Thermal Analysis of Lactose Polymorphs

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Introduction

- The following polymorphic forms of lactose exist: α-Lactose Monohydrate (α-LMH), α-Lactose Anhydrous (α-LA) stable, α-LA unstable, β-Lactose Anhydrous (ß-LA) and amorphous Lactose (L_{amorph}). α-LMH is the thermodynamically most stable form and is not hygroscopic (25 °C, 80 % RH, increase in mass < 0.2 %).
- L_{amorph} can be obtained by rapid drying (freeze/spray drying) but also by mechanical processes like milling ***[3, 7, 8]***.
- L_{amorph} recrystallizes when the temperature exceeds the glass transition temperature of the material. Humidity acts as plasticizer and significantly lowers the glass transition temperature. This results in altered material properties, e.g., sticking and caking ***[5]***.
- The amorphous content could be characterized using different analytical techniques such as Dynamic Vapor Sorption (DVS), Differential Scanning Calorimetry (DSC) and X-ray Diffraction, amongst others ***[7, 9]***.

Objective

Elucidate characteristics of diverse lactose grades (spray-dried, micronized, crystalline and anhydrous) based on several analytical techniques like DVS and DSC.

Material & Methods

Lactose grades (MEGGLE GmbH & Co. KG, Wasserburg, Germany):

- Anhydrous lactose (ß-LA/α-LA): DuraLac® H
- Crystalline lactose (α-LMH): InhaLac® 70
- Micronized lactose (α-LMH + L_{amorph}): InhaLac® 500
- Spray dried lactose (α-LMH + L_{amorph}): FlowLac® 90

Measurements:

- Particle Size Distribution (PSD): Sympatec HELOS/BR (Sympatec GmbH, Clausthal-Zellerfeld, Germany)
- Amorphous Content: DVS proUmid SPS-1µg Advance (proUmid GmbH & Co. KG, Ulm, Germany)
- DSC Measurement: DSC 214 *Nevio* (NETZSCH Gerätebau GmbH & Co. KG, Selb, Germany)
- Specific Surface Area (SSA): BET Method N_2
- ß-Anomeric content: Polarimeter MCP 5100 (Anton Paar Germany GmbH, Ostfildern-Scharnhausen, Germany)
- Water Content KF: according to Ph.Eur. 2.5.12 Method A/USP-NF <921> Method I
- Loss on Drying (LOD): according to USP Monograph Lactose Monohydrate (80 °C, 2h)

Results

- ***Table 1*** gives an overview of the characteristics of each lactose grade.
  The amorphous and ß-Anomeric content of spray-dried lactose FlowLac® 90 is higher than for the other lactose grades. Amorphous lactose is also detected for micronized grade InhaLac® 500. The micronized material has a much smaller particle size and therefore also a higher specific surface area (SSA).
- InhaLac® 70 mainly consists of crystalline α-LMH, whereas DuraLac® H is anhydrous lactose and consists of approx. 80 % β-LA and 20 % α-LA. For both materials, the amorphous content is < LOQ.
- Storage of InhaLac® 500 for six days under ambient conditions (22.8 °C, 43 % RH) influences the product. While a glass transition temperature (T_g) was detected for InhaLac® 500 without conditioning, no T_g was measured for the sample after storage, indicating complete recrystallization of the amorphous portion ***(Figure 1)***.

		InhaLac® 500	FlowLac® 90	InhaLac® 70	DuraLac® H
n		2 - 4	3 - 22	2 - 3	1 - 7
PSD (µm)	x_{10}	0.7 ± 0.0	65.1 ± 3.8	144.8 ± 2.6	10.5 ± 1.2
	x_{50}	3.1 ± 0.3	141.4 ± 4.7	219.0 ± 2.0	147.3 ± 18.0
	x_{90}	7.5 ± 0.8	227.3 ± 5.9	297.8 ± 0.4	338.3 ± 15.4
SSA (m^2/g)		6.0 ± 0.9	0.3 ± 0.1	0.19 ± 0.03	0.33
Amorphous Content (%)		4.2 ± 1.0	5.4 ± 0.4	< LOQ*	< LOQ*
ß-Content (%)		2.7 ± 0.7	9.0 ± 0.7	1.2 ± 0.2	83.1 ± 1.0
Water Karl Fischer (%)		5.2 ± 0.2	4.9 ± 0.1	5.1 ± 0.0	0.5 ± 0.1
LOD (%)		≤ 0.5	≤ 1.0	≤ 0.5	≤ 0.5

Table 1: *Characteristics of different lactose grades. * LOQ: Limit of Quantification: 0.13 %*

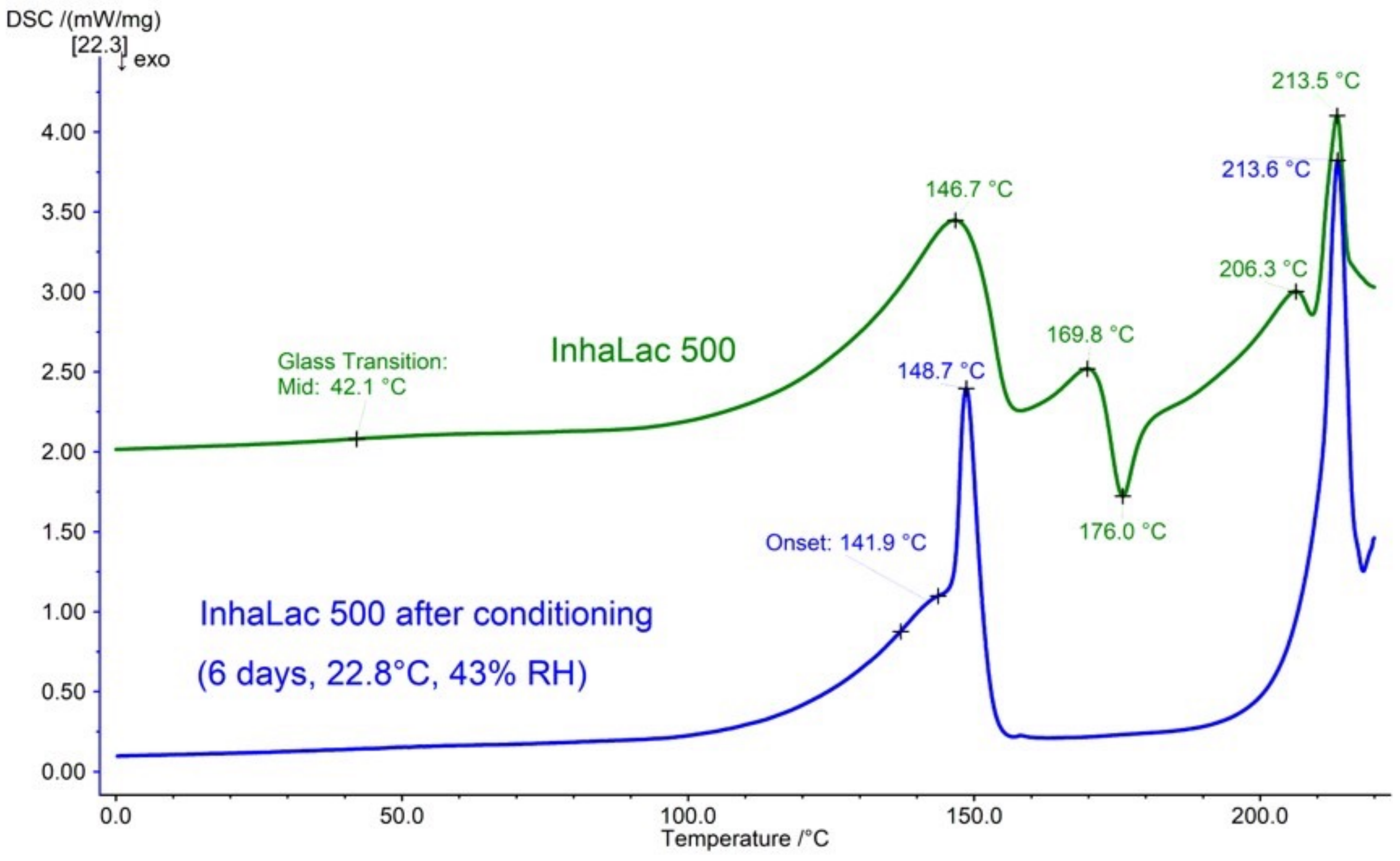

Figure 1: *DSC curves of InhaLac® 500 before and after conditioning.*

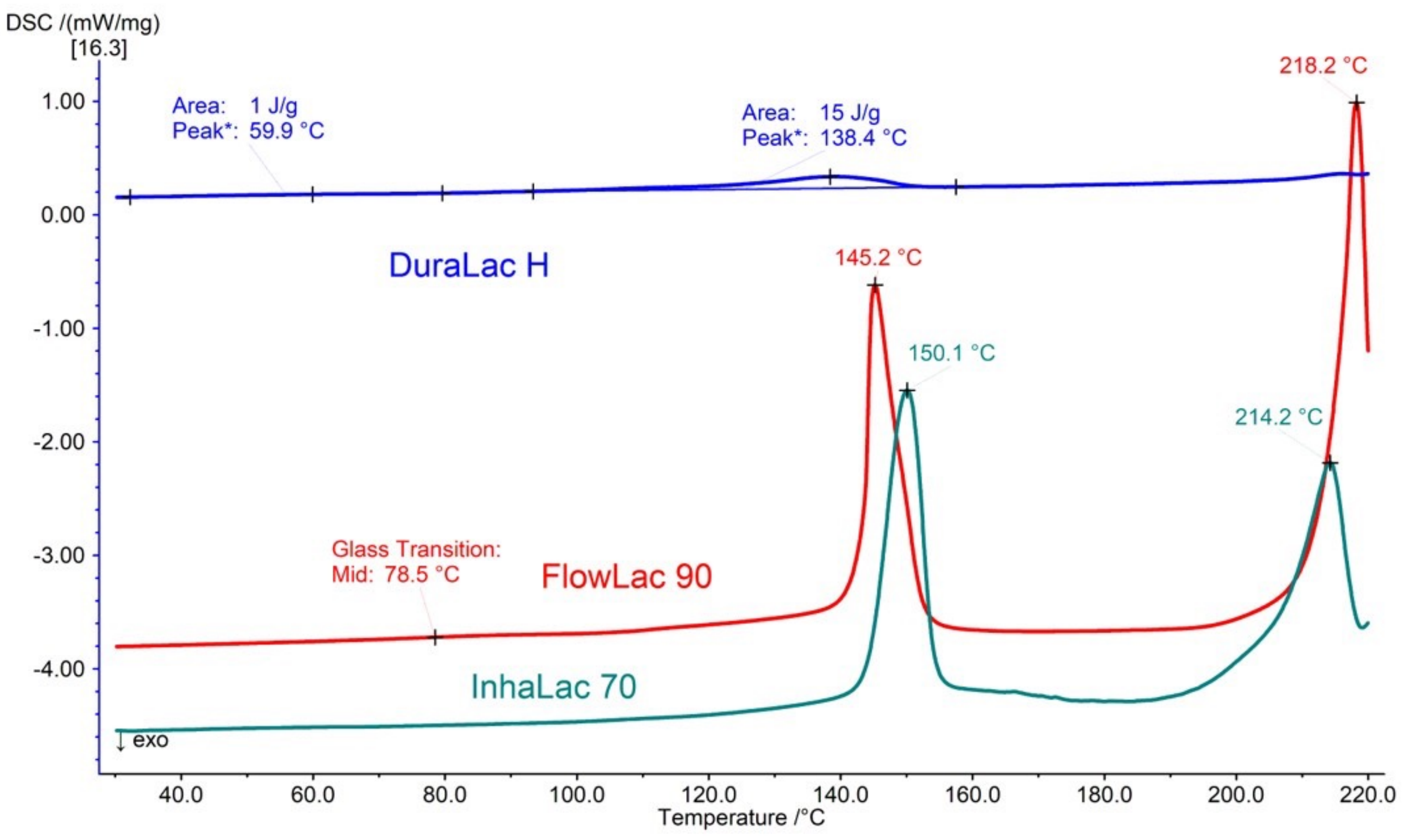

Figure 2: *DSC curves of FlowLac® 90, InhaLac® 70 and DuraLac® H*

- ***Figure 2:*** heat flow curves of DuraLac® H, FlowLac® 90 and InhaLac® 70. The first endothermic peak between 120 °C and 160 °C is observed for all samples ***(Figures 1*** and ***2)*** and can be assigned to the dehydration of the crystal water. As DuraLac® H is an anhydrous lactose grade, the enthalpy is much lower than that of the other investigated lactose grades as only very small amounts of α-LMH are present. The second endothermic peak at temperatures above 200 °C indicates melting and degradation of anhydrous lactose ***[2]***.
- Interestingly, for InhaLac® 500, an additional endothermic and exothermic peak can be detected between approximately 160 °C and 190 °C ***(Figure 1)***. This effect cannot be observed for conditioned (recrystallized) InhaLac® 500. However, the dehydration peak is broader for InhaLac® 500 before and after recrystallization/dehydration than is the case for other lactose grades. Even though FlowLac® 90 initially contains more amorphous material, no additional peaks between 160 °C and 190 °C are observed, nor are they for any other grade.
- This indicates differences in the crystal structure or anomeric composition of micronized lactose. A possible explanation could be that the high micronization energy induces crystal unit structure disruption on the surface and thereby also generates α-LA unstable ***[1, 4, 6]***. The observed exothermic and endothermic peaks then might be assigned to the epimerization of α-LA to β-LA as previously observed by DSC measurements on α-lactose powders. ***[2]***
- Differences between FlowLac® 90 and InhaLac® 500 could be explained by differences in formation (fast solidifying of lactose solution vs high energy, which could induce crystal defects on surface) as well as the location of the amorphous parts within the particles, a phenomenon that has been described previously for L_{amorph} achieved by freeze or spray drying ***[9]***.

Conclusion

Several lactose grades are available, each exhibiting distinct material properties. The differences between polymorphic forms could be measured by using well-known analytical techniques like DVS or DSC. However, there is still a lack of knowledge regarding the differences observed, for example, for L_{amorph} obtained by spray-drying in contrast to micronization. Therefore, further investigations are necessary to gain a deeper understanding of not only polymorphic characteristics but also differences within a given polymorph as a function of processing.

References:

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