Various Pharmaceutical Lactose Grades in a Provocative *Maillard* Environment

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Introduction

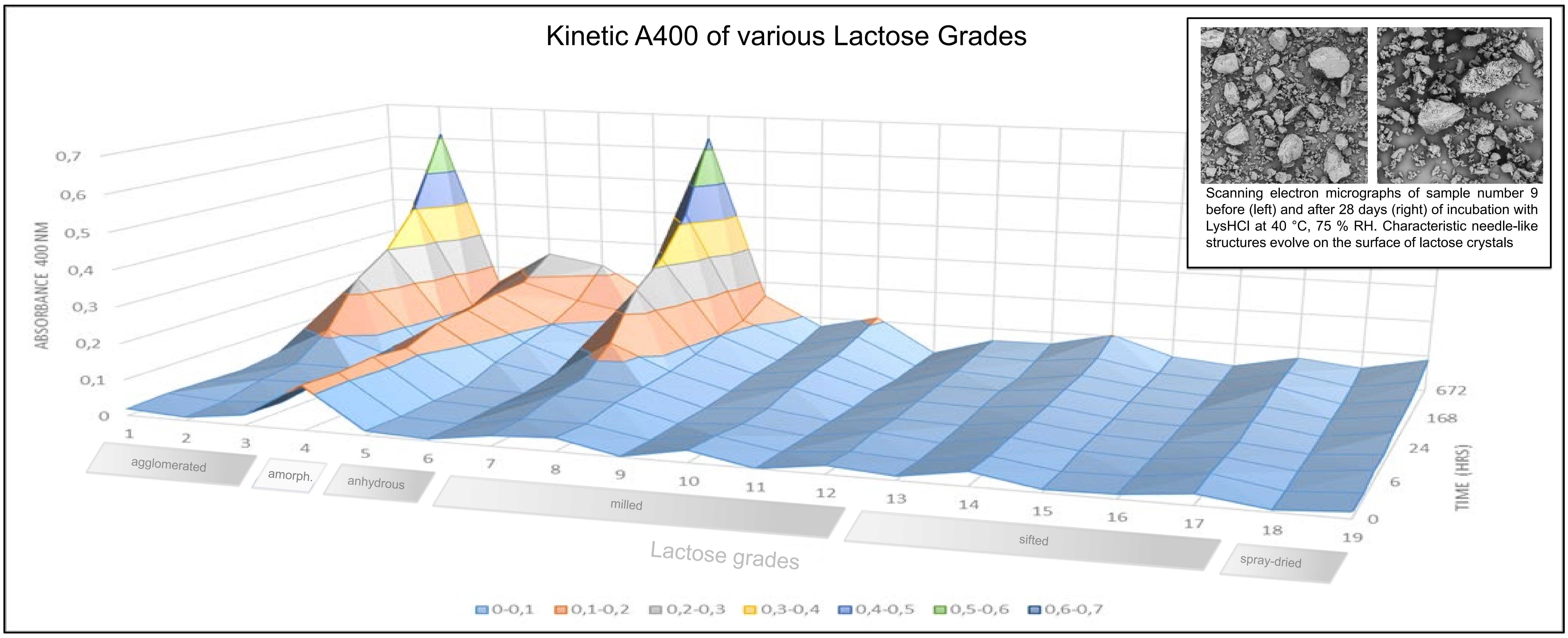
Maillard reaction is a long known chemical, non-enzymatic reaction cascade, caused by the reaction of an amine with a reactive carbonyl group, typically a reducing sugar. An incredibly complex pathway leads finally to brown or dark-colored, polymeric end products with defined taste and texture (Hodge, 1953). The reaction is largely driven by its chemical and physical environment, effects of e.g. metals, pH, pressure, temperature, and water activity have been extensively discussed elsewhere (Nursten, 2005). In nutrition industry this is of utmost functional importance and technological significance. However, in pharmaceutical practice such an outcome is unwanted due to pharmacological reasons when APIs are inactivated, or when the appearance of a dosage form is compromised. Lactose, one of the most frequently used pharmaceutical carriers in inhaled and oral dosage forms, is such a reducing sugar and therefore *Maillard* behavior can be of prime importance. The objective of this work was to elucidate if various, commercially used pharmaceutical lactose grades indicate a different browning tendency in a provocative *Maillard* environment based on their degree of crystallinity, an individual, site-specific manufacturing process, or a specific particle morphology.

Materials & Methods

19 different pharmaceutical lactose qualities (3 agglomerated, 1 amorphous, 2 anhydrous, 6 milled, 5 sifted, and 2 spray-dried grades; Table 1) from 4 different manufacturers (A-D) were investigated using Lysin HCl (LysHCl; Merck) as highly reactive model substance containing two primary amino groups in a 2:1 molar ratio. A Turbula^R mixer (Bachofen, 1l; 10 min, 72 rpm) assisted in the preparation of dry blends, which were incubated in open storage of 5 g aliquots under defined conditions with the aid of a climate chamber (40 °C, 75 % RH). The reaction's progress was monitored by UV absorption at 400 nm (Perkin Elmer, Lambda 25) according to Ph. Eur., and by colorimetry (Hach, LICO^R 690) after complete dissolution in water (70 °C). Results have been corrected for A400 values at t = 0. The explored time period was 28 days, all tests were conducted in triplicate at t = 0, 2, 6, 8, 24, 96, 168, 336, and 672 hrs. Morphological changes of surfaces were investigated with scanning electron microscopy (Phenom^R, ProX Desktop).

Lactose Grade	Sample number	Manufacturer	d_{50}	Span
Agglomerated	1	A	140	1.86
	2	B	171	1.00
	3	C	191	1.28
Amorphous	4	C	n.a.	n.a.
Anhydrous	5	A	50	3.12
	6	C	128	2.31
Milled	7	A	3	2.00
	8	C	8	2.50
	9	C	27	3.26
	10	A	40	2.86
Milled	11	D	48	2.47
	12	A	100	1.95
Sifted	13	C	49	1.59
	14	A	61	1.05
	15	C	126	1.30
	16	A	140	1.35
	17	C	221	0.95
Spray-dried	18	A	110	1.41
	19	C	133	1.11

Table 1. Investigated lactose grades from 4 different manufacturers (A-D), characterized by their d_{50} values and span



Scanning electron micrographs of sample number 9 before (left) and after 28 days (right) of incubation with LysHCl at 40 °C, 75 % RH. Characteristic needle-like structures evolve on the surface of lactose crystals

Figure 1: Response plot of 19 commercially available lactose grades (agglomerated (1-3), amorphous (4), anhydrous (5,6), milled (7-12), sifted (13-17), and spray-dried (18,19)) from 4 different lactose manufacturers and their evolution in UV absorbance at 400 nm (A400) and different time points (t = 0, 2, 6, 8, 24, 96, 168, 336, and 672 hrs) after incubation at 40 °C, 75 % RH. All lactose grades are grouped according to their particle sizes, increasing from left to right

Results

In powder form investigated lactose grades display characteristic, partly colored and textured surface structures when incubated with LysHCl. Dissolving in water at predetermined time points resulted in rather consistent performance of UV spectroscopy at 400 nm and colorimetry. Therefore, only A400 kinetics will be shown comparatively (Figure 1). The **sifted** lactose grades (samples 13-17) displayed only a moderate increase in A400 within 28 days. Sample 14 (d_{50} = 61 μm) reached an A400 maximum in the range of 0.1. Impact of particle size seems to be minor within the sifted lactose grades (particle range: d_{50} between 49 and 221 μm). A very similar behavior is depicted for **spray-dried** lactose grades (samples 18, 19). The changes in A400 are very small, but however there are manufacturer-dependent discrepancies after 672 hrs. For instance, sample 18 (manufacturer A) exhibits a significant lower final A400 value than sample 19 (manufacturer C). **Milled** lactose grades (samples 7-12) show a widely diversified evolution in A400. The finest sample 7 (d_{50} of 3 μm), exhibits a dramatic increase in A400 after 12 hrs, reaching the highest values of all tested samples. This reactivity is lower in coarser milled grades. The reactivity of the milled samples 9-12 is similar to that of sifted and spray-dried grades. In this case, manufacturer-dependent characteristics appear more visible due to materials of similar functionality and morphology. One grade of the **agglomerated** lactose types (samples 1-3) exhibits a very strong increase in A400 (sample 2), whilst the remaining two qualities stayed understated (samples 1, 3). All **anhydrous** lactose grades (samples 5, 6) led to medium A400 values between 0.3 and 0.1, only outperformed by **amorphous** lactose (sample 4). Interestingly, amorphous lactose started already with high initial A400 values at t = 0 and developed a final magnitude slightly above the range of anhydrous lactose.

Conclusion

Commercial lactose grades display a different susceptibility to LysHCl in a provocative *Maillard* system, strongly depending on the investigated lactose grade and its specific manufacturer. An overall ranking in lactose grade reactivity was found: (most stable) sifted > spray-dried > milled > agglomerated > anhydrous > amorphous (less stable), whereby milled lactose grades show a strong dependency on PS/PSD. Fine milled grades tend to develop drastically increased reaction kinetics.

References: [1] Hodge, J. E. Dehydrated Foods, Chemistry of browning Reactions in Model Systems. J. Agric. Food. Chem. 1, 928-943 (1953); [2] Nursten H. The Maillard Reaction. Chemistry, Biochemistry, and Implications, RSC (2005)

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