



Determining the Moisture-Induced Glass Transition in an Amorphous Pharmaceutical Material

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A new method to determine the onset relative humidity for a glass transition in an amorphous material was developed using the DVS. Water vapour can act as a plasticising agent in amorphous materials, causing a recrystallisation event below the glass transition temperature. This method calculates the threshold relative humidity for this moisture-induced glass transition at a particular temperature.

Introduction

The characterisation of amorphous or partially amorphous pharmaceutical materials has been of particular interest in recent years [1]. The existence of amorphous materials can generally be attributed to one of three circumstances [2]. First, the material (drug, excipient, or delivery system) may be deliberately manufactured in an amorphous state. Second, the material may be inherently amorphous or partially amorphous at a processing or delivery temperatures. Third, the amorphous material may be produced unintentionally. This can occur through milling, compression, introduction of impurities, freeze-drying, or spray-drying.

Whether intentional or accidental, the presence of amorphous materials in pharmaceutical systems causes significant challenges in the processing, storage, and delivery of these materials. Thermodynamically, amorphous materials are metastable compared to the crystalline state. Also, amorphous solids have no long-range molecular order or well-defined molecular structure. For these reasons, amorphous materials typically have different properties from their crystalline counterparts.

Some useful properties of amorphous materials can be higher solubility, higher dissolution rate and better compression characteristics. Some typically undesired characteristics of amorphous solids include decreased physical and chemical stability [3].

Due to the unique properties of the amorphous phase, full characterisation of any amorphous material is paramount in the development of drug systems. Of particular concern is the stability during processing and storage. Low molecular weight amorphous materials will typically revert to their crystalline state over a certain temperature or temperature range. To complicate matters, ever-present water vapour can have a significant effect on amorphous materials. Amorphous solids often absorb relatively large amounts of water vapour compared to their corresponding crystalline phases. Sorbed water often acts as a plasticising agent, thus significantly lowering the glass transition temperature causing spontaneous phase transitions and lyophile collapse. In fact, there is often a critical humidity at which the glass transition will occur at room temperature. Therefore, determining the necessary threshold temperature and humidity conditions to prevent a





glass transition is critical for storage and processing of amorphous materials.

This paper describes a technique to determine the critical relative humidity of an amorphous material to prevent a glass transition and a water-induced recrystallisation at a constant temperature.

Theory

As an amorphous material passes through the glass transition it often transforms from a glassy, hard, brittle material to a less viscous, 'rubber' state [4]. Additionally, there is a shift in the molecular mobility of amorphous compounds at the glass transition [5]. Above the glass transition, the molecular mobility increases as evidenced by a decrease in viscosity and increasing flow. Temperature often forces the transformation at a characteristic temperature or temperature range (i.e. T_g). Plasticisers, often at a lower molecular weight than the bulk, can decrease the T_g. The extent of T_g depression depends on the concentration of the plasticiser and its interaction with the amorphous material. Water is a common plasticiser for a range of materials [5], thus the water content in amorphous foods, polymers, and pharmaceutical materials can have a significant lowering effect on the glass transition temperature. For these materials, the glass transition is a direct function of relative humidity.

If the humidity surrounding an amorphous material is linearly ramped from 0% relative humidity (RH) to a humidity above the water vapour induced glass transition, then a shift in vapour sorption characteristics will be evident. Below the glass transition, water sorption will typically be limited to surface adsorption. As the material passes through the glass transition, molecular mobility increases, allowing bulk water absorption. Therefore, the shift in sorption characteristics can be used as a measure of the glass transition. As in determining the T_g [6], the glass transition RH depends on the time scale of the experiment. Faster RH ramping rates will yield higher glass transition RH values. If a series of experiments are completed over a range of relative humidity ramping rates, then the critical

RH for a glass transition can be plotted versus ramping rate. If a correlation exists, then the inherent glass transition RH can be found by extrapolating the correlation to a zero ramping rate.

Above the glass transition, some amorphous materials will relax to their more stable, crystalline state. As mentioned above, the amorphous material will typically have a greater water vapour sorption capacity than the crystalline material, due to increased void space, free energy, and/or surface area. This can be measured directly using gravimetric techniques and used to determine amorphous contents [7-9]. When the material undergoes an amorphous to crystalline transition, the water sorption capacity typically decreases drastically. This results in an overall mass loss as excess water is desorbed during recrystallisation. Therefore, this mass loss can be used to isolate the particular humidity at which recrystallisation occurs. As with the glass transition, a series of experiments at different ramping rates can be performed to elucidate the threshold recrystallisation relative humidity.

Method

Dynamic vapour sorption (DVS) is a well-established method for the determination of vapour sorption isotherms. The DVS instrument used for these studies measures the uptake and loss of vapour gravimetrically using a SMS UltraBalance with a mass resolution of $\pm 0.1 \mu\text{g}$. The high mass resolution and excellent baseline stability allow the instrument to measure the adsorption and desorption of very small amounts of probe molecule. The vapour partial pressure around the sample is controlled by mixing saturated and dry carrier gas streams using electronic mass flow controllers. The temperature is maintained constant at $25 \pm 0.1 \text{ }^\circ\text{C}$, by enclosing the entire system in a temperature-controlled incubator.

Lactose was used as a model pharmaceutical material. Amorphous lactose was obtained by spray drying. The amorphous lactose was stored

over desiccant at 6 °C, to limit any recrystallisation.

The lactose samples were placed into the DVS instrument where they were initially dried in a 200-sccm stream of dry air (< 0.1% relative humidity) for eight hours. The sample was then exposed to a linearly increasing relative humidity environment to 90% RH. The glass transition RH was taken as the inflection point between surface adsorption and bulk absorption. The recrystallisation RH was taken as the point where the sample mass decreases drastically due to relaxation to the crystalline state.

Results

At typical net percent change in mass (based on dry mass) versus time plot is displayed in Figure 1. The red trace follows the net percent change in mass as a function of time, while the blue trace displays the sample relative humidity in the DVS. This particular experiment was done with a 6.0% RH/hour ramping rate. The glass transition relative humidity was measured at the transition point between surface adsorption and bulk absorption (see Figure 1; ~850 minutes). The amorphous to crystalline transition is clearly illustrated by the sharp loss in mass around 1150 minutes. The corresponding relative humidity was taken as the recrystallisation RH. For this particular experiment, the glass transition RH was 37.5% RH and the recrystallisation RH was measured at 65.5% RH. After recrystallisation, the sample has a much lower moisture sorption capacity. The sample retains a significant amount of moisture above the glass transition, due to the formation of a stable hydrate. Under the experimental conditions this hydrate will remain, even if the sample is dried at 0% RH. In its amorphous state, lactose is anhydrous, but when recrystallised, lactose forms a stoichiometric monohydrate. This phenomenon is well characterised and can be used as a means to quantify amorphous contents [9].

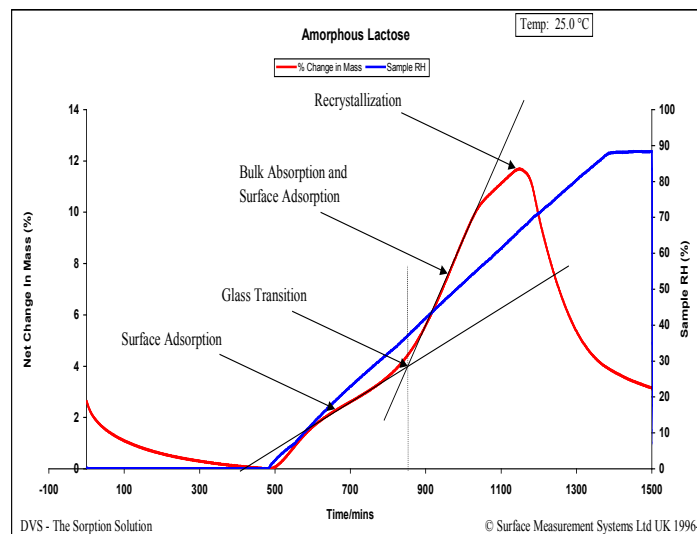


Figure 1. Relative humidity ramping experiment (6.0% RH/hour) for an amorphous lactose sample at 25.0 °C.

Similar experiments were performed over a range of relative humidity ramping rates. The rates and corresponding glass transition relative humidity values and recrystallisation relative humidity values are listed in Table 1 and displayed graphically in Figures 2 (glass transition) and 3 (recrystallisation).

Table 1. Relative humidity ramping rates and corresponding glass transition and recrystallisation RH values.

Rate (% RH/hour)	Glass Transition (% RH)	Recrystallisation (% RH)
10.00	40.8	70.4
8.00	39.4	68.3
6.00	37.5	65.5
4.00	34.4	63.5
2.00	31.7	60.3

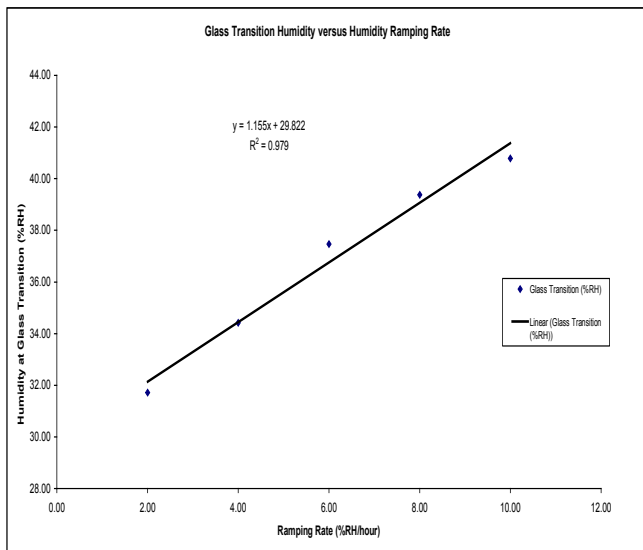


Figure 2. Glass transition RH versus relative humidity ramping rate.

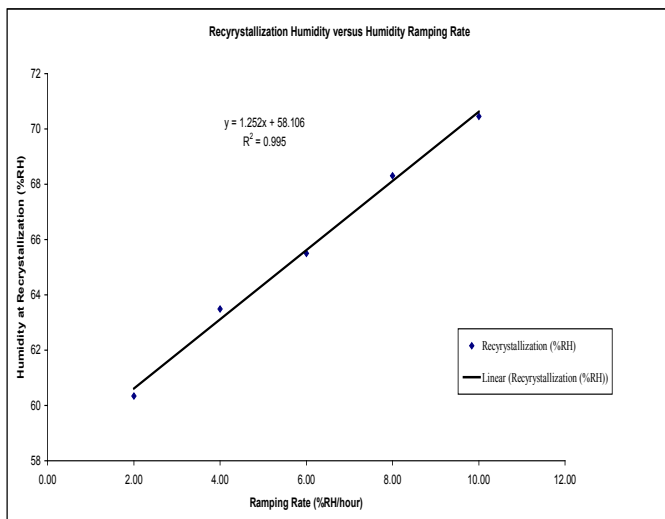


Figure 3. Recrystallisation RH versus relative humidity ramping rate.

As Figure 2 indicates, there is a clear linear relation between the RH ramping rate and the critical, glass transition RH. The graph was fit to a linear equation as shown in Figure 2. The resulting line yields and excellent fit, with a correlation coefficient better than 0.97. Extrapolating the results to a zero ramping rate yields a glass transition of 29.8% RH. Therefore, the critical storage and processing relative humidity for this amorphous lactose sample to prevent a glass transition is 30.0% RH at 25 °C. Figure 3 also shows a linear relationship with the recrystallisation RH and the relative humidity ramping rate.

The results were verified using inverse gas chromatography (IGC). IGC has been previously used to measure glass transition temperatures as a function of relative humidity [10]. Figure 4 shows the amorphous lactose Tg over a range of relative humidity values, indicating a clear relationship between Tg and RH. As the RH increases, the Tg decreases sharply, illustrating the plasticising effect of water. Similar results have been observed using differential scanning calorimetry, where the Tg dropped significantly with increasing lactose water contents [5]. In the IGC experiments at Tg of 22.2 °C (295.2 K) was measured at 30% RH. This value differs slightly from the 30% RH and 25 °C (298 K) value determined via DVS. Considering the different approaches and the uncertainties in measuring the Tg by the two methods, the small differences in the DVS and IGC values are not surprising. Also, the glass transition occurs over a range of temperatures, so the actual glass transition temperature can vary whether reported as the onset, middle, or end of the transformation.

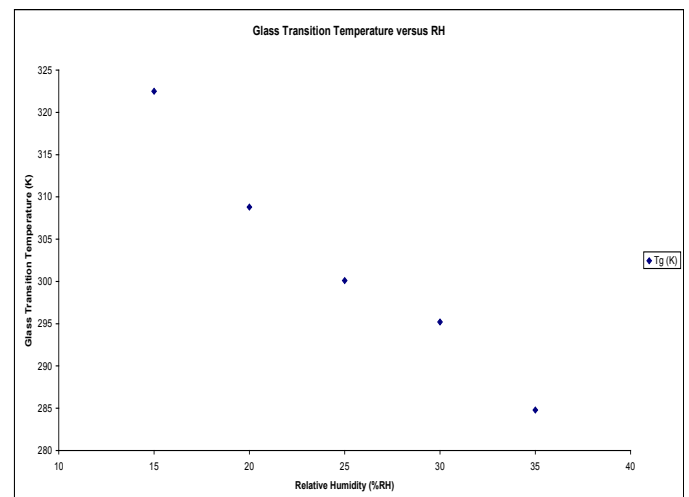


Figure 4. Glass transition temperature (Tg) as a function of relative humidity, measured by IGC on amorphous lactose.

This method could be applied to any system where a water or solvent vapour-induced glass transition and/or recrystallisation event occurs. Additionally, the DVS operates over a wide range of temperatures, so this technique could readily be applied to an array of storage, processing, and delivery conditions.



Conclusion

A new method was developed for determining the critical storage and processing relative humidity for amorphous materials. Using a series of experiments over a range of relative humidity ramping rates, the inherent relative humidity to cause a glass transition and/or recrystallisation can be readily determined at a particular temperature. This technique is applicable to a wide range of pharmaceutical powders provided a solvent-induced glass transition or recrystallisation is possible.

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