DRY POWDER INHALATION →
SIEVED/MILLED/MICRONIZED
LACTOSE

Technical brochure
InhaLac®

MEGGLE
EXCIPIENTS & TECHNOLOGY

MEGGLE's sieved, milled and micronized alpha-lactose monyhydrate for dry powder inhalation: InhaLac®

General information

The delivery of active pharmaceutical ingredients (APIs) via the lung is becoming increasingly important as ever more patients all over the world suffer from chronic respiratory diseases [1].

Dry powder inhalers (DPIs) are widely used in pulmonary drug delivery. This is due to their advantages, such as ease of use, small size, portability, and the lack of requirement of breath-actuation coordination [2]. Because they are propellant-free, they are environmentally friendly. Furthermore, as solid-particle formulations they are comparatively stable [3]. Usually, this dosage form contains a device, one or more APIs and an excipient that improves the powder qualities of the formulation. Features such as particle size are fundamental factors in the design of DPIs.

MEGGLE's alpha-lactose monohydrate grades for inhalation effortlessly fulfill all criteria for achieving the desired quality, safety, and innovation of DPI formulations. Lactose has a long tradition of inhalation application and is proven safe. Thus, lactose is the excipient of choice in pulmonary drug delivery. An established and well-documented production process has lead to this highly specialized product family called InhaLac®. In order to meet formulators' expectations, this product family has a broad range. Sieved, milled, and micronized grades have excellent physio-chemical characteristics and conform with compendial requirements. Beyond that, a highly experienced team of specialists are waiting to support you in matters of processing and process adjustment.

Product description

In DPI formulations, the excipient not only acts as a filler but also contributes to the performance features of the DPI. An extensive knowledge of the physio-chemical properties is a prerequisite to guarantee the functionality and safety of the DPI. This includes an established and well-investigated production process. All InhaLac® grades are produced via crystallization and subsequent sieving or milling. The optimized and standardized production process consistently ensures the highest production quality.

Regulatory & quality information

MEGGLE's InhaLac® grades comply with the current harmonized USP-NF, Ph. Eur. and JP monographs. In order to meet the special requirements for pulmonary drug delivery, additional and in some cases even stricter specification limits are in place for all InhaLac® grades. These exceed even those currently required by the pharmacopoeias. A InhaLac® drug master file (DMF) is available/in process 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. All InhaLac® products are manufactured on product lines exclusively dedicated to inhalation lactose. 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.

international excipients certification

Application

InhaLac® is suitable for use in pulmonary and nasal drug delivery.

BENEFITS

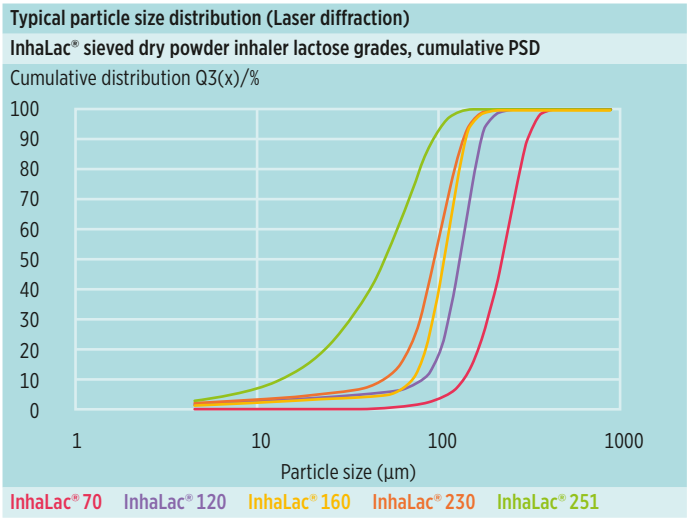
InhaLac®

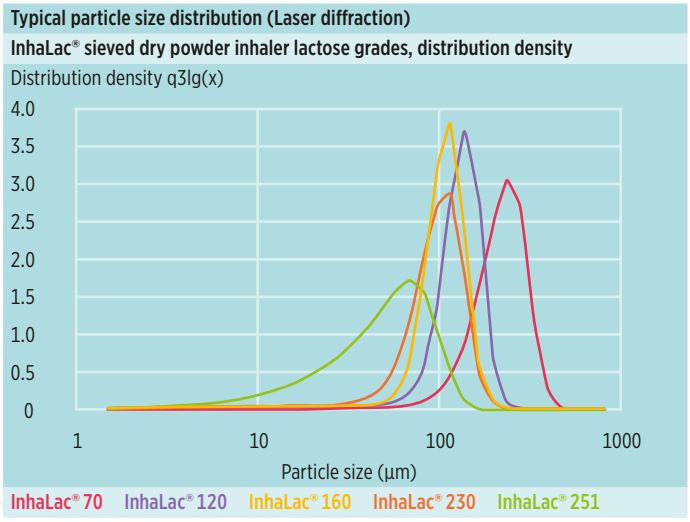
- Highly controlled powder characteristics
- Highest microbial quality including endotoxines
- A broad spectrum of sieve cuts
- Customized grades
- Customized product specifications

Particle size distribution (PSD)

Depending on the API (concentration, particle size and shape, hydrophilicity, lipophilicity, ...), the device (de-agglomeration principle, single- or multi-dose, capsule, blister, container, ...) and the dosage-filling system, different formulation strategies must be applied to guarantee a high and repeatable delivery of the API to the lungs. As the different formulation principles require distinct particle sizes of the excipient MEGGLE offers a range of sieved, milled and micronized InhaLac® grades.

InhaLac® 70, the coarsest, sieved product, has a typical median particle size of approximately 215 µm, is virtually free of fines (particles < 15 µm), shows a narrow particle size distribution (Span: 0.8) and is best suited to cyclone-based inhalation devices. InhaLac® 120 (median particle size: ~130 µm), InhaLac® 160 (median particle size: ~110 µm) and InhaLac® 230 (median particle size: ~100 µm), all three products have a narrowly distributed particle size (Span: ≤ 1.0) and a fines content between 3 – 5 %. InhaLac® 251, the finest sieved lactose grade, has a median particle size of approximately 50 µm.





Figures 1 – 2: *Typical cumulative particle size and density distribution of MEGGLE's sieved inhalation lactose grades InhaLac® 70, InhaLac® 120, InhaLac® 160, InhaLac® 230 and InhaLac® 251. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.*

Sieved InhaLac® grades						
	Lactose type	**InhaLac® 70**	**InhaLac® 120**	**InhaLac® 160**	**InhaLac® 230**	**InhaLac® 251**
		specified/typical	**specified**/typical	**specified**/typical	**specified**/typical	**specified**/typical
Particle size distribution	x_{10}	**110 – 160 µm**/135 µm	**70 – 105 µm**/ 88 µm	**55 – 85 µm**/ 73 µm	**30 – 60 µm**/ 45 µm	**7 – 22 µm**/13 µm
Laser diffraction	x_{50}	**180 – 250 µm**/215 µm	**110 – 155 µm**/132 µm	**90 – 120 µm**/108 µm	**70 – 110 µm**/ 97 µm	**40 – 70 µm**/49 µm
	x_{90}	**270 – 340 µm**/301 µm	**160 – 215 µm**/175 µm	**125 – 165 µm**/144 µm	**110 – 150 µm**/144 µm	**80 – 120 µm**/91 µm
	Span $[(x_{90} - x_{10})/x_{50}]$	/ 0.8	/ 0.7	/ 0.7	/ 1.0	/ 1.6
	% fines < 15 µm	/ 0	/ 3	/ 3	/ 5	/11

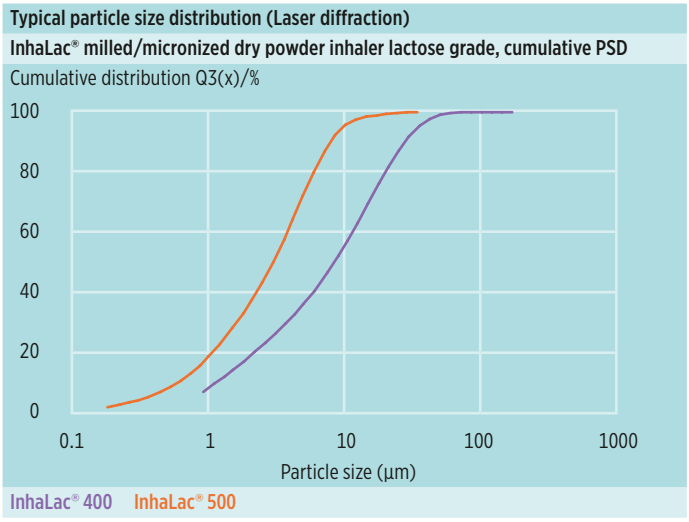
Figure 3: *Specified PSD for MEGGLE's inhalation lactose grades by laser diffraction (in bold letters). Typical values are shown solely for reference.*

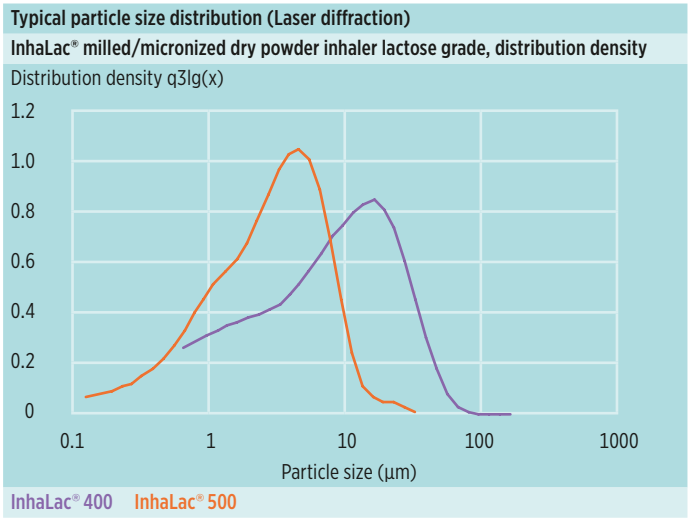
The product is characterized by a higher fines content (particles < 15 µm: > 10 %) and broader particle size distribution. InhaLac® 120, InhaLac® 160, InhaLac® 230 and InhaLac® 251 are mainly used in formulations for capsules or blisters **(figure 1 and 2)**.

InhaLac® 400 is a finely milled alpha-lactose monohydrate with a typical median particle size of x_{50} = 8 µm **(figures 4 and 5)**. InhaLac® 500 is a micronized alpha-lactose monohydrate with a $x_{90} \leq 10$ µm.

Therefore, InhaLac® 500 is well suitable for soft pellet formulations which are known as promising alternative for conventionally applied interactive mixtures for dry powder inhalation.

Further details about the specified particle size and typical values are shown in **figures 3 and 6**. All data was determined by laser light diffraction (Sympatec®/Helos & Rodos).





Figures 4 – 5: *Typical cumulative PSD and distribution density of MEGGLE's milled and micronized inhalation lactose grades, InhaLac® 400 and InhaLac® 500. Analyzed by Sympatec®/Helos & Rodos particle size analyzer.*

Milled/micronized InhaLac® grades			
	Lactose type	InhaLac® 400	InhaLac® 500
		specified/typical	**specified**/typical
Particle size distribution	x_{10}	**0.8 – 1.6 µm/** 1.2 µm	**—/—**
Method: Laser diffraction	x_{50}	**4.0 – 11.0 µm/** 7.7 µm	**NMT 5 µm/** 3.1 µm
	x_{90}	**15.0 – 35.0 µm/**27.90 µm	**NMT 10 µm/** 7.9 µm
	Span $[(x_{90} - x_{10})/x_{50}]$	/ 3.5	/ 2.4
	% fines < 15 µm	/73	/99

Figure 6: *Specified PSD for MEGGLE's milled and micronized inhalation lactose grades by laser diffraction (in bold letters). Typical values are shown solely for reference.*

Batch-to-batch consistency

Batch-to-batch consistency for all lactose products is due to MEGGLE's technical expertise in lactose manufacture. Our stringent release criteria and constant process control ensure our products' consistency and quality.

MEGGLE's sieved dry powder inhaler lactose grades
MEGGLE provides a broad spectrum of sieved inhaler lactose grades. The portfolio includes a variety of products ranging from the coarse InhaLac® 70 to the fine InhaLac® 251. The specification limits of MEGGLE's sieved InhaLac® family are given in **figure 7**.

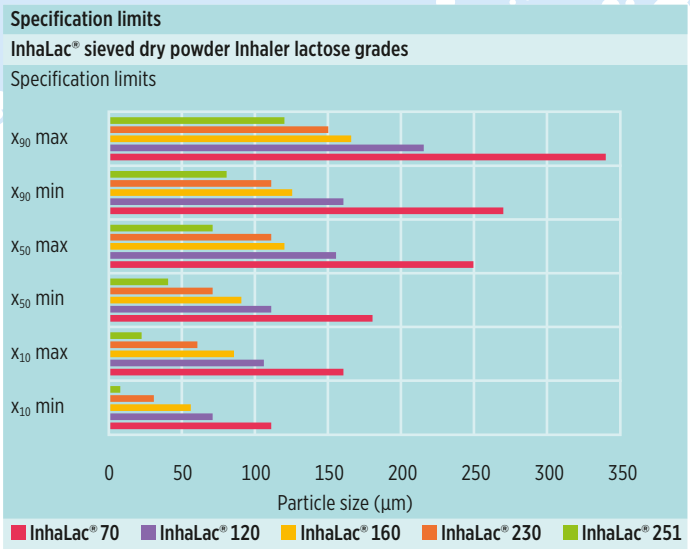


Figure 7: *Specification limits of MEGGLE's sieved dry powder inhaler lactose grades InhaLac® 70, InhaLac® 120, InhaLac® 160, InhaLac® 230 and InhaLac® 251.*

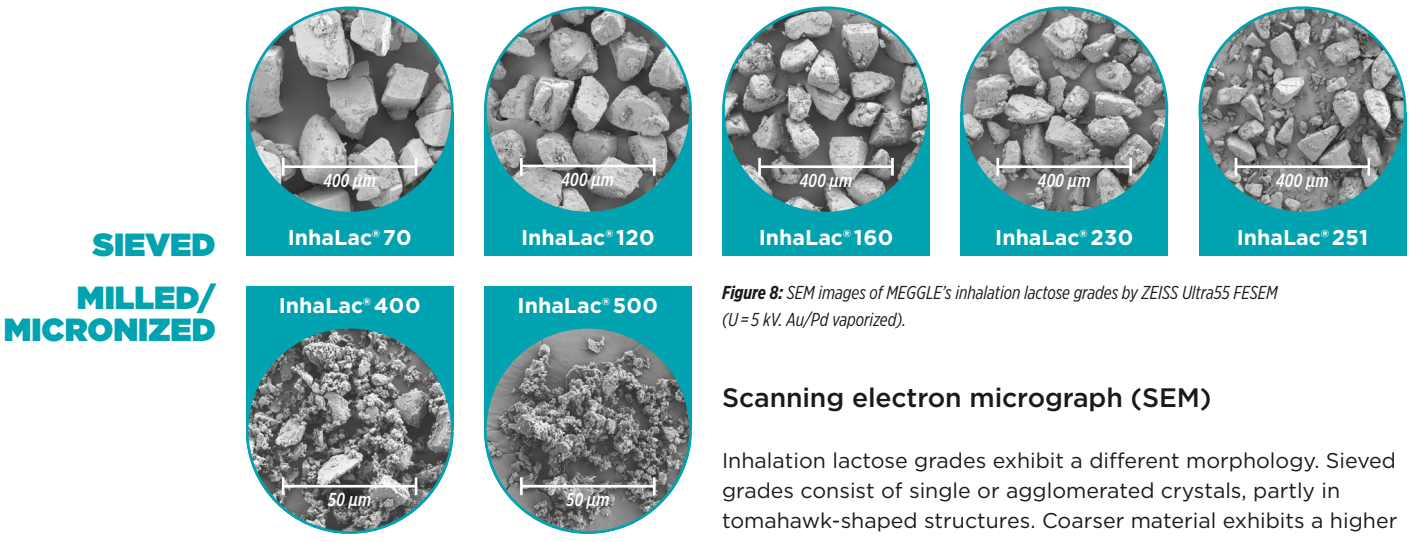


Figure 8: *SEM images of MEGGLE's inhalation lactose grades by ZEISS Ultra55 FESEM (U = 5 kV. Au/Pd vaporized).*

Scanning electron micrograph (SEM)

Inhalation lactose grades exhibit a different morphology. Sieved grades consist of single or agglomerated crystals, partly in tomahawk-shaped structures. Coarser material exhibits a higher share of agglomerate particles. In contrast to the sieved grades, milled and micronized grades consist of lactose particles that are finer, more irregular and sharp-edged due to the manufacturing process **(figure 8)**.

Functional related characteristics

Typical powder technological values

Figure 9 provides additional information on the other functional characteristics of the inhalation lactose grades.

Typical powder technological values					
InhaLac®					
	BET surface (m^2/g)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr's index (%)
Sieved					
InhaLac® 70	0.13[1]	0.60	0.71	1.18	15
InhaLac® 120	0.15[1]	0.72	0.83	1.15	13
InhaLac® 160	0.12[1]	0.70	0.84	1.19	16
InhaLac® 230	0.16[1]	0.70	0.85	1.21	18
InhaLac® 251	0.33[1]	0.64	0.88	1.38	27
Milled					
InhaLac® 400	1.74[2]	0.33	0.53	1.61	38
Micronized					
InhaLac® 500	5.30[2]	0.24	0.37	1.54	35

Figure 9: *Typical technological powder values of MEGGLE's inhalation lactose grades (Quantachrome Autosorb-3, Krypton adsorption[1]/Nitrogen adsorption[2]).*

Microbiology	
InhaLac®	
Parameters	**Specified**
Total aerobic microbial count (TAMC)	NMT 10 cfu/g
Total combined yeasts and molds count (TYMC)	NMT 10 cfu/g
Bile tolerant gramnegative bacteria	absence/10 g
Escherichia coli	absence/10 g
Pseudomonas aeruginosa	absence/10 g
Staphylococcus aureus	absence/10 g
Salmonella spp.	absence/10 g
Burkholderia cepacia	absence/10 g
Bacterial endotoxins	< 5 EU/g

Figure 10: *Specified microbiological parameters of MEGGLE's inhalation lactose grades.*

Packaging and Stability			
InhaLac®			
	Size	Material	Retest
Sieved			
InhaLac® 70	25 kg	Carton box with PE-EVOH-PE double inliner	24 Months
InhaLac® 120			
InhaLac® 160			
InhaLac® 230		Carton box with an aluminium laminated and PE-EVOH-PE inliner	
InhaLac® 251			
Milled			
InhaLac® 400	15 kg	Carton box with an aluminium laminated inliner	24 Months
Micronized			
InhaLac® 500	10 kg	Carton box with an aluminium laminated inliner	18 Months

Figure 11: *Packaging and shelf life of MEGGLE's inhalation lactose grades.*

Microbiology

All of MEGGLE's InhaLac® grades have stricter or additional microbial limits compared to the current monographs of the Pharmacopoeia. This guarantees the highest safety in the use of InhaLac® grades in DPI formulations. All microbiological parameters listed in **figure 10** are part of the product specification. MEGGLE has a validated production process with respect to bacterial endotoxines.

Packaging and Stability

Packaging material complies with Regulation (EC) No.1935/2004 and 21 CFR 174, 175, 176, 177 and 178. Stability tests were performed according to ICH guidelines and an ongoing stability program is in place. **Figure 11** provides information on packaging size, material, and shelf life.

Technical Support

In order to fulfill our customers specific requirements, MEGGLE is open to opportunities for custom-made product solutions. This includes milled and sieved grades as well as customized product specifications. MEGGLE's R&D works in close collaboration with research institutes and universities all over the world. This allows us to continuously increase our capabilities and our product portfolio. Our business is all about collaboration with our customers.

MEGGLE has the necessary know-how for the registering specialty products in the United States.

For more information on our entire InhaLac® portfolio, please contact inhalation@meggle.de

Literature

[1] Bousquet, J., Khaltaev, N. (2007). Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach WHO Library Cataloguing-in-Publication Data: ISBN 978 92 4 156346 8 (NLM classification: WF 140), World Health Organization.

[2] Labris, N.R., Dolovich, M. (2003). Pulmonary drug delivery. Part II: The role of inhalant delivery devices and drug formulations in therapeutic effectiveness in aersolized medications, 56: 600–612.

[3] Pilcer, G., Amighi, K. (2010). Formulation strategy and use of excipients in pulmonary drug delivery. International Journal of Pharmaceutics, 392: 1–19.

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