



Investigating the effect of dehydration conditions on the compactability of glucose

Niraj S. Trasi^{a,*}, Stephan X.M. Boerrigter^{a,1}, Stephen R. Byrn^a, Teresa M. Carvajal^b

^a Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA

^b Department of Agricultural and Biological Engineering/Food Sciences, Purdue University, West Lafayette, IN 47907, USA

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ABSTRACT

Hydrates are commonly found in pharmaceutical ingredients either in excipients or in the active pharmaceutical ingredient form. There is always the possibility that the processing involved in manufacturing can result in the dehydration of the hydrate components. It has been seen that different dehydration conditions can have an effect on the behavior of the final product; however this area has not been fully investigated. In this work, glucose monohydrate powder was dehydrated at four different conditions and then compressed to see the effect on the hardness of the compacts.

Various analytical tools such as inverse gas chromatography, differential scanning calorimetry, X-ray powder diffractometry and scanning electron microscopy were used to determine any differences in the properties of the dehydrates and correlated with the obtained compact hardness.

Annealing studies were performed to determine the effect of storage on the dehydrated materials both before and after compression. It was observed that while annealing of the powders did have an impact, annealing of the compacts did not influence the hardness. The results of the characterization and annealing studies showed that the difference in the behavior of glucose dehydrates were due to the presence of amorphous regions within the particulates.

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1. Introduction

The presence of water as the solvent of crystallization can have an impact in the mechanical properties of the crystal and thus influence its tabletability. Magnesium stearate has been found to have significant batch to batch variability in its properties and the moisture content has been correlated with the ability of the compound to act as a lubricant (Ertel and Carstensen, 1988). The moisture content affected the form of crystal hydration state which influenced the crystal packing of the compound. Also, as seen for thiamine, the crushing strength and disintegration time of the tablets increased upon storage mainly due to the formation of the hemihydrate which is the most stable form at room temperature and ambient humidity (Wostheinrich and Schmidt, 2001). The use of different types of drying techniques such as freeze drying, fluid-bed drying, desiccation and oven drying on microcrystalline cellulose pellets after extrusion–spheronization was also found to have an impact on the tensile strength of the compacts made from those pellets (Bashaiwoldu et al., 2004).

When hydrates are dehydrated as a normal part of the pharmaceutical manufacturing process, the type of hydrate and the processing condition used will result in a certain type of dehydrated hydrate whose properties can be slightly different from the pure anhydrate (Ono et al., 2002). Also, once dehydrated, one would assume that the anhydrous forms would have the same properties as long as their crystal structure (or the lack of it) is the same. But it has been seen in a few cases that when dehydration is performed in different conditions the resulting anhydrate shows varying performance especially when it comes to the rate of moisture sorption and rate of dissolution even though they may show the same X-ray pattern or spectroscopic data (Ono et al., 2001). These are very important parameters in a pharmaceutical product and a variation in these properties can easily result in a change in the ultimate bioavailability. There is also a possibility that the different dehydration conditions can influence the mechanical properties of the solid. Although this has not been reported in detail in any publication it is very important since the changes in compressibility and tablet hardness can not only influence the success of the manufacturing process but also influence its bioavailability.

To study the effect of dehydration conditions we selected glucose monohydrate since this has already been observed to have an effect on compressibility (Lerk et al., 1984). Glucose is a monosaccharide that is commonly obtained in nature and is an important carbohydrate. It exists in two stereoisomeric forms of which the D-

* Corresponding author. Tel.: +1 765 494 9083; fax: +1 765 494 6545.

E-mail addresses: ntrasi@gmail.com, ntrasi@purdue.edu (N.S. Trasi).

¹ Current address: SSCI, a division of Aptuit, 3065 Kent Avenue, West Lafayette, IN 47906, USA.

glucose plays the most important part in nature. In D-glucose, two crystal polymorphs, the α -D-glucose and β -D-glucose, having melting points of 146 and 150 °C respectively have been found to occur (Segal, 1964; Hurtt et al., 2004). Both these forms have very different crystal structures and thus show a difference in their powder diffraction profile.

2. Materials and methods

2.1. Materials

D (+)-Glucose monohydrate (Puriss.) was obtained from Sigma–Aldrich and sieved to obtain particle fractions. The particle size fraction between 125 and 250 μ m was used in this study.

The hydrate was dehydrated at four different conditions, 80 °C (4 h), 100 °C (3 h), 120 °C (2 h) and 140 °C (40 min) in a regular oven. Since the main reason for using higher temperatures for dehydration is to reduce drying time, the times for which the sample was kept for dehydration were reduced as the temperature was increased. Complete dehydration for all the samples was confirmed using TGA.

2.2. Compaction

The dehydrated samples (600 mg) were made into compacts using an automated single punch Carver press (Carver Inc., Wabash, IN). Flat, round punches and dies with a diameter of 15.8 mm were used to make the compacts and the hardness tested using a hardness testing instrument which yielded results in kilo ponds.

2.3. X-ray powder diffraction (XRPD)

The XRPD patterns of the dehydrated powders were generated using a Siemens D5000 diffractometer with a Bragg–Brentano geometry. The scans were taken from 4–40° 2θ at a step scan of 0.04 and a scan rate of 4°/min. The divergent and scattering slits were of 1 mm width and the receiving slit was 0.1 mm. The X-ray generator was run at 40 kV/40 mA.

2.4. Differential scanning calorimetry (DSC)

A DSC 2920 (TA Instruments, New Castle, DE) was used to determine the thermal profile of the dehydrated products. The samples (around 5 mg) were sealed hermetically and run at a rate of 10 °C/min from 25 °C to 180 °C with a nitrogen flow rate of 40 ml/min. The instrument was calibrated for melting point and enthalpy using Indium as a calibrant. Modulated DSC was performed by using about 10 mg of the sample to ensure adequate heat flow and a heating rate of 2 °C/min from –10 to 80 °C with modulation amplitude of 1 °C and a period of 60 s. The data was analyzed using the instrument software Universal Analysis ver. 4.7.

2.5. Surface energy

Inverse gas chromatography (IGC) was used to determine the surface energies of the dehydrated powder samples. These experiments were performed using a commercial IGC instrument (iGC, Surface Measurement Systems Ltd., UK). Samples were packed in a pre-silanized glass column and then equilibrated inside the instrument with dry Helium which was also used as the carrier gas. The column dead volume was corrected using methane. The vapor probes used included a linear hydrocarbon series (C₆–C₁₀) to determine the dispersive surface energy and ethanol, 2-propanol, acetonitrile and ethylacetate to determine the polar component of the surface energy. The probes were used at infinite dilution (0.03 p/p°) and the peaks were measured using a flame ionization

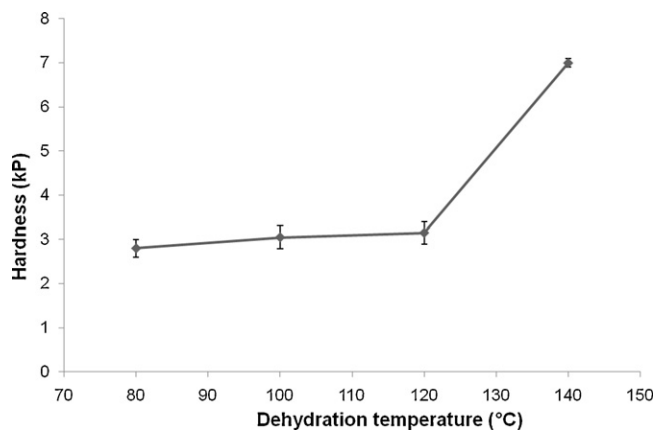


Fig. 1. Compact hardness of glucose dehydrated at different temperatures. Dehydration at 140 °C results in good compact strength.

detector and a thermal conductivity detector. The dispersive and specific surface free energy was calculated using the method of Schultz et al. (1987). The data presented is an average of three replicates.

2.6. Water sorption measurements

The dehydrated powders were placed in relative humidity containers having 75%RH and 93%RH which was obtained by using saturated solutions of NaCl and KNO₃. The weights of the samples were determined periodically for a few hours. Since glucose deliquesces at high RH, only the first few time points were used to look at the differences in water sorption.

2.7. Scanning electron microscopy

Photomicrographs of the dehydrated samples were taken using the JEOL 840 scanning electron microscope (JEOL USA Inc, MA). The samples were attached to an aluminum stub and coated with Au–Pd using a Hummer I sputter coater (Technics, Inc, Alexandria, VA) for 3 min at a voltage of 10 kV and a pressure of 100 mTorr. The samples were then placed in the high vacuum chamber and scanned using an Everhart Thornley detector to obtain the electron micrographs.

3. Results and discussion

3.1. Compact strength

The hardness of the compacts produced from the dehydrated powders at different conditions was determined. While glucose monohydrate and the anhydrate by themselves possess poor compaction behavior, it was seen that the temperature of dehydration has a considerable effect on the hardness of the compact obtained from the dehydrated powder. Compacts of the powders dehydrated using the conditions mentioned showed similar compact strength for the 80, 100 and 120 °C temperature samples where the compacts had low hardness while the 140 °C sample showed a drastic increase in the hardness, up from around 3 kilo ponds to around 7 as shown in Fig. 1. Also, it was observed that while the lower temperature sample formed compacts which laminated and chipped easily, the 140 °C compacts were more robust.

Heckel analysis was attempted to determine if any information on the change in elasticity in the powders could be obtained. Unfortunately the plots were not consistent due to the fact that the compacts did not have uniform thickness. This is most likely due to the fact that the flow of the powders, as observed visually within

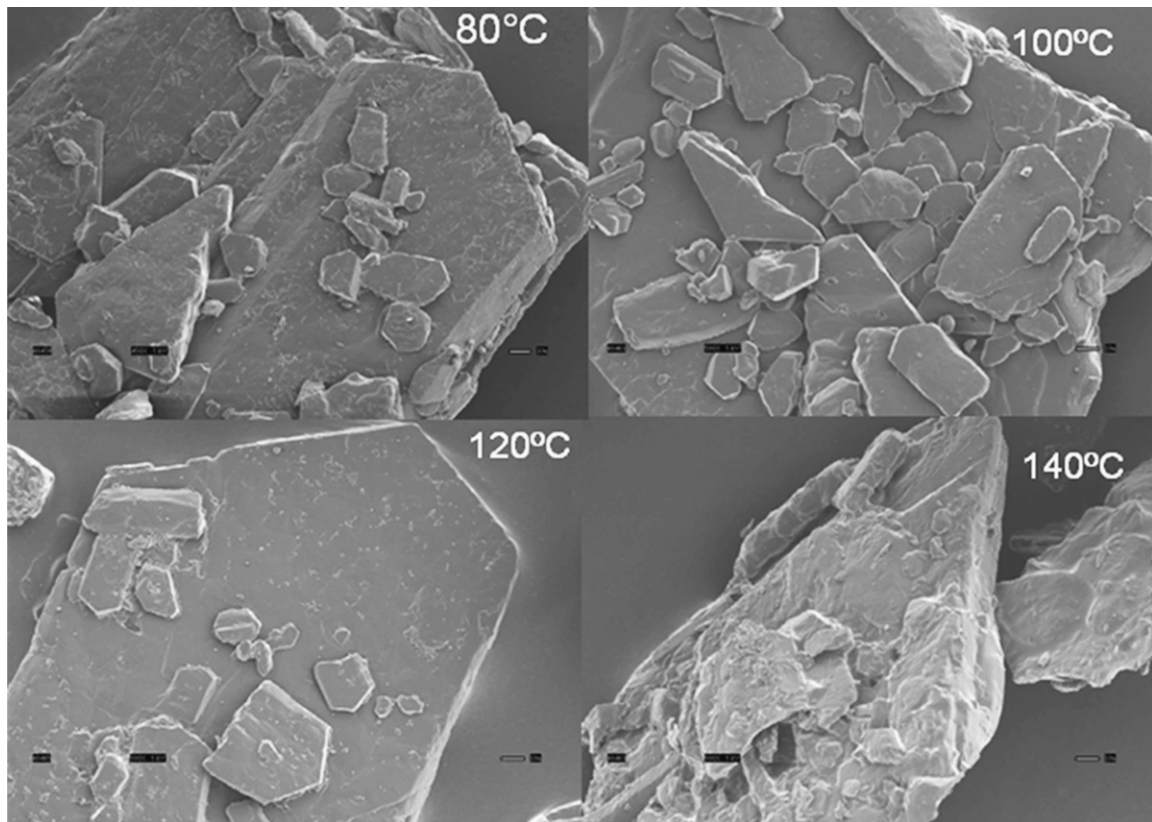


Fig. 2. SEM micrographs of glucose dehydrates showing the similarity of surface for the lower temperature samples and a rough uneven surface for the 140 °C sample.

the die, was not smooth enough to distribute the particles evenly during compression.

3.2. Surface properties

Surface properties of the powders can influence tablet hardness because bonding between particle surfaces which is influenced by surface roughness and surface energy (Fichtner et al., 2008). SEM pictures of the four dehydrates showed that the particles dehydrated at the lower temperatures have a smooth surface and the particles are separate and distinct. The 140 °C samples on the other hand have a rough surface and some of the particles appear to be fused (Fig. 2). Thus there are clearly some changes on the surface due to the dehydration conditions.

All materials have non polar forces acting on the surfaces as well as polar forces which include hydrogen bonding or other forces. For glucose, the hydroxyl groups exposed on the surface contribute to the polar component while the carbon atoms in the backbone have an impact on the non-polar contribution. These forces are most certainly expected to have an impact on inter-particle interaction and therefore the surface energy was determined via the IGC by which both the dispersive (non-polar) and specific (polar) free energies were calculated. In the case of starch, an extra washing step was found to yield much stronger compacts mainly due to the creation of higher surface energy even though other properties remained the same (Chamarthy et al., 2009). However, the results (Fig. 3) for glucose show that the powders dehydrated at lower temperatures had similar dispersive surface energy while the 140 °C sample had significantly lower surface energy. This is contrary to what is expected since the powder showing higher compact strength would have been expected to show higher surface energy. The polar component of the surface energy was determined for four different molecular

probes and it was seen that this also decreases with an increase in dehydration temperature, indicating that the reduction of dispersive surface free energy was not associated with any increase in the specific polar surface free energy.

3.3. X-ray diffraction

It is possible that some transformation occurred during heating which might have resulted in a change in tableting behavior. This was seen in the case of carbamazepine where dehydration at different temperatures resulted in the creation of different polymorphs which had different vapor sorption and dissolution behavior (Ono et al., 2002). Also, it is known that different crystal forms can have different compaction behaviors (Roberts and Rowe, 1996).

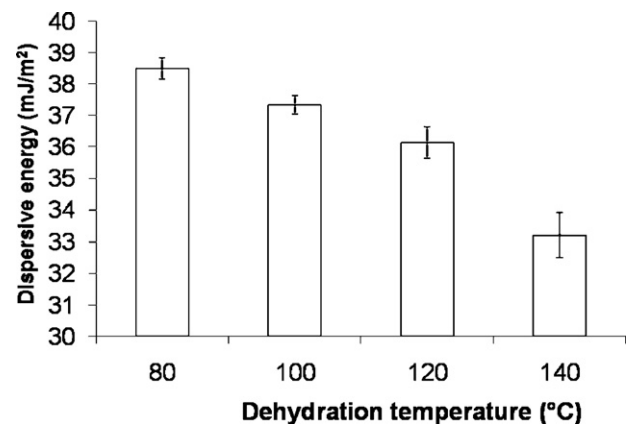


Fig. 3. Dispersive surface energy of glucose dehydrates showing that the high temperature sample has lowest non-polar surface energy.

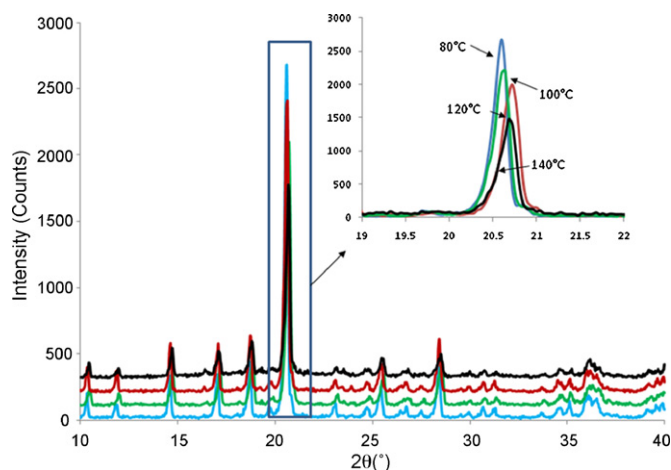


Fig. 4. X-ray powder profiles of glucose dehydrated at 80, 100, 120 and 140 °C (bottom to top) showing that only one polymorph is formed. Inset shows that the intensities are lowered at the higher dehydrated temperature.

To determine if any changes had occurred during the dehydration process, XRPD of the samples were taken on the same day the samples were prepared. The X-ray source was warmed for 6 h before using to avoid any change in the intensity of the resultant peaks due to variation in the source. As mentioned in Section 1, glucose can exist in two polymorphs, α and β -D-glucose.

The X-ray patterns of the experimentally obtained dehydrates are shown in Fig. 4. The X-ray peak positions matched with the alpha form and we see that the crystal form of the different dehydrates is the same indicating that the change in compact hardness is not due to the occurrence of a different polymorph.

A comparison of the intensities was made to see if there was any indication of differences in crystallinity between the samples. The 140 °C sample had considerably lower peak intensity compared to the lower temperature samples indicating the possibility of that sample being of lower crystallinity.

3.4. Water sorption

Water sorption gravimetry is a very sensitive method for the determination of disorder or amorphous content in a sample (Fiebig and Mutz, 1999). Since the X-ray profile indicates possible presence of disordered regions in the 140 °C sample, a difference in the water sorption profile of the powders is expected. When exposed to 75% RH, it was seen that only the 140 °C sample absorbed water up to 3 h with the other samples not increasing much in weight. When the samples were exposed to 93% RH (Fig. 5) all the samples sorbed water with the lower temperature dehydrates sorbing considerably less water than the 140 °C sample. The sample deliquesces upon prolonged storage at 93% RH and thus only the weight changes at the initial time points were taken into consideration. The water sorption data shows that the samples kept at 140 °C are actually more hydrophilic even though the IGC results show that the surface energy is lower, predicting lower surface–water interaction. Thus in this case, the IGC results do not seem to predict the hydrophilicity of the powder accurately.

3.5. Thermal analysis

As shown by both the X-ray and the water sorption studies, there is a difference in the glucose dehydrates with respect to crystallinity. This could be due to the presence of amorphous or nanocrystalline regions. These regions would be expected to have some impact on the thermal behavior of the sample. Thus, DSC scans were taken for the samples at a heating rate of 10 °C/min

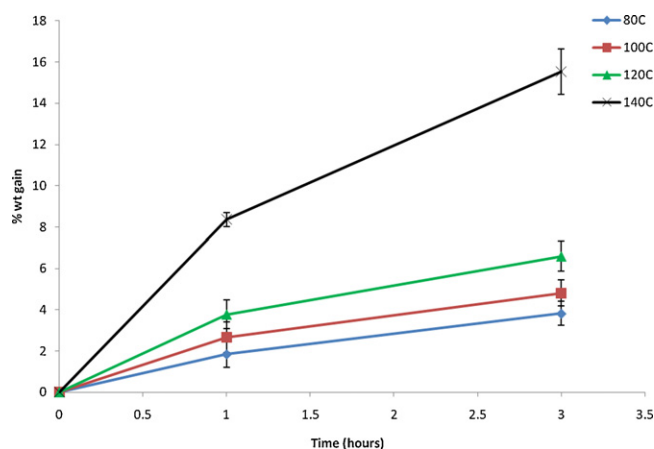


Fig. 5. Water sorption profile at 93% RH shows that the 140 °C sample shows a drastically faster and higher weight gain than the samples dehydrated at lower temperatures.

and the onset of melting temperature and melting enthalpy was determined (Fig. 6). While the melting for glucose anhydrate, as determined by the tangent intersection method by the DSC instrument software, was around 156 °C, the powder actually starts to melt around 146–148 °C as indicated by the onset of the deviation from the baseline due to melting. For the dehydrated samples, the melting temperature was very similar for the lower temperature samples while the 140 °C sample had a drastically lower melting point of 142 °C as per the tangent method (again the actual onset being lower than this due to the broad melting range). The melting enthalpies of the samples dehydrated at 80, 100 and 120 °C were very close to each other at about 192 J/g while the 140 °C sample showed a clear decrease in the melting enthalpy to about 154 J/g. These results indicate that the lower enthalpy for the high temperature sample is due to the lower crystallinity/amorphous regions while the reduced melting point suggests nanocrystalline domains.

The fact that the 140 °C sample has the lowest melting point onset which actually overlaps with the dehydration temperature explains the results obtained in the SEM and the IGC experiments. It is hypothesized that when the sample is being dehydrated, it is also partially melting. Most likely this melting happens specifically at the surface since it is the area with the highest energy. Cooling the sample results in the partially molten regions on the surface solidifying and thus the surface appears uneven in the SEM.

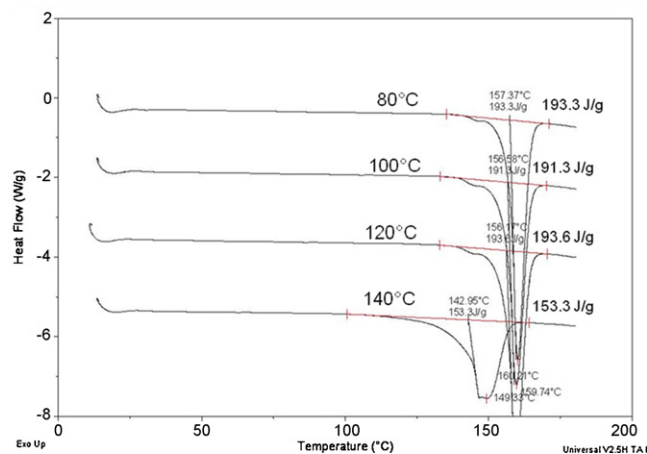


Fig. 6. DSC profiles of the various glucose dehydrates run at 10 °C/min. The onset temperature of melting decreases as the dehydration temperature is increased to 140 °C as does the melting enthalpy.

Also, it is known that any liquid will try to orient itself in a fashion that reduces its surface energy, e.g. water forms drops when it is sprayed. Similarly, the melted glucose on the surface of the particles orients itself in such a way that the overall surface energy is reduced. This orientation is then frozen in place when the sample is cooled. Since the IGC was used in infinite dilution mode, the probe molecules are expected to interact with the crystal faces having the highest energy. For the low temperature samples, the same face of the crystal is being probed by the molecules and therefore shows similar surface energy values. The 140 °C sample, on the other hand, does not have any particular face exposed but instead is melt quenched on the surface which reduces both the polar and non-polar surface energies simultaneously.

The next question is why the sample dehydrated at 140 °C has a lower melting point and whether this should have any effect on the hardness of the compact. Though it is expected that a higher surface energy will result in better compacts, the IGC shows that the powder resulting in better compacts is the one with the lowest surface energy, both polar and non polar. So the reason for improved hardness must lie elsewhere. A possible reason for this could be the formation of small crystallites with amorphous regions between them. It is known that dehydration of a hydrate crystal results in small crystallites (physically observed as darkening of the hydrate crystal) (Byrn et al., 1999). It is possible that dehydration of glucose at all the temperatures results in small crystallites which inevitably have lower melting point of around 125–130 °C. The samples dehydrated at temperatures below 125 °C tend to anneal resulting in the fusion of the nano-domains to give larger crystallite size and thus higher crystallinity. The sample dehydrated at 140 °C on the other hand appears to partially melt at the dehydration temperature itself and then crystallize incompletely when removed from the oven resulting in considerable amorphous regions. There are many studies done on inorganic systems where the amorphous solid has been found to have considerable difference in mechanical behavior when compared to the crystalline form and in the pharmaceutical area, amorphous indomethacin particles were found to have mechanical properties significantly different from the crystalline powder (Hancock et al., 2002; Schuh et al., 2007). Thus the presence of amorphous regions in the dehydrated glucose powder might explain why the 140 °C sample has better hardness as compared to the other powders.

3.6. Modulated DSC

Since the low intensity in the X-ray peaks indicates that there might be some amorphous regions present in the sample, one would expect the presence of a glass transition during heating. To determine this, the 140 °C sample was analyzed by mDSC to clearly identify if a T_g is present. From Fig. 7, we can see that the T_g as well as the relaxation endotherm is clearly visible. This T_g is not seen in the samples dehydrated at lower temperatures. The presence of the T_g confirms without doubt that the samples certainly have amorphous regions.

It is interesting to note that when amorphous glucose is prepared by melting completely in the oven and then cooling by placing at room temperature just as was done for the 140 °C sample, the T_g occurs at a lower temperature than seen for the dehydrated sample.

To see if this difference in T_g remains upon controlled cooling, melt quenched glucose and the sample dehydrated at 140 °C (40 min) were heated to above the T_g and then cooled at 10 °C/min. Since the thermal history is removed by heating above the T_g and the same cooling rate was used for both, one would expect the resulting T_g 's to be very close. Instead we find that the T_g 's are still drastically different (Fig. 8). The reason for this is not clear. It could be due to the possibility that amorphous regions in the 140 °C sam-

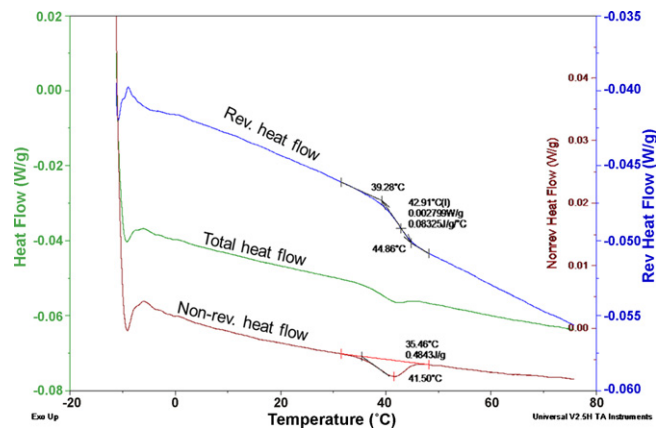


Fig. 7. Modulated DSC profile of glucose dehydrated at 140 °C for 40 min showing the presence of a glass transition temperature in the reversible signal (top) while the non-reversible signal (bottom) shows the relaxation endotherm.

ples exist between small nanocrystalline domains and thus result in an increase in temperature at which they become mobile, similar to how boiling point of water increases when it is present in small capillaries (Lakhanpal et al., 1955).

3.7. Annealing

If amorphous regions and nanocrystalline domains are responsible for the difference in compact hardness, then annealing of the powders would be expected to have some effect on hardness since crystallinity of the powder will increase. To test this, the 140 °C sample powder was annealed at 80 °C for 4 h and 100 °C for 3 h and then analyzed by DSC to determine changes in crystallinity. Compacts were also made from the annealed powders and their hardness determined. The DSC showed that the samples had indeed annealed as seen by the increase in the melting point onset and the melting enthalpy (Fig. 9). The increase in melting enthalpy from 153 J/g to 184 J/g for the 100 °C annealed sample was higher than for the 80 °C annealed sample which increased to around 170 J/g.

The hardness of both the annealed samples decreased relative to the original hardness of the 140 °C sample to an extent matching the increase in melting enthalpy (Fig. 10). The 100 °C annealed sample had hardness similar to the sample dehydrated at 100 °C while the 80 °C annealed sample had a hardness higher than the one dehydrated at 80 °C. To see if annealing can change the hardness of the

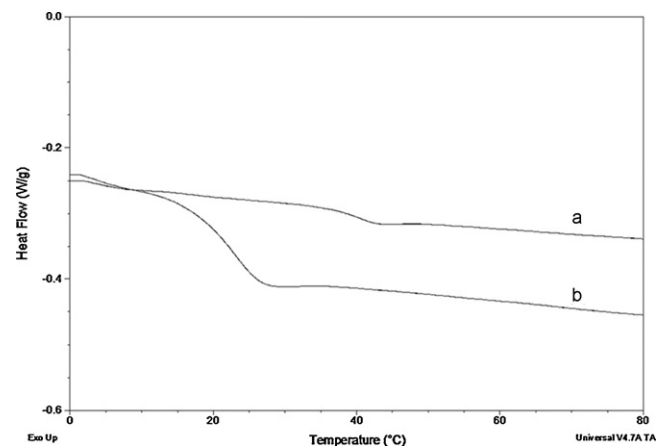


Fig. 8. DSC thermograms of (a) glucose monohydrate dehydrated at 140 °C for 40 min and (b) quench cooled glucose, upon controlled cooling at 10 °C/min from above T_g (to remove thermal history) show very different glass transition temperatures.

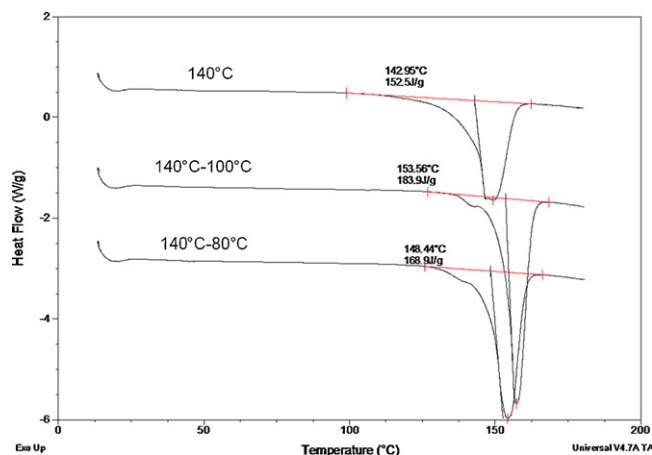


Fig. 9. DSC scans of glucose powder dehydrated at 140 °C for 40 min and annealed at 100 and 80 °C for 3 and 4 h respectively.

compacts after they have been formed, the 140 °C sample was compacted and annealed at the same conditions as the powder. As seen from Fig. 10, the hardness of the annealed compacts was found to be unchanged indicating that once bonds have been formed between the particles, annealing does not cause any changes which would compromise the integrity of the compact.

The water sorption profiles of the annealed samples also showed a similar trend to the hardness, indicating that the effects seen were more or less due to the presence of amorphous regions in the powder.

As another method to confirm that the presence of amorphous regions is responsible for the difference in compact hardness, amorphous glucose was formed by melting the glucose at 155 °C and then quenching by placing over ice. The material produced was then crushed and mixed with crystalline anhydrous glucose in different proportions from 10 to 50% (w/w) to give as uniform a mixture as possible.

These mixtures were then compressed using the same conditions as before and the hardness determined. As seen in Fig. 11, the hardness increases linearly with the amount of amorphous content and seems to level off at 40% amorphous content to around 7.5 kilo ponds, which is the hardness obtained after dehydration at 140 °C. The hardness of the 100% amorphous melt quenched glucose was also around the same value of 7.8 (0.2) and thus it seems that at

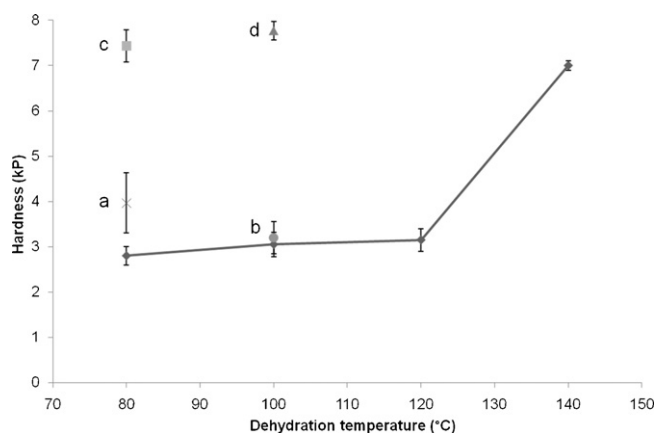


Fig. 10. (a) and (b) represent hardness of compacts made after annealing of the glucose (140 °C) powder samples at 80 °C and 100 °C respectively while (c) and (d) are the hardness of the compacts after annealing of the compacts at 80 °C and 100 °C respectively. These hardness values are overlaid on the original hardness data and show that the powder is more susceptible to annealing effects than the compact.

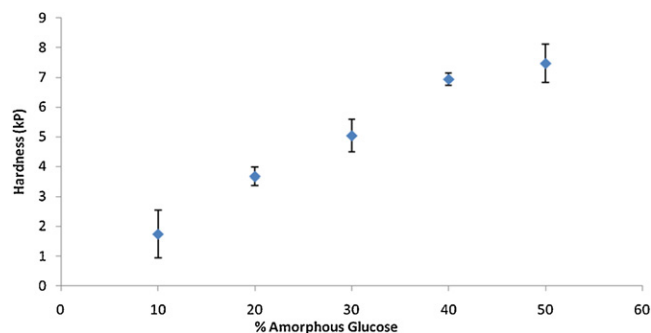


Fig. 11. Compact hardness of glucose anhydrate with different amounts of amorphous content shows that increasing amorphous content results in higher compact hardness which reaches a plateau around 40%.

40% and above, the hardness does not increase anymore. Though the overall amorphous content in the dehydrated sample might be lower than 40%, it behaves as if its amorphous content is much higher. This must be due to the fact that the amorphous regions are concentrated on the surface (since melting starts on the surface) which makes it behave like it is more or less amorphous in its inter-particulate interaction upon compression.

4. Conclusion

Dehydration of glucose monohydrate at different temperatures has clearly shown to have an effect on the hardness of the compacts formed. The main reason for this is apparently due to the formation of disordered/amorphous regions in the sample. The small crystallites formed immediately after dehydration results in melting at temperatures lower than normal. The quench cooling of these molten parts upon removing from the oven results in the formation of amorphous regions. Our findings demonstrate the importance of controlling dehydration temperatures since it can have a drastic effect on the behavior of the dehydrated powders. It also shows that having amorphous regions in the compounds or excipients might improve compactability, thus eliminating or reducing the use of binders.

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