TABLETING →
DIRECT COMPRESSION →
SPRAY-DRIED LACTOSE

Technical brochure FlowLac®

MEGGLE
EXCIPIENTS & TECHNOLOGY

MEGGLE 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 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)**.

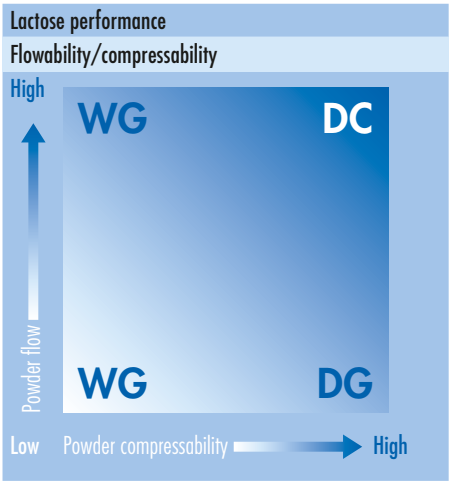


Figure 1: Powder blend compressability and flowability requirements for various tableting technologies (DC is direct compression, WG is wet granulation, DG is dry granulation) [3].

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 compactability 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 compactability [6].

FlowLac® 100 is the standard grade for spray-dried lactose, providing excellent flowability and extraordinary compactability compared to other lactose grades.

FlowLac® 90 was developed to provide greater compactability 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 9001:2008, 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

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

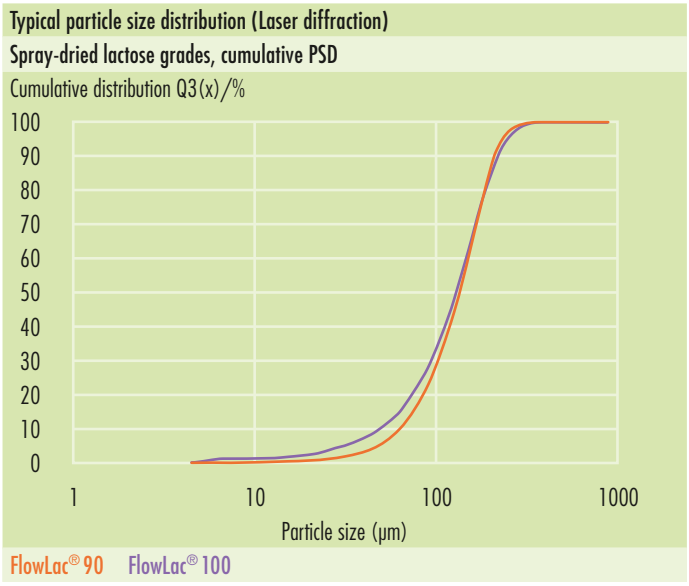
FlowLac®

- Superior flowability
- Excellent compactability
- Low hygroscopicity and high stability
- Fast disintegration times

Particle size distribution (PSD)

Figure 2 shows typical laser diffraction particle size distribution data for MEGGLEs spray-dried lactose grades, FlowLac®. FlowLac®90 offers a tighter particle size distribution compared to FlowLac®100 because of reduced fines content.

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



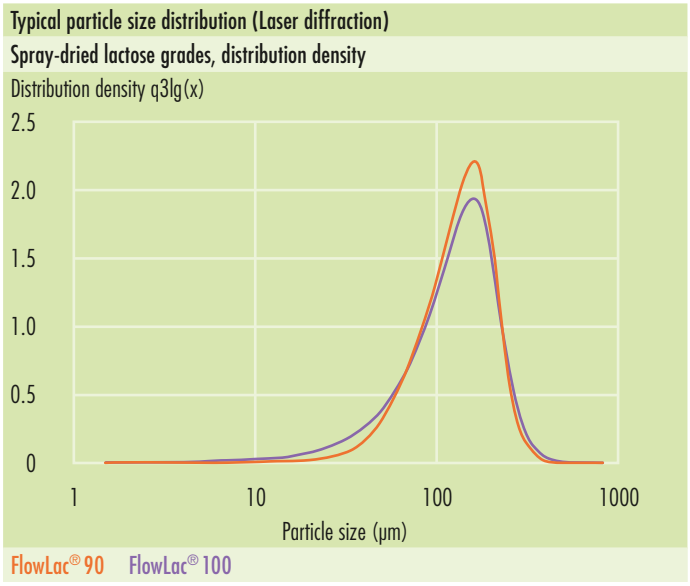


Figure 2: Typical cumulative PSD and distribution density of MEGGLE's FlowLac® 90 and FlowLac® 100. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.

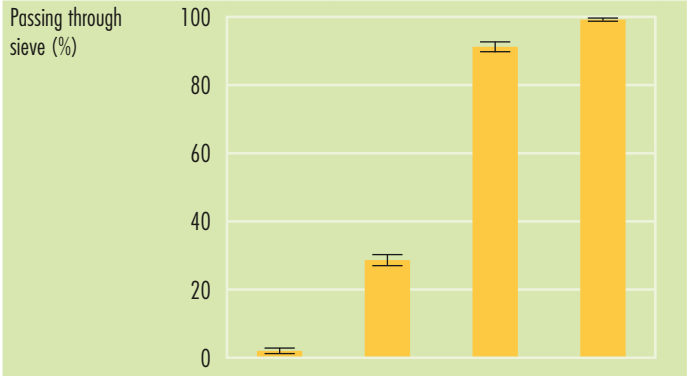
Figure 3: Specified PSDs for MEGGLE's spray-dried lactose grades by air jet sieve in bold letters. Typical values obtained from a permanent in-process-control are shown for orientation.

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

Batch-to-batch consistency

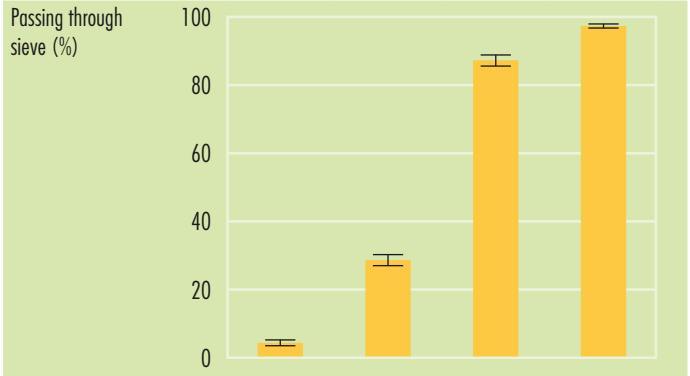
Batch-to-batch consistency for all lactose products can be attributed to MEGGLE's long history and experience in lactose manufacture, and broad technical expertise. Constant in-process and final product testing ensures consistency and quality **(Figure 4)**.

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: *Particle size distribution batch-to-batch consistency of FlowLac® by air jet sieving. 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/80 % relative humidity. **Figure 5** shows sorption and desorption isotherm for FlowLac® 90.

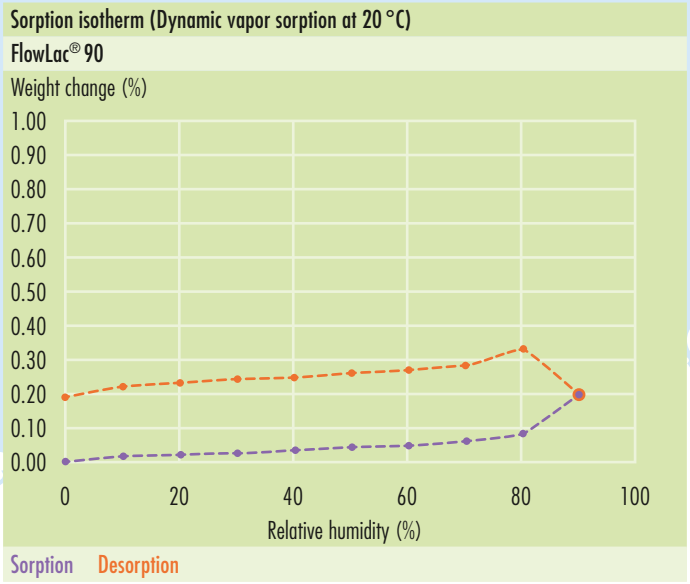


Figure 5: Sorption-desorption isotherm of spray-dried lactose, using FlowLac® 90 as an example.

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 compactability at different storage conditions if packed in aluminum inliners instead of polyethylene inliners.

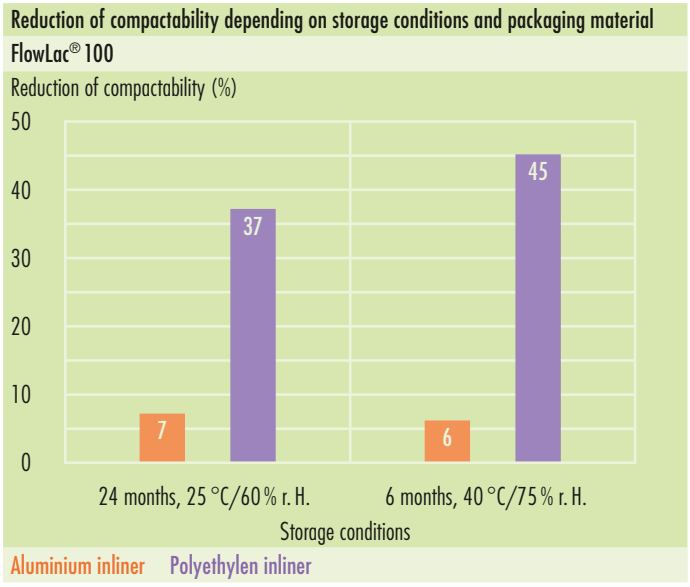


Figure 6: Reduction of compactability of FlowLac® 100 depending on storage conditions and packaging material.

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.

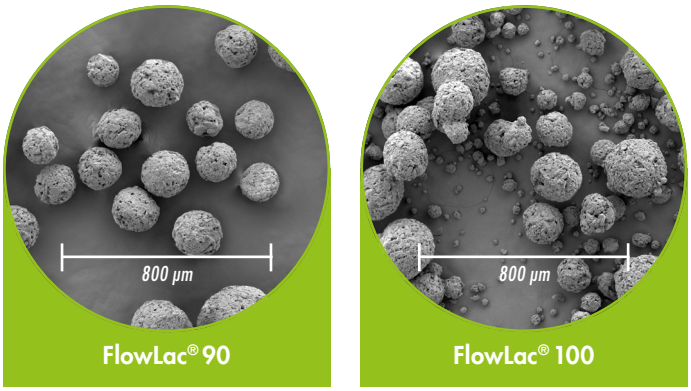


Figure 7: SEM images of various spray-dried MEGGLE lactose grades.

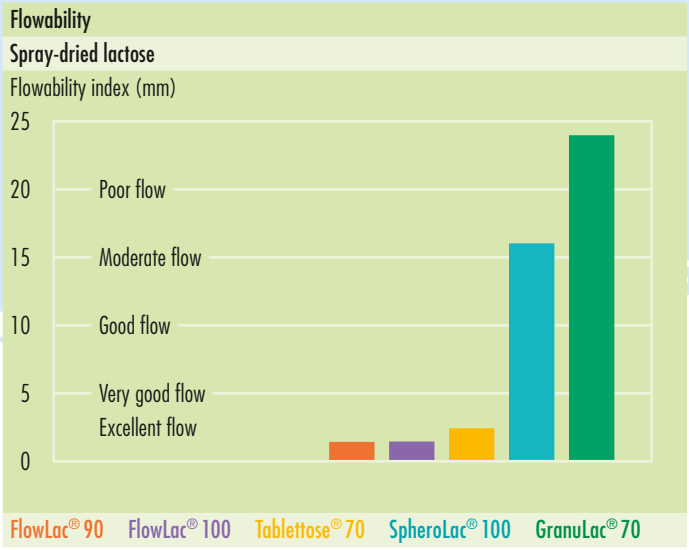


Figure 8: Flowability index of FlowLac® grades compared to other lactose grades.

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 more important than the particle size distribution alone when flowability is considered. Due to its spherical shape, spray-dried lactose possesses the best flowability of all available lactose grades, resulting in a low flowability index FI (powder through an orifice) compared to sieved (SpheroLac® 100) or milled (GranuLac® 70) lactose.

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® grades.

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.

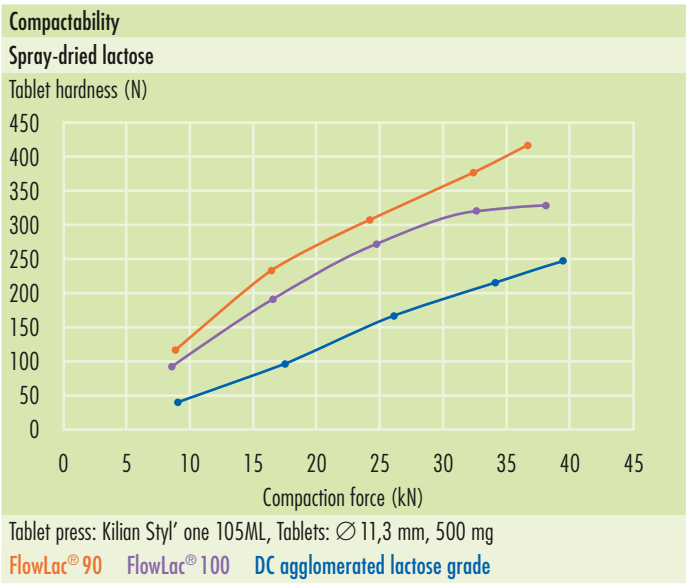


Figure 10: Force-hardness profile of FlowLac® grades compared to DC agglomerated lactose.

Compactability

Figure 10 shows that tablets made with FlowLac® achieve greater tablet hardness compared to 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 compactability. FlowLac® 90's higher amorphous content provides superior compactability when compared to FlowLac® 100. Due to the reduced compaction forces required during tableting, tooling wear can be decreased while tablet hardness can be increased.

Packaging and shelf life
FlowLac®

	Size	Material	Shelf life
FlowLac® 90	25 kg	Corrugated 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.

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.

[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).

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[5] Roos, Y. H. (2002). Importance of glass transition and water activity to spray drying and stability of dairy powders. Le Lait, 82(4), 475–484.

[6] RUANGCHAYAJATUPORN, J., AMORNSAKCHAI, T., SINCHAIPANID, N., & MITREVEJ, A. (n.d.). Compaction behavior and optimization of spray-dried lactose with various amorphous content. Journal of drug delivery science and technology, 21(2), 175–181.

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