DFE pharma

YOUR **INHALATION GRADE LACTOSE**

As a leader in the field of Inhalation, DFE pharma offers pharmaceutical industry the most optimal solution for the development of their Dry Powder Inhalation drug. DFE Pharma is a partner for pharmaceutical companies developing drugs for pulmonary delivery since many years, with a wide range of standard inhalation lactose grades and the option to customize to meet your needs. Our expertise and three dedicated inhalation production sites provide an unique starting point for any advanced pharmaceutical application.

We are DFE Pharma

We are DFE Pharma: the global leader in excipient solutions.

We develop, produce and supply excipients for use in oral solid dose and inhalation formulations, but as a supplier of complete solutions we do a lot more than that.

We work closely with pharmaceutical companies around the world, collaborating in original research, supporting their go to market strategies and fine-tuning our products to ensure that their medicines deliver exactly the right outcomes for patients. That makes us more than just a supplier. We are recognised as a true partner to the pharmaceutical industry in helping people around the world live healthier lives.

We have spent more than 100 years in proving that excellence is not just a word but a deep, long-term commitment to our customers and to the millions of patients who use our products every day.

Our customers respect us for product quality, technical expertise and hands-on market support. We work with your future in mind: today, tomorrow and always.

Our portfolio consists of filler/binders (Lactose, Microcrystalline Cellulose, Starches) and super-disintegrants (Croscarmellose Sodium and Sodium Starch Glycolate) for oral solid dose, as well as carriers for inhalation (Lactose).

DFE Pharma, in pursuit of excipient excellence.

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. Since 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.

DFE Pharma can support you for registration of your Dry Powder Inhalation product in China: for more information, please contact our regulatory specialist. To support our customers, an extensive list of regulatory and quality documents for Lactohale® is available at our website www.dfepharma.com.

Technical Support

DFE Pharma Inhalation team develops pharmaceutical lactose that facilitates delivery of your active 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 pharma-ceutical 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®

Production capabilities

Within DFE Pharma, three production sites are fully committed to the production of inhalation grade lactose, each with their unique capabilities: Veghel (Netherlands) for production of Respitose® products, and Borculo (the Netherlands) and Kapuni (New Zealand) for production of Lactohale®. DFE Pharma is the only excipient supplier with three production sites on two different continents for inhalation-grade lactose, offering customers the possibility of security of supply. All three production sites have been set up to produce a consistent and high-quality inhalation grade lactose, to meet the quality needs of our customers.

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 request.

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 NL	Cardboard Box NZ	HDPE Box	HDPE Drum	Re-test date
Length (cm)	38	36	38.9	38.9	-
Width (cm)	28	32	32.8	32.8	-
Height (cm)	45	42	71.4	71.4	
Product					
- Lactohale® 100	20 kg	-	-	-	3 years
- Lactohale® 200	20 kg	-	-	-	3 years
- Lactohale® 206	20 kg	-	-	-	3 years
- Lactohale® ML001	-	20 kg	-	-	3 years
- Lactohale® 800	-	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® SV001	-	-	-	50 kg	3 years
- Respitose® SV003	-	-	-	50 kg	3 years
- Respitose® SV010	-	-	-	50 kg	3 years

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.

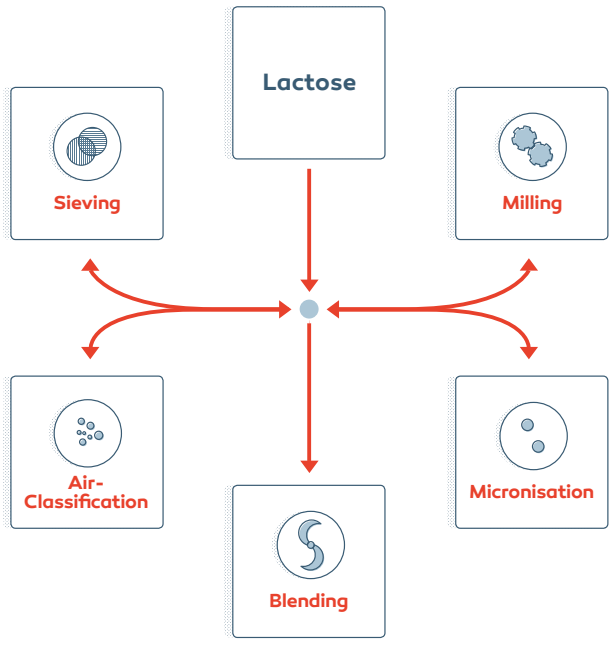
Inhalation lactose is a naturally occurring disaccharide, which is extensively purified to meet the strict requirements for use in an inhaled application. To obtain different functionalities for the inhalation formulation the lactose is further processed by techniques such as sieving, milling, micronisation or air-classification.[1]

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.[2] 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.

More technical information can be found on our website www.dfepharma.com

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

[2] *Kinnunen, H.; Hebbink, H.; Peters, H.; Huck, D.; Makein, L.; Price, P.; Extrinsic lactose fines improve dry powder inhaler formulation performance of a cohesive batch of budesonide via agglomerate formation and consequential co-deposition; 2015 Int J Pharmaceutics 478, 53-59*



Lactohale®

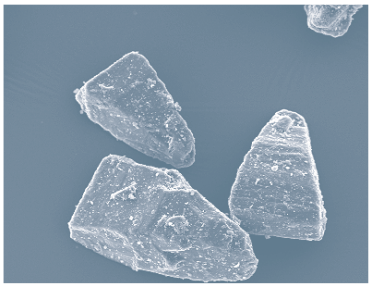
Lactohale® is our high-quality inhalation grade lactose that can be optimized and customized to meet the specific need of customer. Strict and highly consistent particle size control during the production, combined with state of the art particle size measuring techniques form the basis for the success of Lactohale®.

While most customer start their development with the standard Lactohale® grades, many convert to customization to fine-tune the performance of their formulation. In close collaboration, the flow properties can be matched to the correct fines content for an optimal product performance.

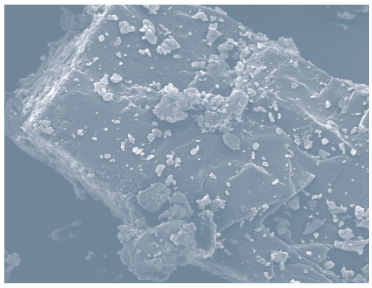
In the final processing step all Lactohale® products are blended in order to ensure that the batch is homogeneous. The resulting customized Lactohale® grade with their specific particle size profiles is unique for each customer.

Lactohale® Inhalation lactose is produced in a dedicated inhalation lactose production sites in Borculo (the Netherlands) and in Kapuni (New Zealand). Both plants were designed to meet the strict quality requirements that are demanded by the FDA and supply to commercialized end-product in regulated markets. We look forward to collaborate closely with pharmaceutical companies to develop, produce and deliver lactose with the required functionality.

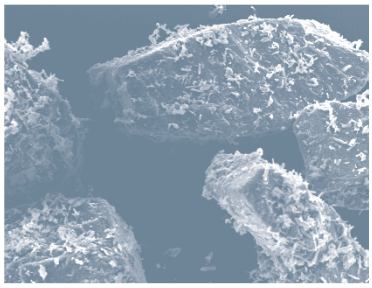
Please, contact your sales representative for more information.



Crystals of alpha monohydrate lactose



Milled alpha monohydrate lactose.



Example of an adhesive mixture of Lactohale® and salbutamolsulphate.

Lactohale® products overview

Product Name	Type of lactose	Production Location	Particle Size Distribution (Sympatec)			Typical values		
			D10 (µm)	D50 (µm)	D90 (µm)	Tapped Density (g/l)	Poured Density (g/l)	Carr's Index
Lactohale® **300**	Fine	Borculo (NL)		< 5	≤10	520	260	>25%
Lactohale® **230**	Fine	Borculo (NL)	1.0 – 3.0	<10	<30	500	310	>25%
Lactohale® **220**	Fine	Borculo (NL)	1.5-3.0	11-15	25-40	660	370	>25%
Lactohale® **210**	Fine	Borculo (NL)	2.0 – 3.5	14 - 19	35 - 50	680	400	>25%
Lactohale® **ML001**	Coarse	Kapuni (NZ)	3-7	37-61	124-194	880	570	>25%
Lactohale® **206**	Coarse	Borculo (NL)	20-50	75-95	115-170	870	720	17%
Lactohale® **200**	Coarse	Borculo (NL)	5-15	50-100	120-160	940	650	>25%
Lactohale® **800**	Coarse	Kapuni (NZ)	5-15	50-100	120-160	940	650	>25%
Lactohale® **100**	Coarse	Borculo (NL)	45-65	125-145	200-250	840	690	19%

NL | The Netherlands NZ | New Zealand

Respitose®

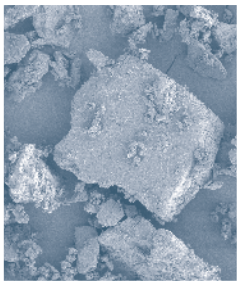
Respitose® Inhalation lactose is a highly consistent product with excellent control of particle size. The offering can be divided in either sieved crystalline lactose grades with tomahawk-shaped articles (Respitose® SV) or milled lactose grades with irregular shaped particles (Respitose® ML).

Respitose® product range include unique lactose grades with good flow and strict control of particle size. Global customers especially favor the standard Respitose® SV003 product because of its unique particle size profile.

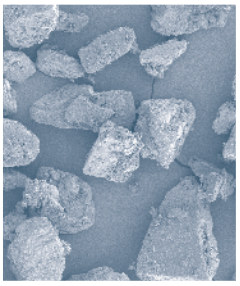
Respitose® Inhalation lactose is produced under GMP conditions at a dedicated inhalation lactose production site in Veghel, the Netherlands. The plant was designed to meet the strict quality requirements that are demanded by the FDA.

Combination of different Respitose® standard grades provide customers a tool to achieve optimal performance for their Dry Powder Inhalation formulation.

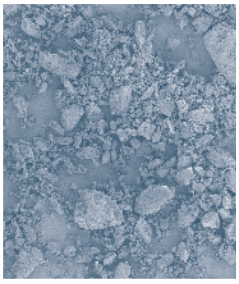
Please, contact your sales representative for more information.



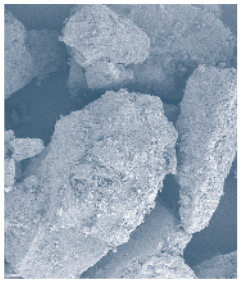
Respitose® **ML001**



Respitose® **SV003**



Respitose® **ML003**



Respitose® **SV010**

Respitose® standard products overview

Product Name	Type of lactose	Production Location	Particle Size Distribution (Sympatec)			Typical values		
			D10 (µm)	D50 (µm)	D90 (µm)	Tapped Density (g/l)	Poured Density (g/l)	Carr's Index
Respitose® **ML003**	Milled	Veghel (NL)	1-6	20-50	65-140	850	560	>25%
Respitose® **ML001**	Milled	Veghel (NL)	3-7	37-61	124-194	880	570	>25%
Respitose® **SV003**	Sieved	Veghel (NL)	19-43	53-66	75-106	780	630	19%
Respitose® **SV010**	Sieved	Veghel (NL)	35-65	95-125	160-190	830	690	17%
Respitose® **SV001**	Sieved	Veghel (NL)	120-160	210-250	290-350	810	700	14%

NL | The Netherlands

DFE Pharma sales offices

Head Office

Klever Strasse 187
P.O. Box 20 21 20
47568 Goch
Germany
T. +49 2823 9288 770
F. +49 2823 9288 7799
pharma@dfepharma.com

India

Plot No. 148
Prestige Featherlite Tech Park
2nd Phase, EPIP Zone
Whitefield, Bangalore 560066
India
T. +91 80 4925 6100
F. +91 80 4925 6150

Singapore

3 Temasek Avenue
#11-01 Centennial Tower
Singapore 039190
T. +65 6580 8100
F. +65 6580 8191

Japan

Taiyo Seimei Bldg. 14F
2-16-2, Konan, Minato-ku, Tokyo
108-0075 Japan
T. +81 3 6260 0740
F. +81 3 6260 0754

North America

61 South Paramus Road
Suite 535
Paramus, NJ 07652
USA
T. +1 551 497 7355
F. +1 551 497 7358

China

Room 302
No. 68 Bohang Road
Pudong Shanghai
China
T. +86 21 6134 5821
F. +86 21 6134 5800

Brazil

Rua Fradique Coutinho, 30 - sala 61
05416-000 São Paulo SP Brazil
T. +55 11 2395 1700

dfepharma.com

In pursuit of excipient excellence

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