MEGGLE

CELLACTOSE

TABLETING →
DIRECT COMPRESSION →
CO-PROCESSED LACTOSE

Technical brochure
Cellactose® 80

MEGGLE's co-processed lactose grades for direct compression: Cellactose® 80

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 cellulose powder are functional excipients used in oral solid dosage forms. Both are naturally derived and well-established for use in the pharmaceutical industry. In an effort to create synergistic functional performance, such as improved compactability and mixing characteristics, co-spray-drying was used to integrate alpha-lactose monohydrate and cellulose powder into a monoparticulate system. Cellactose® 80 was developed to provide the flow and compaction properties necessary for direct compression tableting. Cellactose® 80 comprises 75 % alpha-lactose monohydrate and 25 % powdered cellulose, both maintaining their individual chemical identities.

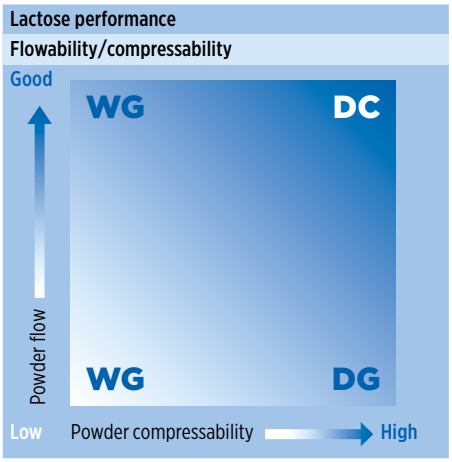


Figure 1: *Powder blend compressability and flowability requirements for various tableting technologies (DC is direct compression, WG is wet granulation, DG is dry granulation) [3].*

Regulatory & quality information

The raw materials used to produce Cellactose® 80, alpha-lactose monohydrate and cellulose powder, comply with Ph. Eur., USP-NF, and JP monograph requirements. Since no chemical modifications result during co-processing and individual chemical identities are maintained, Cellactose® 80 can be considered as a physical blend of alpha-lactose monohydrate and cellulose powder [4].

A Cellactose® 80 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

Cellactose® 80 is designed for direct compression tableting and may be used in other formulation applications such as dry granulation and capsule filling. In comparison with a corresponding physical blend of the individual components, Cellactose® 80 provides improved compactibility, superior flowability, and increased adherence capacity, which reduces segregation tendencies typical of simple powder blends. Due to improved blending characteristics and increased adherence capacity, Cellactose® 80 is ideal for low-dose formulations. Cellactose® 80's superior compaction properties increases tablet hardness in high-dose formulations as well. For low-dose or high-dose applications, Cellactose® 80 maximizes formulation development flexibility.

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

BENEFITS

Cellactose® 80

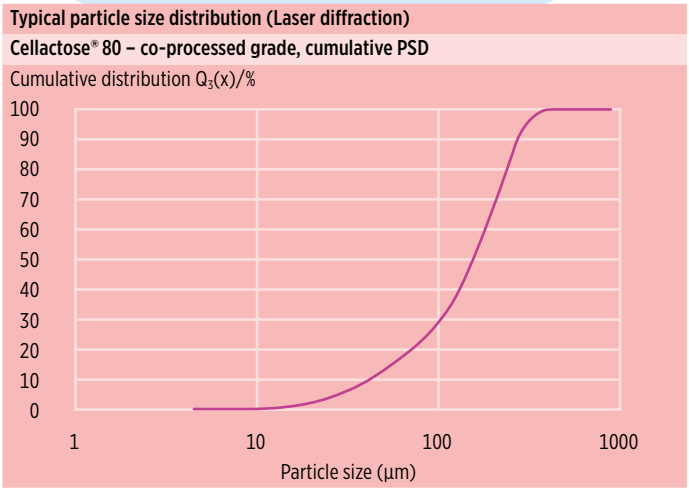
- Excellent compactibility and flowability
- Perfectly suited for poorly compressible APIs (e. g. herbal extracts)
- High adherence capacity to API
- Ideal tablet surface for easy and economical coating
- High adherence capacity may prevent segregation and improves content uniformity

international excipients certification

Particle size distribution (PSD)

Figure 2 shows typical laser diffraction particle size distribution data for Cellactose® 80. Cellactose® 80 possesses a narrow PSD that is effective in preparing homogenous powder blends, a prerequisite in 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 Cellactose® 80 particle size distribution specification.



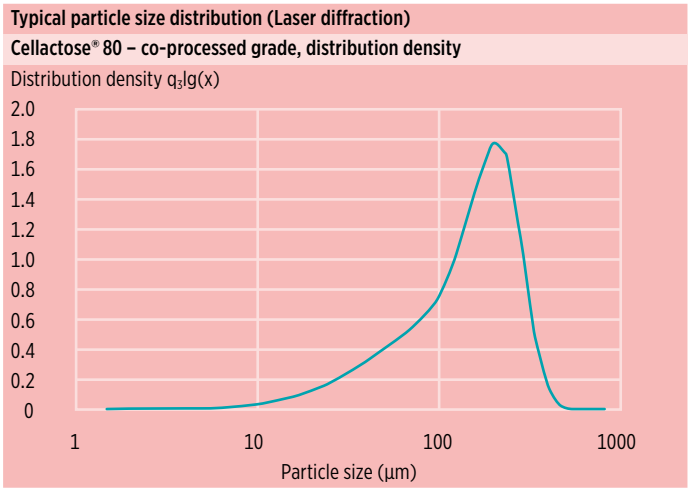


Figure 2: *Typical cumulative PSD and distribution density of MEGGLE's Cellactose® 80. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.*

Sieve data – co-processed lactose		
	Lactose type	Cellactose® 80
		specified/typical
Particle size distribution	< 32 µm	**NMT 20 %**/ 7 %
Method:	< 160 µm	**35–65 %**/54 %
Air-jet sieving	< 250 µm	**NLT 80 %**/93 %

Figure 3: *Specified PSDs for Cellactose® 80 by air-jet sieve in bold letters. Typical values obtained from a permanent in-process control are shown for orientation.*

Batch-to-batch consistency

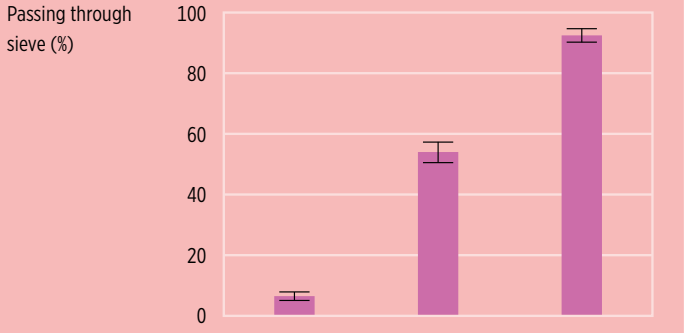
Batch-to-batch consistency for all lactose products can be attributed to MEGGLE's long history and experience in lactose manufacture, and broad technical expertise. Constant in-process and final product testing ensures consistency and quality **(figure 4)**.

Isotherms

Cellactose® 80 exhibits moderate moisture uptake under high relative humidity conditions due to the cellulose powder influence on the observed equilibrium moisture content **(figure 5)**.

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

Cellactose® 80



Particle size (µm)	< 32	< 160	< 250
Specified	NMT 20 %	35 – 65 %	NLT 80 %
Mean IPC value (%)	6.5	53.9	92.5
SD (%)	1.4	3.3	2.3

Figure 4: *A consistent PSD (air-jet sieving) of Cellactose® 80 is illustrated by a low batch-to-batch variability. Data obtained from a permanent in-process control (IPC) of consecutive batches over 12 months.*

Sorption isotherm (Dynamic vapor sorption at 20 °C)

Cellactose® 80

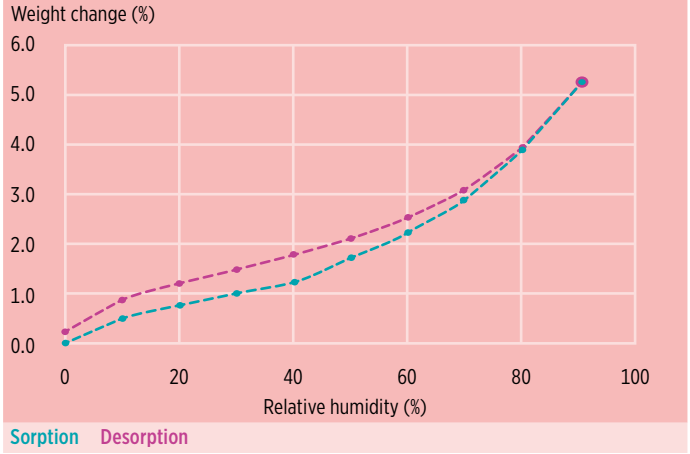


Figure 5: *Sorption-desorption isotherms (20 °C) of Cellactose® 80. Analysis performed by SPSx-1µ moisture sorption test system.*

Figure 6: *SEM image of MEGGLE's Cellactose® 80 by ZEISS Ultra 55 FESEM (U = 5 kV; Au/Pd sputtered).*

Scanning electron micrograph (SEM)

Cellactose® 80 is nearly spherical in shape due to the co-spray-drying manufacturing process. Cellactose® 80's overall morphology reduces blend segregation and improves finished dosage form content uniformity **(figure 6)**.

Functional related characteristics

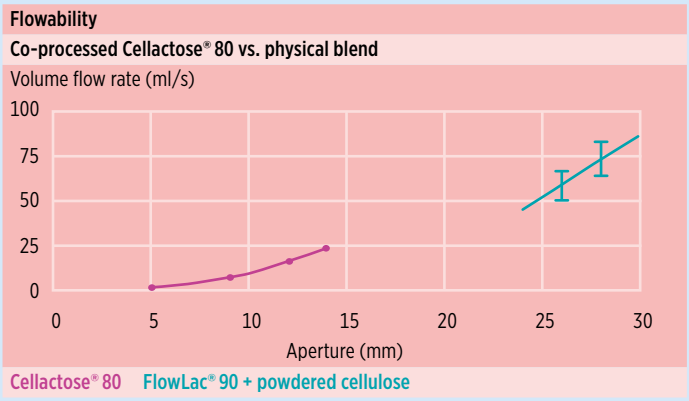


Figure 7: *Volume flow rate (ml/s) as a function of aperture size (mm diameter) for Cellactose® 80 and a comparable physical blend analyzed by a FlowRatex®.*

Powder flow

In assessing powder flow using a FlowRatex® apparatus, Cellactose® 80 exhibited superior flowability compared to a physical blend, made up of spray-dried lactose and powdered cellulose. The simple blend of individual ingredients showed greater flow variation compared to Cellactose® 80 **(figure 7)**. Cellactose® 80 also possessed lower flowability index (Cellactose® 80 = 5 mm, physical blend = 24 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 Cellactose® 80, indicating excellent flowability.

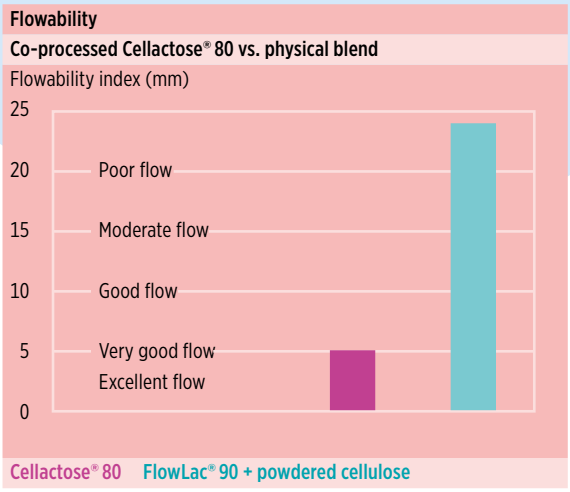


Figure 8: *Flowability index of Cellactose® 80 and its corresponding physical blend. Smaller values indicate better flowability.*

Flowability

Cellactose® 80 – Co-processed lactose

	Angle of repose (°)	Density bulk (g/l)	Density tapped (g/l)	Hausner ratio	Carr's index (%)
Cellactose® 80	34	370	490	1.32	24

Figure 9: *Typical powder technological flowability values of Cellactose® 80. Methods according to Ph. Eur. were used.*

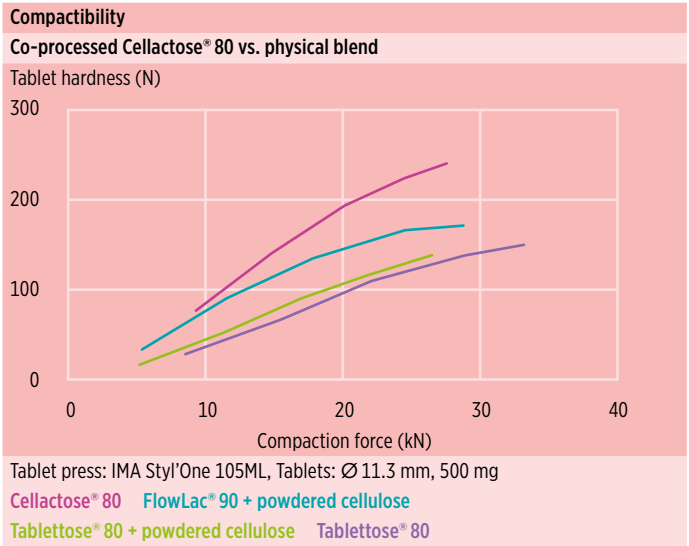


Figure 10: *Tablet hardness profile for Cellactose® 80 compared to a physical blend of the individual components and Tablettose® 80 (granulated lactose). Tablets were produced using a tablet press: IMA Styl'One fitted with 11.3 mm punches. Average tablet weight was targeted at 500 mg.*

Compactibility and friability

Tablet hardness can be increased by combining lactose and cellulose. Results have shown that Cellactose® 80's compactibility is superior to a comparable physical blend of the individual components in the same ratio **(figure 10)**. High-dose formulations were achieved that comprised approximately 70 % drug loading **(figure 11)**. Due to excellent compactibility, low friability (< 1 %) is given **(figure 12)**, eliminating the need for a protective coating.

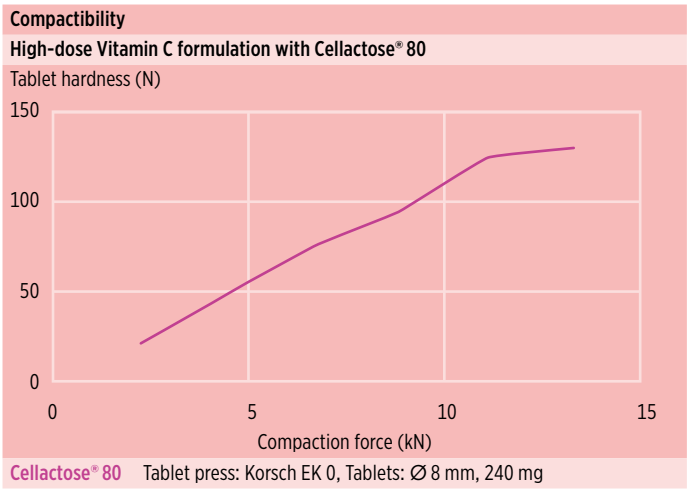


Figure 11: *Tablet hardness profile for tablets comprising 69 % Vitamin C, 30 % Cellactose® 80, and 1 % Compritol® 888. Tablets were produced by Korsch EK 0 tablet press fitted with 8 mm punches. Average tablet weight was targeted at 240 mg.*

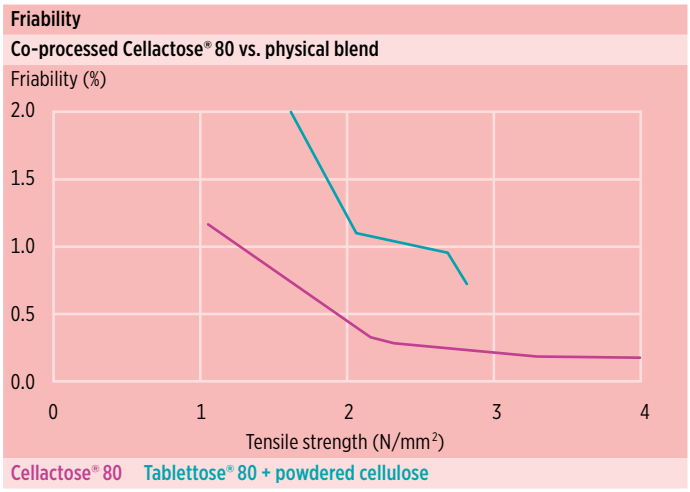


Figure 12: *Friability of tablets produced with either Cellactose® 80 or its corresponding physical blend.*

Adherence capacity

Due to its surface roughness, Cellactose® 80 provides high adherence capacity and is highly recommended for low dosage formulations. Cellactose® 80 mitigates powder segregation during production and assures content uniformity of finished dosage forms. To demonstrate adherence capacity, glibenclamide was blended with different excipients. Non-adhered API was removed by mechanical means, and remaining API was quantified. The following results underscore Cellactose® 80's superior adherence capacity relative to other excipients **(figure 13)**, [5].

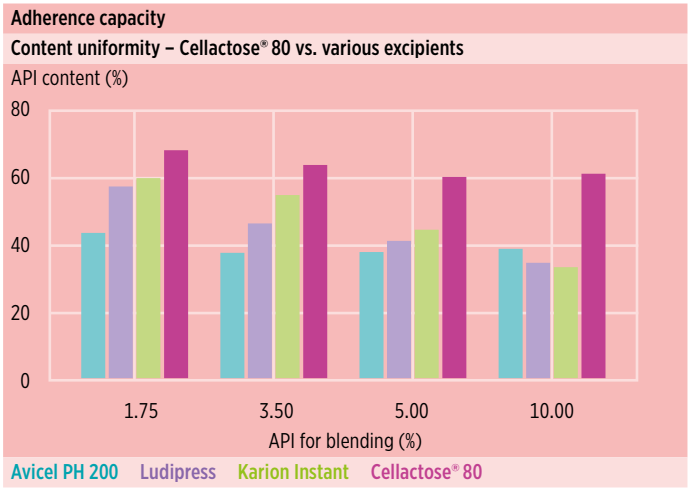


Figure 13: *Adherence capacity of various excipients [5].*

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

Packaging and shelf life

Cellactose® 80

	Size	Material	Shelf life
Cellactose® 80	20 kg	Paper bag with PE-EVOH-PE inliner Carton box with PE-EVOH-PE-inliner	36 Months

Figure 14: *Packaging and shelf life of MEGGLE's Cellactose® 80.*

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 Authorisation Of A Medicinal Product Doc. Ref. EMEA/CHMP/QWP/396951/2006.

[5] P. Schmidt and C. Rubensdörfer (1994). Evaluation of Ludipress as a "Multipurpose Excipient" for DC Part I: Powder Characteristics and Tableting Properties, Drug dev. ind. Pharm. 20(18), 2899–2925.

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