Amorphous Content of Common Pharmaceutical Materials

INTRODUCTION

The processing of pharmaceutical materials is known to introduce small amounts of amorphous material. The physical properties of amorphous structure are quite different from crystalline structure. As a result, amorphous structure can dramatically affect numerous properties such as product stability, compatibility, processing, storage, dissolution rate (faster bioavailability) and hygroscopicity, plus the tendency to absorb moisture or other solvents. It is thus important to know if a drug or drug delivery system has an amorphous component and to be able to quantify it, particularly at low levels.

The most common DSC measurement of amorphous structure is that of the glass transition (Tg). It is important to know the size of the transition in heat flow or heat capacity units and the temperature (Tg) at which it occurs. The size provides quantitative information on the amount of amorphous structure in the sample (when compared to the size of a 100% amorphous sample), while the temperature identifies the point where a large change in physical properties occurs. Below the Tg there is limited molecular mobility, while above it higher mobility results in reduced viscosity and potentially greater chemical interaction between components. This explains the general desire to store samples at least 40 °C below their glass transition temperature.

This paper presents data on the measurement of amorphous content in sucrose and acetaminophen. Sucrose is a sugar that is used as an excipient in many pharmaceuticals. Acetaminophen is an active pharmaceutical ingredient (API) that is used in pain relief medications.

RESULTS and DISCUSSION

One of the most difficult measurements for DSC is the detection of small amounts (<5%) of amorphous material in highly crystalline samples. The transition is small and is often hidden by small variations (nonlinear) in the DSC baseline. Figures 1 and 2 show the results of the outstanding baseline obtained with a Tzero™ DSC on a sample of crystalline sucrose that has less than one percent amorphous phase. Figure 1 shows duplicate runs on a very small (180µg) sample of freeze-dried amorphous sucrose. The value of the second heat is to not only check reproducibility but also to verify that the sample is dry. A wet sample, with even a few percent moisture, would have a lower Tg the first time that it is heated in a crimped (not hermetically sealed) pan. These runs are essentially calibration runs for determining the weight of amorphous material in another sample based on the size of the glass transition.

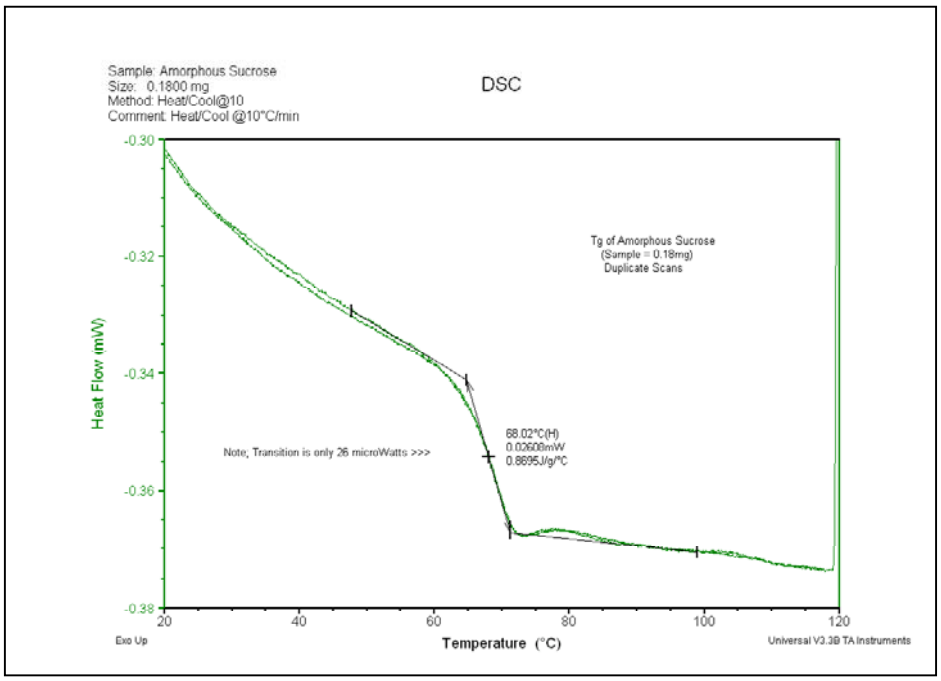

Figure 1 – Repeat runs on crystalline sucrose.

Figure 2 shows an overlay of the data from Figure 1 along with three other experiments. The first experiment was on a relatively large (15mg) sample of sucrose that was thought to be 100% crystalline. A large sample was used to increase the sensitivity of the measurement in detecting small amounts of amorphous content. At the expected glass transition temperature, a very small step change of 8µW is detected. Comparing this change with that of the 100% amorphous sample permits the calculation of the amount of amorphous structure in the crystalline sample.

$$\frac{8.4\mu W}{X} = \frac{24.6\mu W}{180\mu g} \text{ where } X = 61\mu g$$

$$\%\,\text{Amorphous Sucrose} = \frac{61\mu g \text{ x } 100}{15{,}000\,\mu g} = 0.4\%$$

In order to verify that there was a small amount of amorphous material in the crystalline sample, the technique of "standard addition" was applied where a known quantity (80µg) of amorphous material was added to a known quantity (16,000µg) of the crystalline sample. Based on the amount of amorphous material added, a step change of 10.9µW would be expected if there were no amorphous material in the original crystalline sample.

$$\frac{80\mu g}{180\mu g} \text{ x } 24.6\mu W = 10.9\mu W$$

Actual results on duplicate runs shown in the middle of Figure 2 show a step change of 17.3µW. This equates to a weight of:

$$\frac{24.6\mu W}{180\mu g} = \frac{17.3\mu W}{X} \text{ where } X = 126\mu g$$

$$\%\ \text{Amorphous Sucrose} = \frac{126\mu g \text{ x } 100}{16{,}080\mu g} = 0.8\%$$

Since only 0.5% was added, the original crystalline sample must have contained 0.3% which agrees quite well with the 0.4% measured directly.

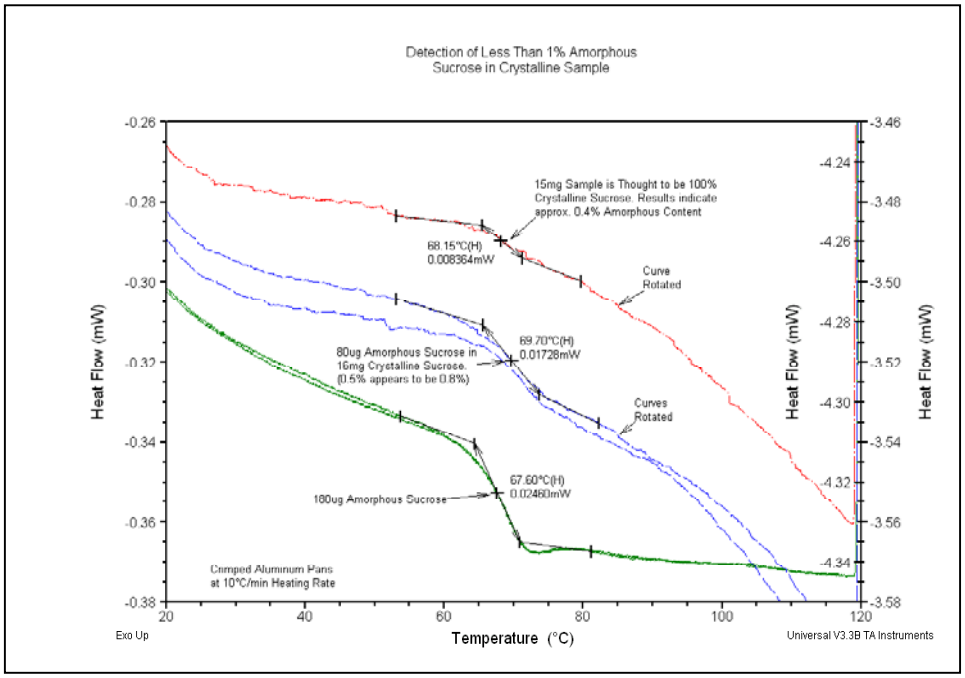

Figure 2 – Overlay of DSC runs on sucrose with varying amounts of amorphous content.

Figure 3 shows an overlay of two DSC experiments on acetaminophen. Both experiments are heating runs performed at 10°C/min. One shows a very large glass transition. This data was collected from a sample that was rapidly cooled from above the melt in order to form a 100% amorphous state. Since the size of the glass transition is proportional to the amount of amorphous material, it is critical to obtain the size of the glass transition for a fully amorphous sample. After this value is obtained, then any sample of intermediate amorphous content can be analyzed and the amorphous content calculated by ratioing the size of the Tg's. The second scan is from a sample that was cooled at 1°C/min from the melt. This slow cooling rate should ensure that a high degree of crystalline structure, or low amorphous content, was formed. The small size of the Tg does indeed indicate that the amount of the sample that is amorphous is quite small. Figure 4 shows the actual calculation of % amorphous content. As mentioned, it is just a straight ratio of the sizes of the glass transitions in heat capacity units. The slow cooled sample is seen to have approximately 6% amorphous content.

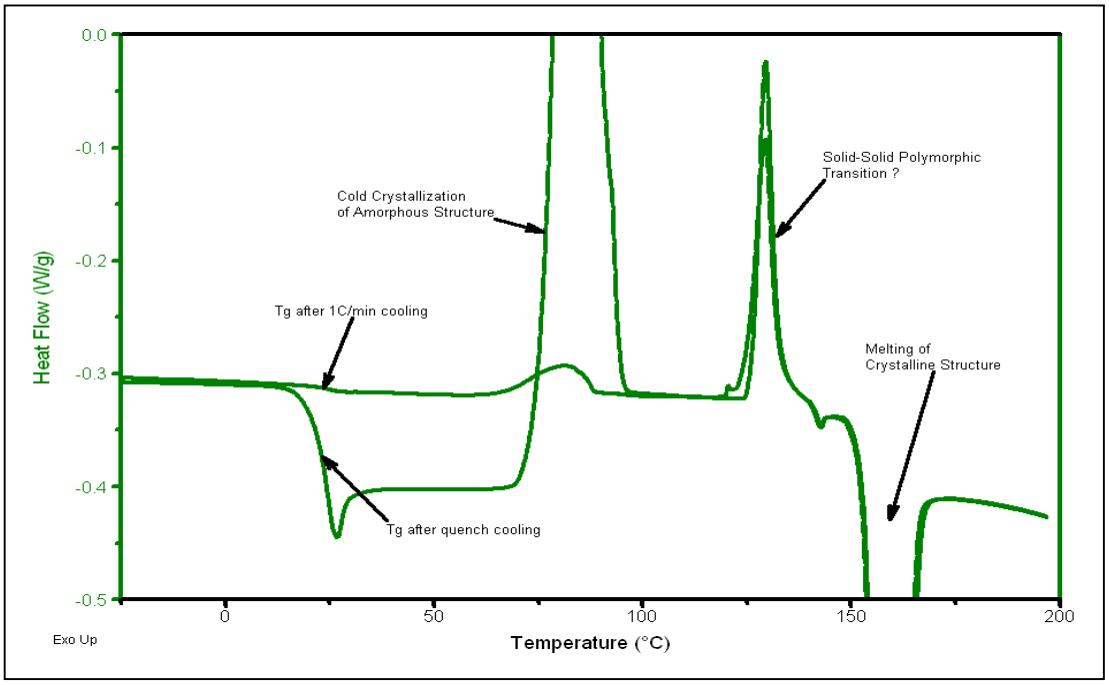

Figure 3 – Overlay of quenched and slow cooled acetaminophen

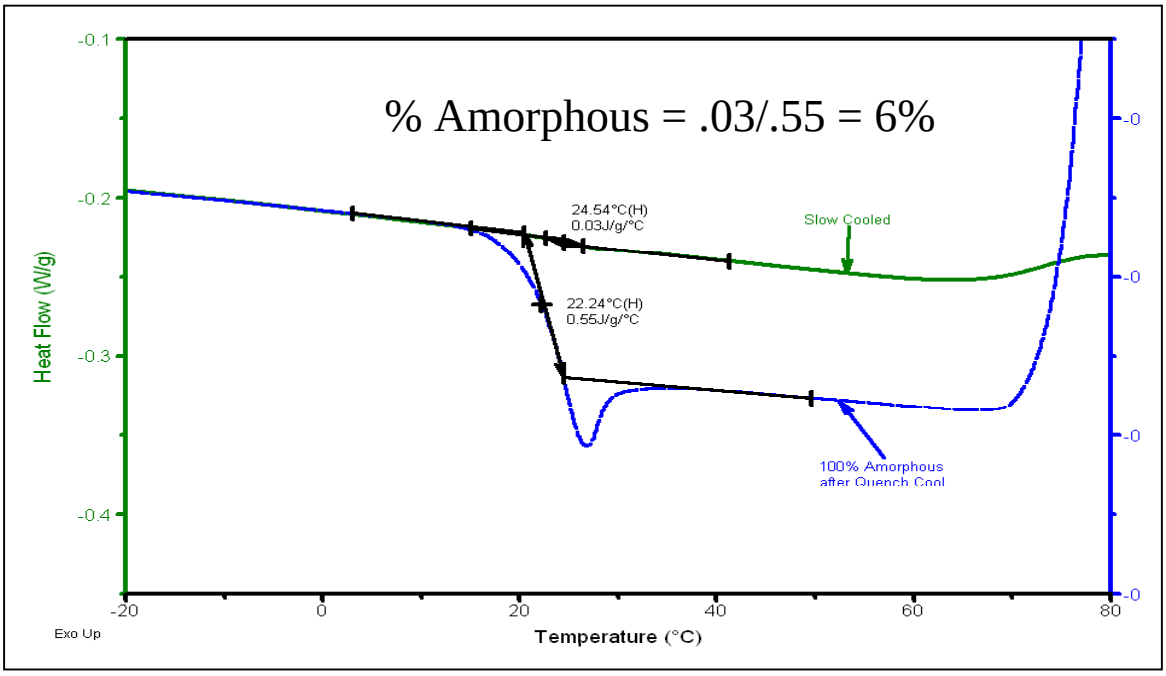

Figure 4 - Calculation of % crystallinity

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