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Evaluation of heat-conduction microcalorimetry in pharmaceutical stability studies. IV. The influence of microcrystalline cellulose on the hydration rate of anhydrous lactose

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Summary

Microcalorimetry at 25.0 ° C, differential scanning calorimetry (DSC) and water uptake measurements were used to monitor the influence of water vapour on a 50/50 mixture of microcrystalline cellulose (MCC) and anhydrous lactose (26% α- and 74% β-lactose), and on MCC alone, after storage at various relative humidities for different lengths of time. It was shown that MCC protects anhydrous lactose when surrounded by abundant water vapour by slowing down the rate of hydration. In a limited amount of water vapour, it was shown that MCC can redistribute its absorbed water through the vapour phase. This extends the duration of incorporation of hydrate water in anhydrous lactose over that seen when anhydrous lactose is alone. In the evaluation of the microcalorimetric technique it was shown that if a process is in progression before the first microcalorimetric measurement in a series, important information can be lost and the result may be difficult to interpret. However, together with other analytical techniques, the microcalorimetric result can give a valuable indication of how the process has proceeded.

Introduction

Interactions between solid-state material and water vapour occur in many stages of the manufacturing of pharmaceuticals, as well as during storage in a humid environment. Several properties of the material in the production process and in the final dosage form, e.g. powder flow, compactability and stability, are dependent on how much water has been taken up by both the active compound and the excipients. The molecular basis of water vapour effects on the physical and chemical stability of solid pharmaceutical materials has been described by Ahlneck and Zografi (1990).

In a previous paper (Angberg et al., 1991), microcalorimetry was used to characterize the

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interaction between water vapour and anhydrous lactose, a crystalline material, in which water can be incorporated to form the monohydrate. The incorporation process ought to be influenced if the lactose is mixed with a material that has the ability to absorb a large quantity of water. Microcrystalline cellulose is hygroscopic but is otherwise stable and shows no incompatibilities according to the *Handbook of Pharmaceutical Excipients* (1986). Several papers on the interaction between water and microcrystalline cellulose have been published (Hollenbeck et al., 1978; Zografi et al., 1984; Zografi and Kontny, 1986; Khan and Pilpel, 1987; Fielden et al., 1988; Blair et al., 1990).

The object of this study was to apply microcalorimetry to the investigation of a complex powder mixture, the components of which show different interactions with water vapour, and to evaluate the microcalorimetric response and the experimental technique used. One of the particular aims was to investigate if, and how, the presence of microcrystalline cellulose influenced the rate of hydration in anhydrous lactose. Differential scanning calorimetry is a complementary analytical technique which has been used extensively to support the microcalorimetric evaluation.

Materials and Methods

Materials

Microcrystalline cellulose, Avicel^R PH 101 (henceforth referred to as MCC), lot no: 6823, FMC Corp., Philadelphia, PA, U.S.A.; Lactose N.F. anhydrous direct tableting 59009 (called anhydrous lactose), lot no: 9NG26, Sheffield Products, Norwich, NY, U.S.A.; and α-Lactose monohydrate, Pharmatose^R 200M, De Melkindustrie, Veghel bv. (DMV), Veghel, The Netherlands, were obtained from the indicated sources.

The anhydrous lactose powder is a mixture of two optically isomeric forms, α- and β-lactose. The batch consisted of 26% α- and 74% β-lactose (determined by gas chromatography at DMV). At the beginning of the experimental period, about 6% of the total lactose content was α-lactose monohydrate (determined by DSC). The water content in untreated MCC is approx. 4% (information from FMC Corp.).

Methods

Sample sizes, mixing and storage conditions at varying humidities. Equal weights of MCC and anhydrous lactose were mixed in a 2 l Turbula mixer (W.A. Bachofen, Switzerland) for 120 min. Samples of 1.50 ± 0.005 g of the MCC/anhydrous lactose mixture and 1.00 ± 0.005 g of MCC alone were stored in humidity chambers at 33, 58, 75, 81, 84 and 94% relative humidity (RH) at 20–23 °C, as in the previous study (Angberg et al., 1991).

α-Lactose monohydrate and MCC were mixed as above, but not stored in humidity chambers.

Water vapour uptake. Water vapour uptake was determined gravimetrically. The weight increases for the MCC/anhydrous lactose mixtures after storage at 33–94% RH and for MCC alone after storage at 75–94% RH were recorded.

Microcalorimetry. The microcalorimeter system used, the 2277 Thermal Activity Monitor (TAM) (Thermometric AB, Sweden), has been described earlier (Suurkuusk and Wadsö, 1982). The heat flow signals (dQ/dt, in $\mu W = \mu J/s$) are monitored as a function of time and are ideally proportional to the rate of the process. The experimental temperature, 25.0 °C, sample preparation and measurement technique were the same as described previously (Angberg et al., 1991). Each measurement lasted for at least 12 h, but the heat flow value after 2 h has mainly been used in the evaluation of the results. Repeated measurements were taken for many combinations of relative humidity and storage time and the mean values and standard deviations were calculated. Exothermic heat flow signals are given positive values in this paper.

Longer measurement times were also investigated. Samples of the MCC/anhydrous lactose mixture were stored for 1 day at 75% or 94% RH and microcalorimetric measurements continued thereafter for 12 days. In other measurements, 0.75 g samples of MCC were stored at 75–94% RH for 1 day. These samples were then poured onto 0.75 g of untreated anhydrous lactose or α-lactose monohydrate, already in the microcalorimetric sample vessels. Microcalorimetric measurements were taken for 40 h.

Differential scanning calorimetry. A DSC 20 (Mettler, Switzerland) was used to investigate the increase of hydrate water in the anhydrous lactose. The powder mixtures were stored at 58–94% RH before the DSC measurements. The measurements were made as described earlier (Angberg et al., 1991), apart from the sample weight (3.1–3.9 mg) and the integration procedure. At least three measurements were made for each combination of storage humidity and storage time. The endothermic heat of dehydration values were given positive signs.

In the book published by Ford and Timmins (1989), it is stated that celluloses display a broad endotherm from 75 to 120 °C, corresponding to the loss of water. However, such an endotherm can influence the interpretation and/or integration of other thermal events in a mixture, e.g., the peak of dehydration for lactose. To allow comparison between the DSC data in this study and the data of anhydrous lactose alone (Angberg et al., 1991), a correction procedure was developed. The following steps were included:

(1) The heat of dehydration is measured in J/g (the DSC sample weight). The weight of water taken up during storage was subtracted from the original sample weight and the difference was used to recalculate the heat of dehydration.

(2) The heat of dehydration value was multiplied by two, as anhydrous lactose was only 50% of the sample.

(3) DSC samples consisting of MCC in one layer and lactose with a known amount of hydrate water in the next layer were prepared. The values of the ratios between the hydrate levels of the lactose alone and those obtained from the two-layer mixtures were plotted on a graph as a function of the heat of dehydration values obtained for the two-layer samples. A smooth curve was drawn in the graph. The values from step 2 were multiplied by factors obtained from this correction curve, in order to correct approximately for the MCC endotherm.

(4) A value of 4 J/g was added, as the batch used previously (Angberg et al., 1991) had a heat of dehydration of 15 J/g at the start of experimentation, compared to 11 J/g in this study.

Results and Discussion

The influence of MCC on the hydration rate in abundant water vapour

In the humidity chambers, the water vapour is in equilibrium with a saturated salt solution. Water vapour that is taken up by the powder mixture will quickly be compensated for by the solution, to regain the equilibrium, which means that all

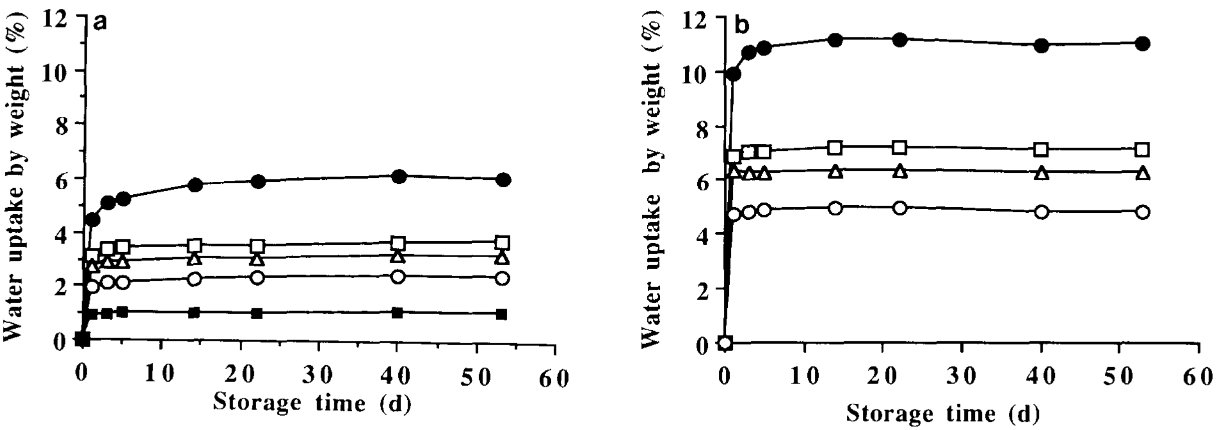

Fig. 1. Percentage water uptake by weight as a function of storage time for (a) 1.5 g of a mixture of MCC and anhydrous lactose at 58 (■), 75 (○), 81 (△), 84 (□) and 94 (●) % RH and (b) 1.0 g of MCC at 75 (○), 81 (△), 84 (□) and 94 (●) % RH.

processes take place in an abundant amount of water vapour. This is in contrast to tests performed in a limited amount of water vapour. The terms abundant and limited amounts of water vapour are from Carstensen (1988).

Water vapour uptake. In Fig. 1a, the water vapour uptake for the MCC/anhydrous lactose mixture is shown as a function of storage time. No change in weight was seen at 33% RH. At 58% RH, the lowest weight increase occurred, at 75–84% RH an intermediate group was formed, and at 94% RH the largest weight increase was seen. In Fig. 1b, the water vapour uptake for MCC alone after storage at 75–94% RH is shown. The percentage increase in weight for MCC alone is approximately double that of the mixture, which shows that most of the water uptake in the mixture is by MCC. For anhydrous lactose alone (Angberg et al., 1991), a saturated level was not reached within the investigation period of 22 days, as hydrate water continued to be incorporated. In this study, the weight of the mixture also continued to increase (Fig. 1a). However, this increase is not very obvious, as the MCC fraction absorbs a large quantity of water quickly, which hides the more subtle weight increase due to the water incorporation.

Microcalorimetry. In Fig. 2, examples of microcalorimetric heat flow curves for the mixtures are shown, as a function of the microcalorimetric measurement time. After 1 day of storage (Fig. 2a), the heat flow curves for the four highest humidities are close to each other, while powders stored at 58% RH have a low heat flow value. Samples stored for 14 days (Fig. 2b) show a lower heat flow level than after 1 day. With anhydrous lactose alone it was concluded that the exothermic heat flow signals monitored were a result of the incorporation of hydrate water (Angberg et al., 1991).

The heat flow levels were low with MCC alone, around 1 μW after 1 day of storage. The signal may have arisen from absorption of water vapour if the MCC was not yet fully saturated, as this is an exothermic process (Blair et al., 1990). As can be seen in Fig. 1b, the absorption of water occurs rapidly and is nearly completed after 1 day of storage, which explains the low microcalorimetric

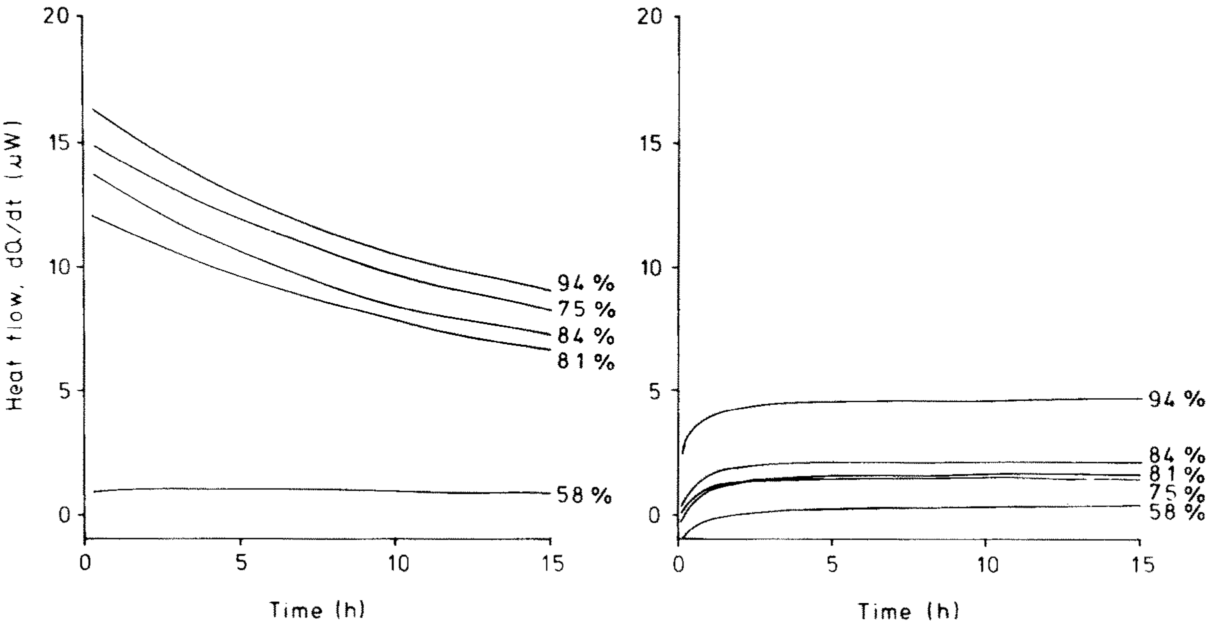

Fig. 2. Primary microcalorimetric heat flow-time curves for 1.5 g of a mixture of MCC and anhydrous lactose after storage at 58–94% RH after (a) 1 day (left) and (b) 14 days (right).

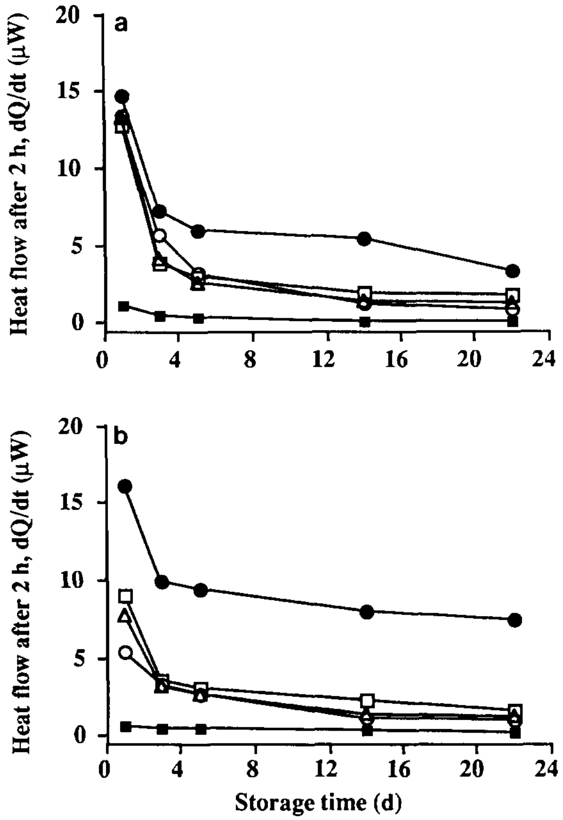

Fig. 3. Heat flow levels after 2 h as a function of storage time for (a) (above) 1.5 g of a mixture of MCC and anhydrous lactose and (b) (below) anhydrous lactose alone, where the values have been calculated as if the samples consisted of 0.75 g, at 58 (■), 75 (○), 81 (△), 84 (□) and 94 (●) % RH. The values in (b) were obtained from Angberg et al. (1991).

signals obtained. After longer storage times the heat flow curves were between zero and 0.5 μW. The measurements showed also that the different humidities were not separated in any special order for the various storage times.

In Fig. 3a, the heat flow levels after 2 h have been plotted as a function of storage time up to 22 days for the various humidities. The 2 h values are used to represent the heat flow curves and thus the incorporation rate. The heat flow values are mean values of five to seven measurements for 1, 3 and 5 days and two to three measurements for 14 and 22 days. As can be seen, the mean heat flow values after 1 day of storage are highest, and similar for the four highest humidities. The mean values at 75% RH are even higher than at 81 and 84% RH for the first 5 days. However, the mean values at 94% RH are higher than the middle group at 75–84% RH for the whole investigated period. For samples stored at 58% RH the heat flow values are very low. At 33% RH the values were approximately zero. The relative standard deviation (S%) ranges between 6 and 31% for 1, 3 and 5 days (33% RH excluded). The higher values are obtained partly because of the loss of water vapour during transfer from the humidity chamber to the sample vessel (Angberg et al., 1991).

To be able to compare the results obtained here with those from anhydrous lactose alone, the latter heat flow values have been normalized to the same weight of anhydrous lactose as in this study (0.75 g) and plotted in Fig. 3b. The appearances of the curves in Fig. 3b are explained by the fact that anhydrous lactose consists of both α- and β-lactose. It is only α-lactose that can incorporate water of hydration directly. β-Lactose cannot incorporate water, since it has a compact molecular structure and must mutarotate to α-lactose before water can be incorporated (Berlin et al., 1971). The result after 1 day of storage was explained by the fact that incorporation occurred mainly in the original α-lactose. The rate-limiting factor was here the relative humidity during storage. The incorporation proceeded then in α-lactose that had mutarotated from β-lactose. This mutarotation is also a rate-limiting factor, but it was only at the highest relative humidity investigated, 94%, that it became an extensive process, shown as a consistently high heat flow level (Angberg et al., 1991).

By comparing Fig. 3a and b, it is shown that the admixture of MCC influences the incorporation of hydrate water. This is especially noticeable after 1 day of storage. The heat flow levels for the mixture were lower at 94% RH and much higher at 75, 81 and 84% RH than for anhydrous lactose alone. This result was difficult to interpret directly, as it did not give a clear indication of whether the hydration rate was slower or faster.

Differential scanning calorimetry. DSC was used to clarify the microcalorimetric result by measuring the increase in hydrate content after

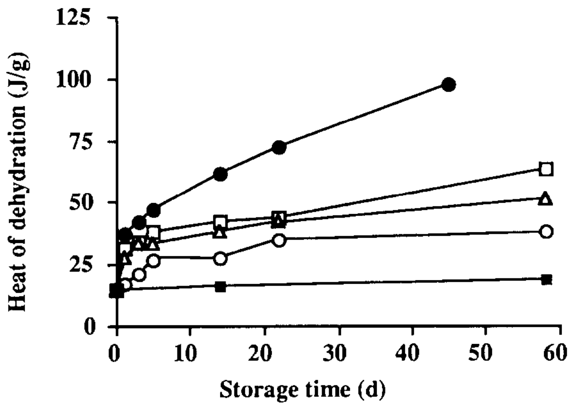

Fig. 4. Heat of dehydration (corrected) from DSC measurements for a mixture of MCC and anhydrous lactose as a function of storage time at 58 (■), 75 (○), 81 (△), 84 (□) and 94 (●) % RH.

storage. However, the desorption of water from the MCC during the measurements influenced the integration procedure, which also made the DSC results difficult to compare with those from anhydrous lactose alone. The appearance of the DSC scan and the changes due to the storage of lactose alone have been described by Angberg et al. (1991).

In Fig. 4, the endothermic heat of dehydration values are shown as a function of storage time in the humidity chamber. The DSC data demonstrate that an increase in both storage time and humidity results in an increased amount of hydrate water formed. Powders stored at 58% RH showed a small increase in the amount of hydrate water after 58 days of storage. The powders stored at 75, 81 and 84% RH form an intermediate group, but the values at 75% RH increase much more slowly at the beginning than those at 81 and 84% RH. The powders stored at 94% RH show the largest increase. Fig. 4 demonstrates that the hydration rates were not the same during the first day for the four highest relative humidities and that the rate of incorporation is slower than when anhydrous lactose alone was analysed after similar storage (Angberg et al., 1991). This means that the MCC protects the anhydrous lactose when water vapour is abundant. The MCC in the mixture rapidly absorbs a large quantity of water (Fig. 1a) but this water does not appear to be directly available for the incorporation process.

The somewhat exaggerated correction procedure was performed merely to certify that the heat of dehydration values in this study did not exceed those when anhydrous lactose was investigated alone. Other DSC parameters were also investigated to verify the protective effect of MCC. With anhydrous lactose alone, the incorporation process had almost reached completion after 76 days of storage at 94% RH, as a plateau of 181 J/g was formed for the heat of dehydration value (Angberg et al., 1991). For the MCC/anhydrous lactose mixture, a plateau had not been formed within 76 days of storage (Fig. 5), which indicates that the hydration rate must be slower. The heat of dehydration was only 148 J/g (corrected value) after 116 days. After such a long time in a high humidity, the samples gave DSC scans that were very much deformed in comparison to anhydrous lactose alone. However, the heat of dehydration peak was not as strongly influenced as the peaks corresponding to the melting of lactose.

The mutarotation of β- to α-lactose was shown earlier to be a rate-limiting factor for the incorporation of water of hydration (Angberg et al., 1991). If all of the original anhydrous α-lactose (26%) had been converted to the monohydrate,

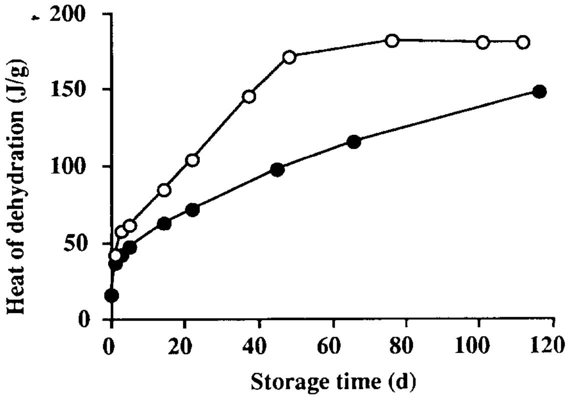

Fig. 5. Heat of dehydration (corrected) as a function of storage time at 94% RH for a mixture of MCC and anhydrous lactose (●) and heat of dehydration for anhydrous lactose alone (○). The data for anhydrous lactose alone were taken from Angberg et al. (1991).

this would have corresponded to a heat of dehydration of 47 J/g (0.26 × 181 J/g). That level is reached within 5 days at 94% RH, within 31 days at 84% and within 58 days for 81% RH, without carrying out step 4 in the correction procedure. As the heat of dehydration value exceeds that corresponding to the original amount of anhydrous α-lactose, it shows that mutarotation also proceeds in the mixture at humidities as low as 81% RH, but at a slower rate than for anhydrous lactose alone.

Explanation of the microcalorimetric result. The microcalorimeter produces a heat flow signal that is ideally proportional to the rate of the process of interest. As the heat flow was low when MCC alone was investigated, the heat flow for the mixture has been interpreted as originating from the incorporation process only. The first heat flow curves were obtained after 1 day of storage. This means that each heat flow signal in Fig. 3a (represented by the 2 h value) was a measure of the incorporation rate at that moment and that the level is influenced by what has happened to the sample during the 1 day storage time. This is equally true for the previous study with anhydrous lactose alone (Fig. 3b), but then the microcalorimetric heat flow curves gave a good reflection of the difference in incorporation rates for the various humidities. The reason that the first value was chosen after 1 day of storage in both studies and not earlier was to ensure proper equilibration time in the humidity chambers.

The microcalorimetric result can be seen as a measure of the distribution of the water vapour taken up within the mixture. If the water vapour is preferentially absorbed in the MCC fraction at the beginning of the storage period, there will be a delay before the water participates in another reaction, i.e., the incorporation process. After a while, when the MCC is nearly saturated, the incorporation process begins slowly in the original anhydrous α-lactose. The rate increases and eventually reaches a maximum. As the amount of original anhydrous α-lactose decreases, the incorporation rate also decreases. When most of the original anhydrous α-lactose has changed to the monohydrate, the incorporation proceeds into anhydrous α-lactose that has mutarotated from β-lactose.

The rate of the incorporation process can be thought of as a continuous microcalorimetric heat flow curve, where the appearance of the imagined curve must vary for the different humidities investigated. This means that after 1 day of storage, the processes had come to different points (or heat flow signals) on their respective curves. This resulted in the high and unexpected order for powders stored at 75, 81 and 84% RH (Fig. 3a), but also in similar values for the four highest humidities, depending on whether the incorporation rate was increasing, at its maximum or decreasing. After 14 days and longer the heat flow levels are in increasing order from 75 to 94% RH. Here, the rate-limiting mutarotation from β- to α-lactose determines the incorporation process, at least for powders stored at 94% RH, which show the strongest signals due to the extensive rate of mutarotation and subsequent incorporation. However, a slower hydration rate occurs for the mixtures stored at 94% RH, i.e. the heat flow levels are lower, than for anhydrous lactose alone (Fig. 3). The explanation for the slower rate also after longer storage times, when the MCC ought to be saturated, could be that the water is retained by the MCC and that extra water is not taken up to allow the mutarotation and subsequent incorporation to proceed as if the lactose was alone.

Influence of MCC on the hydration rate in a limited amount of water vapour

After storage in the humidity chamber, the powder was poured into the microcalorimetric sample vessel, which was closed immediately. The incorporation process occurs in a limited amount of water vapour, because the water consumed cannot be replaced from the surroundings as in the case of the humidity chambers.

As can be seen in Fig. 2a, the heat flow signals commence after 1 day of storage as strong signals that decrease as a function of measurement time in the microcalorimeter. After longer storage times, the heat flow signals start from below, increase slowly and generally stay on a plateau for several hours. The curves appear different from when only anhydrous lactose is monitored. In the latter case the signals always decreased for the four highest humidities investigated as water, one of the reactants, decreased (Angberg et al., 1991). However, the appearances of the heat flow curves for MCC alone showed similarities to the mixture, as they also started from below.

Approx. 37% of MCC is amorphous (Nakai et al., 1977). Amorphous powders that have absorbed water can act as a reservoir of water in a closed system and then promote water-solid interactions with other components through the vapour phase (Zografi et al., 1988). The appearance of the heat flow curves is related to the ability of MCC to redistribute the absorbed water. As anhydrous lactose consumes water by incorporation, the MCC fraction desorbs water vapour. The anhydrous lactose can therefore interact with water for a longer time, as shown in Fig. 6, where powder mixtures were monitored for 12 days in the microcalorimeter after storage for 1 day at 75 or 94% RH. The heat flow signals did not reach zero within this time, and the incorporation process seemed to continue for much longer, in contrast to the results for anhydrous lactose alone (Angberg et al., 1991).

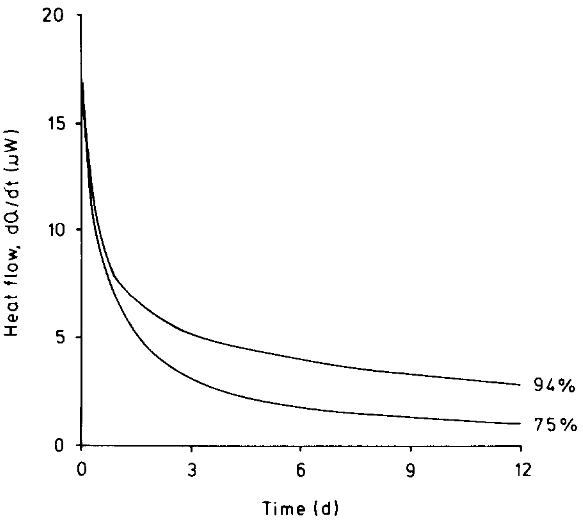

Fig. 6. Microcalorimetric heat flow-time curves for 1.5 g of a mixture of MCC and anhydrous lactose after storage for 1 day at 75 and 94% RH.

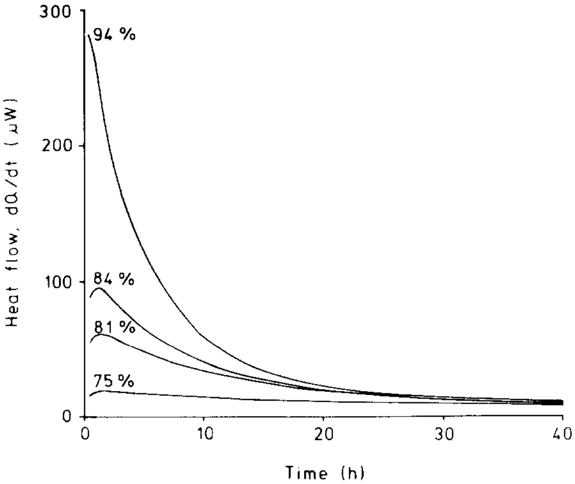

Fig. 7. Microcalorimetric heat flow-time curves for 0.75 g of MCC after storage for 1 day at 75, 81, 84 or 94% RH, when poured onto 0.75 g of untreated anhydrous lactose.

This ability to redistribute water can also be seen in another type of experiment (Fig. 7) where MCC samples were stored at high humidities. The MCC was then poured onto untreated anhydrous lactose, which was already in the calorimetric vessel. The heat flow signals obtained from the incorporation of water into anhydrous lactose reflect the relative humidity created by the MCC. The large size of the signals indicates that much of the incorporation process has passed during the 1 day storage time for the results presented in Fig. 3b. The signals decrease mainly as the amount of water decreases due to incorporation and the MCC loses its water resources, but also due to the fact that the amount of original anhydrous α-lactose decreases. When anhydrous lactose was replaced by α-lactose monohydrate very low heat flow signals were detected, below 12 μW after the MCC fraction had been stored for 1 day at 94% RH. These signals were probably the result of adsorption of water by the untreated α-lactose monohydrate.

Ahlneck and Zografi (1990) suggest that there are mainly two types of interaction between drug and excipient where water is involved. The last experiment (Fig. 7) demonstrates one type, where the water is redistributed through the vapour phase. The other type of interaction is seen in a system where the water located at the points of physical contact facilitates a reaction. This would only have caused low heat flow signals in the last experiment, because the MCC and the anhydrous lactose were separated into two layers.

Conclusions

This study has shown that MCC protects anhydrous lactose when water vapour is abundant by slowing down the rate of hydration, because the water taken up is preferentially absorbed by the MCC. Anhydrous lactose may in this case act as a model substance for drugs that react with water.

In a limited amount of water vapour, it has been shown that MCC redistributes its absorbed water through the vapour phase. The incorporation of water in anhydrous lactose progresses for a long time in a closed container in the presence of MCC.

Measurements with microcalorimetry can lead to erroneous interpretations, if it is not known how far a process has proceeded before the first measurement. This is due to the fact that the microcalorimetric technique gives a real-time measurement of the rate of the process at a particular moment. It is non-specific and therefore gives an overall picture of the rate of both physical and chemical processes in a sample. As the microcalorimetric technique is non-destructive, other analytical methods can be used on the same sample. Together they may give indications of how the process of interest has proceeded.

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