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# Applying dry powder coatings to pharmaceutical powders using a comil for improving powder flow and bulk density

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ABSTRACT

A method for applying nano-sized silicon dioxide guest particles onto host pharmaceutical particles (a.k.a. "dry-coating" or "nanocoating") has been developed using conventional pharmaceutical processing equipment. It has been demonstrated that under selected conditions, a comil can be used to induce sufficient shear to disperse silicon dioxide particles onto the surfaces of host particles such as active pharmaceutical ingredients (API) without significant host particle attrition. In accordance with previous studies on dry coating, the dispersed silicon dioxide adheres to the host particle surface through van der Waals attractions, and reduces bulk powder cohesion. In this work, laboratory and pilot scale comils were used to dry coat pharmaceutical API and excipient powders with 1% w/w silicon dioxide by passing them through the mill with an appropriate combination of screen and impeller. In general, the uncoated powders exhibited poor flow and/or low bulk density. After dry coating with a comil, the powders exhibited a considerable and in some cases outstanding improvement in flow performance and bulk density. This coating process was successful at both the laboratory and pilot scale with similar improvements in flow. The superior performance of the coated powders translated to subsequent formulated blends, demonstrating the benefit of using nanocoated powders over uncoated powders. This particle engineering work describes the first successful demonstration of using a traditional pharmaceutical unit operation that can be run continuously to produce uniform nanocoating and highlights the substantial improvements to powder flow properties when this approach is used.



## 1. Introduction

Many active pharmaceutical ingredients (API) exhibit deficient bulk powder properties such as poor flow or high propensity for adhesion/cohesion due to their small particle size. Small particles (e.g. <20 μm) have a relatively high specific surface area, causing high degrees of adhesion to surfaces and cohesion to neighboring particles. Larger particles (e.g. >100 μm) tend to roll over one another when a shear stress is present and exhibit lower adhesive and cohesive behavior [1,2]. This is because external forces such as gravity significantly exceed interparticle forces due to the cohesive forces arising from electrostatic, capillary or van der Waals interaction for particles in this larger size range [3]. If these cohesive forces can be reduced, the flow properties of the bulk powder can be significantly improved.

The literature has reports that powder flow properties of cohesive powders can be improved by dispersing a very small guest particle such as silicon dioxide over the surface of a host particle such as an API [4–6]. The preliminary hypothesis is that the guest particles act as spacers among host particles, which effectively increase contact distance and therefore decrease van der Waals attractions [5,7,8]. However, the reduction in cohesion by this approach is also greatly influenced the surface area coverage of nano-particle on the guest particle, where in general, higher surface area coverage yields better flow [5,6].

Historically, dry powder coatings have been applied using mechanical processing techniques: impact blenders such as the Hybridizer (Nara Machinery, Tokyo, Japan), high-shear coaters that utilize a high-speed rotor (Hosakawa Mechanofusion, Hosokawa Micron Powder Systems, Osaka, Japan), or magnetic particles in an electric field (Magnetically Assisted Impact Coater – MAIC, Aveka, Inc., Woodbury, MN, USA) to induce shear and dispersion of the guest particles [4,5]. These approaches are required to disperse the nano-sized guest particle agglomerates during processing so that they may discretely adhere to the host particles. Detailed review and description of common batch-processing methods for dry coating may be found in the literature [4].

Although the benefits of dry powder coatings have been demonstrated for improving powder flow and bulk handling performance, the approaches described above for applying dry powder coatings have not

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been widely adopted by the pharmaceutical industry. These approaches often require the aforementioned specialized processing equipment and in some cases require the inclusion and then separation of processing aids (i.e. magnetic particles) which presents a product contamination risk. Although improving formulation powder flow by adding glidants is common in the pharmaceutical industry and conventional pharmaceutical processing equipment such as bin blenders can distribute the guest particle agglomerates throughout the bulk powder mass, low shear mixers do not fully enable the benefit of reduced interparticulate cohesion because they are inefficient for dispersing the nano-sized particles over the entire surface of the host particle [5]. The approach described in this paper is promising as it uses a continuous process that applies the glidant directly to the most cohesive particles (e.g. active ingredients) prior to mixing with other components required for dosage form performance. This work describes the development of a novel method for using a comil for applying dry powder coatings to guest particles.

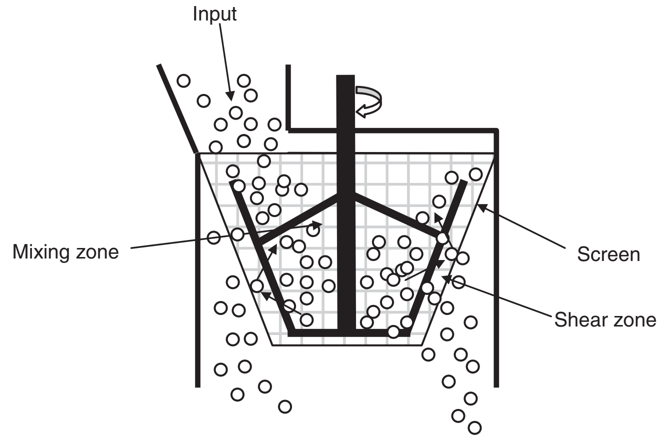


**Fig. 1.** Illustration of comil mixing and shear zones.

## 2. Materials and methods

### 2.1. Materials

A hydrophobic grade of silicon dioxide (Aerosil R972 pharma grade, Evonik/Degussa, Frankfurt, Germany) and a hydrophilic grade of silicon dioxide (Aerosil 200 pharma grade, Evonik/Degussa, Frankfurt, Germany) were selected as the guest particles and have a nominal particle diameter on the order of ~10 to 100 nm. Ibuprofen (50 grade, 2 lots, BASF, Florham Park, NJ, USA), mannitol (powder grade, SPI Polyols Inc., Wilmington, DE, USA), lactose monohydrate (310 grade, Foremost Farms USA, Baraboo, WI, USA) and five proprietary APIs ("A" through "E", Pfizer Inc., New York, NY, USA) were selected as host particles. A 1 wt.% loading of silicon dioxide guest particle with 99 wt.% host particle was used to form the nanocoated particles. This silicon dioxide level has been reported as a typical minimum effective level to achieve bulk property enhancement [5,9]. Ibuprofen formulations were also prepared with additional components as described in Section 2.4 to evaluate the benefit of using nanocoated powders.

### 2.2. Preparation of simple blends

Prior to nanocoating with the comil, the initial blends of silicon dioxide guest particles and host particles were prepared by simple blending for 125 rotations in turbula mixers (Quadro Engineering, Waterloo, Ontario, Canada) for small batches (<50 g) or 2 quart twin-shell blenders for pilot scale batches (100 to 5000 g) prior to the nanocoating unit operation.

### 2.3. Dry powder coating using a comil

A comil can be used for deaggomeration/sieving of bulk powders, sizing of granules, or in some cases controlled sizing of primary particles. They are available with a range of screen sizes, screen types (e.g. round hole vs. rasping) and impeller types (e.g. square edged vs. round edge) and are designed to combine sieving and milling into a single operation [10]. Dry powder coating was achieved using a conventional comil to exploit its capability for deaggomeration with intensified mixing. As powder is charged to the mill, it is retained and mixed in the middle of the conical vessel. Refer to Fig. 1. The conical design and centrifugal forces propel the mixed particles outward and up toward the impeller tip and screen. As the particles become trapped between the screen and impeller edge, significant shear stresses are imparted to deaggomerate the silicon dioxide particles. It is believed that during this time period the larger agglomerates of nano-sized silicon dioxide particles break-down into smaller sub-agglomerates and preferentially attach to the substantially larger host particles through van der Waals attractions. Further residence time is expected to promote repeated collisions between larger host particles having some sub-agglomerates attached and this would lead to transfer/redistribution of nano-particles ultimately resulting in uniform coating of nano-particles. After shearing, some of these coated particles pass through the screen open area and the remaining contained particles are displaced back into the center mixing zone. Eventually all of the particles pass through the screen until the entire charge volume is emptied. This design of the comil enables it to be used as a batch or continuous unit operation. The comil nanocoating sequence is illustrated in Fig. 2.

Overdriven (model 193 and 197, Quadro Engineering, Waterloo, Ontario, Canada) and underdriven (model U3, Quadro Engineering, Waterloo, Ontario, Canada) comils were used to prepare the nanocoated particles. This process requires the selection of comil operating conditions (screens, impeller, operating speed and the powder feeding rate) that are specific to the powder as to maximize dispersion and enable throughput without screen blinding. Typical examples of these conditions are listed here. The comil round hole screen size (0.018, 0.024, and 0.032 inch diameter) was selected to be slightly above the maximum particle size of the host particle lot with the goal of maximizing residence time and minimizing host particle attrition. A round edged impeller rotating at a tip speed of 2.4 m/s was used. Powder was manually charged to the mill at approximately 1 to 10 kg/h.

### 2.4. Formulated blend preparation

To investigate the benefit of using nanocoated particles in a conventional immediate release tableting blends, the as-received ibuprofen (without silicon dioxide) was compared to two types of

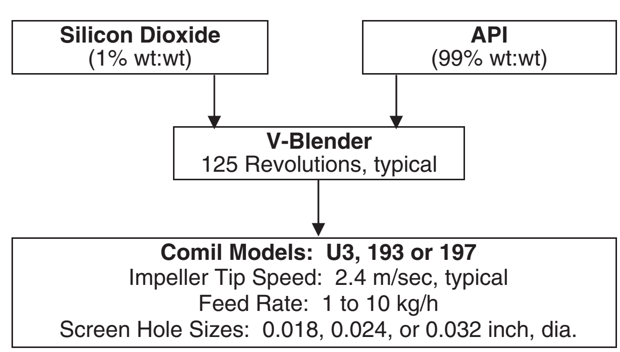


**Fig. 2.** Dry powder coating method using simple blending followed by passing through a comil.