DRY POWDER INHALER →
SIEVED/MILLED/MICRONIZED LACTOSE

Technical brochure
InhaLac®

MEGGLE
EXCIPIENTS & TECHNOLOGY

MEGGLE sieved, milled and micronized alpha-lactose monohydrate for dry powder inhaler: InhaLac®

General information

The delivery of active pharmaceutical ingredients (APIs) via the lung is becoming more and more important as an increasing number of 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 not needing breath-actuation coordination [2]. In addition, they are propellant-free and therefore, environmentally friendly. Furthermore, as solid-particle formulations they are comparatively stable [3]. Commonly, this dosage form contains a device, one or more APIs and an excipient, which improves powder handling during the manufacturing process. Properties, such as particle size are fundamental factors in the design of DPI formulations.

MEGGLE's alpha-lactose monohydrate grades for inhalation effortlessly fulfill all criteria for achieving the desired quality, safety and innovation of a DPI formulation. Lactose has a long tradition of inhalative application and is regarded as being safe. Thus, lactose is the excipient of choice in pulmonary drug delivery. An established, well-documented production process leads to a very special product family, called InhaLac®. In order to meet formulator's expectations this family has a broad product range. MEGGLE's InhaLac® grades are profoundly characterized from a physico-chemical point of view 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 of the DPI. A profound knowledge about the physico-chemical properties is a prerequisite to ensure the functionality and safety of the DPI. This implies an established and well-investigated production process. MEGGLE's InhaLac® grades are produced via crystallization and subsequent sieving, milling or micronization. Due to an optimized and standardized production process highest and consistent product quality is achieved.

Regulatory & quality information

MEGGLE's InhaLac® alpha-lactose monohydrate grades comply with the current harmonized Ph.Eur., USP-NF and JP monographs. In order to meet the special requirements for pulmonary drug delivery additional and/or stricter specification limits above the current ones of the pharmacopoeias are in place for all InhaLac® grades. 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 GMP according to the Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients and USP General Information Chapter <1078>. All InhaLac® products are manufactured on product lines, exclusively dedicated to inhalative lactose. Additionally, MEGGLE is a member of IPEC (International Pharmaceutical Excipients Council).

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

Application

InhaLac® stands for a lactose, which is, in particular, suitable for use in pulmonary and nasal drug delivery.

BENEFITS

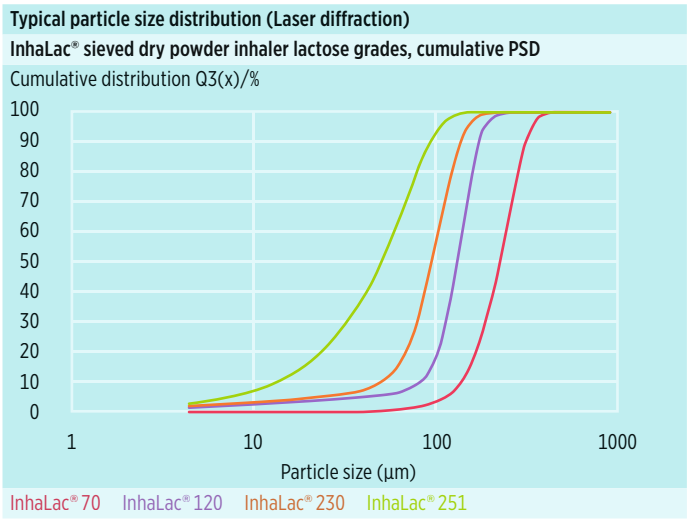
InhaLac®

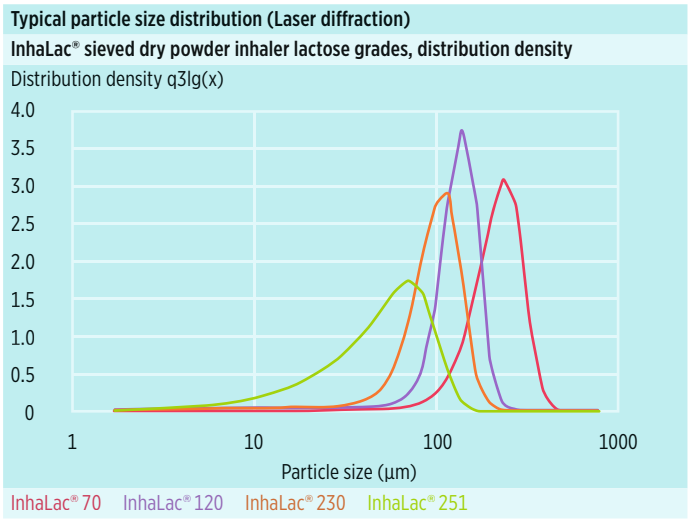
- Highly controlled powder characteristics
- Highest microbial quality including endotoxines
- A broad spectrum of different size ranges
- Tailor-made inhalation grades
- Customized product specifications

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 preferably high and reproducible 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 practically free of fines (particles < 15 µm), shows a narrow particle size distribution (Span: 0.8) and may be best used in cyclone-based inhalation devices. InhaLac® 120 (median particle size: ~ 130 µm) and InhaLac® 230 (median particle size: ~ 100 µm), both sieved products, have a narrowly distributed particle size (Span: < 1.0) and a fines content between 3 – 4 %. InhaLac® 251, the finest,





Figures 1 – 2: *Typical cumulative PSD and distribution density of MEGGLE's sieved dry powder inhaler lactose grades InhaLac® 70, InhaLac® 120, InhaLac® 230 and InhaLac® 251. Analyzed by Sympatec®/Helos & Rodos laser diffraction system.*

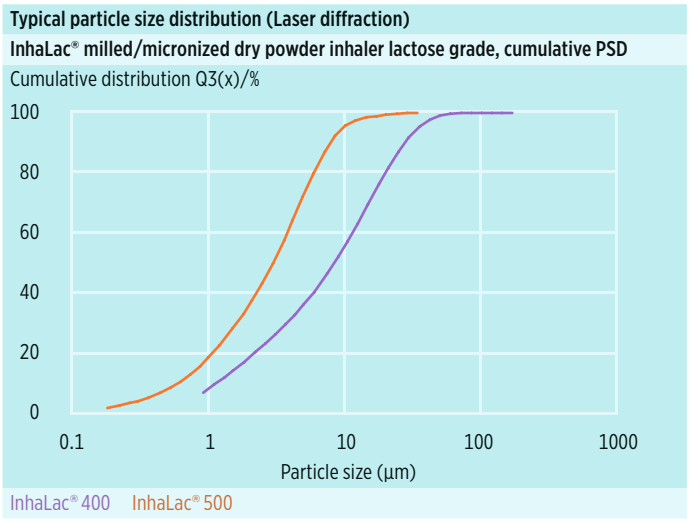
Sieved InhaLac® grades					
	Lactose	InhaLac® 70	InhaLac® 120	InhaLac® 230	InhaLac® 251
		specified/typical	**specified**/typical	**specified**/typical	**specified**/typical
Particle size distribution	x_{10}	**110 – 160 µm**/135 µm	**70 – 105 µm**/ 88 µm	**30 – 60 µm**/ 45 µm	**7 – 22 µm**/ 13 µm
Method: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

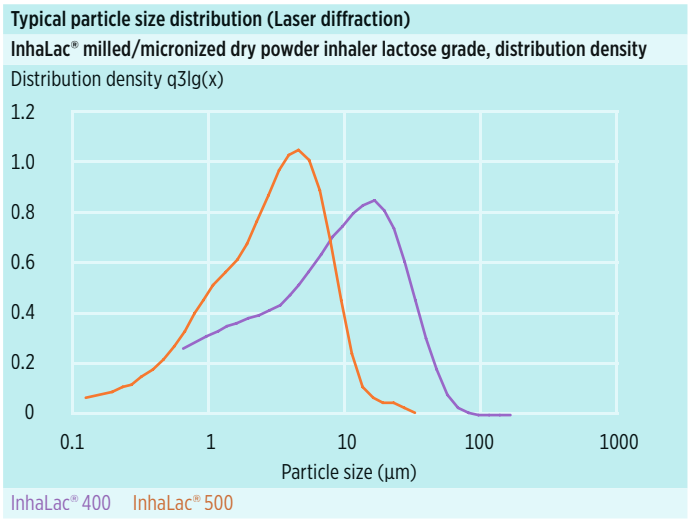
Figure 3: *Specified PSDs for MEGGLE's sieved dry powder inhaler lactose grades by laser diffraction in bold letters. Typical values are shown for orientation.*

sieved lactose quality, has a median particle size of approximately 50 µm. The product is characterized by a higher amount of fines (% fines <15 µm: >10 %) and a broader particle size distribution (Span: 1.6). InhaLac® 120, InhaLac® 230 and InhaLac® 251 are mostly used in capsule- or blister-based formulations **(Figures 1 – 2)**.

InhaLac® 400 is a fine-milled alpha-lactose monohydrate with a median particle size of typically x_{50} = 8 µm **(Figures 4 – 5)**. InhaLac® 500 is the finest grade of the InhaLac® family. The micronized material shows a particle size distribution with 90 % smaller than 10 µm.

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





Figures 4 – 5: *Typical cumulative PSD and distribution density of MEGGLE's milled and micronized dry powder inhaler lactose grade InhaLac® 400 and InhaLac® 500. Analyzed by Sympatec®/Helos & Rodos laser diffraction system.*

Milled/micronized InhaLac® grades			
	Lactose	**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/**27.9 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/micronized dry powder inhaler lactose grade by laser diffraction in bold letters. Typical values 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.

Scanning electron micrograph (SEM)

Sieved, milled and micronized lactose grades for DPIs show different morphology. Sieved qualities contain partly tomahawk-shaped crystals, which can occur as single or agglomerated particles. Coarser material has a higher share of agglomerates. In contrast to sieved qualities, milled and micronized grades consist of fine lactose particles. Their disrupted and sharp-edged appearance derives from a defined milling process **(Figure 7)**.

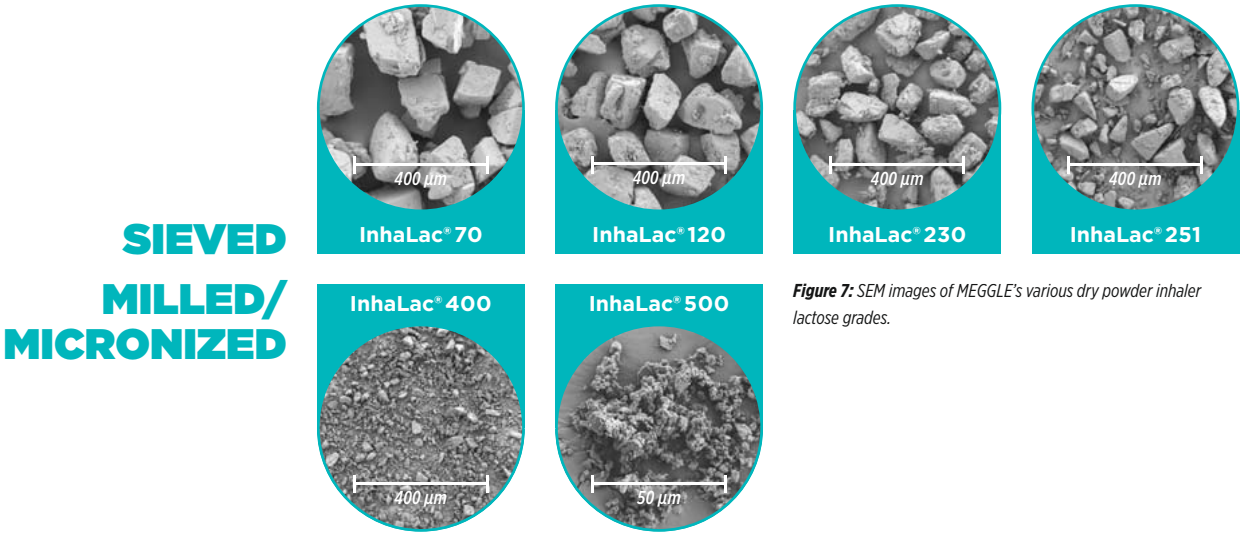


Figure 7: *SEM images of MEGGLE's various dry powder inhaler lactose grades.*

Functional related characteristics

Typical powder technological values
Figure 8 provides additional information on further functional related characteristics of MEGGLE's dry powder inhaler lactose grades.

Typical powder technological values					
InhaLac®					
	BET surface area (m^2/g)	Density bulk (g/ml)	Density tapped (g/ml)	Hausner ratio	Carr's index (%)
Sieved					
InhaLac® 70	0.13	0.60	0.71	1.18	15
InhaLac® 120	0.15	0.72	0.83	1.15	13
InhaLac® 230	0.16	0.70	0.85	1.21	18
InhaLac® 251	0.33	0.64	0.88	1.38	27
Milled					
InhaLac® 400	1.74	0.44	0.64	1.45	31
Micronized					
InhaLac® 500	5.30	0.24	0.37	1.54	35

Figure 8: *Typical powder technological values of MEGGLE's dry powder inhaler lactose grades (Quantachrome Autosorb-3, Krypton adsoption).*

Microbiology	
InhaLac®	
Parameter	**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	negative/10 g
Escherichia coli	negative/10 g
Pseudomonas aeruginosa	negative/10 g
Staphylococcus aureus	negative/10 g
Salmonella spp.	negative/10 g
Burkholderia cepacia	negative/10 g
Bacterial endotoxins	< 5 EU/g

Figure 9: *Specified microbiological parameters of MEGGLE's dry powder inhaler lactose grades.*

Microbiology

All of MEGGLE's InhaLac® grades have stricter or even additional microbial limits compared to the current monographs of the Pharmacopoeia. This provides the highest security for the use of InhaLac® grades in DPI formulations. All the microbiological parameters listed in **Figure 9** are part of the product specification. MEGGLE has a validated production process with respect to bacterial endotoxines.

Packaging and stability			
InhaLac®			
	Size	**Material**	**Retest**
Sieved			
InhaLac® 70 InhaLac® 120 InhaLac® 230 InhaLac® 251	25 kg	Carton box with PE-EVOH-PE double inliner	24 months
Milled			
InhaLac® 400	15 kg	Carton box with an aluminum laminated inliner	24 months
Micronized			
InhaLac® 500	10 kg	Carton box with an aluminum laminated inliner	12 months

Figure 10: *Packaging and retest of MEGGLE's dry powder inhaler lactose grades.*

Packaging and stability

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 10** provides an overview about packaging size and material, and product stability.

Technical Support

In order to fulfill specific requirements of our customers MEGGLE offers the development of tailor-made product solutions. This includes sieved, milled and micronized grades as well as individual 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 knowledge and to improve our product portfolio. A jointly close collaboration with our customers is for us a day-to-day business.

For the registration of tailor-made qualities in the United States, MEGGLE has experience in filing of a DMF Type IV.

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.

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

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