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The physical modification of lactose and its thermoanalytical identification

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Abstract

Using DSC, at least 6 different types of lactose may be distinguished. In addition to the known α- and β-modifications, there are different dehydrated forms. Rapid dehydration yields the probably partly amorphous α_H-type which can reversibly sorb water from the vapour phase. Amorphous lactose can be detected by its characteristic recrystallization peak. Due to the mutarotational state of lyophilized lactose solutions, powders of amorphous lactose with different glass transition temperatures and different recrystallization behaviour may be produced.

LIST OF SYMBOLS

$\vartheta_{P,fus}$	melting, peak temperature
$\vartheta_{on,fus}$	melting, onset temperature
$\vartheta_{P,hyd}$	dehydration, peak temperature
$\vartheta_{on,hyd}$	dehydration, onset temperature
$\Delta_{fus}H$	enthalpy of melting
$\Delta_{hyd}H$	enthalpy of dehydration
RH	relative humidity
β	heating rate
τ	mutarotation time
ϕ	heat flux
$\dot{m}$	mass flux

INTRODUCTION

Lactose (4-*O*-β-D-galactopyranosyl-D-glucose, milk sugar) is one of the main components of cow milk with an average content of 4.8%. The separation of fat and protein from milk yields whey. In the production of lactose, whey is concentrated to 55–60% dry weight and crystallized. By repeated crystallization, purity grades of $\geqslant$99.5% lactose (refined food quality) and $\geqslant$99.8% (pharmaceutical quality) are produced. The main use of lactose in industrial pharmacy is as a filler in tablets and capsules. For direct compressing of tablets, lactose must have a good flowability, proper compressibility and suitable binding properties. From empirical investigations, it is known that lactose samples produced from different industrial processes show distinct powder properties. Presumably this is due to amorphous solidification and partial dehydration of lactose.

EXPERIMENTAL

Thermal analysis

All DSC experiments were carried out using a Mettler TA 4000 system equipped with a DSC-30 cell. Evaluation of the measured curves was made on a micro-computer with a Mettler Graphware TA72.5. (Negative (downward) peaks are endothermic effects, corresponding to ICTA convention.) Powder samples of 3–5 mg were weighed in aluminium crucibles of 40 μl volume. Crystalline samples were scanned in crimped crucibles, and amorphous and partly amorphous samples were analysed in hermetically sealed crucibles. Because of their high hygroscopicity, samples of amorphous and partly amorphous lactose were handled under dry nitrogen. In this work a Ganuk PMMA-glove-box was used. The relative humidity of the N_2 atmosphere was below 8%. TG measurements were made on a Sartorius microbalance M25 D-V. About 50 μg of the samples were weighed into quartz pans and scanned with a heating rate of 0.5 K min^{-1}.

MATERIALS

α-Lactose-monohydrate with a purity of $\geqslant$99.8% (EP D30) was purchased from Meggle, Germany. All other types of lactose described here were prepared by physicochemical treatment of this monohydrate. Pure β-lactose was prepared by crystallization from methanol [1]. Stable α_S-lactose and hygroscopic α_H-lactose were made by dehydration of the α-monohydrate [2]. α_H-Lactose was prepared by vacuum drying for 2.5 h at 120°C.

Amorphous lactose was prepared by lyophilization of aqueous solutions containing 5% lactose by weight. Because of mutarotation of these solutions, the age τ of the solutions was kept constant where τ is the period between dissolution and shock freezing of the solution. Solutions made from α- and β-lactose were lyophilized with $\tau \leqslant 6$ min and $\leqslant 5$ min respectively, and one solution was made from α-lactose with $\tau = 46$ h.

RESULTS

Crystalline samples

Figure 1 shows the DSC curves of different de-hydrates, the non-hydrated β-lactose and the commercially available α-lactose monohydrate. The α- and β-modifications can be distinguished by their different melting points. Tables 1 and 2 give the thermoanalytical data of both modifications.

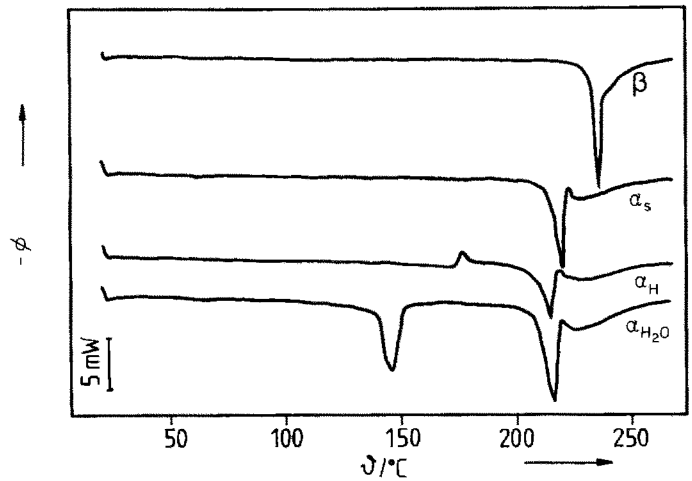

Fig. 1. DSC curves of different lactose types recorded at 5 K min^{-1}. The α- and β-modifications are distinguished by their melting points above 200°C. The dehydrated types α_H and α_S have no water desorption peak at 150°C (water of crystallization).

TABLE 1

Thermodynamic data of α-lactose monohydrate, measured with a heating rate of 5 K min^{-1}

$\vartheta_{P,hyd}$/°C	$\Delta_{hyd}H/(kJ\ g^{-1})$	$\vartheta_{P,fus}$/°C	$\Delta_{fus}H/(J\ g^{-1})$	Ref.
143.6	2.10	210.1	80.6	4
145.2	2.7 ± 0.2	215.9	141.8	This work
–	2.86 ± 0.16	223.0	150.4	3

Key: see list of symbols.

TABLE 2

Thermodynamic data of β-lactose, measured with a heating rate of 5 K min^{-1}

$\vartheta_{on,fus}$/°C	$\vartheta_{P,fus}$/°C	$\Delta_{fus}H/(J\ g^{-1})$	Ref.
220	232	203.6 ± 5.4	3
219.7 ± 0.8	230.2 ± 0.8	–	This work

Key: see list of symbols.

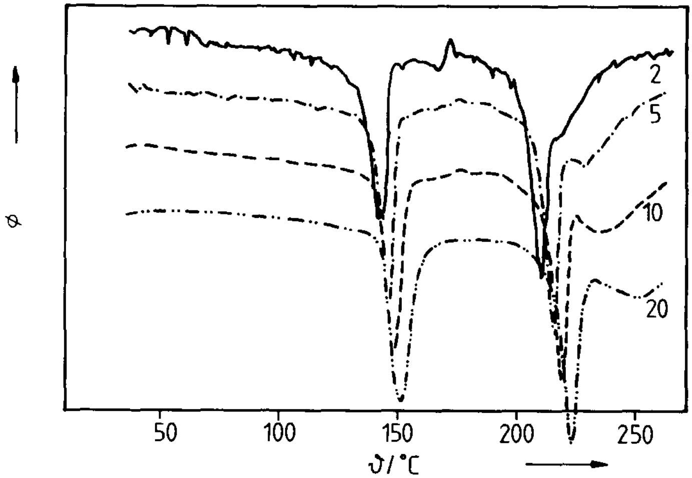

Fig. 2. DSC curves of α-monohydrate at different heating rates (2, 5, 10, 20 K min^{-1}).

The values of Berlin et al. [3] were confirmed in most cases. Although due to the simultaneous melting and decomposition, a reliable determination of the melting enthalpy of β-lactose does not seem posible. Figure 1 shows the characteristic heat flow rate curve of α_H-lactose. As with α_S-lactose, there is no dehydration signal but there is an exothermic peak near 170°C which presumably represents recrystallization of lattice distortions. Thus α_H-lactose, in contrast to α_S-lactose, is partly amorphous due to the preceding dehydration process. X-ray investigations of α_H-lactose samples will clarify this.

Figure 2 compares the DSC curves of α-lactose monohydrate recorded at different heating rates, and Table 3 compares the related onset temperatures of dehydration and melting. A linear correlation between temperature and heating rates does not seem to exist, and a direct extrapolation to $\beta = 0$ [5] is not possible.

Figure 2 shows that heating rates of 10 or 20 K min^{-1} are possible for process control, although a slight baseline-drift at 170°C, possibly related to

TABLE 3

Influence of heatng rate β on measured temperatures of dehydration and melting

β	$\vartheta_{\mathrm{on,hyd}}$/°C	$\vartheta_{\mathrm{on,fus}}$/°C
2	131.3	202.0
5	136.9	207.7
10	139.8	211.2
20	141.4	213.3

Key: see list of symbols.

recrystallization of trace amounts, can be seen at low heating rates only. For precise results, measurements at different heating rates are recommended.

Partly crystalline samples

Vacuum dehydration of lactose monohydrate yields a hygroscopic form, called α_H-lactose. Depending on the preparation technique used in the literature, unstable forms of lactose have been termed α_i (instable) [2], α_u (unstable) [6], α_r (regular) [7], etc. To avoid confusion, the hygroscopic type discussed here, prepared as described above by isothermal vacuum dehydration, is named α_H. The DTG curve of a differential dehydration (Fig. 3) illustrates the onset and end of the vacuum drying process.

An interesting characteristic of the α_H type of lactose is its reversible sorption of vapours. Figure 4 shows the repeated uptake of water by α_H-lactose. Freshly prepared α_H-lactose was stored overnight at 55% RH. The subsequent DSC measurement shows an uptake of about 5% water by the sample. By heating up to 160°C, the sorbed water is lost quantitatively. When the sample is stored once more at the same humidity, a repeated uptake of water takes place. This water can also be thermo-desorbed. Figure 4 shows such a series of re- and dehumidifying, beginning at the top of the figure. The relatively high temperature of the dehumidification is remarkable. This indicates a significant bonding of the adsorbed water [8].

To elucidate the nature of the bonding, a sample of α_H-lactose which was only partly dehydrated was re-humidified. Figure 5 shows the DSC peak (≈140°C) due to water of crystallization and at 120°C, the signal of the

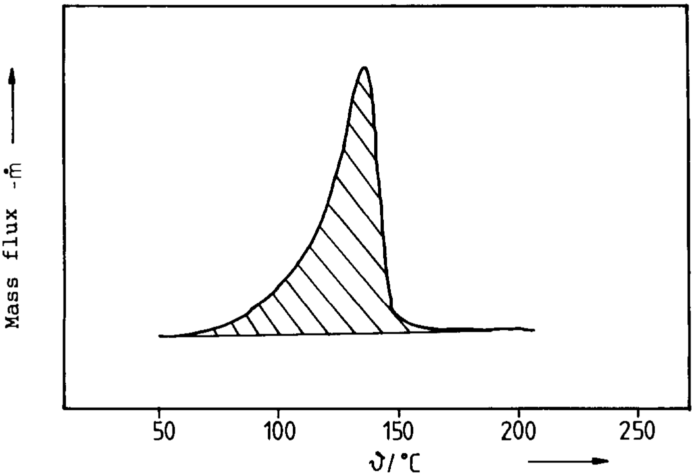

Fig. 3. DTG signal of vacuum dehydration of α-lactose monohydrate. Above 150°C, the water of crystallization is completely desorbed.

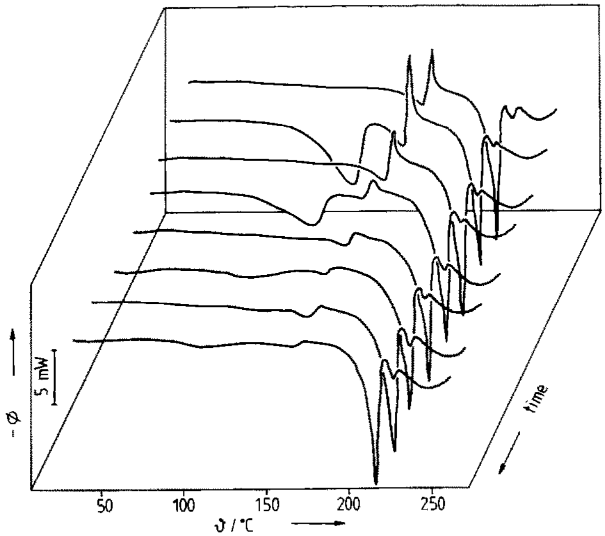

Fig. 4. Reversible re- and de-humidification of α_H-lactose. The top curve is for α_H-lactose which was successively humidified (2), re-dried (3), humidified once more, (4), etc. The temperature of water desorption indicates a significant bonding of the sorbate. DSC heating rate was 5 K min^{-1}.

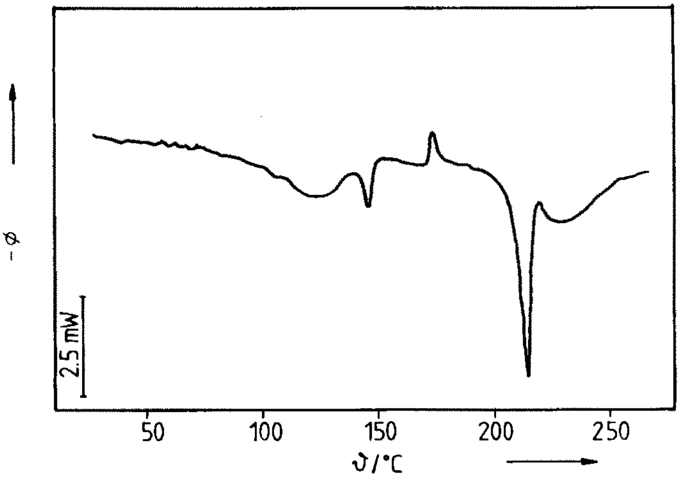

Fig. 5. DSC curve of a partly dehydrated and re-humidified sample of α_H-lactose (5 K min^{-1}). Characteristic effects are melting ($\geq$200°C) and recrystallization ($\approx$170°C). At desorption temperatures of 120°C and 140°C, the water taken up by sorption and water of crystallization are separately detectable.

desorption of the water taken up by rehumidification. This suggests that the water of rehumidification has a bonding character between that of free water and water of crystallization. NMR investigations should give more detailed information about the physico-chemical state of the absorbed water.

To summarize, α_H-lactose may sorb up to 5% water; the bonding of the sorbed water is noteworthy (desorption at 120°C); and the hygroscopic educt may be recovered by thermodesorption.

Other sorptives may display similar behaviour, in which case α_H-lactose would be especially suited as a carrier material for flavours and pharmaceutical agents.

Amorphous samples

Different lyophilized lactose samples were compared by means of DSC (Fig. 6). The samples differed in their mutarotational states. Sample MMO3 was prepared from a solution in mutarotation equilibrium and therefore consists of β- and α-lactose in a ratio of about 1.7. MMO1 was prepared from a fresh α-solution and has a content $\geq$95% of lyophilized lactose in its α-conformation. MMO2 consists of non-crystalline lactose mainly in its β-conformation. The anomer purities and anomer ratios were confirmed by polarimetry, using the method of Sharp and Doob [9], see Table 4.

Figure 6 shows the different glass transition temperatures of the samples in the range 70–100°C. The temperatures of recrystallization (exothermic signal) of the three different samples range from 150 to 180°C. After

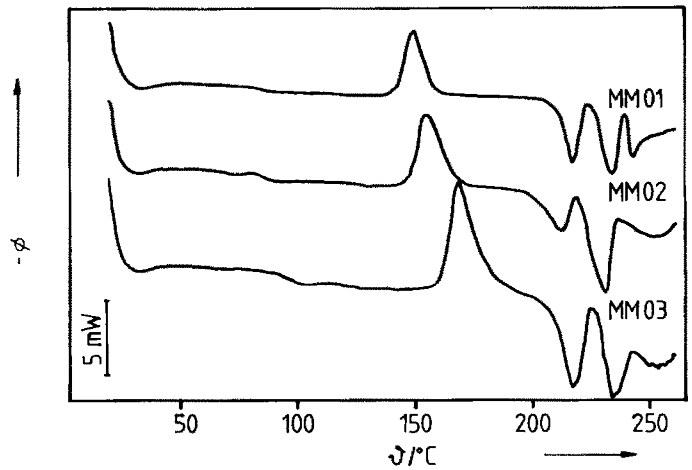

Fig. 6. Comparison of three samples of amorphous lactose with different mutarotational states. The DSC curves differ in their temperatures of glass transition and recrystallization. After recrystallization, the sample exhibit melting peaks of α- and β-lactose of different ratios. Heating rate, 20 K min^{-1}.

TABLE 4

Polarimetrically determined anomer purity of different investigated amorphous lactose samples, where τ is mutarotation time

Probe	τ	Educt	Content of α/%	Content of β/%
MMO1	6 min	D 30	95	5
MMO2	5 min	β after ref. 1	3	97
MMO3	46 h	D 30	37	63

recrystallization, the samples obviously consist of different ratios of crystalline β- and α-lactose, as indicated by the observed melting peaks.

To summarize, different forms of amorphous lactose exist, and differ in their mutarotational state, their temperatures of glass transition and recrystallization, and their recrystallization products.

Further intensive study of the underlying solid state transitions should provide a better understanding of the recrystallization processes of partly amorphous industrial spray products.

The reaction mechanisms and their influencing factors may be elucidated by combined thermoanalytical methods, and NMR and X-ray techniques.

ACKNOWLEDGEMENT

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