50 Shades of White – Lactose in Direct Compression

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Introduction

Looking at an excipient suppliers Lactose portfolio, the variety might be overwhelming. There are many different Lactose types, some are unmodified crystals of Lactose Monohydrate und differ mainly in particle size but others have been modified in their habitus by spray drying or wet granulation, still being mainly Lactose Monohydrate. But also several anhydrous Lactose grades are commercially available. This study is designed to give an easy overview of how powder, compaction and tablet properties change with different Lactose types and sizes.

For comparison, a sieved Lactose grade (CapsuLac® 60), a fine milled (GranuLac® 140), three agglomerated (Tablettose® 70/80/100), two spray dried (FlowLac® 90/100) and one anhydrous grade (DuraLac® H) have been chosen. All commercially available by MEGGLE GmbH & Co. KG.

Material & Methods

Particle size distribution (PSD): HELOS laser diffractometer, RODOS dry dispersion (Sympatec GmbH), Lenses: R5, pressure: Tablettose® 80/100: 0.3 bar, CapsuLac® 60/Tablettose® 70/FlowLac® 90/100, DuraLac® H: 0.5 bar, GranuLac® 140: 1 bar. **SEM Images:** Phenom PRO X, Au-sputtered. **Amorphous content**: DVS (ProUmid). **β-content**: Polarimetric measurement. **Permeability:** FT4 Powder Rheometer (Freeman), Pressure drop at 15kPa. **Compressibility Index:** FT4 (Freeman). **Preparation of blends**: Turbula blender TC2 (Willy A. Bachofen), 72 rpm 2 min, 99.5 % Lactose, 0.5 % MgStearate. **Tablet compaction and characterization**: STYL'One (MEDELPHARM). Five compaction pressures between 100-300 MPa. IPC control and calculation of key performance indicators were done according USP-NF. The software "Uncountable" is used as data base for characterization data and for all calculations.

Results I: Powder Characterization

	x_{10} [µm]	x_{50} [µm]	x_{90} [µm]	Span [µm]	Amorph [%]	Beta [%]	AOR [°]	CAR	CI	PD
CapsuLac® 60 (n=3)	155±21	258±27	403±16	1.0±0.1	0.1±0.0	2.9±0.1	31.8±0.8 good	15.8±1.4 fair	3.7±0.1	0.1±0.0
GranuLac® 140 (n=3)	4.2±0.1	35±5	139±12	3.9±0.2	0.3±0.1	3.0±0.3	46.5±1.3 poor	32.2±1.6 very poor	26.6±2.6	10.8±0.5
Tablettose® 70 (n=6)	120±9	214±9	352±9	1.1±0.0	0.3±0.1	2.4±0.4	31.7±0.6 good	17.5±0.8 fair	3.9±0.3	0.2±0.0
Tablettose® 80 (n=9)	47±7	164±19	418±39	2.3±0.2	0.3±0.1	2.3±0.4	32.5±0.3 good	18.8±1.2 fair	6.0±0.6	0.7±0.1
Tablettose® 100 (n=9)	38±3	136±13	333±28	2.2±0.1	0.3±0.2	3.2±1.5	32.8±0.5 good	19.0±1.4 fair	6.3±0.7	0.8±0.1
DuraLac® H (n=3)	9.9±0.2	135±8	332±16	2.4±0.2	0.1±0.0	83.1±1.3	44.2±0.3 passable	18.5±0.7 fair	12.4±0.2	2.5±0.3
FlowLac® 90 (n=6)	66±2	142±3	227±4	1.1±0.0	5.5±0.3	9.1±0.5	27.2±0.5 excellent	12.4±2.2 good	5.5±0.5	0.4±0.1
FlowLac® 100 (n=6)	41±3	129±6	232±13	1.5±0.1	4.3±0.6	7.5±0.5	29.7±0.7 excellent	12.5±2.3 good	5.8±0.2	0.9±0.1

***Table 1:** Powder properties of different Lactose types (mean+SD). PSD via laser diffraction as x_{10}, x_{50}, x_{90}. AOR = Angle of repose, CAR = Carr's Index, CI = Compressibility Index (FT4), PD = Pressure Drop (FT4)*

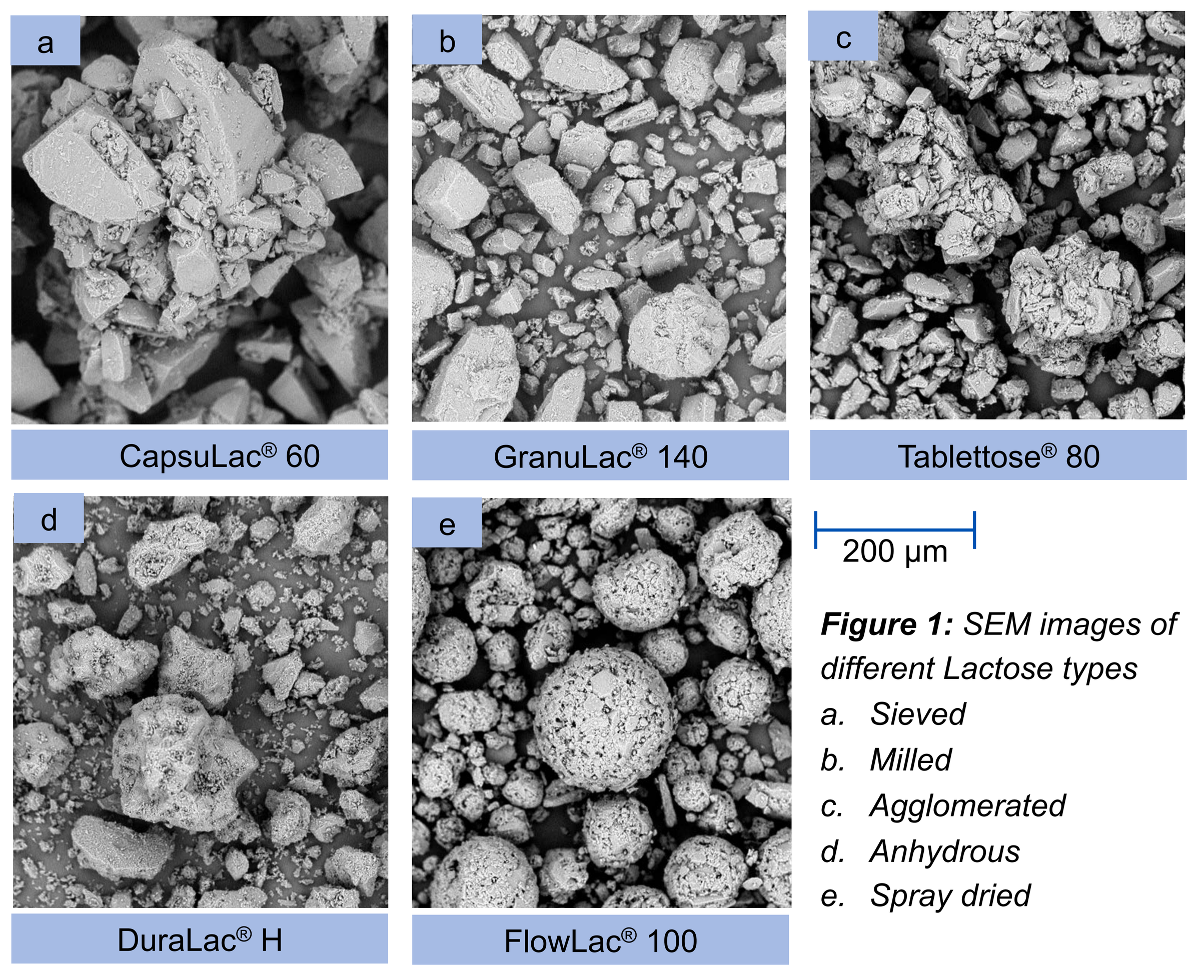

***Figure 1:** SEM images of different Lactose types*
a. Sieved
b. Milled
c. Agglomerated
d. Anhydrous
e. Spray dried

The **amorphous content** was for sieved, milled, anhydrous Lactose and granulated grades (CapsuLac®, GranuLac® 140, Tablettose® 70/80/10, DuraLac® H) below 0.4 %, whereas the amorphous content of spray-dried FlowLac® 90 and 100 was elevated, around 5 and 4 %, respectively.

For those two grades, the **β-content** was also higher (around 8-9 %) compared to the sieved, milled and granulated Lactose (2-3 %). The β-content of anhydrous β-grade DuraLac® H was detected as over 80 %.

According to **Angle of Repose** (AOR) and **Carr Index**, the flow properties of the spray dried grades are superior, followed by CapsuLac® 60 and next the Tablettose® grades.

SEM images help to understand results from flow evaluation, as spray dried Lactose consists of spherical particles. Tablettose®'s agglomerates help to improve flow properties of milled lactose, which is used for Tablettose® production. The coarser, sieved CapsuLac® contains Lactose agglomerates as well, resulting in good/fair flow properties. The anhydrous Lactose surface differs from crystalline Lactose Monohydrate, resulting in more adhesive particles.

Permeability by FT4 powder rheometer is a measure of the powder's resistance to air flow. A vented piston is used to constrain the powder column under a normal stress of 15 kPa, whilst air is passed through the power column. The pressure drop of air between the bottom and the top of the powder column is a function of the powder's permeability. In a tableting process, the efficiency of air removal during the compression step will influence the mechanical properties of the compact, and should air be retained within the tablet due to low powder permeability, capping or lamination may occur ***[1]***. Pressure drop of GranuLac® 140 with 10.78 kPa was significant higher than all other tested products. Despite results of flow evaluation showing similar flow properties of DuraLac® H and GranuLac® 140, a comparatively low pressure drop of 2.1 kPa was detected which is favorable. However, lowest pressure drop was seen for CapsuLac® 60, followed Tablettose® 70 and FlowLac® 90.

Compressibility Index (CI) by FT4: Change in volume after compression [%] was significantly higher for cohesive GranuLac® 140 (26.6 %) followed by DuraLac® H (12.4 %), all other products were between approx. 4-6 %.

Results II: Compaction and Tablet Characterization

	m (kPa/Mpa) Increase kPa TS per MPa	TS@CP150 [MPa]	CP@TS1.5 [MPa]	SF@TS1.5	*FRI@TS1.5 [%]*	*DIS@TS1.5 [s]*
CapsuLac® 60 (n=3)	5.4±0.7	0.6±0.0	319±38	0.94±0.01	--	--
GranuLac® 140 (n=3)	10.7±0.7	1.6±0.0	145±11	0.89±0.01	*3.0±2*	*97±3*
Tablettose® 70 (n=6)	11.0±0.7	1.3±0.0	170±5	0.88±0.01	*1.3±0.2*	*310±116*
Tablettose 80 (n=9)	10.7±0.9	1.3±0.1	171±8	0.88±0.00	*1.2±0.1*	*425±87*
Tablettose 100 (n=9)	12.5±1.4	1.5±0.1	150±11	0.87±0.05	*1.2±0.1*	*256±80*
DuraLac H (n=3)	12.5±1.4	1.6±0.0	146±1	0.87±0.02	*1.2±0.1*	*379±2*
FlowLac 90 (n=6)	19.6±1.3	2.6±0.1	95±7	0.81±0.01	*1.1±0.2*	*134±31*
FlowLac 100 (n=6)	18.8±0.8	2.5±0.2	99±8	0.80±0.01	*1.1±0.0*	*119±24*

***Table 2:** Performance parameters calculated from tabletability curve (m, TS@CP150, CP@TS1.5) and compactability profile (SF@TS1.5). Values for friability and disintegration at tensile strength=1.5 MPa also interpolated.*

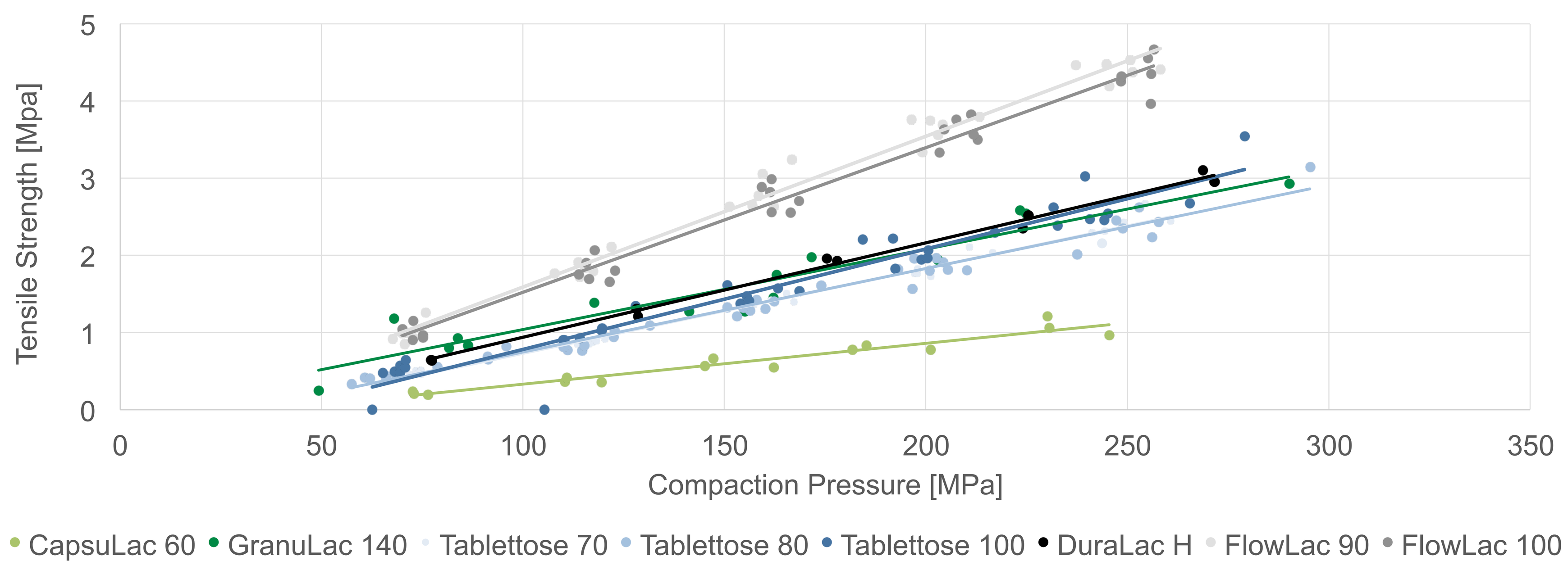

***Figure 2:** Tabletability profile for all included Lactose types.*

Tabletability profile ***(Figure 2)*** shows that for sieved CapsuLac® 60 hardly an acceptable hardness could be achieved whereas for all other Lactose grades sufficient tensile strength (TS) was observed. However, weight uniformity for GranuLac® was with 5% RSD not acceptable. Weight uniformity for all other products was between 0.2-0.3 %, except Tablettose® 80 with 1.2 % RSD in tablet weight. For anhydrous Lactose (DuraLac® H), disintegration time was hardness independent over a wide TS range. At lower TS values, both FlowLac®s showed faster disintegration as the Tablettose®s whereas this was reversed for higher TS values. One reason therefore is that the solid fraction increases for FlowLac® with higher compaction pressure more than for the mainly brittle compacting Tablettose®s.

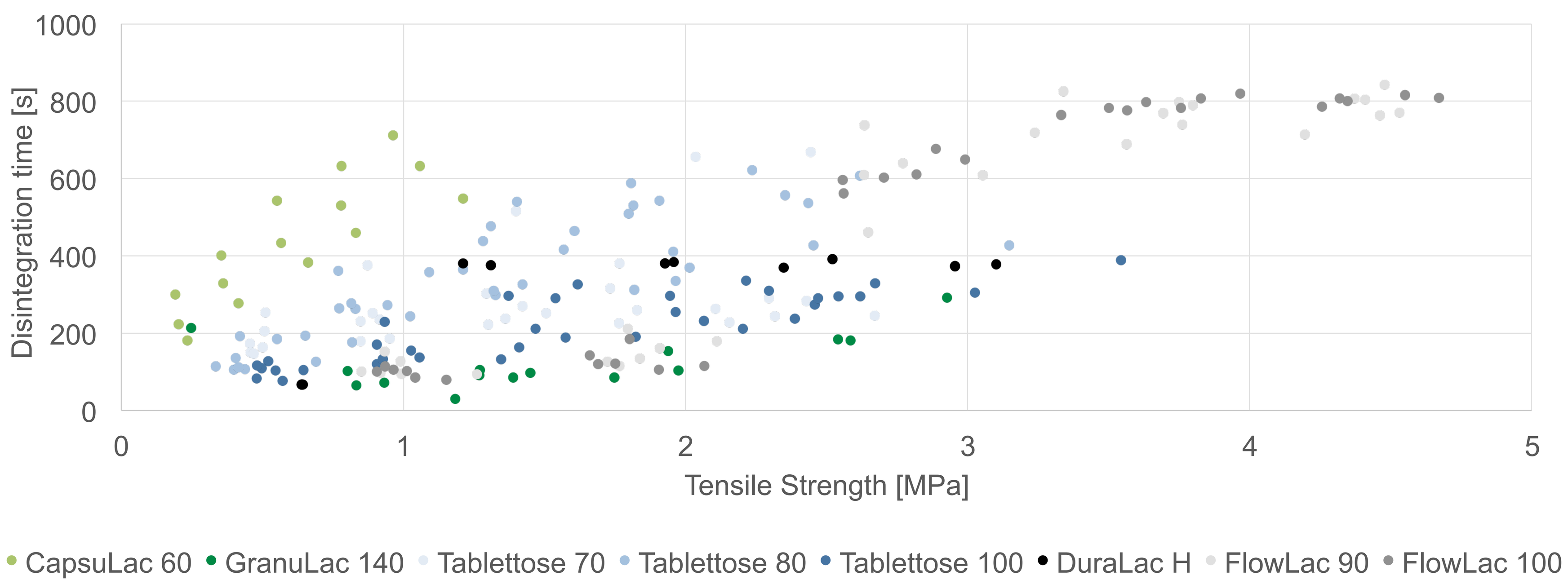

***Figure 3:** Disintegration vs. Tensile Strength for all included Lactose types.*

Conclusion

- Unmodified Lactose like milled or sieved grades are not suitable for direct compression.
- The different approaches to modify Lactose into a direct compressible (DC) excipient – agglomeration, spray drying, roller drying (anhydrous Lactose) – work well. However, this three groups of DC Lactoses do not only show differences in the powder properties but differ significantly in compaction behavior and properties of resulting tablets.
- Within the different groups of DC Lactose grades, differences due to PSD are not as pronounced as between the different groups but not to be neglected.
- This knowledge helps to adjust and optimize formulations.

[1] https://www.freemantech.co.uk/powder-testing/ft4-powder-rheometer-powder-flow-tester/bulk-properties