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Improved blend and tablet properties of fine pharmaceutical powders via dry particle coating

Zhonghui Huang, James V. Scicolone, Xi Han, Rajesh N. Davé *

New Jersey Center for Engineered Particulates, New Jersey Institute of Technology, Newark, NJ 07102, USA

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ABSTRACT

The improvements in the flow and packing of fine pharmaceutical powder blends due to dry coating of micronized acetaminophen (mAPAP, ~11 μm), a model poorly flowing drug, are quantified. Poor flow and packing density of fine excipients (~20 μm) allowed testing the hypothesis that dry coating of cohesive API may counteract poor flow and packing of fine pharmaceutical powder blends. Further, fine excipients could improve compaction and reduce segregation tendency. It was found that flow function coefficient (FFC) and bulk density enhancements for 10%, 30%, and 60% (w/w), API loading blends with dry coated API are significantly higher than those without coated silica. At the highest API loading, for which coarser excipients were also used as reference, the flow and packing of dry coated mAPAP blends were significantly increased regardless of the excipient particle size, exceeding those of a well compacting excipient, Avicel 102. In addition, tensile strength of tablets with fine excipients was significantly higher, indicating improved compactibility. These results show for the first time that dry coating of fine, cohesive API powder leads to significantly improved flow and packing of high API loading blends consisting of fine excipients, while achieving improved tablet compactibility, suggesting suitability for direct compaction.

1. Introduction

The flowability of powders is an important parameter in pharmaceutical processes such as mixing, conveying, feeding, and tablet formation. Since flowability depends on various factors such as particle size (Liu et al., 2008), particle size distribution (Liu et al., 2008), particle shape (Ohta et al., 2003; Podczeck et al., 1996), and humidity (Armstrong and Clayton, 2012; Jonat et al., 2004a; Schulze, 2008; Young et al., 2003), generally it is difficult to optimize the flowability of powders. To further complicate the matter, fine active pharmaceutical ingredients (APIs) (e.g., median particle size <20 μm) are very cohesive and have poor flowability because fine particles experience strong interparticle forces, which exceed the weight of the particles, quantified by their ratio, denoted by the granular Bond number (Castellanos, 2005). Consequently, pharmaceutical blends consisting of fine APIs usually have processing issues at high API dose, or may suffer from poor content uniformity at low API dose because of their poor flowability and presence of API agglomerates (Sun, 2010; Sun et al., 2009). Nonetheless, since fine APIs result in tablets with enhanced dissolution rates because of greater fine particle surface area (Gold et al., 1966; Liversidge and Cundy, 1995; Nalluri and Kuentz, 2010), those in academia and the pharmaceutical industry have shown great interest in overcoming the issues associated with their poor flowability and low bulk densities, which in turn could also facilitate direct compression high-speed tableting (Chattoraj et al., 2011; Davé et al., 2013; Ghoroi et al., 2013a).

Surface modification via dry coating has been established as an efficient approach to improve powder flowability without requiring any solvents or binders, and may be done using many devices, including the conical screen mill (Comil), magnetically assisted impaction coater (MAIC), fluid energy mill (FEM), and resonant acoustic mixer (RAM) (Beach et al., 2010; Chen et al., 2009; Davé et al., 2011,b; Ghoroi et al., 2013a,b; Han et al., 2013, 2011; Huang et al., 2014; Iwasaki et al., 2002; Jallo et al., 2012,b; Mullarney et al., 2011a,b; Otles et al., 2009, 2011; Pfeffer et al., 2001; Ramlakhan et al., 2000; Roth et al., 2011; Yang et al., 2005). In the dry coating process, a layer of nano-sized particles (guest particles), usually nano-silica, is applied onto the surface of a larger particle (host particle), the API or excipient, through mechanical forces. In contrast to typical pharmaceutical blending where silica does not get sufficiently deagglomerated and hence does not get evenly

* Corresponding author. Tel.: +1 973 596 5870; fax: +1 973 642 7088.
E-mail address: dave@njit.edu (R.N. Davé).

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coated on to the drug powders, dry coating leads to more uniform coating of silica, which decreases the natural surface roughness of the host particles down to the nano-scale range, thereby reducing the cohesion between the host particles leading to smaller Bond number values (Chen et al., 2008; Han et al., 2013; Meyer and Zimmermann, 2004; Yang et al., 2005).

Previous studies have showed that dry coating the API in blends did not adversely impact resulting tablets (Mullarney et al., 2011a). In fact, according to (Han et al., 2013), dry coating of ibuprofen in the blends not only improved powder flowability, but also improved tablet hardness and dissolution rate. However, none of the previous studies considered use of very fine excipients, raising a doubt if the blend flow and packing improvements were also because of the use of well flowing coarse excipient serving as "carriers" for fine APIs (Pilcer and Amighi, 2010). In addition, use of fine excipients in blends would be desirable, since that may help improve tablet compaction properties (Kaerger et al., 2004), and may also reduce the potential of segregation driven by particle size difference. However, fine excipients, such as Avicel PH105, have poor flowability, and while they may lead to improved tablet strength, they would lead to poorer flow and packing of the fine API blends. As a major novelty of this paper, instead of typical larger excipients, fine excipients are used due to the greater challenge they pose in terms of achieving sufficient flow and packing improvements in fine API blends. If dry coating of fine API can indeed lead to sufficient blend property enhancements despite use of fine excipients, that would constitute a novel outcome. Consequently, the main objective of this paper is to investigate the improvements in the packing and flow of the blends consisting of very fine micronized acetaminophen (~11 μm) as a model poorly flowing drug in conjunction with use of very fine excipients. These properties will be compared with those of a well-known tableting excipient such as Avicel 102 to assess the suitability for high-speed tableting as suggested by (Sun, 2010). The effect of dry coating on the tablet hardness of the resulting fine API and excipient blends will be also assessed.

A standard tablet formulation consisting of a combination of Avicel and Pharmatose is considered. Avicel PH105 and Pharmatose 450 M, both about 20 μm, are the fine grades of excipients. Packing and flow properties of 10%, 30%, and 60% (w/w) API loading blends, without and with dry coated component(s) are assessed using the powder flow tester. The 60% (w/w) API loading blend of fine excipients, considered as most challenging, is compared with the blends consisting of larger excipients, Avicel PH102 (~122 μm) and Pharmatose DCL11 (~107 μm). Tensile strength for tablets prepared from 60% (w/w) API loading blends of fine as well as coarse excipients are also assessed. The results are expected to help validate the main hypothesis that dry coating can lead to significant improvements in blend and tablet properties, making direct compression feasible for high API loaded blend of fine API and fine excipients.

2. Experimental

2.1. Materials

The API used was a very fine micronized grade of acetaminophen (mAPAP, Mallinckrodt Inc., USA). The excipients were received from their respective manufactures as donated samples. Two grades of lactose were used: milled α-lactose monohydrate Pharmatose 450 and spray-dried monohydrate Pharmatose DCL11 (DFE Pharma, USA). Two sizes of microcrystalline cellulose were used: Avicel PH-105 and Avicel PH-102 (FMC Biopolymer, USA). The mAPAP, Pharmatose, and Avicel were used as the host particles in the dry coating process. Crospovidone (trade name Kollidon-CL, BASF Corporation, USA), a disintegrant, and magnesium stearate (MgSt, Mallinckrodt Inc., USA), a lubricant and flow enhancing agent (glidant), were also added to the blends. Aerosil R972P (Evonik, USA), a nano-sized pharma-grade hydrophobic silica, was used as the guest material for the dry coating process due to its efficacy when compared to hydrophilic silica in decreasing the cohesion force due to the fewer hydrogen bonds as has been previously shown (Huang et al., 2014,b; Jonat et al., 2004a,b). The particle size distributions of the pharmaceutical powders were obtained using a Rodos/Helos system (Sympatec, USA), employing a ventury-tube type device for powder dispersion under different pressures, along with laser diffraction to measure the powder sample particle size distributions. Table 1 contains the information on the particle size distributions of the powders at a dispersion pressure of 0.2 bar. Results are reported based on an average of 3 runs, and since the standard deviation is low, it is not shown.

2.2. SEM

A Field Emission Scanning Electron Microscope (FESEM) (LEO 1530 170, Carl Zeiss SMT Inc., Germany) was used to check the particle morphology and nano silica coating surface coverage. Samples were taken from the blends and sputter-coated with carbon to enhance conductivity during FESEM imaging.

2.3. Dry particle coating

In this work, a vibratory mixer, called resonant acoustic mixer (RAM, Resodyn Corporation, USA), was employed to dry coat the desired powder components. Both host (API or an excipient powder) and guest (nano-sized silica R972P) particles were placed in a 500 mL plastic jar, which was mounted in the RAM vibratory

Table 1
Blend components, particle size distributions, true material densities, and their functions.

Component	Particle size				*Span	ρ_{true} (g/ml)	Function
	[1]D_{10} (μm)	[2]D_{50} (μm)	[3]D_{90} (μm)	[4]$D(3,2)$ (μm)			
Micronized acetaminophen	2.3	11.1	40.8	6	3.5	1.29	API
Avicel PH105	7.2	19.7	43.5	13.44	1.9	1.58	Filler and binder
Pharmatose 450 M	3.6	20.2	51.5	6.9	2.4	1.54	
Avicel PH102	32.0	122.4	244.4	66.6	1.7	1.58	
Pharmatose DCL11	42.3	107.5	194.4	73.8	1.4	1.54	
Crospovidone Kollidon-CL	16.34	75.43	191.55	40.04	2.3	1.2	Disintegrant
Magnesium Stearate	1.4	5.45	13.1	3.74	2.1	1.03	Lubricant
Silica R972P	–	0.02	–	–	–	2.65	Flow agent

[1] D_{10}, [2]D_{50}, [3]D_{90} means 10%, 50% and 90% below this size; [4]$D(3,2)$ = volume/surface mean; span= $(D_{90}- D_{10})/D_{50}$.