



TABLETING | DIRECT COMPRESSION | ANHYDROUS LACTOSE

DURALAC

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 compatible 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 (figure 1).

Anhydrous Lactose

Anhydrous lactose is a water-free form of lactose, typically present predominantly in the β -lactose modification. Due to its good compressibility and the absence of crystal water, anhydrous lactose is widely used as a filler (diluent) in direct compression and is the excipient of choice for dry granulation (roller compaction). Another notable characteristic of anhydrous lactose is that tablets typically exhibit rapid disintegration, largely independent of compaction pressure.

Roller Compaction

Anhydrous lactose is well suited for use in roller compaction. Roller compaction is a dry granulation process that densifies powders without the need for liquids or thermal input. The powder blend is compressed between two counter-rotating rollers to form a compact ribbon, which is subsequently milled and sieved to obtain granules with a defined particle size distribution.

Key advantages of roller compaction include:

- no exposure to moisture or elevated temperatures
- suitability for moisture- and heat-sensitive APIs
- improved flowability and uniform bulk density
- good process scalability for industrial manufacturing

A major benefit of anhydrous lactose in roller compaction is its outstanding recompactability. Unlike many other excipients, such as microcrystalline cellulose, it retains its compactability during a second compaction step without a significant loss in tablet strength, owing to its brittle fracture mechanism.

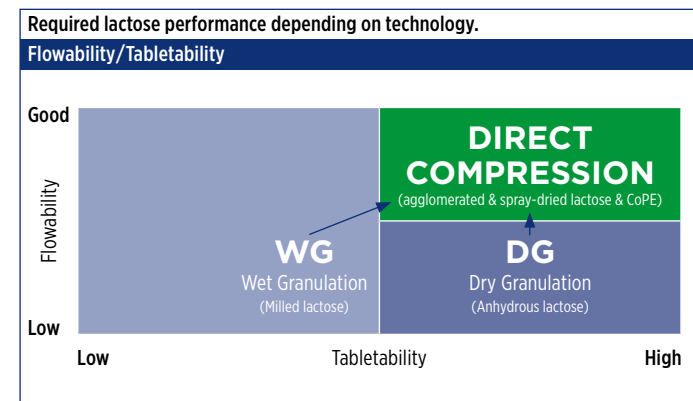


Figure 1: Lactose with high flowability and compressibility leads to DC. Lactose with poor flow needs to be processed with wet or dry granulation.

Product description

DuraLac® H is produced by roller-drying a lactose solution at high temperature to form 70–80% anhydrous beta-lactose crystals (**figure 2**). During anhydrous lactose crystallization, no water is incorporated in the crystal lattice. Subsequent to roller-drying, anhydrous lactose is milled and sieved to the desired particle size distribution, optimizing powder flow and compactibility. DuraLac® H complies with the monograph “Lactose, anhydrous” (USP-NF, Ph. Eur., and JP). Because DuraLac® H deforms by brittle fracture during compaction, it is well suited for directly compressed and dry granulated formulations (roller compaction, slugging).



Figure 2: Shape of anhydrous lactose

DuraLac® H was developed especially for direct compression processes. The following chart provides recommended areas of applications.

APPLICATION

DuraLac® H

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

BENEFITS

DuraLac® H

- Excellent compactibility and recompactibility
- Highest density
- Disintegration independent of compaction pressure
- Good storage stability
- Low water content

Regulatory & quality information

DuraLac® H is MEGGLE's trade name for anhydrous lactose and complies with the current harmonized USP-NF, Ph. Eur., and JP monographs. Specifications and regulatory documents can be downloaded from www.megggle-excipients.com

MEGGLE's new state-of-the-art, pharma-dedicated production facility in Le Sueur, Minnesota, complies with 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 US site in Le Sueur produces milled alpha-lactose monohydrate and anhydrous lactose to equivalent quality standards and provides the same documentation as the Wasserburg facility. 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) & Morphology (SEM)

Figure 3 shows typical laser diffraction particle size distribution data for MEGGLE’s anhydrous lactose grade, DuraLac® H.

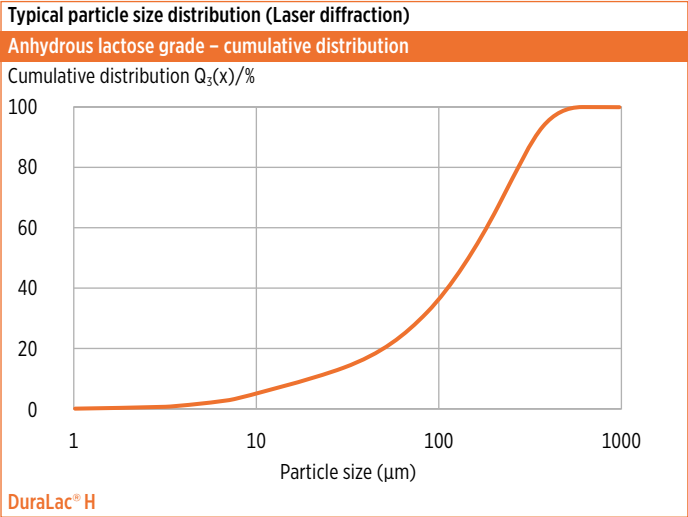


Figure 3: Typical cumulative PSD and distribution density of MEGGLE’s anhydrous lactose grade DuraLac® H. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.

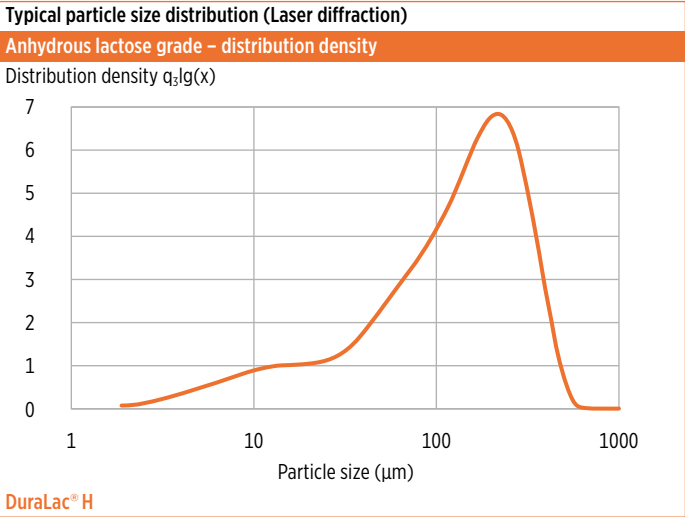
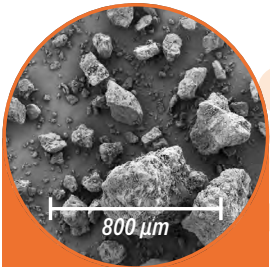


Figure 4 illustrates the specified particle size distribution (PSD) ranges for MEGGLE’s DuraLac® H and its typical Scanning Electron Microscope (SEM) image. The PSD is obtained using air-jet sieving and is shown in bold letters. Typical values generated through continuous in-process control are provided for information only. The SEM images of alpha-lactose monohydrate and anhydrous lactose exhibit different morphology. Where alpha-lactose monohydrate products are defined typically by monoclinic spheroidal, “tomahawk-shaped” monocrystals, anhydrous lactose consists of micro-crystal clusters of beta- and alpha-lactose, both in the anhydrous form. This characteristic shape results from the roller-drying and milling processes.



DuraLac® H

Particle size distribution	
μm	specified/typical
< 45	NMT 20 % / 15 %
< 150	40 – 65 % / 53 %
< 250	NMT 80 % / 84 %

Figure 4: Specified PSDs for MEGGLE’s anhydrous lactose grade DuraLac® H by air-jet sieving in bold letters. Typical values obtained from a permanent in-process control are shown for orientation. SEM images of MEGGLEs anhydrous lactose grade DuraLac® H 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 flowability indices for DuraLac® H, indicating its moderate flowability. DuraLac® H exhibits a fair to moderate flowability, as indicated by a CI of 20 % and a Hausner ratio of 1.25. The angle of repose further supports a limited but still processable flow behavior, with a value of 42.

Flowability					
Anhydrous lactose					
	Carr's Index (%)	Angle of Repose (°)	Hausner ratio	Density bulk (g/l)	Density tapped (g/l)
DuraLac® H	20	42	1.25	710	888

Figure 6: Typical technological values, describing powder flowability, shown for anhydrous MEGGLE lactose grade.

Figure 7 demonstrates that particle shape and structure are more important than particle size distribution. Due to its shape, the anhydrous lactose exhibits moderate flowability, but improves significantly with lubricant and/or glidant addition (0.5 %). Notably, DuraLac® H shows particularly good dynamic flowability during die filling.

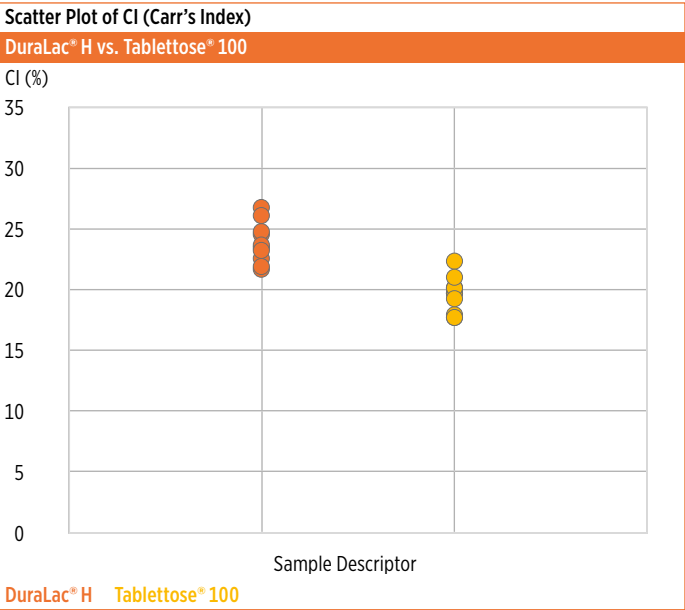


Figure 7: Carr's Index of DuraLac® H in comparison with fine agglomerated lactose Tablettose® 100.

Functional related characteristics – Part 2

During compaction, DuraLac® H fragments, exposing clean surfaces having numerous binding sites. This provides the functional performance needed to produce robust tablets in direct compression and granules having desired characteristics for high-speed tableting and capsule filling processes.

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

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

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

Figure 8 presents the tableability profiles of DuraLac® H and dry-granulated DuraLac® H granules produced at low, medium, and high roller compaction pressures. The results demonstrate the good tableability of DuraLac® H, which remains unaffected by the initial compaction step during roller compaction, in contrast to many other materials.

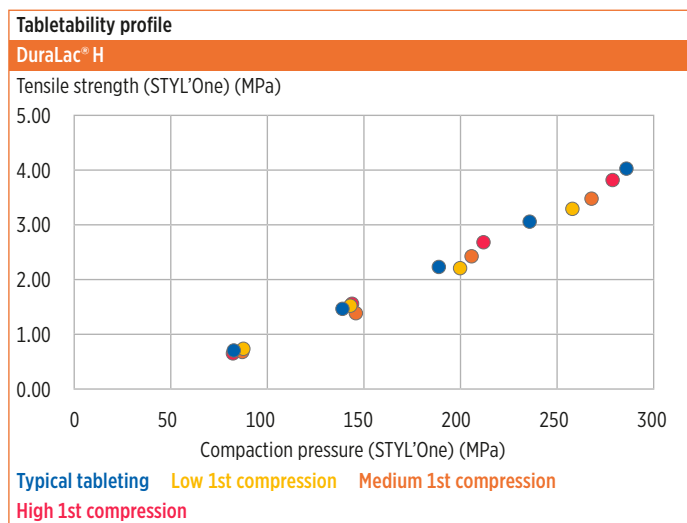


Figure 8: Tableability profile of DuraLac® H showing a good and stable tableability, largely independent of compression force. Tablet press: MEDELPHARM STYL'One, Tablets: Ø 11.3 mm, 500 mg.

Figure 9 compares the disintegration behavior of DuraLac® H with that of agglomerated and spray-dried lactose. Once the minimum compaction pressure required to form stable compacts has been reached, the disintegration time of DuraLac® H tablets does not increase further with increasing compaction pressure. DuraLac® H is therefore largely insensitive to changes in compaction pressure, in contrast to spray-dried lactose, which shows a pronounced increase in disintegration time at high compaction pressures, and agglomerated lactose, which exhibits a slight increase.

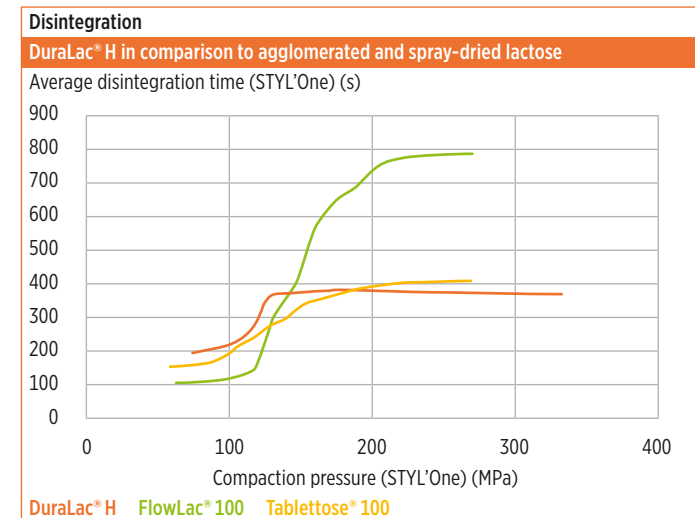


Figure 9: Disintegration of DuraLac® H in comparison to agglomerated and spray-dried lactose.

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 10**).

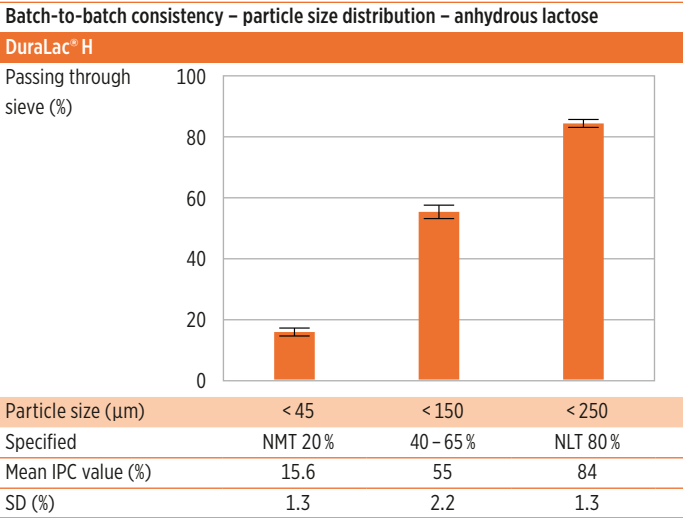


Figure 10: DuraLac® H provides a very consistent particle size distribution (by air-jet sieving), illustrated by low batch-to-batch variability. Data obtained from a permanent in-process control (IPC) of subsequent batches over 12 months.

Isotherm

While alpha-lactose monohydrate shows water uptake of less than 0.2% and hence, could be categorised as non-hygroscopic, slightly hygroscopic anhydrous lactose demonstrates water uptake at higher humidities (shown in **figure 11**). The hysteresis is caused by the conversion of lactose from the anhydrous to hydrated form.

MEGGLE's anhydrous lactose grade, DuraLac® H, contains no water of crystallization and has therefore a lower total water content as alpha-lactose monohydrate. However, the free moisture content of anhydrous lactose and alpha-lactose monohydrate is similarly low, at less than 0.5%. This makes both excipients well suited for formulations containing moisture-sensitive APIs.

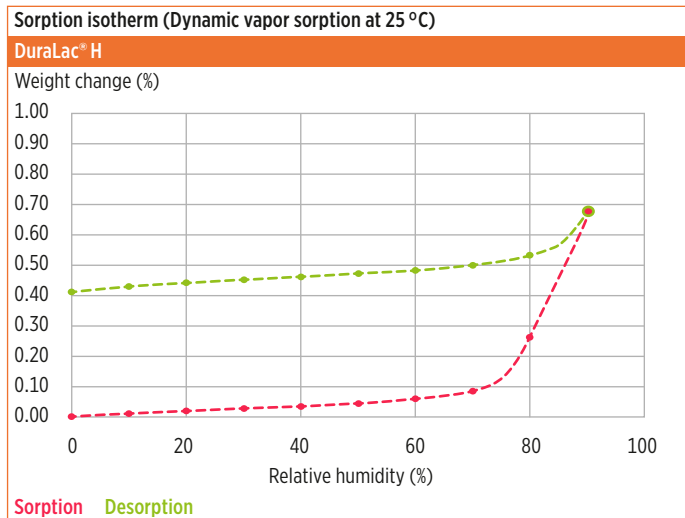


Figure 11: Sorption-desorption isotherms (25 °C) of anhydrous lactose DuraLac® H.
Analysis performed with SPSx-1µ Advance (proUmid GmbH & Co. KG, Ulm, Germany).

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

Packaging and shelf life			
	Size	Material	Shelf life
DuraLac® H	25 kg	Carton box with an aluminium laminated inliner	36 Months

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

DuraLac® H is protected from uncontrolled water uptake, by its aluminium packaging. Therefore, MEGGLE can assure at least 36 months of stability throughout storage (unopened package provided).

Literature

- [1] Meeus, L. (2011). Direct Compression versus Granulation. Pharmaceutical Technology, 23(3). pharmtech.com
- [2] Kristensen, H. G., Schaefer, T. (1987). Granulation: A Review on Pharmaceutical Wet-Granulation. Drug Development and Industrial Pharmacy, 13(4-5), 803-872. tandfonline.com
- [3] Hein, S., Picker-Freyer, K. M., & Langridge, J. (2008). Simulation of roller compaction with subsequent tableting and characterization of lactose and microcrystalline cellulose. Pharmaceutical Development and Technology, 13(6), 523-532. doi.org

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