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Water mobility in amorphous lactose below and close to the glass transition temperature

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Abstract

The water sorption behaviour of amorphous lactose has been investigated gravimetrically. It was found that the kinetics of absorption at (especially) 40% and (also) 50% RH were bi-phasic. Although we have no explanation for this behaviour, it is noted that the inflection point between the two processes is at a 1:1 mole ratio of water:lactose. Equilibration at 40% RH results in an equilibrium uptake of 7% water, which is not sufficient to lower the T_g of lactose to the temperature of the experiment (T). Following from this, desorption is rapid and the rate proportional to the extent to which the RH has been lowered. If the sample is equilibrated to 50% RH the water content exceeds that which lowers the T_g below T, this results in a collapse of the amorphous structure, but not in instantaneous recrystallisation. Exposure to higher humidities in an isothermal microcalorimeter revealed that the heat output for recrystallisation of the collapsed amorphous structure was indistinguishable from that produced on recrystallisation of the original expanded amorphous form. The rate of water desorption from the collapsed amorphous structure is slow and follows square root of time dependency. The rate of this diffusion controlled process is not altered by changing the external RH. The duration of exposure to 50% RH alters the extent of collapse, and hence alters the amount of water which is free to leave the sample rapidly and that which is released by the slow diffusion through the solid. After reducing the RH the water content of the collapsed structure remains high, but the recrystallisation is greatly delayed. These studies show that water can be held in different ways within amorphous lactose and this has implications for physical, chemical and potentially even microbiological stability of products.

Keywords: Lactose; Amorphous; Glass; Diffusion; Water; Gravimetric studies; Absorption; Isothermal microcalorimetry; Stability

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1. Introduction

Many pharmaceutical solids (including low molecular weight drugs and excipients) exist in a thermodynamically stable crystal form, but can also contain metastable regions of amorphous material which may be induced during processing. There has been considerable interest in amorphous content in pharmaceuticals as the presence of even small amounts (as little as 1% of total weight) can have a significant impact on the physico-chemical nature of the material, which in turn can alter product performance.

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It is recognised that the molecular mobility of the amorphous region of the solid will be important in determining its physical stability (Hancock et al., 1995) and that the nature of the amorphous solid will change depending upon the difference between the temperature (T) and the glass transition temperature (T_g). There has been consideration of the great significance of changes in physical state of the solid having an impact on the access to, and diffusion of water in products (e.g. Parker and Ring, 1995). The presence of water is of significance as the T_g is generally lowered by the absorption of water (which acts as a plasticiser) until eventually the material is able to crystallise. As water plasticises the material and the T_g approaches T, the material will clearly start to change structure, which results in a collapse and densification prior to crystallisation. Water entrapped in a collapsed amorphous structure may well give rise to problems of instability.

We have investigated the crystallisation of amorphous lactose using isothermal microcalorimetry and gravimetric vapour sorption (Briggner et al., 1994; Buckton and Darcy, 1995a,b; Buckton et al., 1995), and have identified an area of critical relative humidity (ca. 45% RH) below which the amorphous material does not recrystallise spontaneously. It must be assumed that around this critical RH is the point below which the water content is not, and above which the water content in the amorphous material is, sufficiently high to plasticise it such that $T_g = T$ (in this case T is 298 K). This observation can be checked by calculation, using the equation:

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

Where w represents the weight fraction of the two materials (subscripts 1 and 2) and k is a constant. The values for the T_g of lactose (101°C) and water (− 135°C) and an estimate of k (6.56) are available from the literature (Roos, 1993). From these data and Eq. 1, it can be calculated that the T_g will drop to 25°C when the water content in amorphous lactose is 7.25% of the mass of the lactose. It would be expected, therefore, that sorption experiments at 40% RH (i.e. a value which does not result in spontaneous recrystallisation of amorphous lactose within the time scale of the experiment viz. up to 2 days) would result in water absorption amounting to less than 7.25% weight gain, whilst at 50% RH (which does result in spontaneous recrystallisation of lactose) the water absorbed should be above this value.

The aims and objectives of this current study are to investigate the water content which results in recrystallisation of amorphous lactose and to investigate the water mobility at and close to the point where $T_g = T$. It is expected that the nature and content of water in the sample at these (near ambient) conditions can be expected to have very significant influences on the physical and chemical stability of the product in which the lactose is used. It should be noted that we have already shown that adsorption of water to lactose results in very low water uptake in the region that is studied here, such that it can reasonably be ignored in relation to the amount of water which is taken up by absorption (Buckton and Darcy, 1995a).

2. Experimental details

Samples (15 mg) of spray dried amorphous lactose (as used in the previous publications: Briggner et al., 1994, Buckton and Darcy, 1995a; Buckton and Darcy, 1995b)were loaded onto a quartz pan of an environmental controlled gas flow microbalance (Dynamic Vapour Sorption, Surface Measurement Systems, UK) (DVS), having been desiccated since drying by storage over silica gel. The Dynamic Vapour Sorption system has been utilised previously for studies on lactose crystallinity (Buckton and Darcy, 1995a) and was seen to combine a very accurate control of RH with in situ weight measurement (details of the quality of RH control are in preparation for publication). The sample was initially equilibrated to 0% RH and then to either 40 or 50% RH. After equilibration at the desired RH, the atmosphere was changed to either 20% RH or 0% RH and the rate of desorption determined. The impact of length of time of exposure to 50% RH on the structure of the lactose was also investigated.

The degree of crystallinity of the amorphous lactose was assessed by exposure to 54% RH, by sealing with a saturated solution of sodium dichromate in the glass cell of an isothermal microcalorimeter (Thermal Activity Monitor, Thermometric) at 25°C. The exact experimental method was as reported previously (Briggner et al., 1994).

3. Results

3.1. Rate of absorption

If amorphous lactose is equilibrated in an environment of 40% RH the sorption behaviour is clearly biphasic (Fig. 1). There is relatively rapid sorption until the water content is approximately 3% of the original mass, then there is a slower region of absorption (during which the sorption behaviour of the sample at 40% RH deviates from that for 50% RH), until an inflection point at approximately 5% weight increase which is followed by a further apparent exponential process. Whilst we do not have an explanation for the shape of the sorption data for the sample exposed to 40% RH, it may be linked to the fact that at the inflection point (approximately 5% weight increase) the mole ratio of water to amorphous lactose is 1:1. A similar, but less obvious, inflection is seen in the 50% RH data when replotted on a shorter time scale.

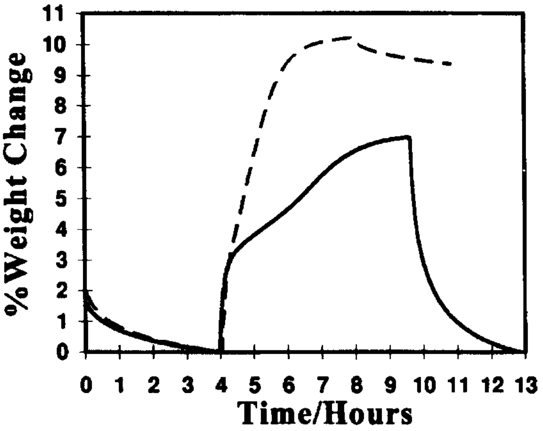

Fig. 1. Water sorption isotherms for amorphous lactose exposed to 40% RH (full line) and 50% RH (dashed line) after 4 h of drying at 0% RH, followed by a desorption isotherm due to exposure to 0% RH (the change from 40 to 0% RH was at ca. 10 h, and for 50–0% RH at ca. 8 h).

For amorphous lactose exposed to 40% RH the water content at equilibrium is 7% weight change over the original sample (Fig. 1). For a 15 mg sample load this equates to a weight increase of 1.05 mg, thus the final sample weight is 16.05 mg of which water is 6.54% w/w. By application of Eq. 1, it can be predicted that this amount of water will lower the T_g of the amorphous lactose to 26.7°C, i.e. just above the temperature of the experiment. This calculated value of T_g is in keeping with the observation that the lactose does not spontaneously recrystallise when exposed to 40% RH. However, when the amorphous lactose is exposed to 50% RH the sample comes to equilibrium with a moisture content of 9.25% w/w water (a 10.2% increase over dry weight). This water content (9.25% w/w) would be calculated to lower the T_g of the lactose to 6.4°C, and as such it is not surprising that the material recrystallises spontaneously at this (50%) RH. It should be noted, however, that the use of the word spontaneous in this text should not be confused with instantaneous, as the lactose does not instantaneously recrystallise at 50% RH, but rather requires approximately 11 h before crystallisation starts. A sample which had been equilibrated at 50% RH, then repeatedly exposed to 0% followed by 50% RH showed only minor fluctuations in water content (due to the slow desorption from the collapsed state), but did not recrystallise for 30 h, indicating that saturation near the surface of the solid may be needed prior to crystallisation. The lag time between water sorption and recrystallisation is dependent upon the water content of the amorphous region, for example, a sample exposed to 75% RH recrystallised before it reached equilibrium moisture content (Fig. 2) 47 min after first being exposed to that environment and with a water content immediately before recrystallisation of 11.2% w/w (12.7% weight increase), which would be expected to lower the T_g of the amorphous lactose to 2.8°C. It should be noted, however, that the sample at 75% RH was never at equilibrium, thus the T_g was varying, but lower than T for sometime before it recrystallised.

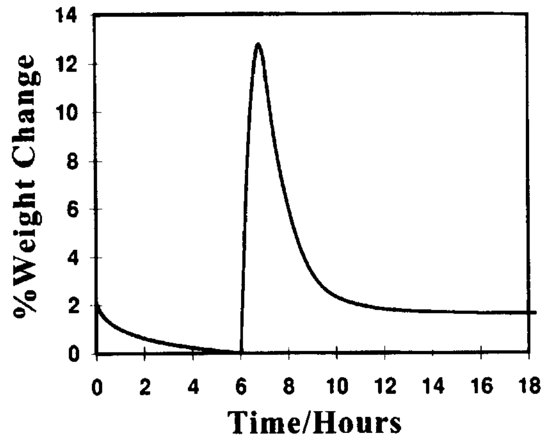

Fig. 2. Water sorption isotherm for amorphous lactose exposed to 75% RH. (The first 6 h show drying at 0% RH, the weight loss at ca. 7 h is due to crystallisation occurring, which causes desorption of the water even thought the sample remains at 75% RH.)

3.2. *Rate of desorption*

The desorption of water from a sample of amorphous lactose which has been exposed to 40% RH is rapid (Fig. 1) and at a rate which is related to the external RH (i.e. the rate is faster if the external RH is 0% than if it is 20% RH (Fig. 3)). This demonstrates that the rate of desorption is linked to the concentration gradient at the surface of the solid.

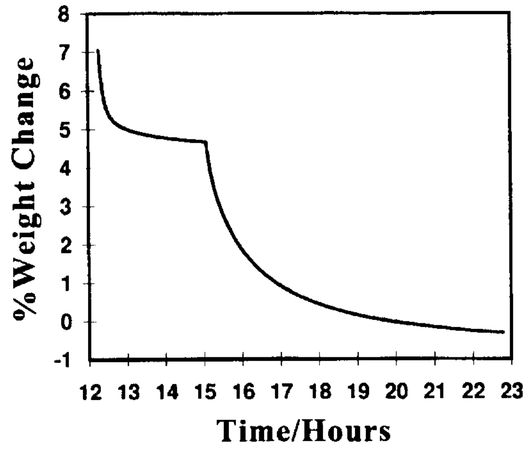

Fig. 3. Desorption of water from a sample which had been equilibrated at 40% RH. For the first 3 h desorption is being driven with the system RH set at 20% and the final 8 h with the RH reduced to 0%.

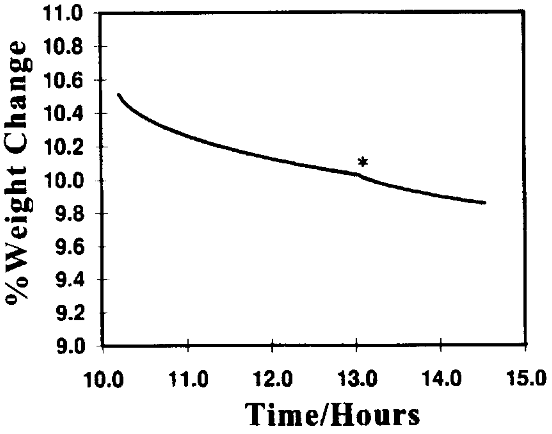

Fig. 4. Desorption of water from a sample of amorphous lactose which has been equilibrated at 50% RH, with the first ca. 3 h at 20% RH and the final section at 0% RH. *The point of the transition from 20 to 0% RH.

For the sample which has been exposed to 50% RH, and allowed to come to equilibrium, the desorption is very slow (Fig. 1) and independent of external RH. This can be seen in Fig. 4, where the RH was reduced from 50% to 20% and then 0% without altering the desorption rate (Table 1). The desorption from this sample is much slower than that from the one which had been exposed to 40% RH. In this instance (50% RH) the desorption data were found to produce a linear relationship when the weight loss was plotted as a function of the square root of time (gradient

Table 1

Gradient of plots of percentage weight change as a function of square root of time for the desorption from amorphous lactose, induced by changing to 0% RH following exposure to 50% RH for different times. (Linear regions taken in each case, for consistency this was always taken as the period after 5 h at 0% RH)

Time at 50 %RH (min)	Slope (% min$^{-0.5}$)
≤60	Not linear
75	0.091; 0.083
90	0.136; 0.135
120	0.100; 0.114
210[a]	0.108; 0.127; 0.132

[a] Slope for external RH of 20% instead of 0% = 0.107, followed by 0% RH = 0.108.

Gradients for repeat runs are shown separately.

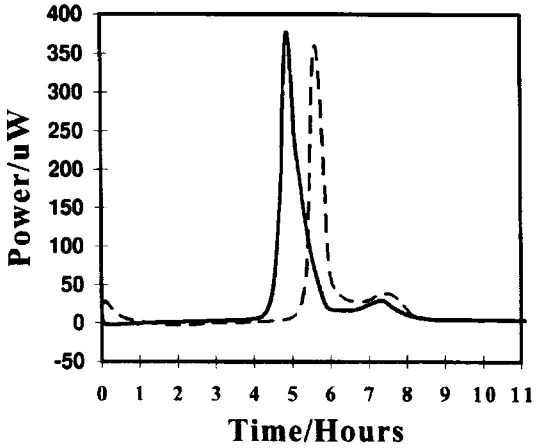

Fig. 5. Isothermal microcalorimetry traces showing the recrystallisation of amorphous lactose following exposure to 54% RH in the cell of the calorimeter. The two samples had previously been exposed to 50% RH in the DVS system for (- - -) 75 min and (——) 120 min.

$-0.107\%/\mathrm{min}^{0.5}$ for the region where the external RH was 20% and $-0.108\%/\mathrm{min}^{0.5}$ where it was 0% RH). These data show that the change in structure which occurs when the T_g falls below T (a collapse of the amorphous structure) results in a desorption of water by a process which is controlled by the diffusion rate through the consolidated structure. It is extremely difficult to get accurate measurements of diffusion in glasses (Parker and Ring, 1995) so these data serves two purposes. Firstly they demonstrate the physical difference between the two metastable states of lactose (with consequential different water loadings and water availabilities within the sample) and secondly that the DVS system can be used to monitor diffusion coefficients (proportional to the gradient of the square root of time relationship) in glasses. It should be noted that the collapsed glassy state is still amorphous, having no long range order. This can be proved by removing the collapsed sample and exposing it to a defined relative humidity in an isothermal microcalorimeter. This procedure was carried out using a sealed glass ampoule containing a saturated salt solution to give a relative humidity of 54%. The data shown in Fig. 5 are for two samples of amorphous lactose which have been exposed to 50% RH in the dynamic vapour sorption apparatus, one for 75 and the other for 120 min. The sample which had been exposed to 50% RH for 120 min had a totally collapsed structure (showing slow diffusion controlled desorption for almost all of the associated water) whilst that which had been exposed for 75 min had only partially collapsed (see below). Both of these samples showed identical recrystallisation events within the isothermal microcalorimeter, with both giving an area under the curve for the major peak of 47 J/g (a value which is the same as that reported previously for spray dried lactose which had been stored dry prior to testing in the isothermal microcalorimeter (Briggner et al., 1994)). It follows that the collapse of the amorphous structure contributes very little towards the total enthalpy change that accompanies recrystallisation. It can be assumed that this collapse is probably chronologically removed from the recrystallisation. It may be true that the collapse of the amorphous structure is contributing to the initial response that is seen during such recrystallisation experiments in the microcalorimeter, as the sample which had been exposed for 75 min showed an initial peak at 0-1.5 h (possibly the collapse), whilst that which had already been seen to collapse showed no such initial response. To check this finding, we exposed amorphous lactose (direct from dry storage, to 33% RH in the isothermal microcalorimeter and obtained only a very minor deviation at the early stages (consistent with heat evolved with lowering an empty ampoule into the measuring site). It follows that the first peak of the calorimetry responses which has previously been described as a wetting response (Briggner et al., 1994) is more likely to be a result of the collapse of the amorphous structure. This is in keeping with the hypothesis that the wetting response should not be seen as the evaporation from the salt solution is approximately matched by the condensation into the solid (an equal exotherm and an endotherm respectively).

The data in Fig. 6 show the desorption from amorphous lactose samples following exposure to 50% RH for different durations. It can be seen that the vapour sorption profile is superimposed

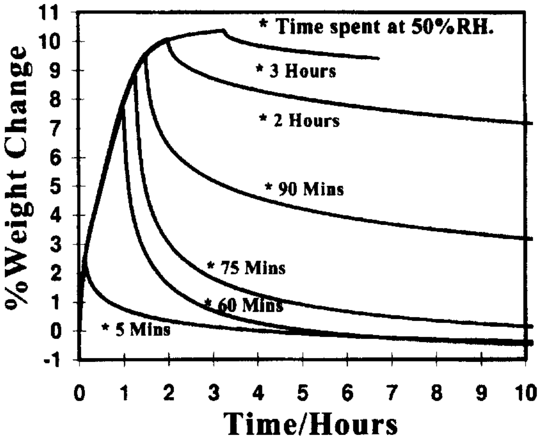

Fig. 6. Desorption of water from samples of amorphous lactose which had been exposed to 50% RH for varying times.

for each sample, whilst the nature of the desorption differs depending upon the time exposed to the elevated RH. Exposure to 50% RH for 60 min results in a water uptake maximum which almost exactly equals the point where $T = T_g$. This water was desorbed immediately when this point is reached, resulting in no collapse of the sample and a relatively rapid desorption profile back to the dry weight. This desorption rate is very similar to that observed following just 5 min exposure to 50% RH. For all longer exposure times, the water content of the sample rises above that required to lower T_g to T, thus the T_g drops below T by varying amounts depending upon the total water uptake, and for varying periods of time. The subsequent desorption from these samples results in a process for which the final loss of water follows a diffusion controlled process with square root of time dependency. The proportion of water loss which is released rapidly and that which follows slow diffusion controlled kinetics gives a good indication of the extent of collapse of the amorphous structure. For example, exposure at 50% RH for 120 min results in total collapse whilst exposure for 90 min allows relatively rapid loss of approximately half the absorbed water before the slow diffusion process starts to dominate the desorption event.

4. Conclusions

The expected consolidation of amorphous material at T_g approximately equal to T can be observed using vapour sorption. The consequence of this change of form is a dramatic effect on the mobility of water in the sample. The change in water mobility in this metastable region can be expect to be significant for the behaviour of the product in which the lactose is used. This will have implications for lyophilised dosage forms as well as any other systems which contain lactose in a partially amorphous state, such as solid oral dosage forms containing spray dried lactose, and inhalation devices.

The shape of the isothermal calorimetry response for recrystallisation of amorphous material is now better understood as being an initial response for collapse of the structure, followed by a lag time prior to the crystallisation.

References

Briggner, L.-E., Buckton, G., Bystrom, K. and Darcy, P., The use of isothermal microcalorimetry in the study of changes in crystallinity induced during the processing of powders. *Int. J. Pharm.*, 105 (1994) 125–135.

Buckton, G. and Darcy, P., The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. *Int. J. Pharm.*, 123 (1995a) 265–271.

Buckton, G. and Darcy, P., The influence of additives on the recrystallisation of amorphous spray dried lactose. *Int. J. Pharm.*, 121 (1995b) 81–87.

Buckton, G., Darcy, P. and MacKellar, A.J., The use of isothermal microcalorimetry in the study of small degrees of amorphous content of powders. *Int. J. Pharm.*, 117 (1995) 253–256.

Hancock, B.C., Shamblin, S.L. and Zografi, G., Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. *Pharm. Res.*, 12 (1995) 799–805.

Parker, R. and Ring, S.G., Diffusion in maltose-water mixtures at temperatures close to the glass transition. *Carbohydrate Res.*, 273 (1995) 147–155.

Roos, Y., Melting and glass transitions of low molecular weight carbohydrates. *Carbohydrate Res.*, 238 (1993) 39–48.