Effects of Magnesium Stearate on the Efficient Dispersion of Salbutamol Sulphate From Carrier-Based Dry Powder Inhaler Formulations

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INTRODUCTION

Dry powder inhaler (DPI) formulations is one of the most useful aerosol preparations in which drugs may be formulated as carrier-based interactive mixtures with micronised drug particles (<5 μm) adhered onto the surface of large inert carriers (lactose powders). The addition of magnesium stearate (MgSt) (1-3), was found to increase dispersion of various drugs from DPI formulations. Recently, some active compounds coated with 5% (wt/wt) MgSt using the mechanofusion method showed significant improvements in aerosolization behavior due to the reduction in intrinsic cohesion force (4). Application of MgSt in powder formulations is not new; however, no studies demonstrated the minimum threshold level for this excipient in efficient aerosolization of drug powders from the interactive mixtures. Therefore, this study investigated the role of MgSt concentration on the efficient dispersion of salbutamol sulphate (SS) from DPI formulations.

METHODS

The powder formulations of SS and lactose carriers (Inhalac 120) were prepared on a laboratory scale using a simple hand mixing method (5). Briefly, the required amounts of MgSt (0.1-2.5% w/w) were placed between two layers of carrier powder in a glass test tube together with three ceramic balls and after sealing, the test tube was vigorously shaken by hand for five minutes. Using the same method, 2.5% SS formulations were prepared by mixing SS powders with the lactose powders pre-blended with varying concentrations of MgSt. The powder formulations were loaded (20 mg) into hard gelatine capsules (size 3, Fawns and McAllan Pty Ltd., Australia).

The dispersion of SS from interactive mixtures was determined by Twin Stage Impinger (TSI) with a Rotahaler at an airflow rate of 60 L/min. The aerodynamic cut-off diameter at 60L/min was 6.4μm. The active drug was quantified by a validated HPLC method (6). The particle size distributions were determined by laser diffraction (Malvern Mastersizer S). The surface morphology of the particles was examined using a Quanta 200 Environmental Scanning Electron Microscope (FEI Company, The Netherlands).

RESULTS AND DISCUSSION

The fine particle fraction (FPF) of 2.5 % w/w SS with Inhalac 120 (without MgSt) was 14.8%; however, no SS particles were aerosolized without lactose carrier in the formulation. Varying concentrations (0.1-2.5%) of MgSt were used as ternary components in the formulations and increased concentrations of MgSt over the range 0.1 to 1.5% resulted in a significant increase (ANOVA, $p<0.05$) in FPF (18-33%) of the loaded dose of SS (Figure1) compared to that of formulation without MgSt. However, a trend was observed where the FPF of SS reduced with increasing concentrations of MgSt ≥ 2.0% (Figure 1). In this study, Inhalac 120 lactose crystals were selected because of their asymmetric shape (Figure 2A). These particles were nearly free from fine lactose associated with large carriers and further removal of the amount of fine lactose was carried out by decantation (6) to eliminate the effect of fine lactose in the drug dispersion processes.

The insufficient dispersion of SS from the formulation without MgSt could be due to the occupation of the preferential binding sites (cavities/valleys) on the carrier surface by the active or strong agglomerates of active. With the introduction of MgSt (0.1-1.5%) in the formulations, the FPF of SS was significantly increased due to the reduction in the cohesive behaviour of SS particles as well as lowering the adhesion between SS and lactose surface.

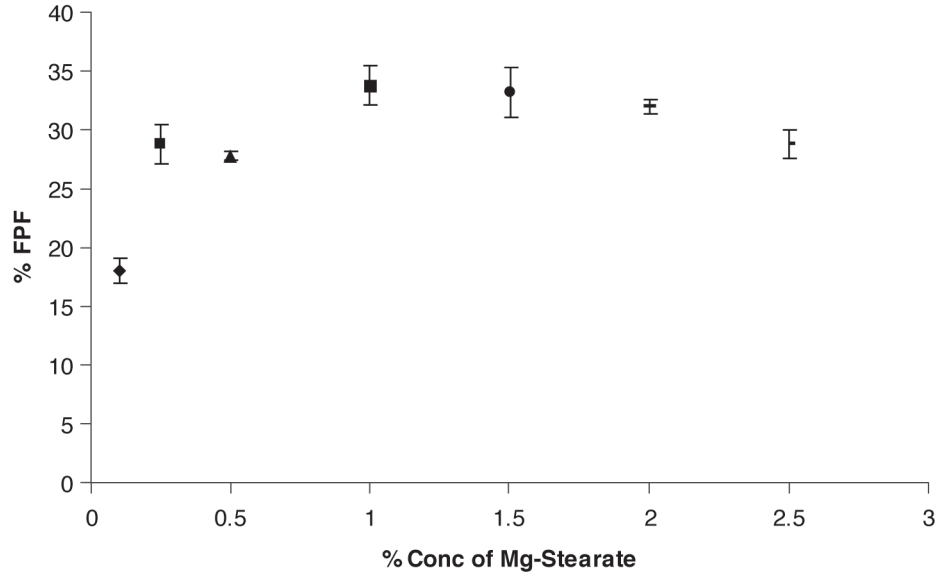

Figure 1. Drug dispersion from the varying concentration of Mg-stearate and 2.5% of SS from the interactive mixtures with Inhalac 120.

It can be emphasised that 0.1% to 0.2% MgSt would be enough to reduce the cohesive forces among SS particles as well as reduce the adhesion between SS and lactose carriers, resulting in easy detachment of SS particles from the lactose surface (3). Before the addition of MgSt in the formulation, the SS particles were present in large and dense agglomerates (Figure 2, B), from where insufficient dispersion occurred. However, loose network structure of SS particles were found upon the addition of a minimum amount of MgSt (Figure 2, C and D), which suggested that the addition of MgSt produced a significant reduction in cohesive interactions of the SS particles. The reduced FPF at higher concentration of MgSt was probably caused due to the transformation of the particle force balance from an adhesive back to a cohesive system resulting in re-agglomeration of SS particles and phase separation of SS agglomerates as illustrated by Figure 2, E and F.

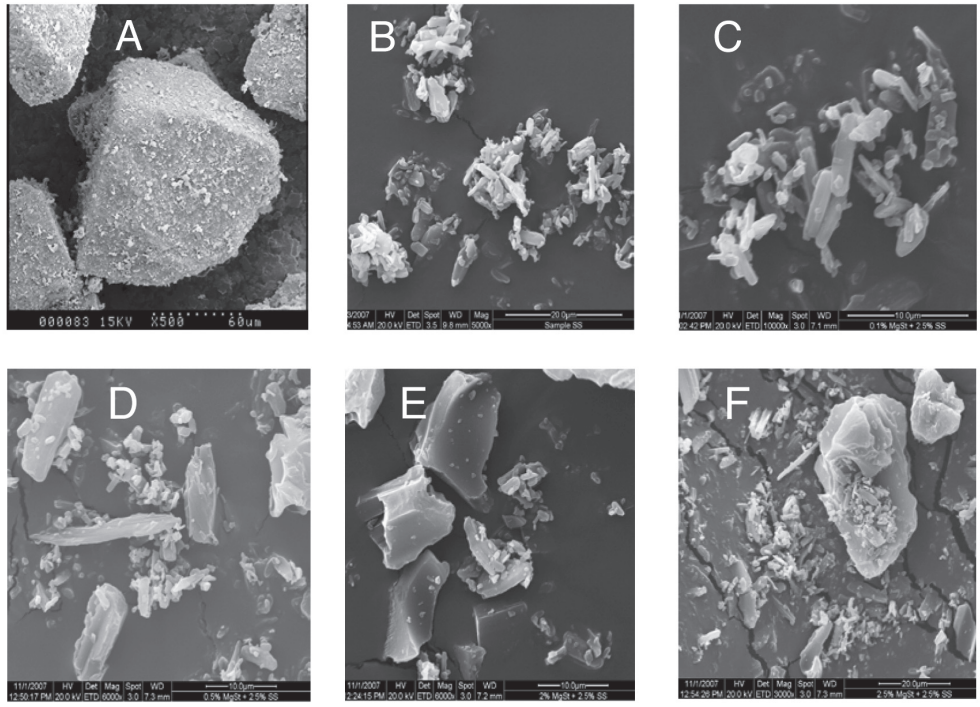

Figure 2. SEM micrograph of various compositions: A. Inhalac 120; B. SS; C. Mixture of 0.1% MgSt; 2.5% SS and Inhalac 120; D. Mixture of 0.5% MgSt, 2.5% SS and Inhalac 120; E. Mixture of 2.0% MgSt, 2.5% SS and Inhalac 120; F. Mixture of 2.5% MgSt, 2.5% SS and Inhalac 120.

The actual mechanism by which fine excipients like MgSt improves the performance of carrier-based DPI formulation is unclear. There is no explanation in the literature how the interparticulate interactions are distributed in the components of ternery formulations and the relationship between deagglomeration processes and subsequent improvement in drug dispersion. Furthermore, no studies demonstrated the theoretical description of the de-agglomeration process that occurs during aerosolization of complex ternary formulations. Thus, it is speculated that the interactive forces in the ternary formulations are changed in the presence of ternary components like MgSt and performance is improved.

CONCLUSIONS

The outcome of this study shows that the addition of a minimum amount of MgSt (0.1% w/w) in the powder mixtures significantly increased the dispersion of SS. It is hypothesised that this may be due to increased de-agglomeration of highly cohesive SS agglomerates via reduction of drug-carrier adhesion. Thus, this minimum amount of MgSt would be considered to be enough to lower the threshold level of the interfacial free energy of interaction between particles, which results in efficient de-agglomeration process. The benefit of adding MgSt to the formulation is questionable due to the potential risk caused by this excipient being delivered to the deep lung. However, an insignificant amount of MgSt from the formulation is expected to be delivered into the deep lungs and would not produce negative effects. The proportion of fine excipient like MgSt added in carrier based DPI systems has an important role in efficient aerosolization of drug particles. Processing of DPI formulation with minimum concentration of this agent is an effective means of improving the de-agglomeration and aerosolization of cohesive powders.

REFERENCES

1. Zeng, X.M, Martin, G.P., Tee, S.-K., and Marriott, C. (1998), "The role of fine particle lactose on the dispersion and deaggregation of salbutamol sulfate in an air stream *in vitro*," *International Journal of Pharmaceutics,* 176, pp. 99-110.

2. Young, P.M., Cocconi, D., Colombo, P., Bettini, R., Price, R., Steele, D.F., and Tobyn, M.J. (2002), "Characterization of a surface modified dry powder inhalation carrier prepared by 'particle smoothing,'" *Journal of Pharmacy & Pharmacology,* 54, pp. 1339-44.

3. Begat, P., Price, R., Harris, H., Morton, D.A.V., and Staniforth, J.N. (2005), "The influence of force control agents on the cohesive-adhesive balance in dry powder inhaler formulations," *Kona,* 23, pp. 109-21.

4. Zhou, Q.T., Qu, L., Larson, I., Stewart, P.J., and Morton, D.A.V. (2010), "Improving aerosolization of drug powders by reducing powder intrinsic cohesion via a mechanical dry coating approach,"*Int J Pharm,* 394, pp. 50-59.

5. Louey, M.D. and Stewart, P.J. (2002), "Particle interactions involved in aerosol dispersion of ternary interactive mixtures," *Pharmaceutical Research,* 19, pp. 1524-31.

6. Islam, N., Stewart, P., Larson, I., and Hartley, P. (2004), "Lactose surface modification by decantation: Are drug-fine lactose ratios the key to better dispersion of salmeterol xinafoate from lactose-interactive mixtures?" *Pharmaceutical Research,* 21, pp. 492-99.