50 SHADES OF WHITE

Lactose in Direct Compression

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

1. 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.

2. Material & Methods

Particle size distribution (PSD):
HELOS laser diffractometer, RODOS dry dispersion (Sympatec GmbH), Lenses: R5, FlowLac® 90/100: 0.5 bar, DuraLac® H: 0.5-1.0 bar, Tablettose® 70/80/100 /GranuLac® 140: 1.0 bar. Malvern 3000 laser diffractometer, CapsuLac® 60: Dispersion pressure 1.0 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 % Mg Stearate.

Tablet compaction and characterization: STYL'One (MEDELPHARM). Five compaction pressures between 100-300 MPa were used. IPC control and calculation of key performance indicators were done according to USP-NF. The software "Uncountable" is used as data base for characterization data and for all calculations.

3. Results I: Powder Characterization

	Amorph [%]	Beta [%]	AOR [°]	CAR [%]	x10 [µm]	x50 [µm]	x90 [µm]	Span [µm]	CI [%]	PD [mbar]
CapsuLac® 60 (n=3)	0.1	2.5	32 good	16 fair	138	241	407	1.1	3.6	0.1
GranuLac® 140 (n=9)	0.5	2.4	49 poor	31 very poor	5	41	142	3.3	22.2	10.8
Tablettose® 70 (n=12)	0.3	2.2	31 good	17 fair	90	183	313	1.3	4.1	0.2
Tablettose® 80 (n=12)	0.3	2.3	33 good	19 fair	36	132	315	2.1	6.2	0.6
Tablettose® 100 (n=12)	0.3	3.3	33 good	18 fair	32	121	293	2.2	6.3	0.8
DuraLac® H (n=8)	0.1	82.5	43 passable	20 fair	18	170	344	2.0	11.3	1.7
FlowLac® 100 (n=12)	4.4	7.5	30 excellent	13 good	41	131	237	1.5	6.0	0.9
FlowLac® 90 (n=12)	5.5	9.1	28 excellent	12 good	66	144	234	1.2	5.6	0.4

Table 1. Powder properties of different Lactose types (mean+SD). PSD via laser diffraction as x10, x50, x90. AOR= Angle of repose, CAR=Carr's Index, CI=Compressibility Index (FT4), PD=Pressure Drop (FT4)

The **amorphous** content for sieved, milled, anhydrous Lactose and granulated grades (CapsuLac® 60, Granu Lac® 140, Tablettose® 70/80/10, DuraLac® H) was below 0.4 %, whereas the amorphous content of spray dried FlowLac® 90 and 100 was elevated, around 5.5 and 4.4 %, 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 is approx 80 % by Polarimetry.

According to **Angle of Repose** (AOR) and **Carr´s 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 the results from the flow evaluation. Spray dried Lactose has superior flowability as it consists of spherical particles. Tablettose®'s agglomerates help to improve flow properties of milled lactose, which is used for Tablettose® production. The sieved CapsuLac® 60 contains coarse Lactose agglomerates resulting in good/fair flow properties. The anhydrous Lactose surface differs from crystalline Lactose Monohydrate, resulting in more adhesive particles under static flow conditions.

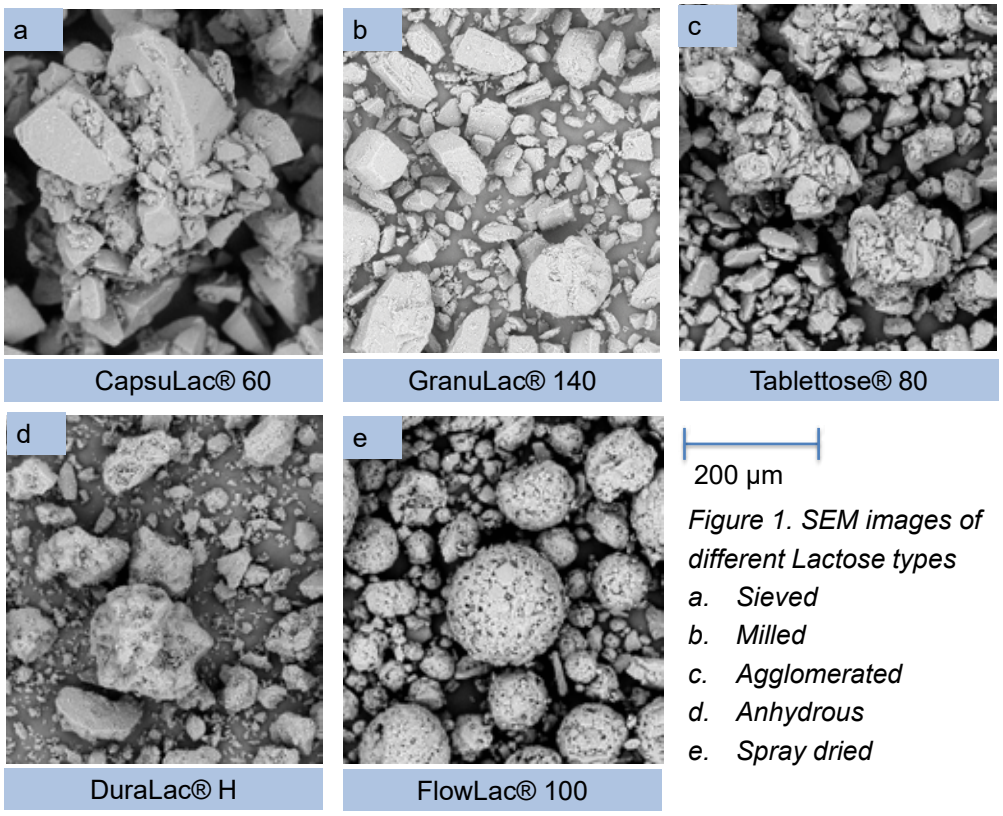

Figure 1. SEM images of different Lactose types

a. Sieved
b. Milled
c. Agglomerated
d. Anhydrous
e. Spray dried

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 10.8 kPa was significant higher than for all other tested products. Despite similar flow properties of DuraLac® H and GranuLac® 140 regarding static flow properties, a comparatively low pressure drop of 2.1 kPa was detected for DuraLac® H, which is favorable. However, lowest pressure drop was seen for CapsuLac® 60, followed by 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 (11.3 %) and all other products were between approx. 4-6 %.

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

4. Results II: Compaction and Tablet Characterization

	Slope m (kPa/MPa) Increase kPa TS per MPa	TS@CP200 [MPa]	CP@TS 2.0 [MPa]	SF@CP 200	SF@TS 2.0	Max. DIS [s]	Max. EF [N]
CapsuLac® 60 (n=3)	5.4	0.9	412	0.91	0. 96	631	380
GranuLac® 140 (n=3)	10.1	2.1	195	0.91	0.91	209	666
Tablettose® 70 (n=12)	10.7	1.8	223	0.89	0.90	384	435
Tablettose® 80 (n=12)	10.9	1.9	214	0.89	0.90	477	510
Tablettose® 100 (n=12)	13.0	2.2	186	0.89	0.87	328	684
DuraLac® H (n=8)	11.9	2.0	197	0,92	0.93	403	683
FlowLac® 100 (n=12)	19.7	3.5	123	0.89	0.83	819	464
FlowLac® 90 (n=12)	19.3	3.6	119	0.89	0.83	779	439

Table 2. KPIs calculated from tabletability curve (Slope, TS@CP 200 or CP@TS 2.0, SF@CP 200, SF@TS 2.0, max. DIS, max. EF). TS=Tensile Strength, CP=Compression Pressure, SF=Solid Fraction, DIS=Dissolution time, EF=Ejection Force

In table 2 common key performance indicators (KPIs) are shown, which have been implemented to allow comparison for large numbers of samples as well as different excipients. They are derived from the profiles defined by USP-NF <1062> Tablet Compression Characterization for tabletability, compactibility and compressibility.

As reference value for Compression Pressure (CP) 200 MPa has been selected. This is a typical value well within normal range of a machine run. The maximum allowed CP depends on the punches, but a typical target is to stay below 300 MPa.

Key reference point for comparison is a Tensile Strength (TS) of 2.0 MPa. This is a typical development target to assure sufficient mechanical strength of tablets for coating/further processing.

As reference value for Solid Fraction (SF) 0.85 has been proposed by the USP-NF. This is a typical value of material with good compressibility at TS of 2.0 MPa. At SF of 0.85 the remaining porosity is 15 %.

The tabletability profile (TS@CP 200 [MPa] or CP@TS 2.0 [MPa]) in table 2 shows the relationship between TS vs. CP. At 200 MPa CP a TS of 2.0 MPa should be achieved. Tablet TS usually increases initially with increasing CP. Depending on tablet composition, TS can either continue to increase or gradually level off at higher pressures. It is also possible that the tablet TS may decrease with increasing pressure, a phenomenon known as overcompression. The tabletability profile of the agglomerated Tablettose® grades show an exact TS value at CP 200 [MPa] between 1.8 and 2.2 which is a sufficient tabletability. CapsuLac® 60, the sieved lactose grade is not sufficient for direct compression, but the achieved TS value at CP 200 [MPa] of 3.5-3.6 of the spray dried FlowLac® grades show a superior tabletability.

The compressibility profile (SF@CP 200) is the dependence of tablet SF on CP. The CP necessary to form a compact with a specified SF (e.g. 0.85) may be used to compare diverse pharmaceutical materials. Use of 0.85 as a reference SF is convenient because many, although not all, pharmaceutical powders can be compressed to this SF, and a reference SF enables comparative assessments of tablet property measurements. All grades show a sufficient compressibility profile.

The compactibility profile (SF@TS 2.0) shows the ability of a powder to form an intact compact with measurable strength. At a TS of 2.0 MPa the goal target should be a SF less or equal 0.85. You can see that all grades have a good compactibility profile, but that the spray dried FlowLac® grades are superior. In comparison with table 1 it can be seen that the intentionally higher amorphous content of FlowLac®, due to the spray drying process, leads to a better compactibility profile (SF@TS 2.0) and superior flowability of these grades.

Other Profiles which can be seen in table 2:
Disintegration Profile (against CP or TS) – Target Disintegration ≤ 15 min *
Max. Ejection Force – Target ≤ 1000 N (max. 1500 N).

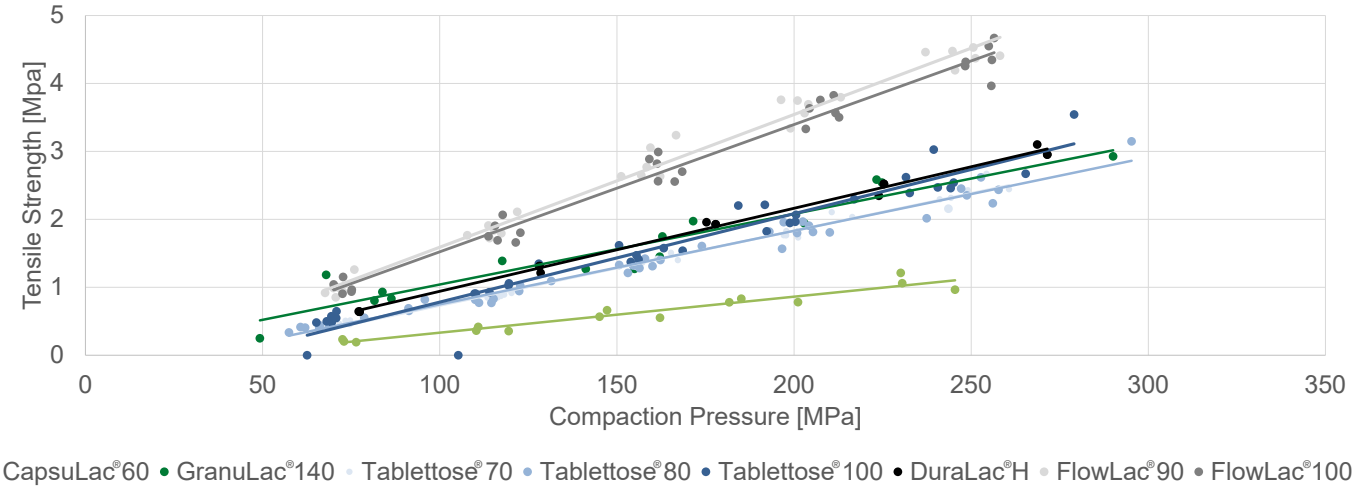

Figure 2. Tabletability profile for all included Lactose types.

For anhydrous Lactose (DuraLac® H), the disintegration time was hardness independent over a wide range. At lower TS values, both FlowLac® grades showed a very fast disintegration, even faster than the Tablettose® s. At higher TS, disintegration time for FlowLac® increases. One reason therefore is that the solid fraction increases for FlowLac® with higher compaction pressure and even more than for the mainly brittle compacting Tablettose®s.

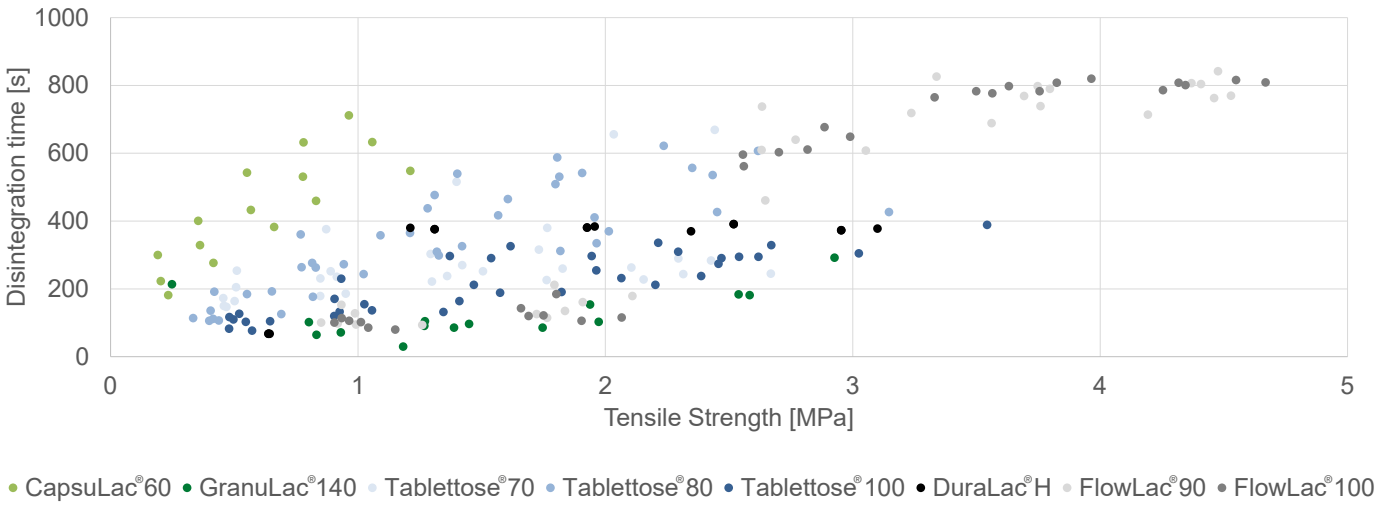

Figure 3. Disintegration vs. Tensile Strength for all included Lactose types.

5. 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, modification of crytallization/polymorphic form (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.
- The intentionally higher amorphous content of spray dried lactose due to the spray drying process, leads to a better compactibility profile (SF@TS 2.0) and superior flowability of these grades.
- With a superior flowability DC lactose grades show advantages in continuous manufacturing, but also may promote segregation in certain cases.
- Even though a product can have inferior flowability (Tablettose® 100 vs. 70) because of the fine partcle fraction, it shows a better blend uniformity in low dose formulations because of the higher amount of fines.

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