Investigating the Effect of the Force Control Agent Magnesium Stearate in Fluticasone Propionate Dry Powder Inhaled Formulations with Single Particle Aerosol Mass Spectrometry (SPAMS)

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Summary

A number of researchers are investigating the role of ternary force control agents (FCA's) in pharmaceutical inhaled products with different analytical techniques. Various application processes such as mechanofusion and particle smoothing have been published to apply FCAs on carrier particles [1–3]. Nevertheless, a thorough mechanistic understanding of the role of FCA's in dry powder inhalation (DPI) formulations is still largely missing.

In this study, the effect and impact on the formulation containing the FCA MgSt has been investigated in a FP, lactose based DPI formulation. Two different mixing methods of lactose and MgSt have been examined. The aerosol performance in terms of APSD and FPF of the DPI formulations was evaluated with cascade impaction studies with the NGI and analyzed with SPAMS.

High-shear blending of the lactose carrier together with the FCA magnesium stearate (MgSt) lead to a shift of the aerodynamic particle size profile (APSD) of the active drug fluticasone propionate (FP) and the total number of particles to a higher number of smaller particles. The blending method applied to pre-blend the excipients strongly impacts the APSD and fine particle fraction (FPF) of FP. Both SPAMS and Next Generation Impactor (NGI) confirmed an increase of FPF for FP when adding MgSt to the formulation by high-shear mixing. Low-shear mixing of the excipient-blend did not increase the pharmaceutical performance of FP. The analytical techniques NGI and SPAMS successfully demonstrated that it is possible to distinguish changes in the formulation of DPI powders blended with different amounts of MgSt.

Introduction

Dry powder inhaled (DPI) products commonly consist of large carrier particles (usually alpha-lactose monohydrate) and a relatively low amount (0.05–10%) of active pharmaceutical ingredient (API) having a particle size typically below 6 µm. Blending lactose together with a ternary force control agent (FCA) such as MgSt prior adding the API has been shown to modify the performance of pharmaceutical inhaled products [3,4].

For this study, active blends with the cohesive drug FP [5] have been manufactured between 0 and 1% (w/w) MgSt-content in the excipient blend by high-shear and low-shear mixing the excipient-blend. A formulation of FP with lactose untreated (0% MgSt) was used as a reference. The effect of the FCA MgSt has been investigated with SPAMS and NGI to assess the aerosol performance of FP and excipient. Another aim of this study was to examine the influence of the two different mixing methods on applying the FCA on lactose and the resulting effect on aerosol performance of FP DPI formulations.

For the evaluation of the aerosol performance of inhaled pharmaceutical products, the current state of the art is the use of the NGI (Copley Scientific, UK), typically with chemical analysis using high performance liquid chromatography (HPLC), to characterize the APSD and FPF of the active substance. But for the total fine particle assessment, a special NGI method has to be developed and carried out in order to determine the distribution of the excipients (e. g. lactose carrier and FCA). SPAMS is an analytical technique where the aerodynamic diameters and chemical compositions of many individual aerosol particles are determined in real-time. The SPAMS technique and its advantages have been published in several articles recently [6,7]. SPAMS is a promising method to explore effects in DPI formulations due to the fact that not only the APSD of the active drug in the formulation is determined. The total number of particles (excipient and API) is determined simultaneously and also the additional information of co-associations between two APIs.

Experimental methods

DPI formulation preparation: For the high-shear manufactured excipient-blends, inhalation grade lactose (Respitose® ML001, DFE Pharma) and MgSt (Peter Greven, 0-1 % w/w) were blended in a Collette MicroGral (GEA Pharma Systems) for 16 minutes at 1400 rpm. The low-shear manufactured excipient-blend was mixed for 16 min at 34 rpm in a Turbula mixer (Willy A. Bachofen AG). The excipient-blend together with the active drug FP was sieved through a sieve with a mesh size of 250 µm in a vessel. The resulting drug-excipient blend was then mixed in a Turbula mixer at 34 rpm for 16 min. The final powder was filled into size 3 HPMC capsules containing dosage strength of 200 mcg FP per capsule. The capsules were stored at 25°C and 55% relative humidity for a period of 7 days prior to the experiments.

FP DPI analysis by NGI: The deposition of the dry powder formulations was investigated using an NGI equipped with a pre-separator. All measurements were conducted at 55% RH and ambient temperature (23 ± 2ºC). The cup trays of the impactor were coated with Brij® reagent (1% v/v solution of Glycerol in Ethanol). The capsules were actuated in a Breezhaler® inhalation device at a flow rate of 90 L/min for 2.7 sec. The amount of powder deposited on the different collection cups was recovered by extracting each cup with solvent. The remaining powder in the capsule and the powder deposited in the throat and the pre-separator was also collected. After dissolution of the particles, HPLC analysis was performed. In this study the mean of three individual determinations was taken for a given NGI result.

FP DPI testing by SPAMS: A Livermore Instruments SPAMS 3.0 was used for this study. The experimental setup of the SPAMS instrument and sample testing has been described earlier by Morrical et al. [6]. For the calibration of the SPAMS instrument in the region of 0.1-10 µm, polystyrene (PLS) microspheres (Thermo-Fisher Scientific) were used. The dry powder formulations samples were acquired using a Breezhaler® inhalation device. The induction port was connected to a pre-separator (Copley Scientific, UK), which was filled with 15 mL of water and then connected to a 4L relaxation chamber. This assembly of pre-separator and sampling chamber was then fitted to the SPAMS inlet. The primary purpose of the pre-separator was to filter out coarse lactose carrier particles (>10 µm) so that they cannot enter the SPAMS instrument to prevent clogging of the inlet interface. The sampling chamber allows for dilution of the particles and flow rate matching. The actuation of the DPIs was made with a simultaneous 2.7 seconds draw of air into the sampling chamber, at a flow rate 90 L/min (i.e. 4 liters of air drawn).

Results and discussion

Figure 1a) shows a comparison of SPAMS APSD histograms of total particles (API, fine lactose and MgSt) for three different FP blends with lactose untreated, lactose with 0.1 and 0.5% MgSt-content (w/w; excipient-blend high-shear manufactured), respectively. By adding MgSt to the formulation, the APSD profile shifts to a higher number of smaller particles with a higher number of particles in the size range from 0-1.9 µm diameter. By increasing the MgSt-content from 0.1 to 0.5% (w/w), the number of smaller particles increases even more and the size distribution shift is more pronounced.

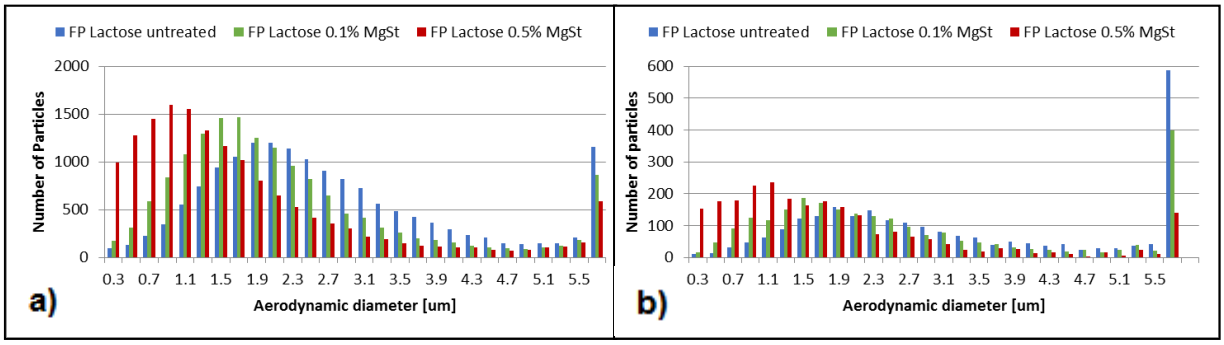

Figure 1 - SPAMS Aerodynamic particle size distribution histograms of three FP blends with lactose untreated, 0.1 and 0.5% MgSt (w/w), respectively (high-shear manufactured).

a) The plot shows the total number of particles measured (active substance FP and excipients).
b) The plot shows the distribution of the active substance FP (no excipients). The size bins were scaled in order to have a comparison between the different formulations.

The APSD histogram of particles containing FP in the two high-shear manufactured formulations and the reference formulation without MgSt is shown in Figure 1b). The size bins in Figure 1b) were scaled in order to compare the three formulations with each other. It can be seen that there is a significant increase in number of FP particles with a small particle size in the range from 0-1.9 µm for the formulations containing 0.1 and 0.5% MgSt, respectively. Interestingly, the same shift observed in the total number of particles (Figure 1a) was also detected for the API FP following the same pattern. SPAMS is indicating that the high-shear manufactured blends containing the FCA MgSt have a higher dispersibility compared to the reference formulation without MgSt.

In Figure 2, a series SPAMS APSD histograms of three FP blends is compared: A high-shear manufactured lactose 0.1% MgSt excipient-blend, a low-shear manufactured lactose 0.1% MgSt excipient-blend and the reference formulation without MgSt. It is clearly evident that there are significant differences between the high- and low-shear manufactured blends. While the APSD of the high-shear manufactured blend shifts to a higher number of smaller particles (0-1.9 µm), the APSD of the low-shear formulation seems to have a slight shift to a larger particle size. A much lower number of particles with a size below 1.9 µm are present. The increase in number of particles in the region of 2.1 µm is probably due to MgSt agglomerates. The histogram indicates that low-shear mixing of the excipient-blend does not increase the dispersibility of the manufactured FP formulation.

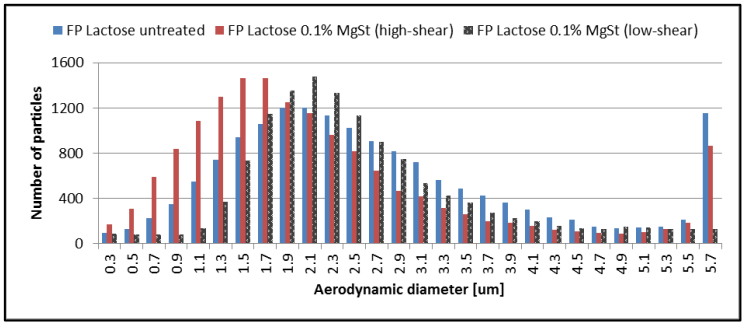

Figure 2 - SPAMS Aerodynamic particle size distribution histogram of three FP blends with lactose untreated, 0.1% MgSt (w/w) high-shear and low-shear manufactured, respectively. The plot shows the total number of particles measured (active substance FP and excipients).

The fine particle fraction (FPF) of FP (particles with a diameter <5 µm) calculated as a percentage of total recovery, is described in Table 1. The FPF increases with the amount of added MgSt for the high-shear manufactured formulations. The tested formulations with amounts of 0.1 and 0.5% (w/w) MgSt increased about 2 and 8% in FPF, respectively. The FPF did not increase for the formulations manufactured with the low-shear excipient-blend.

Formulation	FPF [%]	StDev [%]
FP Lactose untreated	24.4	0.2
FP Lactose 0.1% MgSt (high-shear)	26.3	0.2
FP Lactose 0.5% MgSt (high-shear)	32.2	0.8
FP Lactose 0.1% MgSt (low-shear)	22.0	1.2
FP Lactose 0.5% MgSt (low-shear)	22.3	0.5

Table 1 - Fine particle fraction (% of declared content) obtained by NGI

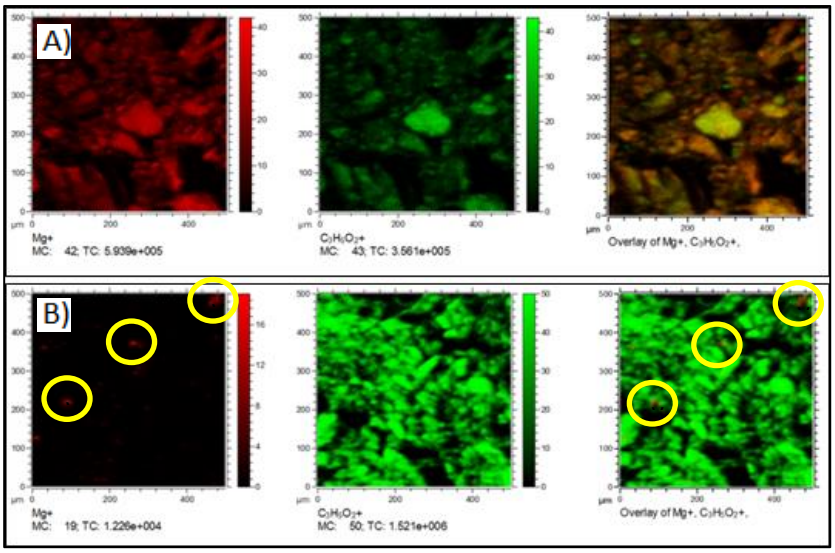

Figure 3 - ToF-SIMS images of lactose 0.1% MgSt (w/w) high-shear (A) and low-shear (B) manufactured

Red: Ion signal for Mg^+ (from MgSt)
Green: Ion signal for lactose ($C_3H_5O_2^+$)
Orange: Overlay of MgSt (red) and lactose (green) ion signals

Characterization of changes on the lactose carrier surface or carrier coating is crucial to examine and difficult to achieve because of particle size and shape and the extremely thin coating layer. Conventional techniques such as Raman spectroscopy penetrate the coating layer and measure both, the coating layer and the host particles. Secondary ion mass spectrometry (ToF-SIMS) images showed ion signals for MgSt all over the measured area in the high-shear manufactured excipient blend (Figure 3A). Therefore, we conclude that MgSt must be evenly distributed on the lactose surface (Figure 3A: Overlay of MgSt and lactose). A thin layer of MgSt covers the lactose surface. While in the low-shear manufactured excipient blend, MgSt agglomerates (yellow circles) were detected by ToF-SIMS imaging as small intense spots (Figure 3B). Low-shear blending did not induce any surface coating of the lactose with MgSt. The overlay of MgSt and lactose shows only some intense spots with ion signals indicating MgSt agglomerates.

The results collected with SPAMS and NGI indicate that there is higher dispersibility of fine particles with an aerodynamic diameter below 5 µm when adding the FCA MgSt to the excipient blend by high-shear mixing. Apparently, the MgSt is modifying the lactose carrier surface in such way that attractive forces, such as van der waals or electrostatic forces [8], between drug and carrier and also between fine excipient and coarse excipient are much reduced. This leads to easier detachment of drug and also fine excipient from the coarse carrier. The likelihood to form smaller agglomerates between drug and fine lactose increases. As a consequence, the amount of liberated drug substance increases [4].

In the investigated DPI blends, the amount of MgSt added to the blend also played an important role. Introducing more MgSt (0.5% compared to 0.1% w/w) into the system resulted in further increase of the aerosol performance in terms of FPF for the formulation when the excipient-blend was manufactured by high-shear mixing. A higher amount of MgSt seems to cover more of the lactose surface area and thus decreases interaction forces even more when applied on the lactose by high-shear mixing. It can be hypothesized that above a certain concentration of MgSt in the excipient blend, different effects may influence the aerosol performance. Various competing effects such as the saturation of activated areas on the carrier surface or the formation of drug–fines agglomerates for easier lift-off could offer an explanation for the observed behaviour [9-11]. However, no conclusive explanation can be given at this point.

Conclusions

The blending method applied to pre-blend the excipients strongly impacts the APSD and FPF of FP. High-shear blending of the lactose carrier together with the FCA MgSt leads to a shift of the APSD profile of the active drug FP and the total number of particles to a higher number of smaller particles overall as detected with SPAMS. There is a better detachment of small particles overall and possibly co-associations of FP with fine MgSt or very fine lactose is formed during the actuation of the capsule. Both SPAMS and NGI showed an increase of FPF for FP when adding MgSt to the excipient blend by high-shear mixing. Low-shear mixing of the excipient-blend did not significantly increase the performance of FP in our formulations. Images from ToF-SIMS indicate that the distribution of MgSt in the excipient blend strongly depends on the blending method. The presence of MgSt as a thin and homogenous layer on the lactose surface in the high-shear blend appears to change the interaction forces between API and lactose carrier. The altered surface properties influence the interaction forces between API and carrier, which leads to easier detachment of FP from the lactose carrier together with higher dispersbility of total fines. For future work it would be interesting to explore, if other FCAs can have a similar effect with the used excipient high-shear mixing method.

It was demonstrated with SPAMS that it is possible to distinguish changes in the formulation of DPI powders. SPAMS provided valuable additional information about the dispersion behavior of our formulations. APSD histograms of total number of particles and particles containing FP could be determined for comparison. Using an upgraded SPAMS setup with a desorption and ionization laser firing at a different wavelength, SPAMS could potentially detect co-associations not only between APIs, but also between API and excipients (lactose and FCA) in future.

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