Effect of Loaded Dose on Delivered Dose in Dry Powder Inhalers

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. 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). Subsequently, the powder properties and performance of a formulation can be significantly determined by properties of the lactose carrier. 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 as ‘active sites’. At a low dosing, most API particles will be attached to such a site with a non-linear behavior of detachment 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.

Materials and methods

Table 2: Particle size distribution of Lactohale100, Respiron SVD30 and Fluticose propionate (FP).

<table>
<thead>
<tr>
<th>Drug</th>
<th>d50 (µm)</th>
<th>d90 (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactohale100</td>
<td>100</td>
<td>157</td>
</tr>
<tr>
<td>Respiron SVD30</td>
<td>112</td>
<td>157</td>
</tr>
<tr>
<td>Fluticose propionate</td>
<td>112</td>
<td>157</td>
</tr>
</tbody>
</table>

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 80 L/min for 2.3 seconds (Figure 1).

Results and Discussion

Figure 2 shows the in vitro results. Fitting the linear regimes for both ranges of formulations with the assumption that mN is calculated from true density and average particle size for FP (d50 = 11.2 µm, d90 = 15.2 µm) and lactose (d50 = 6.8 µm, d90 = 10.3 µm) and from the total weight of the formulation (M = 25 mg) by

\[ mN = \frac{m_{FP}}{\rho_{FP} (d_{FP}/d_{lac})^3} \]

Table 2: Fitted results for the linear regime, for comparison results from Young et al. (salbutamol sulphate with lactose) were fitted and represented. SVD30 did not have a higher fine particle dose, more API particles stay attached to the lactose carrier. This is reflected in the higher value for fp (delivered fraction) but also a higher value for Ndet, although the errors in the results for Ndet are such that differences are hardly significant. Comparison to the previous results of loaded dose study with salbutamol sulphate, it can be observed that the number of attached particles is comparable to SVD30, but the delivered fraction (fp) is substantially higher. This has to do with the different type of API and therefore different interactions with lactose.

Conclusions

In conclusion, modeling of the linear regime was carried out for two different lactose carrier with similar particle sizes. The smoother SVD30 did result in a lower number of attached particles to the carrier than for the rougher SVD30 as was expected. The reason for the lower detached fraction (fp) has probably to do with fluidization dynamics but is still under investigation and for FP doesn’t fit the active site theory.

Acknowledgements


References