

Influence of Fine Excipient Lactose Grades on Powder Fluidization and Performance of Dry Powder Inhaler Formulations

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Summary

The physicochemical properties of different grades of fine excipient lactose were characterised, in addition, to their affect on the performance of ternary dry powder inhaler (DPI) dosage forms. The fine particle delivery of budesonide increased linearly as the fine content was increased from 0 to 15 % w/w using either milled or micronized fine excipient particles. However, the micronized fines had a significantly greater affect on fine particle delivery than milled lactose. This was related to a change in the fluidization behaviour of the powder bulk as a result of inclusion of the different grades of fine excipient material. These data suggest that the grade of fine excipient particles impacts powder fluidization properties, which ultimately affects the performance of DPI formulations.

Introduction

The inclusion of fine excipient particles in dry powder inhaler (DPI) formulations is known to increase liberation of drug particulates, for which a number of mechanisms have been proposed^{1, 2, 3}. However, there remains limited evidence on the role of fines on powder fluidization and elutriation behaviour of the active ingredient, which are critical in generating therapeutic aerosols from such systems. The fluidization of DPI formulations is primarily a function of the relationship between the pressure differential generated between the air flow and the powder bed and the corresponding tensile strength of the DPI formulation⁴. The inter-relationship between these components is complex, however, previous studies have suggested that powders of greater tensile strength are difficult to fluidize and have been reported to lift as 'plugs' and fracture⁵. In the context of DPIs, the effect of fines on the tensile strength of the powder bed and hence fluidization and performance of DPI powder formulations is not known. Recently, a study from our laboratory reported significant differences in bulk powder flow properties of formulations that comprised of different amounts of fine excipient material, which was related to differences in the fluidization and entrainment properties of formulations and hence their performance⁶. However, there remains a paucity of data relating how different grades of fine excipient material influence the bulk physicochemical properties of powder material and fluidization behaviour of DPI formulations.

The aim of the present study was to determine how milled and micronized grades of fine excipient particles affected the fluidization behaviour of bulk lactose powder and how this related to DPI performance.

Experimental

A range of lactose pre-mixes containing a coarse lactose carrier grade (SV010, DMV, Vehgel, Netherlands) and different amounts of either milled lactose (ML006, DMV, Vehgel, Netherlands) or micronized lactose (MC001, DMV, Vehgel, Netherlands) ranging from 2.5 – 15 % were produced by turbula mixing. These pre-mixes of lactose were fully characterised in terms of physicochemical and powder properties such as, particle size, morphology and bulk density. The fluidization behaviour of lactose pre-mixes were characterized using a FT4 Powder Rheometer (Freeman Technologies, Welland, UK). In each case, 20 ml of sample powder was analysed in a 25 mm bore cylinder. The samples were conditioned using a 23.5 mm blade which was moved down a helical path with a helix angle of 5 degrees at 20 mm/s. This provides a gentle displacement of the powder, which removes the packing history of the powder and any operator influence and thus generates a homogenised or uniform low packing stress in the powder. The powders were exposed to increasing airflow velocities and the resistance to powder fluidization quantified as fluidization energy was determined. In all cases measurements were performed in triplicate upon each powder in each test.

Formulations consisting of 0.7 % w/w budesonide were produced using geometric and turbula blending with each pre-mix of lactose. The Cyclohaler™ was used to disperse blends from size 3 HPMC capsules containing 25 mg of blend, into a next generation impactor (NGI) with pre-sep at 90 L.min⁻¹.

Results

The lactose pre-mixes were characterised in terms of their physicochemical characteristics and their performance in DPI formulations consisting of budesonide. Furthermore, the rheological properties of the lactose pre-mixes were related to their affect on formulation performance.

Physicochemical Characterisation

Typical SEMs of the coarse lactose monohydrate carrier SV010 and fine excipient sources ML006 and MC001 are shown in Figures 1A, B and C, respectively. The physicochemical characteristics of the excipients are shown in Table 1. The coarse carrier particles present a median equivalent volume diameter of 112 μm with 2.90 % less than 10 μm by volume. The two fine excipient sources are distinctly different from the carrier material and are markedly different to each other. The MC001 grade of fine excipient material exhibited a median equivalent volume diameter of approximately 3 μm , whereas particles of ML006 are significantly larger with volume median diameter of 17 μm . These data are also supported by SEMs shown in Figure 1. These differences in particle size of the two grades of fine excipient materials is related to their respective process history, where the larger ML006 material was produced by milling whereas the finer MC001 was produced upon high-intensity micronisation most likely carried out using an air-jet mill.

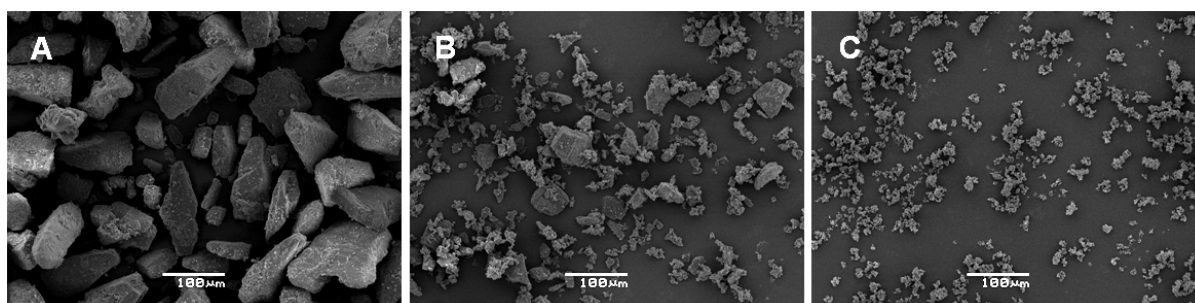


Figure 1. Typical scanning electron micrographs of SV010 (A), ML006 (B) and MC001 (C).

Table 1. Particle size distribution of SV010, ML006 and MC001.

Lactose Grade	Particle Size Analysis (\pm S.D.)			
	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	% < 10 μm
SV010	54.71 (0.56)	112.15 (0.56)	181.88 (1.32)	2.90 (0.03)
ML006	1.71 (0.01)	17.20 (0.25)	45.14 (0.62)	34.04 (0.39)
MC001	0.87 (0.02)	2.82 (0.10)	6.77 (0.14)	98.83 (0.17)

The physicochemical properties of the different lactose pre-mixes containing either ML006 or MC001 are summarised in Table 2. Increasing lactose fines content resulted in lower bulk tap densities and increasing percentage of particles less 10 μm by volume, which is indicative of materials exhibiting increasing cohesivity and thereby increasing tensile strength. However, it is apparent from Table 2 that the inclusion of increasing amounts of MC001 had significantly ($p < 0.05$) reduced the bulk density of the powder mixture than ML006. These data indicate that the inclusion of MC001 in mixtures of coarse lactose would result in powders exhibiting greater cohesivity and tensile strength than powders containing ML006. These data are supported by fluidization energy measurements, which suggest that the more cohesive powders containing MC001 are more resistant to fluidisation than powders containing ML006, as indicated by the larger fluidization values of powders containing increasing amounts of MC001.

Table 2. Physicochemical analysis of lactose pre-mixes of SV010 containing either ML006 or MC001.

Lactose Pre-mix	% < 10 μm (v/v \pm S.D.)	Bulk Density (g/ml)	Fluidization Energy (mJ \pm S.D.)
SV010	2.90 (0.03)	0.74	1.53 (0.24)
+ 2.5 % MC001	8.37 (0.03)	0.72	11.20 (1.85)
+ 5.0 % MC001	11.93 (0.19)	0.68	24.10 (1.14)
+ 10.0 % MC001	22.46 (0.19)	0.65	24.47 (1.16)
+ 15.0 % MC001	35.26 (2.18)	0.57	27.33 (2.49)
Separator			
+ 2.5 % ML006	3.79 (0.03)	0.74	1.55 (0.02)
+ 5.0 % ML006	5.12 (0.01)	0.73	3.03 (1.02)
+ 10.0 % ML006	6.26 (0.02)	0.72	6.08 (0.99)
+ 15.0 % ML006	9.26 (0.02)	0.69	14.30 (1.28)

Functional Attributes of Excipient Material in DPI Formulations

In order to investigate the relationship between the functional properties of the different fine excipient grades, formulations containing budesonide and the different pre-mixes of lactose were. Following acceptable blend uniformity, formulations were included in size 3 HPMC capsules and aerosolised into a NGI at $90 \text{ L}\cdot\text{min}^{-1}$ using a Cyclohaler™. The fine particle dose of budesonide increased linearly from 18 – 50 μg when aerosolized from formulations containing increasing levels of MC001 and ML006 (Table 3). However, a significantly ($p < 0.05$) lower amount of micronized fines was required in comparison to milled lactose to increase fine drug particle delivery.

Table 2. Aerosolisation performance of budesonide (200 μg) using different lactose pre-mixes.

Lactose Pre-mix	Fine Particle Dose ($\mu\text{g} \pm \text{S.D.}$)
SV010	18.5 (2.2)
+ 2.5 % MC001	32.0 (3.2)
+ 5.0 % MC001	46.0 (1.2)
+ 10.0 % MC001	46.1 (3.4)
+ 15.0 % MC001	50.0 (3.1)
+ 2.5 % ML006	20.8 (0.5)
+ 5.0 % ML006	37.4 (2.9)
+ 10.0 % ML006	41.0 (3.8)
+ 15.0 % ML006	43.2 (1.6)

Interestingly, powder rheology studies suggested that there was a relationship between fluidisation energy and fine particle dose, where increasing fluidization energy corresponded to improved drug fine particle delivery (Figure 2). Moreover, the addition of micronized lactose fines significantly ($p < 0.05$) increased the fluidization energy of lactose powders in comparison to milled lactose fines, which correlated to the greater increase in fine particle delivery of formulations containing micronized lactose fines.

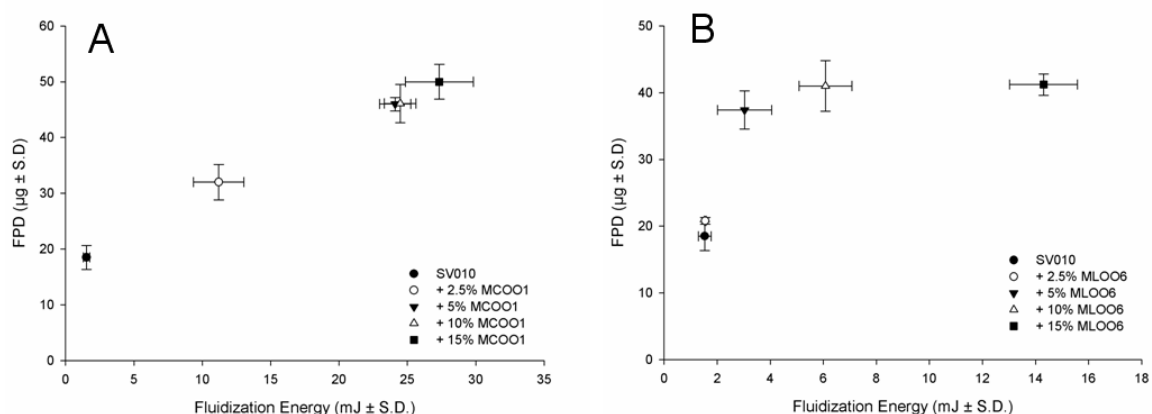


Figure 2. Relationship between fine particle delivery of ternary DPI formulations containing either MC001 (A) or ML006 (B) and fluidization energy.

These data suggest that increasing fines content contribute to increase the cohesivity of the powder bed, thereby making the powder bed less permeable to air. The presence of fines may therefore, increase the tensile strength of the powder bed, which stabilizes it to disturbances from air flow as previously reported⁶. As a result, air is not free to permeate through the powder bed, and therefore, the air flow permeates through channels formed within the powder and/or result in the powder to lift as a plug, which then fractures and collapses⁷. It is conceivable therefore, that the increase in air flow resistance due to the greater tensile strength of the powder would shift the minimum fluidization velocity, resulting in the generation of higher aerodynamic drag forces within a DPI device that may result in increased liberation of fine drug particles. This is supported by Figure 2 which shows that the energy required to aerate the powders increased linearly as the fines content of lactose batches was increased, which was correlated to an increase in FPD of formulations containing fines. However, the presence of MC001 (micronized grade of fines) had a significantly greater impact on powder fluidization properties than the milled

ML006, which corresponded in formulations containing MC001 producing greater fine particle delivery than those containing ML006.

Conclusions

In conclusion, changes to powder fluidization properties as a function of different fine excipient sources was related to DPI performance. We propose that the addition of fine excipient particles effects powder fluidization and entrainment behaviour of the bulk powder formulation and therefore, DPI performance.

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