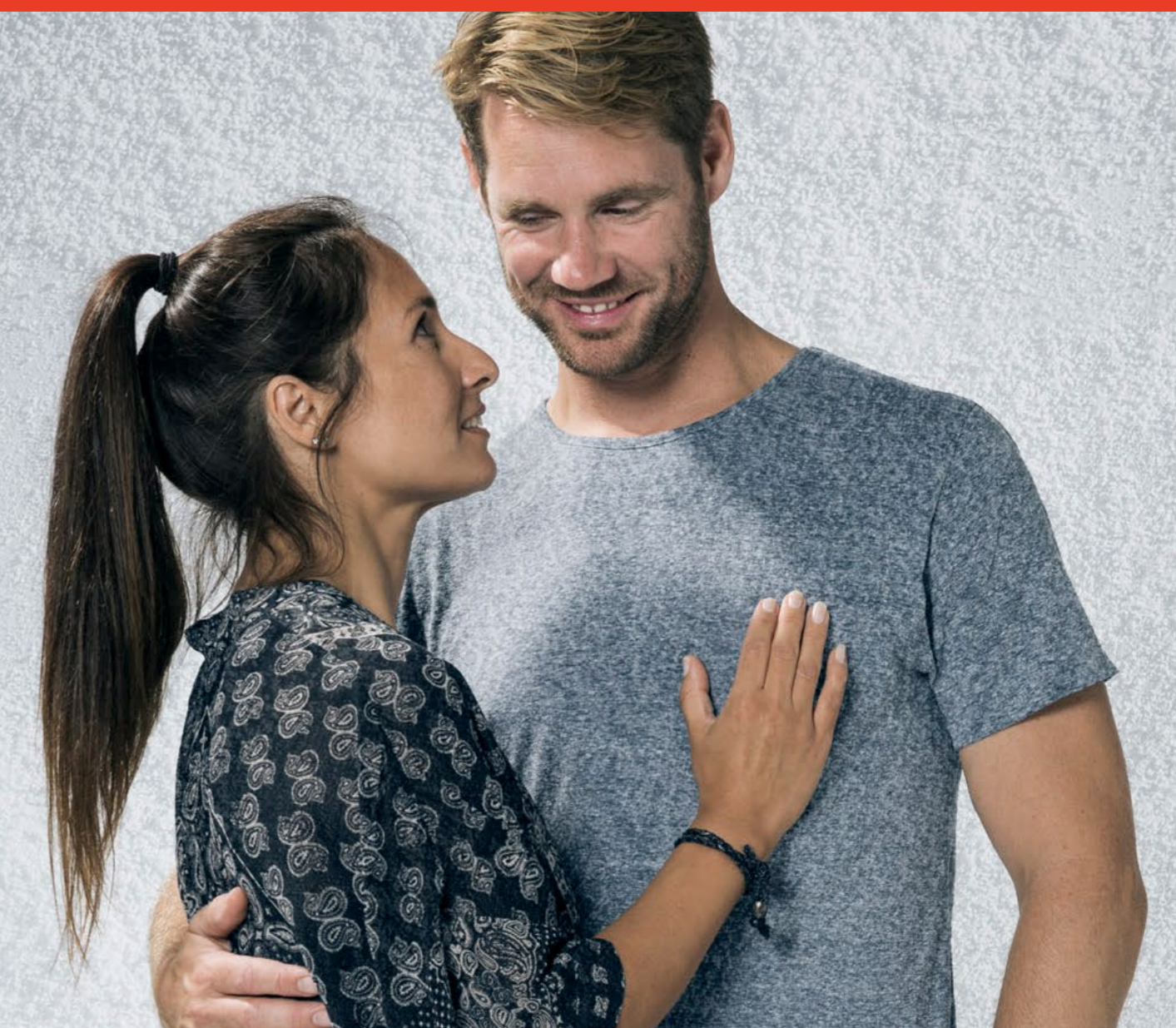


YOUR INHALATION GRADE LACTOSE



Different Types of Lactose Fines Have an Impact on Different Dry Powder Inhalers Properties

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Introduction

The excipient of choice for dry powder inhalers (DPI) is lactose monohydrate. It plays an important role in the whole formulation process from bulking the dose chamber in the devices to facilitate dose delivery by the respiratory action of a patient [1, 2]. A number of scientific papers and opinions have been devoted to the specific role of lactose fines and discussion is still ongoing [3-7]. Commercially, a number of lactose excipients are available with varying amount of fines. In a Quality by Design environment, control of critical attributes of DPI formulations is essential [8]. In this investigation we will demonstrate that, as different sized lactose fines affect different properties, the definition of what we consider 'fines' is of utmost importance.

Materials and methods

Pre-blends of coarse lactose with 2.5, 5, 10, and 20 wt-% of fine type of lactose were prepared in 100 g quantities by sandwiching the fines between three layers of LH100 in an earthed 500 mL stainless steel vessel and blended using a Turbula T2F mixer (Glen Creston Ltd, Middlesex, UK).



Handihaler

The formulations were in-vitro tested for aerosol performance using a Next Generation Impactor (NGI) equipped with a pre-separator (Copley Scientific, Nottingham, UK). Hydroxypropyl methylcellulose capsules, filled with 12.5 mg of the desired formulation, were aerosolized using a Handihaler® (Boehringer Ingelheim, Germany) dry powder device. Flow rates were adjusted to 52 L/min for Handihaler with 4 kPa pressure drop. Fine Particle Fractions (FPFs) of particles less than 5 µm were determined in triplicate.

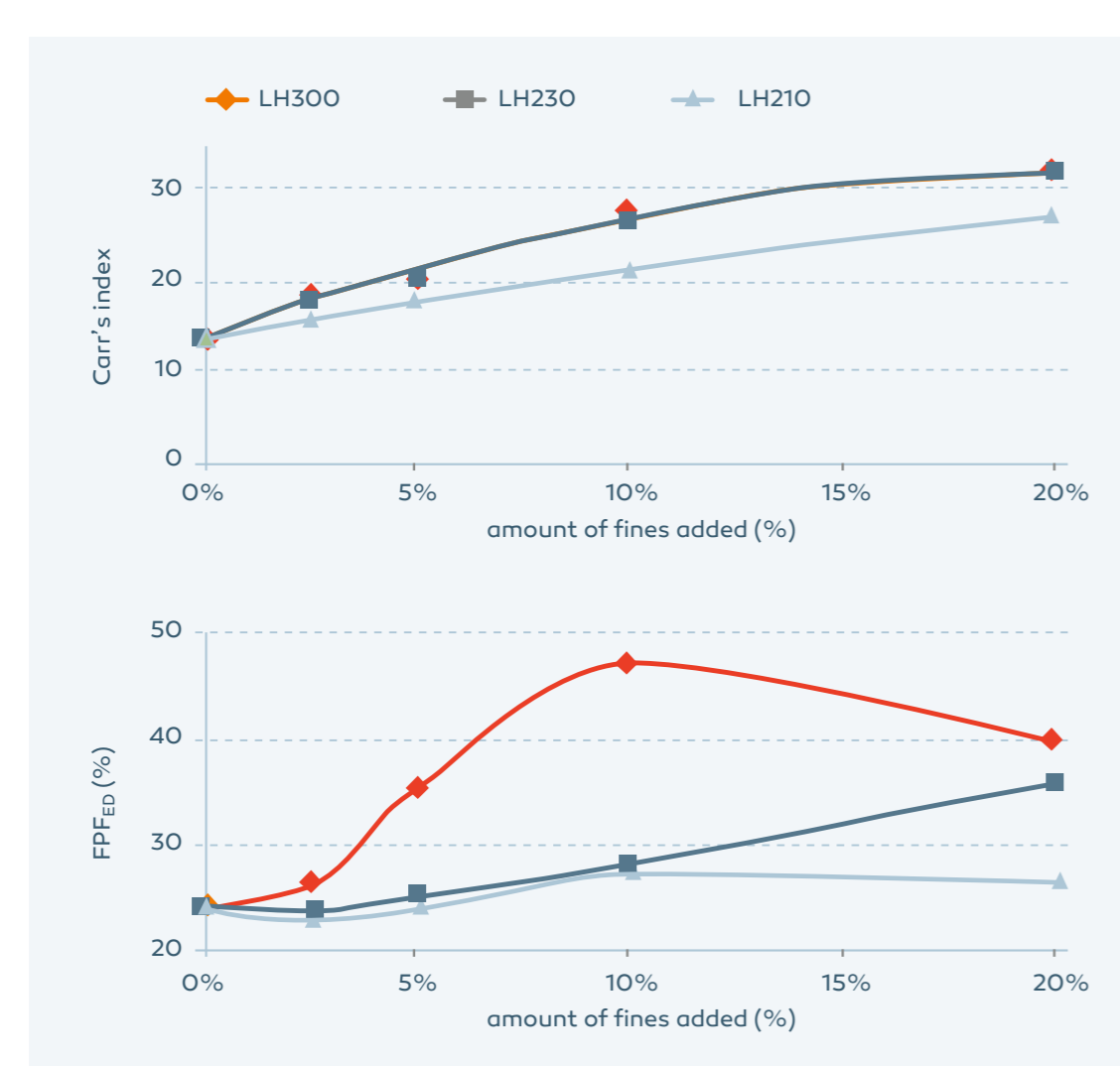


Figure 1: Above Carr's index of lactose formulations. Below FPF_{ED} of emitted dose as function of amount of fines added (n=3, ± StDev).

Results and discussion

The data shows that adding more fines resulted in an increased Carr index, indicating a decreased powder flow. The effect is more pronounced for blends with LH300 and LH230, compared to LH210. Addition of more fines resulted in a significant increase in FPF.

Conclusions

The type of fines, i.e. fine (<30 µm) or very fine (<4.5 µm) is of utmost importance in designing a DPI formulation. In this investigation it has been demonstrated that flow of powders is dominated by lactose fine particles smaller than 30 µm, and that drug deposition is dominated by lactose very fine particles smaller than <4.5 µm. By using combinations of different types of fine grade lactose with coarse grade lactose, a formulation can be fine-tuned on all relevant properties.

	%<4.5 µm	%<30 µm
LH100	1.0±0.2%	5.1±0.3%
LH210	18.1±0.4%	80.2±0.4%
LH230	30.2±0.5%	96.8±0.5%
LH300	61.5±0.5%	100±0.0%

Table 1: Fractions of fines measured in the commercial lactose grades used (n=3±st.dev). By choosing the right combinations, the specific amount and type of fines can be achieved.

Size fraction	Carr	FPF _{ED} (%)
%<4.5 µm	0.68	0.83
%<30 µm	0.95	0.51

Table 2: Pearson Correlation coefficients (R²) for linear correlation of Carrs index and FPF_{ED} versus amount and type of fines.

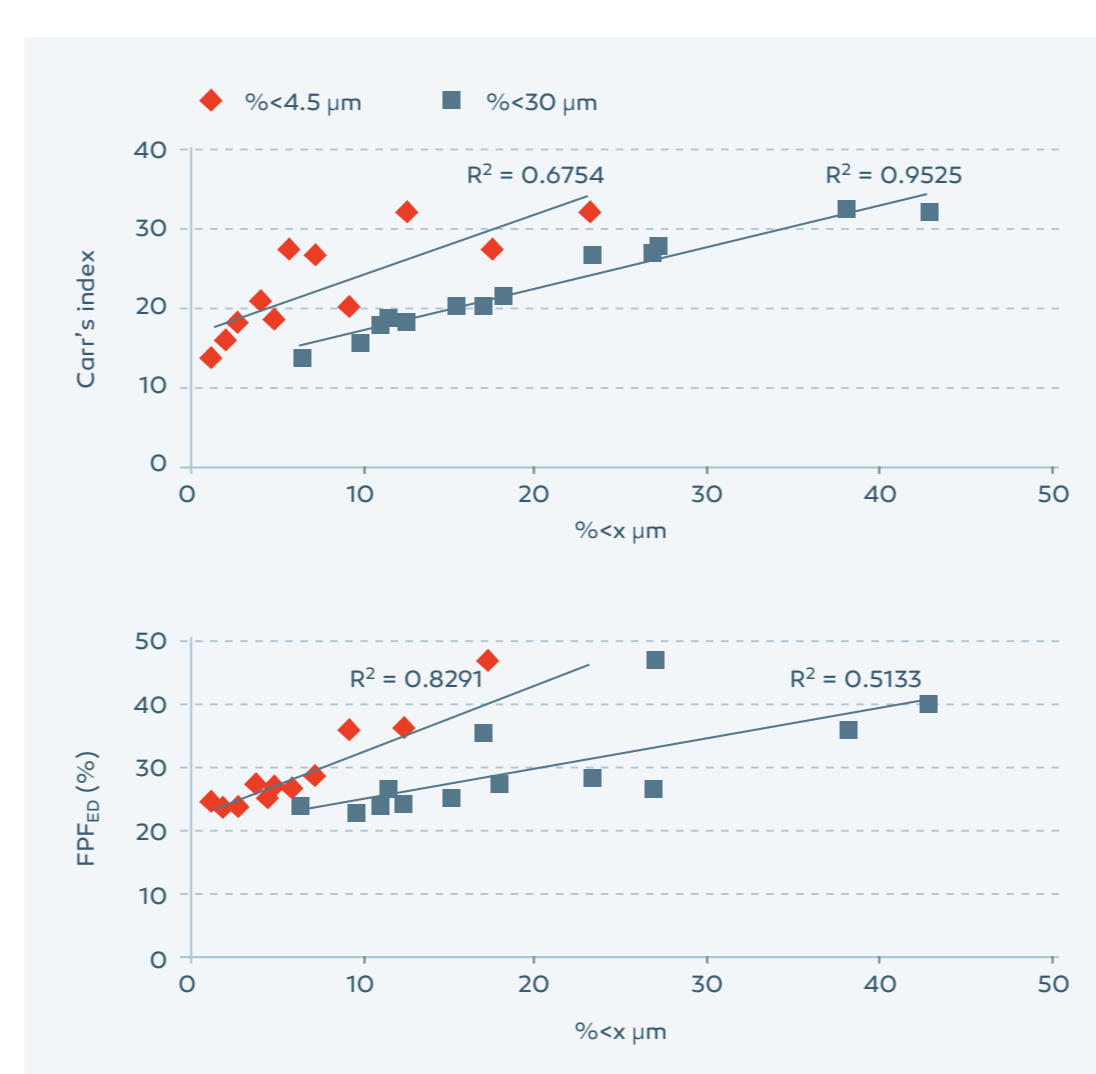
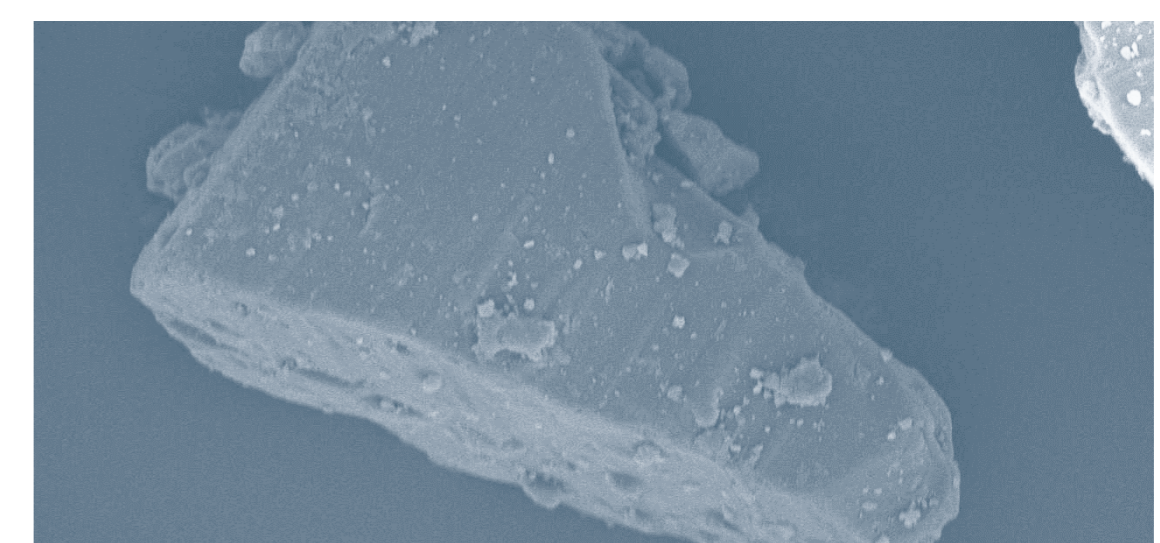
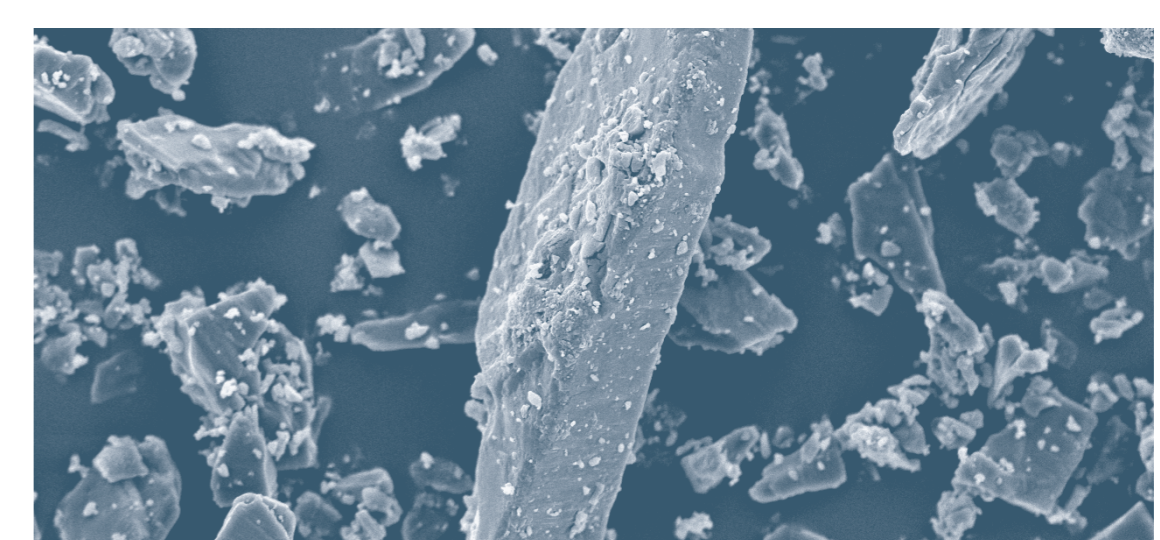


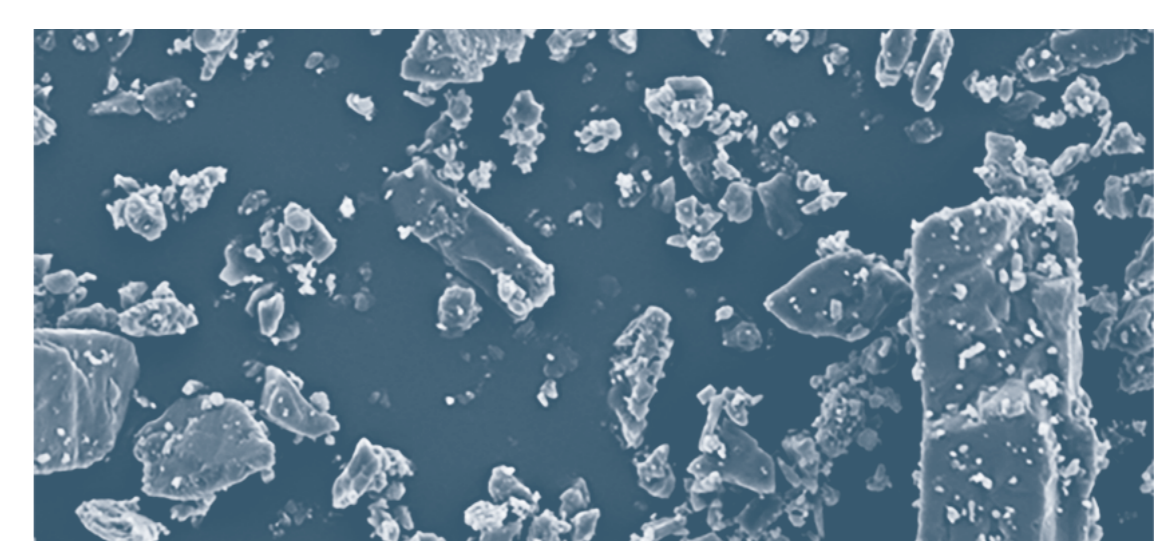
Figure 2: Above Carr's index as function of fraction amount of fines. Below FPF_{ED} of emitted dose as function of fraction of fines from particle size distribution.



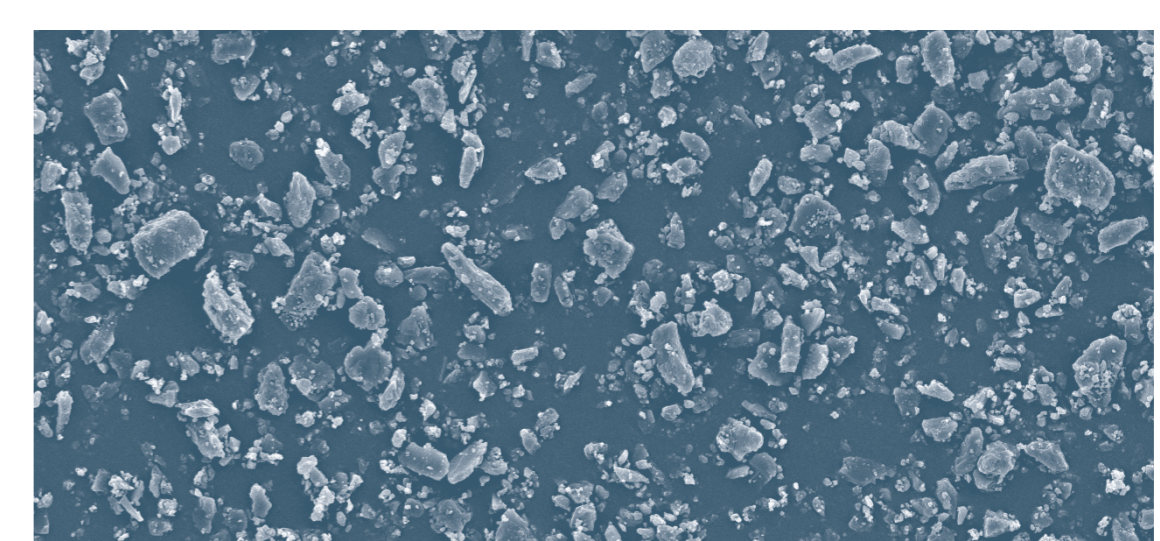
LH100



LH210



LH230



LH300

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