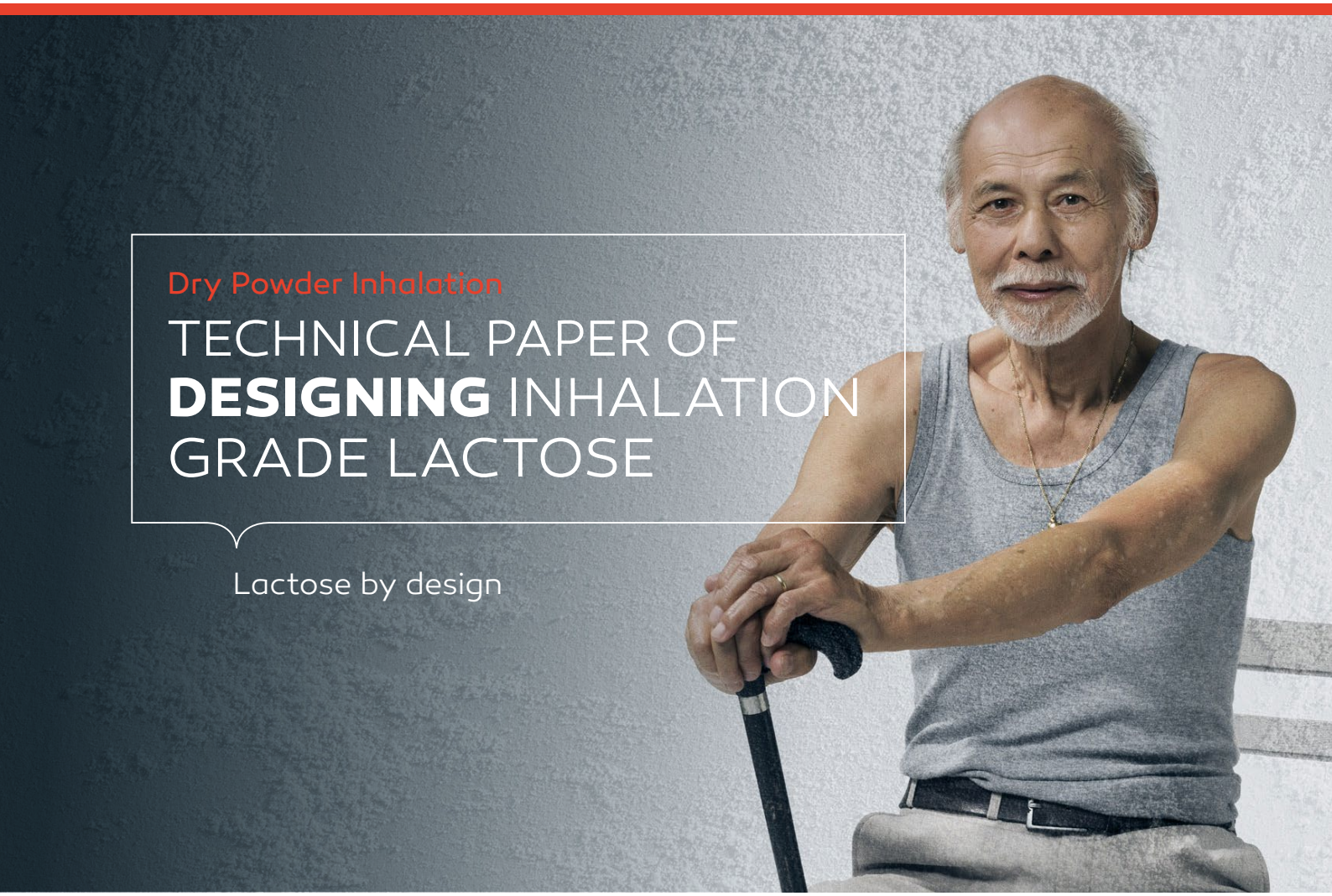
DFE pharma



Dry Powder Inhalation

TECHNICAL PAPER OF **DESIGNING** INHALATION GRADE LACTOSE

Lactose by design

1 Introduction

Lactose is used in DPI devices as carrier. The role of the carrier is to facilitate filling of DPI device with drug and to facilitate the aerosilisation of the drug during inhalation. Lactose is a disaccharide and it major source is mammalian milk in varying amounts from <0.1% to 10% dependent on species. For example, human milk contains about 7% lactose; cow's milk contains 4.5-5% lactose, dependent on breed.[1] For the pharmaceutical industry lactose is isolated from cow's milk and purified to meet strict requirements for use in inhalation.

Several types of devices exist such as reservoir devices, capsule devices and blister devices.[2] Each type of device has particular demands on the powder. In reservoir devices, the dosing from the reservoir in the firing compartment is a key event. In capsule or blister devices, the filling of the capsule or blister is of great importance. All these differences demand for different properties of the powder. The properties of the powder are determined by the constituents and their interaction. In a typical device the powder constitutes of a relative large amount of excipient with a small amount of drug, typically in the order of 1-2% of the loading. These particles are very small because to deposit in the deep lungs the aerodynamic diameter of the particles should be below 5 µm. The larger excipient particles are responsible for flow properties of the powder into the device. Due to the low amount of drug, powder bulk properties such as powder flow are expected to rely largely on the excipient properties.[3]

The second major event is the inhalation process. Here powder properties play again a major role, but the drug should also be detached from the carrier. In this event the interactions between excipient and drug are of great importance as well. On the one hand, the interaction between drug and powder should be strong. The very fine drug particles should be well mixed within the powder. And the very fine drug particles are very cohesive and agglomerates of drug particles should be prevented. On the other hand, the interaction should be weak enough to be broken during the inhalation event. During this event, the powder is aerosolized and by impactions and shear forces the carrier particles are separated from the drug particles.

As has been pointed out already, several types of devices exist with different demands on the powder properties. Although some general demands on powder properties, and therefore the choice of type of lactose, can be pointed out beforehand, each individual device and individual drug will have specific properties and interactions with lactose and therefore, for each device and drug a careful selection of the carrier should be made.

Considering Geldart's classification of powders,[4] lactose powders with median particle sizes varying from 5-500 micron fall in group A or group C or around the boundary of these two classes. Therefore, combining fine lactose (group C) with coarse lactose (group A) makes it able to fine-tune powder properties of the powder blend (see Figure 1 on the next poge).

Deposition of particles in the lung is the parameter that is of interest for describing the functionality drug delivery to the lungs. However, in vivo testing is not very easy and in vitro testing is considered as an alternative. Pharmacopeias describe the use of cascade impactors in order to measure the fraction of particles that enter the lung. These cascade impactors measure the aerodynamic diameter and particles with an aerodynamic particle diameter below 5 µm are considered to be deposited within the lung. The particles that deposit in cascade impactors such as the Anderson Cascade Impactor or the Next Generation Impactor (NGI) is called the fine particle dose (FPD), or if expressed as fraction from the total amount of particles the fine particle fraction (FPF).

Several parameters of the lactose do have a significant effect on the fine particle fraction such as particle size, moisture content and amorphous content. An important parameter is the amount of fine particles within the lactose. Several studies have identified this phenomenon, but despite several attempts to understand the role of these fines, there is still no conclusive theory.[5] Anyway, it is clear that lactose fines play an important role in delivering APIs to the lungs.

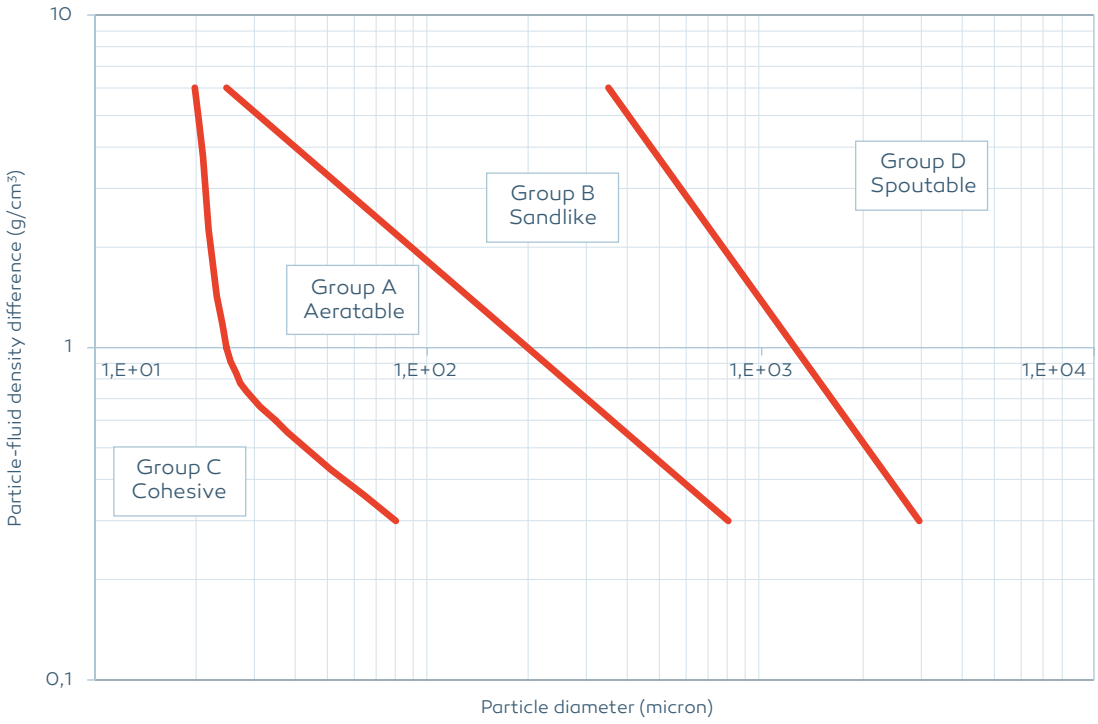


Figure 1
Geldart's classification of powders

Here we will give an example how the particle size distribution can be designed in such a way that important parameters such as median particle size of the powder and the amount of fines can be tuned. The median particle size can be expressed in several ways. Here we will use the volume based median particle size determined by laser diffraction, expressed as d_{50}.

2 Methods

Lactose monohydrate crystals (Lactohale®, DFEpharma) was milled and split into a coarse and a fine fraction by air classification.[6] Blends were made on laboratory scale with varying amounts of fines and coarse ingredients (0-100%). These blends were analyzed on powder properties. The production process is depicted in Figure 2.

Particle size was measured by laser diffraction (Sympatec or Malvern), specific surface area (SSA) was determined by nitrogen adsorption and BET analysis (Micromeritics). Tapped density and bulk density were measured on an Erweka tapped density.

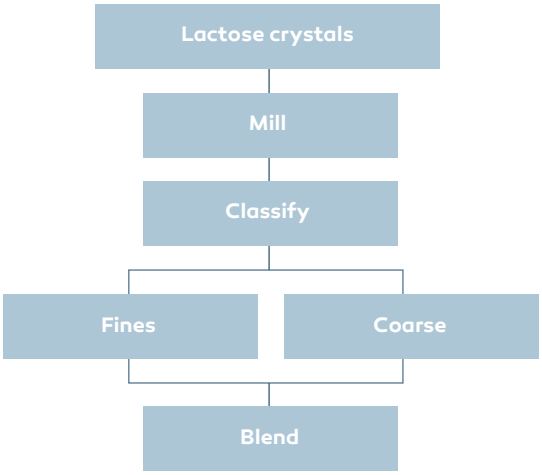


Figure 2
Production scheme of inhalation grade lactose

3 Results and Discussion

The influence of the amount of coarse fraction in the blend on d_{50}, % below 15 micron, density and specific surface area are graphically presented in Figures 3 and 4.

Up to 40% of coarse fraction the d_{50} increases only slightly, at higher coarse fractions the d_{50} increases linearly with the increase in coarse fraction, until about 80%. The amount of lactose particles below 15 µm is not linear correlated over the whole blend range. It is expected that fine lactose particles are not fully deagglomerated during the particle size measurement.

Up to 50% of coarse fractions there is a linear relation with the bulk and tapped density. Above 70% no change in tapped density is measured anymore. The bulk density still increases above 70% coarse material as a consequence of the reduction of the amount of the fines and the improved flowability.

The specific surface area decreases with the increase in the coarse fraction with an almost linear relationship. The fines in the blend still contributes to the specific surface area but are not measured by the particle size measurement.

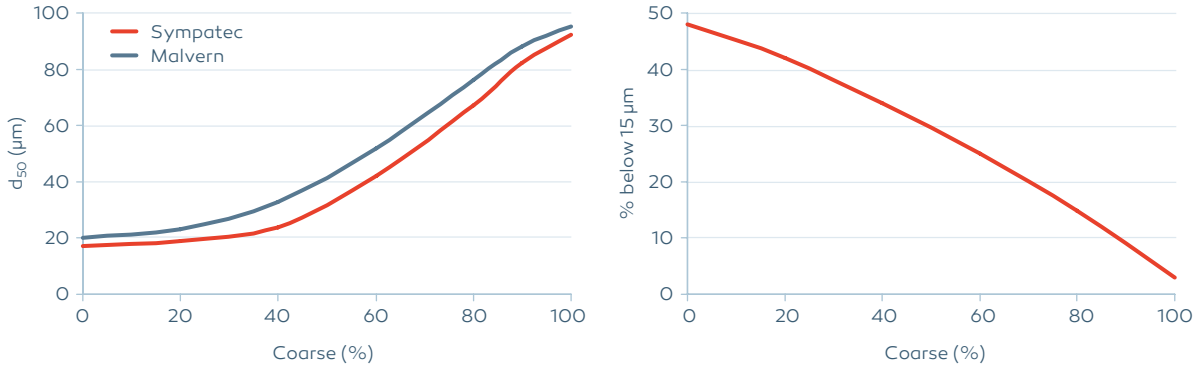


Figure 3
Left: d_{50} as function of coarse content. Right: percentage of particles below 15 µm as function of coarse content

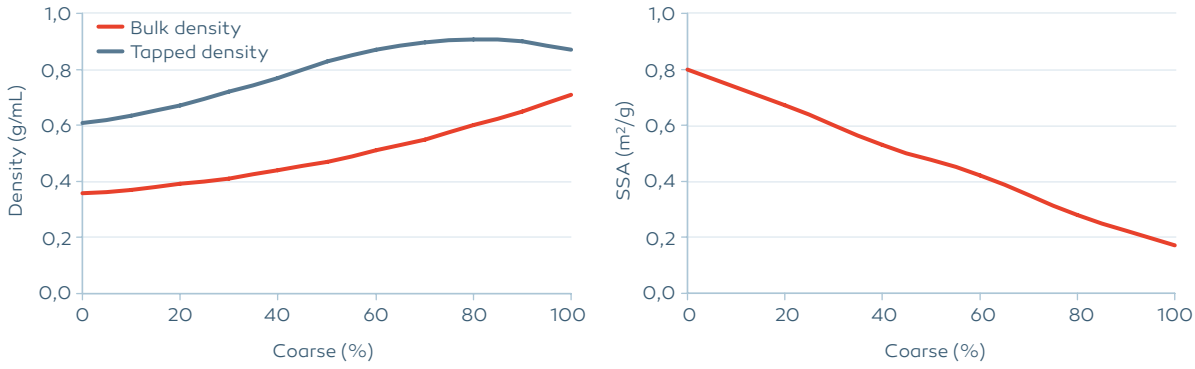


Figure 4
Left: bulk and tapped density as function of coarse content. Right: specific surface area (SSA) as function of coarse content.

4 Conclusions

Blending a fine fraction with a coarse fraction of lactose can control the different physical properties i.e. the fines content in inhalation grade lactose. Detailed knowledge is obtained to predict various physical parameters of the lactose for inhalation out of fine and coarse lactose fractions. The example above is just one of a number of ways that the fines can be adjusted to give a specific result. The choice of fines can be a critical decision point in the development of a DPI.

References

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