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Determining the critical relative humidity for moisture-induced phase transitions

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Abstract

A new method to determine the onset relative humidity for a glass transition and crystallization processes in amorphous or partially amorphous materials was developed using dynamic gravimetric vapor sorption (DVS). Water vapor can act as a plasticizing agent in amorphous materials, thus lowering the glass transition temperature below room temperatures. Additional water sorption can lead to a crystallization event below the glass transition temperature. On spray-dried lactose the glass transition RH and crystallization RH values were 30 and 58% at 25 °C, respectively. Glass transition and crystallization RH values were also measured at 5, 15, 25, 35, and 45 °C on a spray-dried salbutamol sulfate sample. The glass transition RH values for the salbutamol sulfate sample ranged from 64.5% RH (5 °C) to 32.8% RH (45 °C) while the crystallization RH values ranged from 81.0% RH (5 °C) to 50.4% RH (45 °C). The results clearly show that the glass transition and crystallization humidity values decrease as the sample temperature increases.
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Keywords: Vapor sorption; Glass transition; Humidity; Amorphous; Crystallization

1. Introduction

The characterization of amorphous or partially amorphous pharmaceutical materials has been of particular interest in recent years (Hancock and Zografi, 1997). The existence of amorphous materials can generally be attributed to one of three circumstances. 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 processing or delivery conditions. Third, the amorphous material may be produced unintentionally through milling, compression, or introduction of impurities (Graig et al., 1999).

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Whether intentional or accidental, the presence of amorphous materials in pharmaceutical systems can directly affect the processing, storage, bioavailability, and delivery properties of these materials. Therefore, full characterization of any amorphous material is paramount in the development of successful drug systems. Of particular concern is the stability during processing and storage. Even in very small amounts, the presence of amorphous phases may significantly affect the long-term stability and batch-to-batch variations in performance. Changes in temperature or solvent vapor pressure can increase molecular mobility and free volume within the amorphous region, thus lowering the activation energy barrier towards crystallization. In fact, low molecular weight amorphous materials will typically revert to their crystalline state over a certain temperature range. Additionally, ever-present water vapor can have a dramatic effect on amorphous materials. Amorphous solids often absorb relatively large amounts of water vapor compared to their corresponding crystalline phases. Sorbed water can act as a plasticizing agent, thus significantly lowering the glass transition temperature below the storage temperature and cause phase transitions and lyophile collapse (Roos and Karel, 1991). There is often a critical humidity at which the glass transition will occur at a particular 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 storage conditions of an amorphous or partially amorphous material to prevent a glass transition and a water-induced crystallization at a particular temperature. Lactose was used as model pharmaceutical excipient, because its crystallization behavior and polymorphic forms have been well characterized and it is used in a variety of solid dosage forms (Wade and Weller, 1994). Salbutamol sulfate, a common drug used for the treatment of asthma, was chosen as a model pharmaceutical active because its amorphous and crystalline phases have been well characterized (Ticehurst et al., 1994; Ward and Schultz, 1995; Feeley et al., 1998; Columbano et al., 2002; Young et al., 2004). The critical glass transition and crystallization humidities were determined for spray-dried lactose at 25 °C and for spray-dried salbutamol sulfate at 5, 15, 25, 35, and 45 °C using a gravimetric vapor sorption apparatus.

2. 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 (Sperling, 1986). Additionally, there is a shift in the molecular mobility of amorphous compounds at the glass transition (Roos, 1995). This transition will typically occur at a characteristic temperature or temperature range, commonly called the material’s T_g. Above the glass transition, the molecular mobility increases as evidenced by a decrease in viscosity and increasing flow. Plasticizers, often at a lower molecular weight than the bulk, can decrease the overall T_g. The extent of T_g depression depends on the concentration of the plasticizer and its interaction with the amorphous material. Water is a common plasticizer for a range of materials (Roos, 1995), 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 vapor induced glass transition, then a shift in vapor 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 water absorption into the bulk structure. Therefore, the shift in sorption characteristics can be used as a measure of the glass transition. As in determining the T_g (Frick and Richter, 1995), the glass transition RH (RH_g) 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 RH_g can be plotted versus ramping rate. If a correlation exists, then the inherent RH_g can be found by extrapolating the correlation to a zero ramping rate.

Above the glass transition, many low molecular weight amorphous materials will relax to their more

stable, crystalline state. As mentioned above, the amorphous material will typically have a greater water vapor 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 has been used previously to determine amorphous contents (Saleki-Gerhardt et al., 1994; Buckton and Darcy, 1995; Mackin et al., 2002). 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 crystallization. Therefore, this mass loss can be used to identify the particular humidity at which crystallization occurs (RH_c). As with the glass transition, a series of experiments at different ramping rates can be performed to elucidate the threshold crystallization relative humidity.

The determination of both the RH_g and RH_c values are based on detecting a change in moisture sorption properties. Their determination is not related to an absolute amount of water sorbed. Therefore, particle size and surface area differences between samples should have a minimal effect on the RH_g and RH_c determination. Additionally, the material's inherent RH_g and RH_c are determined by extrapolating the ramping rate to zero. Also, the RH_g is the onset glass transition and RH_c is taken as the onset of crystallization. Thus, both water sorption and crystallization kinetic limitations would be minimized.

3. Experimental

Dynamic gravimetric vapor sorption (DVS) is a well-established method for the determination of vapor sorption isotherms. The DVS-1 instrument (Surface Measurement Systems, London, UK) used for these studies measures the uptake and loss of vapor gravimetrically using a Cahn D200 recording ultra-microbalance with a mass resolution of ± 0.1 μg. The high mass resolution and baseline stability below 0.5 μg/h allow the instrument to measure subtle changes in vapor uptake. The vapor partial pressure around the sample is controlled by mixing saturated and dry carrier gas streams using electronic mass flow controllers. The desired temperature is maintained at ± 0.1 °C, by enclosing the entire system in a temperature-controlled incubator.

Partially amorphous lactose was prepared by GlaxoSmithKline (Collegeville, PA, USA) by dissolving crystalline lactose in water (10%, w/w) and spray-drying at 190 °C. Partially amorphous salbutamol sulfate was prepared by Bath University, School of Pharmaceutical Sciences (Bath, UK) by dissolving crystalline salbutamol sulfate in water (10%, w/w) followed by spray-drying at 180 °C. The spray-dried materials were stored over desiccant (anhydrous calcium sulfate) at 6 °C, to limit any crystallization. The same batch of spray-dried lactose and salbutamol sulfate was used for the respective studies to minimize any particle size, surface area, amorphous content, or similar batch-to-batch effects.

For the water sorption experiments, the samples (~10 to 90 mg) were placed into the DVS-1 instrument at the desired temperature where they were initially dried in a 200 sccm (standard cubic centimeters) stream of dry air (< 0.1% RH) for several hours to establish a dry mass. The samples were then exposed to a linearly increasing relative humidity environment up to 90% RH. The glass transition RH was taken as the inflection point between surface adsorption and absorption in the bulk structure of the material. The crystallization RH was taken as the point where the sample mass decreases drastically due to relaxation to the crystalline state. Multiple experiments ($n = 3$) were performed on the spray-dried lactose sample at the same humidity ramping rate to establish the reproducibility of the measurements. Only one run was performed at each temperature and humidity ramping rate for the salbutamol sulfate. Crystallinity of the end material was verified by performing a second humidity ramp from 0 to 90% RH. Absence of the mass loss feature at high relative humidity values was taken as an indication of complete crystallinity of the end material.

For comparison, inverse gas chromatography (IGC) experiments were performed to measure the glass transition temperature, T_g, of spray-dried lactose over a range of relative humidity values. IGC is a gas phase technique used to study the surface and bulk properties of particular and fibrous materials. IGC has been used previously to measure the T_g for a wide range of materials and the theory and details have been described in detail elsewhere (Lavoi and Guillet, 1969; Braun and Guillet, 1976; Hamieh et al., 1995; Thielmann and Williams, 2000). In short, the T_g is determined via IGC by measuring the differential heat of sorption for a par-

ticular probe molecule with the surface under investigation over a range of temperatures. The glass transition (or any second order phase transition) will result in a discontinuity in the relationship of the heat of sorption with temperature. The location of this discontinuity is taken as the glass transition temperature. For this study, an IGC-2000 instrument (Surface Measurement Systems, London, UK) was used to measure the T_g of spray-dried lactose (between 250 and 350 mg) from 15 to 35% RH. Ethanol was used as the probe molecule for all IGC experiments.

4. Results and discussion

4.1. Spray-dried lactose

A typical net percent change in mass (based on dry mass) versus time plot for spray-dried, partially amorphous lactose is displayed in Fig. 1. The solid trace follows the net percent change in mass as a function of time, while the dotted trace displays the sample relative humidity in the DVS. This particular experiment was done with a 6.0% RH/h ramping rate. There are several features in the mass response with linearly increasing RH. At low RH values (below 30% RH), the water uptake is relatively low. The moisture uptake in this region is probably dominated by surface adsorption. Above 40% RH there is a sharp increase in moisture sorption, most likely due to bulk absorption dominating the sorption mechanism. The glass transition relative humidity (RH_g) was measured at the transition point between surface adsorption and absorption into the bulk (denoted by intersection of dashed lines in Fig. 1; ~875 min and 37% RH).

The amorphous to crystalline transition is clearly illustrated in Fig. 1 by the sharp loss in mass around 1150 min. After crystallization, the sample has a much lower moisture sorption capacity. The corresponding relative humidity was taken as the crystallization RH (RH_c). Previous researchers have observed a similar decrease in mass when amorphous lactose was exposed to conditions above 50% RH at 25 °C and attributed this phenomenon to sample crystallization (Buckton and Darcy, 1995; Price and Young, 2004). Using AFM (Price and Young, 2004) and optical microscopy (Buckton and Darcy, 1999) other researchers have confirmed that lactose remains amorphous be-

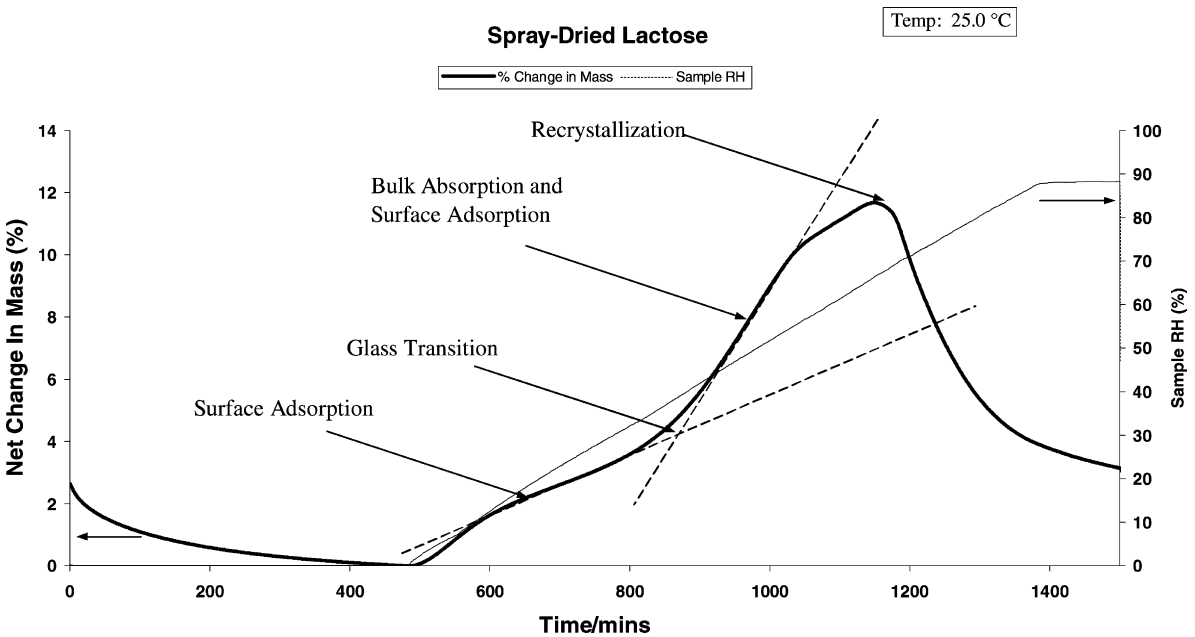

Fig. 1. Relative humidity ramping experiment (6.0% RH/h) for spray-dried lactose sample at 25.0 °C. Solid line shows the net change in mass while the dotted line shows the RH profile.

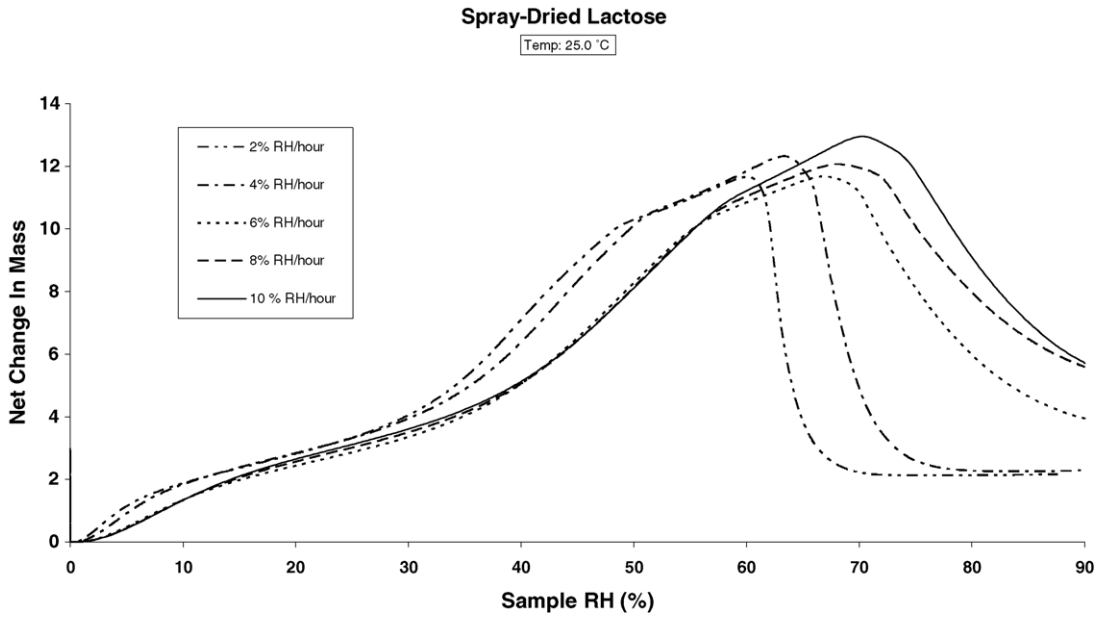

Fig. 2. Net change in mass for spray-dried lactose at 25.0 °C for a range of relative humidity ramping rates.

tween 30 and 50% RH, but crystalline when stored above 60% RH, thus supporting the assignment of the sharp mass loss above 50% RH as the crystallization RH in this study. For this particular experiment, the crystallization RH was measured at 65.5% RH. There is a nearly 30% relative humidity gap between the RH_g and RH_c. Even though the sample passes through the glass transition, molecular mobility must be significantly increased before crystallization occurs.

The sample retains a significant amount of moisture above the glass transition, due to the formation of a stable hydrate. Under the experimental conditions (25 °C in 200 sccm stream of dry air) this hydrate will remain, even if the sample is gently dried at 0% RH. In its amorphous state, lactose is anhydrous, but when it crystallizes, lactose can form a stoichiometric monohydrate. The formation of this hydrate species was observed for all humidity ramping experiments at 25 °C. This phenomenon is well characterized and can be used as a means to quantify amorphous contents (Buckton and Darcy, 1995). By applying this method, it is possible to estimate the amorphous content for this lactose sample. The lactose sample after crystallization and drying retains 1.95% of its weight in water. If the lactose was 100% amorphous and completely crystallizes to form α-lactose monohydrate, the sample would retain 5.26% water (18.01 amu/H_2O molecule/342.35 amu/anhydrous lactose molecule × 100% = 5.26%). Based on the measured uptake compared with the theoretical uptake, the lactose used for this study is 37.1% amorphous (1.95% measured water retention/5.26% theoretical 100% amorphous retention × 100%). Again, the above calculation assumes that the amorphous lactose completely crystallizes to form α-lactose monohydrate.

Fig. 2 displays the results for similar experiments from 2% RH/h to 10% RH/h. In Fig. 2, the net change in mass is plotted versus the sample RH(%) to highlight the effects of changing ramping rates. Notice that all features remain over the entire range of ramping rates. Both the RH_g and RH_c values appear to decrease with decreasing ramping rate. The ramping rates and corresponding RH_g values and RH_c values at 25.0 °C are listed in Table 1 and displayed graphically in Figs. 3 (RH_g) and 4 (RH_c). Multiple runs at the same ramping rate ($n = 3$) indicate error margins for RH_g and RH_c are ±0.5% RH. Error bars have been included in Figs. 2 and 3 to reflect the first standard deviations for these measurements.

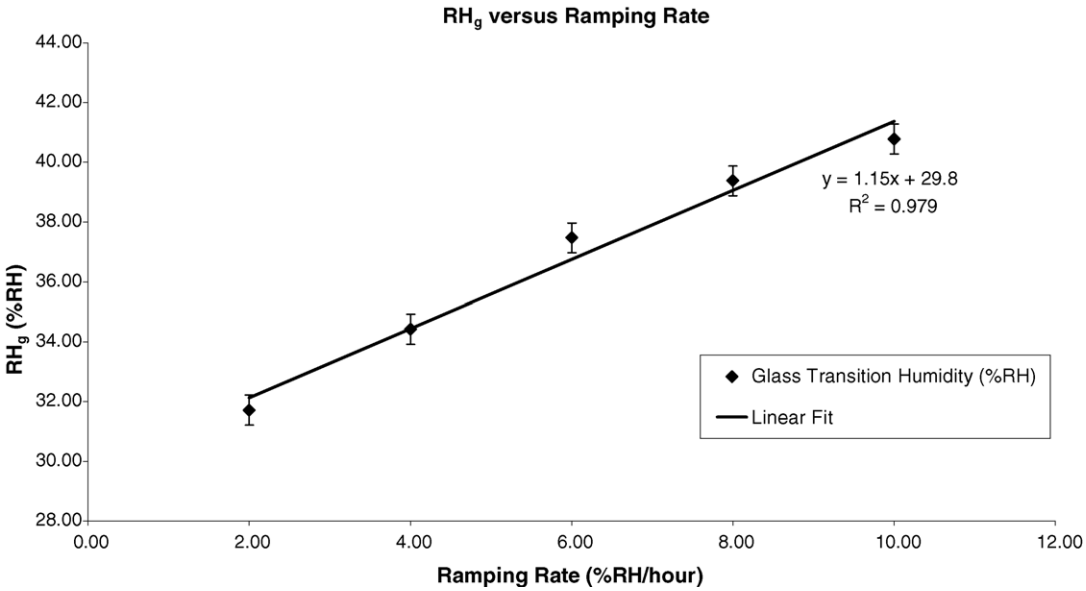

Fig. 3. RH_g vs. relative humidity ramping rate for spray-dried lactose at 25.0 °C. Solid line and equation represent linear fit.

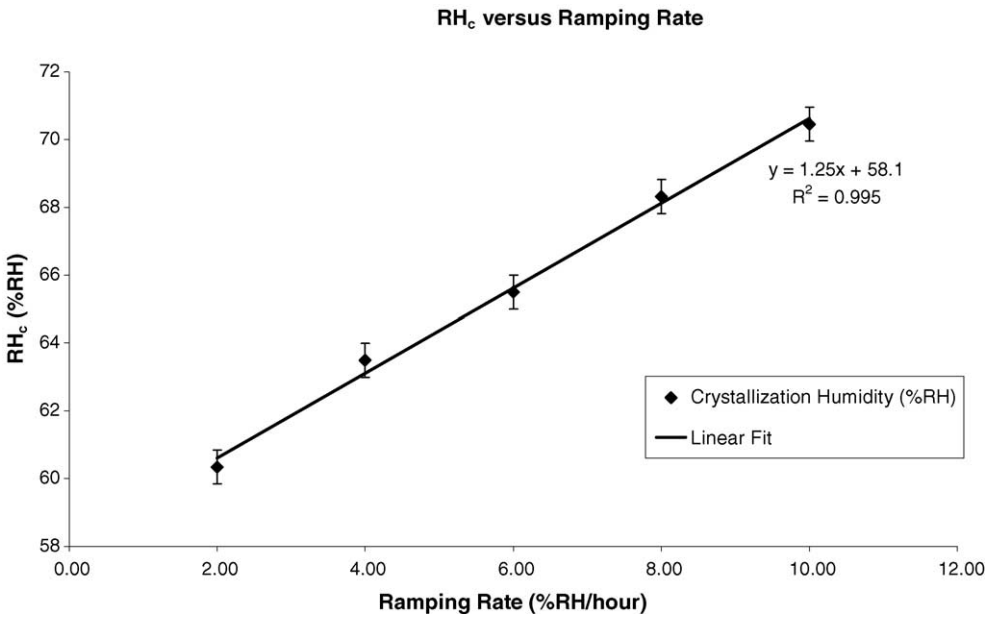

Fig. 4. RH_c vs. relative humidity ramping rate for spray-dried lactose at 25.0 °C. Solid line and equation represent linear fit.

Table 1
Relative humidity ramping rates and corresponding RH_g and RH_c values for spray-dried lactose at 25.0 °C

Rate (% RH/h)	RH_g (% RH)	RH_c (% 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

As Fig. 3 indicates, there is a clear linear relationship between the RH ramping rate and the RH_g. The resulting line yields an excellent fit, with a correlation coefficient better than 0.97. Extrapolating the results to a zero ramping rate yields an RH_g of 29.8% RH. Therefore, the critical storage and processing relative humidity for this partially amorphous lactose sample to prevent a glass transition is 30.0% RH at 25 °C. To prevent any moisture-induced phase changes, the spray-dried lactose should be stored well below 30% RH at 25 °C.

Using atomic force microscopy (AFM) to visualize the crystallization behavior of spray-dried lactose, Price and Young (2004) observed a rapid and distinct morphological change at 30% RH and 25 °C. They attributed this transformation to a rubbery transformation on the surface of the particles. Further, Lechuga-Ballesteros et al. (2003) detected an internal structure change in spray-dried lactose around 30% RH and 25 °C using isothermal calorimetry techniques. The authors define this point as a threshold for molecular mobility. When spray-dried lactose was stored below this point, there were no detectible morphological changes in the material (Lechuga-Ballesteros et al., 2003). Therefore, current results and previous work on spray-dried lactose support the presence of a moisture-induced glass transition in lactose around 30% RH at 25 °C.

The results were verified using IGC. We have previously performed similar experiments to measure glass transition temperatures of maltose as a function of relative humidity (Thielmann and Williams, 2000). The T_g was measured over a range of humidity values. The humidity values were correlated to the amount of water sorbed at each humidity by comparisons with DVS experiments (data not shown). Fig. 5 shows the spray-dried lactose T_g as a function of water content. As the water content (and RH) increases, the T_g decreases sharply, illustrating the plasticizing effect of water. In the IGC experiments a T_g of 22.2 °C (295.2 K) was measured at 30% RH. This value differs only slightly from the 30% RH and 25 °C (298 K) value determined via DVS.

Similar results have been observed using differential scanning calorimetry (DSC), where the T_g dropped significantly with increasing lactose water contents (Roos and Karel, 1990, 1991). DSC results on amorphous lactose at 33% RH yielded a glass transition temperature of 29.1 °C (T_g onset). This value is very close to the 30% RH and 25.0 °C values obtained in this study.

For further comparison, the Gordon–Taylor approximation can be used to predict the glass transition temperature of binary mixtures as shown below:

$$T_g = \frac{w_1 T_{g1} + k w_2 k_{g2}}{w_1 + k w_2} \quad (1)$$

where T_{g1} and T_{g2} are the glass transitions for the pure materials, w_1 and w_2 are the corresponding weight fractions and k is an empirical constant specific to the particular binary system. The glass transition temperatures of lactose (374 K) and water (138 K) and the k value for the lactose/water system (6.56) have been previously determined via DSC experiments (Roos, 1995). Using these values, the predicted Gordon–Taylor T_g values are shown Fig. 5.

The DSC values are slightly higher than IGC and DVS values. Considering the different approaches and the uncertainties in measuring the T_g by the three methods, the small differences in the DVS, DSC, 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. The DVS values presented here would represent the onset of this transformation and the IGC values would be the middle of this transformation. The 4 °C difference between the DVS and DSC results (both based on onset temperatures) may be due to the different approaches to controlling humidity. In the DVS, the humidity is controlled in situ during the experiment, but for the DSC experiments the sample is equilibrated at a particular RH, then sealed and run in the DSC. As the temperature changes during the DSC experiment, the relative humidity inside the DSC pan is not constant. The T_g is strongly dependent on humidity, so even if there is a slight change in humidity, the T_g can change by sev-

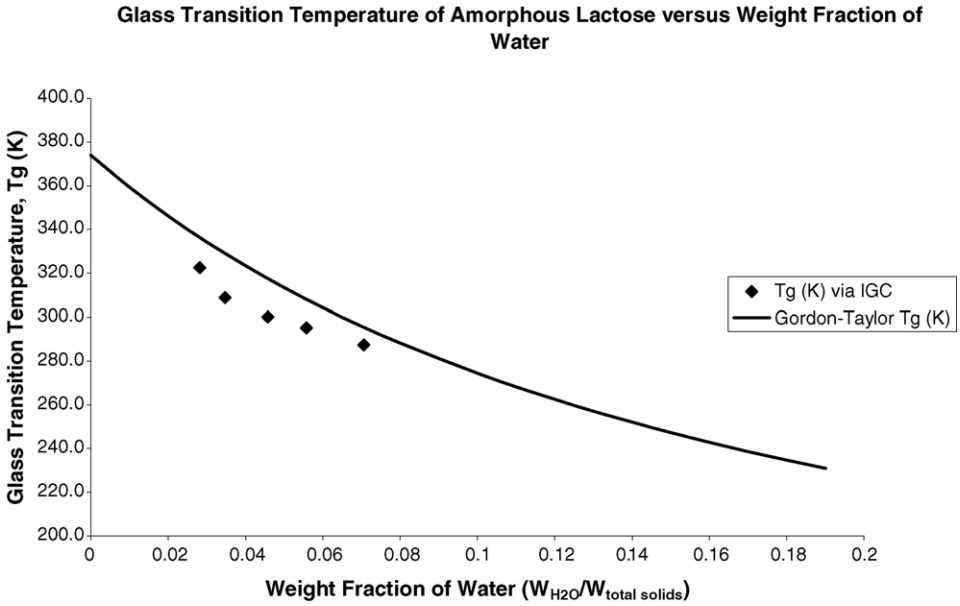

Fig. 5. Glass transition temperature (T_g) as a function of weight fraction of water, measured by IGC on spray-dried lactose. Gordon–Taylor prediction (solid line) for a water/lactose binary system is included for comparison.

eral degrees. Also, the DSC values used a temperature ramp (5 °C/min) while the DVS values were extrapolated to an equilibrium value and the IGC experiments are done at defined, equilibrated temperatures. Faster ramping rates can lead to higher glass transition values, which could help explain the differences between the DVS, IGC and DSC results.

Fig. 4 also shows a linear relationship for the crystallization RH as a function of relative humidity ramping rate. The resulting line shows and excellent correlation coefficient (0.995) with an intercept of 58.1% RH. Therefore, the inherent RH_c measured at 25 °C for this spray-dried lactose sample is approximately 58% RH. The current study favors well with other studies as water-induced crystallization behavior for amorphous lactose samples around 60% RH at 25 °C has been observed previously (Buckton and Darcy, 1995; Price and Young, 2004; Elamin et al., 1995).

4.2. Spray-dried salbutamol sulfate

RH ramping experiments were also performed on a spray-dried salbutamol sulfate sample. A representative mass response is shown in Fig. 6, where approximately 10 mg was exposed to a 5% RH/h humidity ramp at 25.0 °C. The salbutamol sample undergoes similar sorption mechanisms to the lactose sample discussed previously. Initially water sorption is dominated by surface adsorption, which is followed by bulk absorption at higher humidity values. The transition between these two regimes was taken as the glass transition; around 47% RH in Fig. 6. The glass transition temperature for amorphous salbutamol sulfate is 64 °C as measured by DSC (Ward and Schultz, 1995). Therefore, sorbed water acts as a plasticizing agent and lowers the glass transition temperature to the measurement conditions (25 °C). With further increases in humidity, the salbutamol sample shows a sharp mass loss (around 71% RH in Fig. 6). This is most likely due to a water-induced crystallization process. As the sample crystallizes, the surface area and energy of the sample decreases, which leads to a decreased water sorption capacity and a net mass loss. A similar mass loss has been observed previously and attributed to sample crystallization for partially amorphous salbutamol sulfate at 60 °C and 55% RH (Ward and Schultz, 1995) and 25 °C and 75% RH (Columbano et al., 2002). The 71% relative humidity value obtained in these studies at 25 °C agrees quite favorably with previous work at 25 °C. Again, there is a signifi-

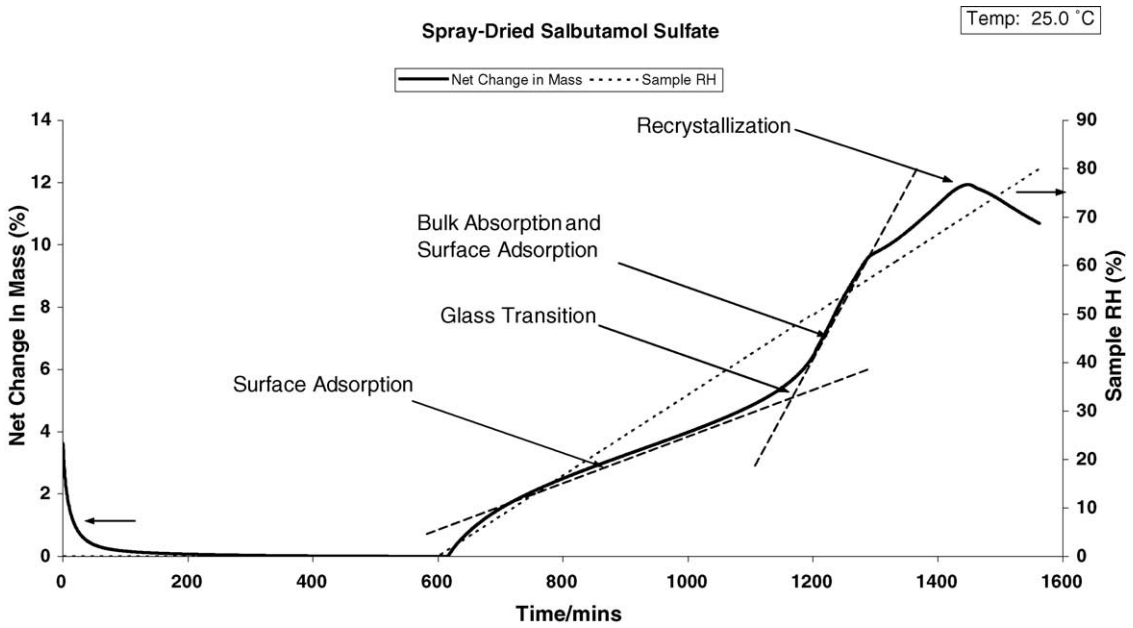

Fig. 6. Relative humidity ramping experiment (5.0% RH/h) for spray-dried salbutamol sulfate sample at 25.0 °C. Solid line shows the net change in mass while the dotted line shows the linear RH profile.

cant humidity gap between the RH_g and crystallization RH_c.

Similar RH ramping experiments were performed on the same spray-dried, partially amorphous salbutamol sulfate material at 2, 5, and 10% RH/h and 5, 15, 25, 35, and 45 °C. The RH_g (Table 2) values were recorded at each ramping rate and temperature. The RH_g values plotted versus ramping rate for each temperature indicate a clear, linear correlation (see Fig. 7). The values at each temperature were fit to a straight line using least squares analysis. The slopes of the fits appear to be relatively unchanged at the five temperatures, indicating the same dominant mechanism over the temperature range studied. From the resulting linear fits, the extrapolated 0% RH/h glass transition RH values were obtained. These values are listed in Table 2. These extrapolated values could be used as the threshold storage humidity (at each temperature) to prevent moisture-induced transformations.

Comparing extrapolated values at 0% RH/h rate reveals that increasing experiment temperature leads to decreasing RH_g values (see Table 2). As temperature is increased, molecular mobility is increased within the salbutamol sulfate samples. Therefore, less water is necessary to induce a glass transition. Clearly there is a strong dependence on both storage temperature and humidity on the sample's glass transition.

The RH_c was also obtained at each ramping rate and temperature (see Table 3) and are plotted versus ramping rate at each temperature in Fig. 8. Again,

Table 2
Relative humidity ramping rates and corresponding RH_g values for spray-dried salbutamol sulfate at 5, 15, 25, 35, and 45.0 °C

Rate (% RH/h)	RH_g at 5 °C	RH_g at 15 °C	RH_g at 25 °C	RH_g at 35 °C	RH_g at 45 °C
0	64.5	58.0	44.4	39.0	32.8
2	65.8	58.8	45.3	39.7	33.0
5	67.0	60.9	47.5	40.7	34.1
10	70.3	63.1	49.8	42.4	34.7

Table 3
Relative humidity ramping rates and RH_c values for spray-dried salbutamol sulfate at 5, 15, 25, 35, and 45.0 °C

Rate (% RH/h)	RH_c at 5 °C	RH_c at 15 °C	RH_c at 25 °C	RH_c at 35 °C	RH_c at 45 °C
0	81.0	74.1	66.4	57.8	50.4
2	82.2	74.8	67.5	58.9	51.5
5	86.8	78.2	70.5	64.3	57.1
10	90	80	73.7	67.3	60.4

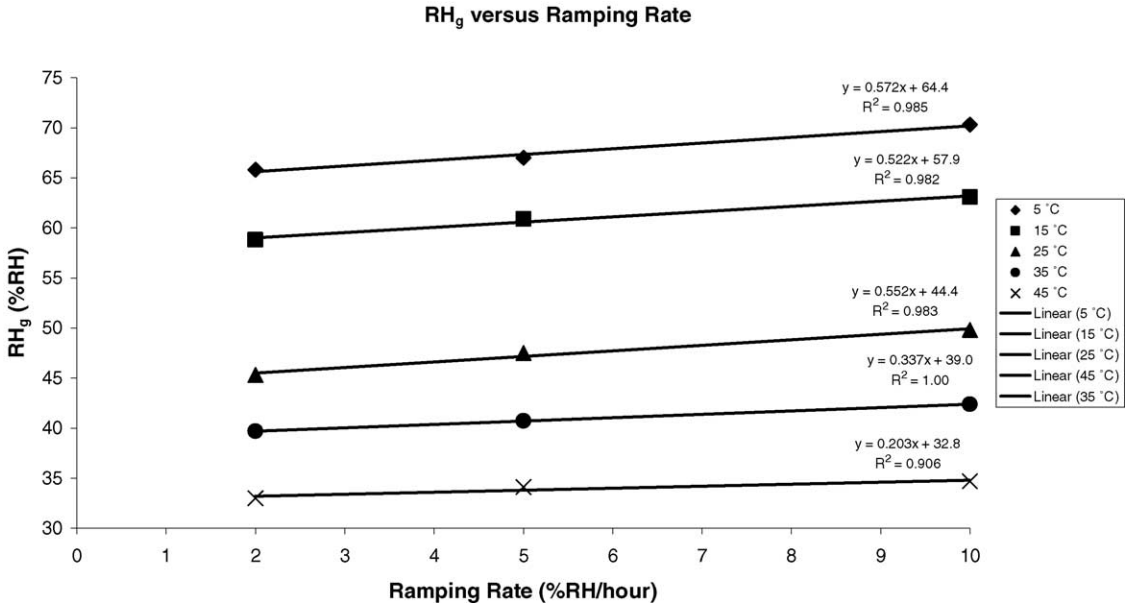

Fig. 7. RH_g values vs. relative humidity ramping rate for salbutamol sulfate at 5, 15, 25, 35, and 45 °C. Solid lines and equations represent linear fits at each temperature.

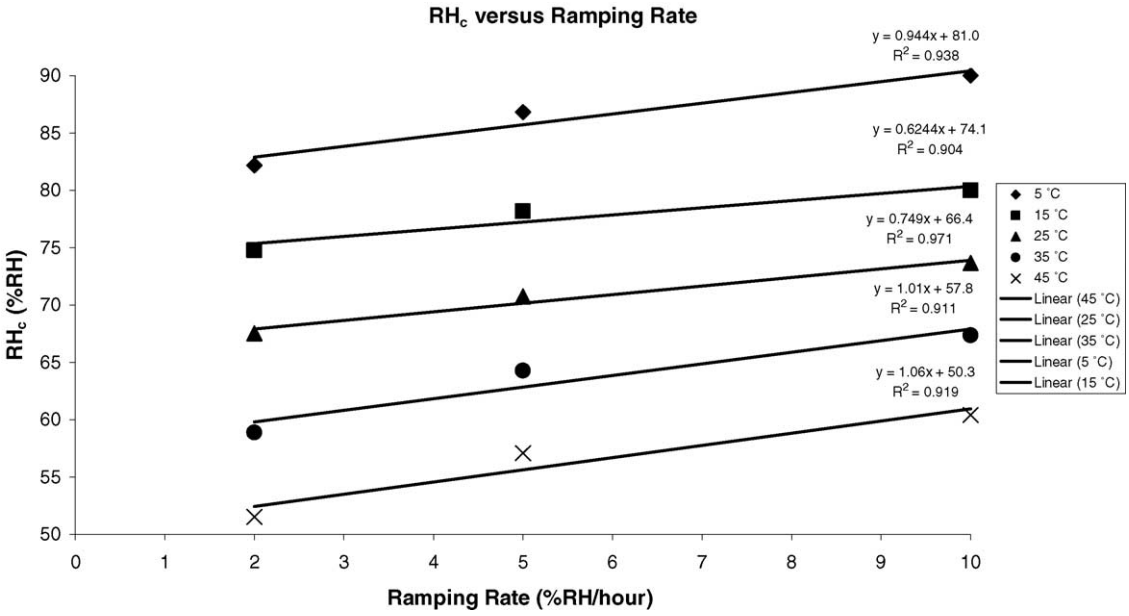

Fig. 8. RH_c values plotted vs. ramping rate at 5, 15, 25, 35, and 45 °C. Solid lines represent linear fits at each temperature.

there is a clear trend: as ramping rate decreases, the RH_c decreases. As before, the trends were subjected to a linear fit to extrapolate the values to a 0% RH ramping rate. The resulting values are given in Table 3. Again, Fig. 8 illustrates there is little change in slope with temperature, indicating the same crystallization mechanism dominates at each temperature.

As with the RH_g, the RH_c decreases dramatically with increasing temperature (see Table 3). Again, the higher temperatures increase the molecular mobility of the sample, thus driving the crystallization process and requiring less sorbed water necessary to force a phase change. Together, these results clearly indicate that the crystallization process is highly dependent on both temperature and relative humidity.

5. Conclusions

A new method based on gravimetric vapor sorption was developed for determining the critical storage and processing relative humidity for spray-dried lactose and salbutamol sulfate. Using a series of experiments over a range of relative humidity ramping rates, the inherent relative humidity to cause a glass transition and/or crystallization event can be readily determined at a particular temperature. Experiments performed over a range of temperatures illustrate the effects of temperature on water-induced transformations. Higher temperatures lead to lower threshold RH values to prevent a glass transition and/or phase change. Also, experiments at different temperatures allow a single, threshold RH to be established that can span a range of processing, storage, and delivery temperatures. This technique is applicable to a wide range of pharmaceutical powders provided a solvent-induced glass transition or crystallization is possible.

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