Fluidised Powder Blending to Control Particle-Particle Interaction – The Future of DPI Formulation

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Summary

Traditional blending processes for dry powder inhaler (DPI) manufacture involve use of equipment that relies upon the solid-solid mixing of powders to deagglomerate and disperse cohesive micronised active pharmaceutical ingredients (APIs) onto the surface of coarser carrier particles, which often generate mechanical shear and are generally inefficient. Researchers at Aston University have developed a novel dry coating process which avoids the limitations of solid-solid blending by micro-fluidising powders held at the surface of a rotating chamber by a strong centrifugal field (high G) through the application of a nitrogen air-blade. Cohesive API is dispersed into primary particles in the fluidised state and coated onto the surface of much larger co-fluidised lactose particles. In a model study, cohesive micronised Rhodamine B was coated onto an inhalation grade lactose to mimic a typical DPI formulation. Blends were manufactured under a range of different processing conditions and the time course of the coating process was studied using confocal microscopy and scanning electron microscopy. This work exposed the nature of the coating process and the transitions through which the fine particles pass to achieve efficient coating. In a further study, a genuine DPI formulation, micronised fluticasone propionate was coated onto lactose (at 0.71%$^{w}/_{w}$) following a design of experiment scheme. The results demonstrate how the technology can control the formulation of DPI blends through manipulation the three process parameters; process speed, air-flow rate and process time. Two-dimensional response maps at set processing times were constructed highlighting how the critical process parameters of the novel methodology control two blend responses, content uniformity and fine particle fraction performance, and illuminate a standard to which DPI performance of the future might be designed and controlled.

Key Message

Particle micro-fluidisation through the novel dry coating process produces consistent dispersion of the API/carrier system to primary particles and delivers concise deposition of API onto the lactose carrier. This results in a controlled DPI formulation process with exquisite control of the critical quality attributes of the resultant blend.

Introduction

DPI formulations are dispersions of fine API particles in carefully engineered coarser inhalation grade lactoses (IGLs) originally added to the formulation to bulk up the dose to facilitate the dispensing of highly potent APIs. It was soon discovered that coating fine API onto carefully selected lactose carriers could enhance aerosolisation [1]. IGLs are typically chemically pure grades of alpha-lactose monohydrate with highly specialised particle size distributions but, despite more than 40 years of research and development, the performance of passive DPI formulations remains poor. Much research has been executed to understand the coating of fine particles on carriers. When fine (guest) particles are coated onto the surface of coarser (host) particles, composite particles result with enhanced properties different from those of the individual particles [2,3]. Current state of the art DPI blending mechanisms, such as high shear blending and turbula mixing, utilise solid-solid interaction between the constituent particles and the physical components of the mixing equipment to disperse API over the carrier to deliver an acceptable aerosol performance [2]. The link between aerosol performance of individual API/lactose systems and the manufacturing process is often poorly understood, which drives a trial and error approach to batch manufacture, with poorly predictable outcomes. Current practice in the formulation of DPIs is to seek to maximise the aerosol performance, by enhancing fine particle fraction (FPF). This is often achieved by the incorporation of fine material into the formulation (termed ternary formulations) either as a fine percentage of the lactose carrier or of other compounds such as magnesium stearate or leucine, known as force control agents. The latter dampen high energy sites on the lactose carrier prior to blending with the API, which results in higher percentages of the API being removable from the carrier during aerosolisation[3]. Additional components in the formulation add further unpredictability to nature of the blending process.

A theoretical picture of the dry particle coating process is relatively simple to deliver schematically. It has been described as follows [4]: (1) deagglomeration of fine guest particles into individual particles; (2) attachment of the individual guest particles onto the host particle surface in close proximity; and (3) - redistribution/rearrangement of the fines between already coated and non-coated host particle surfaces to attain an even distribution of guest on host particles. This is presented in Figure 1.

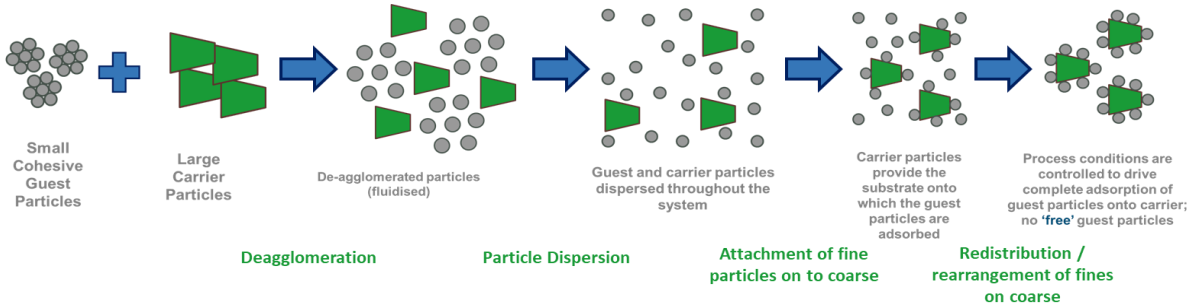

Figure 1: A schematic dry particle coating process

In DPI formulation the critical step in this process is the complete separation of any agglomerated API particles into primary particles. The API primary particles will have been engineered to be in the respirable size range (0.5 – 5 µm) so delivery of a respirable dose requires that the API is formulated and maintained as individual particles. If this level of dispersion is achieved the efficiency of the other two steps in the coating process will also be enhanced. The purpose of this study is to demonstrate that the unique dry particle coating process developed at Aston [5], achieves all 3 steps in the coating process.

The unique dry coating process utilises rotation to generate a centrifugal force at the surface of a chamber which is continuously swept by a dry nitrogen gas air-blade. Powders inside the chamber are forced to this surface during processing. The centrifugal force and the sweeping air-blade cause disruption of any agglomerates in the powder into primary particles. Pockets of micro-fluidisation are formed at the surface in which the fine particles come into contact with the larger particles and are adsorbed. In effect the fine particles are mopped up by the larger particles. Since there is very low shear in the system and little energy is generated by collisions of particles near the surface of the chamber, the coating process occurs at ambient temperature. No increase in temperature is observed during processing due to the significantly reduced solid-solid interactions when compared with a typical blender and the absence of physical attrition. This is mediated through the relatively small set of critical process parameters (CPP) utilised by the process, and it is the intimate control of these CPP's which provides controlled fluidisation and blending of the DPI formulations. The key objective of this work was to investigate the fluidisation principle using a model system and then to show how this can be applied to the controlled manufacture of a real DPI formulation.

Experimental Methods

Materials

Rhodamine B Micronised (VMD – 6.27 ± 0.45 µm) (Sigma-Aldrich, Dorset, UK) used as a model guest cohesive material (utilised for fluorescent nature and resolution under confocal microscopy (CLSM)). Alpha-Lactose Monohydrate (Inhalac 251™ (Meggle, Wasserburg Am Inn, Germany) IGL (non-fluorescent). Fluticasone Propionate (FP) Micronised (VMD 3.22± 0.02 µm) (Discovery Fine Chemicals, Wimborne, UK)

Methods

Model Study: An APT benchtop dry particle coater was used to manufacture 10 g batches of 0.5%$^{w}/_{w}$ rhodamine /IGL powder blend. The coater was operated at 201 G, at 3 different air-flows (0 l/min, 25 l/min and 50 l/min). Blend processing times were varied from 4 to 28 minutes (at 4-minute intervals). CLSM (Leica Microsystems Confocal Microscope TCS SP5 II, 10X dry objective lens - images were obtained between 528-560nm) was used to determine the state of dispersion of rhodamine particles. The blends were also analysed by scanning electron microscopy to visualise the coating of the rhodamine particles attached to the lactose surface.

FP study: A D-optimal design of experiments (DoE) was conducted using FP (0.71%$^{w}/_{w}$) in the IGL and MODDE 10 software was used to design and assess the model. Manufacture of the formulations was conducted using an APT pilot scale dry particle coater, with 500 g batch sizes. Each of the FP blends was tested for content uniformity of 10 micro-samples and the aerosol particle size distribution from a capsule based delivery system (Aerolizer™) incorporating a notional dose of the blended material was measured. The doses were manually filled into size 3 gelatin capsules and tested using a Next Generation Impactor (NGI - Copley Instruments, UK) at 60 l/min.

Results and Discussion

Samples from the model blends containing Rhodamine B were analysed by Confocal Laser Scanning Microscopy (CLSM) and Scanning Electron Microscopy (SEM). CLSM has a major advantage in that the position of the adsorbed rhodamine particles can clearly be identified in the images, and fluorescent image intensity of these particles is a measure of their state of dispersion whether present as agglomerates or primary particles. Figures 2A, B and C present images of powders blended for 4 mins at 0 l/min, 25 l/min and 50 l/min fluidising air-flow respectively. At this short processing time, the adsorbed rhodamine still contains agglomerates at all airflow rates even though at the highest flow rate, the lactose particles have already adsorbed a significant coating of fine particles. At the longer blending time of 20 minutes the agglomerates have completely disappeared and an excellent degree of coating has occurred (the images presented in 2D, E and F). This is true even when no fluidising air-flow was applied.

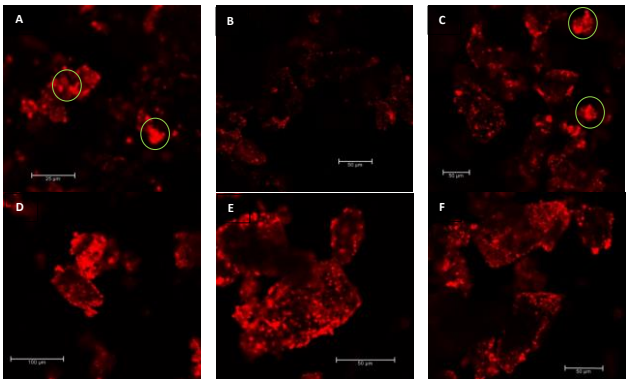

Figure 2: CLSM images of Rhodamine B dry coated at 201 G onto IGL

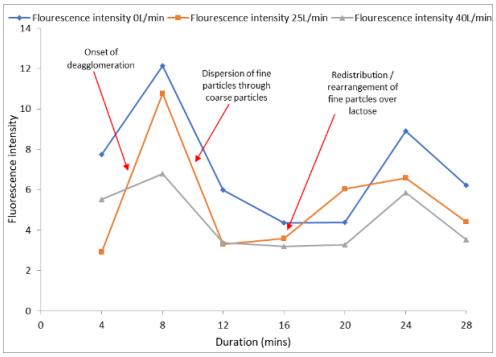

Figure 3: Fluorescence Intensity as a function of processing time

This demonstrates that if the centrifugal force is applied for sufficient time even without the air-blade, the cohesive rhodamine will be reduced to primary particles. With increasing airflow rate, the coating builds up faster due to more rapid and efficient deagglomeration of the fine material through the micro-fluidisation mechanism. A fuller analysis of the intensity of the CLSM images is shown in Figure 3. The variation in fluorescence intensity clearly shows three phases of coating, independent of the fluidising air-flow rates investigated. A first phase, at short processing duration up to 8 minutes, shows a fluorescence intensity maximum most pronounced at low airflow rates. This suggests that although the coating process has commenced many of the rhodamine particles are present as agglomerates. This effect is less pronounced at the highest air-flow perhaps an indication that the presence of agglomerates is less pronounced under these conditions. At intermediate processing times, the fluorescence intensity decreases to a plateau value which suggests that the bulk of the particles have been reduced to primary particle size and are adsorbed onto the carrier particles. At the longest process times investigated, a 2nd peak in fluorescent intensity is seen which suggests that the adsorbed particles are once again in close proximity to each other on the surface. This phase could reflect a re-ordering of the particles on the surface and also that the coating is now becoming more coherent. At the longest process times investigated the intensity has again diminished which suggests that the adsorbed layer has obtained a new equilibrium. A further image analysis of the rhodamine coating at this intermediate processing time is presented in the scanning electron micrographs of Figure 4.

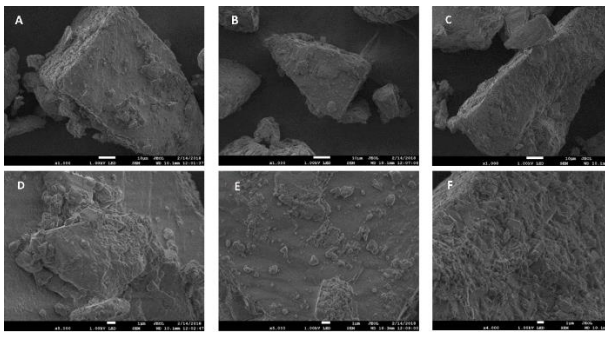

Figure 4: SEM images rhodamine coated lactose (16 minutes processing time) at fluidising airflows (A 0 l/min, B 25 l/min and C 50 l/min airflow at 1000x magnification and D, E, F at the same respective air-flows at 5000x magnification

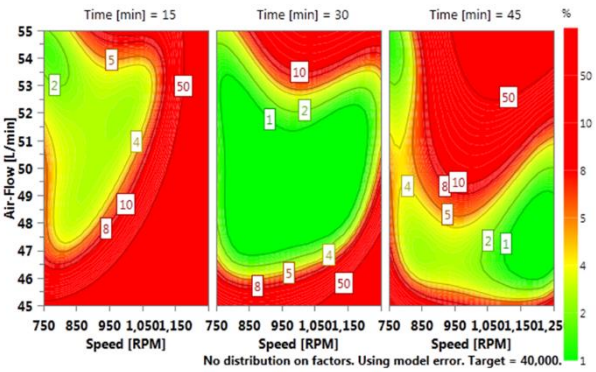

Figure 5: Design space generation using the pilot scale dry particle coating equipment with FP (0.71%$^{w}/_{w}$)

By contrast to the CLSM images, the state of the adsorbed particles shown in the SEM images can only be discerned by changes in monochrome topography. Nevertheless, agglomerates of rhodamine particles are clearly visible on the surface of the IGL in the blend prepared without fluidising air whereas the other samples show the

adsorbed rhodamine as discrete particles. Another important observation in all the images is that all the fine particles are attached to the larger carrier particles, which is evidence that the process causes the carrier particles to 'mop-up' both fine rhodamine particles and the fines from the IGL. Each of the above observations is qualitative in nature and was made with a model cohesive material that had a particle size distribution only barely reflective of a typical respiratory API, so in a second suite of experiments, a commercially sourced API was used to generate quantitative data representative of a true DPI.

The formulation of a commercially available API, fluticasone propionate, at 0.71%$^{w}/_{w}$ was chosen to mimic a product designed to deliver 100 µg/dose with a commercially available grade of IGL, the same grade used in the rhodamine study. The study was deliberately carried out at larger scale (500 g batch size) to be more representative of the scale of batches that might be routinely expected/used in formulation development and product scale up. The seventeen randomized manufacturing runs were performed to investigate whether the new process could be modelled against two chosen responses, critical quality attributes, that would demonstrate how well the new process could control particle-particle interactions in a DPI formulation. With his in mind, content uniformity of the blends and fine particle fraction (FPF) performance of samples from the blends when dispensed via a unit dose capsule-based inhaler were the chosen response factors.

These factors were measured with representative samples of each blend and a working performance model was created from these data and validated with statistical significance. Results from the DoE demonstrate the ability of the technology to deliver dry powder coating of FP on IGL such that the FPF of all the blends was between 21 - 32% of the nominal dose, whilst also maintaining an excellent homogeneity (<3%RSD). A primary finding of the study was that univariately increasing processing speed resulted in increased FPF performance, indicative of a potential to dial up respirable dose through manipulation of the critical process parameters; process speed, air-flow rate and process time. In addition, it was possible to identify a wide and flexible design space for manufacture the FP formulation at various process times as shown in the two-dimensional response maps (Figure 5). Optimal process control settings can be read from these control maps to ensure that the blend attributes fall within the target product profile. The green area at the centre of the model for 30 minutes processing time, delineated by the probability contours, demonstrates a wide degree of flexibility in the optimum processing parameters. It is likely that routine manufacture of batches of the FP formulation will meet the defined critical quality attributes with very small chance of failure. This the level of control is undoubtedly required for DPI formulations of the future.

Conclusion

Researchers at Aston University have developed a novel dry coating process which avoids the limitations of solid-solid blending by micro-fluidising powders held at the surface of a rotating chamber by a strong centrifugal field (high G) through the application of a nitrogen air-blade. Cohesive API is dispersed into primary particles in the fluidised state and coated onto the surface of much larger co-fluidised lactose particles. In a model study, cohesive micronised Rhodamine B was coated onto an inhalation grade lactose to mimic a typical DPI formulation. Blends were manufactured under a range of different processing conditions and the time course of the coating process was studied using confocal microscopy and scanning electron microscopy. This work exposed the nature of the coating process and the transitions through which the fine particles pass to achieve efficient coating. In a further study, a genuine DPI formulation, micronised fluticasone propionate was coated onto lactose (at 0.71%$^{w}/_{w}$) following a design of experiment scheme. The results demonstrate how the technology can control the formulation of DPI blends through manipulation the three process parameters; process speed, air-flow rate and process time. Two-dimensional response maps at set processing times were constructed highlighting how the critical process parameters of the novel methodology control two blend responses, content uniformity and fine particle fraction performance, and illuminate a standard to which DPI performance of the future might be designed and controlled.

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