Investigating Blend Relaxation Effects on Lactose Blends Produced Using a High Shear Process

Andrew Edwards*, John Murphy, Barry Aldous,
Jordan Cheyne, Rachel Brody and Ljiljana Harding

Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent, CT13 9NJ
*School of Life Sciences, University of Hertfordshire, Hatfield, Hertfordshire, AL10 9AB

Summary
High shear blending may induce particle damage, generation of intrinsic fines and subsequent material relaxation, thus causing variable and uncontrollable product performance. Here we examine these effects using an array of powder characterisation techniques. A decrease in surface energy and powder flow was noted over time. Similarly, aeration measurements showed a change in the energy profile, which corresponded with a decrease in Fine Particle Dose when lactose blends were rested prior to blending with drug. The study highlighted the effects of storage on the physical properties of blends. An attempt has been made to identify a set of predictive tools that would enable fast assessment of formulation properties. Whilst high-energy processing remains an industry standard, the effects it may introduce must be understood and controlled.

Introduction
The performance of an inhaled drug formulation will depend on a number of factors, amongst which the blending energy plays an important role. Despite the fact that the high shear energy process being the industry standard, the vast majority of publications describe formulations where low shear blending processes were employed [1, 2]. It is suggested that the use of high shear blending processes can improve dispersion of fine materials, and hence can exert a beneficial effect on dose content uniformity. Conversely, a high shear energy blending process may damage particles thus generating intrinsic fines and/or inducing high-energy sites that can affect the formulation properties. Furthermore, blends manufactured using a high shear process are likely to change over time as material “relaxation” occurs, thus causing variable formulation performance. By relaxation we consider any change in physico-chemical properties of blends on storage.

Aims and objectives
It is not yet clearly known which formulation properties are susceptible to change upon high-energy blending processes. It is the purpose of this investigation to examine these effects using an array of powder characterisation techniques. Furthermore, an attempt has been made to identify a set of predictive tools that would enable fast assessment of formulation properties. More specifically, the surface energy of blends, powder aeration and flow were assessed in the study. Near-infrared (NIR) spectroscopy was also used to detect blend relaxation effects. The results are compared with *in-vitro* aerosolisation performance data generated using Next Generation Impactors (NGIs). Unless otherwise stated, measurements were performed at the initial time point, then after 2 and 4 weeks of blend storage at ambient conditions.

Results and discussion
α-Lactose monohydrate was used to produce test samples. Fine (D50 8μm) and coarse (D50 61 μm) lactose grades were blended in 25/75 fine/coarse ratio. Interactive mixtures were prepared using a Turbula T2F low shear mixer or a Diosna P1/6 high shear mixer/granulator. Low shear blends were manufactured in a 0.5L stainless steel tub by mixing at 46 rpm for 10 minutes. High shear blends were manufactured in a 0.5L bowl by mixing at 1500 rpm for 5 minutes. Blends containing active pharmaceutical ingredient were prepared in order to assess the impact of blend relaxation on drug product performance. Drug A (1% w/w) and 25/75 fine/coarse lactose pre-blend were blended in a Diosna P1/6 blender/granulator. The material was mixed for 5 minutes at 400rpm (no chopper action) using a 0.5L stainless steel bowl. All blends were produced in 150 g quantities.

Surface energy measurements were conducted using Inverse Gas Chromatography (iGC, Surface Measurement Systems, Middlesex, UK). Three replicates were performed per time point at 10 cm^3/min and 303.15K. 1,4-Dioxane, ethanol, acetone, acetonitrile, nonane, octane, heptane and hexane were used as probes. Initial surface energy measured as 45.94 +/- 0.08 mJ/m^2 , seem to drop slightly after 2 week storage to 43.85 +/- 1.39 mJ/m^2. A further smaller drop to 42.75 +/- 0.21 mJ/m^2 was observed after 4 week storage.

NIR spectroscopy measurements were acquired using a Bruker MPA FT-NIR spectrometer. Spectra were collected in reflectance mode between 9994 - 4000 cm^{-1} with a resolution of 8 cm^{-1} and 32 scans. NIR spectra revealed a change in absorbance in the 5540-5100 cm^{-1} and 7500-7100 cm^{-1} regions over time (the spectra having been pre-treated with multiplicative scatter correction to remove the baseline off-set). The two areas of the spectra are associated with water (first overtone of the -OH stretch and -OH deformation combination bands). The spectra demonstrate a decrease in absorbance in these regions over time.

Powder flow testing was conducted using a ring shear tester RST-XS (Dietmar Schulze Schuttgutmesstechnik, Germany). The flow function coefficient (FFC) was measured at 1000 Pa and 4000 Pa pre-shear loads in duplicate with medium cell at ambient conditions. A decrease in the FFC values from 1.85 to 1.6 and from 3.1 to 2.5 over a period of 4 weeks was noted when measured at 1000 Pa and 4000 Pa, respectively.

The FT4 Powder Rheometer (Freeman Technology,Welland, UK) was used to determine flow behaviour at both constant and variable flow rate. A 25 mL of sample powder was analysed in a 35 mm borosilicate split glass cylinder. The samples were conditioned prior to each measurement to remove any effect from sample packing and ensure a homogenous sample prior to measurement. A 23.5 mm blade was moved down a helical path at a velocity of 100 mm/s and the energy required to move the powder was measured as the Basic Flow Energy (BFE; energy required to displace a conditioned powder). This was repeated for seven identical tests to give the Stability Index and then followed by four tests at reducing blade speed. Both the high and low shear blends were analysed twice a week for a period of 4 weeks. The low shear blends had BFE values which showed a general increase over the 4 week time period from 172-199 mJ. The high shear blends had generally lower initial BFE values which did increase over time (from 137-192 mJ) to give values similar to the low shear blends. Differences in the Flow Rate index was also identified between the high and low shear blends indicating that the powders have different response to a change in tip speed.

Additionally, the FT4 Powder Rheometer was used to assess permeability of powders to airflow and resistance to aeration. Aeration measurements were performed by passing air through a sintered vessel base and measuring the BFE whilst the powder is aerated to a set air velocity. Air velocities of 0 to 5 mm/s (in 0.5 mm/s increments), with the powder becoming fluidised at 5 mm/s. Between 0-2 mm/s air velocity, the BFE was larger for the low shear blends indicating more energy required to move the powder. There was also more change in the high shear blends over time, where the energy values increased after 2 weeks to be similar to the initial low shear blend result and then decreased again at the 4 week test. The change in tensile strength of the powder is likely to affect aerosolisation performance as the lowering of aerodynamic drag forces could reduce particle detachment and hence result in a decrease in Fine Particle Dose (FPD) [3]. Indeed, NGI testing of blends at 60 L/min revealed a reduction in FPD values from 45 to 35 µg when lactose pre-blends were allowed to rest prior to blending with drug.

Conclusion

The study highlighted the effects of storage on the physical properties of high shear dry powder inhaler blends. Furthermore, a set of measuring techniques is identified that could serve as predictive tools for rapid evaluation of powder blends. Whilst high-energy processing remains an industry standard, the variability that it may introduce into drug products must be understood and controlled.

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2. Zeng, X.M., et al., *Effects of particle size and adding sequence of fine lactose on the deposition of salbutamol sulphate from a dry powder formulation.* International Journal of Pharmaceutics, 1999. **182**(2): p. 133-144.
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