

TABLETING | DIRECT COMPRESSION | SPRAY-DRIED LACTOSE

FLOWLAC

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 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 DC without modification due to insufficient powder flow or/and compaction properties (figure 1).

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

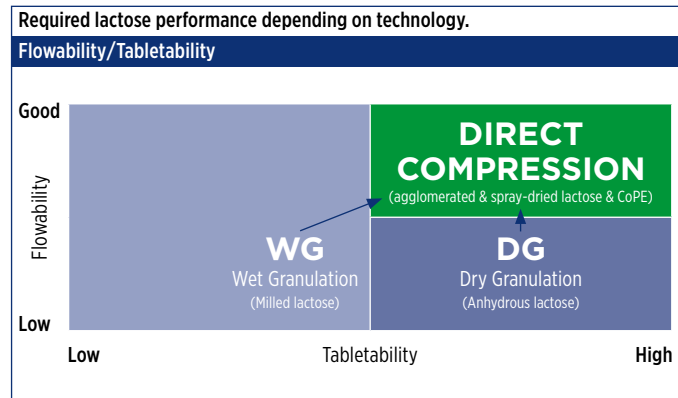


Figure 1: Lactose with high flowability and compressibility leads to DC. Lactose with poor flow needs to be processed with wet or dry granulation.

FlowLac® consists of spray-dried, spherical particles with smooth surfaces, such as shown in **figure 2**. Spray-dried particles show a uniform, spherical morphology with smooth surfaces and a narrow particle size distribution. This morphology enhances flowability and dispersibility, leading to improved handling and consistent performance during tableting and other solid dosage form manufacturing processes.

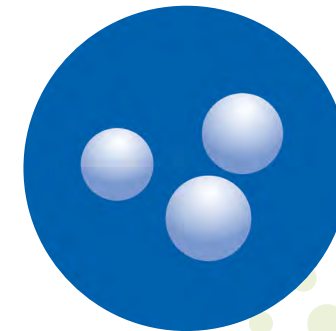


Figure 2: Shape of spray-dried particles

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. Most commercially available, spray-dried lactose products contain 10 to 15% amorphous lactose at the time of manufacturing, 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 [4].

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.

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

APPLICATION

FlowLac®

- Direct compression
- Continuous manufacturing
- Formulations requiring a high flowability
- Capsule and sachet filling
- High speed tableting

BENEFITS

FlowLac®

- Superior flowability
- Best in class tableability
- Very low strain rate sensitivity
- Smooth surface (glossy tablets)
- Fast disintegration times (if moderately compressed)
- Highly consistent particle size distribution
- Virtually dustfree

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

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, 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 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.

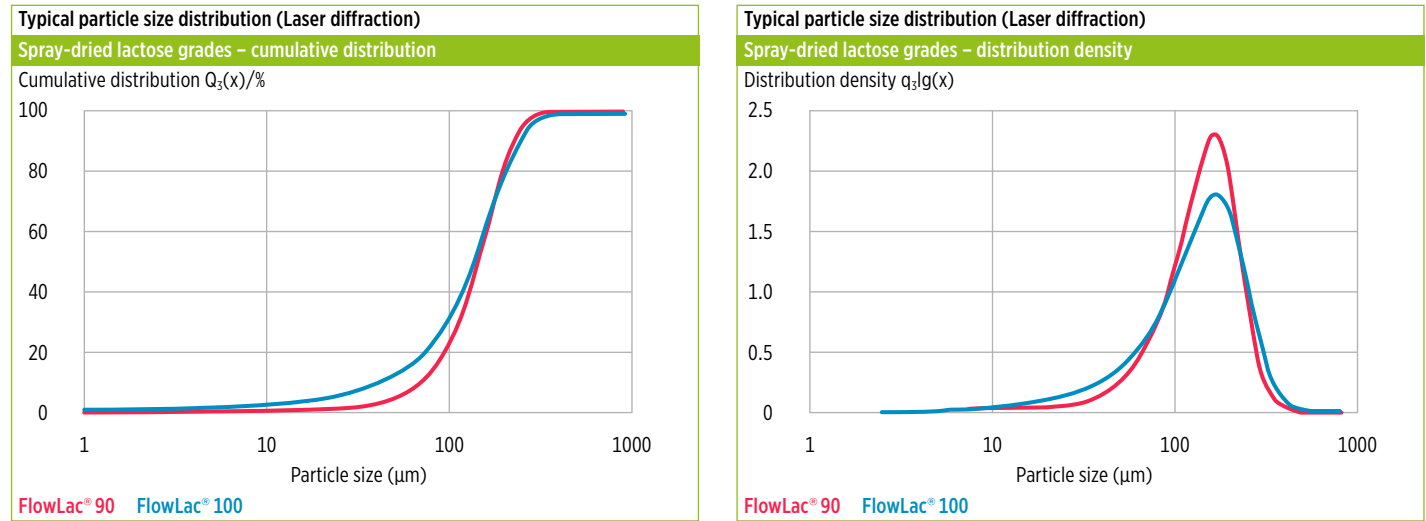


Figure 3: Typical cumulative PSD and distribution density of MEGGLE's spray-dried lactose grades FlowLac® 90 and FlowLac® 100. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.

Particle Size Distribution (PSD) & Morphology (SEM)

Figure 4 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 MEGGLE's spray-dried lactose grades' specification.

Due to the spray-drying process, FlowLac® has a spherical agglomerate shape, consisting of small alpha-lactose monohydrate crystals bound by amorphous lactose, as it can be seen in the different Scanning Electron Microscope (SEM) images. FlowLac®'s spherical shape and narrow particle size distribution result in excellent flow characteristics.

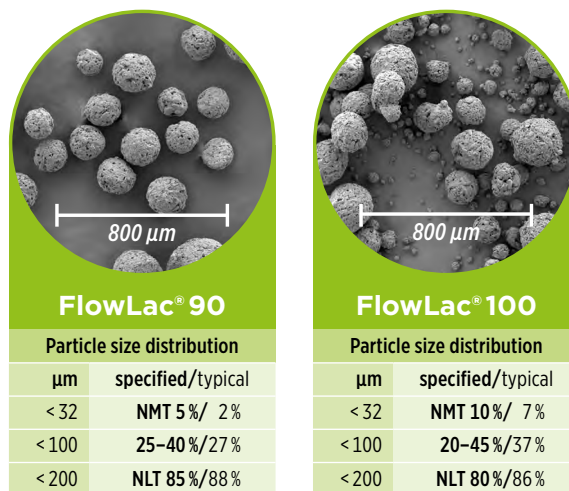


Figure 4: Specified PSD ranges for MEGGLE's spray-dried lactose grades by air-jet sieving in bold letters. Typical values obtained from a permanent in-process control are shown for orientation. SEM images of spray-dried MEGGLE lactose grades by ZEISS Ultra 55 FESEM (U = 5 kV; Au/Pd sputtered).

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 (figure 5).

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 excellent flowability indices for MEGGLE's FlowLac® grades. With a good CI of 12 %, and an excellent angle of repose below 30°, both grades show their excellent flowability values.

Flowability					
Spray-dried lactose					
	Carr's Index (%)	Angle of Repose (°)	Hausner ratio	Density bulk (g/l)	Density tapped (g/l)
FlowLac® 90	12	28	1.14	583	663
FlowLac® 100	12	29	1.14	613	699

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

Figure 7 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 CI compared to sieved (SpheroLac® 100) or milled (GranuLac® 70) lactose.

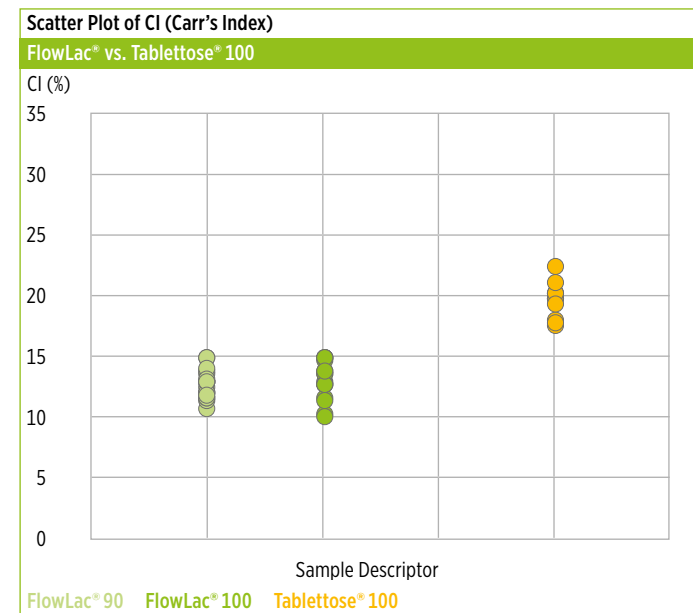


Figure 7: FlowLac®'s flowability index compared to Tablettose® 100. Low flowability indices for FlowLac® 90/100 indicate their excellent flowability.

Functional related characteristics – Part 2

Tabletability profile

Figure 8 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 tabletability when compared to FlowLac®100. Due to the reduced compaction forces required during tableting, tooling wear can be diminished while tablet hardness can be increased.

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

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

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

Tabletability profile

FlowLac® vs. Tablettose® 100

Tensile strength (STYL'One) (MPa)

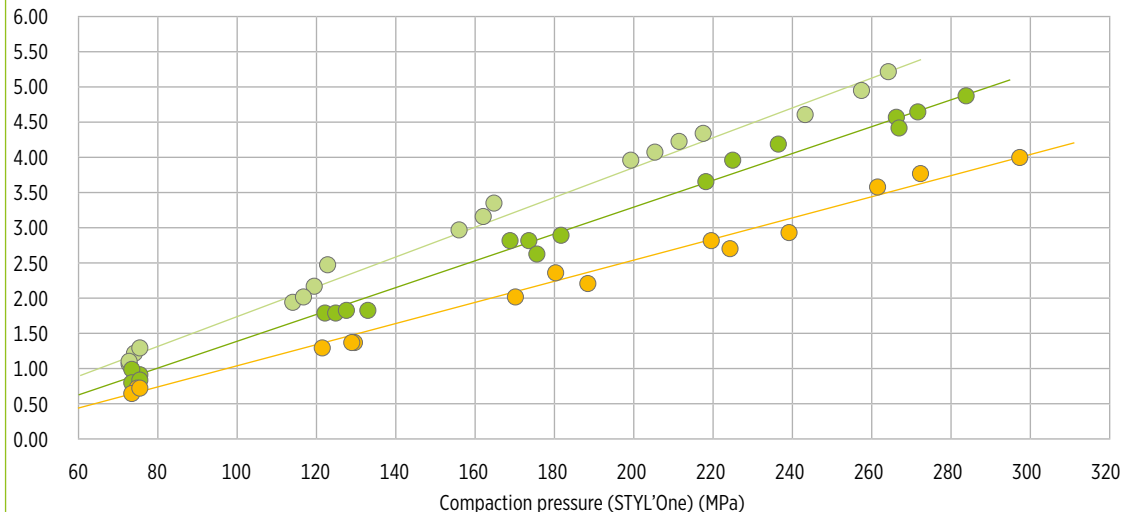


Figure 8: Tabletability profile of FlowLac® compared to DC agglomerated lactose. Tablet press: MEDELPHARM STYL'One, Tablets: Ø 11.3 mm, 500 mg.

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**).

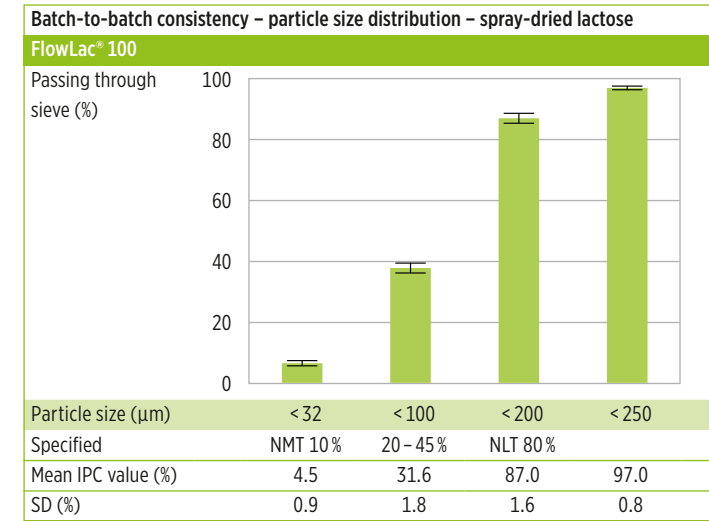
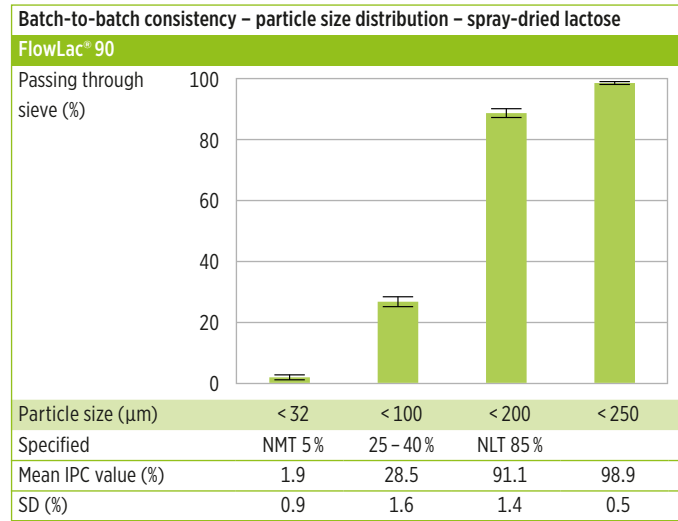


Figure 9: FlowLac® provides consistent particle size distribution (air-jet sieving) indicated by low batch-to-batch variability. Data obtained from a permanent in-process control (IPC) of subsequent batches over 12 months.

Isotherm

MEGGLE's moisture sorption isotherms for spray-dried lactose are shown in **figure 10**, using FlowLac®100 as an example. The peak of the spray-dried lactose grade in **figure 10**, observed at 40 % RH and 25 °C during sorption, indicates the presence of a distinct amount of amorphous lactose in MEGGLE's spray-dried lactose products. Amorphous lactose easily recrystallizes if the glass transition temperature (T_g) is exceeded. Moisture acts as plasticizer and significantly lowers the T_g .

Amorphous lactose has a higher water-uptake capacity than crystalline lactose. Upon recrystallization, part of the absorbed water is incorporated into the crystal structure. In comparison to the spray-dried lactose grade, alpha-lactose monohydrate products, like MEGGLE's sieved SACHELac® 80 do not adsorb significant amounts of water below 90 % relative humidity (25 °C).

For regions with very high relative humidity, MEGGLE offers non-water-permeable packaging materials, such as aluminum inliners, to retain optimal material functionality.

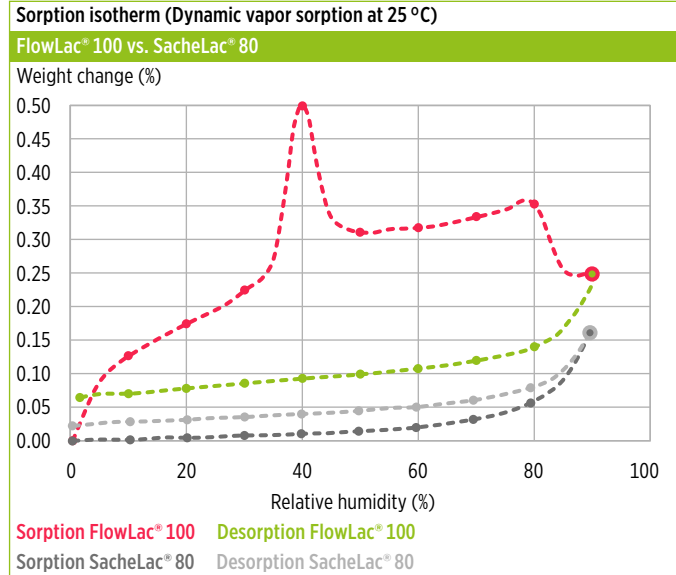


Figure 10: Sorption-desorption isotherms (25 °C) of spray-dried lactose, using FlowLac® 100 in comparison to sieved lactose monohydrate, using SACHELac® 80 as an example.
Analysis performed by with SPSx-1µ Advance (proUmid GmbH & Co. KG, Ulm, Germany).

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			
	Size	Material	Shelf life
FlowLac® 90	25 kg	Carton box with an aluminium	36 Months
FlowLac® 100		laminated inliner	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.

Literature

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- [4] Ruangchayajaturon, J., Amornsakchai, T., Sinchaipanid, N., Mitrevej, A. (2011). Compaction behavior and optimization of spray-dried lactose with various amorphous content. Journal of drug delivery science and technology, 21(2), 175–181. sciencedirect.com

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