Research paper

Assessing the re-crystallization behaviour of amorphous lactose using the RH-perfusion cell

Inga-Lis Timmermann [a], Hartwig Steckel [a,*], Michael Trunk [b]

[a] *Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University Kiel, Kiel, Germany*
[b] *Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany*

Abstract

Many different reports have studied the crystallization behaviour of lactose, e.g., by exposing samples of amorphous lactose to different relative humidity at constant temperatures. However, only few reports are available investigating the formation of α-lactose monohydrate and β-lactose during re-crystallization.

Applying the static ampoule method in the microcalorimeter, the enthalpies of amorphous lactose were reported to be constantly 32 and 48 J/g, respectively, considering the mutarotation of lactose at 25 °C and 58% RH, 75% RH and 100% RH. In this study, an alternative microcalorimetric technique, the relative humidity-perfusion cell (RH-perfusion cell) was chosen. The RH-perfusion cell is able to deliver a constant and controlled flow of humidified air to the sample. Investigated compounds were purely amorphous lactose and different powder mixtures of lactose. They consisted of α-lactose monohydrate (Pharmatose 325M®), β-lactose (Pharmatose DCL21®) or a combination (1:1) thereof as carriers, and different concentrations of amorphous lactose. The determination of the enthalpy of desorption of the just re-crystallization lactose by the RH-perfusion cell was used to discriminate whether the monohydrate or the anhydrous form of lactose was produced. Differences in the re-crystallization behaviour of lactose at 25 °C and 58–100% RH were found. At 60–80% RH purely amorphous lactose showed a high heat of desorption which can be attributed to a very high content of formed β-lactose. Powder mixtures containing high contents of amorphous lactose (8% and 15%, respectively) blended with α-lactose monohydrate as a carrier resulted in similar results at the same RH ranges. The high amount of β-lactose can be due to the equilibrium anomeric composition. Whereas powder mixtures containing β-lactose as a carrier and amorphous lactose in a concentration of 1%, 8% and 15%, respectively, formed less β-lactose than the mixtures containing α-lactose monohydrate as a carrier. At a relative humidity of 90% none of the powder mixtures showed desorption as to the fact that in all cases only α-lactose monohydrate was formed at the surface of the re-crystallized lactose. Furthermore, mixtures of α-lactose monohydrate and β-lactose (1:1) and 8% amorphous lactose were investigated. An increase in formed α-lactose monohydrate by increasing RH was found. To consolidate the results, the same mixtures were re-crystallized at different RH in desiccators and subsequently investigated in the solution calorimeter. The results of the pre-mix were confirmed by the solution calorimeter. In summary, purely amorphous lactose and mixtures containing α-lactose monohydrate as a carrier show different re-crystallization behaviour compared to mixtures containing β-lactose as a carrier.
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Keywords: α-Lactose monohydrate; β-Lactose; Amorphous lactose; Microcalorimetry; Solution calorimeter; Perfusion cell

1. Introduction

α-Lactose monohydrate is a widely used carrier for dry powder inhalations. Inhalation grade lactose may consist of sieved and/or milled α-lactose monohydrate and is typically produced to a customer-tailored specification. Amorphous sites can be present on the surfaces of the raw material or even been generated during milling, micronization or blending processes [1]. These sites can result in different surface energies, different blending behaviour due to changes in their adhesion or segregation properties and, finally, can influence the fine particle fraction of a dry powder

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* Corresponding author. Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University Kiel, Gutenbergstraße 76, 24118 Kiel, Germany. Tel.: +49 431 880 1336; fax: +49 431 880 1352.
 E-mail address: steckel@pharmazie.uni-kiel.de (H. Steckel).

inhalation formulation [2]. Amorphous lactose is thermodynamically instable and as a result of its low ordered range the amorphous state is energetically higher than the solid crystalline states of α-lactose monohydrate or β-lactose [3]. Hence, the amorphous parts can re-crystallize during storage. There have been many different reports studying the re-crystallization behaviour of amorphous lactose while exposing the samples to different relative humidity by thermal analysis [4–8]. Using the static ampoule technique in the microcalorimeter, enthalpies of re-crystallization were stated to be 32 and 48 J/g, respectively, considering the mutarotation at 58% RH to 100% RH. In spite of different enthalpies of desorption of the re-crystallized lactose at different RH, the net area under the curve was found to be constant [9,10].

In order to verify these results, the RH-perfusion unit was utilized in this study. The RH-perfusion cell has the advantage of eliminating saturated salt solutions from the ampoule. Therefore, the endothermic process of evaporation of water or an exo- or endothermic heat flow due to the dissolution of the salt in the micro-hygrostat is avoided and does not influence the heat flow signal of the microcalorimeter. Lechuga-Ballesteros and Bakri [11] found out by investigating different sugars, e.g., sucrose, lactose and raffinose, in the RH-perfusion unit that sometimes the large exothermic peak of re-crystallization is followed by an endothermic peak which is even larger than the exothermic one. This large endotherm appears for substances re-crystallizing into anhydrates as the amount of the expelled water from the amorphous parts is large and the heat of desorption is high in order to equal the relative humidity in the steel ampoule. In comparison to the anhydrate form, hydrates do not show this endotherm, e.g., α-lactose monohydrate, raffinose-pentahydrate, as the adsorbed water is used for the formation of the hydrates. This current study considers the different desorption characteristics of the formed α-lactose monohydrate and the β-lactose, respectively. Different powder mixtures with varying amorphous contents were investigated by isothermal microcalorimetry. First, experiments were made by applying the static ampoule method, followed by experiments using the RH-perfusion cell and, finally, for consolidation of the results, the solution calorimeter was used. It was the aim of this study to determine the influence of factors such as the relative humidity, the amount of amorphous lactose and the presence of α-lactose monohydrate or β-lactose as nucleates on the re-crystallization behaviour of amorphous lactose.

2. Materials and methods

2.1. Materials

For preparation of the powder mixtures, α-lactose monohydrate (Pharmatose 325 M®, Lot No. 19980407-196) and β-lactose (Pharmatose DCL21®, Lot No. 10124925, both from DMV International, The Netherlands) were used as carriers. Amorphous lactose was

gained by spray-drying (Batch Nos. 310103_sp; 110803_sp). The following salts (NaBr, BaCl$_2$, MgCl$_2$ and NaCl) were received from Merck KGaA in standard analytical quality (Darmstadt, Germany) and used as saturated aqueous solutions in glass ampoules or in desiccators to adjust a given relative humidity (RH) of 33%, 58%, 75% and 90%, respectively, at 25 °C. Furthermore, NaCl, Tris, and HCl 36% in analytical grade (both Merck KGaA Darmstadt, Germany) were used for calibration of the solution calorimeter. Water was used in double-distilled quality and in the static ampoule experiments to give a relative humidity of 100%.

2.2. Methods

2.2.1. Preparation of the amorphous lactose

The amorphous lactose was prepared by spray-drying a 15% (w/w) aqueous solution of α-lactose monohydrate in a Büchi 190 mini spray-dryer (Büchi Labortechnik, Flawil, Switzerland). Due to the fact that variability of the spray-drying parameters can result in different re-crystallization behaviour [12], a standard protocol was applied with drying conditions of 145 °C inlet temperature, 80 °C outlet temperature and dial settings of 11 and 10 for the air flow rate and the heating rate, respectively. The atomizer flow rate was set to 500 Normlitres/h. The dried material was collected and immediately desiccated over silica gel. PXRD was used as an additional tool to verify amorphicity of the powders; the X-ray patterns at 5–45 2θ were featureless and only showed the typical amorphous halo (data not shown).

2.2.2. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (PXRD) patterns were collected in transmission using an X-ray diffractometer with a rotating anode (Stoe and Cie GmbH, Darmstadt, Germany) with Cu-Kα1 radiation (monochromator: graphite) generated at 200 mA and 40 kV. Powder was packed into a rotating sample holder between two films (PETP).

2.2.3. Preparation of powder mixtures

Powder mixtures were prepared by blending (Typ Turbula, Willy A. Bachofen Maschinenfabrik, Swizerland) according to a standardized protocol in a sealed container and at dry conditions (RH ≤55%, 25 °C). The mixtures consisted of different ratios of crystalline and amorphous lactose (Table 1). The amorphous content varied from 1 to 20% (w/w). The powder mixtures investigated by the static ampoule method consisted of α-lactose monohydrate and amorphous lactose (Batch No. 110803_sp) at a concentration of 4.5%, 13% and 20% (w/w), respectively. Powder mixtures investigated in the RH-perfusion contained α-lactose monohydrate or β-lactose as carriers (Table 1). The amorphous content varied for both sets between 1%, 8% and 15% (w/w). Furthermore, a pre-mix was prepared by blending both carriers (1:1) in advance. This pre-mix was blended with 8% of amorphous lactose. In total, seven

Table 1
Composition of powder mixtures examined in the static ampoule, in the RH-perfusion cell and in the solution calorimeter, respectively

Isothermal method	Mix	Amorphous content (% w/w)	Carrier	Mass of amorphous lactose (mg)	Sample weight (mg)
Static ampoule	A	13	α-Lactose monohydrate	16	123
Static ampoule	A II	13	α-Lactose monohydrate	48	370
Static ampoule	B	20	α-Lactose monohydrate	16	360
Static ampoule	C	4.5	α-Lactose monohydrate	16	80
Static ampoule	D	100	–	48	48
RH-perfusion	100%	100	–	48	48
RH-perfusion	1%	1	α-Lactose monohydrate	2.1	210
RH-perfusion cell/solution cal.	8%	8	α-Lactose monohydrate	16.8	210
RH-perfusion cell/solution cal.	15%	15	α-Lactose monohydrate	31.5	210
RH-perfusion	1%	1	β-Lactose	2.1	210
RH-perfusion cell/solution cal.	8%	8	β-Lactose	16.8	210
RH-perfusion cell/solution cal.	15%	15	β-Lactose	31.5	210
RH-perfusion cell/solution cal.	Pre-mix	8	α-Lactose monohydrate β-lactose (1:1)	16.8	210

powder mixtures were analyzed in the RH-perfusion cell. Some of these powder mixtures were also investigated by solution calorimetry (Table 1). Two grams of each mixture with an amorphous content of 8% and 15% was conditioned by storing them at a relative humidity of 58% RH, 75% RH and 90% RH, respectively, and at ambient temperature.

2.2.4. Isothermal microcalorimetry using the static ampoule

For isothermal microcalorimetry, the Thermal Activity Monitor TAM 2277 (Thermometric AB, Järfälla, Sweden) was utilized. To determine the heat of re-crystallization, the static ampoule method was applied as formerly described by Angberg et al. [13,14]. For the experiments 3 ml glass ampoules and implemented micro-hygrostats of saturated NaBr and NaCl, respectively, or double-distilled water for adjusting 58% RH, 75% RH or 100% RH were used. Table 1 shows the powder mixtures and their concentrations of amorphous lactose. It also lists the different masses of each investigated mixture. All samples were accurately weighed into the 3 ml glass ampoules. To keep the equilibrium time as short as possible, saturated salt solutions, micro-hygrostatics, vials and caps were stored at a temperature of 25 °C; therefore, the equilibrium time could be shortened to 10 min. The TAM was equipped with the Digitam 4.1 Software (Thermometric AB, Järfalla, Sweden); calculations were carried out by the software origin Pro 7 G® (OriginLab Cooperation, Northampton, USA).

2.2.5. Isothermal microcalorimetry using the RH-perfusion cell

To determine the heat of desorption, a relative humidity (RH-) perfusion cell, type 2269 (Thermometric AB, Järfalla, Sweden), was utilized. The cell consisted of a 20-ml steel ampoule that had been connected to a flow pipe of Nitrogen (5.0, Messer Griesheim GmbH, Germany). A flow-switch-valve adjusts the programmed relative humidity by mixing dry (0% RH) and the saturated (100% RH) Nitro-

gen flow. The RH-perfusion cell was used in a step-mode in contrast to the method described by Lechuga-Ballesteros and Bakri [11] and Lechuga-Ballesteros [15]. The amount of the investigated mixtures was 210 and 48 mg for purely amorphous lactose, respectively (Table 1). All samples were accurately weighed into the steel ampoule, followed by a drying step for 240 min at which the chosen RH was set to 0%. Subsequently the relative humidity was set to 60%, 75%, 80% and 90%, respectively. To calculate the heat of desorption (J/g) at the given RH (%), the endotherm heat flow, following the re-crystallizing exotherm, was subtracted from the baseline. This generated area under the curve was integrated (see Fig. 1, hatched area) and normalized to weight, thus, comparison between the different mixtures was possible. The RH-perfusion cell was calibrated by using a micro-hygrostat filled with a saturated sodium chloride solution. At a programmed RH of 75% the measured heat flow was equal to the baseline. These experiments were repeated for the programmed RH of 60% and 90%, respectively.
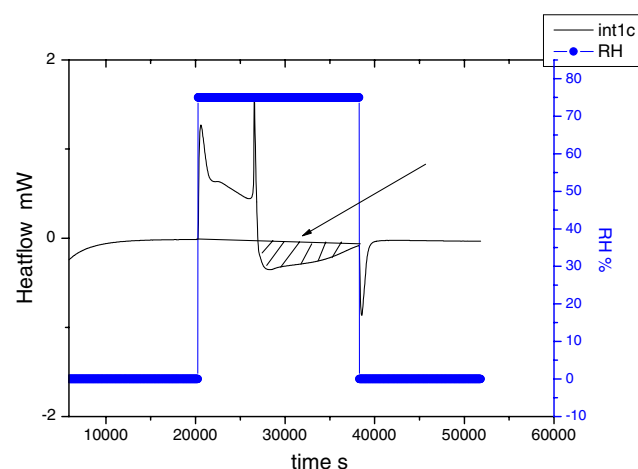

Fig. 1. Exemplary heat flow curve of re-crystallized lactose in the RH-perfusion cell. The hatched area is correlated to the enthalpy of desorption. The RH was adjusted to 0%, subsequently 75% and finalized at 0%.

2.2.6. Solution calorimetry

The enthalpy of solution was measured by a solution calorimeter (type 2225, Thermometric AB, Järfalla, Sweden) in the isothermal microcalorimeter. Samples of the above-mentioned powder mixtures were chosen for experiments (Table 1). The powder mixtures contained 8% and 15% amorphous lactose, respectively, and α-lactose monohydrate or β-lactose as a carrier, just as the pre-mix containing 8% amorphous lactose. The amorphous content was re-crystallized in desiccators at various RH (58%, 75% and 90%, respectively). In order to reduce the amount of adsorbed water after re-crystallization, all 15 samples were stored at 20 °C/<10% for a period of 48 h. Approximately 50 mg of each sample was weighed into a breakable glass ampoule, closed with a rubber stopper and dried for further 24 h, before the glass ampoule was accurately re-weighed and hermetically sealed with wax. The solvent was 100 ml of double-distilled water in the glass reaction vessel. At heat signals with fluctuations lower than 10 μK the experiment was started. A calibration by an electrical impulse was conducted before and after the break of the glass ampoule. The calibration was performed in order to adjust the signal to the environment. Furthermore, experiments with empty sealed glass ampoules, glass ampoules filled with NaCl (double-distilled water as the solvent) and Tris (0.1 M HCl as the solvent) were carried out for calibration. The heat of solution (J/g) calculated by the Solution Calorimeter System®-Software was normalized to weight by the mass of each dried sample. The results are the calculated mean of four determinations. Enthalpies of solution were determined for Pharmatose 325M® and Pharmatose DCL21®. Pharmatose 325M® had an enthalpy of solution of 55.3 J/g (±3.8%) which is well in accordance with the result described by Hogan and Buckton [16] who measured 56.2 J/g. Due to the fact that Pharmatose DCL21® does not completely consist of β-lactose [17], but also contains small amounts of α-lactose monohydrate, the investigated Pharmatose DCL21® had an enthalpy of solution of 11.0 J/g (±10.8%).

3. Results and discussion

3.1. Static ampoule calorimetry

Microcalorimetric measurements using the static ampoule method resulted in a heat of re-crystallization of 41 J/g for purely amorphous lactose regardless of the experimental RH in the ampoule used for re-crystallization (Table 2, Mix D). These results comply with those formerly described by Darcy and Buckton [2]. The curves of the heat flow vs. time do not differ between purely amorphous lactose and the powder blends apart from Mix B at 58% RH (data not shown). The mix contains 20% amorphous lactose. The shape of the heat flow curve is identical to that of the heat flow curve formerly described by Gustaffson et al. [6] for a 4% blend at the same RH. Analysing the heat of re-crys-

Table 2
Enthalpies of re-crystallization (J/g) of powder mixtures re-crystallized by the static ampoule technique at different RH (%)

Mix	ΔH 58% RH (J/g)	ΔH 75% RH (J/g)	ΔH 100% RH (J/g)
A	31.6	36.8	40.5
	(±6.3%)	(±1.9%)	(±1.2%)
A II	36.7	36.2	38.3
	(±3.0%)	(±1.2%)	(±2.6%)
B	30.9	31.4	28.3
	(±2.7%)	(±2.0%)	(±2.9%)
C	29.6	30.2	34.5
	(±2.0%)	(±1.7%)	(±1.9%)
D	41.4	40.9	40.6
	(±3.1%)	(±2.2%)	(±2.8%)

tallization of the powder blends, they varied between 30 and 40 J/g at different RH and with different amorphous content (Table 2 Mixes A, A II, B and C). In summary, the heat of re-crystallization is lower than the heat of re-crystallization for purely amorphous lactose. However, the heat of re-crystallization values are above the stated 32 J/g [10] and below 48 J/g [9] and do not follow any tendency to correlate. As the calculated enthalpies are a sum of many simultaneously occurring endo- and exothermic processes, any conclusion on the re-crystallization behaviour of amorphous lactose and lactose in powder blends should be carefully drawn.
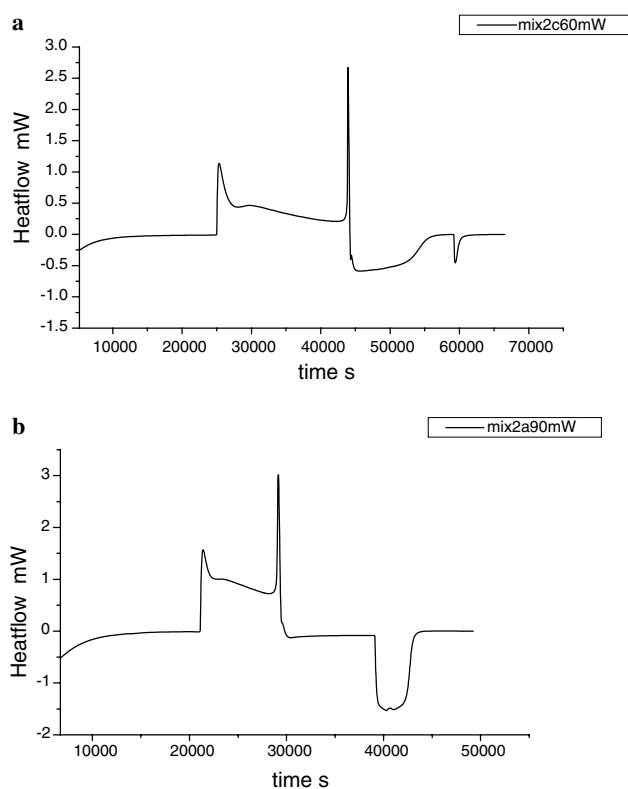

Fig. 2. Heat flow (mW) of 15% amorphous lactose and α-lactose monohydrate as carrier at 60% RH (a) and at 90% RH in the step-mode RH-perfusion cell (RH% not shown).
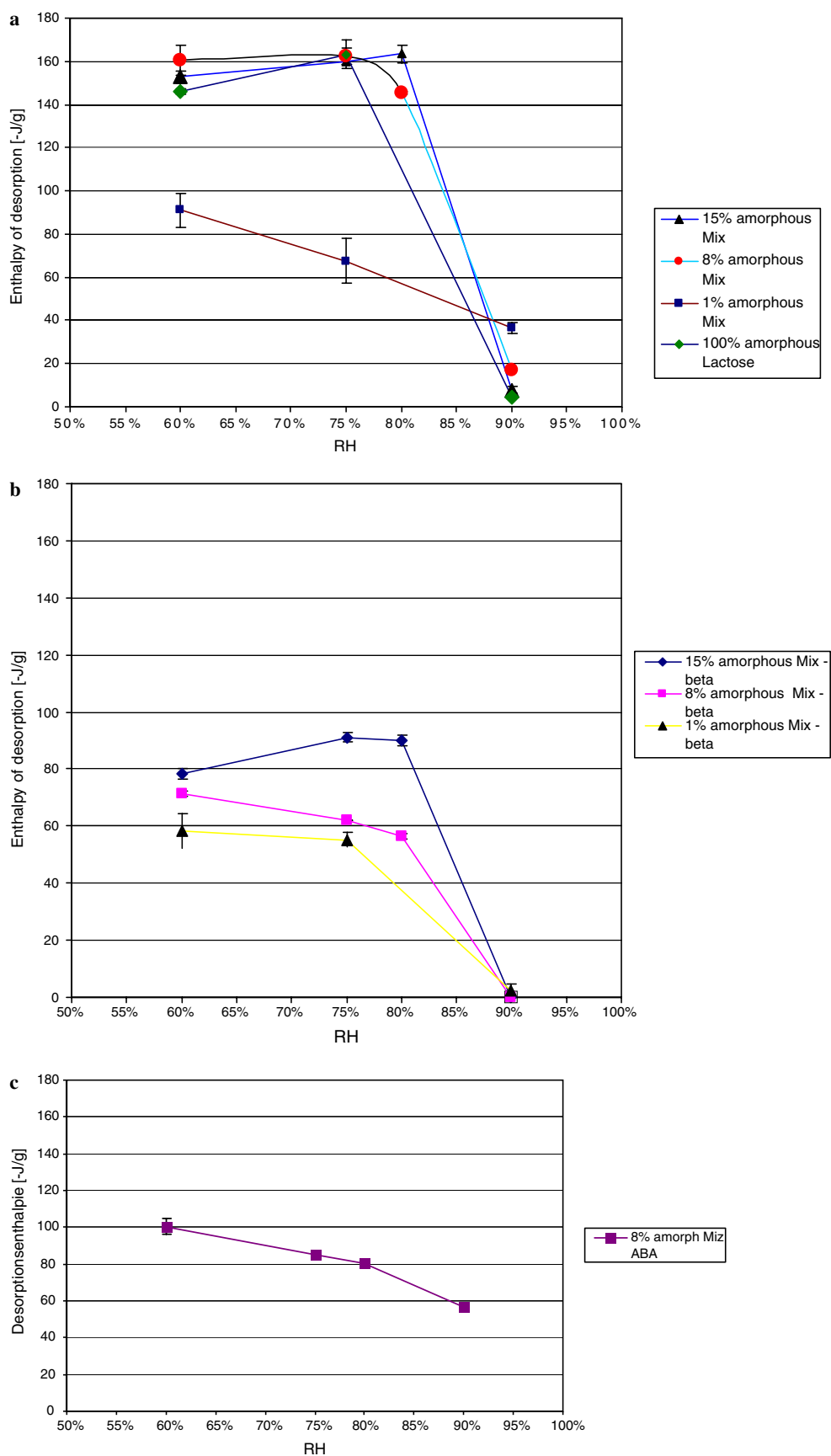
Fig. 3. Enthalpy of desorption (J/g) at different RH (%) for (a) the mixtures of amorphous lactose and α-lactose monohydrate and 100% amorphous lactose; (b) the mixtures of amorphous lactose and β-lactose; and (c) for the mixtures containing 8% amorphous lactose and the α-/β-pre-mixture.

3.2. RH-perfusion cell

The main part of this work was the experimental determination of the heat of desorption of various powder blends in the RH-perfusion cell. All samples were dried over a period of 240 min by the dry nitrogen flow (RH 0%) (Fig. 1). The drying time was considered attentively and controlled by the heat flow signal. The signal always reached the baseline before the drying step was completed. Therefore, the amount of adsorbed water at the surface of the sample was assumed to be negligible. Figs. 2a and b show exemplarily the results of the powder blends of 15% amorphous lactose and α-lactose monohydrate, re-crystallized at 60% RH and 90% RH, respectively, to display the different endothermic heat flows related to the desorption. At 90% RH (Fig. 2b), following the exothermic peak of re-crystallization, no desorption endotherm is visible for the powder blend. The sharp endothermic peak after the re-crystallization is the change from 90% RH to 0% RH at the end of the experiment. It represents the desorption of the complete sample.

Plotting the results of the heat of desorption (J/g) vs. the investigated RH [%] a different re-crystallization behaviour can be for the analysed powder mixtures. Powder mixtures containing α-lactose monohydrate as a carrier and amorphous contents of 8% and 15%, respectively, and even purely amorphous lactose show heats of desorption between 160 J/g ($\pm$6.7 J/g) and 152 J/g ($\pm$3.0 J/g) at 60% RH, and 145 J/g ($\pm$0.8 J/g) to 162 J/g ($\pm$3.9 J/g) at 75% RH to 80% RH (Fig. 3a). These heats of desorption can be related to a very high content of β-lactose. Powder mixtures containing α-lactose monohydrate and 1% amorphous lactose re-crystallize into a similar proportion of α-lactose monohydrate to β-lactose, showing a lower heat of desorption 91 J/g ($\pm$7.8 J/g) at 60% RH and 68 J/g ($\pm$10.6 J/g) at 75% RH. At a RH of 90% the heat of desorption decreases with an increase of the freshly re-crystallized amount of lactose. All physical powder mixtures and the purely amorphous lactose show nearly no desorption as to the fact that only α-lactose monohydrate has been formed at the surfaces of the powder mixtures. These results are in accordance with the findings of Steckel and Bolzen [18] who analysed the re-crystallization behaviour of amorphous lactose by differential scanning calorimetry and concluded that at 100% RH amorphous lactose always re-crystallizes to the monohydrate form. The results of the RH-perfusion cell demonstrate that already a RH of 90% is sufficient for a re-crystallization into the monohydrate. Yu et al. [19] describe that spray-dried amorphous lactose re-crystallizes at normal climatic conditions (25 °C/60% RH) into a proportion of 71% of β-lactose to 29% of α-lactose monohydrate measured by gas-chromatography. The experiments of purely amorphous lactose and blends of 8% and 15% amorphous lactose seem to re-crystallize into the proportion of the mutarotation at 60–80% RH. The re-crystallization

behaviour of amorphous lactose differs from the crystallization behaviour of the solution at temperatures <93 °C, at which only α-lactose monohydrate is formed. At a low amorphous content ($\leqslant$1%), it seems as if the carrier, in this case α-lactose monohydrate, can act as a nucleate and the proportion turns to a higher formation of α-lactose monohydrate than in the higher concentrated mixtures.

Powder mixtures containing β-lactose as a carrier show heats of desorption between 72 J/g ($\pm$1.0 J/g) and 55 J/g ($\pm$2.7 J/g) at 60–80% RH (Fig. 3b). Mixtures with a high amount (15%) of amorphous lactose display heats of desorption of 91 J/g ($\pm$1.8 J/g). None of these mixtures shows desorption at 90% RH. The mixtures com-
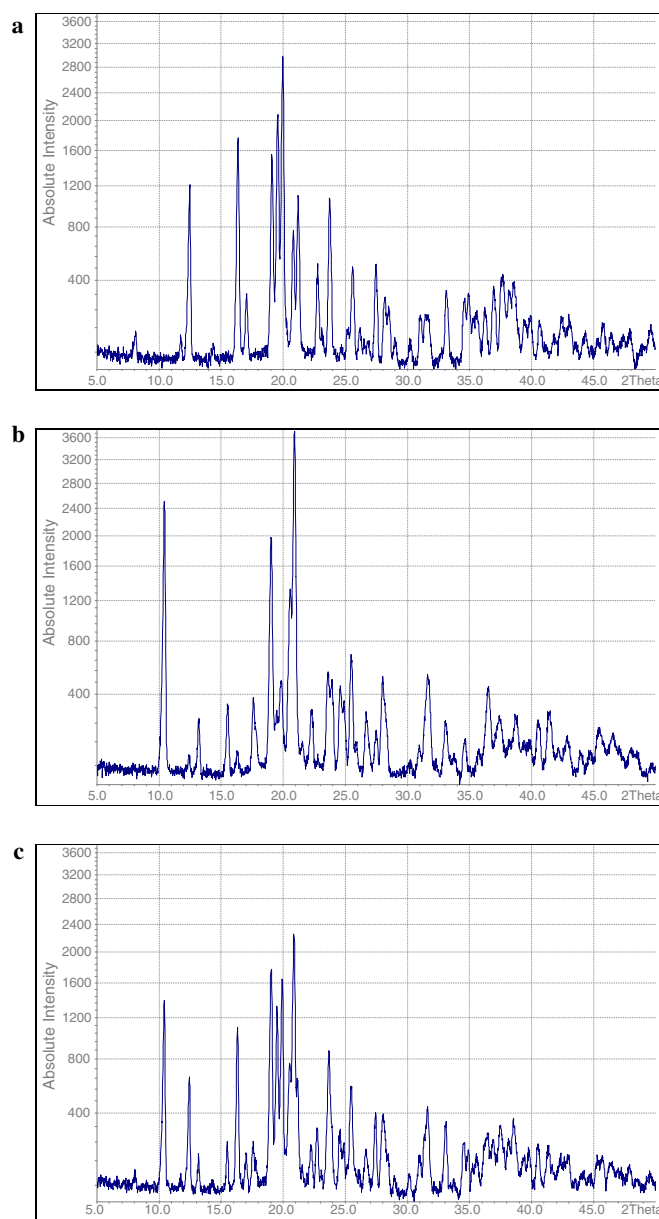

Fig. 4. Powder X-ray patterns of (a) α-lactose monohydrate, (b) β-lactose and (c) re-crystallized amorphous lactose at 60% RH in the RH-perfusion cell.

pletely re-crystallize into the monohydrate. Comparing the two different sets of mixtures, the carrier β-lactose demonstrates lower heats of desorption at 60–80% RH than the mixtures blended with α-lactose monohydrate. This is remarkable because amorphous lactose with β-lactose as a nucleate does not re-crystallize into β-lactose or the equilibrium anomeric composition as expected, but into α-lactose monohydrate. Moreover, it re-crystallizes to an even higher extent to α-lactose monohydrate than the α-lactose monohydrate blends. Raghavan et al. [20] have published data which can help to explain these findings: their data show that a high β-lactose content in a crystallizing lactose solution leads to the crystallization of α-lactose monohydrate in the shape of a tomahawk. They confirm that this shape arises from growth inhibition due to the incorporation of β-lactose and β-lactose restricts under these conditions the new formation of the β-isomer. In this study, the present β-lactose also led to a higher amount of α-lactose monohydrate.

Fig. 3c shows the mixture of 8% amorphous lactose and the α-/β-mixture. At 60–80% RH the heats of desorption show values between 100 J/g (±4.5 J/g) and 80.7 J/g (±0.4 J/g). These results are in between those of the former mixtures, demonstrating an increase in formed α-lactose monohydrate with increasing RH. At 90% RH there is still a considerable amount of formed β-lactose 57 J/g (±0.7 J/g).

These findings could be confirmed by collecting the powder X-ray diffraction patterns of the re-crystallized samples (Fig. 4). Fig. 4 shows exemplarily the diffraction patterns of α-lactose monohydrate, β-lactose and re-crystallized amorphous lactose at 60% RH. The measured X-ray patterns of the re-crystallized sample clearly indicate the formation of β-lactose (Fig. 4c) when compared to the standards of α-lactose monohydrate and β-lactose (Figs. 4a and b, respectively).

3.3. Solution calorimetry

Furthermore, the above-investigated powder mixtures were re-crystallized at various RH and subsequently dried before they were analysed by solution calorimetry. Results are shown in Fig. 5. The heat of solution, ΔH_s, of mixtures with α-lactose monohydrate as a carrier increased from 49 to 52 J/g for the 15% re-crystallized lactose and ΔH_s: 51–53 J/g for 8% re-crystallized lactose at 58–90% RH, respectively. Differences between the investigated RH are not significant ($p = 0.05$). Nevertheless, mixtures with α-lactose monohydrate as a carrier and re-crystallized contents exhibit lower enthalpies of solution than the pure monohydrate (ΔH_s: 55.3 J/g) at all investigated RH. The lower enthalpies of solution can be referred to an amount of formed β-lactose that was formed during the re-crystallization at the different RH.
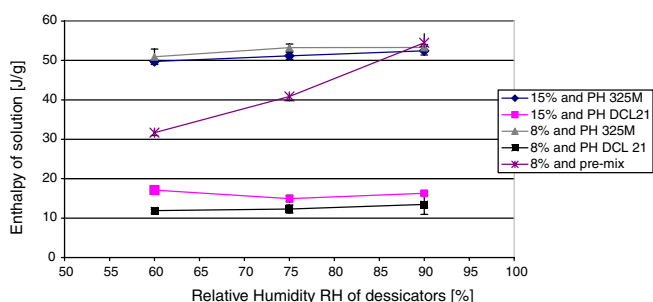

Fig. 5. Enthalpies of solution (J/g) of different powder mixtures after re-crystallization at different RH (%) as determined in the solution calorimeter.
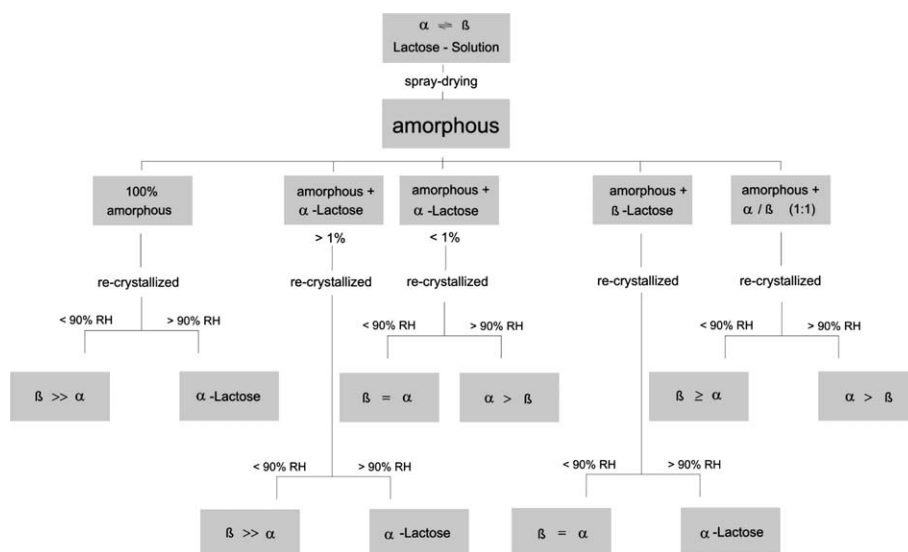

Fig. 6. Summary of the re-crystallization behaviour of amorphous lactose at varying RH and with varying carriers derived from the enthalpies of desorption.

Re-crystallized powder mixtures with β-lactose as a carrier show lower enthalpies of solution than mixtures with α-lactose monohydrate as a carrier, due to the higher solubility of β-lactose in water. This was confirmed in pre-tests in which Pharmatose DCL21® (β-lactose) exhibited a heat of solution of 11.0 J/g. The 8% mixture exposes heats of solution from ΔH_s: 11.9–13.4 J/g at a re-crystallization humidity of 58%, 75% and 90% RH, respectively. In addition, the 15% mixture exhibits heats of solution from ΔH_s: 17.1–16.3 J/g for 58–90% RH. Parts of the amorphous content re-crystallized into α-lactose monohydrate during storage. These α-lactose monohydrate crystals lead to higher enthalpies of solution than Pharmatose DCL21®. These findings support the observations during the re-crystallization in the RH-perfusion cell. A change in the re-crystallization behaviour could not be correlated to the difference in relative humidity ($p = 0.05$). The results of 8% amorphous lactose blended with both carriers in the ratio 1:1 (pre-mix) show a significant increase ($p = 0.05$) from ΔH_s: 32–55 J/g with an increase in the RH from 58% RH to 90% RH, due to the increase of formed α-lactose monohydrate.

4. Conclusions

The present study used a new method to characterize the re-crystallization behaviour of amorphous lactose at varying RH by determining the enthalpies of desorption after re-crystallization of the amorphous parts. All results are summarized schematically in Fig. 6. The figure exhibits that 100% amorphous lactose and mixtures blended with α-lactose monohydrate as a carrier show similar re-crystallization behaviour as long as the amorphous content is ⩾1%. At 60–80% RH the amorphous lactose re-crystallizes in a high proportion to β-lactose, probably in the proportion of the anomeric equilibrium, whereas at 90% RH, a high amount of α-lactose monohydrate is determined. In contrast, mixtures consisting of β-lactose as a carrier show a higher amount of formed α-lactose monohydrate than the mixtures consisting of α-lactose monohydrate as a carrier. In conclusion, the relative humidity, the amount of amorphous lactose and the presence of an excess of α-lactose monohydrate or β-lactose influence the re-crystallization behaviour of amorphous lactose. Re-crystallization at RH higher than 90% RH would be the optimum to achieve α-lactose monohydrate at the surfaces, only. This is an important finding because lactose is often conditioned at elevated relative humidity to re-crystallize process-induced changes in the crystallinity (see Fig. 6).

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