TABLETING →
DIRECT COMPRESSION →
SPRAY-DRIED LACTOSE

Technical brochure FlowLac®

MEGGLE
EXCIPIENTS & TECHNOLOGY

MEGGLE's spray-dried lactose grades for direct compression: FlowLac®

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 compactable 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)**.

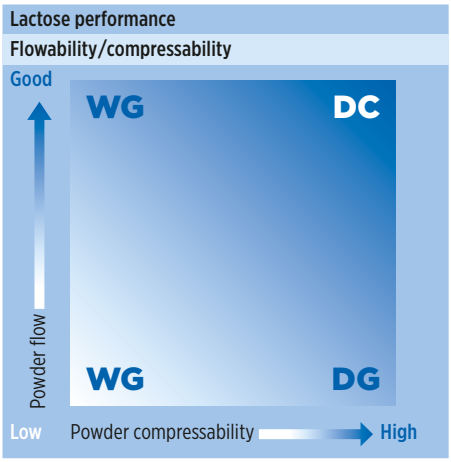


Figure 1: *Powder blend compressability and flowability requirements for various tableting technologies (DC is direct compression, WG is wet granulation, DG is dry granulation) [3].*

In the early 1960's, the introduction of spray-dried lactose changed tablet manufacturing processes and increased direct compression tableting possibilities [4]. Today, MEGGLE is a leading spray-dried lactose manufacturer with the FlowLac® brand.

Product description

FlowLac® is produced by spray-drying a fine milled alpha-lactose monohydrate suspension. When lactose is spray-dried, the rapid water evaporation causes amorphous lactose to form [5]. Most commercially available, spray-dried lactose products contain 10 to 15 % amorphous lactose at the time of manufacture, depending on the solids content and process conditions.

Compared to crystalline alpha-lactose monohydrate, FlowLac®'s compactibility is superior. Unlike alpha-lactose monohydrate and anhydrous beta-lactose, which are known to exhibit brittle fracture during compaction, amorphous lactose plastically deforms. Therefore, due to the synergistic plastic and brittle nature of amorphous and crystalline forms in spray-dried lactose, the result is superior compactibility [6].

FlowLac® 100 is the standard grade for spray-dried lactose, providing excellent flowability and extraordinary compactibility compared to other lactose grades. FlowLac® 90 was developed to provide greater compactibility compared to FlowLac® 100 by optimizing the amorphous lactose content. In addition, the particle size distribution makes FlowLac® 90 virtually dust-free.

Regulatory & quality information

FlowLac® 90 and FlowLac® 100 are MEGGLE's trade names for spray-dried 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 9001:2015 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 remains is our highest priority.

Application

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

- Low to medium dose DC formulations
- Formulations with poorly flowing API's
- Capsule and sachet filling

BENEFITS

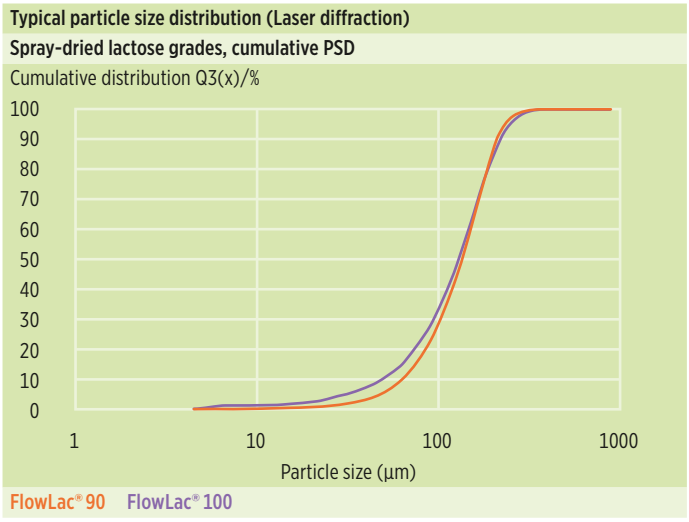
FlowLac®

- Superior flowability
- Excellent compactibility
- Low hygroscopicity and high stability

Particle size distribution (PSD)

Figure 2 shows typical PSD data by laser diffraction for MEGGLE's spray-dried lactose grades, FlowLac®. FlowLac® 90 offers a narrower particle size distribution than FlowLac® 100 because of its reduced fines content.

Figure 3 depicts typical the specified PSD data by air-jet sieving. These parameters are specified and are part of in-process control (IPC).



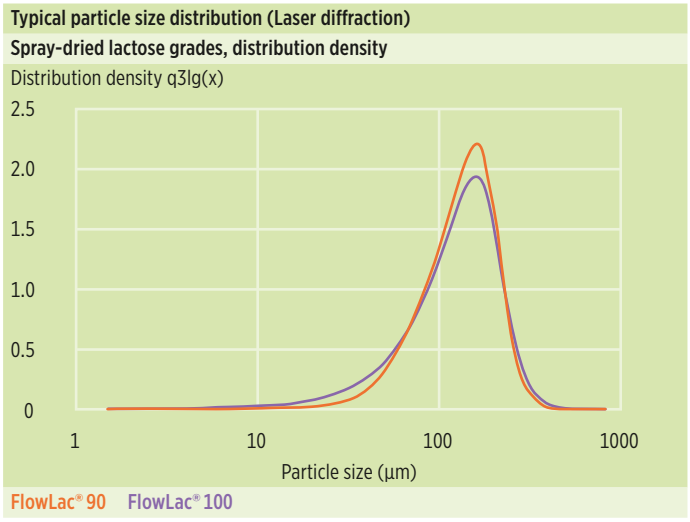


Figure 2: *Typical cumulative PSD and distribution density of MEGGLE's FlowLac® 90 and FlowLac® 100. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.*

Sieve data – spray-dried lactose			
	Lactose	FlowLac® 90	FlowLac® 100
		specified/typical	**specified**/typical
Particle size distribution	< 32 µm	**NMT 5 %**/ 2 %	**NMT 10 %**/ 5 %
Method: Air-jet sieving	< 100 µm	**25 – 40 %**/29 %	**20 – 45 %**/32 %
	< 200 µm	**NLT 85 %**/91 %	**NLT 80 %**/87 %
	< 250 µm	/99 %	/97 %

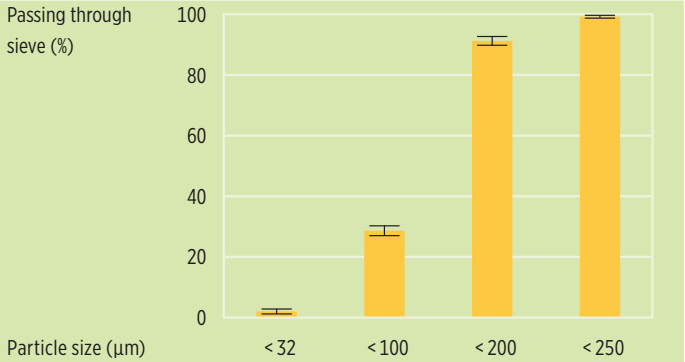
Figure 3: *Specified PSDs by air-jet sieving for FlowLac® 90/100 in bold letters. Typical values obtained from a permanent in-process control are shown for orientation.*

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 – spray-dried lactose

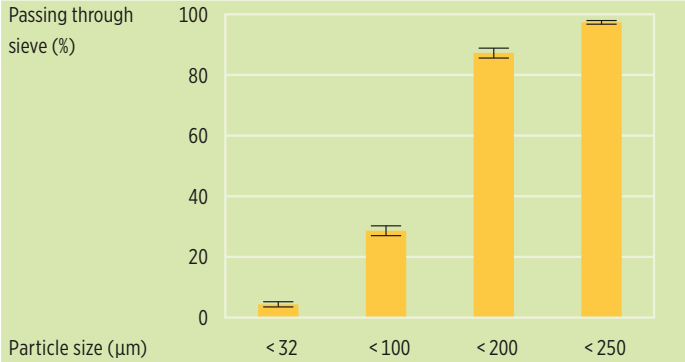
FlowLac® 90



Particle size (µm)	< 32	< 100	< 200	< 250
Specified	NMT 5 %	25 – 40 %	NLT 85 %	
Mean IPC value (%)	1.9	28.5	91.1	98.9
SD (%)	0.9	1.6	1.4	0.5

Batch-to-batch consistency – particle size distribution – spray-dried lactose

FlowLac® 100



Particle size (µm)	< 32	< 100	< 200	< 250
Specified	NMT 10 %	20 – 45 %	NLT 80 %	
Mean IPC value (%)	4.5	31.6	87.0	97.0
SD (%)	0.9	1.8	1.6	0.8

Figure 4: *FlowLac® provides consistent particle size distribution (air-jet sieving) indicated by low batch-to-batch variability. Data obtained from a permanent in-process control (IPC) of subsequent batches over 12 months.*

Isotherms

MEGGLE's spray-dried lactose products do not adsorb significant amounts of water below 20 °C/90 % relative humidity. **Figure 5** shows sorption and desorption isotherm for FlowLac® 90.

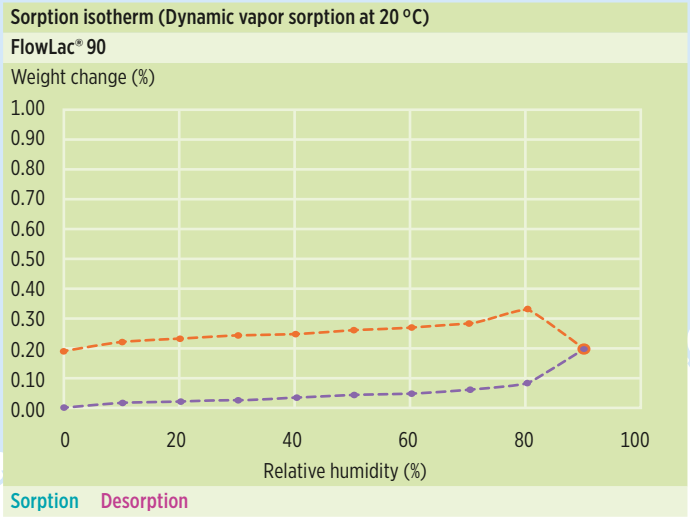


Figure 5: *Sorption-desorption isotherms (20 °C) of spray-dried lactose, using FlowLac® 90 as an example. Analysis performed by SPSx-1µ moisture sorption test system.*

While pure, crystalline lactose monohydrate demonstrates equivalent equilibrium moisture content during sorption and desorption, spray-dried lactose demonstrates hysteresis, having different equilibrium moisture content upon sorption and desorption. The hysteresis is caused by the conversion of lactose from the amorphous to crystalline form. Therefore significant changes in relative humidity during storage should be avoided. For regions with very high relative humidity, MEGGLE offers and recommends non-water-permeable packaging materials, such as aluminum inliners, to retain optimal material functionality. **Figure 6** demonstrates FlowLac® 100's superior compactibility at different storage conditions if packed in aluminum inliners instead of polyethylene inliners.

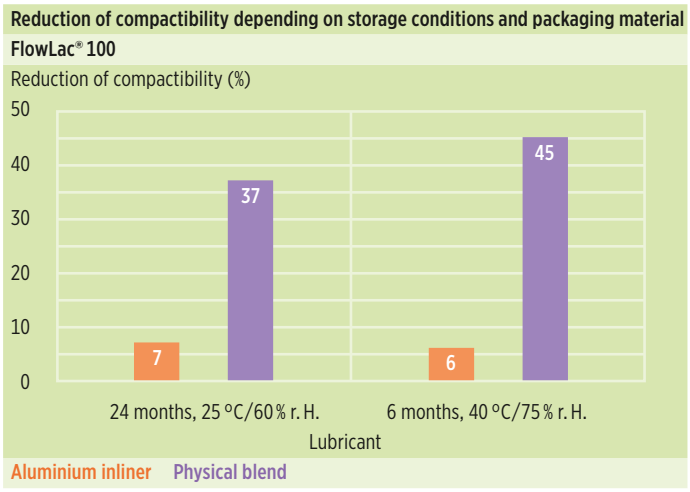


Figure 6: *Deminished compactibility of FlowLac® 100, which depends on storage conditions and packaging material.*

Scanning electron micrograph (SEM)

Due to the spray-drying process, FlowLac® has a spherical agglomerate shape, consisting of small alpha-lactose monohydrate crystals bound by amorphous lactose **(figure 7)**. FlowLac®'s spherical shape and narrow particle size distribution result in excellent flow characteristics.

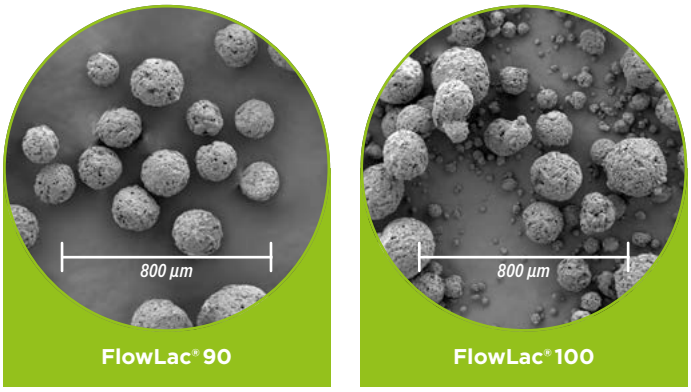


Figure 7: *SEM images of MEGGLE's FlowLac® by ZEISS Ultra 55 FESEM (U = 5 kV; Au/Pd sputtered)*

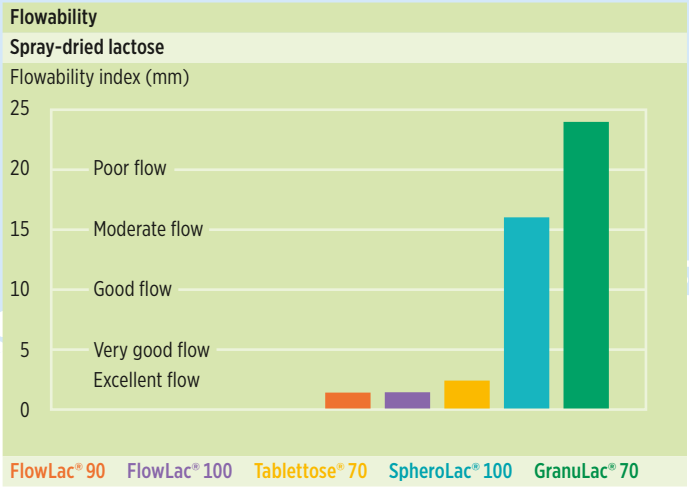


Figure 8: *FlowLac®'s flowability index compared to various lactose grades. Low flowability indices for FlowLac® 90/100 indicate their excellent flowability.*

Flowability
Spray-dried lactose

	Angle of repose (°)	Density bulk (g/l)	Density tapped (g/l)	Hausner ratio	Carr's index (%)
FlowLac® 90	27	560	670	1.20	16.42
FlowLac® 100	28	590	710	1.20	16.90

Figure 9: *Typical powder technological flowability values for FlowLac® 90/100. All methods were performed according to European pharmacopoeial standards.*

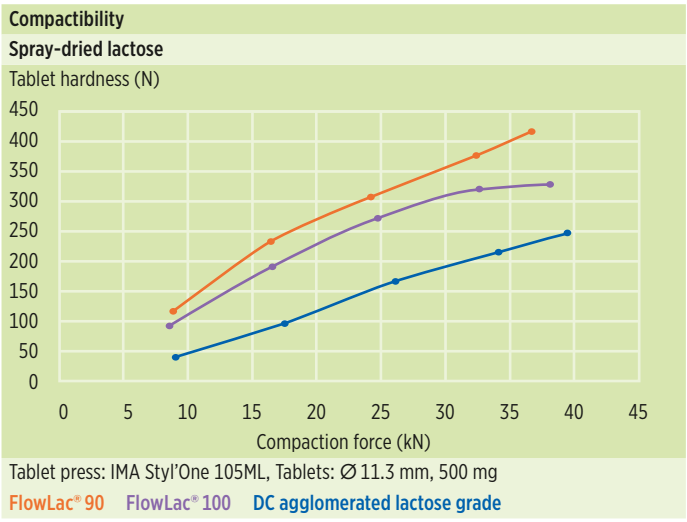


Figure 10: *Force-hardness profile of FlowLac® 90/100 compared to DC agglomerated lactose.*

Packaging and shelf life
FlowLac®

	Size	Material	Shelf life
FlowLac® 90	25 kg	Carton box with an aluminium laminated inliner	36 Months
FlowLac® 100			24 Months
FlowLac® 100		Paper bag with PE-EVOH-PE inliner	18 Months

Figure 11: *Packaging and shelf life of MEGGLE's spray-dried 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 8** demonstrates that particle shape and structure are as important as particle size distribution for powder flowability. Due to its spheroidal structure, spray-dried lactose provides the best flowability among all lactose grades. Therefore, FlowLac® 90 and FlowLac® 100 have 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 9** shows typical flowability indices for FlowLac® grades, indicating the excellent flowability possessed by spray-dried lactose.

Powder compressability

Figure 10 shows that tablets made with FlowLac® achieve greater tablet hardness compared to agglomerated DC alpha-lactose monohydrate. This results from the plastically deforming amorphous lactose present in spray-dried lactose, which is not present in agglomerated lactose. The plastically deforming amorphous lactose and brittle crystalline lactose work synergistically to increase compactibility. FlowLac® 90's higher amorphous content provides superior compactibility when compared to FlowLac® 100. Due to the reduced compaction forces required during tableting, tooling wear can be demi-nished while tablet hardness can be increased.

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.

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.

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