MEGGLE

COMBILAC

TABLETING →
DIRECT COMPRESSION →
CO-PROCESSED LACTOSE

Technical brochure CombiLac®

MEGGLE's 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 compaction properties **(figure 1)**.

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 is made up 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.

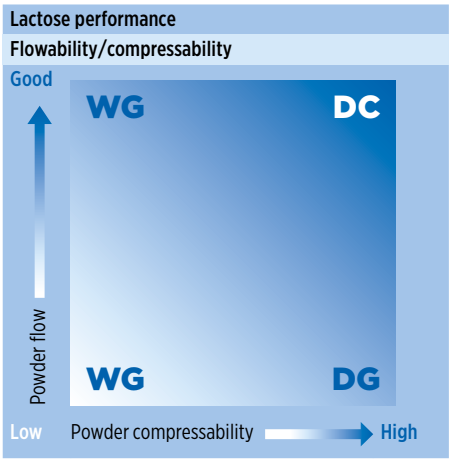


Figure 1: *Powder blend compressability and flowability requirements for various tableting technologies (DC is direct compression, WG is wet granulation, DG is dry granulation) [3].*

Regulatory & quality information

The raw materials used to produce 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 [4]. 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 Chapters <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

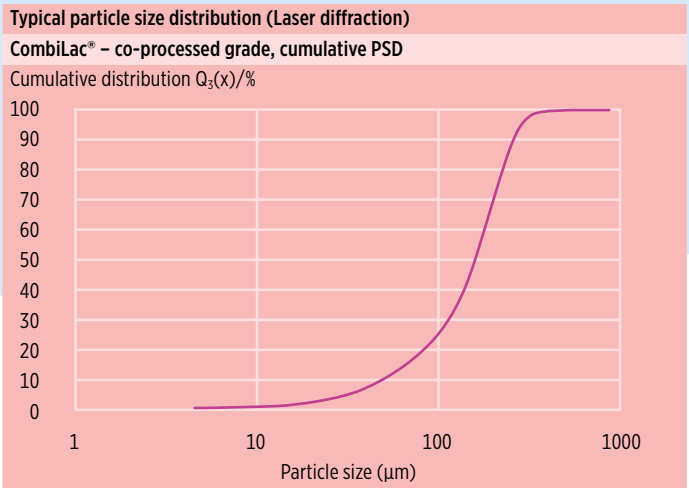
CombiLac® is designed for DC and may be used in other formulation development approaches, such as dry granulation. In comparison to a physical admixture of individual components, CombiLac® provides enhanced compaction properties, as well as the flow performance necessary for increased production rates 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 (Roller compaction, slugging)

BENEFITS

CombiLac®

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



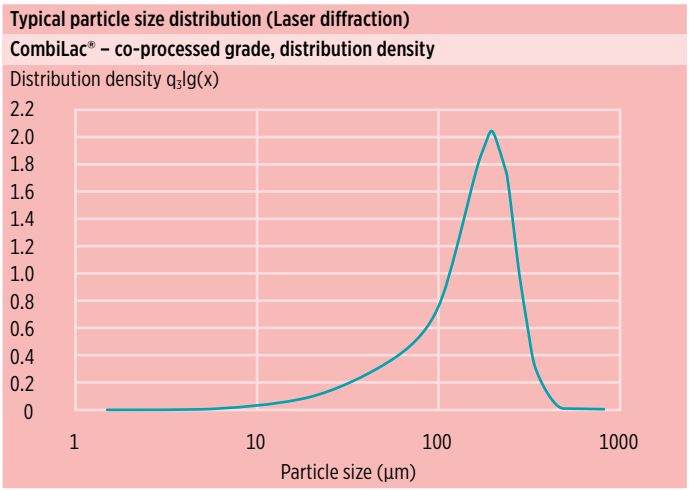


Figure 2: *Typical cumulative PSD and distribution density of MEGGLE's CombiLac®. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.*

Particle size distribution (PSD)

Figure 2 depicts 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:	< 160 µm	**35–65 %**/56 %
Air-jet sieving	< 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 benefits of CombiLac®			
	CombiLac®	MicroceLac® 100	StarLac®
Flowability	+++	+++	+++
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)**.

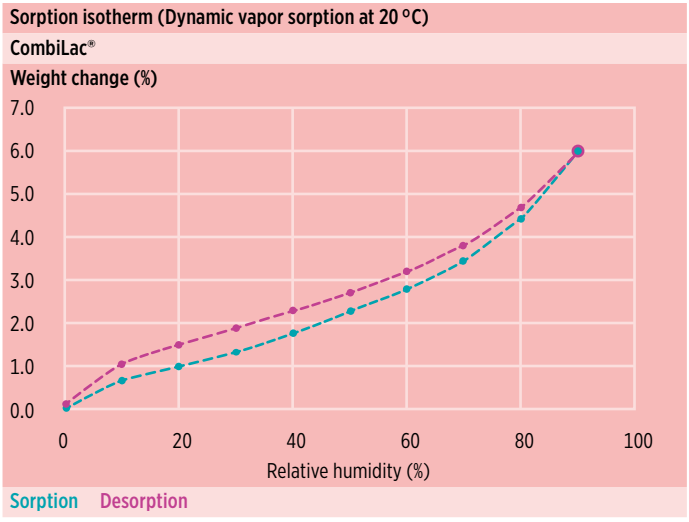


Figure 4: *Sorption-desorption isotherms (20 °C) of CombiLac®. Analysis performed by SPSx-1µ moisture sorption test system.*

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 and surface structure of alpha-lactose monohydrate, MCC and corn starch yield in CombiLac®'s excellent flow and compaction performance in DC.

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

Functional related characteristics

Powder flow

Evaluation of flow properties according to FlowRatex® (powder flow through an orifice) is an integral part of drug development and subsequently impacts production process and product quality. CombiLac® exhibits excellent flow properties, indicated by a small flowability index of 2 (mm) and high volume flow rate as shown in **figure 6**. Index, which describe compressibility as well as angle of repose, commonly used, are shown in **figure 7**.

Specific surface

Compared to the physical admixture, comprising 70 % alpha-lactose monohydrate, 20 % MCC, and 10 % white, native corn starch, CombiLac®'s BET specific surface area is fairly small at 0.5 m^2/g.

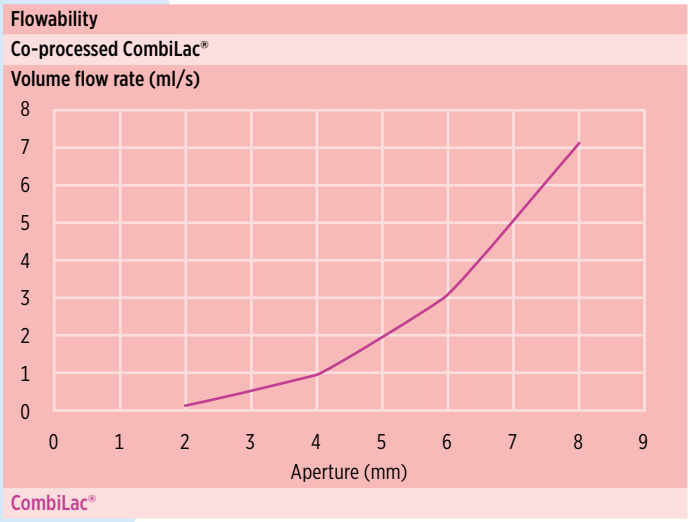


Figure 6: *Volume flow rate (ml/s) as a function of aperture size (mm) for CombiLac® analyzed by a FlowRatex®. Flowability index of MEGGLE's triple co-processed excipient CombiLac® is 2 (mm).*

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 functional powder values for CombiLac®. All methods were performed according to compendial standards. BET surface area determination was conducted by Quantachrome Autosorb® iQ (adsorbent Kr_2, outgas time and temperature: 7 h at 50 °C, in vacuo).*

Powder compressibility

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)**.

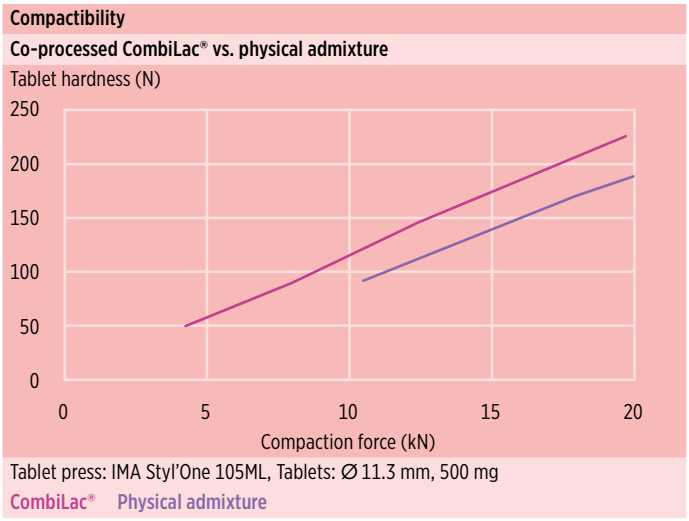


Figure 8: *Tablet hardness profile for CombiLac® compared to a physical admixture of individual components (spray-dried lactose grade FlowLac® 100, MCC 102, and pregelatinized DC starch grade Starch® 1500). Tablets were produced using a tablet press IMA Styl'One 105 ML, with a tablet diameter of 11.3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

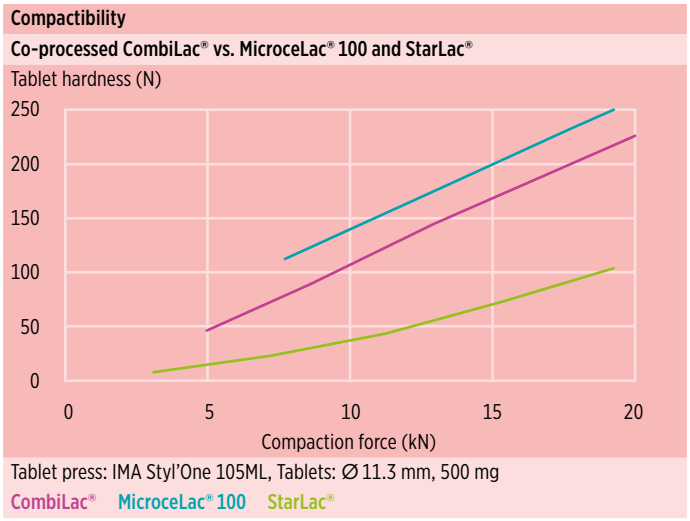


Figure 9: *Tablet hardness profile for CombiLac® compared to co-processed excipients MicroceLac® 100 (75 % alpha-lactose monohydrate and 25 % MCC), and StarLac® (85 % alpha-lactose monohydrate and 15 % native corn starch) are depicted for reference. Tablets were produced using a tablet press IMA Styl'One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

Tablet disintegration

CombiLac® is ideal when rapid disintegration at high tablet hardness is desired. CombiLac®'s disintegration is quick does not depend on tablet hardness. A co-processed excipient consisting of alpha-lactose monohydrat 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)**.

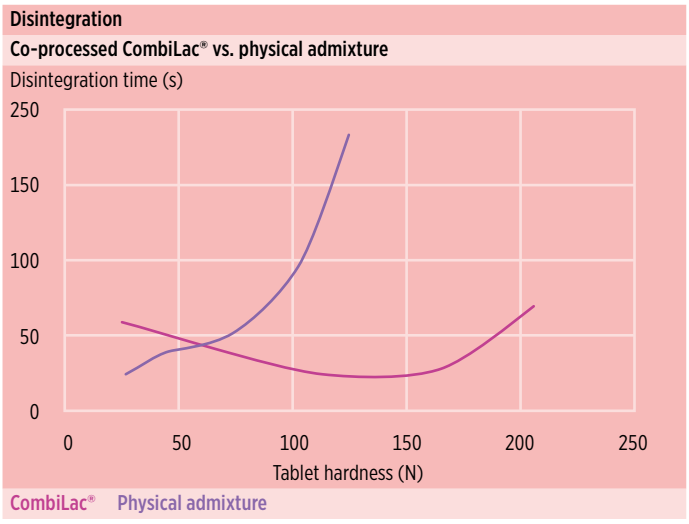


Figure 10: *Tablet disintegration of CombiLac® compared to a corresponding physical admixture (spray-dried lactose grade FlowLac® 100, MCC 102, and pregelatinized DC starch grade Starch® 1500). Tablets were produced using a tablet press IMA Styl'One 105 ML, with a tablet diameter of 11.3 mm, and a weight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

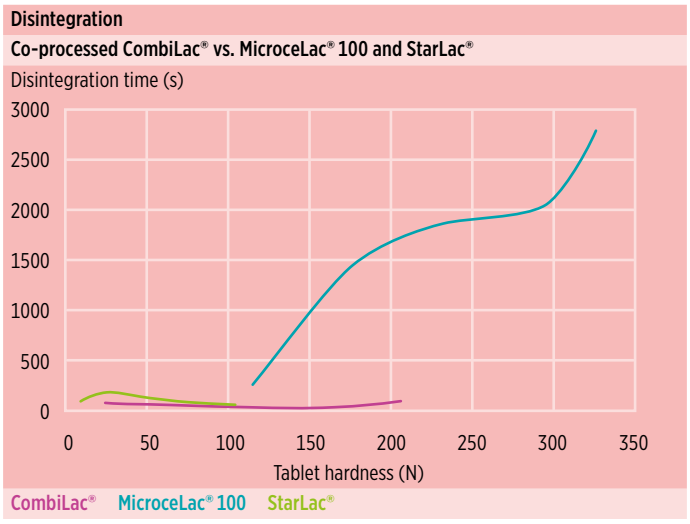


Figure 11: *Tablet disintegration of CombiLac® compared to the co-processed excipients MicroceLac® 100 (75 % alpha-lactose monohydrate and 25 % MCC), and StarLac® (85 % alpha-lactose monohydrate and 15 % native corn starch). Tablets were produced using a tablet press IMA Styl'One 105 ML, with a tablet 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 and, material as well as 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).

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

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