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Improvement of flow and bulk density of pharmaceutical powders using surface modification

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ABSTRACT

Improvement in flow and bulk density, the two most important properties that determine the ease with which pharmaceutical powders can be handled, stored and processed, is done through surface modification. A limited design of experiment was conducted to establish a standardized dry coating procedure that limits the extent of powder attrition, while providing the most consistent improvement in angle of repose (AOR). The magnetically assisted impaction coating (MAIC) was considered as a model dry-coater for pharmaceutical powders; ibuprofen, acetaminophen, and ascorbic acid. Dry coated drug powders were characterized by AOR, particle size as a function of dispersion pressure, particle size distribution, conditioned bulk density (CBD), Carr index (CI), flow function coefficient (FFC), cohesion coefficient using different instruments, including a shear cell in the Freeman FT4 powder rheometer, and Hansen flowability index. Substantial improvement was observed in all the measured properties after dry coating relative to the uncoated powders, such that each powder moved from a poorer to a better flow classification and showed improved dispersion. The material intrinsic property such as cohesion, plotted as a function of particle size, gave a trend similar to those of bulk flow properties, AOR and CI. Property improvement is also illustrated in a phase map of inverse cohesion (or FFC) as a function of bulk density, which also indicated a significant positive shift due to dry coating. It is hoped that such phase maps are useful in manufacturing decisions regarding the need for dry coating, which will allow moving from wet granulation to roller compaction or to direct compression based formulations.

1. Introduction

Manufacturing of pharmaceutical solid dosage forms involves several processes including flow through hoppers, sieving, pouring, blending, die-filling, and compaction (Guerin et al., 1999). These processes are highly sensitive to powder properties like flowability and bulk density, which are to some extent inter-related, and thus affect the quality of the final product. For example, the die-filling process is affected by the cohesiveness of the powder, which determines the ease with which the powder can be fed into the die (Guerin et al., 1999). Cohesiveness also causes the non-uniformity of the API mass in the tablets (Lindberg et al., 2004). Powder bulk properties and its compressibility also impact the pre-compaction and compaction processes. Thus, flow properties of pharmaceutical powders are critical to manufacturing. Poor flow often causes undesirable process breakdown thereby directly impacting the product uniformity.

Most active pharmaceutical ingredients (APIs) used these days are fine powders 100 μm or less which typically have a wide size distribution. Further, particles smaller than 30 μm are extremely difficult to handle and are a generic problem for the industry (Yang et al., 2005). This is due mostly to the presence of strong inter-particle interactions like van der Waals, capillary and electrostatic forces. For fine dry particles, the van der Waals interaction is the most significant force responsible for cohesiveness of powder (Jallo et al., 2011). To ease the handling of these fine powders, methods like aeration and vibration are used along with the addition of small amounts of flow additives or glidants (Molerus, 1978; Kono et al., 1990; Kaya et al., 1983; Elbicki and Tardos, 1998; Wassgren et al., 2002; Fraige et al., 2008; Pingali et al., 2011). However, these methods could also result in segregation, or non-uniform distribution of the flow additives in the bulk. The use of flow additives may also lead to other disadvantages such as inconsistency in performance and difficulty in predicting the flow behavior a priori. In order to alleviate such disadvantages, dry coating via surface modification has been proposed as an alternate approach where nano-particles are uniformly coated on the surface of the carrier particles (Beach et al., 2010; Yang et al., 2005; Pfeffer et al., 2001).

Surface modification is a technique that reduces the cohesiveness of fine particles substantially by forming a film or thin coating of nano particles on the surface of the particles (Chen et al., 2008, 2009). Surface modification can be achieved through wet or dry

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methods (Jallo et al., 2010; Pfeffer et al., 2001). The wet processes however, are not environmentally friendly as compared to the dry ones, which are environmentally benign (Lecoq et al., 2011; Pfeffer et al., 2001). Further, for the purpose of flow improvement, dry processes may be more favorable as shown through previously proposed contact models (Chen et al., 2010; Jallo et al., 2011). The dry method has been successfully used to coat different types of cohesive powders and improve their flow (Ramlakhan et al., 2000; Yang et al., 2005; Jallo et al., 2010; Han et al., 2011; Zhou et al., 2011; Lecoq et al., 2011; Mullarney et al., 2011). In the dry coating technique, nano-size (guest) particles are successfully attached to the surface of the cohesive (host) particles to reduce the inter-particle forces without using any solvent, binder or involvement of water (Ramlakhan et al., 2000). The force of attraction between the host and guest particles, which keeps them in contact, is the van der Waals force. The guest particles stay on the surface of the host particle because the force of attraction between the two is greater than the weight of the guest particle (Yu et al., 2003). In addition to inter-particle force reduction, the dry coating technique also results in the improvement of bulk properties such as flowability, bulk density, compressibility. Pharmaceutical powders having these tailor-made properties are most desirable for successful process and product design (Thalberg et al., 2004).

Dry coating generally involves high impaction mechanical force (Pfeffer et al., 2001; Lecoq et al., 2011), which attaches nano-size guest particles to the surface of the host particle. However, since pharmaceutical powders are organic, they are relatively soft or brittle in nature and also sensitive to the heat generated during the high impaction by the coating process (Ramlakhan et al., 2000). Severe processing conditions can lead to reduction in size of the API particles, which is counter-productive to the goal of improving the flow properties. Thus, it is desirable to investigate and employ the standardized use of a dry coating method which can attach the nano-size guest particles onto the host API particles with minimum degradation of particle size, shape and composition for pharmaceutical applications (Ramlakhan et al., 2000). Yang et al. (2005) studied several dry coating devices like the hybridizer, V-blender, and magnetically assisted impaction coating (MAIC) and even dry coating by hand mixing. They found that the MAIC device is the most effective dry coater among the above-mentioned devices, and may cause the least attrition while providing very good property improvement. Previously, under certain processing conditions, MAIC has been utilized to coat some organic host particles (mostly spherical in shape with a narrow size distribution) without causing major changes in the material shape and size (Ramlakhan et al., 1998). However, those powders, such as cornstarch were found to be naturally resistant to attrition due to their elastic properties. The earlier studies also established that to reduce the cohesive force among fine host particles, a discrete coating of nano-size guest particles is sufficient, with surface area coverage (SAC) of as little as 10–20% (Yang et al., 2005). However, those reports did not examine the use of MAIC and other devices for coating active pharmaceutical ingredient (API) powders. Recently, Beach et al. (2010), dry coated acetaminophen as a model API powder in the MAIC and examined the flow properties of different blends of lactose and the surface modified API powders. Most importantly, Beach et al. (2010), demonstrated successful use of Near-IR in-line imaging to examine flow and flow uniformity for regular and dry coated API blends. It was shown that examination of the flow intensity from NIR spectra (inverse signal to noise ratio of spectra) and its standard deviation revealed that dry particle coated blends showed better uniformity of flow as compared to the other methods. Thus they showed that Near-IR may be used as a Process Analytical Technology tool helping promote quality by design. In addition, flow rates of 100% APIs and their blends were also measured and reported, indicating that dry coated powders exhibited enhanced flow rates. In terms of other flow indices, they only utilized the angle of repose measurements, which corroborated Near-IR results, showing that the majority of the blends prepared from coated APIs stayed in either passable or fair category. However, in that study, the MAIC operating condition was not optimized for API coating and particle sizes were not examined to investigate the extent of attrition. Nonetheless, all these studies showed that there are several critical operating parameters affecting the coating performance of the MAIC device (Ramlakhan et al., 2000; Beach et al., 2010). According to those studies, once the host and guest particles are specified, the key parameters that control the operation and performance of the MAIC are mass ratio of host and guest particles, magnet to powder mass ratio, operating voltage, and processing time.

The main objective of this paper is to carry out a comprehensive investigation of the dry coating approach to improve flow and several other related properties of API powders, while limiting the extent of attrition that is expected from such dry coating devices. MAIC is selected as the model dry coating device, which is also considered to be a material-sparing dry coating device based on our recent work (Ghoroi et al., 2010a, 2010b). These studies along with previous reports indicated that the MAIC, when used in conjunction with selected powder flow testers, works as a screening device to determine the feasibility of certain host–guest combinations for achieving the desired improvement of flow properties. Improvement of flow properties of both uncoated (original; as received) and surface modified APIs were quantified via bulk properties using different powder flow testers. Since one of the objectives is to limit attrition, we also evaluated particle size and size distribution before and after coating. This was done using a venturi-tube type device, namely, the Rodos system coupled with laser diffraction measurements where the powder sample was subjected to varying dispersion pressures. This allows for examination of attrition as well as the extent of powder dispersion, when d_{50} and d_{90} particles sizes are plotted as a function of dispersion pressure.

The presentation in this paper is divided into two parts. The first part of the paper is devoted to the optimization of the operating parameters of the MAIC for dry coating of model cohesive APIs using a limited design of experiments (DOE). The model drugs used for the optimization study were Ibuprofen 110, and Acetaminophen (both micronized and coarse grade) which covers particle sizes from 10 to 120 μm. The major contribution of the paper is in the second part, where several API powders like Ibuprofen 110, Ibuprofen 90, Ibuprofen 50, Coarse Acetaminophen, Micronized Acetaminophen, ascorbic acid crystalline grade and ascorbic acid ultrafine grade were dry coated in the MAIC using the optimal operating conditions. Their flow and related properties were evaluated by flow from orifice through the Flodex device indicated as index (FI), angle of repose (AOR), conditioned bulk density (CBD), flow function coefficient (FFC) evaluated via shear testing, Carr index, as well as material properties such as the cohesion coefficient or the intrinsic shear strength using the Hosokawa powder tester, Quantachrome autotap, and the FT4 powder rheometer. Since flow and bulk density are two of the most important properties that determine the ease with which pharmaceutical powders can be stored, handled and processed, the results are presented as a phase map of inverse of cohesion which is a measure of flowability (Geldart et al., 2009) (or FFC) as a function of bulk density (Mullarney et al., 2011). Such phase maps are expected to provide quick, visual assessment of the extent of property enhancement due to dry coating.

2. Experimental

2.1. Materials

All of the raw materials used in this work are listed in Tables 1 and 2. Table 1 lists the average particle diameters, bulk