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ANHYDROUS α-LACTOSE
A study with DSC and TXRD

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Abstract

The dehydrated lactose forms α_H and α_S were investigated by time- and temperature-resolved X-ray powder diffractometry and differential scanning calorimetry. We found different X-ray structures for these two forms, which is probably related to the different dehydration processes. The rapidly dehydrated form α_H obviously has the same X-ray structure as the starting material α-lactose monohydrate, although the crystallinity is reduced. A thermally induced transition of the α_H-form into the α_S-form was observed. This transition should allow one to "switch" between the physicochemical properties of the excipient, which may be important for applications in pharmaceutical and food industries.

Keywords: anhydrous α-lactose, DSC, TXRD

Introduction

Lactose is one of the most important excipients in processing of pharmaceutical tablets. For direct tableting different forms of agglomerated lactose such as spray-dried lactose are used. The drying step in the manufacturing of spray-dried α-lactose monohydrate is a very sensitive operation because of the possibility of physical modifications of lactose occurring during the drying process [1, 2]. Some possible modifications are:

* partial crystallization of β-lactose
* partial solidification of amorphous lactose
* partial dehydration of α-lactose monohydrate

Two different anhydrous forms of α-lactose are known [3]:

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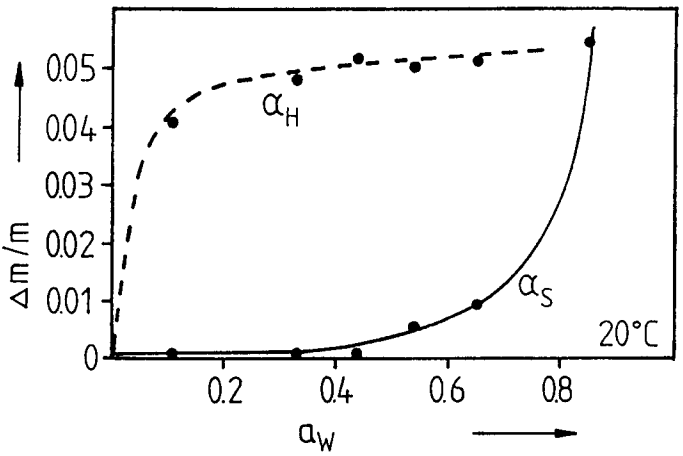

Fig. 1 H_2O adsorption isotherms of α_H- and α_S-lactose. Plotted are the relative mass changes $\Delta m/m$ of lactose samples *vs.* the water activity in the vapour phase a_w (i.e. the relative humidity divided by 100). α_H-lactose shows a strong water uptake at only $a_w \approx 0.1$ whereas α_S-lactose is not hygroscopic until $a_w \approx 0.5$. The calculated mass change for hydration to a monohydrate is $\Delta m/m$=0.05

Stable α-lactose (α_S) and unstable, hygroscopic α-lactose (α_H). Figure 1 shows the completely different hygroscopic behaviour of these two forms. The absorption isotherms were obtained by storing the samples in small exsiccators at room temperature under defined humidity. After equilibration the weight gain of the samples was recorded. While α_S-lactose shows a water uptake below 1% during storage under ca. 50% relative humidity (r.h.), the α_H-form is very hygroscopic and exhibits a water uptake of ca. 4% at only 10% r.h. It was the aim of this work to investigate the physicochemical reasons for the different behaviour of excipients which are identical from a purely chemical point of view. To better understand these differences it is necessary to examine the energetic as well as the structural properties of both forms.

Previous research in this field was reported by [4–8] who also used DSC to characterize different forms of lactose raw materials. Olano found alterations in the anomeric composition of solid lactose when heated under the equilibrium vapour pressure of water up to 165°C [9]. Solid state transitions of the powder were also seen by Conflant and Guyot-Hermann by means of coupled XRD and DSC [10].

Preparation

α_S-lactose was prepared by quasi-equilibrium dehydration. It was heated for 5.5 h at 120°C in a covered petri dish according to the method reported by

Nickerson [2]. α_H-lactose was prepared by a rapid dehydration process. It was heated at 120°C and vacuum-dried at 20 hPa for 3 h. The starting material for both forms was highly crystalline α-lactose monohydrate, commercially available as EP D30 from Meggle, Germany. Because of the preparation process we suggest that both forms should be named as "dehydrated lactose" instead of "anhydrous lactose". This is preferable because the preparation of anhydrous lactose is also possible by crystallization from organic solvents [11].

Methods

In this study differential scanning calorimetry (DSC), conventional X-ray powder diffractometry (XRD), and time- and temperature-resolved X-ray powder diffractometry (TXRD) were used to investigate the samples described above. DSC was carried out with a Mettler TA 4000 system equipped with the DSC 30 cell. Samples were heated in sealed crucibles (aluminium, 40 μl) with heating rates between 2 and 20 deg·min^{-1}. If dry purge gas is used in the DSC cell no difference between measurements made with sealed crucibles and crucibles with pin holes can be seen. X-ray diffractograms were recorded on a Philips PW 1710/00 goniometer. TXRD measurements were made with a self-constructed heatable sample holder for the Philips instrument, which allowed a precise control of the sample temperature. Details may be found in [12].

Results

The X-ray diffractogram of α-lactose monohydrate at room temperature was recorded. Peaks were identified and indexed using the data published by Buma [13]. Figure 2 shows the characteristic monohydrate diffractogram.

Figure 3 shows the comparison between the diffractograms of the monohydrate and the α_S form. From the peak positions it can be seen that both samples have different crystal lattices although there are similarities between the diffractograms.

Figure 4 compares two samples of anhydrous α_S-lactose, prepared by quasi-equilibrium thermal dehydration (1) and by crystallization from dry methanol (2). From the X-ray pattern it can be seen that both preparation techniques lead to products which have most likely the same crystal structure.

The Fig. 5 the X-ray diffractograms of α_H- and α-lactose monohydrate are shown. Surprisingly, the anhydrous form α_H exhibits the same peaks and peak positions as the monohydrate. This suggests that the anhydrous α_H-lactose still contains the crystal structure information of the monohydrate. Additionally, one may conclude that the dehydrated forms α_S and α_H have different crystal structures.

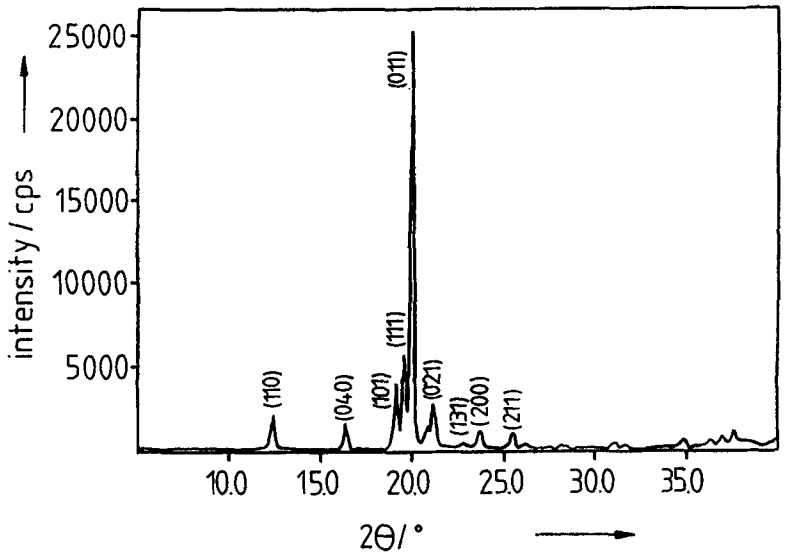

Fig. 2 The X-ray diffractogram of α-lactose monohydrate. The peaks were identified and indexed using data of [13]

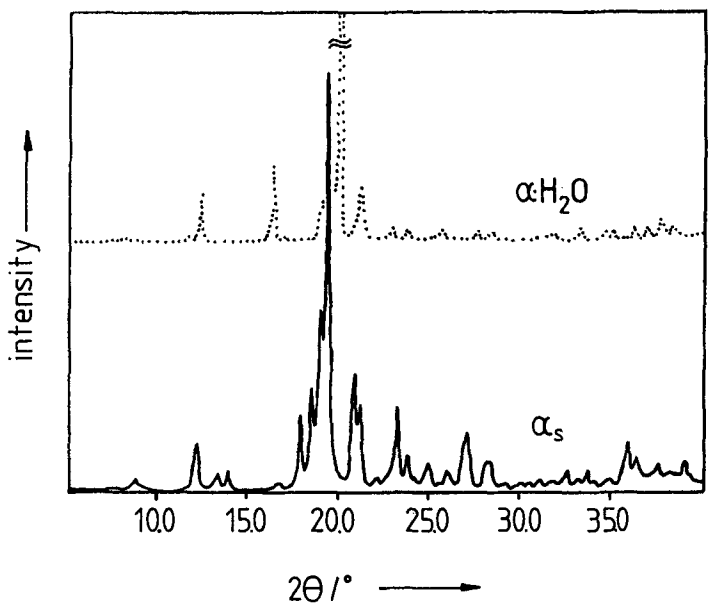

Fig. 3 The diffractograms of α-lactose monohydrate and dehydrated α_S-lactose. The crystal structures are different, although not in a very distinct way

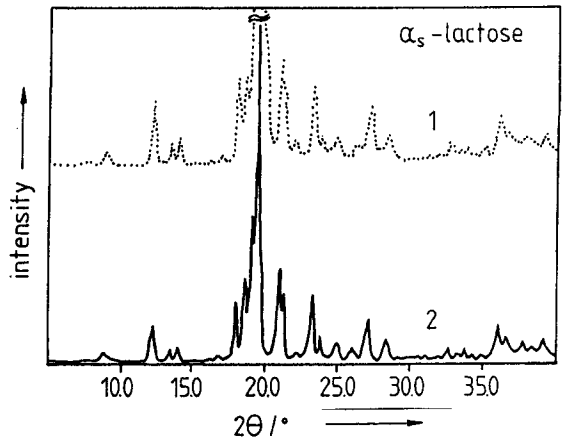

Fig. 4 Comparison of the X-ray diffractograms of α_S-lactose prepared by thermal dehydration (1) and by crystallization from methanol (2). The X-ray diffractograms of both samples are very similar, which suggests that both crystal structures are identical

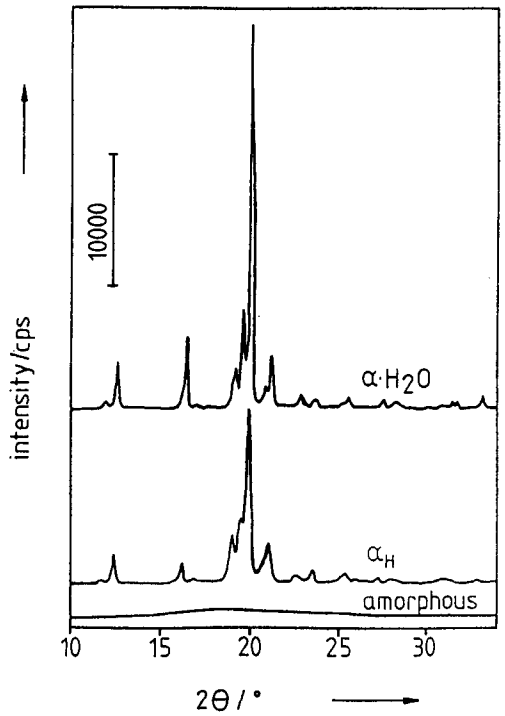

Fig. 5 α-lactose monohydrate and α_H-lactose show identical peak positions in the X-ray powder diffractogram. An intensity decrease in α_H compared to the monohydrate probably indicates lattice faults created during the dehydration process. At the bottom the diffractogram of a completely amorphous sample is shown

Because of the different crystal structures of α_S and α_H a lattice transformation from the monohydrate to the anhydrous α_S-type must have taken place during the slow dehydration process. During rapid dehydration (α_H) this transition seems not to occur quickly enough, so that the structure of the monohydrate is preserved. Figure 5 also indicates a general decrease in peak intensities and therefore in crystallinity from α-lactose monohydrate to α_H-lactose. This can be related to lattice faults generated during the dehydration process. For comparison, the X-ray diffractogram of completely amorphous lactose is shown at the bottom of Fig. 5.

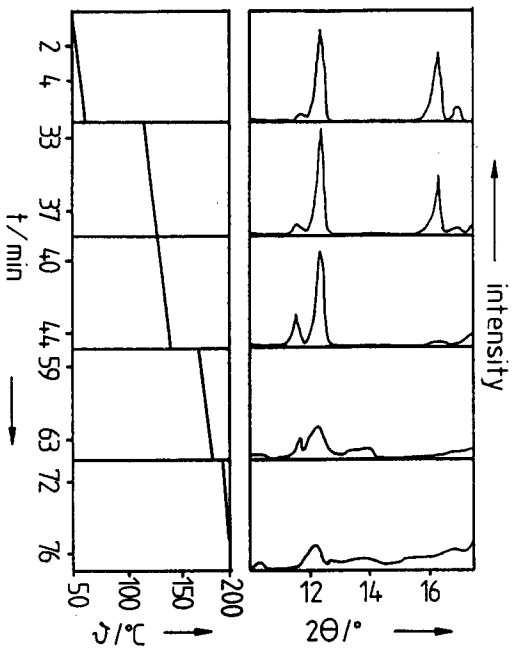

Fig. 6 While heating α_H-lactose with 2 deg·min^{-1} X-ray diffractograms were taken subsequently (left picture: temperature, right picture: X-ray scans). The time runs from the top to the bottom (see scale far left). Typical peaks disappear near 170°C

To investigate possible temperature-induced transitions α_H-lactose was continuously heated (2 deg·min^{-1}) and scanned by powder diffractometry. Before starting the TXRD measurement a stability test of α_H-lactose filled in the sample holder was performed. At 20°C the X-ray diffractograms showed no alteration over a period of 2 h.

During TXRD a diffractogram was recorded every 10 minutes. Figure 6 shows selected X-ray scans of the angular range 10–17° 2Θ between 50 and 170°C. Subsequently two typical monohydrate peaks disappear at 12.5° 2Θ and 17° 2Θ. The transformation obviously consists of at least two

steps. DSC measurements do not reveal this effect. DSC scans of four different forms of lactose are shown in Fig. 7. The DSC curve of α_H-lactose shows only one exothermic effect near 170°C, which is generally ascribed to a "recrystallization". To further investigate this process we performed TXRD-measurements in an angular range of 16–22° 2Θ. The results shown in Fig. 8 point to a complicated recrystallization process between ca. 120 and 170°C, most likely not in one step. At 170°C the transition seems to be complete, in good accordance with the DSC data. The product shows the same X-ray peaks as the α_S form. Therefore it can be assumed with high probability that the α_H form is converted to the α_S form by heating to temperatures above 170°C.

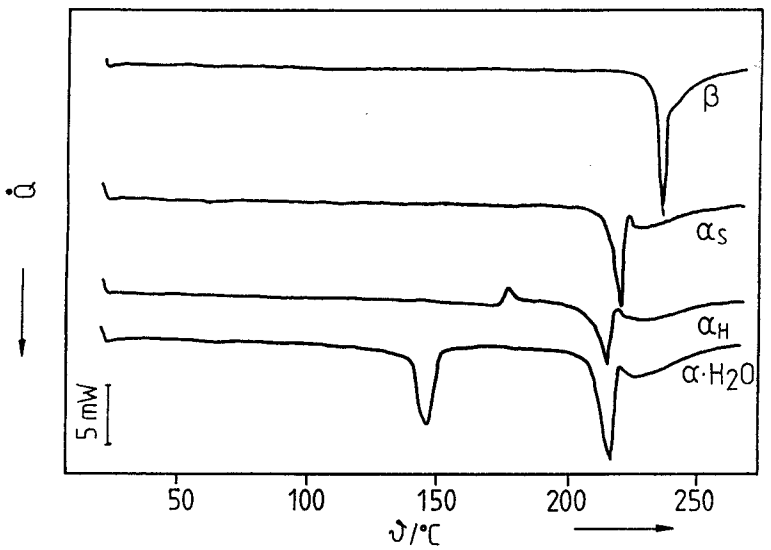

Fig. 7 DSC-curves of different lactose forms, measured with a 5 deg·min^{-1} heating rate; α_H-lactose shows a thermal effect at ≈170°C which is probably due to the transition $\alpha_H \rightarrow \alpha_S$

The thermal effect at about 170°C seen by [10] by means of coupled DSC and X-ray measurements (GUINIER-technique) has been interpreted as transformation of the α-lactose-monohydrate. Our results seems to indicate that this transformation corresponds to a modified lactose material. Indeed we were able to repeat their DSC-results when measuring with the same starting material they used. A comparison of the results of both investigations will be reported later [14].

Many questions still remain about the nature of this phase transformation which certainly can not be resolved with DSC alone, but require additional techniques like TXRD.

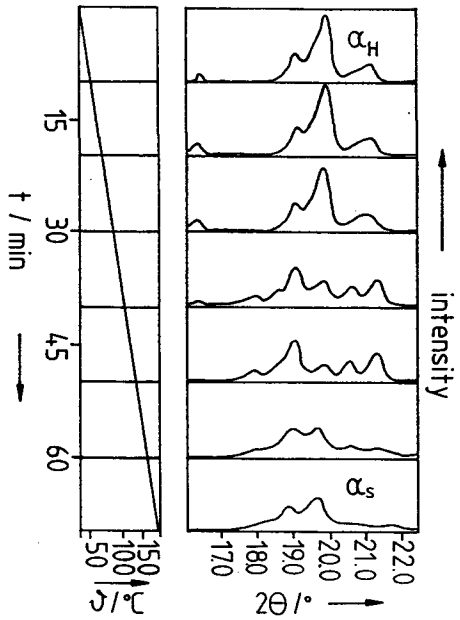

Fig. 8 Performing TXRD at angles of $2\Theta \approx 20°$ confirms that the transition consists of some steps between 120 and 170°C. The heating rate was 2 deg·min^{-1}

Conclusion

The anhydrous lactose forms α_H and α_S were found to have diametral sorption behaviour. By X-ray diffractometry two different crystal structures were found for these forms. The α_S-modification produced by low dehydration of α-lactose monohydrate had the same structure as anhydrous lactose prepared by crystallization from dry methanol. The α_H form obtained after rapid dehydration of the monohydrate exhibits the same X-ray peaks as the monohydrate, although the crystallinity is reduced. Thus the structural information of the monohydrate is preserved in this anhydrous form. However, α_H is unstable with respect to transformation into α_S. The expected thermally induced transition was found by TXRD to consist of multiple steps in the temperature range of 120–170°C. DSC measurements revealed only a small exothermic peak near 170°C related to this transformation. Economic benefit may be drawn from the sorption-active behaviour of α_H-lactose, e.g. when using it as a carrier of flavours or in pharmaceutical drugs. With the above described transformation of α_H into α_S-lactose it should in principle be possible to "switch" between the physicochemical properties of the excipient, thereby adjusting the hygroscopicity to a desired value.

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Zusammenfassung — Die dehydratisierten Lactose-Formen α_S und α_H wurden durch zeit- und temperaturaufgelöste Röntgendiffraktometrie sowie durch Dynamische Wärmeleitfähigkeits-Differenz-Kalorimetrie (DSC) untersucht. Beide Formen besitzen unterschiedliche Röntgenstrukturen, die wahrscheinlich auf die unterschiedlichen Dehydratationsbedingungen zurückzuführen sind. Das schnell dehydratisierte Material α_H zeigt die Röntgenstruktur des Ausgangsmaterials, α-Lactose-Monohydrat, jedoch ist die Kristallinität gegenüber dem Ausgangsmaterial reduziert. Die fest-fest Umwandlung der α_H-Form in die α_S-Form läßt sich thermisch induzieren. Die Umwandlung ermöglicht ein "Umschalten" zwischen den unterschiedlichen physikalisch-chemischen Eigenschaften der Materialen und könnte für Anwendungen in der Pharmazeutischen Industrie und der Lebensmitteltechnik interessant sein.