

The custom-made solutions of DFE Pharma Inhalation



MCC

Starch

Lactose

Inhalation

Superdisintegrants

The pursuit of excipient excellence

We are DFE Pharma



We are the global leader in excipient solutions. We develop, produce and market excipients for oral solid dose and dry powder inhalation formulations. Our customers are pharmaceutical companies, operating globally, regionally and locally.

The pursuit of excipient excellence

Excipient excellence is a pursuit that will never be fully achieved. What is excellent today will be outdated tomorrow. That's why to us the pursuit of excipient excellence is a way of life. A source of inspiration. Excipient excellence is what guides us on our way to developing and producing the best possible excipient solutions for our customers. Today, tomorrow, always.

- **Leading in expertise**

We are here to help you create pharmaceutical products that set the new standard.

- **Leading in supply**

We are here to ensure you can always produce your products. No matter what happens.

- **Leading in time to market**

We are here to help you grow by minimising the time to market.

We invite you to join us in our pursuit of excipient excellence.

Pursuit 'the act of striving towards an ideal with strong determination.'

Inhalation

Your Inhalation Grade Lactose by DFE Pharma

A growing number of diseases are being treated with inhaled medicines. Many treatments now use Dry Powder Inhalers, which invariably need a high quality inhalation grade of lactose to power the formulation. Each Dry Powder Inhaler device is different, they often need a specific grade of lactose to ensure correct product performance, particularly for highly regulated markets. Due to regulatory demands, all our inhalation grade lactose is produced in dedicated inhalation production sites.

Quality and Regulatory Support

All production sites for inhalation lactose operate under GMP-standards and meet the high quality standards that are demanded by the FDA and other regulatory bodies. In addition, DFE Pharma fully supports the quality requirements demanded by our customers.

A Drug Master File is available to assist in the registration of a new formulation in the United States. For optimal control on the functionality and to comply with regulatory requirements, additional testing above the current pharmacopoeia is in place.

Technical Support

DFE Pharma Inhalation develops pharmaceutical lactose that facilitates delivery of your active ingredient to the lung. We work closely with pharmaceutical companies to design lactose particles with the required functionality for the drug, device and filling-platform.

Research and Development

Through our own research and close co-operation with research institutes and universities, we are continuously expanding our knowledge of lactose and other excipients that can be used for inhaled delivery. Of particular interest to us is the physiochemical behaviour of lactose under conditions relevant for use as an excipient in advanced pharmaceutical applications. With this knowledge we can advise our customers on the latest scientific developments. DFE Pharma offers the following inhalation grade lactose brands:

- Lactohale®
- Respitose®

Lactose-by-Design

Dry Powder Inhalation Formulations

A dry powder inhaler formulation should contain drug particles with an aerodynamic particle size of less than 5 µm for an optimal pulmonary delivery. Due to the high surface area to mass ratio of the particulates, the powdered drug is highly cohesive. Therefore a larger carrier, such as lactose, is applied to de-agglomerate the drug particles and optimize the deposition of the drug in the lung. In addition, the use of a lactose carrier has the added benefit of making the formulation manageable on an industrial scale by boosting the amount of powder in each dose. Summarizing, both the filling of a device and the deposition of the drug in the lung are strongly influenced by the quality of the carrier.

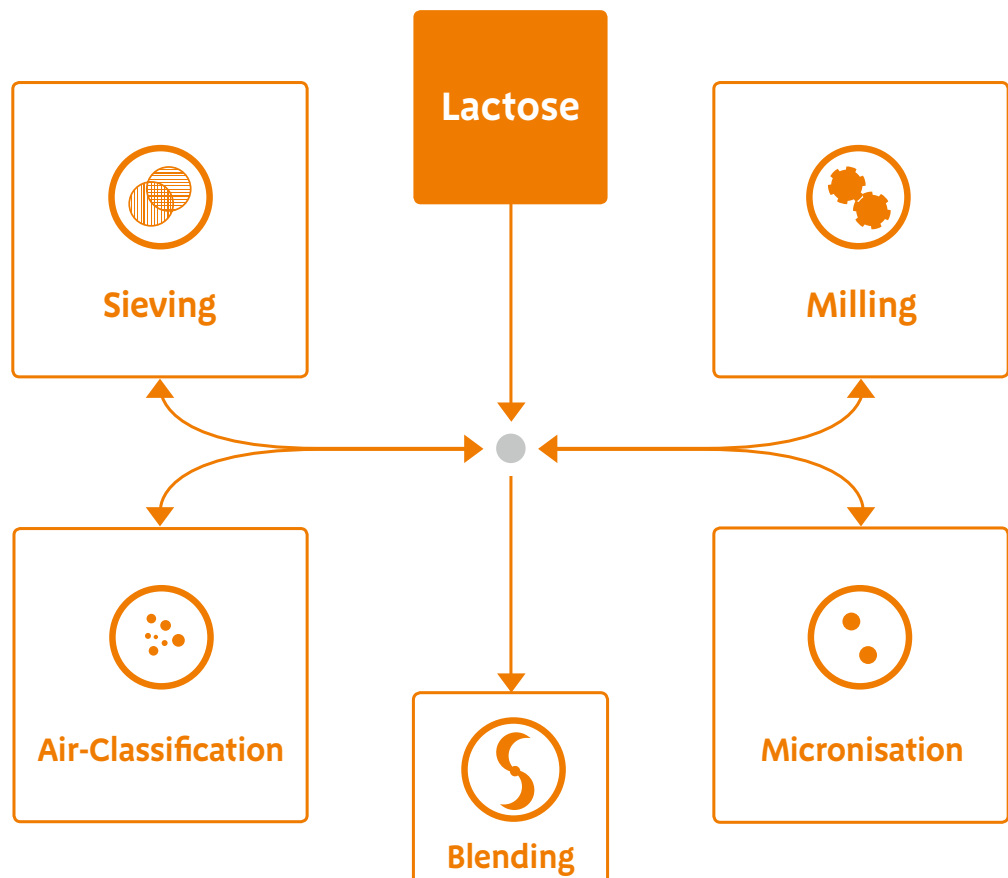
Role of Lactose in inhaled formulations

Lactose is one of the few excipients that have been accepted by all authorities to be used in inhaled formulations. The properties of the inhalation lactose are chosen based on the different parameters, like the device (flow of lactose), filling platform (flow of lactose), type of drug and how it is processed and the required drug release (fine lactose particles). In practice, this means that DFE Pharma can deliver customized inhalation lactose to meet the specific requirements of their customers.

Inhalation lactose is a naturally occurring disaccharide, which is extensively purified to meet the strict requirements for use in an inhaled application. To obtain different functionalities for the inhalation formulation the lactose is further processed by techniques such as sieving, milling, micronisation or air-classification¹.

The technical publications of DFE Pharma show how the different physical properties of inhalation lactose can be controlled by blending a fine fraction with a coarse fraction, i.e. the fines content in inhalation grade lactose. The choice of fines is a critical decision point in the development of a DPI formulation. The detailed knowledge of the experts of DFE Pharma can support customers to predict various physical parameters of the lactose for inhalation out of fine and coarse lactose fraction.

¹ Steckel, H; Markefka, P; teWierik, H; Kammelar, R; 2004, Functionality testing of inhalation grade lactose. Eur. J. Pharm. Biopharm. 57: 495-505



Packaging of Inhalation Lactose

Packaging of the inhalation products offered by DFE Pharma is important to guarantee the quality and stability of the material. In the table below, the standard packaging options for Lactohale® and Respitose® are listed. Additional packaging options might be available on demand.

Storage

It is recommended to store inhalation lactose in the closed original packaging under normal warehouse conditions.

Packaging overview Respitose® and Lactohale®

Packaging attributes	Cardboard Box	HDPE Box	HDPE Drum	Re-test date
Length (cm)	38	38.9	38.9	
Width (cm)	28	32.8	32.8	
Height (cm)	45	71.4	71.4	
Diameter (cm)	n.a.	32.7	n.a.	
Product				
Lactohale® 100	20 kg	-		3 years
Lactohale® 200	20 kg	-		3 years
Lactohale® 210	15 kg	-		3 years
Lactohale® 220	15 kg	-		3 years
Lactohale® 230	10 kg	-		3 years
Lactohale® 300	12.5 kg	-		6 months
Respitose® ML001			50 kg	3 years
Respitose® ML003			40 kg	3 years
Respitose® SV003			50 kg	3 years
Respitose® SV010			50 kg	3 years



Lactohale®

Lactohale® Inhalation lactose is produced in a dedicated inhalation lactose production site in Borculo, the Netherlands. The plant was designed to meet the strict quality requirements that are demanded by the FDA.

Lactohale® is positioned in three categories, each of which reflects the primary manufacturing technique that is used in its production. Lactohale® 100 is produced by sieving, Lactohale® 200, 210, 220 and 230 by milling and Lactohale® 300 by micronising.

Lactohale® can also be customised in order to meet specific particle size profiles. This can include combining the products mentioned above in the final blending stage so that the flow properties can be matched to the correct fines content for product performance. In the final processing step all Lactohale® products are blended in order to ensure that the batch is homogeneous.

Lactohale® 100

Coarse Lactose particles with good flow

Lactohale® 100 is predominantly crystalline lactose with Tomahawk-shaped particles with a smooth surface where the particle size profile has been controlled by sieving as the primary process. It provides good flow properties and the fines content can also be controlled to achieve the correct performance. Typically Lactohale® 100 has a mean particle size above 100 microns.

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	840 g/l
Poured density	690 g/l
Carr's index	19%

Specification

Particle size	(Sympatec)
d10	45 - 65 µm
d50	125 - 145 µm
d90	200 - 250 µm

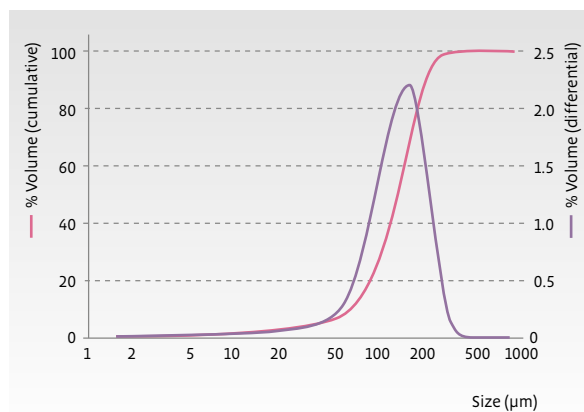


Figure 1: Typical Lactohale® 100 particle size distribution.

Lactohale® 200

Milled Lactose that has a degree of cohesion

Lactohale® 200 is milled lactose which enables the mean particle size to be tightly controlled. Lactohale® 200 is primarily controlled by gentle milling. This means that different D50's can be produced depending on the degree of milling that can match the customer's requirement. The fine content can also be controlled by removing the fines by air classifying and then blending fines back in with the coarse to meet a particular target.

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	950 g/l
Poured density	650 g/l
Carr's index	> 25%

Specification

Particle size	(Sympatec)
d10	5 - 15 µm
d50	50 - 100 µm
d90	120 - 160 µm

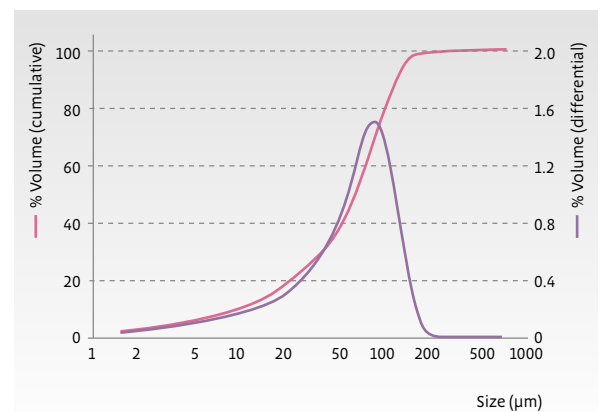
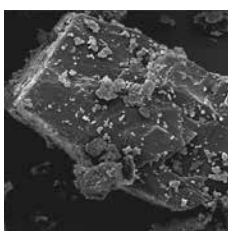


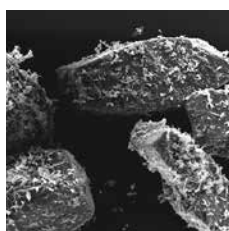
Figure 2: Typical Lactohale® 200 particle size distribution.



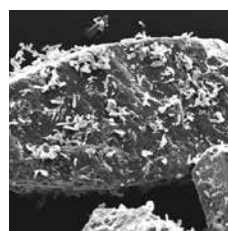
Crystals of alpha monohydrate lactose.



Milled alpha monohydrate lactose.



Example of an adhesive mixture of Lactohale® and salbutamolsulphate.



Lactohale fine grades

DFE Pharma offers different fine grades of Lactohale with a particle size where the d50 is below 20 microns. These grades allow our customers to control the functionality of the DPI formulation by fine tuning of the drug deposition and of the flow properties.

Lactohale® 210

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	680 g/l
Poured density	400 g/l
Carr's index	> 25%

Specification

Particle size	(Sympatec)
d10	2 - 3.5 µm
d50	14 - 19 µm
d90	35 - 50 µm

Lactohale® 220

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	660 g/l
Poured density	370 g/l
Carr's index	> 25%

Specification

Particle size	(Sympatec)
d10	1.5 - 3.0 µm
d50	11 - 15 µm
d90	25 - 40 µm

Lactohale® 230

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	500 g/l
Poured density	310 g/l
Carr's index	> 25%

Specification

Particle size	(Sympatec)
d10	1 - 3 µm
d50	< 10 µm
d90	< 30 µm

Lactohale® 300

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	520 g/l
Poured density	260 g/l
Carr's index	> 25%

Specification

Particle size	(Sympatec)
d10	
d50	< 5 µm
d90	≤ 10 µm

Respitose®

Respitose® Inhalation lactose is produced under GMP-conditions at a dedicated inhalation lactose production site in Veghel, the Netherlands. The plant was designed to meet the strict quality requirements that are demanded by the FDA.

Respitose® products are characterized by the excellent control of the particle size of the lactose. Respitose is produced by using a sieving process from a range of starting materials. The ML range is produced from milled lactose and the SV range is produced from crystalline lactose. The application of various sieving steps allows DFE pharma to offer an extended range of sieved inhalation lactose. On request of customers, the different grades can be blended to achieve an optimal performance.

Respitose® ML001

Respitose® ML001 is a milled inhalation grade lactose, containing irregular shaped particles with various amount of fine particles.

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	880 g/l
Poured density	570 g/l
Carr's index	> 25%

Particle Size Distribution Specification

Particle size	(Sympatec)
d10	3 - 7 µm
d50	37 - 61 µm
d90	124 - 194 µm

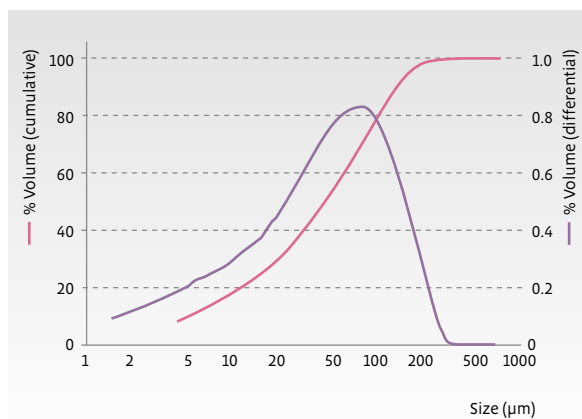


Figure 3: Typical Respitose® ML001 particle size distribution.

Respitose® ML003

Respitose® ML003 is a fine milled inhalation grade lactose with irregular shaped particles.

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	850 g/l
Poured density	560 g/l
Carr's index	> 25%

Particle Size Distribution Specification

Particle size	(Sympatec)
d10	1 - 6 µm
d50	20 - 50 µm
d90	65 - 140 µm

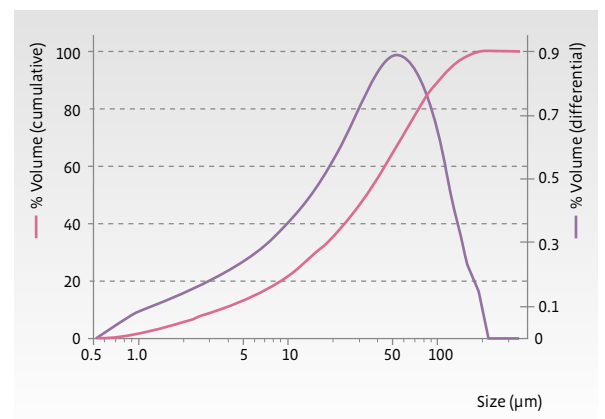
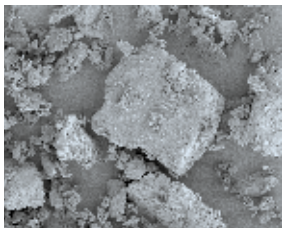
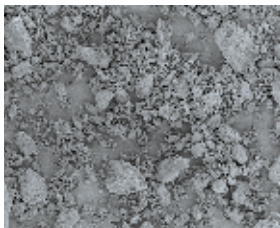


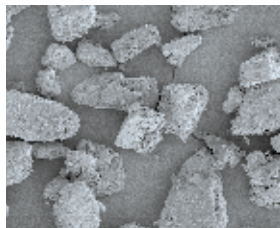
Figure 4: Typical Respitose® ML003 particle size distribution.



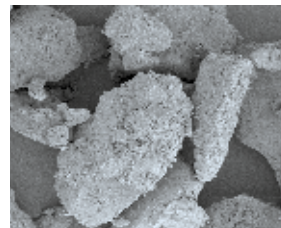
SEM of Respirose® ML001



SEM of Respirose® ML003



SEM of Respirose® SV003



SEM of Respirose® SV010

Respirose® SV003

Respirose® SV003 is a fine sieved inhalation grade lactose containing tomahawk shaped particles.

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	780 g/l
Poured density	630 g/l
Carr's index	19%

Particle Size Distribution Specification

Particle size	(Sympatec)
d10	19 - 43 µm
d50	53 - 66 µm
d90	75 -106 µm

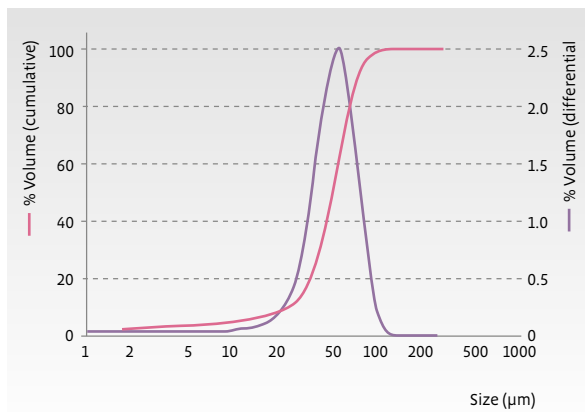


Figure 5: Typical Respirose® SV003 particle size distribution.

Respirose® SV010

Respirose® SV010 is a coarse sieved inhalation grade lactose.

Typical product characteristics

Parameter	Typical
Tapped density (1250 taps)	830 g/l
Poured density	690 g/l
Carr's index	17%

Particle Size Distribution Specification

Particle size	(Sympatec)
d10	35 - 65 µm
d50	95 - 125 µm
d90	160 -190 µm

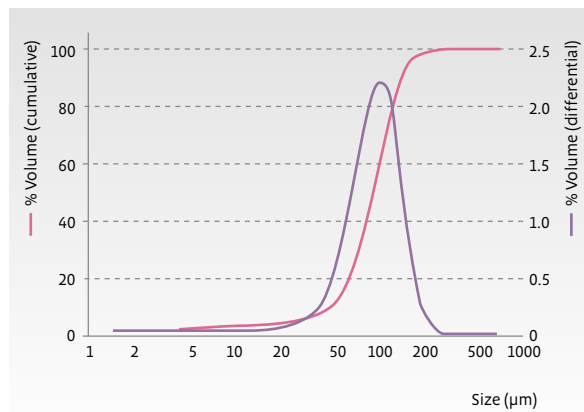


Figure 6: Typical Respirose® SV010 particle size distribution.



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DMV-Fonterra Excipients GmbH & Co. KG - Warranty

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