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The use of gravimetry for the study of the effect of additives on the moisture-induced recrystallisation of amorphous lactose

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Abstract

The moisture sorption of amorphous lactose was monitored gravimetrically in a humidity controlled microbalance system (CISORP Automated Sorption Monitor). The effects of the adding of hygroscopic (polyvinyl pyrrolidone, PVP) and non-hygroscopic excipients (crystalline lactose and colloidal silicon dioxide) on the ability of amorphous lactose to recrystallise above its glass transition temperature, i.e. at 55 and 75% relative humidity, were studied. PVP was found to delay the time for onset of weight loss, i.e. the 'apparent' recrystallisation. This is explained by PVP acting as an internal desiccant, prolonging the time until recrystallisation occurs. However, this time was significantly reduced when non-hygroscopic excipients were admixed, which is explained by isolation and a deaggregating effect on the amorphous lactose. Thus, gravimetrical studies are well suited for screening the effect of additives on the moisture-induced recrystallisation of amorphous materials. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Amorphous materials; Additives; Recrystallisation; Moisture sorption; Gravimetrical studies

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1. Introduction

It is well-known that the energy content of crystalline materials such as lactose can be altered during pharmaceutical processing, giving rise to disorders in the form of crystal defects or amorphous regions. The free energy of such products is relatively high when compared to the initial crystalline material, which means that their capacity for moisture sorption is increased. The moisture sorbed acts as a plasticiser and lowers the glass transition temperature (T_g) of the material. There

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has recently been a renewed interest in studying the glass-to-rubber transition of lactose, since it is expected that the product performance of pharmaceuticals containing amorphous or partially amorphous lactose may be explained by such studies. Sebhatu et al. (1994a) and Stubberud et al. (1996b) have observed an increase in tablet strength during storage. This was explained by a moisture-induced reduction of T_g to a level below the operating temperature, which allowed the molecules in the amorphous regions freedom of motion. The ensuing crystallisation proceeded as soon as the thermal conditions were in favour for the formation of a stable nucleus. This process gave rise to improved bonding through solid bridge formation.

Whilst it is known that additives can influence the crystallisation of amorphous spray-dried lactose and that these events can be followed calorimetrically (Buckton and Darcy, 1995a), there is little literature on the use of gravimetric studies to follow such events in the presence of additives. Buckton and Darcy (1995b) primarily used gravimetric studies to determine the degree of crystallinity for mixtures of amorphous and crystalline lactose. Using amorphous lactose as an example and by extending the range of additives evaluated from the one used by Buckton and Darcy (1995b), this paper considers the general utility of gravimetry to screen formulation additives for their ability to promote or inhibit crystallisation of amorphous or partially amorphous materials. Emphasis is placed on homogeneous mixes to reflect industrial practice. The layering of excipients, following the method of Buckton and Darcy (1995a), is more amenable to the calorimetric study they conducted, and has not been evaluated.

2. Materials and methods

2.1. Materials

Approximately 100% amorphous lactose was prepared by spray drying (Stubberud et al., 1996b). The material was sieved through a 0.425-mm sieve and stored in a desiccator over P_2O_5 prior to use. It was verified to be amorphous by X-ray diffraction. Lactose α-monohydrate (Pharmatose 350M, DMV, the Netherlands), 100% crystalline, polyvinyl pyrrolidone (Plasdone K-25, GAF, USA), 100% amorphous, and colloidal silicon dioxide (CAB-O-SIL M5, Cabot, Germany) were used as additives in binary blends containing amorphous lactose.

2.2. Methods

Moisture sorption was monitored gravimetrically in a humidity-controlled microbalance system (CISORP Automated Sorption Monitor, C.I. Electronics Ltd., Salisbury, UK). The flows of dry and of humidified nitrogen are thereby controlled by switching valves before entry into the humidification chamber. The CISORP monitor is designed to bring a gas stream of controlled temperature and humidity into a computer-controlled weighing chamber containing the microbalance. Thus, any changes in the sample mass can be monitored and recorded, revealing moisture uptake or loss.

Binary blends of amorphous lactose/additive in the ratios 100:0, 100:25, 100:100 and 200:0 (w/w) were studied. For amorphous lactose/PVP, the ratios 80:20 and 50:50, were also chosen. The blends were mixed for 20 min, using a cubic mixer. In some experiments the fraction of amorphous lactose was kept constant while the sample size was varied, while in others the size was kept constant and the fraction was varied. Thus, sample amounts ranging from 7.5 to 15 mg ($\pm$5%) were loaded onto the weighing pans. They were dried for 30 min under dry nitrogen to obtain a vapour pressure above the samples of less than 10%. The RH of the chamber was raised to 10% and the samples were allowed to equilibrate. Equilibrium was defined as having been reached when the weight change was less than 0.0025% between three measurements taken at 60-s intervals. The humidity was then raised to either 55 or 75% RH. All the experiments were performed at 25°C. Both test humidities are greater than 50% RH, above which amorphous lactose is known to recrystallise spontaneously (Briggner et al., 1994; Buckton and Darcy, 1996).

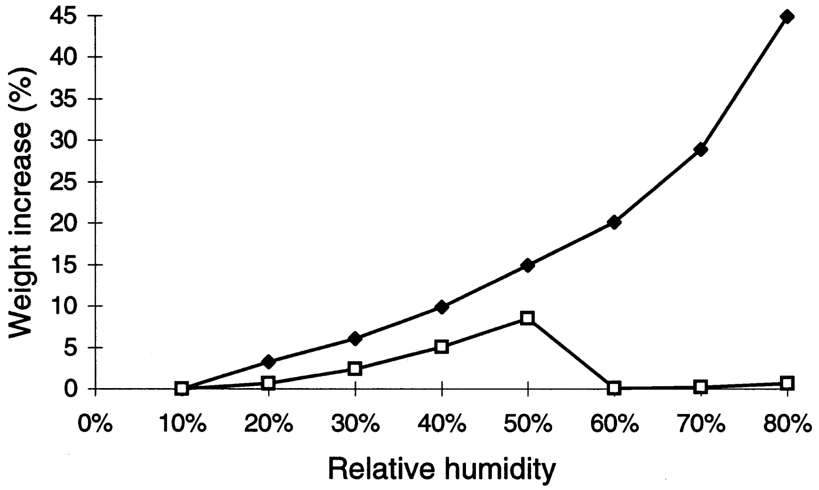

Fig. 1. Moisture sorption, i.e. thermodynamic hygroscopicity, for amorphous lactose and PVP. (◆), PVP; (□), Amorphous lactose.

The initial weight increase caused by moisture sorption was recorded. After peak moisture uptake had been attained, the corresponding time to the onset of weight loss of the sample was also determined. This weight loss is associated with recrystallisation, and the time taken to its onset was defined as the 'apparent' onset of recrystallisation. The time was found to be reproducible to within 1 min ($n = 2$).

For the studies of the hygroscopicity of amorphous lactose and PVP, the samples (10 mg) were initially dried for 240 min under dry nitrogen. The RH was then raised in steps of 10% starting at 10% RH, and the weight increase as well as time to reach equilibrium was recorded. The program feedback was set to increase the humidity when a weight change of less than 0.0025% was recorded between three measurements taken at 60-s intervals.

Table 1
Time to reach EMC, i.e. kinetic hygroscopicity, for amorphous lactose and PVP

% RH	Amorphous lactose (min)	PVP (min)
20	31	115
30	170	138
40	95	54
50	69	45
60	108	72
70	–	142
80	–	280

Powder X-ray diffraction was used to analyse the crystal lattice in the powder samples of amorphous lactose alone and of the binary mixtures containing PVP after recrystallisation in desiccators at 55 and 75% RH. A Siemens Model D5000 diffractometer fitted with a scintillation counter and a CuKα radiation source (wavelength = 0.15418 nm) was used. Differential scanning calorimetry was performed using a Perkin Elmer, Model DSC 7, to observe the thermal properties of the amorphous lactose alone and the binary blend containing PVP (100:100). Finally, 2–4 mg samples were weighed into standard aluminium pans and scanned at a rate of 10°C/min.

3. Results and discussion

3.1. Hygroscopicity

Fig. 1 shows the moisture sorption isotherms for amorphous lactose and PVP. Data is presented as the weight increase above the Equilibrium Moisture Content (EMC) of the samples obtained at 10% RH. In the case of amorphous lactose there is an increase in weight up to an RH of 50%. This process is followed by a weight loss

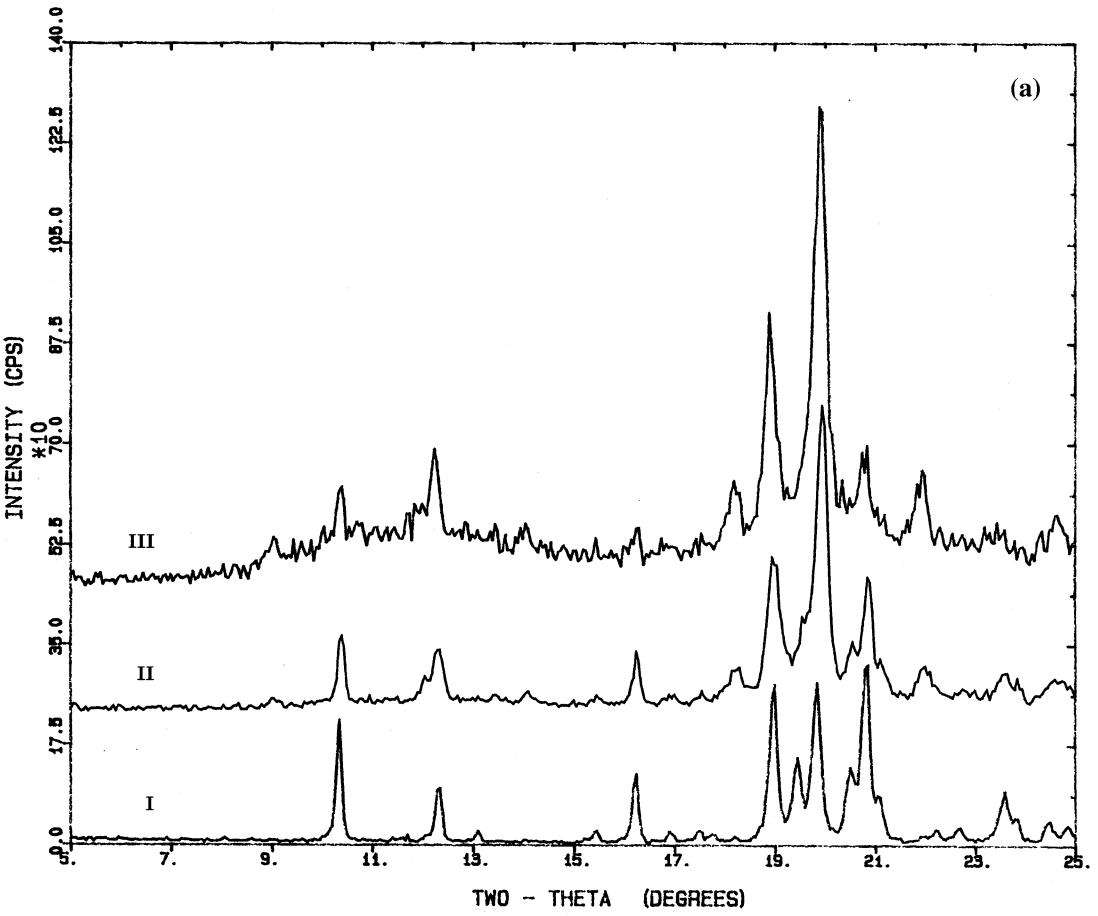

Fig. 2. X-ray diffraction pattern of amorphous lactose and binary mixtures after recrystallisation at (a) 55% RH: (I) amorphous lactose, (II) amorphous lactose/PVP (80:20), (III) amorphous lactose/PVP (50:50); (b) 75% RH: (I) amorphous lactose, (II) amorphous lactose/PVP (80:20).

of water and a return to the starting weight when the RH is increased from 50 to 60%. The observation confirms the event reported by Buckton and Darcy (1995b), and is explained by recrystallisation of the amorphous lactose as the T_g is depressed below the operating temperature (Sebhatu et al., 1994b). Unlike lactose, PVP does not show the characteristic weight loss associated with recrystallisation and expulsion of sorbed moisture from the lattice. The weight increases are higher than those for lactose at the same RH, suggesting that PVP is more hygroscopic when applying a thermodynamic approach to the interpretation of the results. This is also true when the hygroscopicity is considered on the basis of the kinetic aspects (Table 1). In absolute terms, the time for the lactose sample to reach EMC is longer than for PVP at all humidites below 70%, except 20%, which means that for PVP sorption takes place at a faster rate. At higher humidities, however, the time to reach equilibrium for PVP is significantly increased. This may be explained by a change in the physical structure from a glassy state to a rubbery state (Stubberud et al., 1996a).

3.2. Apparent onset of recrystallisation

Fig. 2a, b present the X-ray diffraction patterns of amorphous lactose after recrystallisation following storage in desiccators at 55 and 75% RH.

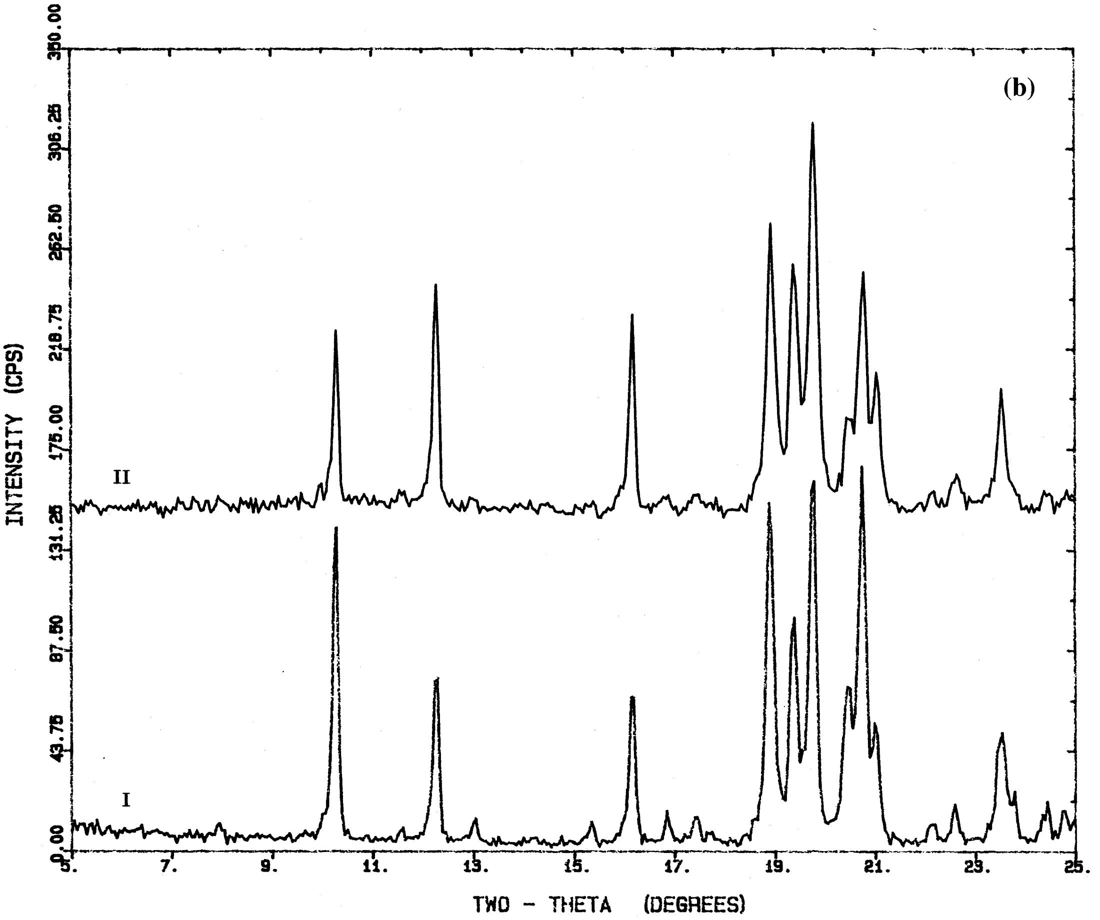

Fig. 2. (*Continued*)

It has previously been reported (Briggner et al., 1994; Stubberud et al., 1996b) that amorphous lactose recrystallises to form a mixture of anhydrous β-lactose and lactose α-monohydrate. The peak observed at 10.5° is characteristic for the anhydrous β-lactose, lending further support to these findings. Identical behaviour was observed when the material was recrystallised as a physical mixture containing 20 or 50% PVP. These results confirm that PVP does not modify the lactose crystal form produced under these conditions.

3.2.1. *Amorphous lactose/PVP*

Table 2 shows the times for recrystallisation and the weight increases for amorphous lactose, PVP and the binary blends containing PVP when increasing the ambient RH from 10 to 55% and 75%, respectively. Fig. 3a, b show the weight changes of the samples.

The time to the onset of weight loss of amorphous lactose alone, i.e. the time to the apparent onset of recrystallisation, decreases with increasing humidity (weight ratio 100:0). The same observation has previously been made by using microcalorimetric techniques (Briggner et al., 1994), and the behaviour was explained as being due to a delay in saturating the powder bed with decreasing humidity. In addition, Table 2 also shows, as expected, that when the sample amount is increased (weight ratio 200:0), the time to the apparent onset of recrystallisation is prolonged.

Table 2
Time for recrystallisation of amorphous lactose alone and in binary blends containing PVP

Amorphous lactose/PVP (m/m)	Sample amount (mg)	75% RH			55% RH		
		Time to recrystallise (min)	Calculated weight increase (%)	Actual weight increase (%)	Time to recrystallise (min)	Calculated weight increase (%)	Actual weight increase (%)
0/100	6.5	–	–	37.2	–	–	18.7
100/0	6.5	14	–	11.5	42	–	8.4
200/0	13	16	–	9.9	52	–	7.8
80/20	6.5	23	17.1	17.6	51	11.5	12.0
50/50	6.5	41	24.8	22.6	46	14.2	14.7
100/25	8.1	22	17.1	16.0	51	11.5	12.9
100/100	13	189	24.8	22.9	60	14.2	15.2

The weight increases when changing the ambient humidity from 10% to 55% and 75% RH, respectively, are also shown.
The calculated values for the binary mixtures are based upon the actual values for pure amorphous lactose and pure PVP, respectively.

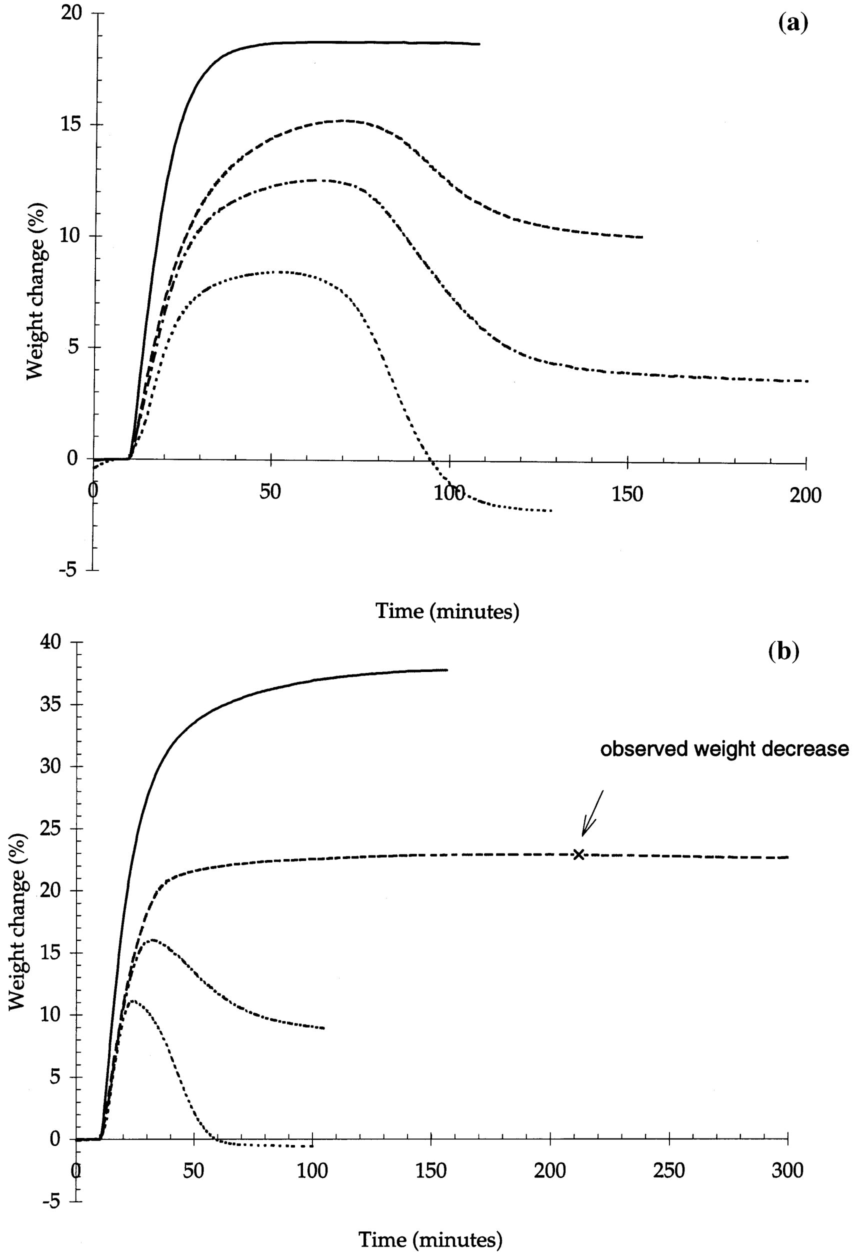

Fig. 3. (a) Weight change (%) for amorphous lactose, PVP and binary mixtures when increasing the ambient RH from 10% to 55%. (b) Weight change (%) for amorphous lactose, PVP and binary mixtures when increasing the ambient RH from 10% to 75%. (——), Amorphous lactose/PVP (0:100); (- - -), amorphous lactose/PVP (100:100); (– · –), amorphous lactose/PVP (100:25); (···), amorphous lactose/PVP (100:0).

The addition of PVP further delays the time for recrystallisation at 55 and 75% RH (weight ratio 100:25), which is to be expected. PVP, acting as an internal desiccant, delays the saturation of the powder bed or parts of it, thereby prolonging the time elapsing before recrystallisation. Identical be-

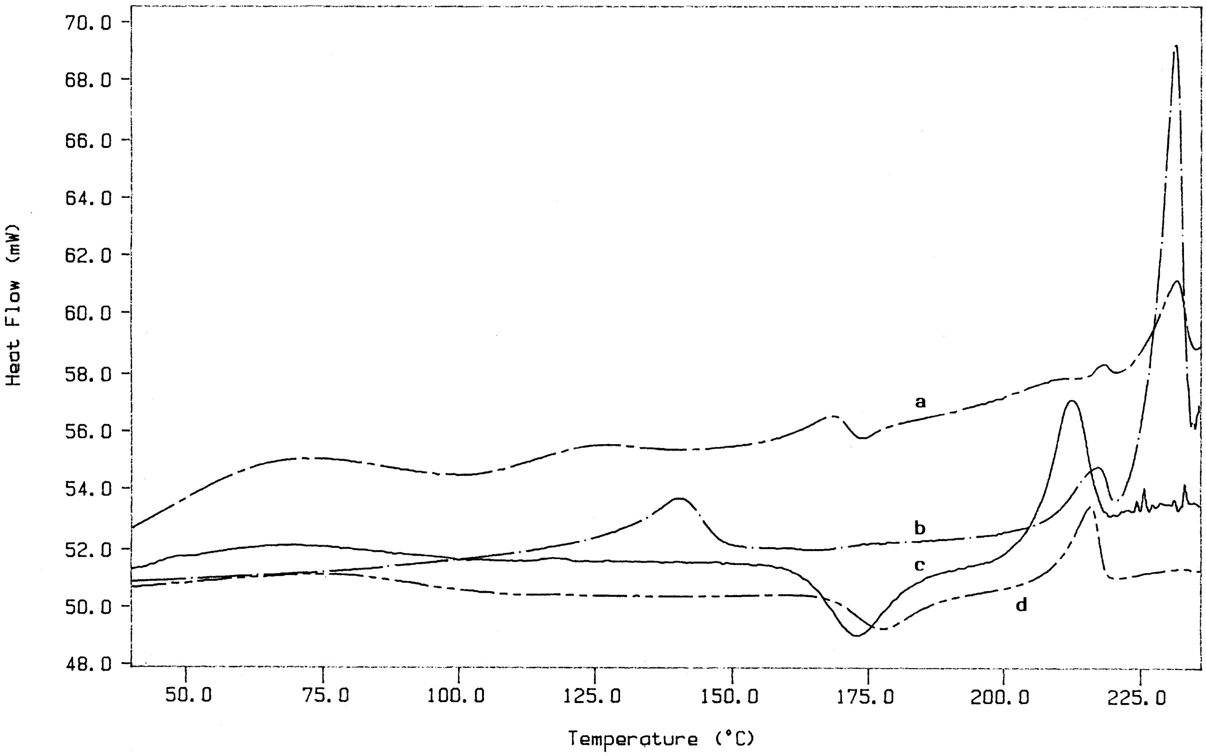

Fig. 4. DSC thermograms of samples exposed to 75% RH: (a) amorphous lactose/PVP (100:100), (b) recrystallised amorphous lactose. Thermograms of samples which were not exposed to humidities which induce recrystallisation are also shown: (c) amorphous lactose, (d) amorphous lactose/PVP (100:100).

haviour is observed when the total sample size is kept constant (weight ratio 80:20), showing that this is a true effect of PVP and is not due to the increase in the sample weight. The effect of PVP as a desiccant is significantly stronger at higher blend concentrations where the PVP content is further increased (weight ratio 100:100). Buckton and Darcy (1995a) have shown a similar increased delay in the time for recrystallisation of amorphous lactose in mixtures containing microcrystalline cellulose using microcalorimetric techniques, showing that this hygroscopic substance also effectively acts as a desiccant.

It is probable that different processes are occurring simultaneously when the weight of the powder is changing, i.e. on the one hand a sorption of moisture by PVP and by amorphous lactose, and on the other hand a recrystallisation of lactose when a moisture increase which depresses T_g below the operating temperature is reached. As illustrated by the kinetic hygroscopicity (Fig. 3a and Table 1), PVP equilibrates faster than pure lactose at humidities below 60%. Thus, it might be supposed that the EMC is obtained for PVP in the blend prior to the onset of the recrystallisation process. At 75% RH, however, the time to obtain EMC is significantly prolonged, and the recrystallisation of lactose will probably start before the EMC is obtained for PVP (Fig. 3b). Weight increases are shown in Table 2. The calculated theoretical values are derived from the actual weight increase for pure amorphous lactose and pure PVP, respectively, and seem to be close to the actual values obtained for the blends. At 75% RH, there is a tendency towards lower actual values relative to those theoretically estimated. This supports the hypothesis that recrystallisation of the amorphous lactose starts before the saturation of PVP is reached.

Table 3
Time for recrystallisation of amorphous lactose in binary blends containing lactose α-monohydrate and colloidal silicon dioxide

	Sample amount (mg)	75% RH		55% RH	
		Time to recrystallise (min)	Weight increase (%)	Time to recrystallise (min)	Weight increase (%)
Amorphous lactose/lactose α-monohydrate (m/m)					
100/0	6.5	14	11.5	42	8.4
200/0	13	16	9.9	52	7.8
100/25	8.1	10	8.4	21	7.2
100/100	13	8	7.4	16	6.9
Amorphous lactose/colloidal silicon dioxide (m/m)					
100/25	8.1	10	7.5	18	5.9
100/100	13	10	5.7	17	4.7

The weight increases, calculated as the increase for amorphous lactose, when changing the ambient humidity from 10 to 55% and 75% RH, respectively, are also shown.

When studying the weight change at 75% RH for amorphous lactose/PVP (100:100), no significant weight loss can be seen (Fig. 3b). The weight increase which depresses T_g below the operating temperature and thereby induces recrystallisation for amorphous lactose alone, is shown to be about 10% (Table 2). If lactose recrystallises instantaneously (Briggner et al., 1994) to a mixture of lactose α-monohydrate and anhydrous β-lactose, the weight loss would thus be expected to be in the range 3–5%, which corresponds to 6–10% when based on amorphous lactose alone. This may indicate that no recrystallisation of the sample (amorphous lactose/PVP, 100:100) takes place. However, after about 3 h (189 min) there is a tendency for a slight continuous decrease. Therefore, the weight change was monitored for another 100 minutes whereupon its thermal properties were characterised by using DSC (Fig. 4a), in order to probe its solid state properties. The curves for recrystallised amorphous lactose (Fig. 4b), i.e. sample exposed to 75% RH, as well as for unexposed amorphous lactose (Fig. 4c) and unexposed amorphous lactose/PVP (100:100) (Fig. 4d) are included as references. An exothermic peak is observed at 170°C, which is most probably the result of recrystallisation of the amorphous parts of lactose. In addition, two separate melting peaks are observed for the binary sample stored at 75% RH (Fig. 4a), which must correspond to the melting peaks observed at about 220° and 230°C, for recrystallised amorphous lactose. The X-ray data presented in Fig. 2a, b confirms that the bulk lactose/PVP blends studied crystallised on exposure to moisture to produce some β-lactose. Whilst DSC cannot prove that recrystallisation had occurred, since in-pan transitions are possible during sample analysis, the presence of the β-melting endotherm (around 220°C) in the sample exposed to humidity and the reduction in the magnitude of the exotherm at around 170°C, when compared to the unexposed sample run, are consistent with the sample of amorphous lactose/PVP (100:100) containing a mixture of amorphous lactose and recrystallised lactose after exposure to 75% RH for 290 min.

It has previously been proposed that the recrystallisation of amorphous lactose occurs on one occasion immediately after saturation of the powder bed at 75% RH (Briggner et al., 1994; Buckton and Darcy, 1995a). However, other results point to the fact that the recrystallisation process in larger or bulk sample amounts occurs gradually during the time of exposure of the sample to moisture (Stubberud et al., 1996b). By adding PVP to the amorphous lactose, a similar gradual process seems to occur. The reason for this is most probably that PVP, which exists in rubbery state at 75% RH (Stubberud et al., 1996a), sorbs

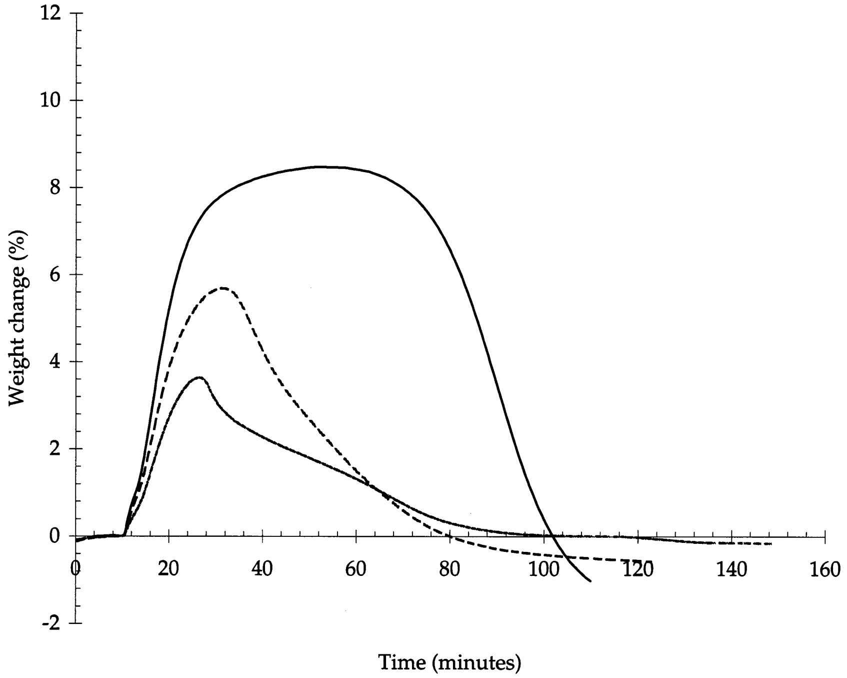

Fig. 5. Weight change (%) for amorphous lactose and binary mixtures with lactose α-monohydrate when increasing the ambient RH from 10% to 55%. (——), Amorphous lactose/lactose monohydrate (100:0); (- - -), amorphous lactose/lactose monohydrate (100:25); (···), amorphous lactose/lactose monohydrate (100:100).

the moisture which is expelled from lactose, thereby preventing the cooperative recrystallisation process.

3.2.2. Amorphous lactose and lactose α-monohydrate/colloidal silicon dioxide

Table 3 shows the times for recrystallisation and the weight increases for the binary blends of amorphous lactose with lactose α-monohydrate and with colloidal silicon dioxide at 55% and 75% RH. The time for recrystallisation of amorphous lactose is significantly reduced when these excipients are admixed, the effect being most apparent at 55% RH (see representative data in Figs. 5 and 6). It may be explained by isolation and a deaggregating effect on the amorphous lactose making it more available for moisture sorption, and thereby reducing the time for saturation of the powder bed and the recrystallisation. Additional supporting evidence for such behaviour arises from the observation that less moisture is sorbed prior to the onset of recrystallisation when the fraction of amorphous lactose is decreased in the sample (Table 3). Table 3 further shows that the weight increase prior to recrystallisation is higher for the mixture with lactose α-monohydrate relative to the mixture with colloidal silicon dioxide. The BET-surface area for lactose α-monohydrate and colloidal silicon dioxide was found to be 0.6 m^2/g and 200 m^2/g, respectively. Thus, it seems probable that the isolation effect is greater for colloidal silicon dioxide because its smaller particles are better able to penetrate the amorphous lactose powder bed and bring about a higher level of dispersion of primary amorphous lactose particles. On crystallisation of the amorphous lactose particles, the expelled moisture may also be able to more readily diffuse through the powder bed created with colloidal silicon dioxide than that created with crystalline lactose monohydrate.

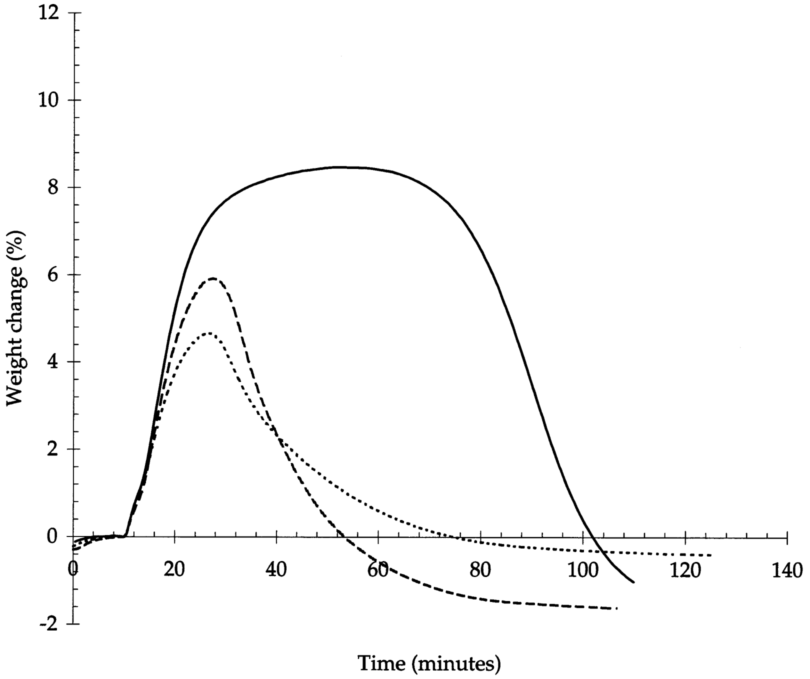

Fig. 6. Weight change (%) for amorphous lactose and binary mixtures with colloidal silicon dioxide when increasing the ambient RH from 10% to 55%. (——), Amorphous lactose/colloidal silicone dioxide (100:0); (- - -), amorphous lactose/colloidal silicone dioxide (100:25); (···), amorphous lactose/colloidal silicone dioxide (100:100).

4. Conclusion

Gravimetry, e.g. by using commercially available moisture sorption balances, is well suited for screening the effect of additives on the moisture-induced recrystallisation of amorphous materials. It is shown that the hygroscopic excipient PVP acts as an internal desiccant to delay the 'apparent' onset of recrystallisation of amorphous lactose, while the addition of the non-hygroscopic excipients crystalline lactose and colloidal silicon dioxide significantly reduce the time for recrystallisation. The use of additives is thus expected to significantly affect the behaviour of a powder mass during formulation, production and storage if it contains amorphous or partially amorphous materials. Accordingly, careful control of humidity and an understanding of its influence in such situations are required.

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