DFE pharma

Dry Powder Inhalation

TECHNICAL PAPER OF **INFLUENCE ON PERFORMANCE**

The influence of lactose particle size

1 Introduction

In most dry powder inhalation (DPI) formulations carriers are used. Lactose is the most common used carrier[1]. A DPI formulation could contain lactose for more than 99%. It is used as a flow aid and it facilitates the dose of the active into the lungs. The properties of lactose play an important role in the formulation of a dry powder inhaler and have extensively been investigated and described in the literature[2-5]. The selection of lactose is based on the type of device, the filling process of the device and the final release of the active. The formulator for a DPI has various challenges. He should be able to get a homogeneous mixture where the drug particles adhere to the lactose. The adhesion should not be too strong as the drug will not be able to release from the lactose particle during inhalation. Furthermore, a low dose of powder should be filled into the device and the drug should always be released in the same way. One of the important parameters for the formulation is the particle size of the lactose. The role of the particle size of lactose in dry powder inhalers is discussed.

2 The role of particle size of lactose

The particle size of lactose is one of the parameters for inhalation lactose that has been studied and reviewed extensively[6,7]. The particle size of lactose influences parameters like flow, specific surface area, bulk and tapped density and emitted dose. In general a decrease in particle size will decrease the flow and increase the specific surface area. Flow, bulk and tapped density are important for filling the formulation into the device. The requirement to fill low dose of powder into a device (10-20 mg) makes it important to have these parameters under control.

A reduction in mean particle size increases the aerosolisation of various drugs[6,7]. A reduction in particle size increases the fluidization energy and this could explain the increase of the amount of drug particles that will get into the lung[8].

The addition of fine lactose particles has extensively been studied and has been reviewed by Jones[6]. Fine lactose particles have been reported to be of influence for the fine particle mass of drug. In Figure 1 (see next page) the effect of addition of micro fine lactose and milled lactose to sieved lactose on the fine particle fraction is given. It can be seen that the addition of micronized or milled fines increase the fine particle fraction of Albuterol[9].

Different theories and effects have been described and investigated to explain the role of the fine lactose particles. One theory explains the increase in fine particle fraction to co-agglomeration of the fine lactose particles with the drug particles on the carrier surface. Another theory describes that the fine lactose particles occupies the carrier surface areas of high adhesion. The drug particles will then adhere to the lower adhesion sites and will be easier released during inhalation. With the addition of fines also the surface area increases significantly and the payload will be reduced. When the fine lactose particles are slightly coarser then the drug particles it could eliminate the friction forces between drug and carrier in the mixing process. Fines are often characterized as particles below 5 µm, 10 µm or 15 µm.

Kinnunen showed that the presence of micronized lactose has an influence on the residue of powder that stays into the mouthpiece. This is depicted in figure 2 (see next page). As a higher amount of powder stays into the mouthpiece the final dose into the lung is lower.

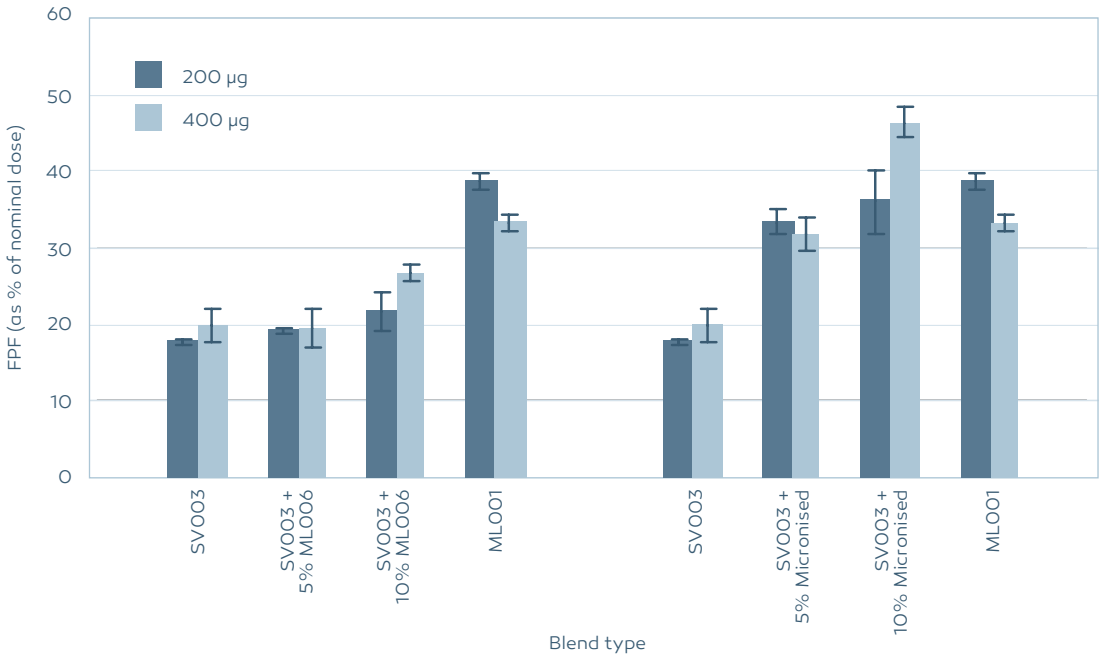

Figure 1
Effect of addition of fine lactose on the fine particle fraction (FPF) of Albuterol[9]

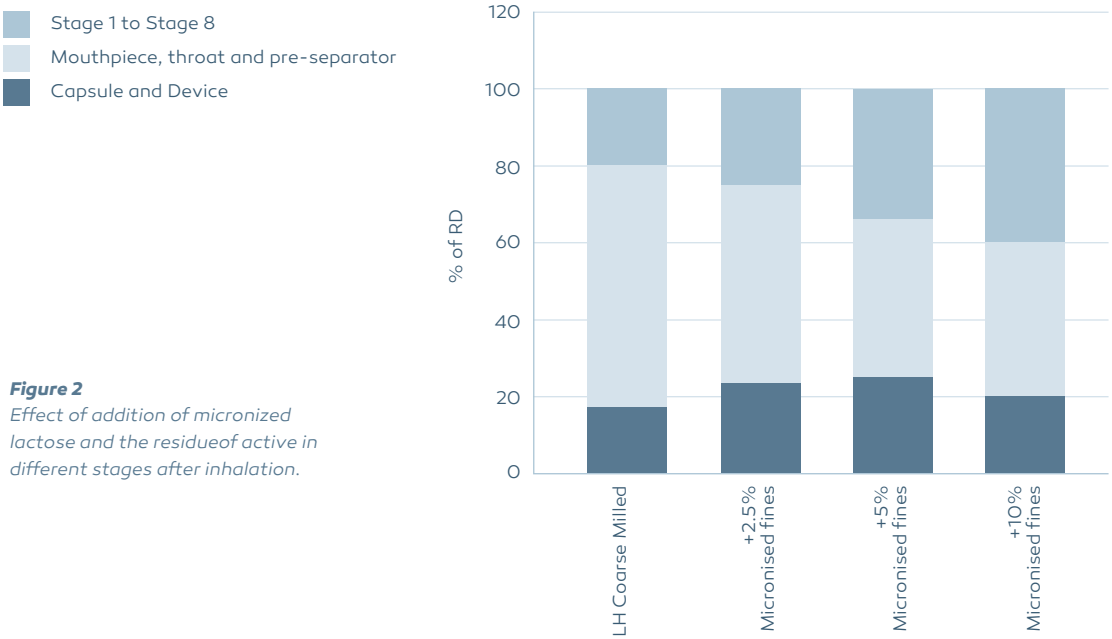

Figure 2
Effect of addition of micronized lactose and the residueof active in different stages after inhalation.

3 Conclusions

The particle size of lactose is very important in the behavior of a dry powder inhalation formulation. Lactose should be carefully selected, designed and controlled for the use in a dry powder inhalation formulation.

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