# The Mechanism of Magnesium Stearate to Modify Aerosol Performance in Dry Powder Inhaled Formulations

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## Summary

The potential of the force control agent (FCA) magnesium stearate (MgSt) to enhance the aerosol performance of lactose-based dry powder inhaled (DPI) formulations was investigated in this study. Two different blending methods of lactose and MgSt (0.5% w/w) have been examined. The in vitro aerosol performance in terms of aerodynamic particle size distribution (APSD) and fine particle fraction (FPF) of the fluticasone propionate (FP) and salmeterol xinafoate (SX) DPI formulations were evaluated with the Next Generation Impactor (NGI) and also with single particle aerosol mass spectrometry (SPAMS). Furthermore, the electrostatic behaviour of the FP and SX formulations was investigated. The aim was to generate insights in electrostatic charge generation during powder manufacturing and capsule actuation in the inhalation device (i.e. unit dose capsule inhaler) and its effect on the aerosol performance.

The dispersion of MgSt in the binary mixture with lactose carrier strongly depends on the blending method, and the particle interactions between drug and carrier particles are substantially affected by the choice of blending technique. Measurements of the dynamic electrostatic charge show that there is a significant difference in electrostatic charge between the different formulations tested. This affects particle detachment from the carrier and thus impacts aerosol performance for FP. SX did not show significant electrostatic effects for any of the blends. Compared to blends with pure lactose, low-shear blending of MgSt increases the FPF of the adhesive model drug SX, while high shear blending significantly increases FPF of both SX and FP. This allows fine control of aerosol performance of a DPI by an adequate choice of the blending technique.

## Introduction

Dry powder inhaler (DPI) products commonly consist of large carrier particles (usually alpha-lactose monohydrate) and a relatively small amount (0.05–10%) of micronized active pharmaceutical ingredient (API) having a particle size typically below 6 µm. A variety of factors such as particle size distribution, shape, surface morphology (roughness) and surface energy (adhesive/cohesive properties) can influence the deposition of the aerosol particles in the respiratory tract [1]. In addition to the formulation composition and material properties, the choice of blender, order of mixing of ingredients, the process parameters and storage also play an important role [1]. The presence of fine lactose particles in a DPI formulation improves the formulation performance in terms of delivered dose and fine particle fraction up to some extent. Numerous articles on the topic of adding lactose fines to coarse carrier with different blending methods have been published [1, 2], demonstrating the effects of adding fines. Surface modifications of carrier particles have been reported to improve inhalation performance of DPI formulations [3]. Blending lactose together with a FCA such as MgSt prior to adding the API has been shown to modify the performance of pharmaceutical inhaled products [1, 4]. Various application processes such as mechanofusion and particle smoothing have been used to apply different FCAs on carrier particles or APIs [1, 5].

The fundamental attractive forces/mechanisms of interaction between particles in DPI formulations are including: van der Waals, electrostatic and capillary forces [1]. Besides the mentioned adhesive/cohesive forces, friction and mechanical interlocking also play important roles in power flow and deaggregation [6]. Extensive research has been conducted on aerosol characteristics of DPIs such as particle size and mass output, but their electrostatic properties are only poorly studied [7]. Triboelectrification showed to have a significant effect on inhaler function, separation of drug from carrier particles and lung deposition [8].

The aim of this study was to investigate the impact of the FCA MgSt on the mechanism of interaction and physico-chemical characteristics of the DPI carrier particles and the performance of active substances in pulmonary formulations using engineered excipient-blends. A variety of analytical techniques, including single particle aerosol mass spectrometry (SPAMS), time-of-flight secondary ion mass spectrometry (ToF-SIMS) and a dynamic electrostatic charge measurement were employed.

## Materials and Methods

The high-shear excipient-blend (inhalation grade lactose and MgSt) was blended in a Collette MicroGral (GEA Pharma Systems) for 16 minutes at 1400 rpm. The low-shear excipient-blend was mixed for 16 min at 34 rpm in a Turbula mixer (Willy A. Bachofen AG). The excipient-blends together with the drug FP or SX were sieved through a sieve with a mesh size of 250 µm in a vessel. The resulting drug-excipient blends were then mixed in a Turbula mixer at 34 rpm for 16 min. The final powder was filled into size 3 HPMC capsules containing a dosage strength of 200 mcg drug per capsule. FP capsules were stored at 25°C and 55% relative humidity for a period of 7 days prior to the experiments to optimize the performance. SX capsules were not conditioned as SX showed poor stability when exposed to temperature and humidity [9]. A formulation of FP or SX with untreated lactose (0% MgSt) was used as a reference.

The in vitro aerosol performance of the DPI formulations in terms of fine particle fraction (FPF; <5 µm) was investigated using an NGI equipped with a pre-separator. Experiments were conducted at 55% RH and 23 ± 2ºC. The impactor cup trays were coated with Brij® (1% v/v Glycerol in Ethanol). Capsules were actuated in a Breezhaler® inhaler device at a flow rate of 90 L/min for 2.7 sec. The amount of powder deposited on the collection cups was recovered by extracting each cup with solvent. After dissolution of the particles, HPLC analysis was performed. The mean of three individual determinations was taken for a given NGI result.

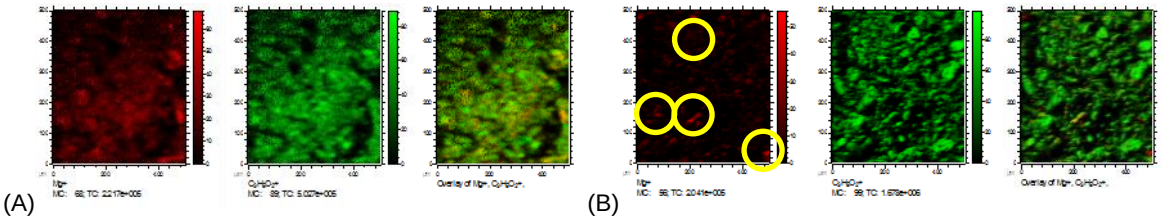
Time-of-flight secondary ion mass spectrometry (TOF-SIMS 5, ION-TOF) was used to detect the chemical composition of surfaces by scanning the sample with a focused ion beam of Bi3+ primary ions in spectrum mode.

The experimental setup of the SPAMS instrument (SPAMS 3.0; Livermore Instruments Inc.) and sample testing has been described earlier by Morrical et al. [10]. For the calibration of the SPAMS instrument in the region of 0.1-10 µm, polystyrene (PLS) microspheres (Thermo-Fisher Scientific) were used. The DPI samples were acquired using a Breezhaler® device. The induction port was connected to a pre-separator (Copley Scientific), which was filled with 15 mL of water and connected to a 4L relaxation chamber. The primary purpose of the pre-separator was to filter out coarse lactose carrier particles (>10 µm) to prevent clogging of the SPAMS 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 L of air drawn).

The dynamic electrostatic emitted charge (DEEC) measurements were performed using an in-house designed dynamic Faraday cage with a mesh screen inside that is isolated from external fields by being placed inside a metal can acting as a Faraday cage. Actuated particles fly through the screen and impart a charge that is detected by a JCI 178 charge measuring unit electrometer (Chilworth) to record the electrostatic charge that the powder generated on the mesh screen. An average from 5 capsules was taken as a DEEC result.

## Results and Discussion

ToF-SIMS images showed ion signals for MgSt over the entire measured area in the high-shear excipient-blend (Figure 1A). From this result, we conclude that MgSt is evenly distributed by the high-shear blending on the lactose surface (overlay of MgSt and lactose) with a thin layer of MgSt that is covering the lactose surface (80% relative coverage with MgSt). While in the low-shear excipient-blend, MgSt agglomerates were detected by ToF-SIMS imaging as small intense spots (Figure 1B; yellow circles). Low-shear blending did not induce any surface coating of the lactose with MgSt.



(A) (B)

**Figure 1 ToF-SIMS micrographs at scanning area of 500µm×500µm for (A) Lactose 0.5% MgSt (high-shear) and (B) Lactose 0.5% MgSt (low-shear). Red = Signal for MgSt ($Mg^+$). Green = Signal for Lactose ($C_3H_5O_2^+$). Orange = Overlay.**

The fine particle fraction (FPF) of FP and SX (particles with a diameter <5 µm) from NGI analysis is calculated as a percentage of total recovery, described in Table 1. Compared to pure blends with lactose, low-shear blending of MgSt increases the FPF of SX, while high-shear blending significantly increases FPF of both SX and FP.

**Table 1 Fine particle fraction of FP and SX formulations (FPF; % of declared content; ± one standard deviation, SD) obtained by NGI with Breezhaler® device.**

| Formulation | FPF [%] ± SD | Formulation | FPF [%] ± SD |
|---|---|---|---|
| **FP Lactose untreated** | 24.4 ± 0.2 | **SX Lactose untreated** | 39.2 ± 1.3 |
| **FP Lactose 0.5% MgSt (high-shear)** | 32.2 ± 0.8 | **SX Lactose 0.5% MgSt (high-shear)** | 54.2 ± 0.7 |
| **FP Lactose 0.5% MgSt (low-shear)** | 22.3 ± 0.5 | **SX Lactose 0.5% MgSt (low-shear)** | 56.3 ± 2.0 |

The results collected with SPAMS indicate that there is higher dispersibility of fine particles with an aerodynamic diameter below 5 µm when adding the MgSt to the excipient blend by high-shear mixing for both FP and SX (Figure 2). Interestingly, the SX low-shear formulation also had similar dispersibility to high-shear blending as compared to no MgSt in the formulation. It has been reported that FP is adhesive to lactose while SX shows cohesive behaviour with regards to lactose [11]. Thus it is possible that SX is not forming strong agglomerates with either lactose or MgSt and therefore the blending technique has only a very limited influence on the aerosol performance in case of SX. While for FP, the interaction with lactose is much reduced in the high-shear blend as the outermost surface is covered with MgSt. This results in lower interaction forces and facilitated detachment of drug and also fine excipient from coarse carrier. Comparing the reference formulations of FP and SX, the performance of SX was already substantially higher than observed for FP (Table 1). This can also be explained with the adhesive/cohesive behaviour of the APIs.

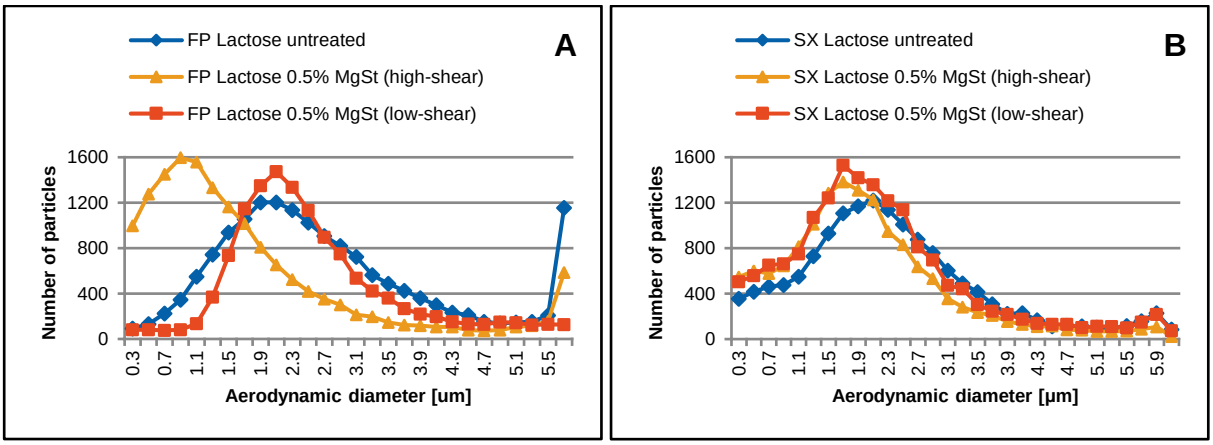



**Figure 2 SPAMS Aerodynamic particle size distribution histogram of FP (A) and SX (B) blends with lactose untreated, 0.5% MgSt (high- and low-shear), respectively. The plot shows the total number of particles measured (APIs and excipients).**

Measurements of the dynamic charge show that there is a significant difference in electrostatic charge between the different formulations tested in this study for FP (Figure 3A). High-shear blending of MgSt seems to modify the lactose surface so that electrostatic forces, between drug and carrier and also between fine excipient and coarse excipient are much reduced as witnessed by the increase in fine particles observed for FP with SPAMS (see Figure 2A). Low-shear blends with FP seem to have a reduced drug detachment from the carrier due to high interactive forces and therefore a lower FPF. The results in Figure 3A show that the addition of MgSt changes the overall polarity of the powder with low-shear having a high and positive charge upon actuation. This might be because MgSt with low-shear is still present as discrete particles and MgSt is an electrical insulator and therefore strongly retains charge. However, when applied through high-shear blending, the thin layer of MgSt is in direct contact with lactose, which could act as an effective sink (based on the rapid charge decay measured for lactose) for the charge, thus lowering the overall impact of having MgSt in the formulation.

SX does not have the same propensity to charge as FP and in fact seems to dissipate charge quite effectively as all three SX formulations have weak electrostatic forces and therefore exhibit a relatively high in vitro aerosol performance (as compared to the highly electrostatic FP) as could be verified with SPAMS and NGI. A recent study indicated that the electrostatic properties are directly related to the surface functional group chemistry, with hydrophobic groups accumulating greater quantities of charge than hydrophilic groups. Florine-rich surfaces, such as Fluticasone accumulate much greater charge upon tribocharging than the hydroxyl-rich surfaces in Salmeterol [12].

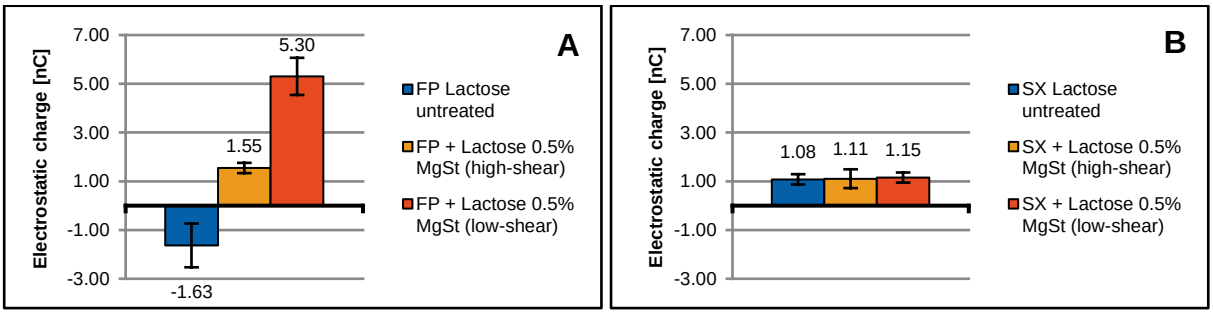



**Figure 3 Dynamic charge measurement with Breezhaler® device for FP (A) and SX (B) blends (n=5 capsules).**

In the high-shear formulations there is a significant change of surface characteristics as the outermost surface consists more of MgSt and not of lactose anymore as determined with ToF-SIMS (Figure 1). The drug-to-carrier interaction has now changed from lactose-API to primarily MgSt-API. This may result in a reduced surface energy and altered electrostatic behaviour for APIs that show a strong adhesive tendency towards lactose. Measurements with inverse gas chromatography by Das et al. explained that the dispersive surface energy of MgSt is significantly lower compared to lactose [13]. The drug-to-carrier interparticulate forces must be weak enough to allow substantial drug detachment during the inhalation process while strong enough to maintain powder blend homogeneity. Particle interactions and aerosolization are prone to change when surface characteristics of the drug or carrier particles such as surface energy, coating with an FCA, additives or electrostatic behaviour, are changed [1]. During powder mixing, drug particles are distributed between the surface of carrier and fines, forming weak agglomerates of drug and fines that can be dispersed and disaggregated easily during aerosolization as “soft-agglomerates” [1]. Experiments using the SPAMS technology demonstrated that high-shear blending of lactose carrier with MgSt greatly improved the dispersibility of the high-shear formulations. The addition of MgSt to the formulations resulted in apparent changes in particle size, size distribution, morphology, and drug/fine ratio. We also hypothesize that the addition of MgSt by high-shear mixing is modifying the surface roughness and reducing the true contact area between drug and carrier and therefore the in vitro aerosol performance is increased.

While in the FP and SX high-shear formulations an excess of fine and very fine particles could be detected with SPAMS as compared to the reference formulations, a much lower number of smaller particles were detected in the FP low-shear formulation. Particles seem to agglomerate in part due to high electrostatic interparticulate forces in the FP low-shear blend and therefore a lower performance results. The “active site” theory could possibly explain the effects in the SX low-shear formulations. The drug/carrier ratio and drug/fines ratio may be involved in saturation of “active sites” on the particle surface and/or a redistribution of agglomerates, so that an optimum drug/carrier and drug/fine ratio exists [1]. The addition of ternary fines such as MgSt or lactose preferentially binds to these “active sites”, forcing the drug to the weaker binding site, thus drug particles are more easily liberated from the surface of the carrier particles after actuation. In addition, the electrostatic charge did not seem to be a significant ($p>0.05$) factor for the SX aerosol performance as can be seen in Figure 3B. Furthermore, the affinity between API and carrier is substantially different for FP and SX. FP shows adhesive behaviour with respect to lactose while the drug SX is known to show cohesive behaviour with respect to lactose [11]. It might be possible that the high-shear process is changing the cohesive-adhesive balance in the formulation system.

## Conclusions

The blending method applied strongly impacts the APSD, electrostatic charge and FPF of FP. For SX, the important factor seemed to be the presence of MgSt in the blend since both blending techniques were nearly equally effective to increase the aerosol performance. In addition, the electrostatic charge was unaffected by the presence of MgSt or the blending technique. The presence of MgSt as a coating layer on the lactose surface in the high-shear blends appears to change the interaction forces between API and lactose carrier and alter surface properties. This appears to lead to easier detachment of API from the lactose carrier, adding to the higher dispersibility due to the higher number of total fines. Measurements of the dynamic emitted electrostatic charge showed that there is a significant difference ($p<0.05$) in electrostatic charge between the different FP formulations tested and this seems to play a substantial role for the aerosol performance. In contrast, SX did not show any significant electrostatic effects between the three blends tested.

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