

Investigation of Fundamental Powder Flow Properties of Fine Lactose Particles Following Mechanical Surface Modification

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Summary

It is crucial for dry powder inhaler formulations to exhibit satisfactory powder flow during production and administration. In this study, fine lactose carrier particles were modified by dry coating to alter their interparticulate interactions therefore improve their powder flow. Six lactose samples with different size fractions were coated either with colloidal silica or magnesium stearate using either a mechanofusion processor or a conventional mixer. Powder flow behaviours were characterized using bulk densities and powder rheology methods. The greatest improvement in powder flow was obtained after mechanofusion treatment with magnesium stearate, as determined by both methods. Changes were the most significant for particles with mean size ranges 8-20 μm . Powder rheometry appeared to have strong potential in optimising powder flow for future studies.

Introduction

Powder flow properties are of prime concern when developing and producing dry powder inhaler formulations (DPI) in pharmaceutical industries (1). In most cases, carriers with primary particle sizes arranging from 60 to 150 μm are incorporated to improve the flow of cohesive micronized drug. It has been reported that binary formulations using carriers with smaller particle sizes have better delivery performance compared with those using larger carriers (2). Also, many researchers indicate that adding fine additives with particle sizes of 5-10 μm into a binary formulation markedly alter the net adhesive forces experienced by the drug, and thus improved drug delivery efficiency (3). However, it is also well known that both reducing the carrier size and adding increased fine additives will result in poorer flow of the formulation (1). In a recent paper, Price et al also suggested a mechanism by which altered flow by addition of fines might improve performance (4). Thus, such aspects are highly complex, with only specific device-formulation being well characterised, and this is often limited to an empirical understanding. Despite this, in general terms it could be anticipated that there might be an advantage to generating carriers with smaller particle sizes, but which also exhibit good powder flow, and we have shown some indication of this recently (5).

Dry coating techniques are widely used to modify particulate interactions and improve the flow of cohesive powders. In general, dry coating is simpler, cheaper, safer and more environment-friendly than solvent-based alternatives (6). Mechanofusion is a recently developed dry coating approach that has gained interest for particle and powder modification (7).

The flow behaviour of DPI formulations has been examined using several methods (1, 8). Bulk densities have been widely used for evaluating flow characteristics of cohesive powders. Recently, a novel powder rheometer system has been successfully developed to evaluate powder flow by measuring their powder rheological properties. It has been found that rheological properties of powders are intrinsically associated with their flow behaviours and it can provide a very effective tool for characterizing powder flow (9).

In this study, a series of model fine lactose particles were dry coated with colloidal silica and magnesium stearate via mechanofusion. The initial characterisation of some flow properties of these lactose powders was conducted looking at bulk densities and selected powder rheological methods. This paper reports our initial findings in this area, and represents the start of a larger study to characterise relationships between surface modification, powder rheology and its characterisation, and formulation design for dry powder inhalers.

Materials and methods

Six commercially-available fine milled lactose samples were studied: Respitose MC001 (DMV), Lactohale LH 300 (Domo), Sorbolac 400 (Meggler), Pharmatose 450M, Pharmatose 350M, and Pharmatose 200M (DMV). The powders were coated with an estimated minimum (5%, 2%, 2%, 1%, 1% and 0.5% respectively) of magnesium stearate (MgSt) (Mallinckrodt Chemicals) and colloidal silica (Cabosil, Cabot Co.), using a Nobilta-130 (Hosokawa Micron Corporation, Japan) "mechanofusion" processor. All samples were also mixed with the same additive material using a conventional tumbling mixer (Turbular, Glen Mills Inc.) at the same concentration as for the mechanofusion batch. Volume median diameters (VMD) were also determined (n=3) using a Mastersizer "S" (Malvern Instruments, UK). Mean bulk aerated and tap densities were evaluated (n=5) in a calibrated measuring

cylinder. Aerated density was determined by pouring the powder via funnel immediately above and into the measuring cylinder. Tap density was determined using a tapping machine (Autotap, Quantachrome Instruments) by standard tap procedure until no further compaction was obtained. Hausner ratio values (HR) were calculated based on densities.

Powder rheological properties have been characterized using a Freeman FT4 rheometer (Freeman Technology, UK). For the currently reported study, the rheometer operating principle was to force a twisted blade along a helical path through a powder sample so that a required flow rate and pattern of flow is established. The forces causing the deformation and flow of the powder are those imposed by the moving blade and these are measured continuously and used as the basis of the flowability assessment. Specific energy (SE) is then defined and determined as the energy per mass needed to displace a conditioned powder using a gentle shearing and lifting mode of displacement. Higher SE values can then be used as an indication of poorer powder flow.

Results and discussion

The average aerated density, tapped density, and HR results as function of VMD are shown in Figures.1, 2, and 3 respectively (error bars represented 2 standard deviations). For samples mixed and mechanofused with Cabosil, it was interesting to note that very little changes in densities and HR were found for the more cohesive powders of Respirose MC001, Lactohale LH 300, and Sorbolac 400. Changes from untreated powder increased as the particle sizes increased.

Markedly increased densities and HR values were observed for all lactose samples after mechanofusion treatment with MgSt. However, virtually no changes from untreated powder for any of the size distributions or measured parameters were found after tumbling mixing with MgSt. This indicates that after mechanofusion treatment with MgSt, flow of cohesive lactose powders are changed dramatically while suggesting that conventional tumbling mixing with lubricants would not modify the flow behavior of lactose powders involved in this study.

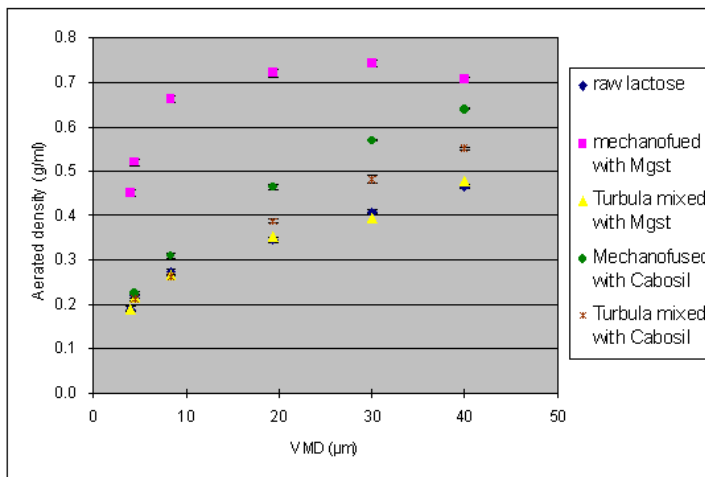


Figure 1. Aerated density results of untreated and processed lactose samples

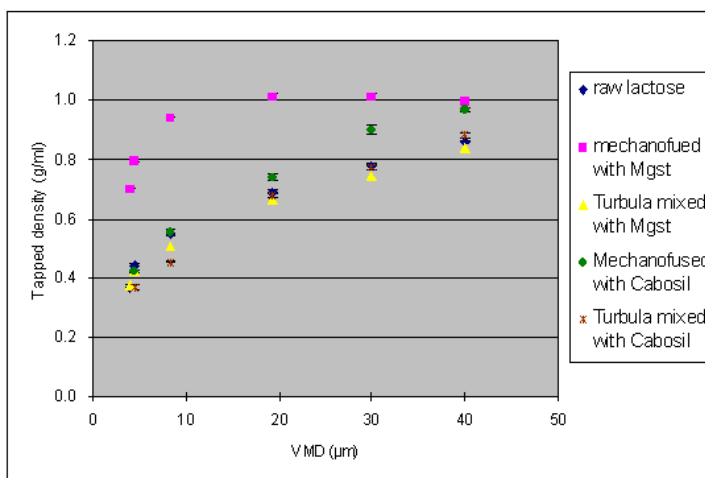


Figure 2. Tapped density results of untreated and processed lactose samples

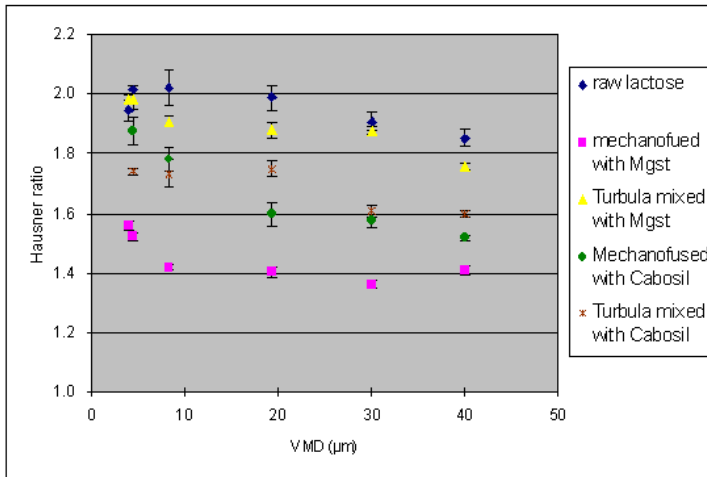


Figure 3. HR results of untreated and processed lactose samples

The greatest changes in densities and HR values after mechanofusion treatment are found for Sorbalac 400 and Pharmatose 450M, which have VMD of approximately 8 and 19 µm, respectively. This suggested that fine particles with median sizes around 8-20 µm have properties of specific interest in the context of our study, and deserved further examination.

We considered it very interesting to observe that greater powder change is achieved for the mechanofused batches with MgSt than with colloidal silica. This study indicated that mechanofusion treatment with lamellar type lubricants enabled greater improvement in powder flow than seen for adding traditional glidants, for such fine particles with sizes smaller than 30 µm. We can conclude that the coating principles are different for families of lubricants and glidants during the mechanofusion process, and believe this finding deserves further investigation. In future studies we want to examine the mechanism of coating and the chemical and physical structure of formed surfaces, in order to relate to resulting powder flow.

Sorbalac 400 and Pharmatose 450M samples of untreated, mixed and mechanofused with MgSt were then chosen for specific powder rheological evaluation, using the rheometer. SE values in Figure 4 showed that much less energy was required for mechanofused powder to be moved by the rheometer blade than the untreated batch, which indicated better powder flow after the mechanofusion treatment. However, we noted that subtle decreases in SE were shown after conventional mixing with MgSt, which were not detected by density data.

We also note from the rheology results that test repeatability of the mechanofused samples is much better than that of untreated and mixed batches, represented by smaller standard deviation. This good repeatability may contribute to the homogenous powder bed structure for high density or good flow powders such as mechanofused lactose samples.

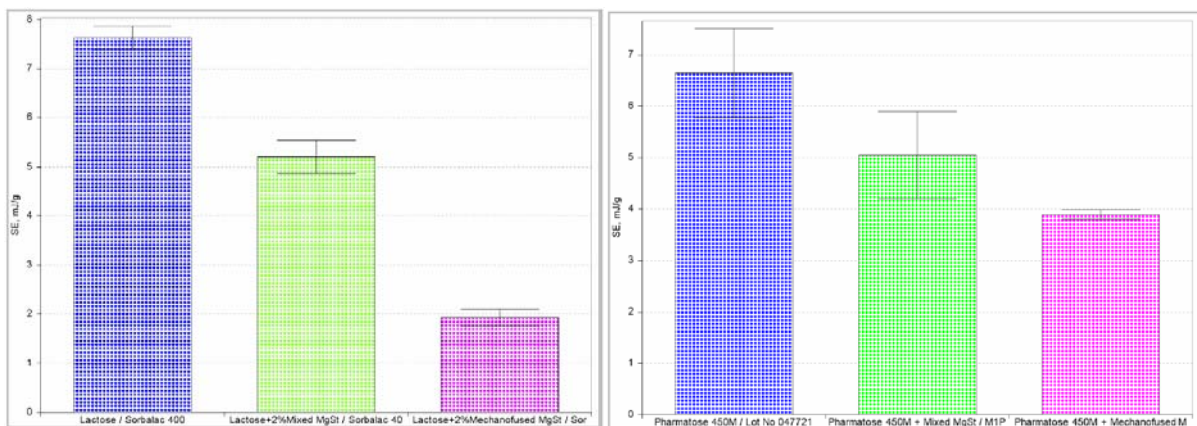


Figure 4. Powder rheological property of untreated, mixed and mechanofused lactose samples.

Conclusions

Significant changes in powder flow indicators were observed for cohesive lactose powders with specific size ranges after appropriate surface treatment using mechanofusion technique. Changes in densities and HR values are notably in the median size region from about 8 to 20 μm . We observed large differences between traditional lubricant and glidants used, as well as a much greater change when a mechanofusion approach is used. These aspects demand further study.

The FT4 Rheometer provided some similar patterns in change to the powders compared to the density based methods, but this work indicated that powder rheometry may offer access to more subtle aspects of powder flow. These powders will now be studied in greater detail using the FT4 rheometer, in order to derive parameters with the aim to help predict both flow behaviour, and aerosolisation behaviour in inhaler devices.

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References

1. Thalberg, K., Lindholm, D., & Axelsson, A. (2004). Comparison of different flowability tests for powders for inhalation. *Powder Technology*, 146(3), 206-213.
2. Zeng, X. M., Martin, G. P., Marriott, C., & Pritchard, J. (2000). The effects of carrier size and morphology on the dispersion of salbutamol sulphate after aerosolization at different flow rates. *Journal of Pharmacy and Pharmacology*, 52(10), 1211-1221.
3. Jones, M. D., & Price, R. (2006). The influence of fine excipient particles on the performance of carrier-based dry powder inhalation formulations. *Pharmaceutical Research*, 23(8), 1665-1674.
4. Shur, J., Harris, H., Jones, M. D., Kaerger, J. S., & Price, R. (2008). The role of fines in the modification of the fluidization and dispersion mechanism within dry powder inhaler formulations. *Pharmaceutical Research*, 25(7), 1631-1640.
5. Morton, D. A. V., Stewart, P. J., & Zhou, Q. (2008). Investigating the flow modification of fine lactose carrier particles. *Proceeding of Respiratory Drug Delivery 2008, Scottsdale, USA*, pp. 655-659.
6. Bose, S., & Bogner, R. H. (2007). Solventless pharmaceutical coating processes: A review. *Pharmaceutical Development and Technology*, 12(2), 115-131.
7. Pfeffer, R., Dave, R. N., Wei, D. G., & Ramlakhan, M. (2001). Synthesis of engineered particulates with tailored properties using dry particle coating. *Powder Technology*, 117(1-2), 40-67.
8. Iida, K., Hayakawa, Y., Okamoto, H., Danjo, K., and Leuenberger, H. (2001). Evaluation of flow properties of dry powder inhalation of salbutamol sulfate with lactose carrier. *Chemical & Pharmaceutical Bulletin*. 49(10), 1326-1330.
9. Freeman R. (2007). Measuring the flow properties of consolidated, conditioned and aerated powders - A comparative study using a powder rheometer and a rotational shear cell. *Powder Technology*, 174(1-2), 25-33.