TABLETTOSE

TABLETING →
DIRECT COMPRESSION →
AGGLOMERATED LACTOSE

Technical brochure Tablettose®

MEGGLE
EXCIPIENTS & TECHNOLOGY

MEGGLE agglomerated lactose grades for direct compression: Tablettose®

General information

Direct compression (DC) tablet manufacture 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 excellent 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 direct compression without modification due to insufficient powder flow or/and compaction properties **(Figure 1)**.

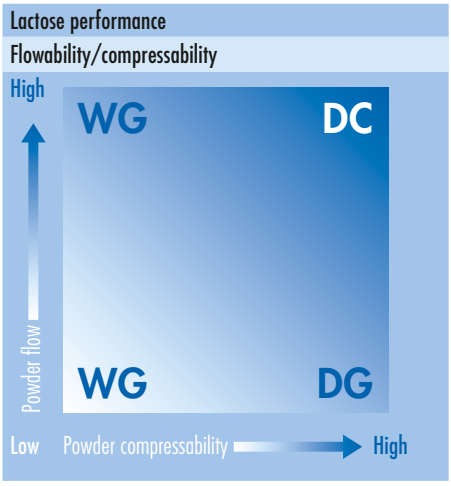
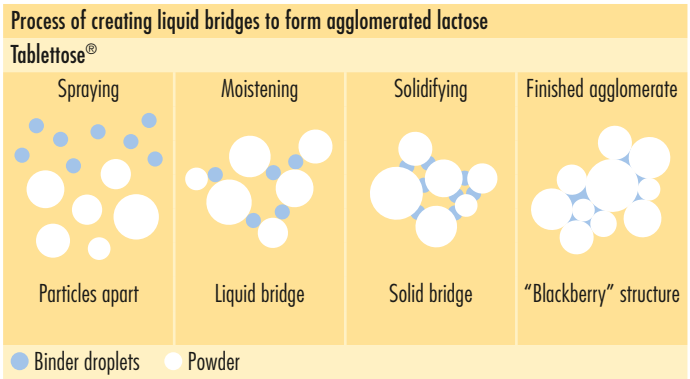


Figure 1: Powder blend compressability and flowability requirements for various tableting technologies (DC is direct compression, WG is wet granulation, DG is dry granulation) [3].

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 direct compression. Coarser particle size alpha-lactose monohydrate sieve fractions show good flow properties, but very poor compressability [4].

For these reasons, MEGGLE developed directly compressable, 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. Water is used as the binder and is sprayed onto fluidized fine milled lactose particles, creating liquid bridges to form agglomerated lactose. 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.



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® 80 and Tablettose® 70. As a result, Tablettose® 100 has a higher dilution potential compared to Tablettose® 70 and Tablettose® 80 due to increased compactibility.

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, and JP monographs. Specifications and regulatory documents can be downloaded from www.meggle-pharma.com.

Our pharma-dedicated production facility in Wasserburg, Germany is certified according to DIN ISO 9001:2008, has implemented cGMP according to the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients and USP General Information Chapter <1078>. 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 raw material resource sustainability, production standards, efficiency and is actively engaged in environmental protection. Lactose meeting pharmaceutical standards is our first priority.

Application

Tablettose® was developed especially for direct compression processes. The following chart provides recommended areas of application.

- Low dose DC formulations
- Capsule and sachet filling
- Effervescent tablets
- Artificial sweetener tablets

BENEFITS

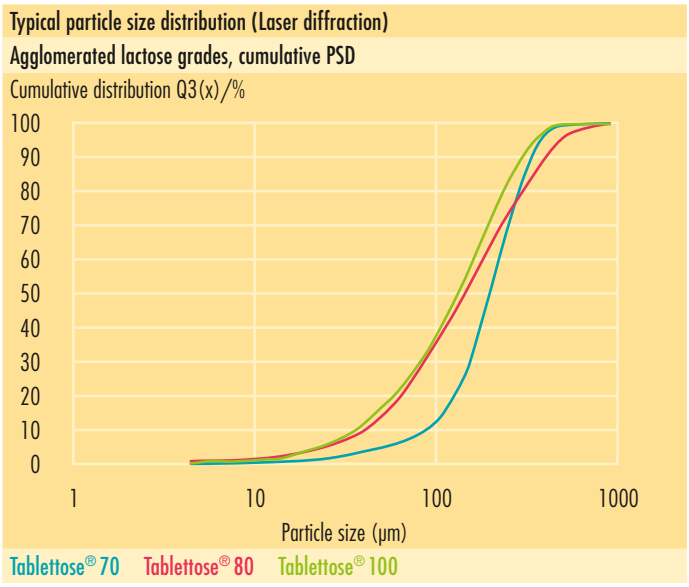
Tablettose®

- Very good flowability
- Very good compactibility
- Low hygroscopicity
- Excellent stability
- Superior blending characteristics
- Fast disintegration times

Particle size distribution (PSD)

Figure 2 shows typical laser diffraction particle size distribution data for MEGGLES agglomerated lactose grades Tablettose®. Tablettose® 80 and Tablettose® 100 exhibit similar particle size distributions. Comparatively, Tablettose® 70 demonstrates a narrower particle size distribution due to fewer fines.

Figure 3 depicts the specified PSD range and typical average values by mechanical sieve shaker. These parameters are constantly monitored through in-process-control (IPC) testing and are part of Tablettose®'s particle size distribution specification.



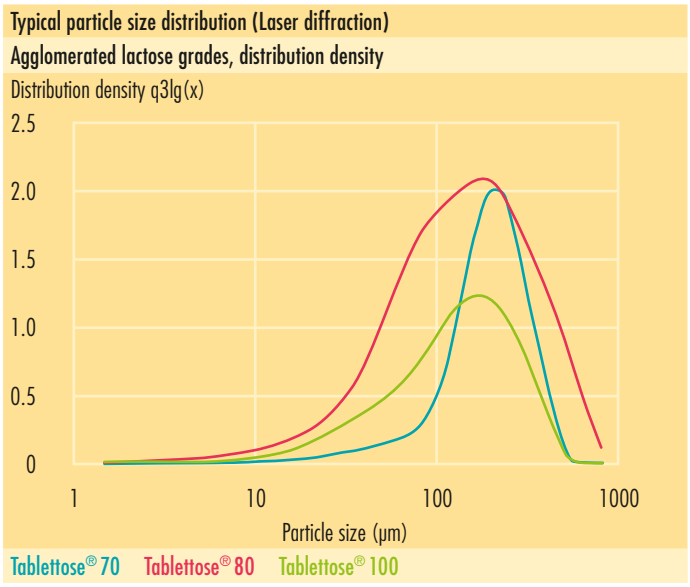


Figure 2: Typical cumulative PSD and distribution density of MEGGLE´s agglomerated lactose grades Tablettose® 70, Tablettose® 80, and Tablettose® 100. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.

Sieve data – agglomerated lactose

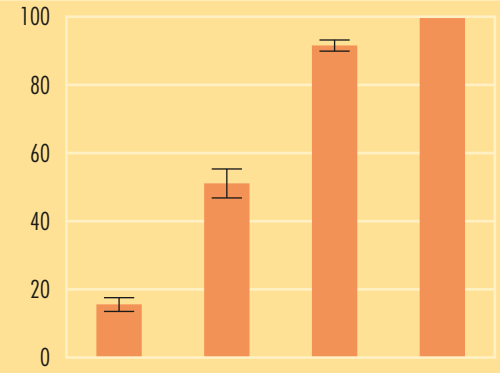
	Lactose type	Tablettose® 70	Tablettose® 80	Tablettose® 100
		specified/typical	specified/typical	specified/typical
Particle size distribution	< 62 µm	**NMT 6 %**/3 %	**NMT 20 %**/16 %	**NMT 25 %**/14 %
Method:	< 150 µm	/20 %		/49 %
Mechanical sieve shaker	< 180 µm		**40 – 75 %**/51 %	
	< 200 µm	**30 – 70 %**/49 %		
	< 250 µm			**60 – 90 %**/82 %
	< 400 µm	/97 %	**NLT 85 %**/92 %	
	< 500 µm	**NLT 98 %**/100 %		**NLT 96 %**/100 %
	< 630 µm		**NLT 97 %**/100 %	

Figure 3: Specified PSDs for MEGGLE's agglomerated lactose grades by mechanical sieve shaker in bold letters. Typical values obtained from a permanent in-process-control are shown for orientation.

Batch-to-batch consistency

Batch-to-batch consistency for all lactose products can be attributed to MEGGLE's long history and experience in lactose manufacture, and broad technical expertise. Constant in-process and final product testing ensures consistency and quality **(Figure 4)**.

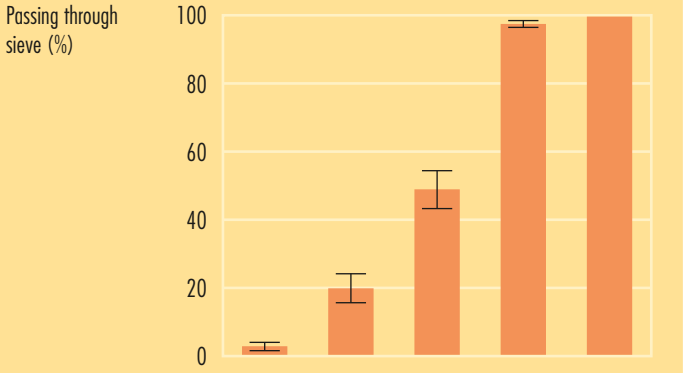
Batch-to-batch consistency – particle size distribution – agglomerated lactose Tablettose® 80



Particle size (µm)	< 63	< 180	< 400	< 630
Specified	NMT 20 %	40 – 75 %	NLT 85 %	NLT 97 %
Mean IPC value (%)	15.7	51.0	92.0	100.0
SD (%)	2.1	4.2	1.5	0.0

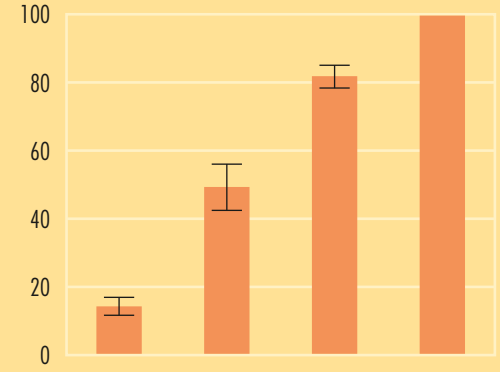
Figure 4: Particle size distribution batch-to-batch consistency of Tablettose® by mechanical sieve shaker. Data obtained from a permanent in-process-control (IPC) of subsequent batches over 12 months.

Batch-to-batch consistency – particle size distribution – agglomerated lactose Tablettose® 70



Particle size (µm)	< 63	< 150	< 200	< 400	< 500
Specified	NMT 6 %		30 – 70 %		NLT 98 %
Mean IPC value (%)	2.8	19.9	48.8	97.3	100.0
SD (%)	1.2	4.2	5.6	0.9	0.0

Batch-to-batch consistency – particle size distribution – agglomerated lactose Tablettose® 100



Particle size (µm)	< 63	< 150	< 250	< 500
Specified	NMT 25 %		60 – 90 %	NLT 96 %
Mean IPC value (%)	14.2	49.1	81.6	99.9
SD (%)	2.6	6.8	3.3	0.1

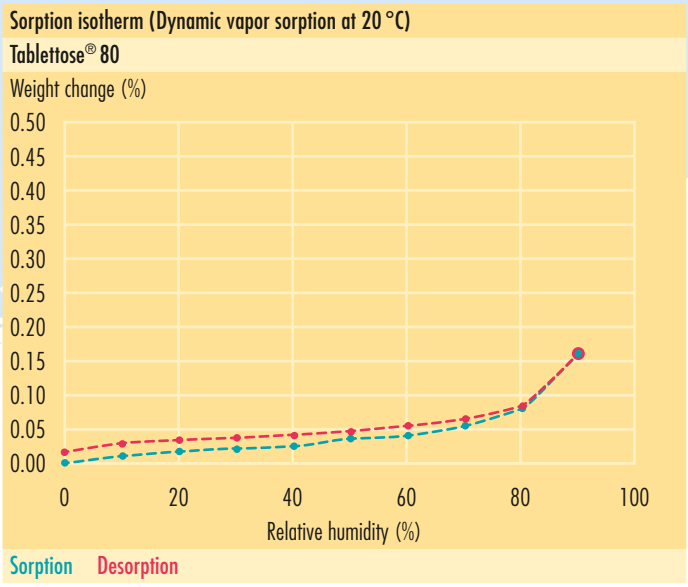


Figure 5: Sorption-desorption isotherm of agglomerated lactose, using Tablettose® 80 as an example.

Isotherms

All alpha-lactose monohydrate-based grades do not adsorb water significantly below 80 % relative humidity at 20 °C.
Figure 5 shows sorption and desorption isotherms for Tablettose®. This demonstrates that agglomerated alpha-lactose monohydrate is non-hygroscopic, and therefore very stable and pure.

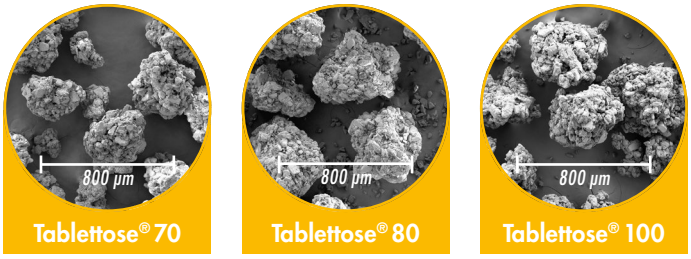


Figure 6: SEM images of various agglomerated MEGGLE lactose grades.

Scanning electron micrograph (SEM)

Tablettose® agglomerates typically have a rough, structured surface, which can be seen in **Figure 6**. Due its characteristic shape, Tablettose® provides stable, homogenous mixtures with other excipients and APIs.

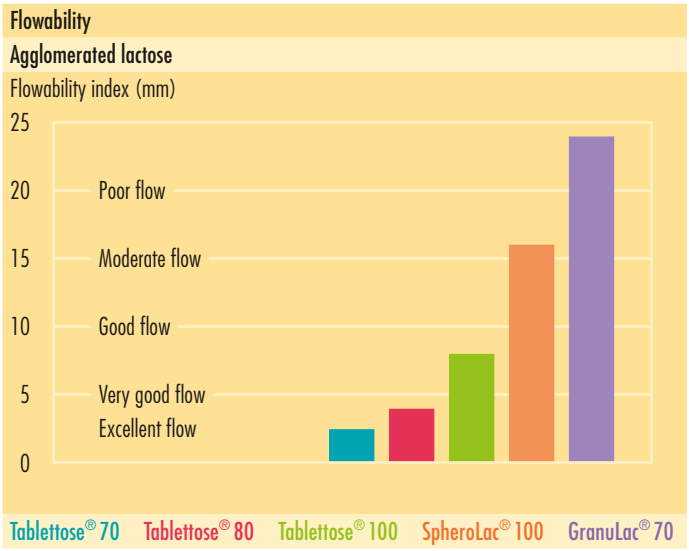


Figure 7: Flowability index of Tablettose® grades compared to unmodified lactose grades.

Functional related characteristics

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. **Figure 7** demonstrates that particle shape and structure are as important as particle size distribution for powder flowability. Due to its "blackberry" or "popcorn" structure, agglomerated lactose has a nearly spherical shape, resulting in a lower flowability index FI (powder through an orifice) compared to sieved (SpheroLac® 100) or milled (GranuLac® 70) lactose.

Flowability can also be described by the Hausner ratio, Carr's index, or angle of repose. A Hausner ratio below 1.25 or Carr's index below 20 indicates that powders are freely flowing. Angle of repose describes "good flowability" between 31–35°, and in general, worsens with steeper angles. **Figure 8** shows typical flowability indices for Tablettose® grades, indicating the very good flowability possessed by agglomerated lactose.

Flowability

Agglomerated lactose

	Angle of repose (°)	Density bulk (g/l)	Density tapped (g/l)	Hausner ratio	Carr's index (%)
Tablettose® 70	31	530	640	1.21	17.19
Tablettose® 80	34	620	770	1.24	19.48
Tablettose® 100	32	580	720	1.24	19.44

Figure 8: Typical powder technological flowability values for Tablettose® grades.

Compactibility

Figure 9 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 force range. This is due to the finer initial particle size, which increases the material's binding capacity.

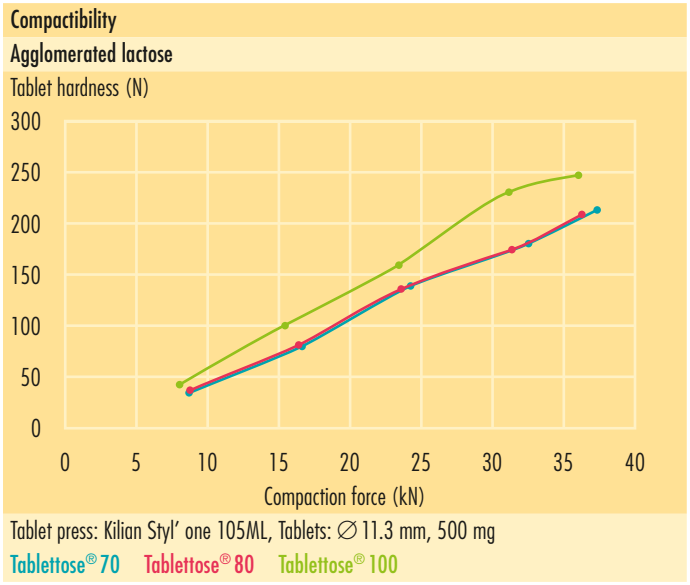


Figure 9: Force-hardness profile of Tablettose® grades.

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 10** provides an overview about packaging size and material, and product shelf life.

Packaging and shelf life

Tablettose®

	Size	Material	Shelf life
Tablettose® 70	20 kg	Paper bag with PE-EVOH-PE inliner	36 months
Tablettose® 80	25 kg		
Tablettose® 100	20 kg		24 months

Figure 10: Packaging and shelf life of MEGGLE's agglomerated lactose grades.

Literature

[1] Meeus, L. (2011). Direct Compression versus Granulation. Pharmaceutical Technology, 23(3).

[2] Kristensen, H. G., & Schaefer, T. (1987). Granulation: A Review on Pharmaceutical Wet-Granulation. Drug Development and Industrial Pharmacy, 13(4–5), 803–872.

[3] Mîinea, L. A., Mehta, R., Kallam, M., Farina, J. A., & Deorkar, N. (2011). Evaluation and Characteristics of a New Direct Compression Performance Excipient, 35(3).

[4] Bolhuis, G. K., & Zuurman, K. (1995). Tableting Properties of Experimental and Commercially Available Lactose Granulations for Direct Compression. Drug Development and Industrial Pharmacy, 21(18), 2057–2071.

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