



TABLETING | DIRECT COMPRESSION | AGGLOMERATED LACTOSE

TABLETTULOSE

Technical brochure

General information

Direct compression (DC) tablet manufacturing is a popular choice because it provides the least complex, most cost effective process to produce tablets compared to other tablet manufacturing approaches. Manufacturers can blend APIs with excipients and compress, making dosage forms simple to produce [1, 2].

DC technology and the use of modern tableting equipment require that excipients and APIs form a compactible mixture with good flowability and low particle segregation tendency [3].

In the pharmaceutical industry, lactose is one of the most commonly used excipients; however, like many other excipients, lactose may not be suitable for DC without modification due to insufficient powder flow (**figure 1**).

The brittle alpha-lactose monohydrate compactibility is strongly dependent on the powder surface area before compaction and the fragmentation produced during the compaction event. The binding capacity increases with increasing powder surface area, suggesting that the smaller the lactose particles become, the more compactibility improves. While the small particles offer relatively good dry binding properties, poor flowability makes milled alpha-lactose monohydrate unsuitable for DC.

Coarser particle size alpha-lactose monohydrate sieve fractions show good flow properties, but very poor compressibility.

For these reasons, MEGGLE developed directly compressible, agglomerated alpha-lactose monohydrate in the mid 1970s, combining the good flowability of coarse lactose and good compactibility of fine milled lactose. The product is marketed as the brand name Tablettose®. Tablettose® is manufactured by a continuous spray agglomeration process.

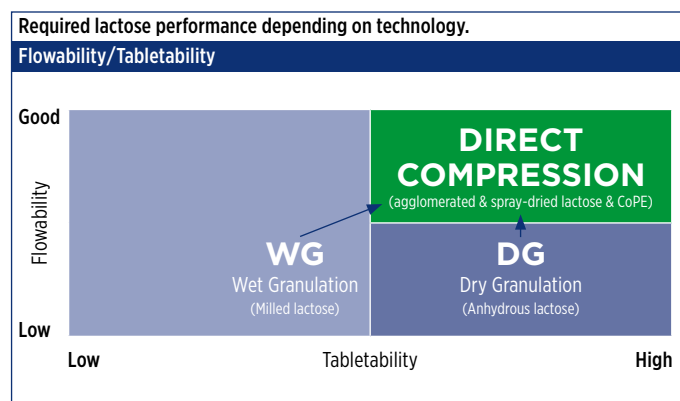


Figure 1: Lactose with high flowability and compressibility leads to DC. Lactose with poor flow needs to be processed with wet or dry granulation.

Water is used as the binder and is sprayed onto fluidized fine milled lactose particles, creating liquid bridges to form agglomerated lactose (**figure 2**). The added water is later evaporated and the liquid bridges are maintained. With this process, no amorphous lactose is produced, resulting in a very stable, non-hygroscopic, pure alpha-lactose monohydrate powder.

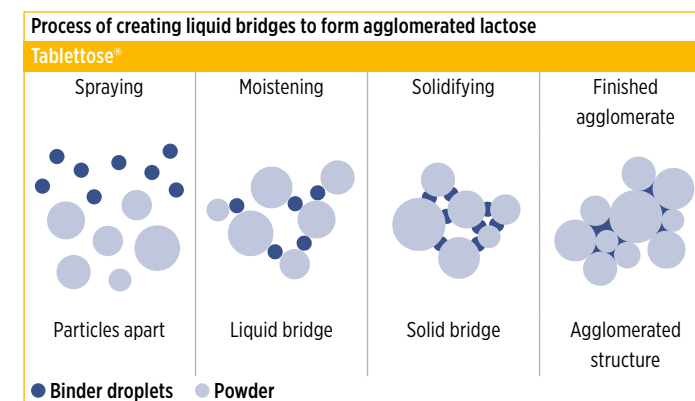


Figure 2: Different stages of the agglomeration process using milled grade lactose plus water to create liquid bridges between the particles.

Product description

MEGGLE's Tablettose® 80 was the first available agglomerated alpha-lactose monohydrate of its kind. Its agglomerates possess a size ranging from 0 – 630 µm. Tablettose® 80 is suitable for most low dosage formulations. Tablettose® 70 is manufactured using identical starting material; however, the particle size distribution is narrower. The content of fines smaller than 63 µm is reduced significantly and there are no particles larger than 500 µm, making Tablettose® 70 the excipient of choice for narrow particle size distribution and dust free production.

Tablettose® 100 is produced from a smaller starting particle size than the material used for Tablettose® 70 and Tablettose® 80. As a result, Tablettose® 100 with its increased binding capacity has a higher dilution potential compared to Tablettose® 70 and Tablettose® 80 due to increased compressibility. Therefore Tablettose® 100 is the excipient of choice for formulations requiring enhanced compactibility and content uniformity. In addition, its fine particle size and superior adhesion make it particularly suitable for low-dose, fine API blends, reducing segregation and ensuring consistent dosing.

Tablettose® was developed especially for direct compression processes.

APPLICATION

Tablettose®

- Direct compression
- Continuous applications
- Capsule and sachet filling
- Effervescent tablets
- Artificial sweetener tablets

BENEFITS

Tablettose®

- Low hygroscopicity
- Excellent stability
- Superior blending characteristics
- Good flowability
- Good compactibility
- Low moisture content
- Fast disintegration times
- Economic efficient

MEGGLE Low Nitrite grades

Due to the nitrosamine issue, the risk assessment and review of nitrite content in excipients have become essential. Pharmaceutical manufacturers must take appropriate measures, especially for critical products. MEGGLE supports manufacturers by offering Low Nitrite grades with nitrite content measured for every production lot. The specified nitrite limit is part of the official product specification and the corresponding Certificate of Analysis (CoA), making risk assessments easier and ensuring compliance with regulatory expectations.

Regulatory & quality information

Tablettose® 70, Tablettose® 80, and Tablettose® 100 are MEGGLE's trade names for agglomerated alpha-lactose monohydrate and comply with the current harmonized Ph. Eur., USP-NF, JP and ChP monographs. Specifications and regulatory documents can be downloaded from www.meggle-excipients.com.

Our pharma-dedicated production facility in Wasserburg am Inn, Germany, is certified according to DIN EN ISO 9001 and has implemented GMP according to the Joint IPEC-PQG (Good Manufacturing Practices Guide for Pharmaceutical Excipients) and USP-NF General Chapter <1078>. GOOD MANUFACTURING PRACTICES FOR BULK PHARMACEUTICAL EXCIPIENTS. MEGGLE has been an EXCiPACT™-certified excipient manufacturer and supplier since 2014.

The Wasserburg facility demonstrates MEGGLE's complete lactose production capability range, including sieving, milling, agglomeration, spray-drying, and co-processing. Additionally MEGGLE is a member of IPEC (International Pharmaceutical Excipients Council).

MEGGLE invests considerably in the sustainability of raw material sourcing, production standards, and efficiency. We are actively engaged in environmental protection. In order to guarantee the quality of our products, our commitment and adherence to established pharmaceutical standards is our highest priority.



Particle Size Distribution (PSD)

Figure 3 shows typical PSD data (obtained by laser diffraction) for MEGGLE's agglomerated lactose grades Tablettose®. Tablettose® 80 and Tablettose® 100 exhibit similar PSDs. Comparatively, Tablettose® 70 demonstrates a narrower PSD due to fewer fines.

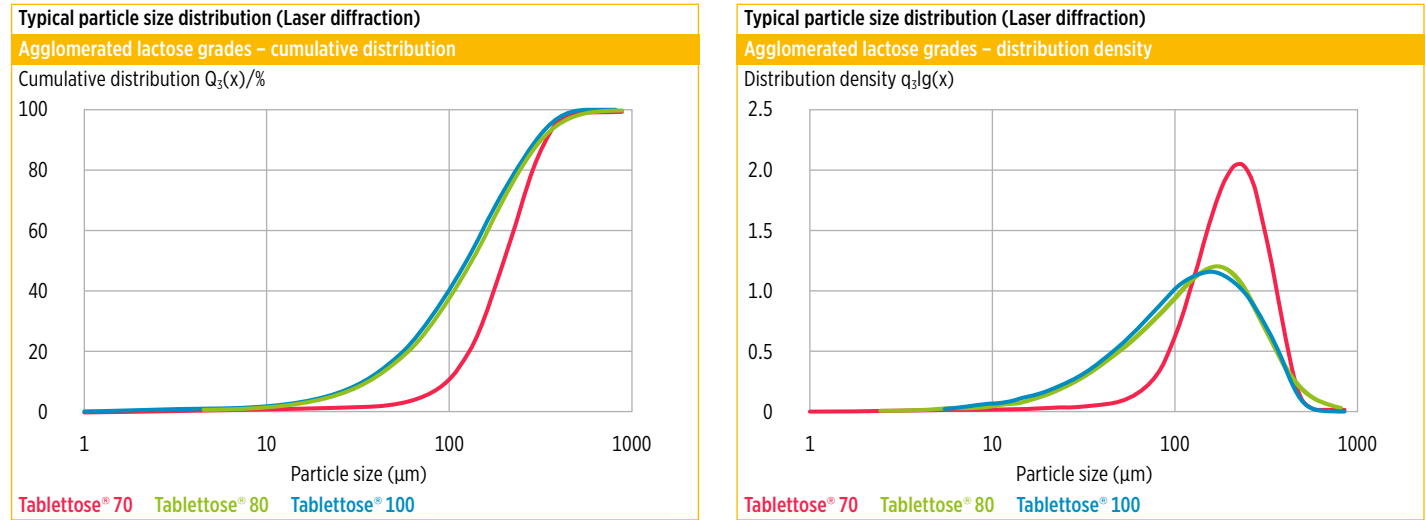


Figure 3: Typical cumulative PSD and distribution density of MEGGLE's agglomerated lactose grades Tablettose® 70, Tablettose® 80, and Tablettose® 100. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.

Particle Size Distribution (PSD) & Morphology (SEM)

Figure 4 illustrates the PSD ranges for MEGGLE's Tablettose® grades and their typical Scanning Electron Microscope (SEM) images. The PSD is obtained using a mechanical sieve shaker and is shown in bold letters. Typical values generated through continuous in-process control are provided for information only. The SEM images show the typical rough, structured surface of Tablettose® agglomerates. Due to its characteristic shape, Tablettose® provides stable and homogeneous mixtures with other excipients and APIs.

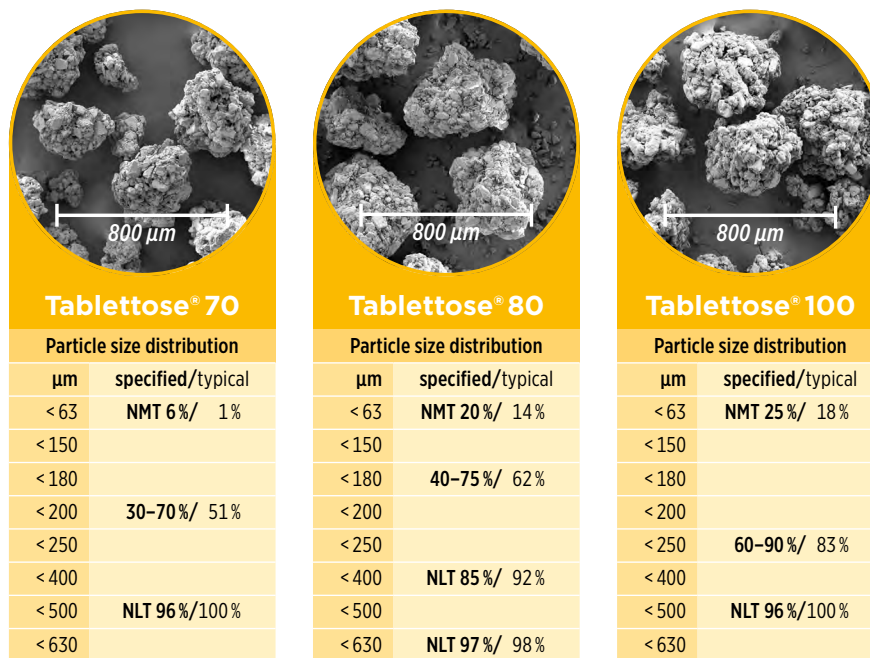


Figure 4: Specified PSD ranges for MEGGLE's agglomerated lactose grades by mechanical sieving in bold letters. Typical values obtained from a permanent in-process control are shown for orientation. SEM images of all agglomerated MEGGLE lactose grades by ZEISS Ultra 55 FESEM (U = 5 kV; Au/Pd sputtered).

Functional related characteristics – Part 1

Powder flow

It is well known that particle size and shape influence powder flowability. Particles less than 100 µm tend to be more cohesive and less freely flowing, whereas larger, denser particles tend to be more freely flowing. Particle morphology also significantly affects powder flow characteristics.

Classification of powder flow according to Ph. Eur.

Flow property	Carr's Index (%)	Angle of Repose (°)	Hausner ratio
Excellent	1 – 10	25 – 30	1.00 – 1.11
Good	11 – 15	31 – 35	1.12 – 1.18
Fair	16 – 20	36 – 40	1.19 – 1.25
Passable	21 – 25	41 – 45	1.26 – 1.34
Poor	26 – 31	46 – 55	1.35 – 1.45
Very poor	32 – 37	56 – 65	1.46 – 1.59
Very, very poor	> 38	> 66	> 1.60

Figure 5: Calculation of the CI, the Angle of Repose (AoR) and the Hausner ratio. Classification according to Ph. Eur. 2.9.36. A CI below 11, a AoR of 25 – 30 and a Hausner Ratio below 1.12 implies excellent flow property of the material. A value between 21 – 25 (CI), 41 – 45 (AoR) and 1.26 – 1.34 (Hausner Ratio) implies passable flow property.

$$\text{Carr's Index (CI)} = \left(\frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \right) \times 100$$

$$\text{Angle of Repose (°)} = \left(\frac{\text{height of the cone}}{\frac{1}{2} \text{ fixed base}} \right)$$

$$\text{Hausner ratio} = \left(\frac{\rho_{\text{tapped}}}{\rho_{\text{untapped}}} \right)$$

Figure 6 shows typical flowability indices for Tablettose® grades, indicating the very good flowability possessed by agglomerated lactose. All agglomerated lactose grades show good to fair flowability, with CI values between 17 – 18%, angle of repose values between 32 – 33° and a Hausner ratio between 1.20 and 1.22.

Flowability					
Agglomerated lactose					
	Carr's Index (%)	Angle of Repose (°)	Hausner ratio	Density bulk (g/l)	Density tapped (g/l)
Tablettose® 70	17	32	1.20	540	649
Tablettose® 80	18	33	1.22	599	731
Tablettose® 100	18	33	1.22	584	714

Figure 6: Typical technological values, describing powder flowability, shown for agglomerated MEGGLE lactose grades.

Figure 7 demonstrates that particle shape and structure are as important as particle size distribution for powder flowability. Due to its structure, Tablettose® has a nearly spherical shape, resulting in a lower CI compared to milled (GranuLac® 70) lactose. Additionally GranuLac® 70 after granulation (GranuLac® 70 Granules) shows also a lower CI than just milled grade lactose, but still a worse flowability than Tablettose® 70.

Scatter Plot of CI (Carr's Index)

Tablettose® vs. GranuLac®

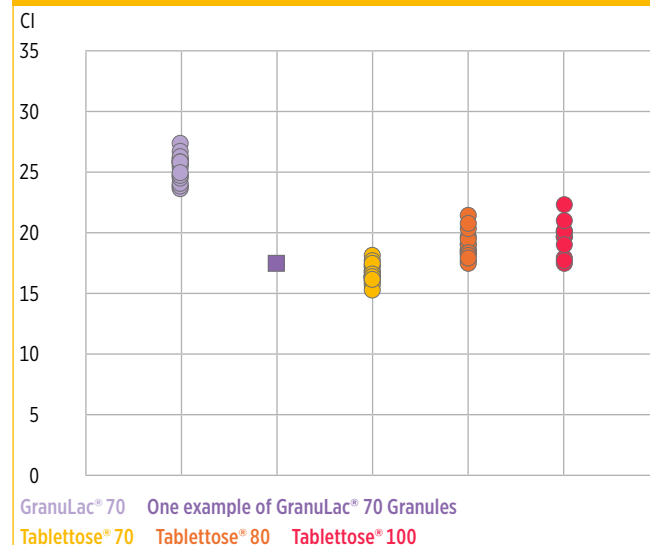


Figure 7: Carr's Index of Tablettose® grades compared to one example of GranuLac® 70 Granules and GranuLac® 70

Functional related characteristics – Part 2

Tabletability profile

Figure 8 shows that tablets made with Tablettose® 70 and Tablettose® 80 possess similar compaction profiles. Tablettose® 100 exhibits increased compactibility as shown by harder tablets over the same compaction pressure range. This is due to the finer initial particle size, which increases the material's binding capacity.

Calculation of Compaction Pressure (CP) and Tensile Strength (TS) for cylindric tablets

$$CP = 4 \times \frac{F_{Comp}}{\pi \times D^2} \times 1000 \quad [\text{kN} \times 1000/\text{mm}^2 = \text{MPa}]$$

$$TS = 2 \times \frac{F_{Tablets}}{\pi \times D \times H} \quad [\text{N}/\text{mm}^2 = \text{MPa}]$$

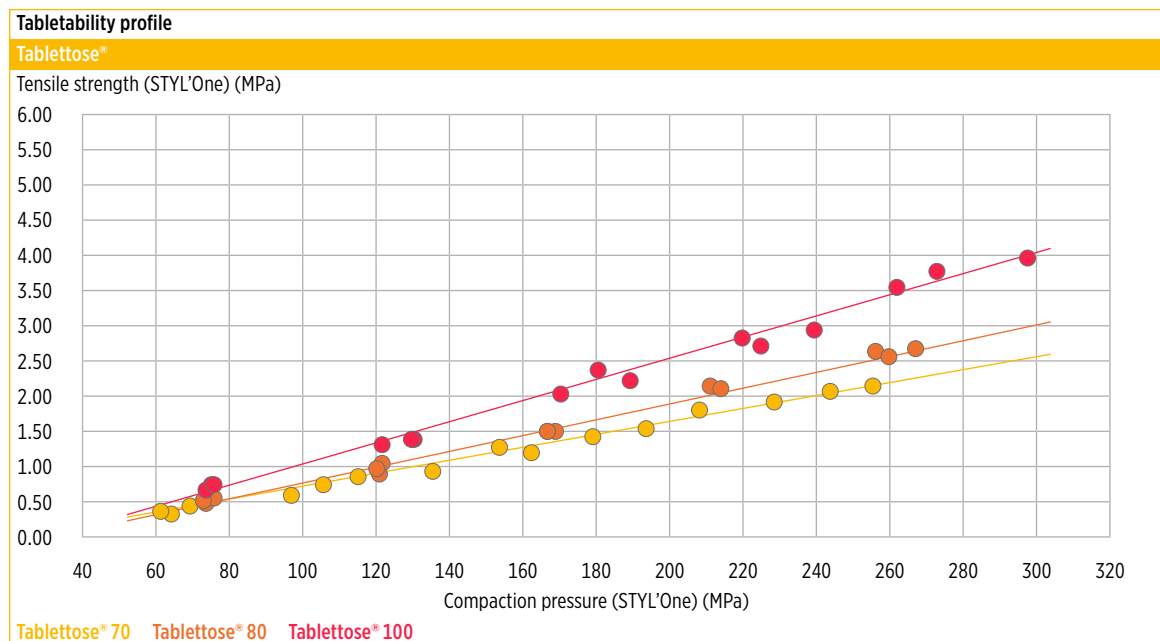


Figure 8:

Tabletability profile of Tablettose®, showing a better tabletability as finer the material. Tablet press: MEDELPHARM STYL'One, Tablets: Ø 11.3 mm, (Tablettose® 100: Ø 11.4 mm), 500 mg.

Batch-to-batch consistency

Batch-to-batch consistency for all lactose products can be attributed to MEGGLE's long history and experience in lactose manufacturing, and broad technical expertise. Constant in-process and final product testing ensures consistency and quality (**figure 9**).

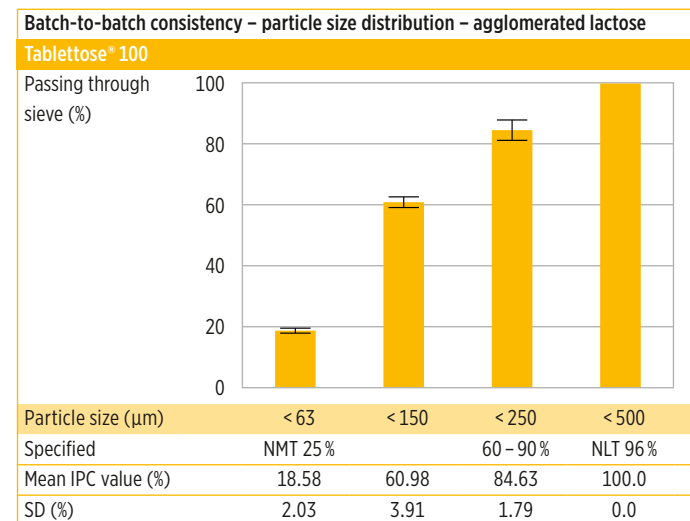
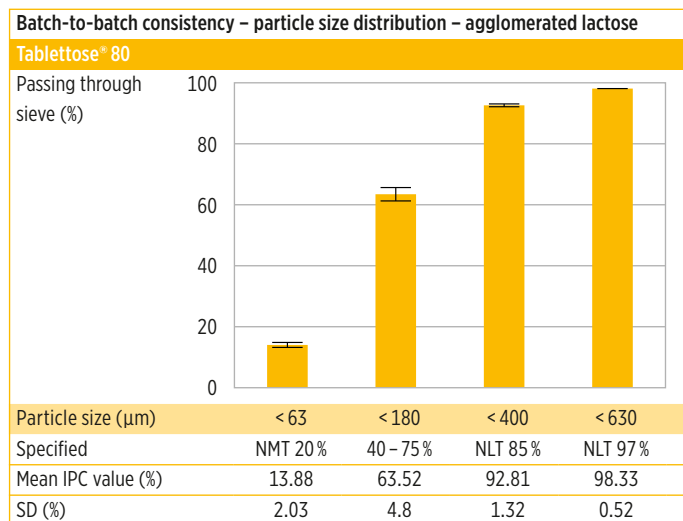
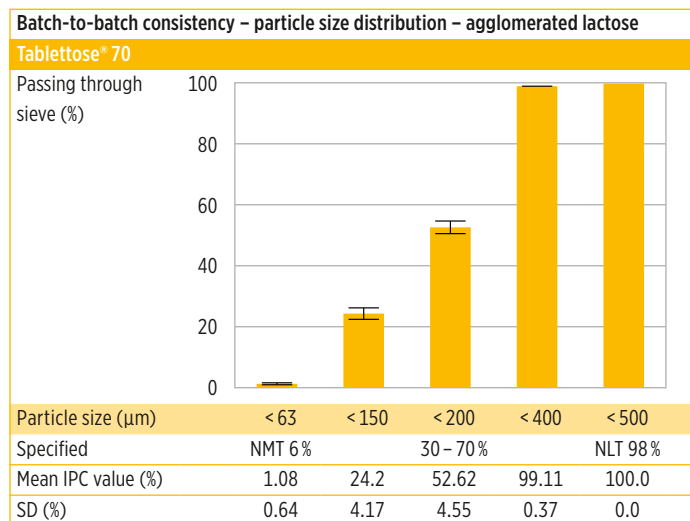


Figure 9: Particle size distribution batch-to-batch consistency of Tablettose® by mechanical sieve shaker. Data obtained from a permanent in-process control (IPC) of subsequent batches over 12 months.

Isotherm

MEGGLE's agglomerated lactose products do not adsorb significant amounts of water below 90 % relative humidity (25 °C). **Figure 10** shows sorption and desorption isotherm for Tablettose® 80.

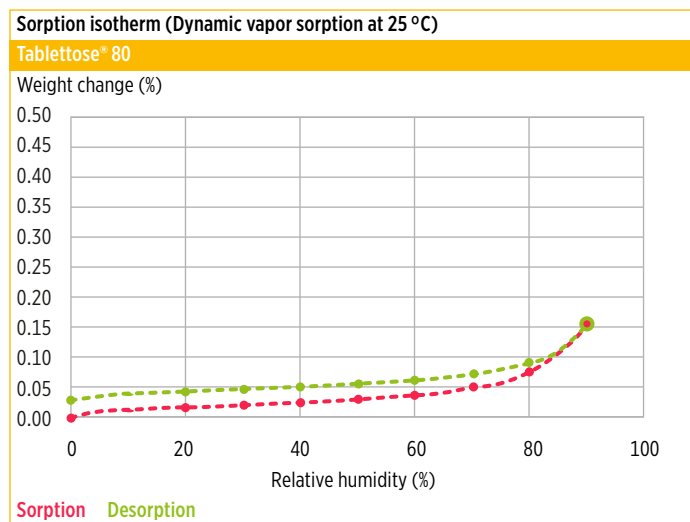


Figure 10: Sorption-desorption isotherm (25 °C) of Tablettose® 80. Analysis performed with SPSx-1µ Advance (proUmid GmbH & Co. KG, Ulm, Germany).

Packaging and shelf life

Packaging material complies with Regulation (EC) No.1935/2004 and 21 CFR 174, 175, 176, 177 and 178. Stability tests have been performed according to ICH guidelines and an ongoing stability program is implemented. **Figure 11** provides an overview about packaging size and material, and product shelf life.

Packaging and shelf life – agglomerated lactose			
	Size	Material	Shelf life
Tablettose® 70	20 kg	Paper bag with PE-EVOH-PE inliner	36 Months
Tablettose® 80	25 kg		
Tablettose® 100			24 Months

Figure 11: Packaging and shelf life of MEGGLE's agglomerated lactose grades.

Literature

- [1] Meeus, L. (2011). Direct Compression versus Granulation. Pharmaceutical Technology, 23(3). pharmtech.com
- [2] Kristensen, H. G., Schaefer, T. (1987). Granulation: A Review on Pharmaceutical Wet-Granulation. Drug Development and Industrial Pharmacy, 13(4-5), 803-872. tandfonline.com
- [3] Hein, S., Picker-Freyer, K. M., & Langridge, J. (2008). Simulation of roller compaction with subsequent tableting and characterization of lactose and microcrystalline cellulose. Pharmaceutical Development and Technology, 13(6), 523-532. doi.org

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