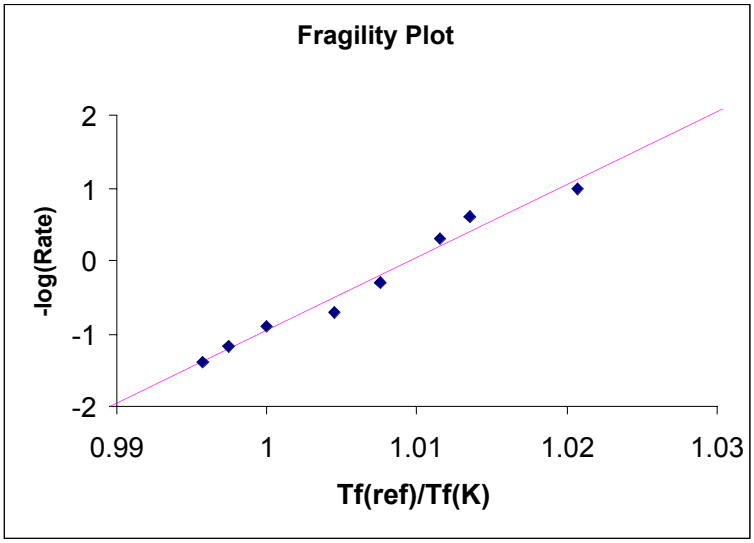

Figure 4 - Fragility Plot of Sucrose

SUMMARY

The fragility of sucrose is determined. This approach may be extended (by choice of heating and cooling ranges) to the determination of the fragility parameter for other glass formers, such as excipients, amorphous drug substances or amorphous formulations. The Q1000 DSC with Advanced Tzero™ Technology has a considerable advantage for this analysis because of its improved temperature control, accuracy, and baseline stability.

REFERENCES

1. *Assignment of the Glass Transition*, Special Technical Publication 1249, R. J. Seyler (Ed.), American Society for Testing and Materials, West Conshohocken, PA, **1984.**
2. A. Q. Tool, "Relaxation Between Inelastic Deformability and Thermal Expansion of Glass in Its Annealing Range," *Journal of the American Ceramic Society*, **1946**, 29 , p. 240.
3. C. G. Robertson, P. G. Santangelo, C. M. Roland, "Comparison of Glass Formation Kinetics and Segmental Relaxation in Polymers", *Journal of Non-Crystalline Solid*, **2000,** 275, pp. 153-159.
4. C. T. Moynihan, A. J. Easteal, M. A. DeBolt, "Dependence of the Fictive Temperature of Glass on Cooling Rate", *Journal of the American Ceramic Society* **1974,** 59, pp. 12-16.

5. R. L. Danley, “New DSC Apparatus and Heat Flow Measurment Technique”, *Thermochimica Acta*, accepted for publication 2002.
6. TA 283, “How Tzero™ Technology Improves DSC Performance: Part V: Reducing thermal Lag”, TA Instruments, New Castle, DE.
7. E1356, “Assignment of the Glass Transition Temperature by DSC and DTA”, American Society for Testing and Materials, West Conshohocken, PA.

KEYWORDS

differential scanning calorimetry, food and food products, glass transition, pharmaceuticals

APPENDIX

DSC Method

ProcName Multi-cool-Ramp
Sample sugar fragility
Size 19.900 mg
PanMass 23.620 23.000 mg
1: Equilibrate at 140.00 °C
2: Isothermal for 4.00 min
3: Ramp 25.00 °C/min to -30.00 °C
4: Isothermal for 3.00 min
5: Mark end of cycle 0
6: Isothermal for 3.00 min
7: Ramp 15.00 °C/min to 140.00 °C
8: Isothermal for 2.00 min
9: Mark end of cycle 0
10: Isothermal for 2.00 min
11: Ramp 15.00 °C/min to -30.00 °C
12: Isothermal for 3.00 min
13: Mark end of cycle 0
14: Isothermal for 3.00 min
15: Ramp 15.00 °C/min to 140.00 °C
16: Isothermal for 2.00 min
17: Mark end of cycle 0
18: Isothermal for 2.00 min
19: Ramp 8.00 °C/min to -30.00 °C
20: Isothermal for 2.00 min
21: Mark end of cycle 0
22: Isothermal for 2.00 min
23: Ramp 15.00 °C/min to 120.00 °C
24: Sampling interval 2.00 sec/pt
25: Isothermal for 3.00 min
26: Mark end of cycle 0
27: Isothermal for 3.00 min
28: Ramp 5.00 °C/min to -15.00 °C
29: Isothermal for 2.00 min
30: Mark end of cycle 0
31: Isothermal for 2.00 min
32: Ramp 15.00 °C/min to 100.00 °C
33: Isothermal for 2.00 min
34: Mark end of cycle 0
35: Isothermal for 2.00 min
36: Sampling interval 2.00 sec/pt
37: Ramp 2.00 °C/min to 10.00 °C
38: Isothermal for 2.00 min
39: Mark end of cycle 0
40: Isothermal for 2.00 min
41: Ramp 15.00 °C/min to 100.00 °C
42: Isothermal for 2.00 min
43: Mark end of cycle 0
44: Isothermal for 2.00 min
45: Ramp 0.50 °C/min to 20.00 °C
46: Isothermal for 2.00 min
47: Mark end of cycle 0
48: Isothermal for 2.00 min
49: Ramp 15.00 °C/min to 100.00 °C
50: Isothermal for 2.00 min
51: Mark end of cycle 0
52: Isothermal for 2.00 min
53: Sampling interval 10.00 sec/pt
54: Ramp 0.25 °C/min to 20.00 °C
55: Isothermal for 2.00 min
56: Mark end of cycle 0
57: Isothermal for 2.00 min
58: Sampling interval 0.50 sec/pt
59: Ramp 15.00 °C/min to 140.00 °C
60: Isothermal for 2.00 min
61: Ramp 4.00 °C/min to 85.00 °C
62: Sampling interval 10.00 sec/pt
63: Ramp 0.10 °C/min to 25.00 °C
64: Sampling interval 0.50 sec/pt
65: Isothermal for 2.00 min
66: Ramp 15.00 °C/min to 140.00 °C
67: Isothermal for 4.00 min