TABLETING →
DIRECT COMPRESSION →
CO-PROCESSED LACTOSE

# Technical brochure
# MicroceLac® 100

MEGGLE
EXCIPIENTS & TECHNOLOGY

# MEGGLE's co-processed lactose grades for direct compression: MicroceLac® 100

## 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)**.

## Product description

Alpha-lactose monohydrate and microcrystalline cellulose are functional excipients used in oral solid dosage forms. Both are naturally derived and commonly used in the pharmaceutical industry, either individually or in combination. To develop synergistic functional performance, such as increased compactability and powder flow, alpha-lactose monohydrate and microcrystalline cellulose were co-spray-dried, creating a monoparticulate system having two compaction mechanisms, brittle fracture and plastic deformation, within individual particles. MicroceLac® 100 provides the flow and compaction properties desired for direct compression tableting. MicroceLac® 100 comprises 75 % alpha-lactose monohydrate and 25 % microcrystalline cellulose (MCC), both maintaining their individual chemical identities.

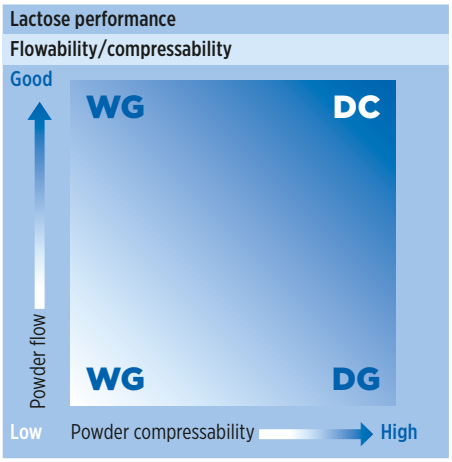



***Figure 1:*** *Powder blend compressability and flowability requirements for various tableting technologies (DC is direct compression, WG is wet granulation, DG is dry granulation) [3].*

## Regulatory & quality information

The raw materials used to produce MicroceLac® 100, alpha-lactose monohydrate and microcrystalline cellulose, comply with Ph. Eur., USP-NF, and JP monograph requirements. Since no chemical modifications result during co-processing and individual chemical identities are maintained, MicroceLac® 100 can be considered as a physical blend of alpha-lactose monohydrate and microcrystalline cellulose [4].

A MicroceLac® 100 drug master file (DMF) is available during FDA (Food and Drug Administration) drug product submission review and approval. 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

MicroceLac® 100 is designed for direct compression and may be applied to other formulation development approaches such as dry granulation and capsule filling. In comparison to a physical blend of the individual components, MicroceLac® 100 provides enhanced compaction and superior flowability. These attributes improve blending and mitigate API content variability typical of simple powder blends. MicroceLac® 100's superior blending characteristics make it ideal for low-dose formulations where API content uniformity is critical. Excellent compaction properties help increase tablet hardness, making it well-suited for high-dose formulations as well. MicroceLac® 100 maximizes formulation development flexibility.

- Direct compression
- Dry granulation (Roller compaction, slugging)
- Capsule filling

## BENEFITS

### MicroceLac® 100

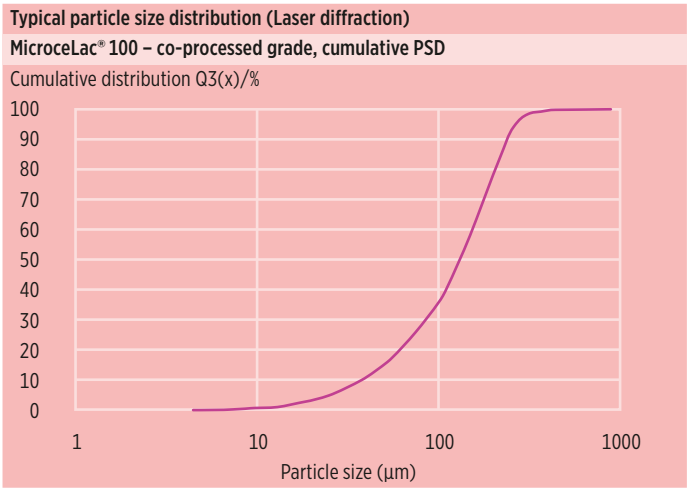
- Excellent compactability and flowability
- Ideal for poorly compactable APIs, e.g. herbal extracts
- Ideal tablet surface for straight forward and economical coating
- High adherence capacity prevents segregation and subsequently improves content uniformity

international excipients certification

## Particle size distribution (PSD)

**Figure 2** shows typical laser diffraction particle size distribution data for MicroceLac®100. MicroceLac®100 possesses a narrow PSD that supports homogenous powder blend preparation, a requirement for achieving good tablet quality.

**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 the MicroceLac®100 particle size distribution specification.



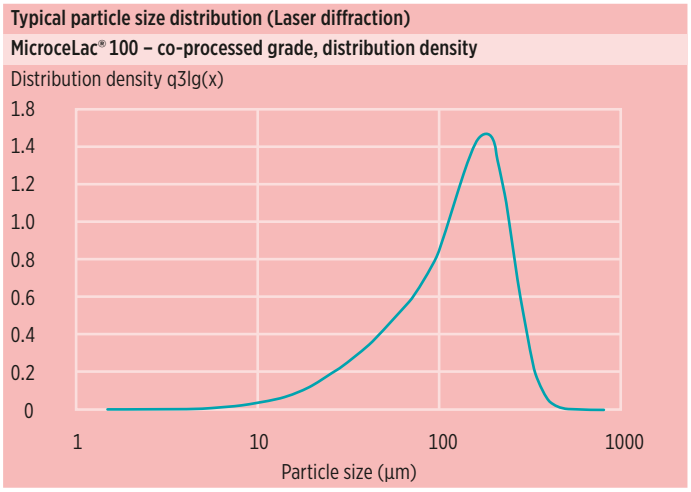




***Figure 2:*** *Typical cumulative PSD and distribution density of MEGGLE's MicroceLac® 100. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.*

| Sieve data – co-processed lactose | | |
|---|---|---|
| | Lactose | MicroceLac® 100 |
| | | **specified**/typical |
| **Particle size distribution** | < 32 µm | **NMT 15 %**/ 7 % |
| Method: Air-jet sieving | < 160 µm | **45 – 70 %**/59 % |
| | < 250 µm | **NLT 90 %**/95 % |

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

## Batch-to-batch consistency

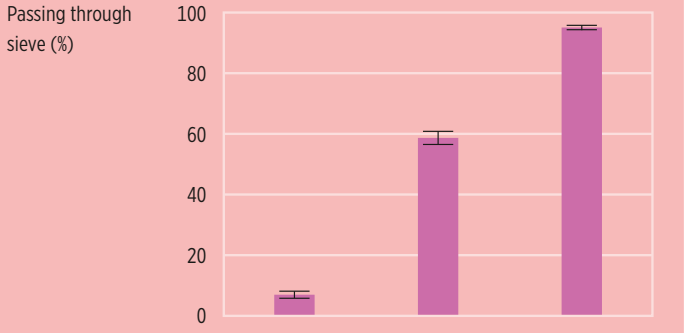
Batch-to-batch consistency for all lactose products can be attributed to MEGGLE's long history and experience in lactose manufacture, and broad technical expertise. Constant in-process and final product testing ensures consistency and quality **(figure 4)**.

## Isotherms

MicroceLac®100 exhibits moderate moisture uptake while exposed to high relative humidity conditions due to the MCC influence on observed equilibrium moisture content **(figure 5)**.

**Batch-to-batch consistency – particle size distribution – co-processed lactose**

**MicroceLac® 100**




| Particle size (µm) | < 32 | < 160 | < 250 |
|---|---|---|---|
| Specified | NMT 15 % | 45 – 70 % | NLT 90 % |
| Mean IPC value (%) | 7.0 | 58.8 | 95.2 |
| SD (%) | 1.2 | 2.2 | 0.8 |

***Figure 4:*** *MicroceLac® 100 particle size distribution batch-to-batch consistency by air-jet sieve analysis. Data obtained from a permanent in-process control (IPC) of subsequent batches over 12 months.*

**Sorption isotherm (Dynamic vapor sorption at 20 °C)**

**MicroceLac® 100**

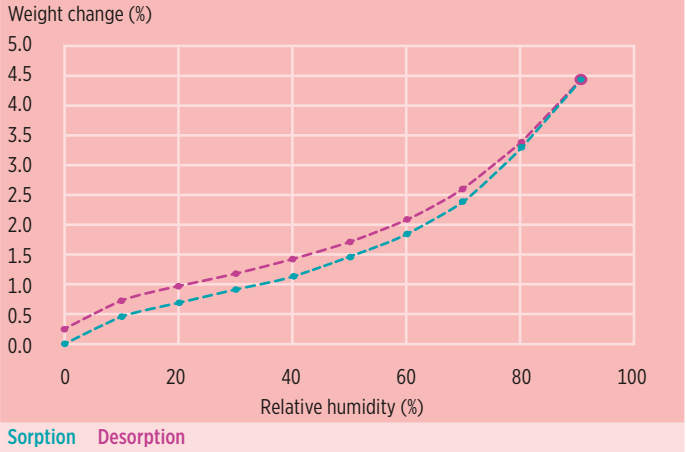



***Figure 5:*** *Sorption-desorption isotherms (20 °C) of MicroceLac® 100. Analysis performed by SPSx-1µ moisture sorption test system.*


***Figure 6:*** *SEM image of MEGGLE's MicroceLac® 100 by ZEISS Ultra 55 FESEM (U = 5 kV; Au/Pd sputtered).*

## Scanning electron micrograph (SEM)

MicroceLac®100 is nearly spherical in shape due to the co-spray-drying manufacturing process. MicroceLac®100's overall morphology reduces blend segregation and improves finished dosage form content uniformity **(figure 6)**.

## Functional related characteristics

### Powder flow

In assessing powder flow using a FlowRatex® apparatus, MicroceLac®100 exhibited superior flowability compared to a physical blend, made up of spray-dried lactose and microcrystalline cellulose. The simple blend of individual ingredients showed greater flow variation compared to MicroceLac®100 **(figure 7)**. MicroceLac®100 also possessed lower flowability index (MicroceLac®100 = 2 mm, physical blend = 9 mm), indicating superior flowability **(figure 8)**.

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 MicroceLac®100, indicating excellent flowability.

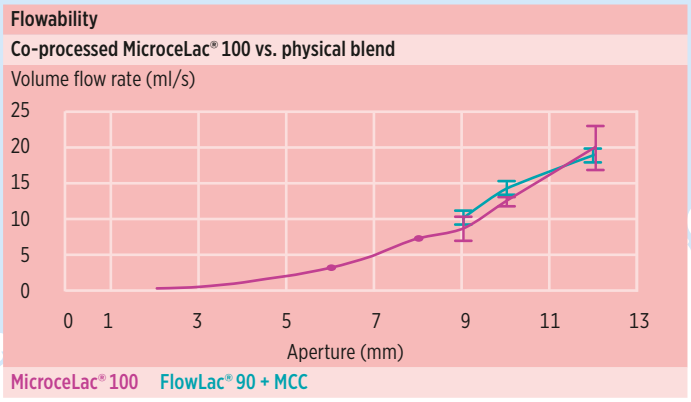



***Figure 7:*** *Volume flow rate (ml/s) as a function of aperture size (mm diameter) for StarLac® and a comparable physical blend analyzed by a FlowRatex®.*

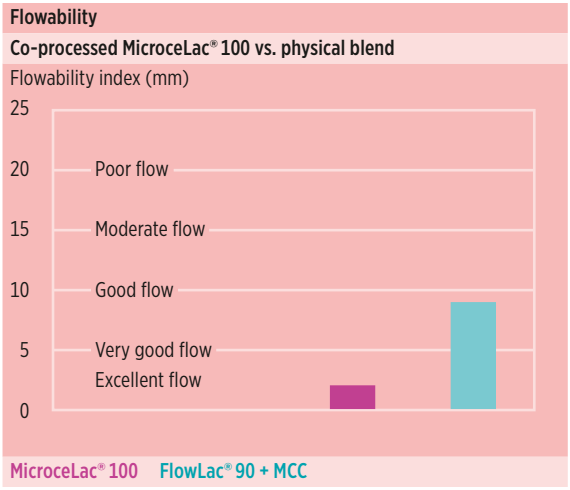



***Figure 8:*** *Flowability index of MicroceLac® 100 and its corresponding physical blend. Smaller values indicate better flowability.*

**Flowability**

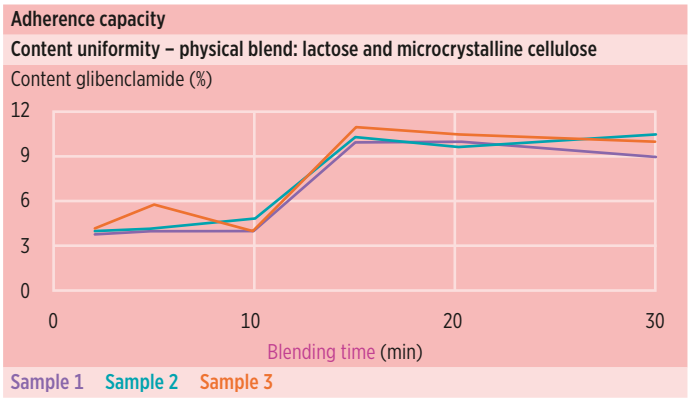
**MicroceLac® 100 – co-processed lactose**

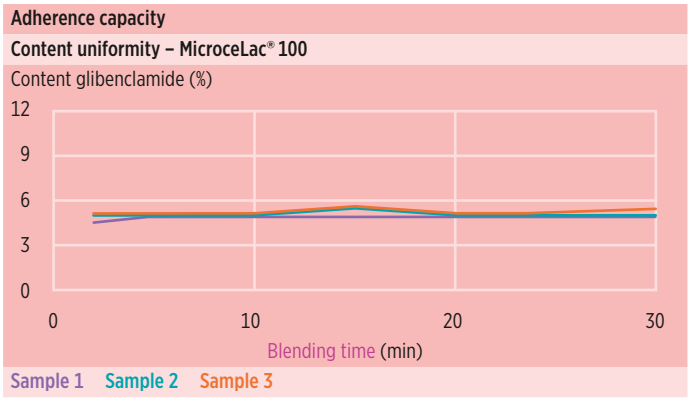
| | Angle of repose (°) | Density bulk (g/l) | Density tapped (g/l) | Hausner ratio | Carr's index (%) |
|---|---|---|---|---|---|
| MicroceLac® 100 | 34 | 460 | 580 | 1.26 | 20.69 |

***Figure 9:*** *Typical powder technological values for MicroceLac® 100. Pharmacopoeial methods were used.*

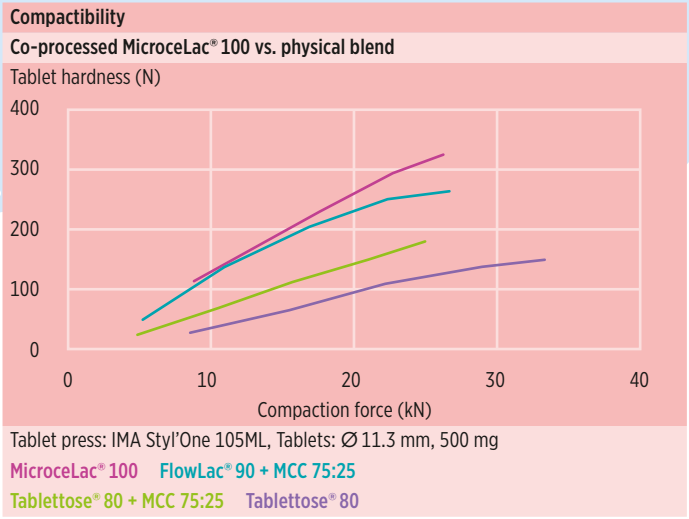
### Adherence capacity

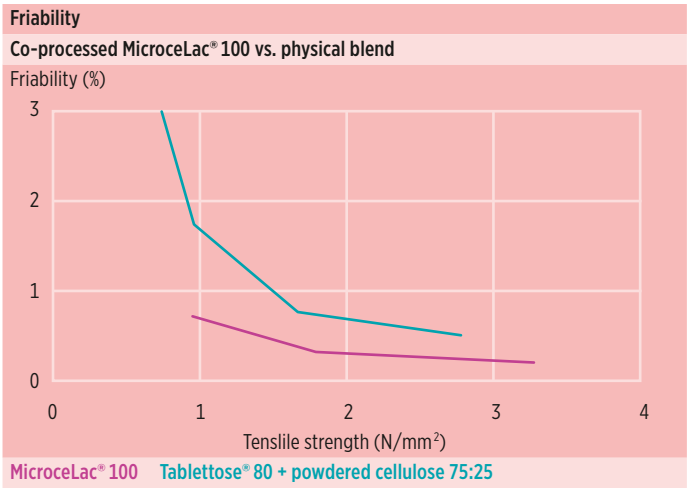
Due to its particle morphology, MicroceLac®100's excellent flow properties create the shear necessary to disperse API during low-dose blending operations thereby improving content uniformity. Studies have shown that a homogenous powder blend comprising 5% glibenclamide can be achieved using MicroceLac®100 **(figure 10b)** compared to the use of a simple physical blend **(figure 10a)**, [5].




***Figures 10a and 10b:*** *Content uniformity of a powder blend comprising 5% glibenclamide and either MicroceLac® 100 or the individual components, lactose and MCC [5].*




## Compactibility and friability

Tablet hardness can be increased by combining lactose and microcrystalline cellulose. Results have shown that MicroceLac® 100's compactibility is superior to a comparable physical blend of the individual components in the same ratio **(figure 11)**. Due to excellent compactibility, low friability (<1%) is given **(figure 12)**, eliminating the need for a protective coating.

***Figure 11:*** *Tablet hardness profile for MicroceLac® 100 compared to a physical blend of the individual components and Tablettose® 80 (granulated lactose). Tablets were produced using a tablet press: IMA Styl'One fitted with 11.3 mm punches. Average tablet weight was targeted at 500 mg.*

***Figure 12:*** *Friability for tablets produced either with MicroceLac® 100 or its corresponding blend.*

**Packaging and shelf life**

**MicroceLac® 100**

| | Size | Material | Shelf life |
|---|---|---|---|
| MicroceLac® 100 | 20 kg | Paper bag with PE-EVOH-PE inliner | 18 Months |

***Figure 13:*** *Packaging and shelf life of MEGGLE's MicroceLac® 100.*

## 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 13** 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).

[4] Guideline on Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product. EMEA/CHMP/QWP/396951/2006.

[5] By courtesy of Prof. Sunada, Meijo University, Nagoya.


*Submitted by*


**MEGGLE Group Wasserburg**
**BG Excipients & Technology**
Megglestrasse 6 –12
83512 Wasserburg
Germany

Phone +49 8071 73 476
Fax +49 8071 73 320
service.pharma@meggle.de
www.meggle-pharma.com





DE 2019-09 Sai