INTRODUCTION

In inhalation therapy, the typical size of respirable particles is generally less than 5 micrometers. Due to their small size, drug particles are very cohesive and naturally form agglomerates that could prevent good aerosolisation. Thus, formulations with fine drug particles and coarse carrier particles, usually α-lactose monohydrate have been commonly used to facilitate aerodynamic dispersion and flow. Interactions between particles are mainly dependent on the physicochemical characteristics of the interacting particles that will influence the drug/carerrier blend process and also drug delivery from the carrier and its dispersion. Among these properties, the influence of the carrier particle size on aerodynamic performance of DPI formulations was extensively performed. However, its influence on agglomeration behaviour of drug particles was not investigated further.

The aim of this work was to assess the influence of carrier size on the drug particle characteristics in DPI interactive mixture and on its aerodynamic performance.

EXPERIMENTAL METHODS

Materials: Intrinsic fine particles of lactose were removed from Lactohale LH200 (Frieslands Foods Domo, The Netherlands) by air-jet sieving through a 32 μm sieve for 30 minutes with an airflow that produces a pressure drop of 4 kPa. This lactose without small particles was further sieved through 40, 63, 90, and 125 μm sieves to obtain 3 fractions: 40-63 μm; 63-90 μm and 90-125 μm. Fluticasone Propionate (FP) (Volume Mean Diameter (VMD) of 2.65 μm at a concentration of 2.5% w/w) was mixed with each lactose fraction in a low shear blending (Turbula) for 2 hours at 90 rpm under controlled relative humidity. Each blend was prepared in 50 g quantity. The quality of the blends was expressed by the uniformity of drug content (n=15). Quantitative analysis was carried out by validated HPLC method.

Characterisation of the lactoses

Particle size was determined by dispersion in ethanol with a laser size analyser MasterSizer 8 (Malvern) and the small sample dispersion unit.

The true density of powder was measured by helium pycnometer (AccuPyc 1330, Micromeritics, USA) using a 3 cm³ sample cell. Apparent bulk volume (V0) and ant particles after 10 taps (V10) and 500 taps (V500) for 50 g powder were determined using the method described in the European Pharmacopoeia. The packing ability V0 - V0/500 was also calculated.

As depicted in Table 1, the agglomerate size is a function of pore size formed between carrier particles and decreases with increasing carrier size. This observation can be explained by particle-particle interaction force proposed by Hamaker. A further decrease of the lactose fraction (32-40 μm) improves the FPF but it remains much lower than the one obtained with the Lactohale LH200 used as received. By dissolving lactose in the measurement liquid, the size of agglomerates of fluticasone can be assessed by laser size analyser. It can be noted that even after mixing with lactose for 120 minutes, drug particles still remain in agglomerate form. Agglomerates were found in good correlation with the pore size between carrier particles (R2=0.9431). It can be speculated that during mixture, the natural agglomerates of drug should be dispersed and divided to small agglomerates according to the interstitial space size between the bigger particles of carrier.

CONCLUSION

Carrier particle size plays an important role on the inhalation performance of interactive powder mixtures. Decreasing carrier particle size leads to a decrease of particulate interaction between drug-carrier. The reduced adhesion between drug and carrier particles increased drug detachment. In this study, drug agglomeration in mixture was investigated. Besides adhesion on the carrier particles, drug particles could distribute in the interstitial space between carrier particles and therefore it is more difficult for the air to move through the powder bed.

REFERENCES


Table 1. characteristics of the lactose fractions

<table>
<thead>
<tr>
<th>Lactose Lactose/FP Mixtures</th>
<th>FP size in mixture</th>
<th>Emitted dose (%)</th>
<th>FPF</th>
<th>Fluticasone particle size in mixture</th>
<th>Aerodynamic Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction</td>
<td>150-90 μm</td>
<td>90-63 μm</td>
<td>63-40 μm</td>
<td>Lactohale LH200</td>
<td></td>
</tr>
<tr>
<td>125-90 μm</td>
<td>75.54</td>
<td>5.43</td>
<td>9.46</td>
<td>25.2</td>
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</tr>
<tr>
<td>90-63 μm</td>
<td>72.17</td>
<td>5.43</td>
<td>25.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63-40 μm</td>
<td>71.54</td>
<td>7.67</td>
<td>9.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-60 μm</td>
<td>71.54</td>
<td>7.67</td>
<td>25.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Air permeability of lactose fraction and its mixtures with Fluticasone

<table>
<thead>
<tr>
<th>Air flow time (s)</th>
<th>Lactose</th>
<th>Lactose/FP Mixtures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction</td>
<td>125-90 μm</td>
<td>90-63 μm</td>
</tr>
<tr>
<td>1.25</td>
<td>1.99</td>
<td>2.67</td>
</tr>
</tbody>
</table>

Figure 1. Blaine’s Apparatus - Powder Cell

Pore distribution of lactose fractions was assessed by mercury intrusion porosimetry (Micromeritics® Autopore IV 9500). Mercury pressure range was from 0.04 Mpa to 15 Mpa in order to avoid particle compression or collapse due to high pressure. The interparticular pore size was calculated based on pressure at which the porosization begins.

Figure 2. Alpine Air-Jet Siever for Adhesion Evaluation

Figure 3. Percentage of FP remaining in the blend in relation to the functioning time of the air-jet siever

The quantity of drug remaining after 30 seconds is an indicator of the quantity that adheres to the carrier. It was observed that the bigger the carrier particle size is, the greater is the fraction of drug that remains attached to the carrier. This is confirmed by the assays carried out using the TSI (Table 3).

When blends are submitted to the Alpine air-jet sieve, drug is rapidly carried away by the airflow.

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