Particle engineering by practical and scalable, intensive, mechanical, dry coating processes to develop highly efficient dry powder inhaler formulations

Dry coating may be a promising strategy in DPI development.

Li Qu
Monash University
David A. V. Morton
Monash University
Qi (Tony) Zhou
Purdue University

Limitations of fine particle manufacturing

Although the first decade of the 21st century has seen significant pharmaceutical innovation in producing inhalable aerosol particles, the mainstay industrial manufacturing route has largely remained unchanged over the last 30 years. API particles are crystallized, followed by jet milling, then either agglomerated or mixed with carriers and/or other inert excipients. Jet-milled particles are notoriously problematic; being created in a violent attritional process, they can be extremely cohesive, variable, physically unstable and unpredictable. These cohesive milled powders possess poor flowability and low dispersibility, which cause difficulty in manufacturing and aerosolization.[1] High surface-energy sites on the particle surface are generated during collisions and are recognized as being a primary factor in such undesirable properties.[2]

In practice, carriers are often added to improve flow but may cause even poorer dispersion efficiency as a result of strong adhesion between milled drug particles and carrier surfaces.[3] Marketed carrier-based dry powder inhaler (DPI) products typically have low fine particle fractions in the range of 15-50%.[4] This is highly dependent on the formulation and inhaler device and especially on the user's handling and aerosolization environment. Furthermore, use of a carrier may be limited in high-dose DPI products such as inhaled antibiotics. A large amount of carrier or other excipient present in a formulation inevitably increases the mass and bulk volume of the powder in a single dose, which may make the inhaler larger or increase the number of inhalation maneuvers (i.e., a large single dose may need to be divided into multiple inhalation maneuvers such as with the Tobi® Podhaler™ (Novartis Pharmaceuticals).[5]

Besides a relatively low aerosolization efficiency caused by the cohesive nature of the powder, the consistency of aerosol performance may also be compromised.[6] Typically, the fine particle fraction (FPF) and emitted dose will decrease, sometimes to a substantial extent, after storage.[7] The changes in aerosolization behavior can occur over weeks or even months. While such reduction in FPF upon storage is believed to be associated with contact bridging changes from re-crystallization of the disordered sites on milled particle surfaces, it is important to appreciate that no absolute mechanism for this instability affecting aerosolization has ever been directly proven.[7,8]

Despite this, and on a largely empirical basis, pharmaceutical scientists have made attempts to solve this stability problem, for instance by introducing controlled conditioning processes and storing products for a fixed period of time prior to their deployment to the market. These conditioning periods may last several months and consequently add significant cost to the supply chain. Therefore, a practical, cost effective and efficient process that removes or minimizes the instability, variability and low-efficiency problems of jet-milled particles would be attractive.

Figure 1

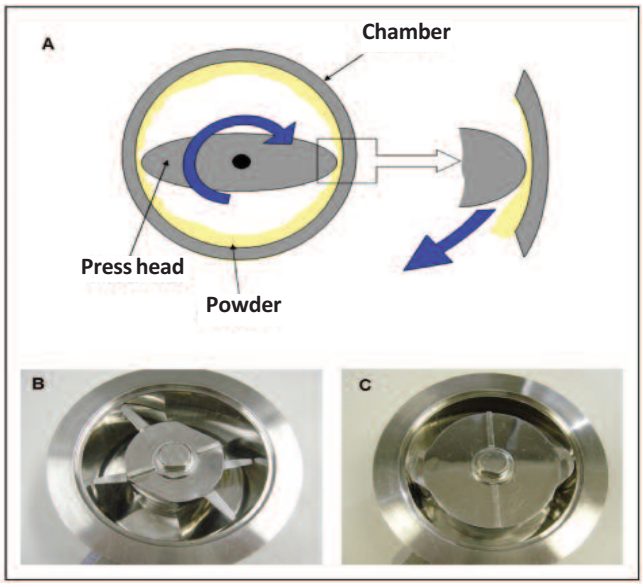

Figure 1. (A) Diagram of dry coating process; (B) Image of mechanofusion AMS-Mini system with a Nobilta processor; (C) Image of mechanofusion AMS-Mini system with a Nanocular processor. Figures B and C are reprinted from reference 29 with permission from Elsevier.

Table 1

	Batch 1	Batch 2	Batch 3
FPF (%)	68.6 ± 1.6	66.4 ± 2.7	67.5 ± 2.1
ED (%)	68.0 ± 1.2	69.2 ± 1.0	67.4 ± 0.7

Table 1. Powder properties of mechanofused salbutamol sulfate from three different batches have shown process reproducibility in fine particle fraction (FPF) and emitted dose (ED). Mean ± SD, n = 4. Data are adopted from reference 15.

Wet coating of particles

One such option is to coat milled particles with a thin (even down to nano-scale) layer of an additive or "force control agent," notably a pharmaceutical lubricant such as magnesium stearate. The aim is to address the stability and low-efficiency issues with one step. The concept is simple: put a ubiquitous, ultra-thin coating onto the cohesive milled particles to make them not only achieve much improved flowability and dispersibility than the uncoated milled particles, but also perform more consistently over the time of storage. Traditionally, pharmaceutical coating has been dominated by wet coating approaches (e.g., using a fluid bed) which have been used extensively to coat much larger particles or pellets. For example, Chan, et al. coated coarse lactose carriers (64 µm) with micronized lactose fine particles (4 µm).[9] However, it is extremely challenging to wet-coat fine inhalable particles with aerodynamic diameters < 5 µm in a relatively scalable and cost effective process.[10] For example, as the consequence of liquid bridging, either the aggregates (rather than the individual particles) are coated or granules are formed. Even at the laboratory scale, success in coating ultra-fine particles is rare and can be associated with inability to scale up.

Dry coating

In contrast, dry coating has proven to be a relatively simple and easy-to-control process, with proven scale-up feasibility in the manufacture of toners and cosmetics and in the powder metallurgy industries. As a single step process, without solvents to handle and remove, dry coating is quicker, safer, lower cost and more environmentally friendly, compared to the solvent-based coating approaches.[11]

After approximately 40 years of development of mechanical dry coating technology, there are several systems available including the Hybridizer (Nara), Magnetically Assisted Impaction Coater (MAIC, New Jersey Institute of Technology), Mechanofusion (Hosokawa Micron) and Theta-Composer (Tokuju).[12] Other equipment such as the high shear mixer Cyclomix® (Hosokawa Micron)[13] and the Quadro® Comil®[14] for co-milling have also been employed to coat cohesive powders. The configurations of various dry coating equipment vary, but the general principles are the same: high-shear and high-energy interactions between particle/particle or particle/device are used to coat the surface of host particles with guest material. For example, the Nanocular mechanofusion system (Hosakawa Micron) comprises a solid circular blade with two semi-circular press heads that compress powders against the internal vessel wall (Figure 1C). Literally, the dry coater is a highly energetic variant of a high-shear mixer, employing maximum surface interactions and minimum milling effects.

The operation of these dry coating systems is relatively simple, involving loading the powder, processing for a set time (often around 5-15 minutes) then unloading the powder. Each process is optimized and validated. Continuous manufacturing is also feasible for some dry coating devices. Studies have shown that batch variation is low (Table 1)[15] and scaled-up bulk properties are comparable between, for example, milled lactose powders coated with a lab-scale mechanofusion system (Nobilta-AMS Mini, powder load up to 0.1 L) and a pilot-scale system (Nobilta-130, powder load up to 0.5 L) (Hosokawa Micron) (Table 2). By comparison, a commercially available mechanofusion system may have a processing capacity of 1,000 L.

Mechanofusion has been the most extensively examined process for inhalation formulations, likely due to its high efficiency and ease of use. Other techniques have also been attempted. For example, co-jet-milling of micronized salbutamol sulfate with magnesium stearate has shown a reduced dispersive surface energy and more homogenous energy distribution.[18]

Table 2

Mechanofusion system	Cohesion (kPa)	Flow Function
Nobilta-AMS Mini (lab scale)	0.36	11.7
Nobilta-130 (pilot scale)	0.47	10.7

Table 2. Shear cell data for coated lactose powders with 1% w/w magnesium stearate using pilot and lab-scale mechanofusion systems. Data are adopted from references 16 and 17.

Theoretically, guest particles should be smaller than those of the host so the guest material (i.e., colloidal silica) can form a layer of fine particles. Alternatively, the guest material is soft and lamellar (i.e., magnesium stearate) so it can be laminated and smeared onto the surface of host particles. Both glidants and lubricants are popular coating materials for oral solid dosage forms. For inhalation purposes, the use of colloidal silica may raise concerns about pulmonary cytotoxicity while magnesium stearate has been accepted as safe for use in inhalation and been approved in several inhalation products (i.e., Pulmicort® CFC-free metered dose inhaler (previously marketed by AstraZeneca) and Foradil® Certihaler® (Novartis)).[19]

Several patent applications describe the problem solving and applied nature of intensive dry coating techniques for inhalable powder formulations.[20-22] Related preliminary work was conducted at Bath University, showing the potential for improving aerosol performance of carrier-based DPI formulations using mechanofusion-based processing.[23,24] A Japanese group also investigated the feasibility of coating a coarse carrier via such a dry coating approach.[25,26] However, a true fundamental understanding of the process and effect of dry coating on aerosolization of coated powder had not been elucidated. Many critical questions remained, notably: What occurs at the particle surface during the coating process? What are the key characteristics of the coating quality and the relationship to bulk behavior?

Studies of dry coating

To address the later question, systematic and mechanistic investigations in the pharmaceutical application of dry coating have been conducted at Monash University, Australia since 2007.

In the first series of studies by the Monash University team, milled lactose monohydrate powders with a size range of 5-100 µm were coated with magnesium stearate. Substantially improved flowability and fluidization were reported for these cohesive powders (from very poor flow to free flow), as measured by both traditional characterization tools of Carr Index and angle of repose, and modern techniques of FT4 powder rheometry.[16,27]

The optimized coating parameters were identified for various milled lactose powders; for example with a D_{50} of 20 µm: 0.5-1% w/w magnesium stearate as a coating material; rotation speed of 3,000 rpm; coating time of 5-10 minutes.[28]

It was found the coating efficiency depends on the host particle size, with the most dramatic improvement in flowability observed in the median particle size range of approximately 7-20 µm for milled lactose powders.[28] Larger lactose particles typically bigger than 40 µm flowed well without coating and ultra-fine lactose particles (i.e., approximately 5 µm and below) were not free-flowing even after coating. Optimized coating parameters are likely dependent on the properties of both host and guest materials.

In subsequent studies, micronized drug particles were coated with magnesium stearate, aiming to engineer DPI powders with improved aerosolization and superior stability. Coating lactose monohydrate particles (D_{50} of 4 µm) with 5% w/w magnesium stearate demonstrates substantial improvement in fluidization and dispersion.[27] Additional model inhalation drugs were also tested, including triamcinolone acetonide, salmeterol xinafoate and salbutamol sulfate.[29] Interestingly, all of the coated drug powders had significantly higher aerosol efficiency but the extent of improvement varied and differences were attributed to the effect of particulate properties (i.e., particle size, shape, surface chemistry, etc.) on coating efficiency.[29]

In a subsequent study, an optimal magnesium stearate concentration was found to be 2% w/w for coating a micronized salbutamol sulfate powder (with a D_{50} of 3 µm).[19] Coating quality measured by x-ray photoelectron spectroscopy (XPS) was shown to have a strong impact on aerosolization.[19] A recent patent application has disclosed the usefulness of dry coating to improve the aerosol performance of high-dose antibiotics.[30] After dry coating of 1% w/w magnesium stearate for 10 minutes, the emitted dose and FPF of a micronized tobramycin powder improved from 71% to 82% (emitted dose) and 33% to 66% (FPF). This opens a new window for design of high dose DPI products with aerosol performance superior to that of traditional jet-milled formulations.

Surface energy of coated powders

The improvements in flowability and dispersibility are attributable to the reduced cohesive forces, as the outcome of decreased free surface energy. Surprisingly, an early study reported that the surface dispersive energy was increased for lactose particles coated with magnesium stearate, as measured by the infinite dilution method of inverse gas chromatography (IGC).[25] These data appeared contradictory to the observed improvements in flowability and dispersibility of coated lactose particles. It was believed that such a contradiction could be due to the limitation of the infinite dilution method of IGC in that it only measures the highest surface energy.[31] To resolve this, a finite dilution method of IGC was employed to measure the distribution and hetero-

Figure 2

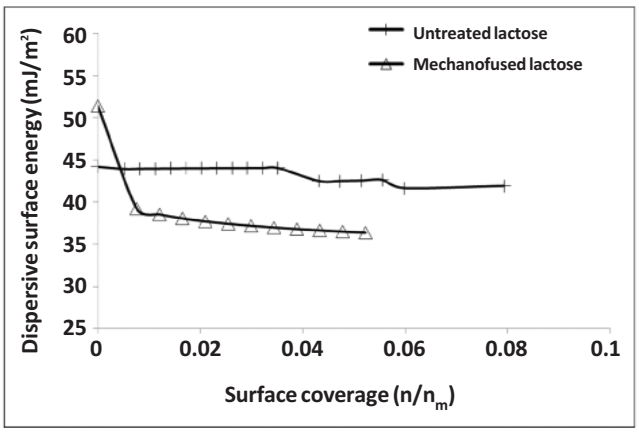

Figure 2. Only less than 1% of the mechanofused lactose particle surface has high dispersive energy; more than 99% of the surface has a lower dispersive energy than that of the milled lactose powder. Reprint from reference 32 with permission from John Wiley and Sons.

geneity of surface energy. This indeed confirmed that the high dispersive surface energy was only detected on a very small surface area of dry-coated particles (< 1%) (Figure 2).[32] These data explain that reduced cohesion and improved flowability are the outcomes of decreased free surface energy by dry coating.

Characterization of coating quality

Characterization of coating quality is crucial to examine the effect of coating on bulk behavior. However, it is very difficult to achieve because of fine particle size, complex shapes and extremely thin coating layers, typically of nanometers. Ideal measurements should have both sufficient sensitivity and high spatial resolution in detecting the low mass of coating material at the uppermost surface. Conventional equipment, such as energy dispersion x-ray spectroscopy (EDXS), has poor spatial resolution. Other techniques, such as Raman spectroscopy, penetrate the coating layer and measure both the coating and host particles.

Recently, the state-of-the-art characterization techniques of time-of-flight secondary ion mass spectrometry (ToF-SIMS) and x-ray photoelectron spectroscopy provide highly sensitive measurements of the surface chemistry of dry-coated particles. Both instruments measure the outermost surface of <10 nm, which ensures the data are confined to the coating layer regions. ToF-SIMS is capable of providing mapping of the coating layer at a spatial resolution down to 20-100 nm. Alternatively, XPS offers a more quantitative measurement of surface coating coverage.[33-35] By combining the data obtained with these two powerful tools, for the first time, both qualitative and quantitative characterizations of ultra-thin coating layers on fine particles have been achieved and the correlation between coating quality and bulk behavior has been established.[17, 19, 32]

Figure 3

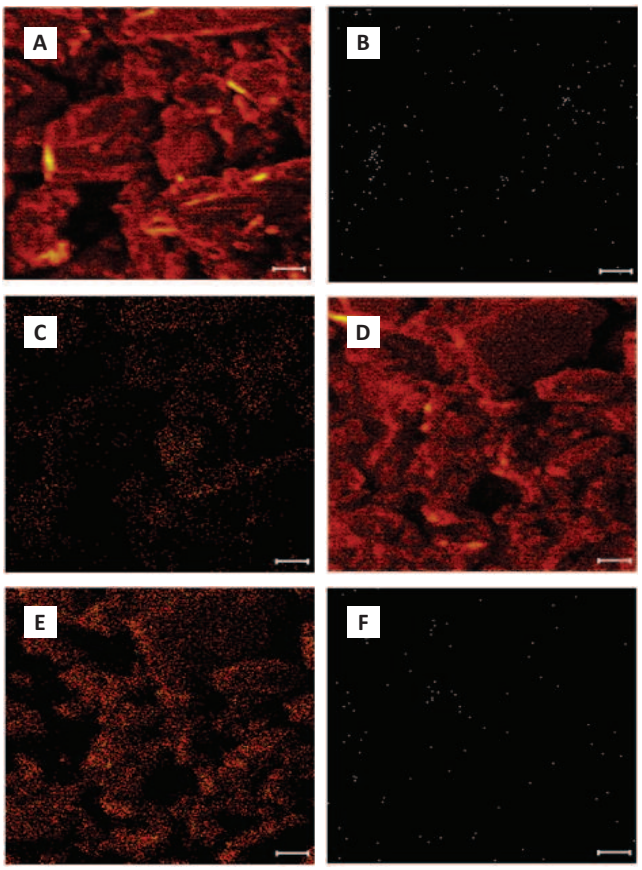

Figure 3. TOF-SIMS micrographs: (A) total ion signals (red dots) of untreated lactose show the shape of particles; (B) untreated lactose has no Mg signals (m/z 24), thereby showing a black background; (C) untreated lactose shows lactose signals ($C_6H_{11}O_5$ m/z 163) as red dots; (D) total ion signals of mechanofused lactose; (E) mechanofused lactose shows Mg signals (m/z 24, red dots) on the particle surface indicating a coating of MgSt; (F) lactose signals are not shown on the particle surface of the mechanofused lactose (leaving a black background), indicating lactose is not found on the uppermost particle surface and a MgSt coating covers the whole surface of the mechanofused lactose. Scale bars = 10 µm. Reprinted from reference 32 with permission from John Wiley and Sons.

Potential opportunities through dry coating

Developing DPIs for new indications with challenging doses, such as inhaled antibiotics, require the products to possess high aerosolization efficiency and superior performance consistency. To achieve such efficient DPI formulations, particle engineering appears necessary. In this article, the application of intensive, mechanical, dry coating approaches to improve the aerosol performance and manufacturability of DPIs has been discussed and evidenced by current reported research. The operation of dry coating equipment appears highly effective, simple, scalable and economical. Dry coating can also be an additional step that complements current industrial manufacturing processes. Therefore, this approach appears to be a promising strategy for design and manufacture of next-generation, high-performance DPI products.

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Li Qu, MSc is a PhD candidate at Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC 3052, Australia. David A.V. Morton is an Associate Professor at Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC 3052, Australia. Qi (Tony) Zhou is an Assistant Professor at the Department of Industrial and Physical Pharmacy, College of Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN, 47907-2091, US, tonyzhou@purdue.edu.