COMBILAC

TABLETING →
DIRECT COMPRESSION →
CO-PROCESSED LACTOSE

Technical brochure CombiLac®

MEGGLE
EXCIPIENTS & TECHNOLOGY

MEGGLE co-processed lactose grades for direct compression: CombiLac®

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 compressability properties **(Figure 1)**.

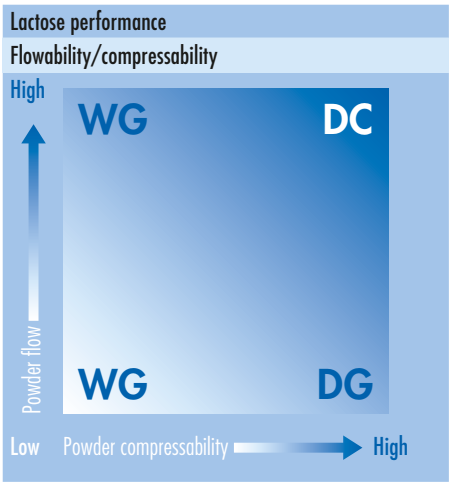


Figure 1: Powder blend compressability and flowability requirements for various tableting technologies (DC is direct compression, WG is wet granulation, DG is dry granulation) [3].

Product description

The high-functionality excipient, CombiLac® is an integrated, lactose-based, co-processed excipient, specifically designed to ease oral solid dosage form development and manufacture. It consists of 70% alpha-lactose monohydrate, 20% microcrystalline cellulose (MCC) and 10% white, native corn starch, each conforming with Ph.Eur., USP-NF, and JP compendial requirements. The three individual components are integrated into a monoparticulate structure, which is not separable by physical means. CombiLac® shows improved compaction properties compared to an equivalent admixture of individual ingredients, providing robust tablets with minimal friability. It assures rapid, hardness-independent tablet disintegration for effective API release, and features powder flow characteristics necessary to enhance dosage form weight uniformity and throughput in DC.

Regulatory & quality information

The raw materials used to produce CombiLac®, alpha-lactose monohydrate, MCC and native corn starch, comply with Ph.Eur., USP-NF and JP monograph requirements. Since no chemical modification results during co-processing and individual chemical identities are maintained, CombiLac® can be considered as a physical blend of individual ingredients. 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 Practice 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). It has also implemented GDP according to the IPEC Good Distribution Practices Guide for Pharmaceutical Excipients. Both IPEC standards have been certified according to EXCiPACT™ for manufacturing, testing, storage and distribution of lactose and co-processed excipients used as pharmaceutical excipients or claimed for pharmaceutical use.

MEGGLE invests considerably in raw material resource sustainability, production standards, efficiency and is actively engaged in environmental protection. Excipients meeting pharmaceutical standards is our first priority.

international excipients certification

Application

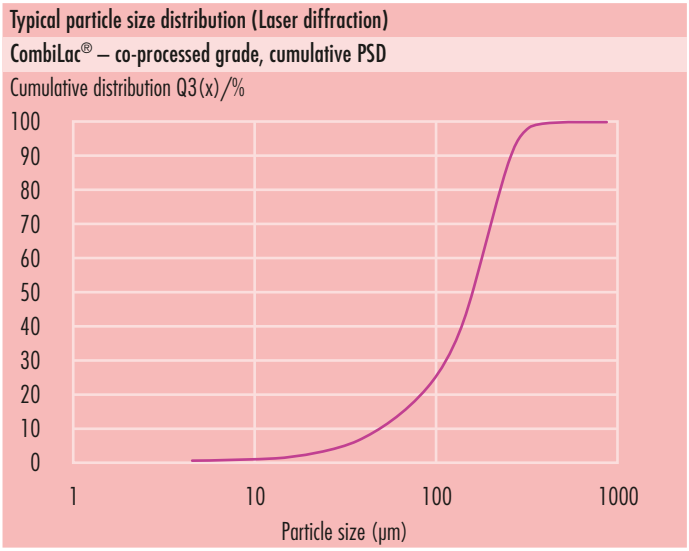
CombiLac® is designed for DC and may be used in other formulation development approaches, such as dry granulation. In comparison to a physical admixture of individual components, CombiLac® provides enhanced compaction properties, as well as the flow performance necessary for increased production rates and decreased weight variation. If robust, time saving development of frequently used formulation ingredients is a top priority, ready-to-use CombiLac® is the best choice. During production, reduced raw material testing is required due to its ternary combination.

- Direct compression
- ODT formulations
- Dry granulation

BENEFITS

CombiLac®

- Excellent compactibility
- Excellent flowability
- Fast, hardness-independent tablet disintegration for effective API release
- Low friability
- Overcomes individual ingredient compaction and handling limitations



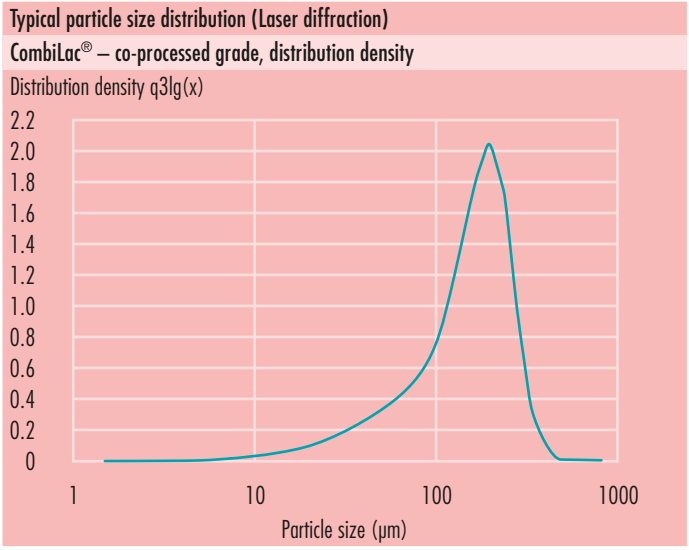


Figure 2: Typical cumulative PSD and distribution density of MEGGLE's CombiLac®. Analyzed by Sympatec®/Helos & Rhodos Particle size analyzer.

Particle size distribution (PSD)

Figure 2 shows typical laser diffraction particle size distribution data for CombiLac®. The narrow PSD supports homogenous powder blend preparation, an important requirement in tableting manufacture.

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 CombiLac® particle size distribution specification (Typical values shown for orientation only).

Sieve data – co-processed lactose		
	Lactose type	CombiLac®
		specified/typical
Particle size distribution	< 32 µm	NMT 15 %/5 %
Method: Air jet sieving	< 160 µm	35 – 65 %/56 %
	< 250 µm	NLT 85 %/93 %

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

Core benefit

CombiLac® is highly appropriate for DC, as it synergistically combines the benefits of its individual components through intelligent particle design. The monoparticulate structure of CombiLac® clearly outperforms the physical blend in flow, hardness, and disintegration performance.

Core benefit of CombiLac®			
	CombiLac®	MicroceLac® 100	StarLac®
Flowability	++	++	++
Compactability	+++	+++	++
Tablet hardness	++	+++	+
Tablet disintegration	++	+	+++

Isotherms

CombiLac®'s moisture sorption isotherms at 20 °C exhibit a moderate water uptake due to the MCC and corn starch content, as shown by dynamic vapor sorption (DVS). Increase and subsequent decrease of equilibrium moisture content demonstrates hysteresis **(Figure 4)**.

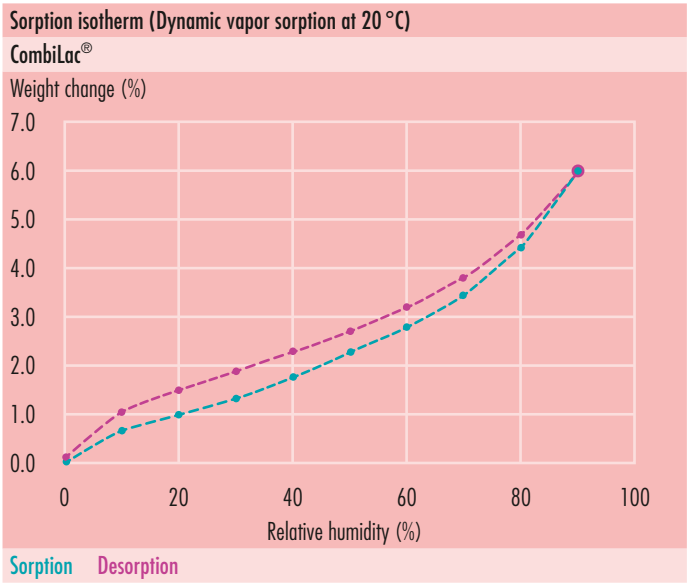


Figure 4: CombiLac®'s moisture sorption isotherms at 20 °C. Moisture uptake is driven by MCC and corn starch and is proportional to the surrounding atmosphere. Analysis performed by SPSx-1µ moisture sorption test system.

Scanning electron micrograph (SEM)

MEGGLE's triple co-processed excipient, CombiLac®, appears as a white, or almost white, odourless powder. It is a spray-dried composition of 70% alpha-lactose monohydrate, 20% MCC, and 10% GMO-free, white, native corn starch, where each component meets Ph.Eur., USP-NF, and JP compendial standards. It is freely flowing and partially soluble in cold water. A well-defined production process generates a porous, spherical morphology. Although triple in composition, it is monoparticulate structurally.

CombiLac®'s SEM demonstrates the conversion of the irregularly shaped lactose, MCC and corn starch particles into a highly spherical, integrated system **(Figure 5)**. The individual components cannot be separated by physical means. Flow and compaction performance is improved in comparison to a simple physical admixture of the individual ingredients.

Morphology of irregularly shaped lactose, MCC and corn starch is adjusted to the particle requirements needed for excellent flow and compaction performance in DC.

Figure 5: SEM of MEGGLE's triple co-processed excipient CombiLac®.

Functional related characteristics

Powder flow

Flow assessments are routinely completed in solid dosage form development and strongly impact production and product quality. Amongst the various methods used to evaluate powder flow, a FlowRatex® apparatus (Powder flow through an aperture) is widely used. CombiLac® shows good flowability, reflected by a low Flowability Index, FI = 2 (mm), and high volume flow rates as shown in **figure 6**. Also, compressibility related indices and angle of repose are common and had been used for comparison **(Figure 7)**.

Specific surface

If the physical admixture comprising 70 % alpha-lactose monohydrate, 20 % MCC and 10 % white, native corn starch is compared to the triple co-processed excipient CombiLac®, only a marginal impact on BET surface area is observed. The overall BET surface area is measured to be 0.5 m^2/g.

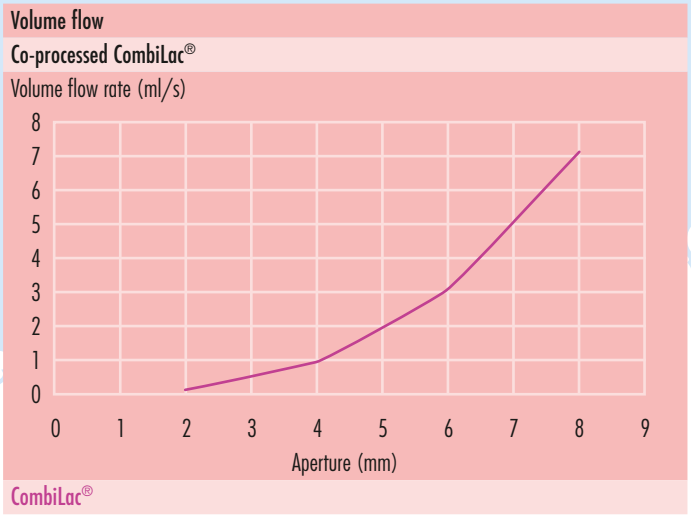


Figure 6: Volume flow rate (ml/s) as a function of aperture size (mm) for CombiLac® analyzed by a FlowRatex®. Flowability Index (FI) of MEGGLE's triple co-processed excipient CombiLac®, is 2 (mm).

Flowability

Co-processed lactose

	Angle of repose (°)	Density bulk (g/l)	Density tapped (g/l)	Hausner ratio	Carr's index (%)	BET-surface (m^2/g)
CombiLac®	30	450	540	1.19	16	0.49

Figure 7: Typical powder functional values for triple co-processed excipient CombiLac®. All methods were performed according to compendial standards. BET surface area determination was conducted by an instrumented Quantachrome Autosorb iQ (Adsorbent K_2, outgas time and temperature: 7 hrs at 50 °C, in vacuo).

Compactability

Material fill characteristics and compression behavior of formulation ingredients impact tablet quality. Generally, compaction performance is enhanced by combination of brittle and plastically deforming materials. However, addition of elastically deforming components, e. g. various starches, seems to be diametrically opposed. Pharmaceutical practice is often positioned to balance the integrity of a solid dosage form and its function as a pharmacological vehicle. CombiLac® is well-balanced by insuring sufficient tablet hardness and, simultaneously, fast disintegration time. Additionally, CombiLac® offers superior hardness yield in comparison to the physical admixture of individual ingredients. An increase of approximately 20 % is achieved **(Figure 8)**.

Tablet hardness profiles of co-processed excipients MicroceLac® 100 (75 % alpha-lactose monohydrate and 25 % MCC) and StarLac® (85 % alpha-lactose, and 15 % native corn starch) are provided for reference **(Figure 9)**.

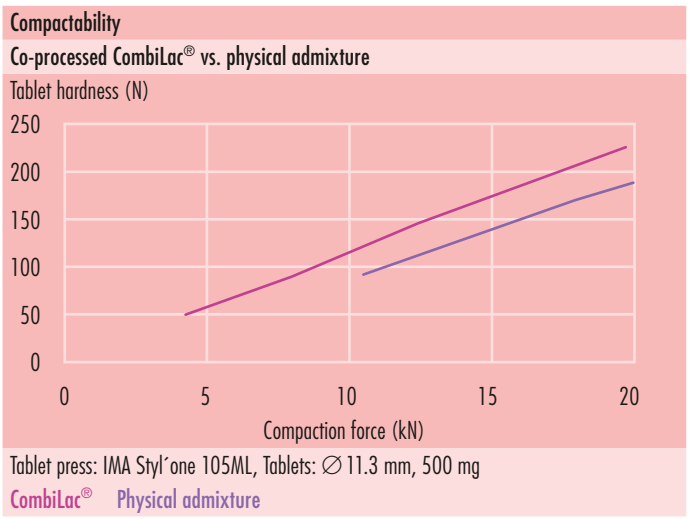


Figure 8: Tablet hardness profile for CombiLac® compared to a physical admixture of individual components (spray-dried lactose grade FlowLac® 100, MCC 102, and pregelatinized DC starch grade Starch® 1500). Tablets were produced using a tablet press IMA Styl'One 105 ML, with a tablet diameter of 11.3 mm, a weight of 500 mg, and 0.5 % Mg-stearate.

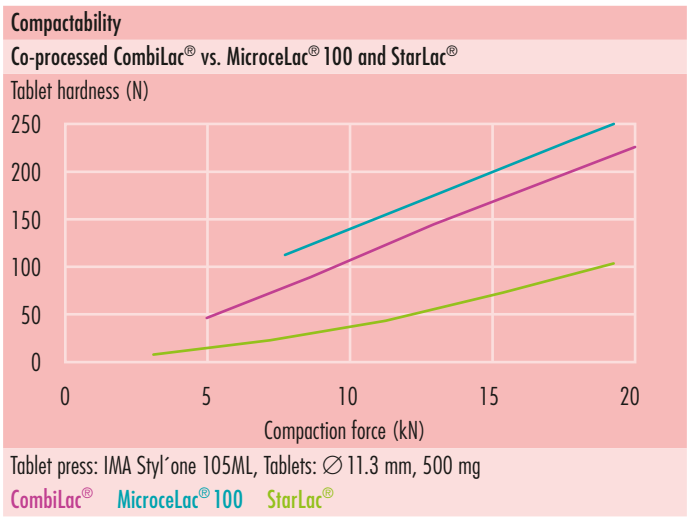


Figure 9: Tablet hardness profile for CombiLac® compared to co-processed excipients MicroceLac® 100 (75 % alpha-lactose monohydrate and 25 % MCC), and StarLac® (85 % alpha-lactose monohydrate and 15 % native corn starch) are depicted for reference. Tablets were produced using a tablet press IMA Styl'One 105 ML, with a tablet diameter of 11.3 mm, a weight of 500 mg, and 0.5 % Mg-stearate.

Disintegration

CombiLac® is ideal when rapid disintegration at high tablet hardness is desired. CombiLac®'s disintegration is quick and independent of tablet hardness. A co-processed excipient consisting of lactose and MCC shows a significant disintegration time dependence on tablet hardness, challenging the limits of immediate release formulations.

Corn starch, as a traditional disintegration agent, may be helpful by ensuring rapid water uptake, either in a classical physical admixture or incorporated in a co-processed excipient (CombiLac®, StarLac®), but at the expense of tablet hardness. In CombiLac® high tablet hardness and low disintegration time have been balanced **(Figure 10, 11)**.

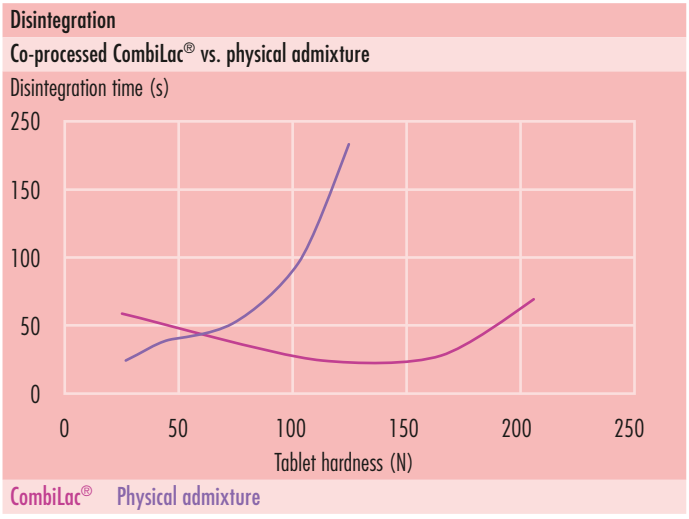


Figure 10: Tablet disintegration of CombiLac®, MEGGLE's triple co-processed excipient compared to the corresponding physical admixture (spray-dried lactose grade FlowLac® 100, MCC 102, and pregelatinized DC starch grade Starch® 1500). Tablets were produced using a tablet press IMA Styl'One 105 ML, with a tablet diameter of 11.3 mm, and a weight of 500 mg, 0.5 % Mg-stearate.

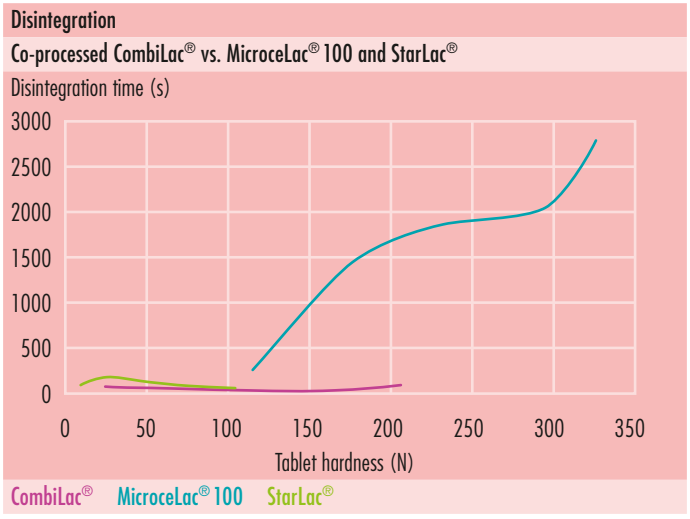


Figure 11: Tablet disintegration of CombiLac® compared to the co-processed excipients MicroceLac® 100 (75 % alpha-lactose monohydrate and 25 % MCC), and StarLac® (85 % alpha-lactose monohydrate and 15 % native corn starch). Tablets were produced using a tablet press IMA Styl'One 105 ML, with a tablet diameter of 11.3 mm, and a weight of 500 mg, 0.5 % Mg-stearate.

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

Packaging and shelf life

	Size	Material	Shelf life
CombiLac®	20 kg	Carton box with PE-EVOH-PE-inliner	24 months

Figure 12: Packaging and shelf life of MEGGLE's CombiLac®.

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).

MEGGLE App:

MEGGLE Consultant

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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