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Communication

Surface Modification of Micronized Drug Powders to Improve Aerosolization via Mechanical Dry Powder Coating

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Abstract: Objective: To improve the efficiency of aerosolisation of two model micronized drug powders by dry mechanical modification of particle surfaces. **Method**: Two model drugs, micronized salbutamol sulphate (SS) and salmeterol xinaofoate (SX) powders were dry coated with magnesium stearate using a mechanofusion approach. The powder re-suspension and de-agglomeration behaviours were evaluated using a real-time particle sizer (Spraytec) and a twin stage impinger (TSI). **Results and discussion**: The Spraytec results indicated that a substantial improvement in de-agglomeration efficiency during the aerosolization could be achieved, with a decrease of D_{50} from 8.1 µm to 5.0 µm for SS and from 7.7 µm to 4.5 µm for SX, after the mechanofusion processing. The fine particle fraction values from the TSI were also increased significantly from 51% to 69% for SS and from 59.9% to 73.1% for SX. **Conclusions**: This study indicated that the aerosolization performance of carrier-free powder formulations can be substantially improved by reducing the intrinsic cohesion of the powder via appropriate particle surface modification.

Keywords: dry powder inhaler; micronized drug; aerosolization; mechanical dry powder coating; magnesium stearate.

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1. Introduction

In a dry powder inhaler (DPI) delivery system, it is commonly regarded that only drug-containing particles with aerodynamic sizes around 5 μm and below can be efficiently delivered into the target sites in the lungs [1]. Such fine particles substantially exist as agglomerates in a bulk powder, due to the strong inter-particle cohesive forces present. This intrinsic cohesive nature contributes to the poor flowability, fluidization and aerosolisation behaviours of such fine powders. This creates problems in handling, transportation, dose accuracy and drug delivery efficiency [2]. It has been shown that intensive mechanical dry coating can substantially change the flow, fluidization and dispersion behaviours of model fine lactose powders [3]. With a view to using with or without such carriers, the aim of this paper is to further investigate the effect of dry coating on the formulation performance of two model drug powders, one is hydrophobic and tabular in shape (SX) and the other is hydrophilic and elongated in shape (SS).

2. Experimental Section

Micronized drug powders, salbutamol sulphate (SS) (Cambrex Profarmaco) and salmeterol xinafoate (SX) (GSK) were coated with 5% w/w of magnesium stearate (MgSt), using an AMS-mini "mechanofusion" processor (Hosokawa Micron Corporation). Morphology of lactose samples was investigated using SEM. Mean tap densities were also evaluated (n=4). The cohesion of each sample was characterized using the Freeman FT4 system in its shear module (Freeman Technology).

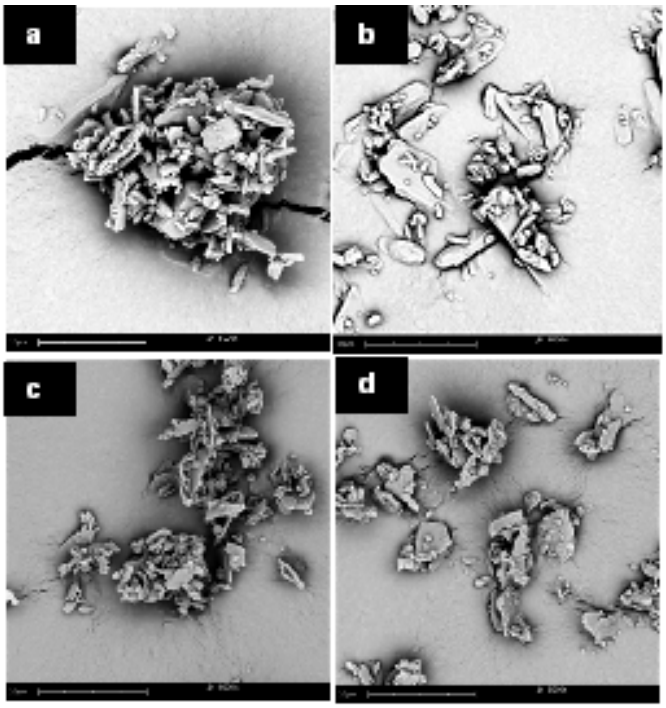
Powder aerosolization behaviour was evaluated using a real-time particle sizer (Spraytec, Malvern Instruments). 10 mg of each powder was loaded into capsules and was aerosolized using a Monodose inhaler (Miat S.p.A.) at 60 L/min. Median particle size (VMD) was measured using the Spraytec. *In vitro* performance was evaluated using a TSI under equivalent conditions. The fine particle fraction (FPF) was calculated.

3. Results and Discussion

3.1 SEM

No apparent shape or size changes were observed after mechanofusion. The SS particles exhibited an elongated shape while SX exhibited a tabular shape. The mechanofused powders were less agglomerated than the unprocessed drug powders (Fig 1).

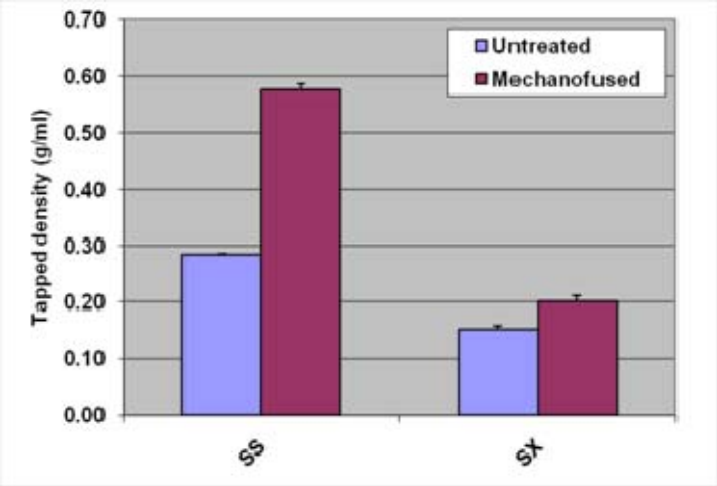
Figure 1 SEM micrographs of (a) SS untreated; (b) SS mechanofused; (c) SX untreated; (e) SX mechanofused.



3.2 Powder Densities

Fig 2 showed that the tapped densities of the mechanofused powders for both drugs were higher than the untreated batches. The increases in densities after mechanofusion were less for SX than for SS.

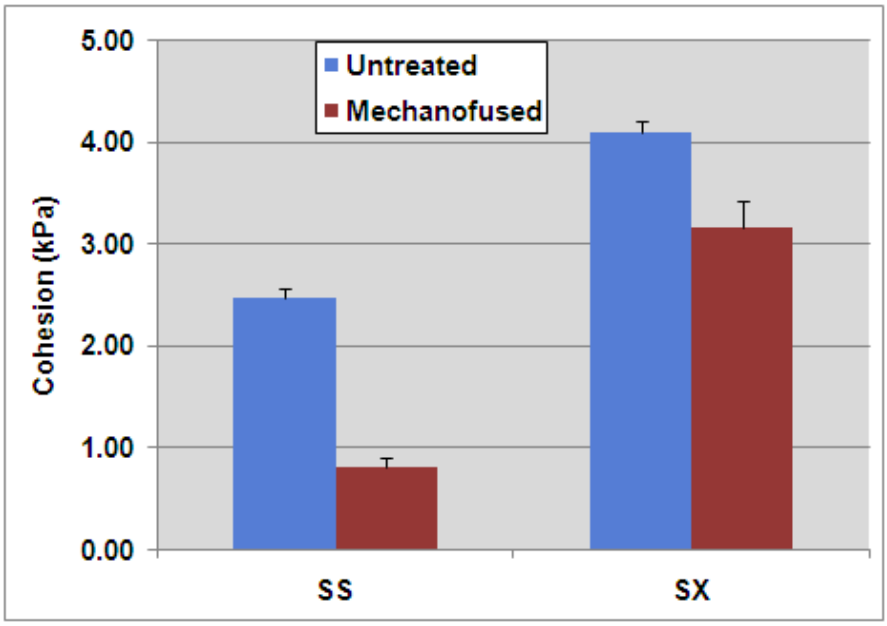
Figure 2 Tapped densities.



3.3 Shear Tests

Fig 3 showed that after mechanofusion, cohesion values of both drug powders were significantly reduced, demonstrating that surface modification contributed to the reduction in cohesion. The reduction in cohesion for SS was observed to be less than for SX: this indicated that surface modification may be influenced by particle shape.

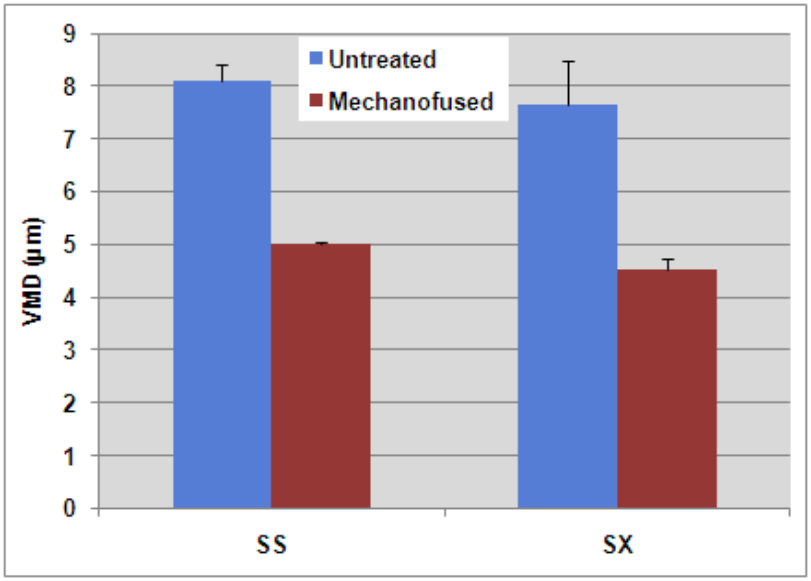
Figure 3 Cohesion results from shear cell test.



3.4 Powder Dispersion

Fig 4 showed that after mechanofusion processing, the drug powders were better dispersed than the untreated batches.

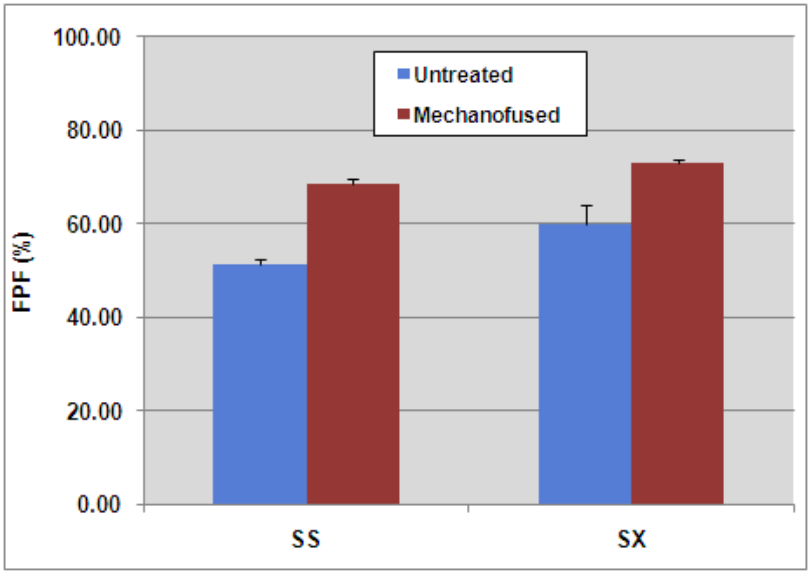
Figure 4 VMD of the aerosolized drug powders from Spraytec.



3.5 Twin stage impinger

After mechanofusion, the aerosolization performance of both drug powders were substantially improved (Fig 5). The improvement of the aerosol performance for both model drugs after mechanofusion can be attributed to the reduction in cohesive forces.

Figure 5 TSI *In vitro* results.



4. Conclusions

This work indicated that a substantial improvement in aerosolization behaviours could be achieved for the two model micronized drug powders used here by appropriate surface modification, and in isolation of carriers. Evidence of the modification of inter-particulate interactions is further provided by changes in the bulk densities and results from shear testing. It also suggests that the coating efficiency or coating effects may be dependent on particle properties such as shape or size. This work will be extended by examining the detailed relationship between the bulk powder behaviours using powder shear and rheometry methodology, and the formulation performance, with the aim to better understanding the relationship between fundamental powder properties and the aerosolization performance of formulations with or without carriers.

References and Notes

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