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Effect of Loaded Dose on Delivered Dose in Dry Powder Inhalers

Inhalation

Lactose plays an important role in dry powder inhalers where it functions as a carrier to aid filling of the powder in the device and fluidization of the powder out of the device[1]. In general, lactose is present in large excess when compared to the active drug (where drug loads below 1-2% of the formulation mass are common)[2]. Subsequently, the powder properties and performance of a formulation can be significantly determined by properties of the lactose carrier [3]. Performance of an inhalation device is determined by the amount of active pharmaceutical ingredient (API) that is delivered to the lung.

Different types of interactions will result in particles that are stronger attached to the carrier, also referred to 'active sites'. At a low dosing, most API particles will be attached to such a site with a non-linear behavior of de-tachment during fluidization as a result. At higher dosing the active sites get saturated and the detachment during fluidization will be dominated by the particles at 'normal' lactose surface. Increasing the dosage even more will result in a linear behavior of fine particle dose versus loaded dose.[5,6]

$$FPD = f*LD - f*N_{as}*m*N$$

with

FPD	the fine particle dose[4],
LD	the loaded API dose and with,
f	the probability of detachment of a API particle from the lactose surface,
m	the (average) mass of a drug particle,
N_{as}	the average number of drug particles that do not detach from the lactose surface,
N	the total number of carrier particles in a blend.

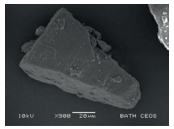
Materials and methods

Table 1: Particle size distribution of Lactohale100, Respitose SV010 and Fluticasone proprionate (FP).

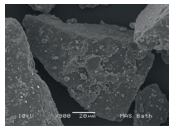
	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
LH100	38	100	157
Respitose SV010	51	111	177
FP	0.9	2.1	4.1

Formulations were prepared by blending 40 g of lactose with 0.02-2% (wt/wt) of FP in a Turbula blender. Content uniformity was checked by sampling 10 random aliquots of 25 mg and quantifying the drug content in each aliquot.

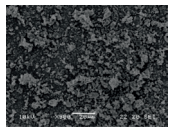
In vitro testing was performed by hand filling size 3 HPMC capsules (Qualicaps, Spain) with 25 mg of the formulations. The capsules were loaded in a Cyclohaler and fired into a Next Generation Impactor (Copley Scientific, Nottingham, UK) equipped with a pre-separator at a flow rate of 90 L/min for 2.7 seconds. (figure 1)



LH100



SV010



Fluticasone Propionate (FP)

Figure 1: *SEM pictures of LH100, SV010, and micronized FP.*

Results and Discussion

Figure 2 shows the *in vitro* results. Fitting the linear regimes for both ranges of formulations with the assumption that $m*N$ is calculated from true density and average particle size for FP (ρ_{FP} = 1.32 g/cm³; d_{lac} = 2.1µm) and lactose (ρ_{lac}=1.55 g/cm³; d_{lac} = 100µm (LH100) or 111µm (SV010)) and from the total weight of the formulation (M = 25 mg) by[6]

$$m*N = M*\rho_{FP}/\rho_{lac}*(d_{FP}/d_{lac})^3$$

Table 2: Fitted results for the linear regime, for comparison results from Young *et al*[5] (salbutamol sulphate with lactose) were fitted and represented. SV010 had a higher fine particle dose, more API particles stay attached to the lactose carrier. This is reflected in the higher value for f (delivered fraction) but also a higher value for N_{as}, although the errors in the results for N_{as} are such that differences are hardly significant. Comparison to the previous results of loaded dose study with salbutamol sulphate[5], it can be observed that the number of attached particles is comparable to SV010, but the delivered fraction (f) is substantially higher. This has to do with the different type of API and therefore different interactions with lactose.

	f	N_{as}
LH100	0.10±0.01	47±17
SV010	0.14±0.01	67±17
Young *et al*[5]	0.19	58±6.5

Conclusions

In conclusion, modeling of the linear regime was carried out for two different lactose carriers with similar particle sizes. The smoother LH100 did result in a lower number of attached particles to the carrier than for the rougher SV010 as was expected. The reason for the lower detached fraction f has probably to do with fluidization dynamics but is still under investigation and for FP doesn't fit the active site theory.

References

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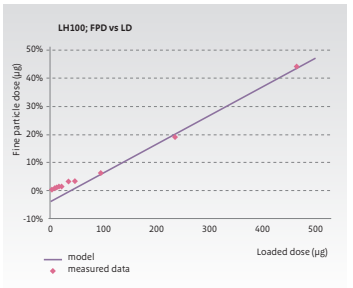

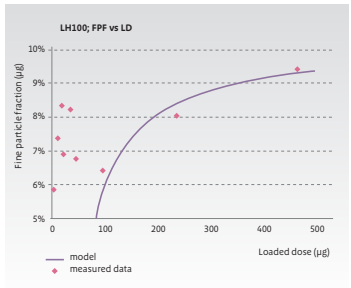

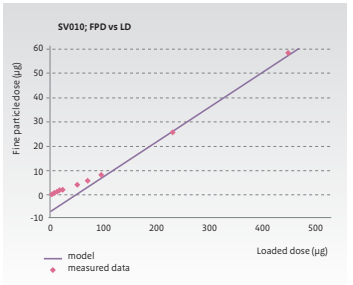

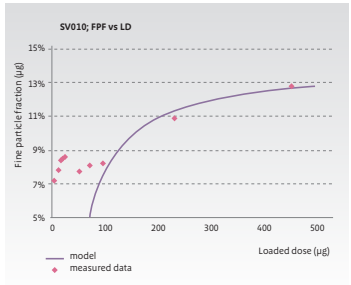

Figure 2: *In vitro results for the loaded dose studies FPD (left) and FPF (right) for LH100 (top) and SV010 (bottom) loaded with 0.02-2% FP with fit for the higher loading regime (solid line) which illustrates linearity at the higher dose. Non-linearity to loaded dose at lower values is emphasized by plotting FPF versus loaded dose (LD) (i.e. FPF=FPD/LD).*