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THE SORPTION AND DESORPTION OF WATER IN LACTITOLS

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Anhydrous lactitols (A1, α- and β-lactitol), lactitol monohydrate, lactitol dihydrate and lactitol trihydrate were kept for varying times in atmospheres of different relative humidity at 20°C in equivalent size plastic desiccators. The relative humidities (8–95%) were maintained with saturated salt solutions and drying agents (silica gel and phosphorous pentoxide). The composition of the samples was monitored by thermogravimetry, differential scanning calorimetry and X-ray powder diffraction.

According to these measurements both lactitol monohydrate and lactitol dihydrate were substantially stable under the conditions used. Lactitol monohydrate converts to lactitol dihydrate at the highest relative humidity used. All phases of anhydrous lactitol convert into a form of lactitol monohydrate but not to lactitol dihydrate, even at the highest relative humidity used. At a high relative humidity lactitol trihydrate easily loses part of its crystal water and converts partly to lactitol dihydrate. At a lower relative humidity, the phase forming from trihydrate is difficult to identify.

Keywords: *desorption, lactitol, 4-O-β-D-galactopyranosyl-D-glucitol, phase transition, sorption*

Introduction

According to literature lactitol exists in five polymorphic and pseudopolymorphic forms: α-lactitol [1], β-lactitol [2], lactitol monohydrate [3], lactitol dihydrate [4] and lactitol trihydrate [5]. It has also been observed that in drying of crystalline lactitol monohydrate by heat a third form of anhydrous lactitol called A1* is formed, and in drying with P_2O_5 a fourth form called A1 is formed [6]. The A1 phase transforms into A1* at about 105°C; this phase melts at 120°C while the other anhydrous lactitols melt at about 150°C.

Sugar alcohols are industrially produced for food and pharmaceutical applications. They may exist in several polymorphic and pseudopolymorphic forms having different physicochemical properties and being stable under certain conditions [7, 8]. Therefore it is often advantageous to choose the proper polymorph for different applications. Polymorphic and pseudopolymorphic forms can convert to each other in the solid-state [9–11].

Many properties of sugars and sugar alcohols are well known but their phase transitions are not well understood. This causes unexpected surprises in their production, conserving, industrial use and analysis. Moisture is the most significant contributor in conversion. Also dehydration causes phase transitions. In some solvates the solvent plays an important role in holding the crystals together. When these solvates lose solvent, the crystal collapses producing amorphous material that afterwards recrystallizes in a new crystal form. In other solvents, the solvent molecules are fillers that occupy voids in the crystals and desolvation of these solvates does not destroy the crystals. In this case the diffraction pattern does not change substantially, leading to the most similar possible packing so that at least a part of the initial structural information is preserved [9, 12, 13]. Also during the processing of various pharmaceutical substances the crystalline lattice can be disordered leading to a partially or fully amorphous structure. Possible routes for producing amorphous solids during pharmaceutical processing are vapour condensation, supercooling of liquid, precipitation from solution (rapid crystallization) and disruption of crystalline lattice (i.e. grinding, desolvation, compaction). Non-crystalline amorphous forms are energetic states which tend to crystallize to a more stable form and decompose more easily than crystalline forms [9, 14, 15].

Different techniques are available for the characterization of moisture sorption [16–19]. In this work the sorption and desorption of lactitols was studied by using humidity chambers prepared with aqueous salt solutions [20, 21]. New information of the phase transitions of lactitols was obtained.

Experimental

Reagents

Anhydrous lactitol A1 was prepared by drying lactitol monohydrate at 40°C over phosphorous pentoxide in a

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desiccator. Anhydrous α-lactitol (A2 Lot. 21695), anhydrous β-lactitol (anhydrous lactitol crystallization 8 25.5.2000), lactitol monohydrate (lactitol MC L125 T8L27) and lactitol dihydrate (crystallization 10.9.1998) were obtained from Danisco Sweeteners, Kotka. Lactitol trihydrate was crystallized at 15°C. Because α-lactitol contained 0.2–0.3% water, it was dried at 100°C overnight and stored over silica gel before preservation tests.

Sorption and desorption

About 0.5 g of each lactitol form was spread uniformly in open Petri dishes (diameter 5 cm). The humidity chambers were prepared with aqueous saturated salt solutions at 20±1°C. The salts used were LiCl (RH 11.31%), $CaBr_2$ (RH 18.50%), NaBr (RH 59.14%), KI (RH 69.90%), NaCl (RH 75.47%), KCl (RH 85.11%) and KNO_3 (RH 94.62%). Also two solid drying agents, phosphorous pentoxide and silica gel, were used in glass desiccators. Each sample was immediately transferred to a plastic desiccator with 500 mL of the saturated solution in its base. Preservation times varied from 1 to 90 days. With preservation times of less than 30 days only one sample was kept in each desiccator in order to avoid opening its cover during the experiment. After storage each sample was mixed thoroughly into a homogenous mixture, moved to a small plastic-decked tin and analyzed immediately with TG, DSC and X-ray powder diffraction methods.

Measurements

The TG measurements were done on a Perkin-Elmer TGA 7 with sample masses of 4–8 mg in open Pt pans in a flowing nitrogen atmosphere with a flow rate of about 50 mL min^{-1}. The heating rate used was 0.5 K min^{-1} and the temperature range was 25–180°C. Temperature calibration of the TG was done by using the Curie-point temperatures of alumel, nickel, nicoseal, perkalloy and iron.

The DSC-measurements were carried out on a Perkin-Elmer DSC Pyris 1 with sample masses of 4–9 mg using 50 μL aluminium pans with capillary holes and a heating rate of 2 K min^{-1} from 30 to 170°C. The measurements were done in a flowing nitrogen atmosphere with a flow rate of about 50 mL min^{-1}. Temperature calibration of the DSC was carried out by indium and benzoic acid standards and energy calibration by an indium standard.

The X-ray powder diffraction patterns were recorded using a Huber G670 Imaging Plate Guinear camera. Germanium crystal monochromatized $CuK_{\alpha 1}$-radiation (λ=1.54056 Å) was produced at 45 kV and 25 mA. Transparency measurement geometry was used with an angle between sample and incident X-ray beam of 45°. The samples were prepared on Mylar film using vaseline. The sample was oscillated horizontally for about 20 mm. The exposure time was 30 min and the imaging plate was scanned six times. ZDS software was used to locate the peak positions of diffraction patterns [22]. The refinement of unit cell dimensions was carried out using program PIRUM [23].

Results and discussion

Anhydrous lactitols derived from the monohydrate

In the DSC curve of anhydrous lactitol A1 (Fig. 1), prepared from monohydrate by drying over phosphorous pentoxide, a small sharp reversible phase transformation peak is seen at 103–104°C from transformation A1↔A1*, the melting peak of A1* with melting onset and its standard deviation for six repeats at 120.9±0.3°C, and melting peak at about 123.9±0.4°C under extrapolated isothermal conditions. The melting enthalpy of 102±1 J g^{-1} was calculated from 30 repetitions with five different heating rates. Anhydrous lactitol A1 transforms to lactitol monohydrate (theoretical water content of 4.97 mass%), even when it was stored 40 days over silica gel at 20°C. The water contents of preservation tests for A1 are shown in Fig. 2.

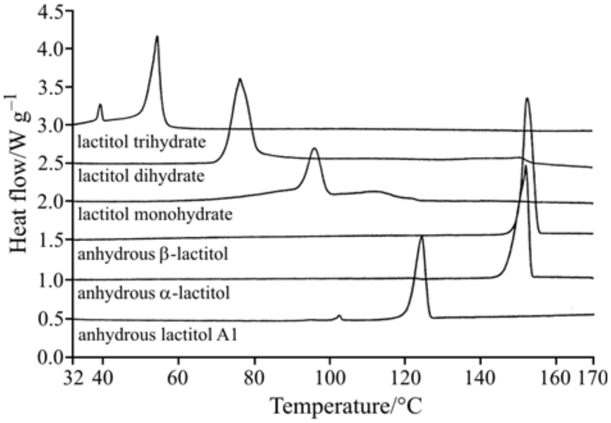

Fig. 1 DSC curves of anhydrous lactitol A1, anhydrous α-lactitol, anhydrous β-lactitol, lactitol monohydrate, lactitol dihydrate and lactitol trihydrate

The DSC curve of highly crystalline lactitol monohydrate (Fig. 1) shows melting and the evaporation of water. The onset of the melting of lactitol monohydrate is at 93.3±0.1 and it peaks at 97.1±0.1°C under isothermal conditions [24]. If a structurally imperfect monohydrate sample has a slightly lower crystal water content or the crystal water evaporates easily, the endothermic peak of anhydrous A1 lactitol is seen

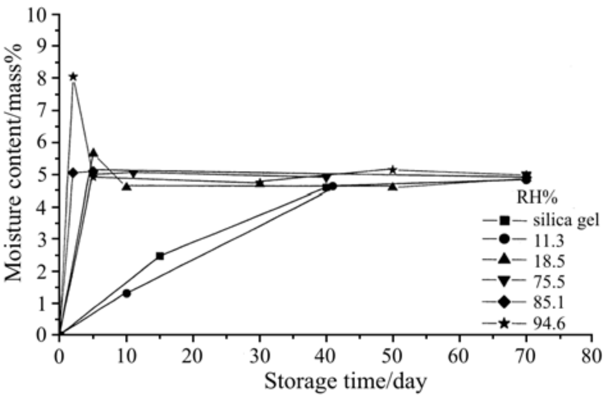

Fig. 2 The moisture content of anhydrous A1-lactitol in the storage tests

in the DSC curve as a solid–solid transformation. When the original sample contains a small amount of amorphous substance, the melting peak of anhydrous α-lactitol (melts at 150°C measured at 2 K $\min^{-1}$) is generally seen as well. It forms nuclear centers more easily than the other anhydrous polymorphs of lactitol. The seed crystals strongly promote the crystallization and the sample crystallizes to anhydrous α-lactitol during a DSC measurement. Sometimes the crystallization occurs in a short temperature range after the melting of anhydrous lactitol A1* and there is a sharp exothermic recrystallization peak right after the melting peak of anhydrous lactitol A1*.

When A1 is stored in a relative humidity of 18.5% or below, there is only a small melting peak at about 150°C. In more humid conditions the melting peak at 150°C is remarkable. According to the powder diffraction method all the crystalline samples correspond to pure monohydrate or mixtures of A1 and monohydrate. The unit cell parameters of monoclinic A1 are a=7.78 Å, b=12.83 Å, c=14.77 Å and β=91.20° determined from powder diffraction data while those for orthorhombic monohydrate are a=7.808 Å, b=12.685 Å and c=15.931 Å [3]. The unit cell dimensions of A1 and lactitol monohydrate are quite the same, and therefore the phases could change to each other in a solid–solid transformation of the unit cell. However, it seems that anhydrous lactitol A1 can convert to lactitol monohydrate also through the amorphous phase because the water content of the sample stored at RH 94.6% is considerably higher for some days than that of lactitol monohydrate (Fig. 2). Thus the sample could dissolve in the additional water and recrystallize as lactitol monohydrate [13]. After that, the additional water evaporates and the water content of the sample corresponds to that of lactitol monohydrate. The DSC curve of such a sample has a much bigger melting peak at about 150°C than other samples. It seems that there are some amorphous areas left in the structure and they offer a possibility for the recrystallization of α-lactitol. According to the X-ray powder diffraction all these samples correspond to the monohydrate or to a mixture of anhydrous lactitol A1 and the monohydrate, depending on the water content of the samples.

Crystallized anhydrous lactitols

In the DSC curve of anhydrous α-lactitol (Fig. 1) there is only one sharp melting peak with a melting onset and its standard deviation for six repeats at 147.7±0.3°C and the melting peak at 150.2±0.3°C under isothermal conditions. The melting enthalpy calculated from 30 repetitions is 154±3 J g^{-1}. The lowest relative humidities used for α-lactitol were 69.9% because our former tests show that it is relatively stable at ≤59 RH%. However, α-lactitol reached at least the water content of lactitol monohydrate in all test points. Drying before the experiments could cause slight water sorption. The water contents in the storage tests of α-lactitol are shown in Fig. 3.

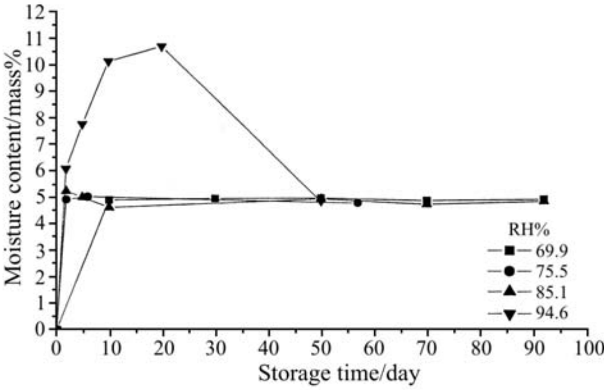

Fig. 3 The moisture content of anhydrous α-lactitol in the storage tests

Samples with a short storage time produce DSC curves with melting peaks of lactitol monohydrate and anhydrous α-lactitol formed during the measurement. Although the melting peaks of anhydrous α-lactitol and anhydrous β-lactitol occur at about the same temperature, it was found out in our investigation that this kind of lactitol monohydrate forms anhydrous α-lactitol upon drying. The melting peak of lactitol monohydrate formed from α-lactitol is situated about 10°C lower than that of lactitol monohydrate formed from anhydrous lactitol A1 by absorption of moisture. The lower melting peak of this lactitol monohydrate form is caused by water evaporation taking place at a lower temperature. At the highest humidity level used (RH% 94.6) the sample absorbs over 10 mass% water (Fig. 3) so that substantial amorphous areas which could easily absorb water, can be formed. Despite of a water content in excess of that of lactitol dihydrate, all the samples corresponded quite well to monohydrate according to X-ray powder diffraction (unindexed lines 0–2 and M(20) and F(20) values are 8–15 and 17–30, respectively). Because water evaporates in two steps at a lower temperature than the decomposition temperature of the dihydrate, the sample does not behave like dihydrate, the TG curve of which is shown in Fig. 4. Probably the storage time was not long enough to produce seed crystals of dihydrate although the storage temperature was suitable for the crystallization of dihydrate from an aqueous solution. We also tested the effect of seed crystals on the crystallization by adding 1 mass% of dihydrate into α-lactitol. This sample was stored for 50 days at a RH of 94.6%. The resulting phase was a mixture of dihydrate and monohydrate.

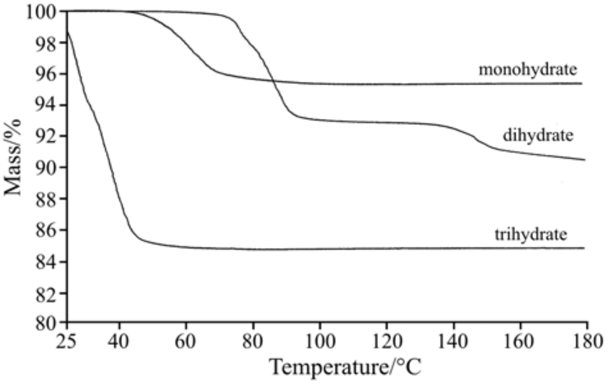

Fig. 4 The TG curves of lactitol monohydrate, lactitol dihydrate and lactitol trihydrate

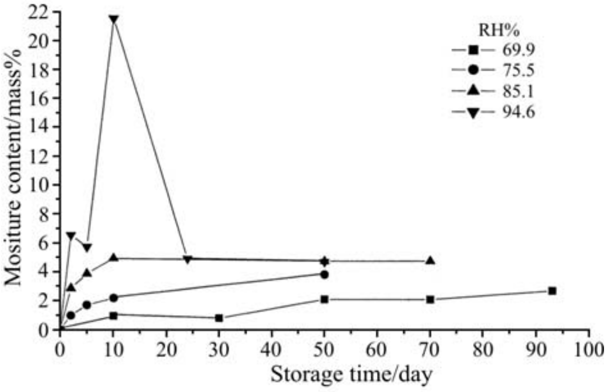

Fig. 5 The moisture content of anhydrous β-lactitol in the storage tests

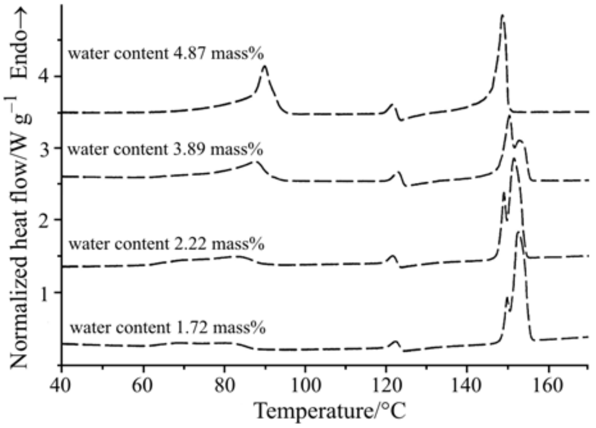

Fig. 6 DSC curves of storage tests of anhydrous β-lactitol

Samples having a high water content, which resulted from α-lactitol, were also wet and sticky, so that all the additional water was not in the crystal structure. After recrystallization the additional water evaporates and the water content of samples become that of lactitol monohydrate. Lactitol monohydrate formed through moistening of α-lactitol was found to have a lower level of crystallinity than that of lactitol monohydrate formed by moistening of anhydrous lactitol A1. As mentioned earlier these amorphous areas cause a recrystallization to α-lactitol during DSC measurements. When monohydrate samples that give also the melting peak of α-lactitol are stored for long periods, they tend to crystallize and the melting peak of α-lactitol disappears from the DSC curve.

β-lactitol absorbs water at all humidity levels, but more slowly than α-lactitol (Fig. 5). Also, β-lactitol absorbs water over the water content of lactitol monohydrate, although the crystal structures of these samples correspond quite well to lactitol monohydrate in accordance with X-ray powder diffraction. The melting peak at about 150°C has split ends so that the melting peak of α-lactitol grows with the crystal water content (Fig. 6). Therefore it is likely that the amorphous substance crystallizes to α-lactitol, which forms crystals easier than β-lactitol, during the DSC measurements. At the highest moisture levels, the sample absorbs substantially more water than the water content of lactitol monohydrate. Despite a water content higher than that of lactitol dihydrate all the sample corresponded quite well to monohydrate according to X-ray powder diffraction (unindexed lines 0, M(20) and F(20) values were 12 and 24, respectively).

Lactitol monohydrate

Our investigation shows that lactitol monohydrate is very stable towards moisture. Also the TG curve of the monohydrate shows that the crystal water does not evaporate easily (Fig. 4). Earlier in our examination it became evident that by drying monohydrate by phosphorous pentoxide it changes to anhydrous lactitol A1 [6]. This change occurs probably via a solid–solid transformation because if there were amorphous areas, the anhydrous α-lactitol would crystallize much

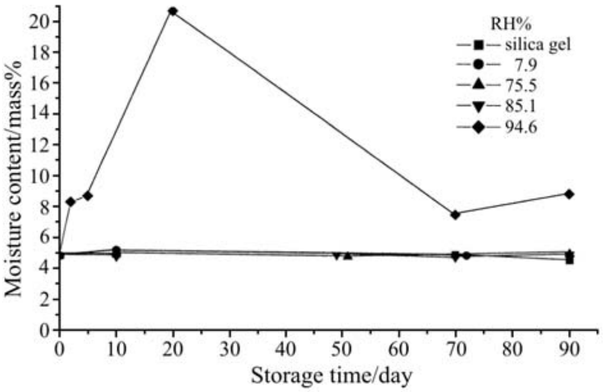

Fig. 7 The moisture content of lactitol monohydrate in the storage tests

more easily than anhydrous lactitol A1. In these dehydration tests it was shown that silica gel could not remove the crystal water. The water content of lactitol monohydrate samples was increased substantially only at a high relative humidity of 94.6% (Fig. 7). The DSC and TG curves of these samples show typical lactitol dihydrate-like behaviour. According to the powder diffraction method these samples were partly converted to dihydrate in the storage time of 90 days.

Lactitol dihydrate

In the DSC curve of lactitol dihydrate (Fig. 1) there is only one melting peak with melting onset at 73±1 and a melting peak at 77±1°C when measured under a heating rate of 2 K min^{-1}. Sometimes there exist several random endotherms at 120–150°C, caused by water vapour bubbling from the melt.

The dihydrate is the stable phase of lactitol at 20°C. Even phosphorous pentoxide is unable to remove much of the water content of the dihydrate during 50 days. On the other hand the water content did not increase noticeably in a relative humidity of 94.6% during 70 days (Fig. 8). Also, the DSC and powder diffraction methods show that these samples consisted mostly of dihydrate, although there were 2–24 unindexed low peaks (<5%) in the diffraction patterns of dihydrate samples. Most of these peaks were transferred peaks of dihydrate, which became unindexed during the Pirum analysis. A few of these peaks belonged to diffraction patterns of other lactitol phases. Thus these samples did not change to lactitol trihydrate during these storage tests. It is also noticed that if lactitol dihydrate partly converts to an amorphous state, the storage temperature used was suitable for the crystallization of dihydrate. If these tests had been carried out, for instance, at 10°C, the results could be different.

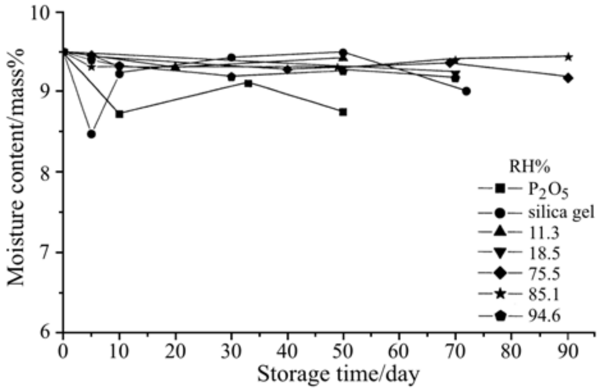

Fig. 8 The moisture content of lactitol dihydrate in the storage tests

Lactitol trihydrate

In the DSC curve of lactitol trihydrate (Fig. 1) there is a sharp little melting peak with melting onset at about 41°C and melting peak at about 42°C, when measured with the heating rate of 2 K min^{-1}. After this melting peak there is the melting peak of lactitol dihydrate formed by drying from trihydrate during the measurement. Sometimes there is also a third melting peak in the DSC due to the melting of dihydrate formed by crystallization during the measurement. In that case the sample consists of a little more water than calculated for the trihydrate (13.57 mass%). That extra water produces amorphous areas, which could crystallize during the DSC measurement. From the TG curve of trihydrate it can be seen that crystal waters are removed at low temperature range (Fig. 4). A part of the crystal water of lactitol trihydrate evaporates easily at all test points (Fig. 9). Some DSC curves of these samples were difficult to interpret. Although in some cases the water content of samples corresponds to the water content of lactitol dihydrate, the DSC behaviour may correspond to that of trihydrate. According to the powder diffraction the samples contain trihydrate, dihydrate or the mixture of

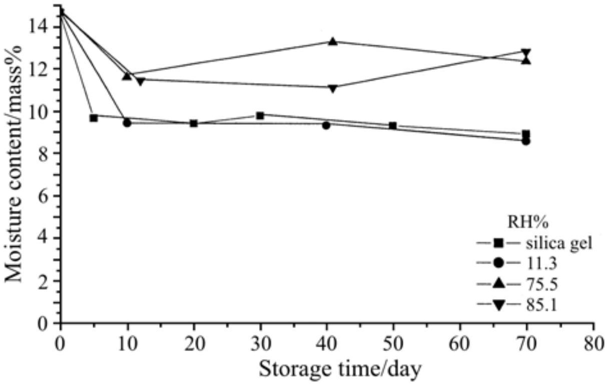

Fig. 9 The moisture content of lactitol trihydrate in the storage tests

different lactitol phases (mostly dihydrate and trihydrate). In the storage tests done under high humidity the resulting phase is mostly lactitol dihydrate, but in some cases it is an unidentified mixture. None of the unindexed peaks in the powder diffraction pattern belonged to any of known lactitol phases. This creates a suspicion of a new lactitol phase, possibly a new phase of dihydrate.

Conclusions

It is found that all anhydrous phases of lactitol convert to monohydrate form during sorption tests. The monohydrate formed loses its crystal water more easily than crystalline monohydrate, which was used as the initial material. It is interesting that the resulting monohydrates does not change further to dihydrate as crystallized monohydrate did, even at conditions of higher humidity. The temperature of 20°C is suitable for crystallizing the dihydrate from a water solution and it is likely that the seed crystals promote the crystallization. It appears that the required seed crystals do not build up during the storage times used unless some seed crystals are added before the storage test.

In conditions of high humidity the lactitol monohydrate, which seems to be very stable in most conditions, partly converts to dihydrate. Lactitol dihydrate was the most resistant against all conditions used; it did not convert to trihydrate even at high humidity at 20°C. If the conditions of storage produce amorphous areas in the structure, they will crystallize back to dihydrate under those conditions. At a lower temperature the formation of trihydrate could be presumed. Lactitol trihydrate behaves in a way that is very complicated to explain. Also the DSC behavior of trihydrate is complex. At a lower relative humidity the melting peak of trihydrate disappears before the melting peak of dihydrate formed by drying. However, according to powder diffraction these samples consisted trihydrate and dihydrate. At a higher relative humidity there is also the melting peak of trihydrate in the DSC curves.

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