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Fluid bed film coating of fine ibuprofen particles

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ABSTRACT

Fine pharmaceutical powders pose significant challenge in fluid bed (FB) film coating due to their high cohesion. Ibuprofen powders, considered as model Geldart group C powders with Sauter mean diameters of 41 μm (coarse) and 22 μm (micronized), could not be fluidized due to severe agglomeration, solid-bridging, and poor flowability. Dry coating, applied as a pre-processing method that coats nano-silica on the surface of ibuprofen, enabled sufficiently improved flow, hence fluidization via reduced cohesion. Resulting coarse and micronized ibuprofen powders were successfully polymer film coated in a top spray fluidized bed. As a major novelty, apart from pre-processing through 20 nm silica surface coating that enabled fluidization, agglomeration during FB processing was minimized by introducing 180 nm colloidal silica particles that were pH stabilized in polymer spraying suspension using NaOH. In contrast, lack of or poorly stabilized colloidal particles led to significant agglomeration. Spray rate and fluidization velocity were both investigated to understand their effect on agglomeration of the coarse ibuprofen powders. Increased spray rate led to increased agglomeration due to the overly wet conditions, while increased fluidization velocities unexpectedly led to increased agglomeration resulting from electrostatic charging. To simplify the experimental design, a simple scaling relationship was introduced to estimate the coating conditions for the micronized ibuprofen powders based on the processing conditions of the coarse ibuprofen powders. This relationship, based on the minimum fluidization velocity, led to comparable agglomeration levels for powders with Sauter mean diameters of 21 and 42 μm. To the author's knowledge these are the first successful results where micronized pharmaceutical powders were polymer coated in a traditional top spray fluidized bed.
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1. Introduction

Fluidized bed techniques are commonly used for coating and agglomeration of active pharmaceutical ingredients (API) to enhance their powder flow and handling capabilities as well as to impart desirable characteristics associated with the coating material, such as modified release behavior, protection from the environment or to mask unpleasant tastes or odors [1–5]. Incorporating fine active particles into pharmaceutical products is highly desirable because of their high specific surface area, which can enhance the dissolution and therefore the bioavailability of most poorly water soluble materials [6]. Unfortunately, fluidized bed coating is typically limited to particle sizes appreciably greater than 100 μm without severe agglomeration [7]. These fine API particles can often be categorized as Group C (cohesive) by the Geldart classification system, which are extremely difficult to fluidize due to their high relative cohesion [8]. Attempts to fluidize these powders generally lead to the formation of channels or ratholes. To overcome these processing issues, small particles are commonly granulated with much larger, easily fluidizing powders to enhance processing [9–12]. While such approaches are capable of producing well coated products, it has the disadvantages of limited potency ranges, due to the high concentration of the well fluidizing excipients and can be problematic for products requiring high drug loadings. Additionally, these granules are typically on the size of several 100s of microns which may have a larger size than is desirable or could lead to size segregation [13].

Several methods have been developed to fluidized bed coat or agglomerate fine cohesive particles without the addition of significant amounts of excipient materials, however most of these methods require complicated and potentially expensive modifications to the typical fluidized bed configuration. Kawaguchi et al. [14] showed that a rotating fluidizing bed configuration was capable of fluidizing and granulating cohesive API particles to prepare reproducible acetaminophen granules (~500 μm), which were difficult to produce in a conventional fluidized bed. Later Watano and collaborators showed that 15 μm cornstarch particles could be granulated [15] or individually coated [16] in a rotating fluidized bed. They explained that the centrifugal forces exerted onto the normally cohesive cornstarch particle increased the apparent particle weight and made them behave like well fluidizing Geldart group A (aeratable) particles. In another study, Hamashita et al. also showed that micronized core particles containing ibuprofen could be granulated using an impeller agitated conventional fluidized bed [17–19]. A similar apparatus was used to produce micro-granules of ibuprofen particles by Miyadai et al. [20]. While these methods were capable of producing reproducible agglomerates with high loadings of active materials, the

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resulting granules had median sizes larger than 200 μm. In addition, such processing requires expensive and potentially complicated technologies that can be difficult to integrate into pharmaceutical manufacturing.

Ichikawa and Fukumori showed in a series of studies that micronized and cohesive powders could be successfully coated and agglomerated in a bottom spray Wurster type spouted bed [13,21,22]. However, because of the cohesive nature of these micronized particles, they could not be fluidized in a strict sense; hence, high superficial velocities were required to make them spout and a draft tube was used to enhance the circulation. The authors, however, also cited problems maintaining a steady circulation of these cohesive powders, due to their inability to be fluidized in a traditional sense, which can make process development difficult. Therefore an easier and more effective method of fluidized bed coating these fine cohesive powders needs to be established if it is to be widely used in industry.

Fluidization of Geldart Group C powders is typically not possible using conventional fluidized beds. However, analysis of the cohesive forces versus other forces such as buoyancy or resultant drag forces indicate that in order to easily counteract cohesion, one may need to either increase the body weight of the powders, which was performed by Watano et al. [15,16], or one can find ways to reduce cohesion. In present work, latter is considered as a practical way to enhance fluidization of Group C powders. Although cohesion reduction via introducing flow additives to the fine powders has been known for several decades, it could also be used to promote fluidization as was shown in US patent 6833185 [23]. However, surface modification through dry coating of nano-sized flow additives, which is a simple and practical method, has been shown to provide more significant and reliable results as compared to additive blending [24]. Consequently, it has been shown to make cohesive powders behave like well flowing, thus potentially fluidizable [24]. In dry coating, a discrete, fairly uniform layer of nano-silica particles is applied onto the surface of the cohesive host particles. In contrast, the simple addition of glidants through conventional blending methods could leave most of the additives in the form of agglomerates, which are incapable of significantly impacting the flow [24]. Several methods have been developed to achieve high quality surface coatings in a dry process [6,23–29]. These methods have been shown to offer substantial flow improvements by simultaneously deagglomerating the cohesive nano-silica, i.e., glidant powders, and dispersing the nano-silica particles across the host or carrier particle surface, which include Magnetically Assisted Impaction Coating [24,30–34], Acoustic Mixing [26], and Fluid Energy Milling [6,27]. Yang et al. derived a simple equation that showed that the reduction in cohesion due to the introduction of the nano-sized surface asperity in the form of the nano-silica coating is inversely proportional to particle size [24], hence coating of nano-silica would lead to improvements in the flow properties. Chen and collaborators [30–32] later showed that indeed the surface asperities, the level of coating (expressed in terms of surface area coverage, SAC) as well as the surface energy, play a major role in the cohesion reduction, and that the addition of a nano-silica surface coating can reduce the granular bond number (the ratio of the cohesive forces to the inertial forces) by over an order of magnitude for aluminum particles under 5 μm. In addition to flow improvement, this cohesion reduction also allowed fine cohesive particles to be fluidized in a conventional fluidized bed [31,32] and led to fluidized bed coated product without significant agglomeration. While this is a promising development, the type of particles considered were aluminum, having relatively high density and hence body weight, or cornstarch, which is highly spherical and had relatively narrow size distribution. In contrast, drug particles typically have higher levels of cohesion, irregular shapes, and wider size distributions. Recent work on dry coating drug powders indicate that their cohesion can be reduced, albeit less significantly than materials like cornstarch, via dry coating of silica, however, their fluidization behavior has not been investigated [35]. More importantly, film coating of such particles via fluidized bed processing had not been investigated, including examination of conditions that allow for maintaining fluidization during coating, while avoiding particle agglomeration. Thus the major objective of this work is to examine fluidization and subsequent polymer film coating of very fine pharmaceutical powders.

In this study silica nanoparticles were dry coated onto the surface of as received and micronized ibuprofen particles with a median size in the range of 41 to 74 μm and corresponding Sauter mean diameter of 21 to 41 μm, respectively. Ibuprofen was selected as a model drug because of its poor flowability and hence poor fluidizability. It will be shown that dry coating, while not strictly necessary for fluidizing larger API particles, is necessary for fine micronized particles, which are Geldart group C powders. It is shown that the dry coating of the nano-silica particles allows these previously cohesive particles to be fluidized bed coated with minimal agglomeration. It will also be demonstrated that while simple blending with nano-silica can improve the flow properties, it could not offer the same fluidization enhancements as dry coating. To the author's knowledge, the work presented here represents the first successful study of fluidized bed coating of fine, micronized ibuprofen particles in a top spray fluidized bed, without the necessity of equipment modification or the presence of coarse excipient particles.

2. Experimental

2.1. Materials

Ibuprofen, IBU50 ($d_{10} = 24$, $d_{50} = 70$, $d_{90} = 160$ μm) and IBU90 ($d_{10} = 21$, $d_{50} = 113$, $d_{90} = 295$ μm), was a generous gift from BASF (NJ, USA); nano-silica (Aerosil R972p, $d_p = 16$ nm) and Eudragit RS100 were a generous gift from Evonik Degussa (NJ, USA); and HPMC (Methocel E15) was a generous gift from Dow Chemicals (Delaware, USA). ACS reagent grades of ethanol (EtOH), sodium hydroxide (NaOH) and nitric acid (HNO3), tetraethyl orthosilicate (TEOS), ammonium hydroxide (NH4OH) were purchased from Sigma-Aldrich and used without further purification.

3. Methods

3.1. Preparation of 180 nm silica particles

Colloidal silica particles were synthesized according to a process introduced by Stober et al. [36], which allows for fabricating mostly monodisperse spherical particles in sizes from tens to thousands of nanometers. Through this process, TEOS was hydrolyzed to form silica particles in ethanol with an NH4OH catalyst. In each batch, TEOS, ethanol, NH4OH, and deionized water were mixed according to certain molar ratios and stirred for 2 d at room temperature.

3.2. Preparation of uncoated and dry coated powders

Uncoated, dry coated and v-blended powders produced in this study are summarized in Table 1, along with their sizes and the coating methods used. These powders were investigated to determine the preconditioning steps, namely, v-blending or dry coating, necessary to produce well flowing and fluidizable powders. Uncoated ibuprofen was produced by sieving as received IBU50 through a 60 mesh sieve (250 μm) to break up and remove large chunks that formed during storage. V-blended powder was prepared by blending the sieved powder

Table 1
Dry coated and uncoated powders.

Sample	Size (μm) d_{10}, d_{50}, d_{90}, $d_{(3,2)}$	Coating method
UC-74		Uncoated
VB-74	24, 74, 170, 41	V-blender
DC-74		LabRAM
UC-41		Uncoated
VB-41	10, 41, 130, 22	V-blender
DC-41		LabRAM

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