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Improving aerosolization of drug powders by reducing powder intrinsic cohesion via a mechanical dry coating approach

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ABSTRACT

The aim of this study was to investigate the effect of coating on the aerosolization of three model micronized powders. Three model powder materials (salbutamol sulphate, salmeterol xinafoate, triamcinolone acetonide) were chosen not only for their different chemical properties but also for their different physical properties such as shape and size distribution. Each powder was coated with 5% (w/w) magnesium stearate using two different dry mechanofusion approaches. After mechanofusion, both poured and tapped densities for all three model drug powders significantly increased. There were significant improvements in aerosolization behavior from an inhaler device for all model powders after mechanofusion. Such improvements in aerosolization were attributed to the reduction in agglomerate strength caused by decreasing powder intrinsic cohesion via surface modification. The work also indicated that the effect of the coating was dependant on the initial particle properties.

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1. Introduction

Only drug-containing aerosol particles with aerodynamic diameter below about 5 μm can be efficiently transported through the upper airways to reach the target sites in lungs (Timsina et al., 1994). However, as dry powders in isolation, such fine particles will generally exhibit poor flowability and poor aerosolization behaviors, given the inherent strong cohesive forces as a result of their small particle size and high relative surface area (Chan and Chew, 2003). Thus, in practice, dry powder inhaler (DPI) formulations are frequently developed as ordered mixtures which include a coarse lactose carrier to improve the flowability and ensure consistency of aerosolization of the formulations (Smyth and Hickey, 2005).

However, there are some disadvantages of carrier-based DPI formulations which may limit the use of such a lactose carrier. Undesired chemical reactions may occur between the lactose and certain drugs, for example some peptides or proteins (Patton and Platz, 1992). Moreover, lactose intolerance restricts its use, and protein contaminants of lactose may restrict use in the formulation for those patients who are allergic to such substances (Kretchme and Faber, 1972). Furthermore, for those medications requiring high-dose drug treatment, the use of carriers will, in practice, substantially limit the drug load of the formulation to a maximum in the order of a few milligrams or often much less. In the absence of a carrier, drug pelletization may be used to overcome flow issues; however, the control of agglomerate strength is critical since it needs a favorable balance in agglomerate strength between the formation and de-agglomeration of loose agglomerates (Smyth and Hickey, 2005). The precise control of the agglomerate strength during the pelletization process is a challenge. Alternatively, new technologies can be used to generate highly porous low density particles with large physical size but small aerodynamic size (Edwards et al., 1997). This concept provides an elegant solution, but such particles are generally complex and challenging to produce and handle in practice, and such low density can require an impractically large volume of powder. Moreover, the delivery of such physically large particles to the lungs may experience difficulty given that the peripheral airway of the lungs is relatively small (Smyth and Hickey, 2005). Therefore, there is a motivation to develop simple and practical technologies that could lead to carrier-free high-dose DPI formulations with suitable flow, fluidization and de-agglomeration behaviors.

A general aim has long been recognized to reduce the intrinsic cohesion of a fine powder. This concept was recognized as far back as the 1850s, when active substances were attached to the pollen of the lycopodium forming a low cohesion vehicle for powder inhalation (Collins and Collins, 1851). Several recent studies have explored various strategies to develop appropriate formulations by modifying particle surface properties. Increasing the corrugation of the drug particle surfaces through spray drying has been demonstrated to result in better aerosolization behavior of bovine serum albumin (BSA) (Chew and Chan, 2001). Such improvements were attributed to the reduced cohesive forces between fine drug particles caused by decreasing their contact area (Adi et al., 2008).

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Coating tobramycin-containing powder with lipids via a spray drying approach also was shown to improve the aerosolization (Pilcer et al., 2006). Similarly, modifying the surface of drug particles with amino acids such as leucine, using spray drying or a physical vapor deposition approach, has also been shown to improve the drug delivery efficiency of dry powder inhaler formulations (Ganderton et al., 2000; Najafabadi et al., 2004; Rabbani and Seville, 2005; Raula et al., 2008). This improved efficiency was attributed to an enrichment of leucine at the surface of the drug particles, reducing the inter-particle cohesive forces (Chew et al., 2005). However, using the spray drying route in developing DPI formulations, particularly for those containing small organic molecules, may bring general concerns over forming meta-stable amorphous structures that are generally characteristic of the spray drying approach (Chow et al., 2007).

Recently, mechanical dry coating techniques have attracted interest. These techniques appear well suited to modifying inter-particulate interactions of dry powders by changing their surface characteristics. A single-step mechanical dry coating method that is solvent-free should be simpler, cheaper, safer, easier to scale up and more environment-friendly than liquid-based alternatives (Bose and Bogner, 2007). "Mechanofusion" is a generic term used for several types of mechanical dry coating approaches for particle and powder modification (Pfeffer et al., 2001). A number of different mechanofusion systems and mechanisms are available, but in general they consist of a cylindrical chamber and a process head which rotate relative to each other at high speed to create intense shear and compression of the core (host) and coating (guest) particles both via impaction with the face of the process head and via compression as the particles are pushed between the edge of the head and the chamber wall. The process head motion will break-up agglomerates of the cohesive host particles to expose their surfaces as it rotates at high speed. A considerable amount of thermo-mechanical energy is generated which coats the guest material onto the exposed surfaces of the host particles (Alonso et al., 1989). However, unlike more conventional milling and co-milling processes, the energy input in mechanofusion is more tightly controlled because the process head geometry, speed and gap from the wall are fixed and the process can be tuned to encourage coating but not size reduction, thus, excess heat or damage kept to a minimum (Morton, 2006). Several reports have demonstrated that the powder flowability can be improved by coating host particles with the traditional glidant fumed silica (Ramlakhan et al., 2000; Yang et al., 2005). The reduction in inter-particulate attractive forces after dry coating with silica is believed to occur by the increasing the distance of closest approach of the host particles or by reducing the contact area between two or more host particles. In previous studies, we have demonstrated that the flowability of a range of fine lactose powders can be improved substantially via mechanofusion with the lubricant magnesium stearate (and to a greater extent than that observed with fumed silica) (Zhou et al., 2010). Given that the improvements in powder flowability have been demonstrated to be attributed to the reduction in intrinsic powder cohesion after coating (Zhou et al., 2009), mechanofusion appears a potential technology to improve aerosol performance of high-dose DPI formulations by modifying drug particles. There are very few published studies that have applied the dry coating approach in carrier-free DPI formulation development, although it has been used to engineer the much larger lactose carrier particles (Kumon et al., 2006), but these powders already have good flow properties in their original state. Kawashima et al. (1998) reported the co-processing of micronized pranlukast hydrate particles with anhydrous silicic acid, but there are concerns about the safety issues of inhaling nanoparticles of silicic acid (Rogueda and Traini, 2007).

An earlier study reported a preliminary investigation on improving dispersibility of drug powders using mechanofusion (Begat et al., 2009). However, the relationship between powder aerosolization behaviors and their intrinsic cohesion has not been explored. In this work, a detailed study was undertaken using a more diverse range of drug powders, with a selected variation in particle properties. Three micronized drug powders (salbutamol sulphate, salmeterol xinafoate, triamcinolone acetonide) were selected based not only on the differences in their chemical properties but also in their physical properties such as particle shape and particle size. Salbutamol sulphate exhibits hydrophilic nature (Brodka-Pfeiffer et al., 2003) while salmeterol xinafoate and triamcinolone acetonide are hydrophobic (Murnane et al., 2008; Williams et al., 1999). Furthermore, these micronized drug powders were believed to possess different particle shapes. In the preliminary part of this study, examination of the shapes and size distributions of each respective material is reported, and confirms a number of such differences. It should also be noted that although each of these drug materials are well known for their use in inhaled therapy, their use here was solely as model materials and no attempt was made to formulate them to specific realistic dose levels or into a final optimized formulation: in contrast, they were selected as three different models to assess how efficiently a hypothetical high-mass of powder (i.e. $\geq$10 mg) could be aerosolized from a simple device. The powder cohesion was modified by mechanofusing drug particle surfaces with a pharmaceutical lubricant, magnesium stearate. The intrinsic cohesion was characterized using a well established shear cell method. The relationship between the aerosolization behavior of model powders from a simple inhaler device and their intrinsic cohesion was therefore investigated.

2. Materials and methods

2.1. Materials

Micronized triamcinolone acetonide (TA) was supplied by (Farmabios S.p.A., Gropello Cairoli, Italy). Micronized salmeterol xinafoate (SX) was donated by GlaxoSmithKline, Middlesex, UK. Micronized salbutamol sulphate (SS) was supplied by Cambrex Profarmaco, Milan, Italy. Magnesium stearate (MgSt) was supplied by Mallinckrodt Baker Inc., Phillipsburg, NJ. Cyclohexane and methanol were supplied by Scharlau Chemie S.A., Barcelona, Spain. All samples were used as received.

2.2. Methods

2.2.1. Intensive mechanical dry coating

Dry coating of drug powders with MgSt was carried out in an AMS-Mini mechanofusion system with either the Nobilta or Nanocular process module (Hosokawa Micron Corporation, Osaka, Japan). The two processors have different geometries in design (Fig. 1) and the effect of processor geometry on the coating was evaluated in this study. Fig. 1 illustrates the contrasting blade geometries. The Nanocular system comprises a solid circular blade with two semi-circular rounded protrusions or "press heads" that are configured largely to compress powders against the internal vessel wall. The Nobilta system in contrast is configured as a series of "propeller" blades that will cause more impact collisions with powder particles as the blades rotate, as well as compression as powders are thrown outwards and interact between the edge of the blades and the internal vessel walls. No previous studies were found that compared these two blade configurations for the coating of micronized powders.

Each drug sample (approximate 10 g) was combined with 5% (w/w) of MgSt and then was transferred to the process vessel. The minimum quantities of the coating material required for a success-

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