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Engineered particles demonstrate improved flow properties at elevated drug loadings for direct compression manufacturing

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ABSTRACT

Optimizing powder flow and compaction properties are critical for ensuring a robust tablet manufacturing process. The impact of flow and compaction properties of the active pharmaceutical ingredient (API) becomes progressively significant for higher drug load formulations, and for scaling up manufacturing processes. This study demonstrated that flow properties of a powder blend can be improved through API particle engineering, without critically impacting blend tabletability at elevated drug loadings. In studying a jet milled API (D_{50} = 24 μm) and particle engineered wet milled API (D_{50} = 70 μm and 90 μm), flow functions of all API lots were similarly poor despite the vast difference in average particle size ($ff_c < 4$). This finding strays from the common notion that powder flow properties are directly correlated to particle size distribution. Upon adding excipients, however, clear trends in flow functions based on API particle size were observed. Wet milled API blends had a much improved flow function ($ff_c > 10$) compared with the jet milled API blends. Investigation of the compaction properties of both wet and jet milled powder blends also revealed that both jet and wet milled material produced robust tablets at the drug loadings used. The ability to practically demonstrate this uncommon observation that similarly poor flowing APIs can lead to a marked difference upon blending is important for pharmaceutical development. It is especially important in early phase development during API selection, and is advantageous particularly when material-sparing techniques are utilized.

1. Introduction

Particle size and morphology of active pharmaceutical ingredients (APIs) are two of the most influential properties that affect powder flow and compaction for a tablet manufacturing process (Hou and Sun, 2008). Understanding the factors affecting powder flow and compaction is important for ensuring blend and tablet uniformity, efficient material transfers, powder encapsulation, manufacturing scale-up, and tablet integrity for downstream processes such as storage and coating (Liu et al., 2008; Prescott and Barnum, 2000; Saleem et al., 2014). Generally, it is understood that larger, rounded particles with narrow particle size distributions express better bulk flow properties than smaller, finer particles (Kim et al., 2005; Liu et al., 2008; Schulze, 2008). Fine, needle or plate-like particles with wide distributions exhibit increased friction and cohesive interactions through their larger surface area (Prescott and Barnum, 2000). Cohesiveness due to size or shape can also affect flow during blending as well as tableting processes. Nonetheless, the higher surface area of smaller particles promotes inter-particle bonding and interlocking, optimizing compactibility and increasing tablet strength (Li et al., 2004; Liu et al., 2013).

When an API exhibits cohesive properties that hinder flowability, actions must be taken to improve flow and facilitate manufacturing operations to maximize efficiency and reduce cost. Several methods exist for improving flow properties of poorly flowing APIs, such as blending with glidants, coating the particles to reduce cohesion, and aerating or fluidizing the powder bed to facilitate transport (Jallo et al., 2012). Processing techniques such as wet and dry granulation are other approaches also commonly used to improve bulk powder flow and compactibility (Šantl et al., 2011). However, granulation is not always desirable, because it involves additional unit operations that increase cost and can further complicate the manufacturing process (Hou and Sun, 2008; Liu et al., 2013). Additionally, diluting with excipients is not a viable option for high drug load formulations that may be required for

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multiple dosing studies during clinical development, or for product lifecycle management. Lifecycle programs often desire to reduce dosing frequencies from multiple daily dosing to once-a-day dosing, in an effort to improve patient compliance (Morningstar et al., 2002; Roda et al., 2002). For high drug load formulations where blending with excipients cannot alleviate processing issues, particle engineering the API itself can assist in achieving improved flow properties. Particle engineering could involve manipulating the crystallization process to better control physical properties of the API crystals, such as size distribution and particle morphology, both of which impact flow properties of the material (Kim et al., 2005; Lee et al., 2004). Other engineering approaches involve milling the API crystals. These processes impact the mechanical properties of the crystals, ultimately affecting their behavior. Understanding the performance of API post-milling is of long standing interest in the pharmaceutical industry (Mackin et al., 2002; Rasenack and Müller, 2004).

This study aimed to use material sparing techniques to evaluate bulk flow and compaction properties of a particle engineered API, to determine if the manufacturability can be improved for a direct compression process, particularly at high drug loads. Two different particle engineering approaches were considered; jet milling and wet milling. During product development for this compound, coarse API was jet milled to reduce the average particle size to improve compaction properties. Jet milling is a common engineering approach for reducing particle size, yet the process micronizes particles with less control of distribution and morphology as the targeted average particle size is increased. Thus, by micronizing our API through jet milling, powder flow was greatly reduced. Wet milling was explored as an alternative particle engineering method in attempt to optimize API physical properties for improving both compaction and flow.

One of the common features of drug development, particularly in early stages, is scarcity of material. For this reason, availability of material sparing characterization tools is critical to the development process. Without tools that use limited material to understand powder properties, it would be impossible to design a material science-based formulation (Sun, 2009). Material sparing characterization techniques for both neat API and the powder blends included flow function analysis by ring shear testing, powder bed permeability by FT4, tabletability by compaction simulation, and tablet mechanical stress resistance by friability test (Çelik and Marshall, 1989; Freeman, 2007; Fu et al., 2012; Pharmacopoeia, 2005; Schulze, 2008).

2. Materials and methods

2.1. Materials

All jet and wet milled API lots, labeled A, B and C were manufactured for Biogen by an external contract manufacturing organization. Lots A and B are wet milled API with different mass median particle sizes (D_{50}) while Lot C is jet milled (Table 1). Croscarmellose Sodium (AcDiSol® SD-711) was sourced from FMC BioPolymer (Philidelphia, PA), Prosolv® SMCC HD90 Silicified Microcrystalline Cellulose was purchased from JRS Pharma (Charlotte, NC), magnesium stearate was purchased from Mallinckrodt Hyqual (St. Louis, MO), and silica colloidal anhydrous (Aerosil® 200) was purchased from Evonik Industries (Essen, Germany).

2.2. Jet milled processing

The coarse API was passed through a jet mill after crystallization to reduce the particle size. Mill pressure, feed pressure, and feed rate were adjusted during the process to reduce particle size from 400 μm to roughly 30 μm. Jet milling typically produces average particle sizes between 20 μm and 50 μm.

Table 1
API and blend descriptions.

Name	Description	Blends	Drug Load
A	Wet milled (D_{50} = 90 μm)	A1	80% API A
		A2	50% API A
B	Wet milled (D_{50} = 70 μm)	B1	80% API B
		B2	50% API B
C	Jet milled (D_{50} = 24 μm)	C1	80% API C
		C2	50% API C

2.3. Wet milled processing

A high-shear mixer was used for wet milling during the API synthesis process to obtain a targeted particle size distribution (PSD). During the final synthesis step, the warm product was recirculated through the high-shear mixer while being simultaneously cooled for crystallization. Particle size of the final drug product can be controlled by milling time or number of recirculations through the high-shear mixer. In-process measurements can also be performed to track particle size until the target is achieved (Lee et al., 2004). Wet milling, as commonly known in the industry, typically produces average particle sizes between 50 μm and 90 μm.

2.4. Scanning electron microscopy

The surface features and morphology of the three API lots were analyzed by scanning electron microscopy (SEM) (JEOL USA Inc. Peabody, MA). Samples of each lot were prepared by placing a thin layer of particles on carbon adhesive tabs and mounting them onto a brass sample holder. The sample holder assembly was then submerged in liquid nitrogen prior to analysis. During imaging, the samples were analyzed with low vacuum using backscatter detector in shadow mode at 15 kV with 100× and 250× magnifications.

2.5. Blend preparation

Croscarmellose sodium was used as a disintegrant in the tablet blends. SMCC, a composition of microcrystalline cellulose and colloidal silicon dioxide, was used as a diluent. Silica colloidal anhydrous was used as a glidant, and magnesium stearate was used as a lubricant. The description of API lots and drug loads used in each blend are listed in Table 1. Table 2 shows the formulation by percent composition for 50% and 80% drug load blends.

The API, silica colloidal anhydrous, and croscarmellose sodium were charged into a 1-quart MaxiBlend V-blender (GlobePharma; New Brunswick, NJ) and blended at 25 rpm for 10 min. This blend was then screened through a 35 mesh sieve (500 μm) to de-lump any potential large agglomerates. The sieved material was placed back into the V-blender and blended with SMCC at 25 rpm for 5 min. Finally, magnesium stearate was added to the mixture and the material was blended at 25 rpm for an additional 2 min.

2.6. Tablet preparation

Tablets were compressed at target forces, 2, 6, 10, 14, 18, and 22 KN of main compression force on a single punch compaction simulator (Romaco Kilian STYL'ONE; Cologne, Germany). A 11.28 mm flat round punch (TSM B) and an instrumented die