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ABSTRACT

EFFECT OF DRY PARTICLE COATING ON THE PROPERTIES OF COHESIVE PHARMACEUTICAL POWDERS

**by
Lauren Elizabeth Beach**

Engineered particles, which have undergone surface modification via dry coating, have been previously shown to have improved flow and handling properties. The improvements in these properties can be applied and are very useful for a number of industrial applications, in this case the pharmaceutical industry. This work investigates the effect of dry particle coating to improve the flowability of cohesive active pharmaceutical ingredient (API) powders and their blends. Improving the flow properties of cohesive API powders can significantly improve their handling and subsequent use for pharmaceutical processes such as formulation and manufacturing processing operations. Although it has been shown that these surface modified powders flow better as indicated by reduced angle of repose and faster or more uniform flow out of a funnel, more quantitative methods of characterization are needed to fully understand the mechanism of coating and extent of improvement.

Acetaminophen, ibuprofen and other powders were the APIs considered in this work. They were surface modified via dry coating of nano-additives using several different devices. The study considered the use of both hydrophobic and hydrophilic nano-additives. Since the dry coating process is not easily achieved by simple mixing of the API and nano additives, high and/or sustained levels of shear are required to disperse the silica over the API particle. There is a need to develop a new dry coating process that is reproducible, scalable and continuous so that dry coating can be applied to (1) simplify formulations, (2) enable higher API levels, and (3) improve overall powder and drug product manufacturing performance.

In contrast to previous studies that only employed angle of repose to evaluate flow improvement, in this work various quantitative flow characterization techniques are used to assess the changes in flow properties. In addition to use of MAIC and hybridizer which are batch devices, this work also includes development of continuous dry coating

methodology which is based on a typical pharmaceutical powder processing device, namely comil. The comil is found to be fast and efficient, as it is a continuous process with little loss of material. The comil has also been scaled up to pilot scale, indicating that it could easily be implemented in existing formulation and manufacturing processes.

The powders that have undergone surface modification via dry coating techniques are first analyzed for the extent of coating using scanning electron microscopy (SEM) and then the powders are analyzed for their particle size distribution using the Sympatec Helos/Rodos system under varying dispersion conditions to ensure there was no attrition during the coating process. Additionally, a variety of techniques are employed to characterize the powder flow and bulk handling properties, which are important for large scale pharmaceutical manufacturing. Extensive characterization of the powder's flow properties were performed using both novel methods, such as vibrated packed density, as well as industry standard techniques such as shear testing via the Schulze tester, the Freeman FT4 Rheometer and the Hosokawa Powder Tester. Other powder properties such as bulk and tapped densities are also evaluated. The results of these tests are compared with those for untreated API powders in order to examine the enhancement of the powder properties due to the surface modification. This work also clearly illustrates that the pharmaceutical materials undergo significant attrition if the dry coating devices are not optimized.

This work intends to position dry coating as a platform technology and show that dry coating based surface modification has the potential to become a routine tool for use in pharmaceutical industry to enable better formulations and aid in manufacturing.

**EFFECT OF DRY PARTICLE COATING ON THE PROPERTIES OF
COHESIVE PHARMACEUTICAL POWDERS**

**by
Lauren Elizabeth Beach**

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in Partial Fulfillment of the Requirements for the Degree of
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**Otto H. York Department of
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APPROVAL PAGE

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COHESIVE PHARMACEUTICAL POWDERS**

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“If I have seen further it is by standing on the shoulders of Giants.” –Sir Isaac Newton

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CHAPTER 1

INTRODUCTION AND BACKGROUND

1.1 Introduction

Most drug powders used in pharmaceutical industries have very poor flowability, which affects manufacturing and other operations like blending and tableting and leads to problems such as lack of content uniformity and low bulk powder density requiring additional operation which can result in significant loss of revenue. The flow behavior is mainly dependant on the powder cohesiveness due to strong Van der Waal's forces and plays a very important role in development of powder formulation, manufacturing processes, and handling procedures [1]. For example, in the case of tableting, cohesiveness of powder mixtures affects the die filling and the uniformity of the mass of the tablets [2]. The cohesiveness of powders could also make the subsequent powder handling and processing operations very difficult as reported in [3]. By positively influencing the flow characteristics of these cohesive powders through dry particle coating with nanoparticles, these manufacturing processes can be improved, and by using various powder testing methods would further help formulations by quantifying the improvement [4-6]. It has been also shown that coating fine particles with nanoparticles helps reduce interparticle adhesion for a given consolidation force; however, it was clearly emphasized by Prof. Castellano group that it is critical that powder history is minimized while characterizing the flow properties and additives are used in proper amounts so that the flowability is enhanced [4].

It is clear that there is need in the pharmaceutical industry for API flow improvement, which is based on systematic, quantitative assessment of the improvement.

Based on the results from [4-8], it is also evident that in contrast to adhoc addition of glidants and flow-aides, dry coating based surface modification leads to predictable flow improvement and there are reports such as [5], that pave the way towards systematic powder flow characterization. However, there are few reports in the literature that address dry coating based surface modification and subsequent characterization of improved flow properties and subsequent impact on product performance, for example on tablets. Thus the main topic of this thesis is to apply dry particle coating techniques to improve API and excipient properties, and address development and usage of quantitative characterization techniques to assess the change in flow properties.

1.2 Background

1.2.1 Granular Material

A granular material is a conglomeration of discrete solid, macroscopic particles characterized by a loss of energy whenever the particles interact [5]. Most industries handle granular materials in some way. Granular materials exhibit a vast amount of interesting phenomena which are poorly understood. There are no unifying equations or laws and this makes the field exceedingly hard and thus very challenging.

- Granular materials cannot be defined as a single phase of matter
- Bulk flow characteristics of granular materials do differ from those of both fluids and solids
- Granular materials occur widely in nature and are second only to water as the most manipulated and used material in industry [5]

“The physics of granular materials is governed by interparticle forces, gas–particle interaction, geometry of particle positions and geometry of particle contacts. For dry fine powders of micron and sub-micron particle size, interparticle attractive forces are typically much higher than particle weight, and particles tend to aggregate. Because of this, cohesive powders fracture before breaking, flow and avalanche in coherent blocks much larger than the particle size. These two features, strong attractive forces and strong gas interaction make powder behavior differ qualitatively from the behavior of large, noncohesive grains.” [5]

1.2.2 Interparticle Interactions

Interparticle attraction leads to cohesiveness, which can severely hamper flowability overall and contributes to poor handling properties of powders. [9] Major factors influencing interparticle attraction are discussed below.

1.2.2a Van der Waal’s Attractions

Van der Waal’s attractions have a major effect on fine powders (those that are micron size and smaller). [9] While not as strong as the covalent bond or Coulombic interactions, van der Waal’s interactions are always present and play a central role in surface force interactions between two particles. [5] As will be evident later, this is the main attraction force that is affected by dry particle coating [10], which is the topic of this work.

1.2.2b Electrostatic Forces

These forces play a major role in liquids, and allow colloidal stability through electrostatic repulsion, thus they do not play a major role in cohesion reduction via dry particle coating of pharmaceutical powders in dry state. [9]

1.2.2c Liquid Bridge/Capillary Forces

Liquid bridge forces are significant for dry powders. The liquid bridge forces between fine particles can possibly become more significant than van der Waal's forces, and can be a cause of problems in handling and dispersion of particles in presence of humidity. The forces can be controlled by manipulating the amount of liquid and its surface tension and viscosity. Unlike van der Waal's forces, the liquid bridge forces include dynamic effects and also dissipative effects. [9]

While these forces are very important in terms of evaluating the influence of humidity or added binder to pharmaceutical powders, detailed examination is deemed to be outside the scope of this work.

1.3 Approach

As stated before, engineered particles, which are surface modified via dry coating processes have been shown to have improved flow and handling properties, and hence are very useful for a number of industrial applications. [6-8]

In the case of pharmaceutical powders, they often consist of nonuniform size and include significant amount of fine powders which further exaggerates the flow-related problems [1-3]. This is true for most APIs but also for some excipients as well. In addition, due to the poor solubility of many new drug molecules, there is an increased need for improving the bioavailability; one of the ways to do so is to reduce the particle size [11-14]. One major bottleneck in incorporating particles with smaller size in tablet formulation is increasingly poor flowability as particles become finer and bulk density is also reduced. In addition, poor flowing powders significantly agglomerate and result in nonuniform API content. Hence, improved flow for fine powders is very desirable. In

addition, many pharmaceutical powders even in size range of 50-100 μm have poor flow behavior which requires special efforts during manufacturing processes [1-3]. Besides utilizing aeration and vibration, addition of a flow agent is an effective way to improve the flowability of cohesive particles, as discussed in the pioneering work of Molerus [15] and other researchers [16-18]. One of the most effective methods to improve the flowability of highly cohesive powders is surface modification, which usually involves particle coating to alter the surface properties of micron to nano-size particles/powders. It is typically carried out by wet-coating techniques (e.g., pan coater, fluidized bed coaters, wet chemistry techniques, etc.). However, these methods are not suitable for very fine powders; the main disadvantages include cost of drying and solvent removal, caking and agglomeration after drying, added steps such as milling and sieving, solvent residues, and potential environmental impact. Dry-particle coating is a promising alternative approach to coat fine size particles with the nano-size particles by the application of mechanical forces [7-8, 19]. In dry-particle coating, nano or submicron size “Guest” particles are brought in contact with relatively larger micron size “Host” particles (in this case API particles) by means of mechanical forces. Due to the high number of collisions between the host particles and the walls, guest particles are coated on the surface of host particles as the Van der Waal’s forces are dominant in creating a strong cohesive bond between the host and guest particles. Since there are multiple collisions that take place, there is a possibility of attrition, in particular if processing time is extensive and depending on the coating method. It has been shown that such surface modification allows for modifying and controlling properties such as cohesion, flow, sinterability (coated material can be made to sinter at a lower or higher temperature than

normal), etc. [6, 20]. It was also shown that dry coating is more effective than simple addition of nano silica to the cohesive powder [6]. There are many other factors besides van der Waal's forces, which can influence powder flow and cohesivity, e.g., particle size, surface area, amount of fines, roughness, absorbed moisture, etc. In general, these properties are very difficult to control once an API form and manufacturing process are specified. Therefore, dry-powder coating is an attractive approach to engineering the API particles and customizing them for dosage form and manufacturing requirements.

The flow behavior of granular materials can be broadly classified into four different flow regimes: plastic behavior, inertial flow, fluidized flow, and entrained flow, determined by particle size, density, and gas flow [21]. Since a single physical model or a device is not capable of explaining the behavior of granular material in all four dynamic regimes, it is better to utilize a flow characterization instrument that closely matches the expected flow regime in the process of interest; e.g., die filling, mixing, feeding, storage in a hopper and subsequent discharge, etc. Cohesive powders are particularly more challenging and cannot be tested by a single testing device since it is very difficult to quantify and predict the cohesive powder behavior [22-25]. In order to understand the flow behavior of cohesive (poor flow) powders, various techniques have been proposed [23-25], including the Carr's index, based on its angle of repose (AoR), compressibility, angle of spatula, and the uniformity/cohesion index. These methods may have limitations, as uncoated powders and coated powders may have different flow regimes. Thus the choice of flow testing device is crucial, in particular for the dry coated powders because typically these are fine powders that have been made weakly cohesive as opposed to strongly cohesive due to surface modification, and may require additional

considerations in powder testing as they would follow different flow regimes. For example, toner powders that are fine but due to particle engineering, they are made less cohesive and exhibit fluidization and suspension regime, which was not previously observed for fine cohesive powders. Thus it is likely that standard tests that are decades old yet very useful such as the angle of repose or packed density measurements may need to be revisited when they are used to characterize surface modified powders.

Thus the overall approach taken in this investigation will employ lessons learnt from other fields in the area of surface modification for flow improvement as well as their characterization. This leads to main objectives of this work as discussed next.

1.4 Objectives

The main objective of this work is to address systematic flow improvement of poor flowing pharmaceutical powder materials, both APIs and excipients, through application of dry coating techniques. The work will examine what types of nano-particle or other additives may be surface coated on the API and excipient particles to improve flow, what are the optimum amounts, which types of devices from those reported in the literature [6-8] may be used and how they differ in general performance, which characterization methods are most relevant from those reported in the literature to assess the flow improvement, and evaluate the influence of surface modification of API particles on the final products, more specifically the tablets to examine if surface coating adversely impacts properties such as tablet strength, dissolution, etc. In addition, since the commercially available dry coating devices are mostly batch type and somewhat specialized and unknown to the pharmaceutical practitioners, evaluation and adapting of typical high-shear devices used in pharmaceutical industry will be attempted, with a goal

of achieving scalable continuous dry coating operation. Finally, the thesis will also identify the need for alternate ways to evaluate the flow and examine available approaches to utilize multiple powder flow measures to assess not only the flow improvement but propose framework for making decisions regarding formulation of the tablet dosage depending on the flow related properties.

1.5 Materials and Methods

We have examined several APIs and excipients, more specifically, Acetaminophen and ibuprofen have been considered as model active pharmaceutical ingredients (APIs), and are surface modified via dry coating of nano-additives in several dry coating devices. The study considers use of hydrophobic as well as hydrophilic nano-additives. The types of powders and the grades used are shown in Table 1.1.

Table 1.1 Host Materials

Host Powder	Type of Powder
Acetaminophen	
<i>Micronized</i>	Active Ingredient
<i>Semi-micronized</i>	Active Ingredient
<i>Coarse</i>	Active Ingredient
Ibuprofen	
<i>50 Grade</i>	Active Ingredient
<i>90 Grade</i>	Active Ingredient
<i>110 Grade</i>	Active Ingredient
Pfizer A	Active Ingredient
Pfizer B	Active Ingredient
Pfizer C	Active Ingredient
Cornstarch	Excipient
Celphere MCC	Excipient
Mannitol	
<i>Powder Grade</i>	Excipient
Lactose	
<i>310 Grade</i>	Excipient

The types of guest powders used and their properties are shown in Table 1.2.

Table 1.2 Guest Materials

Guest Powder	Type of Powder
Silica	
<i>Evonik-Degussa A200</i>	Excipient-Hydrophilic
<i>Cabot Cab-o-Sil M5P</i>	Excipient-Hydrophilic
<i>Evonik-Degussa R972</i>	Excipient-Hydrophobic
Magnesium Stearate	
<i>Vegetable Grade</i>	Excipient-Hydrophobic

The resulting powders are analyzed for their particle size distribution, coating coverage, and dispersibility; the latter is evaluated using the Sympatec Helos/Rodos system under varying dispersion conditions. In addition, a suite of techniques are employed for powder flow and other properties which are important for large scale pharmaceutical manufacturing. Extensive powder flow property characterization is done, ranging from novel methods such as vibrated packed density measurements to industry standard technique such as shear testing via the Schulze tester. In addition, other powder properties such as sticking tendency are evaluated, and several flow testers are also employed, including the Aeroflow, Freeman Rheometer, and the Hosokawa Powder Tester. Lastly, tableting and dissolution studies will be completed. The results of these tests are compared with those for untreated API powders in order to examine the influence of surface modification on property enhancements.

As will be shown in subsequent chapters, dry coating makes it possible to impart improved flowability of various APIs and their blends with very high API contents (higher than 75 %) even for very cohesive micronized API powders. Special attention has been made also to minimize the attrition of the particles during the surface modification,

as a reduction in particle size would be detrimental to the flow. It is hoped that the results of this work will be useful for pharmaceutical processing including flow, handling and downstream processing.

CHAPTER 2

SURFACE MODIFICATION

2.1 Introduction

Dry coating is an innovative technique in which nano particles are mechanically coated onto surface of larger (from a micron to about 200 microns) host particles to impart useful properties to the final product, which are engineered particles. Dry coated engineered particles can have improved flow and handling properties, and hence are very useful for a number of industrial applications.

Besides utilizing aeration and vibration, addition of a flow agent is an effective way to improve the flowability of cohesive particles, as discussed in the pioneering work of Molerus [15] and other researchers [16-18]. One of the most effective methods to improve the flowability of highly cohesive powders is to modify the surface properties of the particles.

Surface modification usually involves particle coating to alter the surface properties and functionality of micron to nano size particles/powders. Typically surface modification of particles is carried out by wet coating techniques (e.g., Pan Coater, Fluidized bed coaters, wet chemistry techniques, etc.) to form a barrier or a film of host particle with its surrounding environment to extend or delay release, separation of incompatibles, protection of water vapor, taste masking etc. However, in addition to the environmental concerns resulting from the formation of hazardous waste and VOC emissions, these methods are not suitable for very fine powders. Dry particle coating is a promising alternative approach to coat fine size particles with the submicron size particles by the application of mechanical forces [7-8, 19].

In dry particle coating, sub-micron size “Guest” particles are brought in contact with relatively larger micron size “Host” particles by means of mechanical forces. Due to the high number of collisions between the particles, guest particles are coated on the surface of host particles as the Van der Waal’s forces are dominant in creating a strong cohesive bond between the host and guest particles, which results in the formation of value added and engineered composites. Thus, the dry particle coating is used to deposit a very small amount of nano-sized additives with high degree of precision onto drug or excipient particles in order to change their flow and other properties. A schematic showing the dry coating process is shown in Figure 2.1.

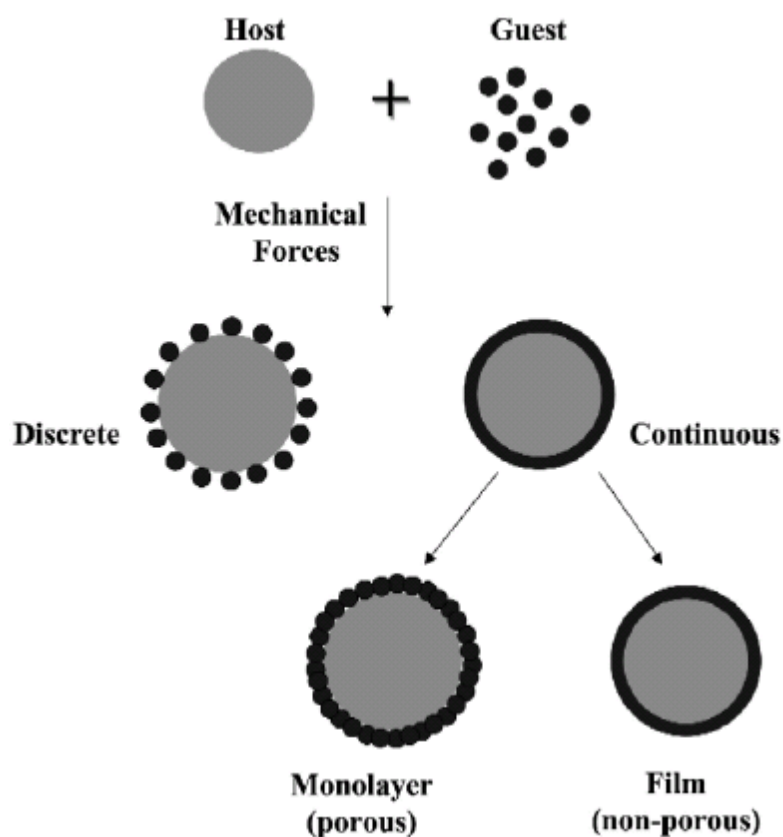


Figure 2.1 Overview schematic of coating process.

Dry coating method allows the deposition of nano-additives directly onto a particle with as little as 0.01 % by weight. It has been shown such surface modification

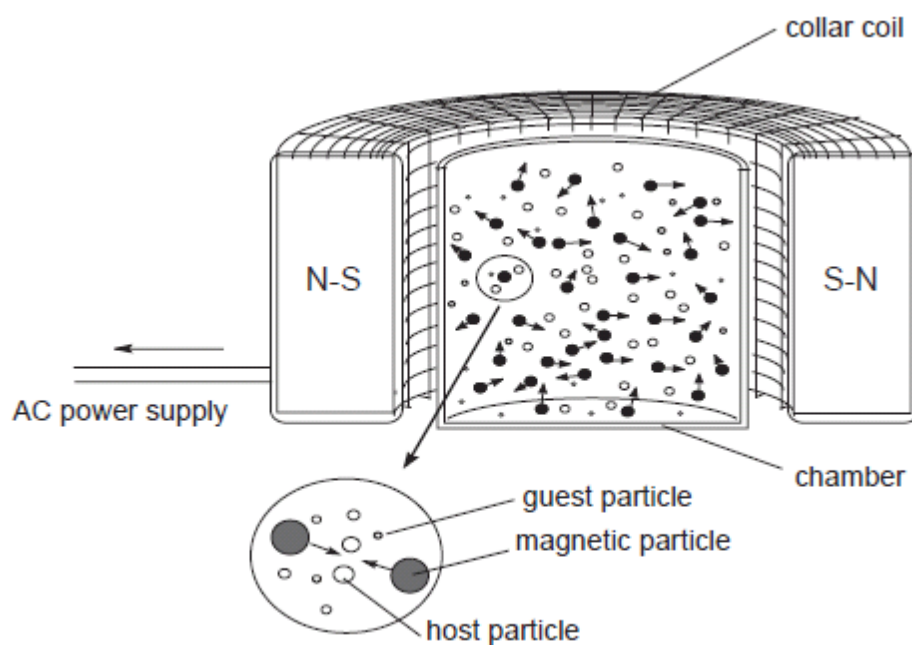
allows for modifying and controlling properties such as cohesion, flow, sinterability (coated material can be made to sinter at a lower or higher temperature than normal), etc [6, 20]. It was also shown that dry coating is more effective than simple addition of nano-silica to the cohesive powder [6].

Surface modification of APIs by coating with silica is carried out in dry-coating equipment as illustrated in the following sections. Dry coating devices commonly employed for the coating of smaller size particles (guest) onto the surface of relatively bigger size particles (host) are based on the principle of application of high impact and shear forces. Schematics of four dry coating devices are shown in the following sections, including magnetically assisted impaction coating (MAIC), Hybridizer, v-blender and Comil. Many of these dry coating devices have been reviewed in the literature [6-8]; however, they are also briefly outlined in the next subsections for the sake of completeness. In addition to being used as a dry coating devices, the V-blender (Patterson-Kelley, BlendMaster, East Stroudsburg, PA,USA), the most commonly employed blending device in the pharmaceutical industries, is used for preparing the blends of uncoated and nano-size silica-coated APIs and the excipients to mimic drug formulations.

2.2 Magnetically Assisted Impaction Coating Device

MAIC (Fig.), patented by Aveka, Inc., Woodbury, MN, USA, is an environmentally benign dry-coating technique that does not require any solvents or binders, conditioning steps, or subsequent drying time [8]. A measured mass of both host and guest particles is placed into a processing vessel. A measured amount of magnetic particles is also placed in the processing vessel. The magnetic particles are made of barium ferrite and coated

with polyurethane to help prevent contamination of the coated particles. Magnets used in the study had particle size range of 800 to 1,400 μm . An external oscillating magnetic field is created using a series of electromagnets surrounding the processing vessel. Consequently, the magnetic particles are excited and gain translational and rotational speed with high mobility inside the vessel resembling a gas-fluidized bed system, but without the flowing gas. These agitated, spinning magnetic particles then impart energy to the host and guest particles, causing collisions and allowing coating to be achieved by means of impaction of the guest particles onto the host particles. A schematic of the MAIC is shown in Figure 2.2a while a closeup of the coating process is shown in Figure 2.2b.



Experimental set-up of MAIC

Figure 2.2a MAIC process.

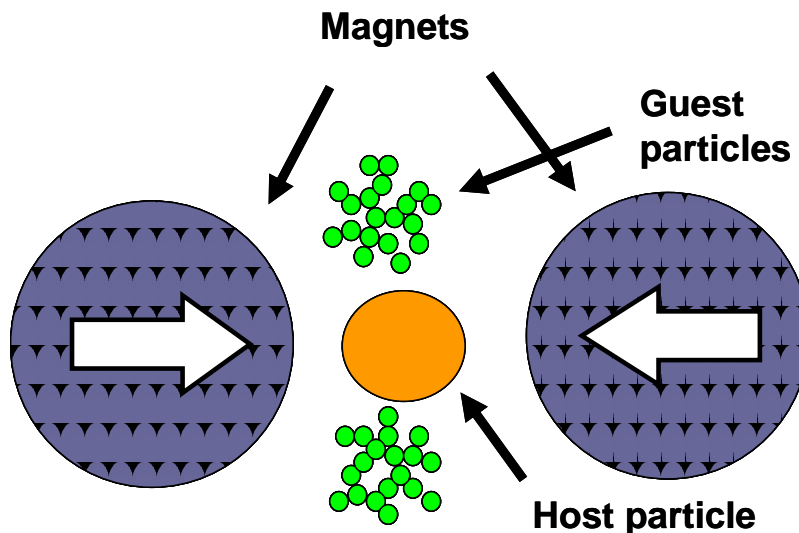


Figure 2.2b Close-up of the actual coating process.

There are several unique features of MAIC that make it advantageous as a dry-particle coating device. The MAIC as overall is a simple operation and is capable of coating host particles without causing significant change in the powder shape, morphology, and size [7-8, 19]. Next, heat generation is insignificant at a macroscopic level although there could be some heat generated at a microscopic level [15-18]. This fact was verified by the measurement of the temperature of the glass bottle used in the MAIC that contains the powder, and it was found that it stayed at room temperature during the process. This is in contrast to most other processing equipment where high heat is generated and in some cases where water cooling is employed to eliminate or reduce temperature rise, such as the hybridizer. In these experiments, a magnet to sample weight ratio of 0.5:1 was employed and the process was run for 10 min. These coating conditions have been previously optimized [8].

Positron Emission Particle Tracking (PEPT) was used as a tool to determine the differences in mobility of powders with no additive compared to powders that had been coated with a specific level of additive. Previous results [6-8] indicate that increasing the

level of additive caused an increase in the flowability and essentially the mobility of the powder. PEPT was used as a tool to quantify the increase in mobility of the powder.

PEPT is a tool derived from the positron emission tomography (PET) nuclear technology used most commonly in medical imaging. Instead of imaging as with PET, PEPT uses the same triangulation principle to track a positron emitting tracer particle. The triangulation principle works using the pairs of gamma rays emitted from the particle to track the exact location of the particle at that time.

PEPT tracks a single radioactive tracer, in this case a 70 micron ion-exchange resin, onto which is adsorbed a positron emitting F_{18} radioisotope. The tracking of this tracer particle produces a trajectory of Cartesian coordinates as a function of time.

During the radioactive decay of the adsorbed radioisotope, a high-energy positron is emitted, a nearby electron annihilates said positron, and two nearly collinear gamma rays are emitted. The PEPT camera, which is comprised of two parallel plates of solid scintillating crystals of sodium iodide, can detect and locate the gamma rays from this decaying isotope. The annihilation glows and the position is determined by an array of photomultiplier tubes behind the crystal. If both the gamma rays are absorbed by detector elements on each plate, then a line can be drawn between the detector element on which the tracer theoretically lies. However, due to the scattering of gamma rays, erroneous locations might also be calculated. To exclude these erroneous locations, an algorithm has been developed to process the data as follows: each discrete location is obtained from a fixed number of events (detected photon pairs). The location is obtained as the centroid of the lines of response (LORs) joining photon pairs. One-by-one, the furthest lines are removed until a tight bunch of LORs centering on the location remain.

Knowing that a large number of events are used for each location means that each location is an average position over the duration of a time interval. The accuracy of this approach has been examined by the creator of the technology [26-27] who previously showed that the particle can be tracked within 1 mm distance. [28]

A Magnetically Assisted Impaction Coating (MAIC) device was transported to the University of Birmingham, UK to determine how the powder behaves during the coating process and to investigate the changes in mobility of the powder when there is no additive and when there is varying amounts of silica added.

Cornstarch powders were used as host powders for experimentation, with hydrophobic fumed silica as the additive. Powders had been previously prepared using the Magnetically Assisted Impaction Coating (MAIC) process. Different percentages of silica additive were used, ranging from 0.5% to 1%. Using previously obtained SEM images, the cornstarch powder was shown to be coated by the silica at every percentage of additive. Additionally uncoated cornstarch was used as a baseline case to assess degree of mobility improvement based on additive percentages.

Initially, a cornstarch particle was to be used as a tracer, since it is a commonly used material in the current and previous coating work. However, due to the small size of the cornstarch particle, it was unable to be labeled as radioactive, and hence a 70 micron ion exchange resin and gamma alumina were used as tracers to simulate the cornstarch in the MAIC system. These materials are comparable with the cornstarch in density, though their size is larger. A magnetic particle was also able to be labeled as a tracer particle and that was also used in a secondary set of experiments to see if there was any change in the magnets movement when there was an additive in the system, despite the motion of the

magnet being caused by an external force, the oscillating magnetic field. The magnets are specially prepared barium ferrite magnets coated with polyurethane.

The MAIC apparatus was set up within the special PET cameras and a cooling fan was used to maintain a constant temperature. A jar was placed within the MAIC apparatus, per standard operating procedure, and the coated powders were placed in the jar with magnets in a 2:1 ratio to the powder. The MAIC and the PET cameras were turned on simultaneously and ran for 15 minutes, with up to 500 data points recorded and locations triangulated per second.

There was a significant difference in the tracer's mobility when coated cornstarch was used as opposed to the uncoated cornstarch. Figure 2.3 shows the motion of the tracer particle when there is no silica in the system.

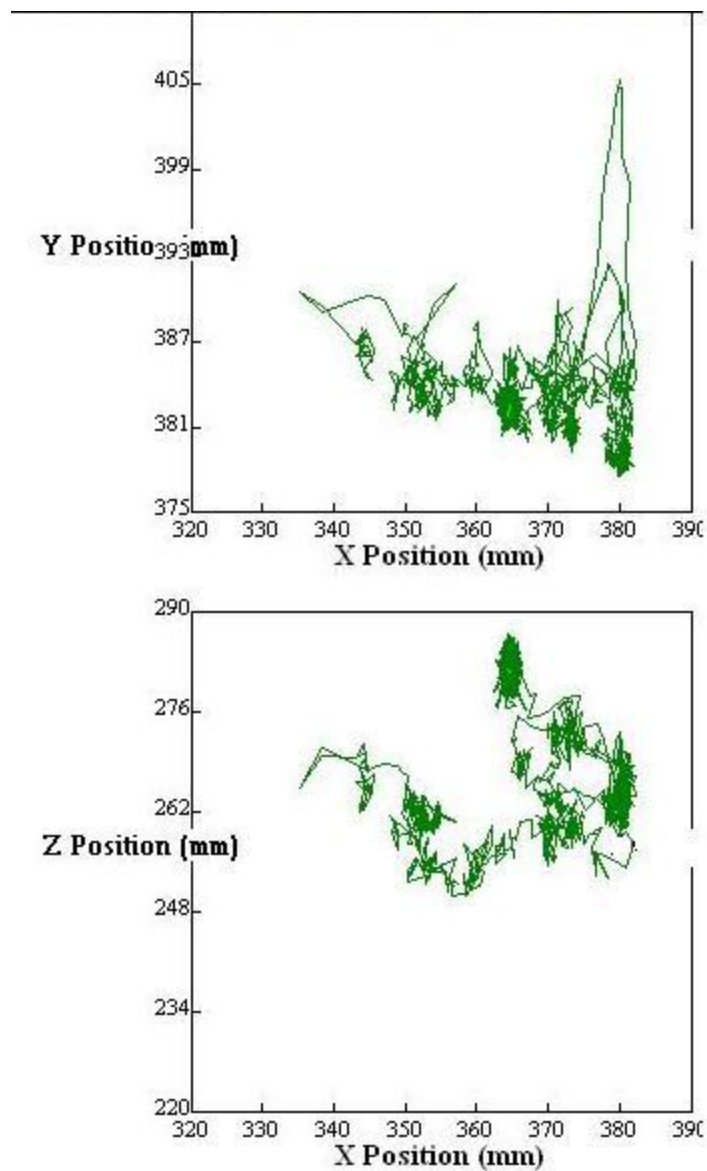


Figure 2.3 Tracking of a single particle in the MAIC system when there is only uncoated cornstarch present.

Figure 2.3 shows the overall motion of the tracer particle at 36 seconds. The motion of the particle is scattered and sporadic throughout the system. Figure 2.4 shows the motion of the coated cornstarch in the system.

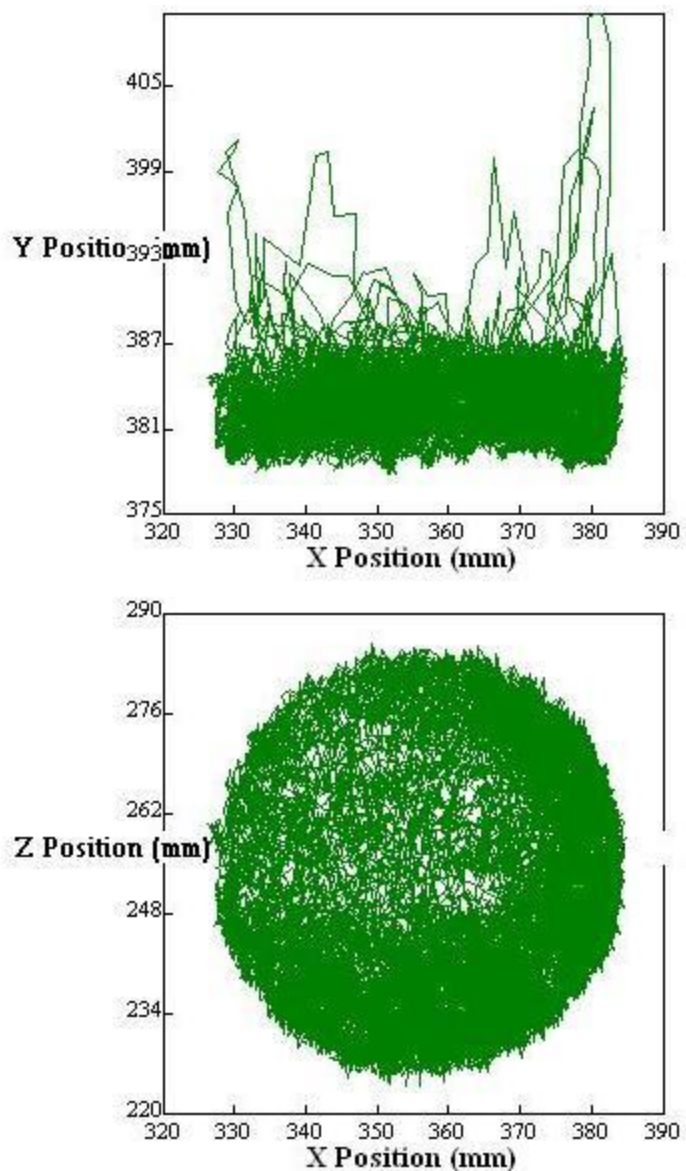
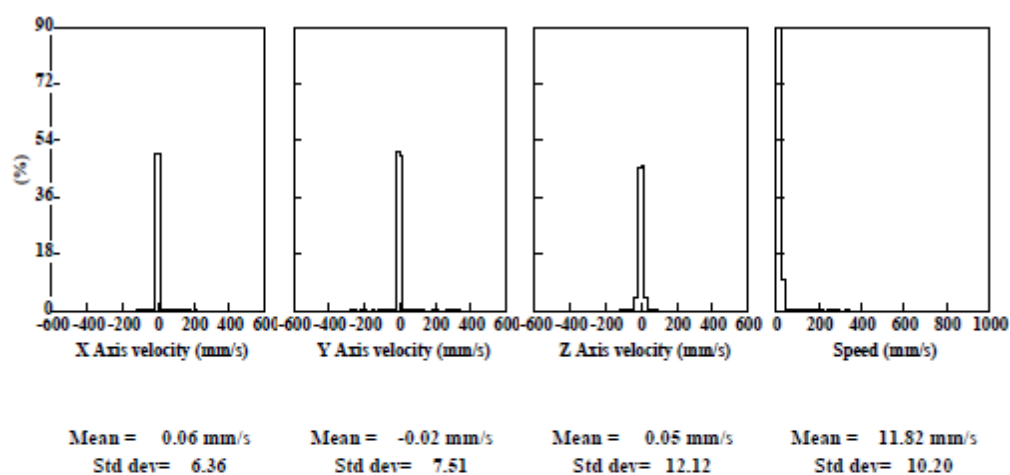


Figure 2.4 Tracking of a single particle in the MAIC system with coated cornstarch present.

Figure 2.4 shows a snapshot of the movement of the tracer particle at only 6 seconds. In comparison to Figure 2.3, there is significantly more motion of the tracer in the coated powder system than the uncoated. In the 6 short seconds, the tracer is able to cover the entire effective area of the cell where the coating takes place. In contrast, the particle in the system without silica has very limited movement, even in a time period 6

times longer. Both Figures 2.3 and 2.4 show the movement of ion-exchange resin as the tracer.

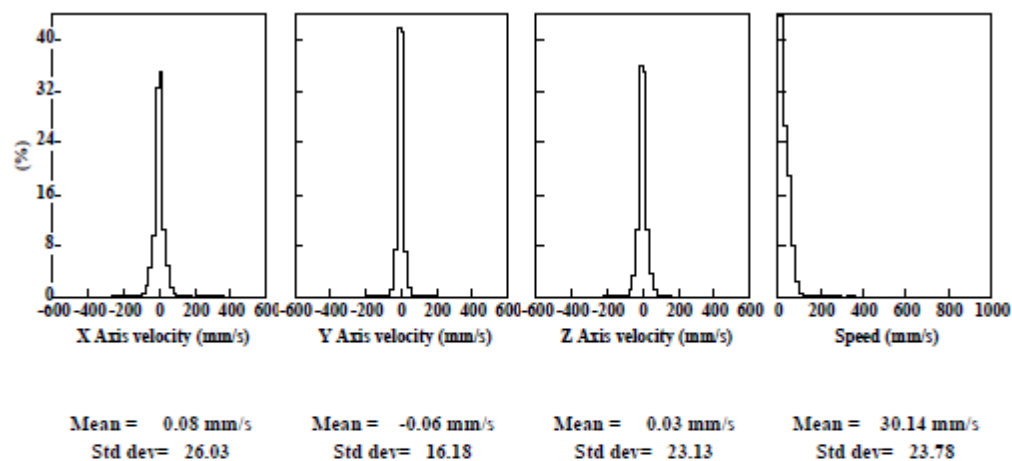
Using the proprietary tracking software developed at the University of Birmingham, UK, the velocity of the tracer particle can be determined. Based on the movement of the tracer as shown in the mobility plots above, there should be an increase in tracer velocity in the system with the coated cornstarch.



LAUREN01.A03

Repeat R1 50 V

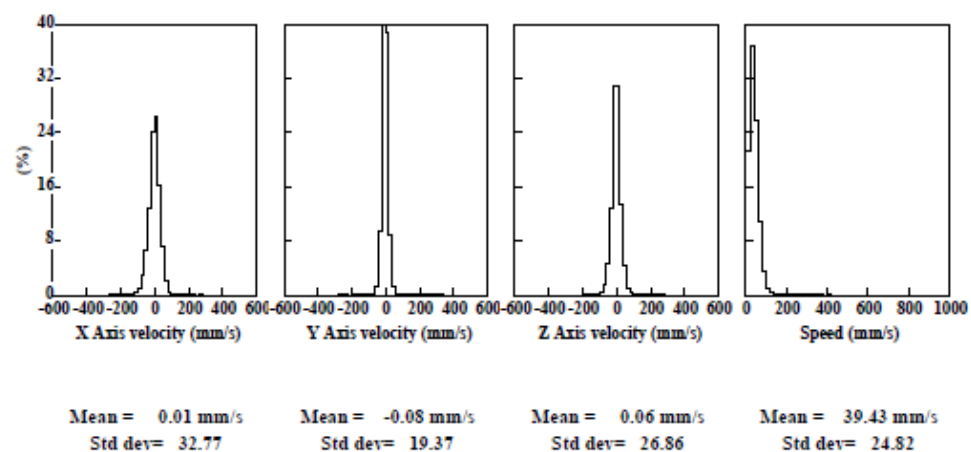
Figure 2.5 Velocity plots of ion-exchange resin as a tracer with no silica additive with a voltage of 50.



LAUREN01.A04

Transient R2 0.05% 50 Volts

Figure 2.6 Velocity plots of ion-exchange resin as a tracer with 0.05% silica additive with a voltage of 50.



LAUREN01.A09

R3 0.5% 50 V

Figure 2.7 Velocity plots of ion-exchange resin as a tracer with 0.5% silica additive with a voltage of 50.

Figure 2.5 shows the velocity of the tracer particle with no silica in the system. The tracking software estimates the velocity as about 12 mm/s. Figure 2.6 shows the velocity of the tracer particle with 0.05% silica in the system. Here, the velocity is about 30mm/s, which is a significant increase, nearly double the velocity of the system with uncoated cornstarch. When the amount of silica is increased to 0.5%, the velocity increases even further to nearly 40mm/s as shown in Figure 2.7. It can be concluded that the addition of silica to the system significantly affects the mobility of the powder, increasing the mobility as the amount of silica is increased. Further processing of the data and new experiments may be required to adequately understand the phenomenon completely.

2.3 Hybridizer

The Hybridizer from Nara Machinery, Tokyo, Japan, shown below consists of a high-speed rotor with six blades, a stator, and a powder recirculation circuit. The powder (host and guest articles) placed in the processing part of the vessel is subjected to high impaction and dispersion due to the high rotating speed of the rotor. The particles undergo many collisions, and this allows for break-up of fine agglomerates and powder coating due to the embedding or smearing of the guest particles onto the surface of the host particles. One of the important advantages of this device is its capability of providing a high-speed rotation in the range of 5,000 to 16,000 rpm. A schematic of the Hybridizer is shown in Figure 2.8.

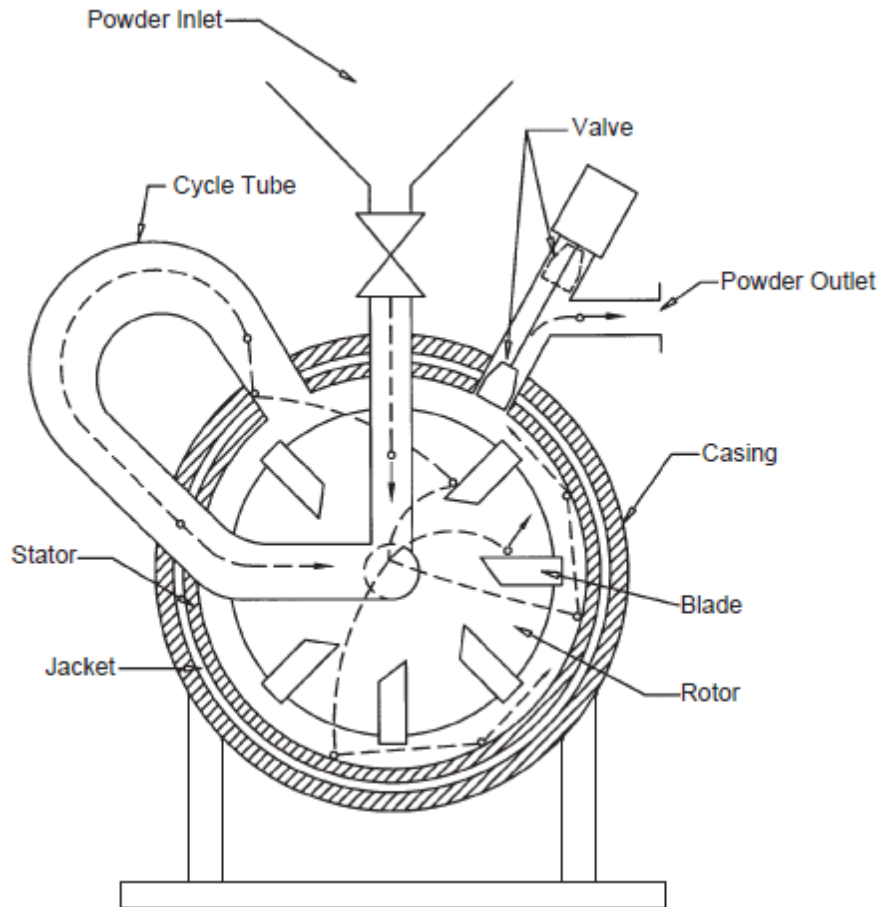


Figure 2.8 Schematic of Hybridizer coating device.

Due to the strong forces applied to the materials at such high rotational speeds, very short processing times are required to achieve either a discrete or uniform coating. Also, it consists of a recirculating unit that continuously moves the particles in and out of the processing vessel and against the blades of the rotor, thus enabling a homogeneous coating or mixing of particles. [29]

During this process, there is a significant amount of heat generated and the unit is jacket cooled with water, but there is still a noticeable amount of heat imparted to the system which could affect the particles being coated. Additionally, due to the rotor shearing at above 5,000 RPM, there is the potential for significant particle attrition. [29]

2.4 V-blender

The v-blender is a commonly known and widely used device in the pharmaceutical industry. It is a twin shell mixing system and may or may not have a separate agitator bar running in the center of the shells, which in general increases shear and promotes mixing. In terms of dry coating, the device does have the potential to process the powders and produce a coating, but generally the level of shear is relatively low and thus the coating process may take an extended period of time (>1 hour). This time would increase even further without the use of an intensifier bar. Thus the v-blender is a rather inefficient system to dry coat powder particles. [29] The v-blender is shown in Figure 2.9a while a schematic with the intensifier bar is shown in Figure 2.9b.



Figure 2.9a Overview of the v-blender.

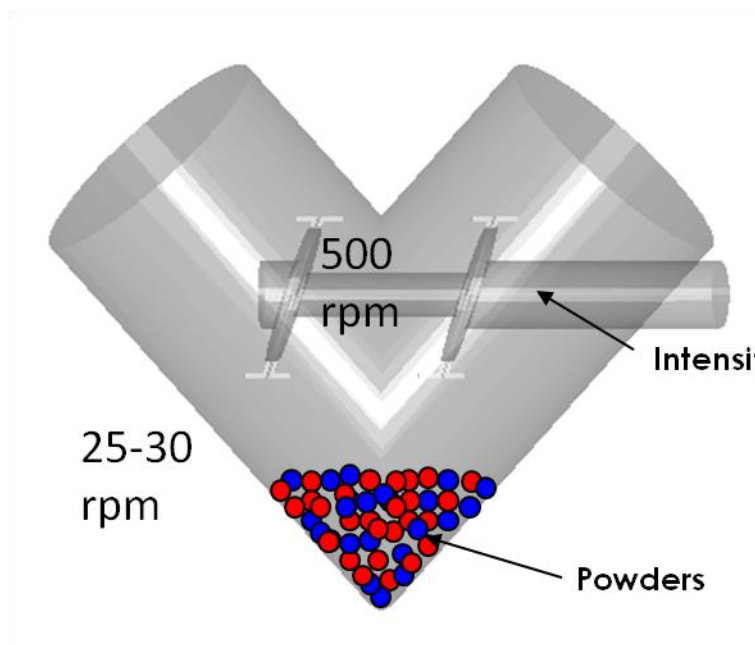


Figure 2.9b Working view of the v-blender.

2.5 Quadro U3 Comil

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 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 significant product contamination risk. Also, these techniques would not be practical for large-scale manufacturing of drug products as they can only accommodate relatively small batch sizes. Therefore, a method for applying these dry powder coatings to host particles using a conventional pharmaceutical unit operation to minimize capital investment and allow for large-scale or continuous processing is desired. This section will describe the novel method for using a comil for quickly and efficiently applying dry powder coatings to APIs. [30]

A comil can be used for deagglomeration/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 [31]. Dry powder coating was achieved using a conventional comil to exploit its capability for deagglomeration with intensified mixing. As powder is charged to the mill, it is retained and mixed in the middle of the conical vessel. The comil coating procedure is shown in Figure 2.10.

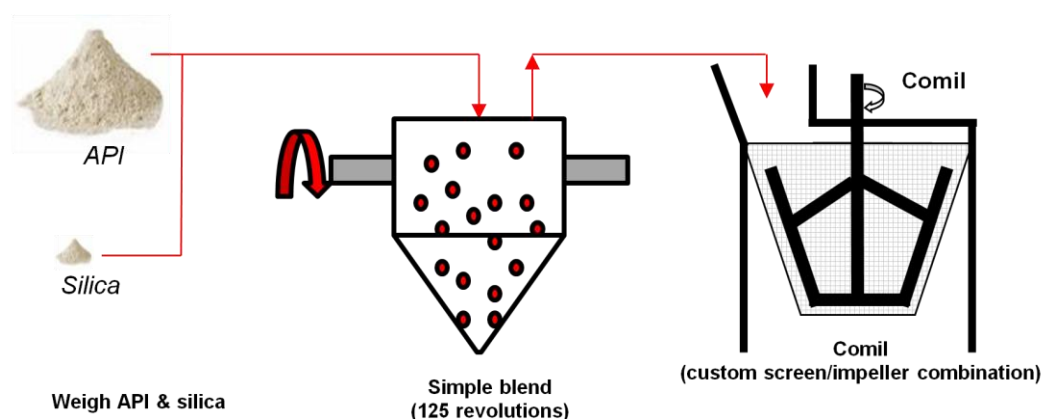


Figure 2.10 Comil coating device procedure.

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 deagglomerate the silica particles. It is believed that during this time period the larger agglomerates of nano-sized silica particles break-down into smaller sub-agglomerates and preferentially attach to the substantially larger API particles through van der Waals attractions. [30] A close up of the comil device in action is shown in Figure 2.11.

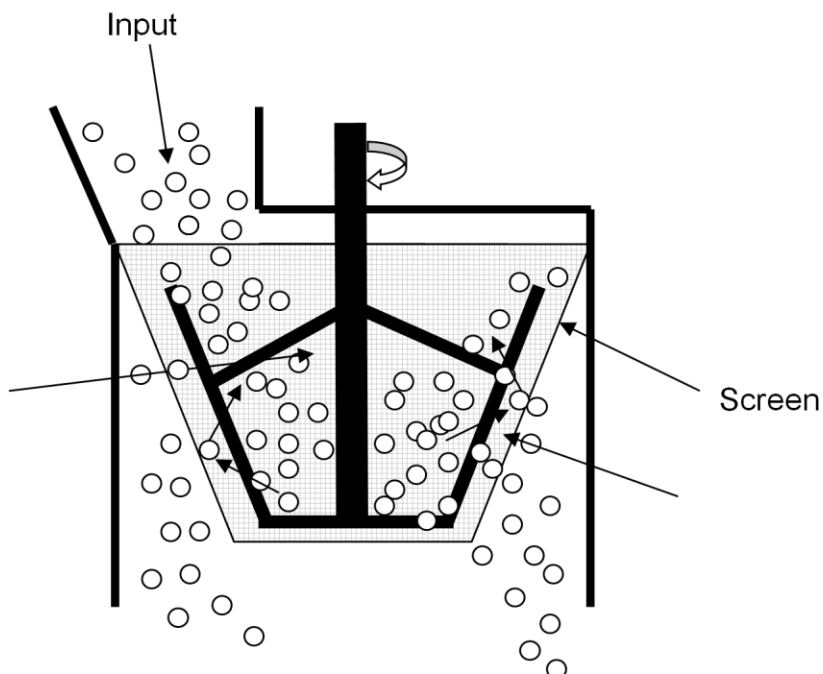


Figure 2.11 Close-up of the Comil device in action.

Further residence time is expected to promote repeated collisions between larger API 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. [30]

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 to maximize residence time and minimize 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 10 to 200 grams per minute. [30]

2.6 Confirming the Coating

The first step after the processing has been completed is to determine if particle coating has taken place. It is important to examine the powder that has not been processed (the original powder) to have a comparison to see if there is a coating on the surface of the powder. The most effective way to determine if the coating is there is using a scanning electron microscope (SEM). Using the SEM allows images to be taken of the surface in great detail which shows the changes due to processing and the extent of the coating. The SEM in use at NJIT can image the silica guest nano particles on the surface of the host particle with great detail which is shown in the following sections.

2.6.1 Cornstarch

Most of the previous work done with nanocoating used cornstarch. Cornstarch is very smooth, extremely spherical and has a tight particle size distribution. Due to those factors, it coats very well in many of the processes previously. Cornstarch was also used in the original optimization study of the MAIC and a secondary optimization study to determine the extent of the attrition to particles in the MAIC. Both are out of the scope of this work but cornstarch has been used in this work to reveal more information about the coating process itself using PEPT in section 2.2.1. Figures 2.12a and 2.12b show the

cornstarch prior to the coating process at two different magnifications, 10KX and 20KX, respectively.

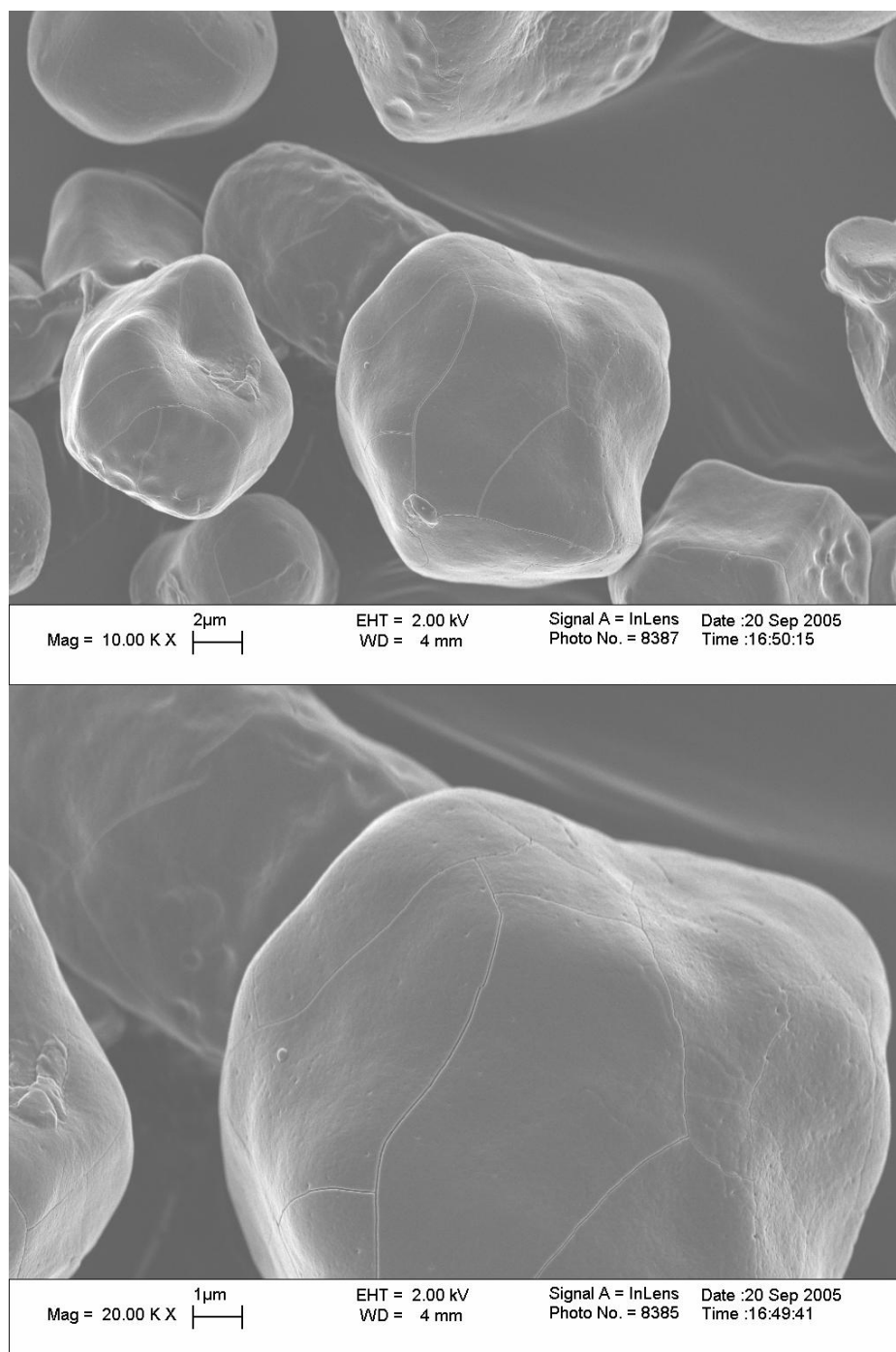


Figure 2.12a (top) and 2.12b (bottom) Various magnifications of uncoated cornstarch.

Figures 2.13a and 2.13b show the cornstarch after coating in the MAIC with 1% R972 silica at two different magnifications, 2KX and 5KX respectively. Figure 2.8b shows the very distinct, discretized coating of the silica nanoparticles coated on the surface.

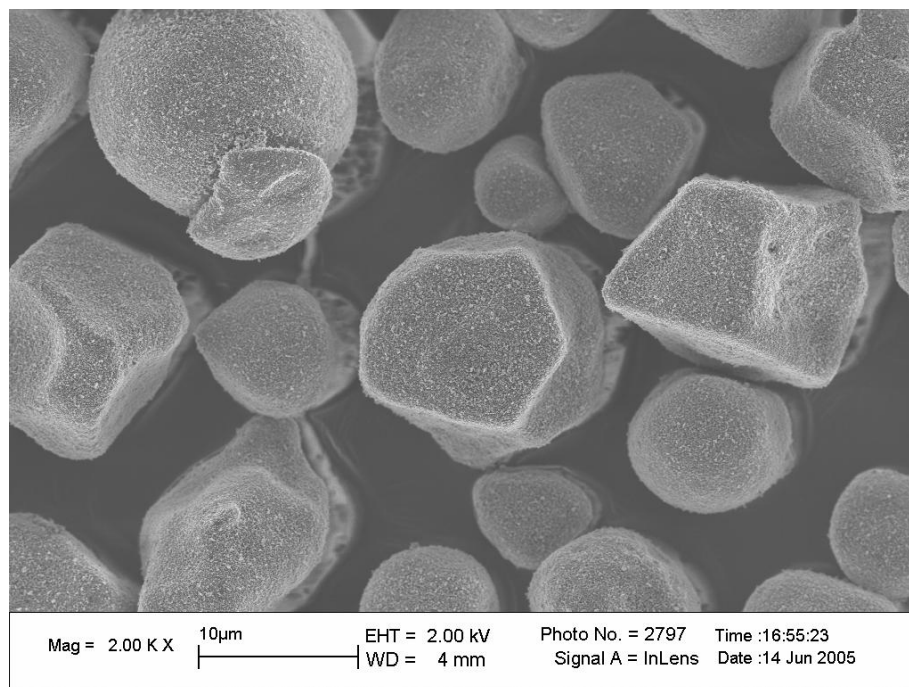


Figure 2.13a (top) and 2.13b (bottom): Various magnifications of cornstarch coated in the MAIC with 1% R972.

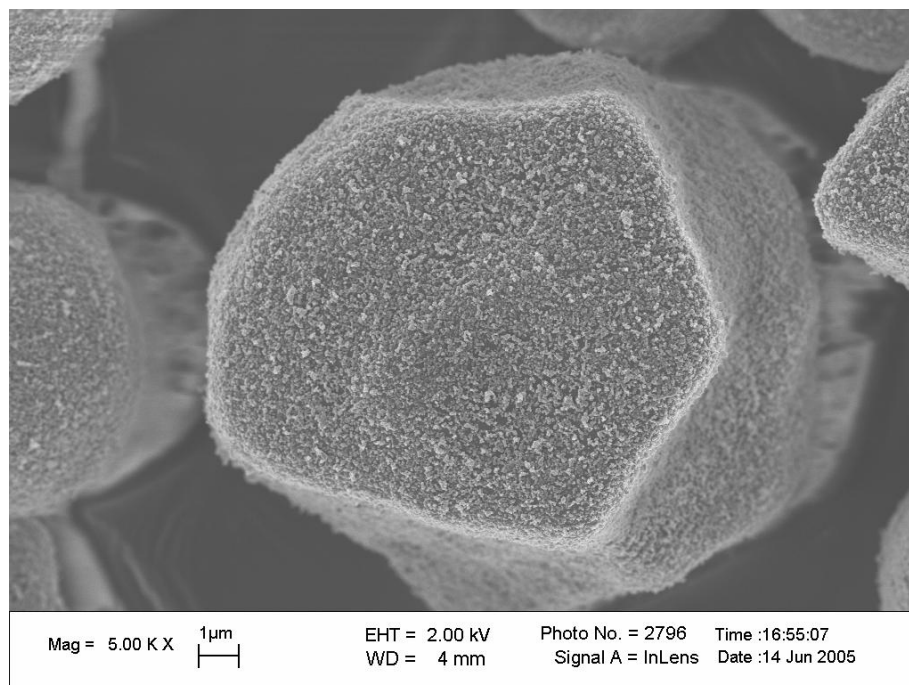


Figure 2.13a (top) and 2.13b (bottom): Various magnifications of cornstarch coated in the MAIC with 1% R972. (Continued)

2.6.2 Acetaminophen

The initial active pharmaceutical ingredient chosen to try to coat was acetaminophen. Acetaminophen is a widely used and recognized drug and has very poor handling properties, including a high cohesivity. Additionally it comes in different grades that each have different properties and is inexpensive overall.

2.6.1.1 Semi-micronized Acetaminophen. Semi micronized acetaminophen is a micron sized powder made up of irregularly shaped needles. The particle distribution is very wide. The surface of the particle is also rough, especially relative to the cornstarch. The as-is material is shown in Figures 2.14a and 2.14b at 500X and 3KX magnifications, respectively.

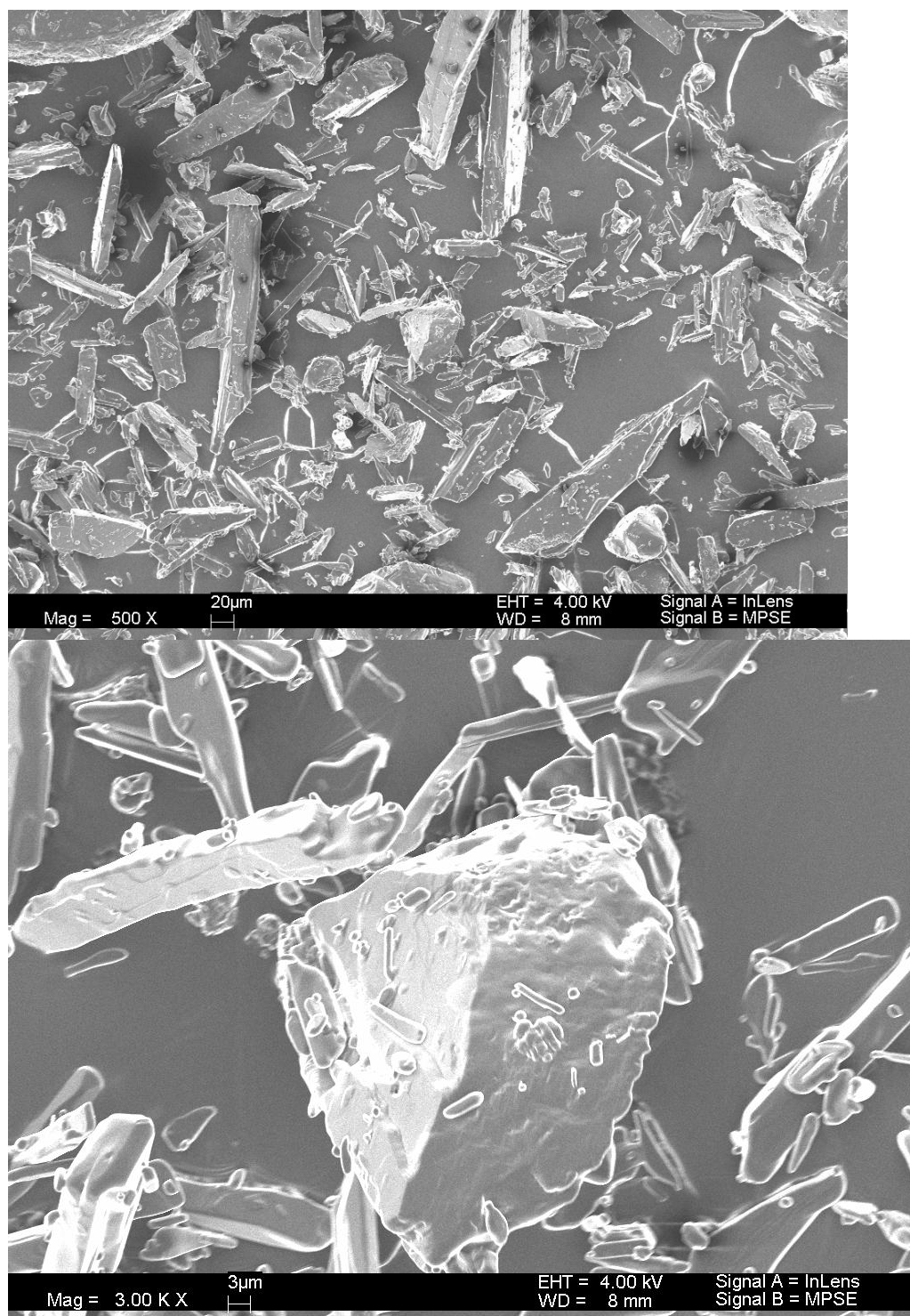


Figure 2.14a (top) and 2.14b (bottom): Various magnifications of uncoated semi-micronized acetaminophen.

Semi-micronized acetaminophen coated well in the MAIC with little size change, however after processing, the particles became more spherical. The coated powders are shown in Figures 2.15a and 2.15b at 2KX and 18.15KX magnifications, respectively. In Figure 2.10b, the nanosilica coating is especially noticeable.

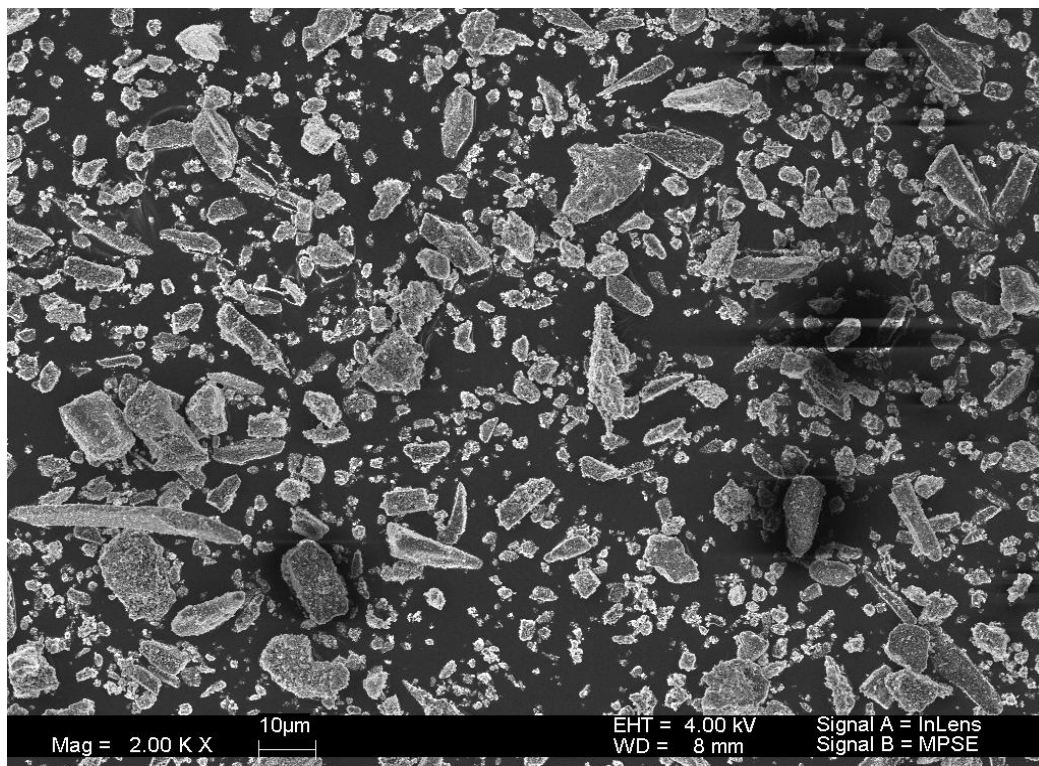


Figure 2.15a (top) and 2.15b (bottom): Various magnifications of semi-micronized acetaminophen coated in the MAIC with 1% R972.

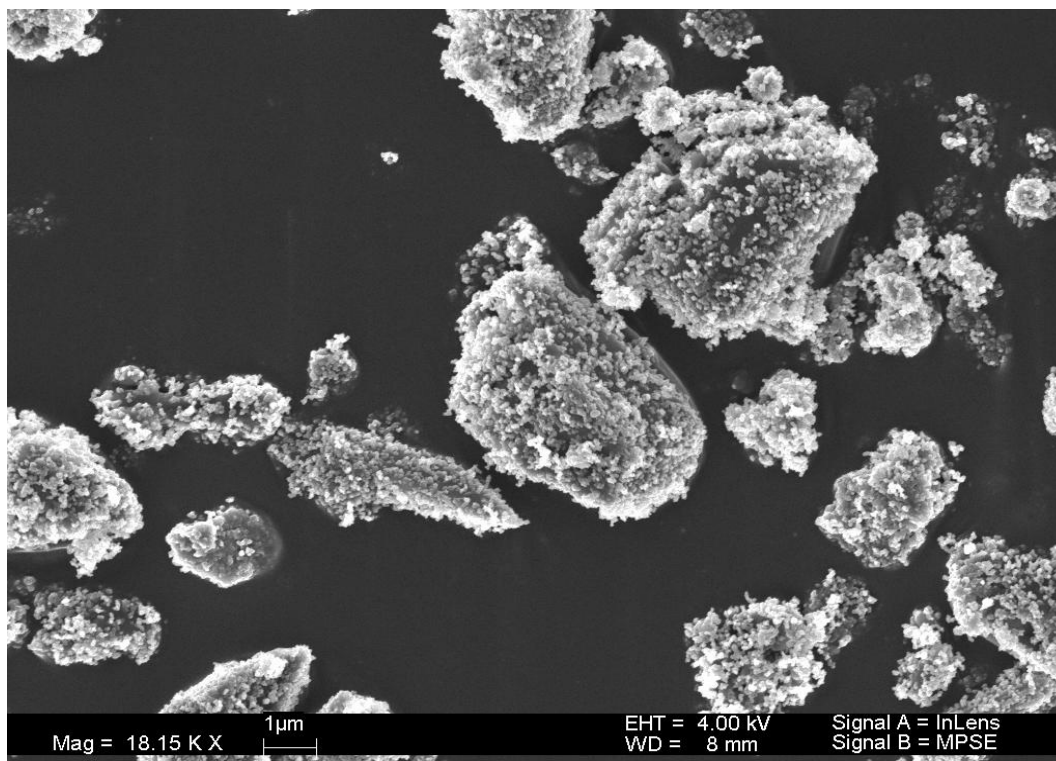


Figure 2.15a (top) and 2.15b (bottom): Various magnifications of semi-micronized acetaminophen coated in the MAIC with 1% R972. (Continued)

2.6.1.2 Micronized Acetaminophen. Micronized acetaminophen is the finest grade of acetaminophen used in this work. It is very small overall with the average particle size around 10 microns. The particle size distribution is not as wide as the semi-micronized powder, but overall this powder is the most difficult to work with due to its small size and extremely cohesive nature. Figure 2.16 shows the as received micronized acetaminophen.

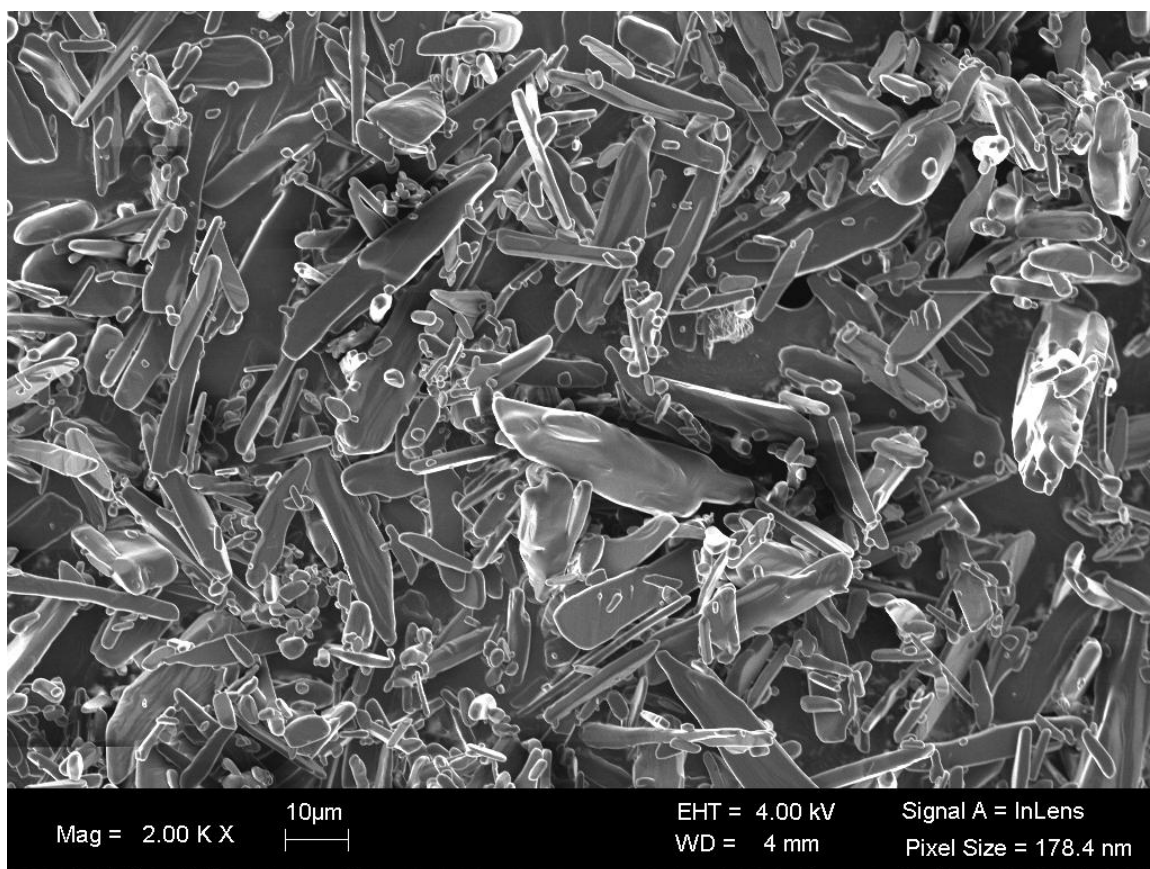


Figure 2.16 As received micronized acetaminophen.

The particles are very needle shaped and have a somewhat smooth surface. Figure 2.17 shows the micronized acetaminophen coated in the MAIC with 1% R972 silica. At this close view, it is easy to see the nanosized silica particles coated onto the surface of the acetaminophen particle.

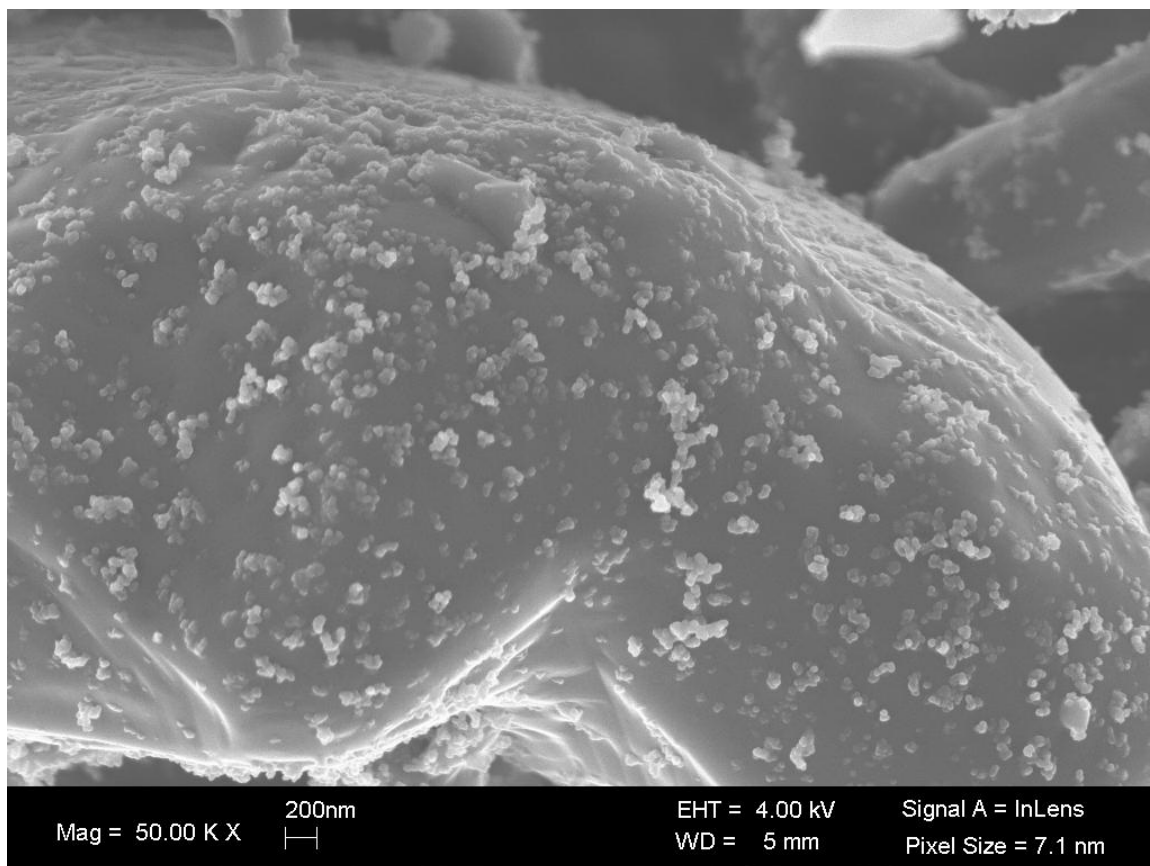


Figure 2.17 Micronized acetaminophen coated in the MAIC with 1% R972.

2.6.3 Ibuprofen

Ibuprofen is another drug used prominently in this work. This was the original model drug chosen, as it notoriously has very poor flow, even with varying grades. Again, as with the acetaminophen, it is widely available and also relatively inexpensive. In this work, Ibuprofen grades 110, 90 and 50 are used.

2.6.3.1 Ibuprofen 50. Ibuprofen 50 is the smallest of grades of commercially available ibuprofen. The powder is made up of flat, needle shaped particles with a size of about 60-70 microns. The surface is somewhat smooth which indicates that a good coating is possible. The as received Ibuprofen is shown in Figure 2.18.



Figure 2.18 Uncoated as received ibuprofen 50.

Note that there is a wide range of particle shapes and sizes. In Figure 2.19, Ibuprofen 50 is shown after coating in the Comil with 1% R972.

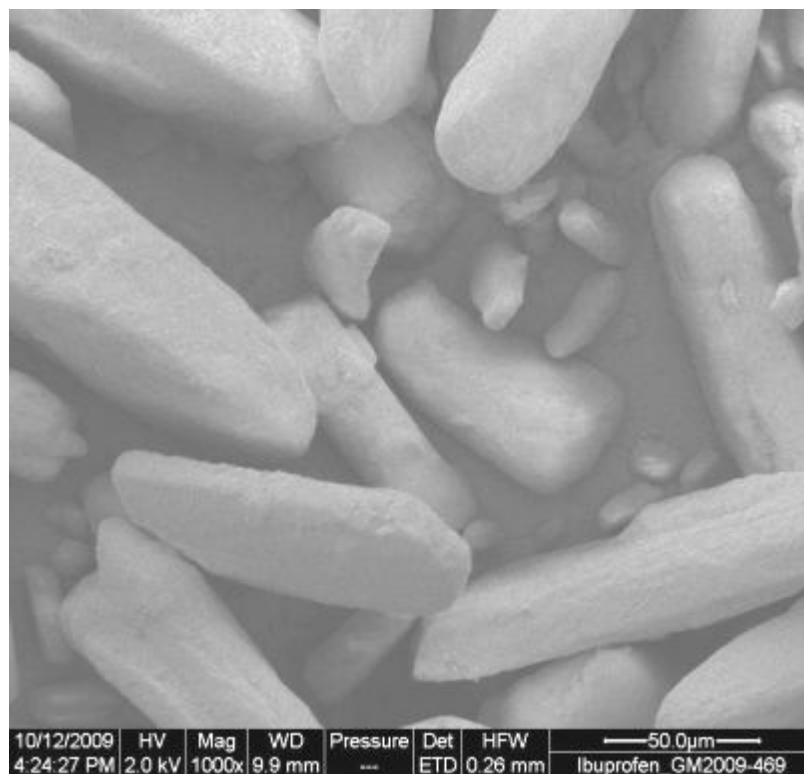


Figure 2.19 Ibuprofen 50 coated in the Comil with 1% R972.

The brighter white color that the particles seem to possess is actually the silica coating on the surface. The silica fluoresces brighter than the ibuprofen using the SEM. This figure shows that there is a very hearty and uniform coating on the particles.

2.6.4 Celphere

Celphere is a specially made spherical multi crystalline cellulose particle. It possesses an extremely smooth surface and is often used for drug layering and film coating. Figures 2.20a and 2.20b show the as-is Celphere particles at 750X and 2KX magnifications.

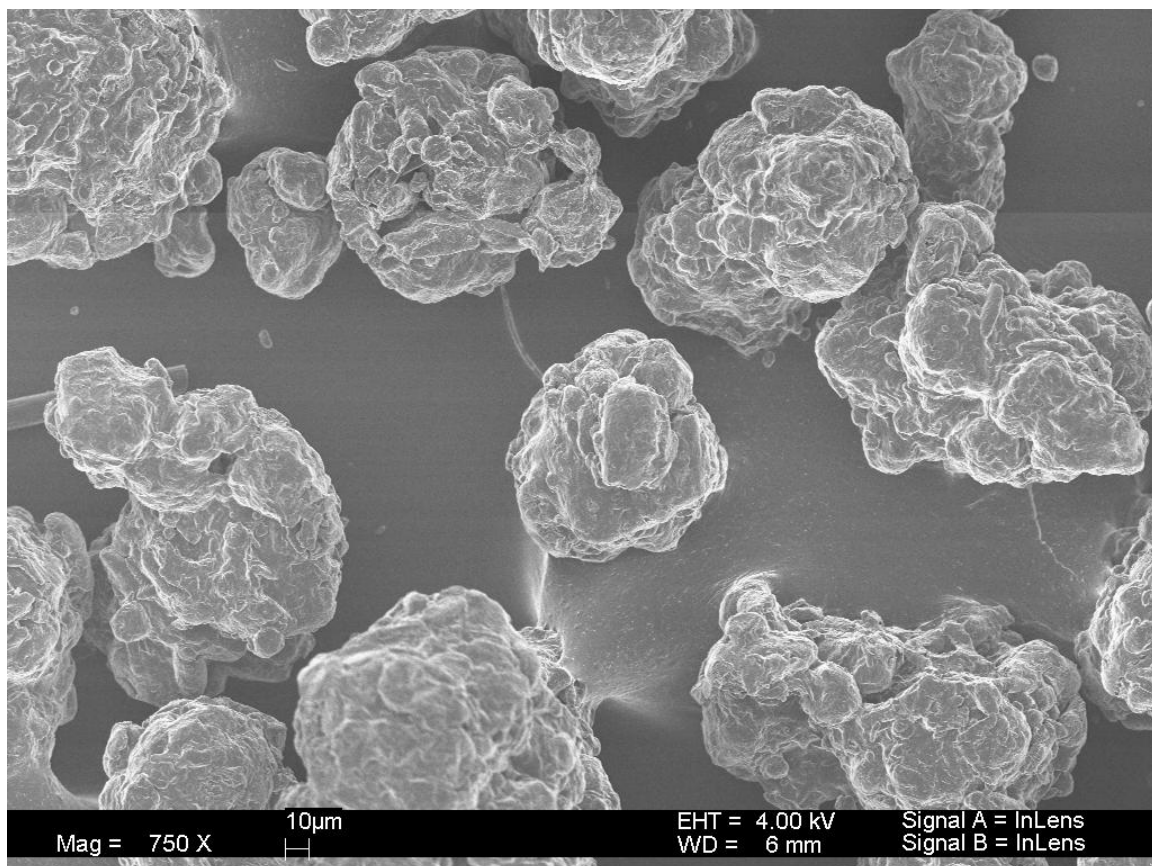


Figure 2.20a (top) and 2.20b (bottom) Various magnifications of uncoated Celphere.

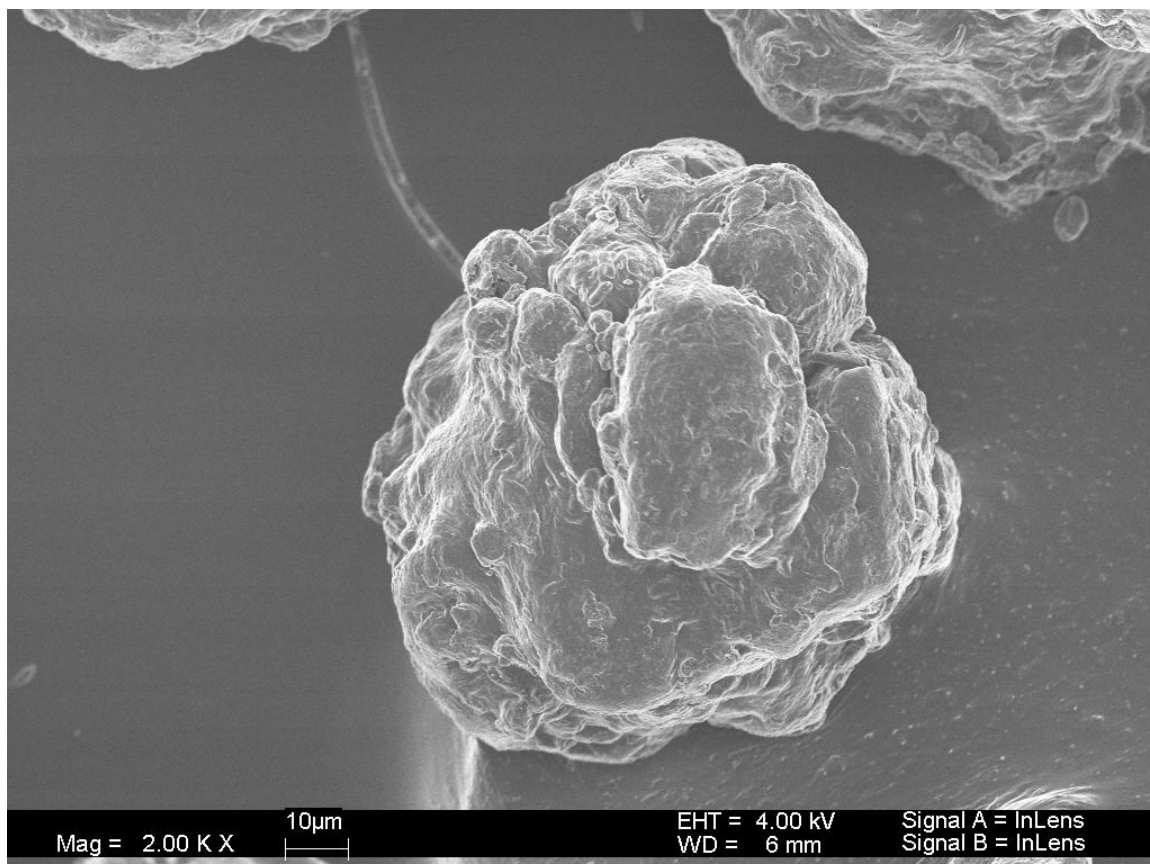


Figure 2.20a (top) and 2.20b (bottom) Various magnifications of uncoated Celphere. (Continued)

In this case, Celphere was coated with magnesium stearate, a lubricant commonly used to aid in tableting processes. Magnesium stearate causes many problems in the blending processes and can also affect dissolution and bioavailability. Using as a guest particle and precisely coating it onto the Celphere could isolate the magnesium stearate and help to maintain the original properties of the blend which in turn will not negatively affect the dissolution. Figures 2.21a and 2.21b show Celphere coated with 5% magnesium stearate in the MAIC at 500X and 2.5KX magnifications.

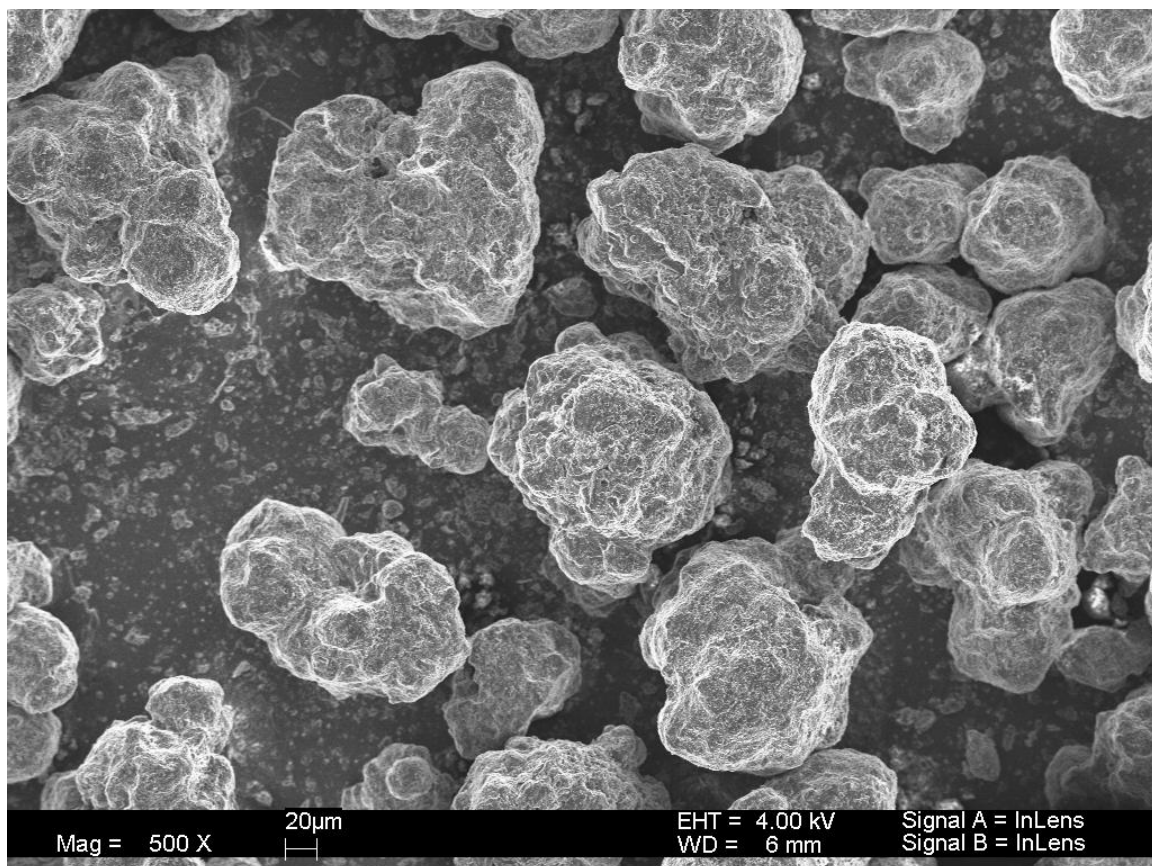


Figure 2.21a (top) and 2.21b (bottom) Various magnifications of Celphere coated with 5% MgSt in the MAIC.

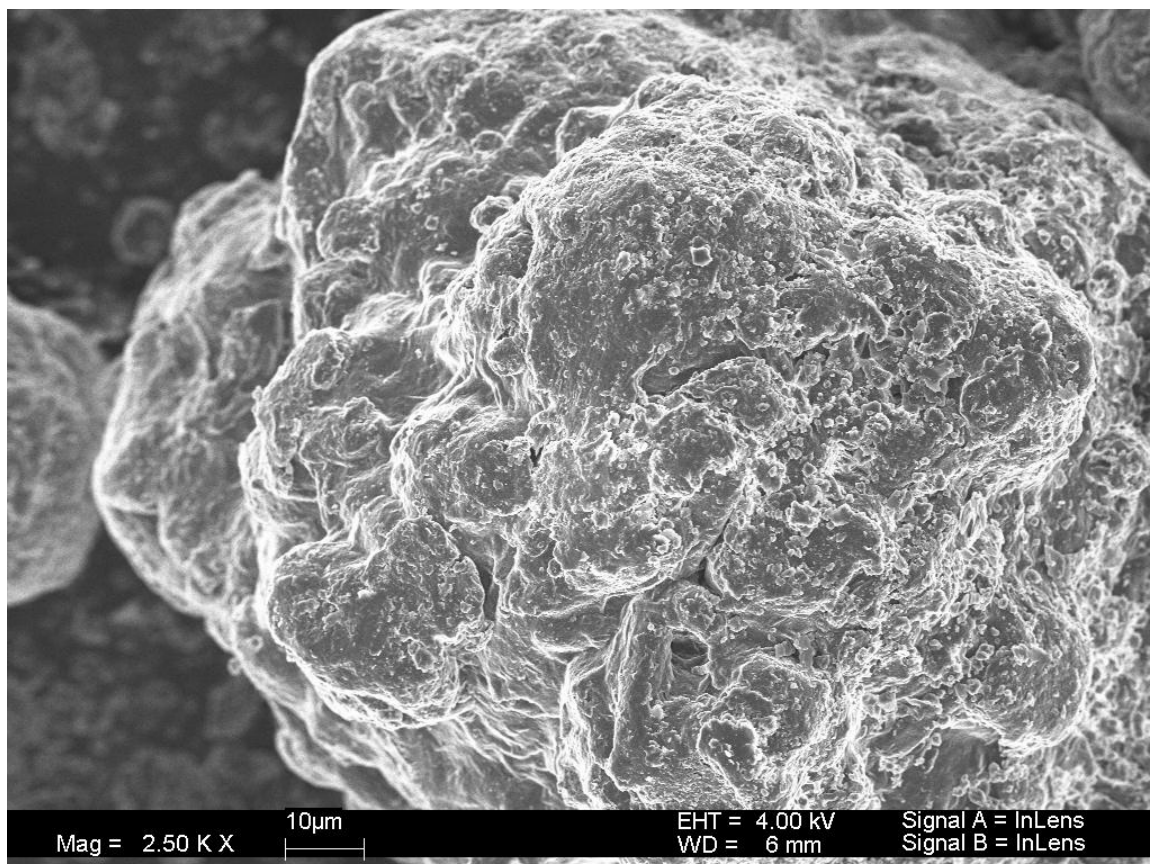


Figure 2.21a (top) and 2.21b (bottom) Various magnifications of Celphere coated with 5% MgSt in the MAIC. (Continued)

Magnesium stearate is a very waxy substance and it coats smoothly onto the surface of the Celphere.

2.7 Shear Intensity

The next step in this work is to investigate the overall shear rate of each coating device. An overall summary of the coating conditions of each instrument is shown in Table 2.1. These conditions will help determine the shear intensity of each instrument.

Table 2.1 Coating Process Parameters

Devices	Process Parameters
MAIC	10 minutes; 20-50% Voltage Magnet/sample ratio: 2:1, 1:1, 05:1
Hybridizer	3-5 minutes; 5000-15000 rpm
V-blender	Shell: 60-120 minutes, 30 RPM. With intensifier bar: 10-60 minutes, 500 RPM.
Comil	1-10 minutes; 798 RPM Screen sizes: 0.018in, 0.024in, 0.032in

Once the strain rate is determined, the overall strain of each device will be known. Then, preliminary conclusions can be drawn as to which device coats in the least amount of time and is most efficient based on the threshold shear rate for coating. The particle size or reduction in particle size can also be linked to the shear intensity and the higher the shear intensity, the more opportunity for particle attrition. At the end, a dimensionless number may be developed for each of the dry coating processes along with a classification scale to show the process to process variability. [32-33]

In general, the overall strain rate of a system can be estimated as

$$\text{Strain Rate} = \frac{V_1 + V_2}{L}$$

Where v_1 is the velocity of one moving part and v_2 is the velocity of the other moving part. L is the distance between the two moving parts which is the shear zone. This equation is based on two surfaces moving in opposite directions, as shown in Figure 2.22. The overall displacement of each moving surface will be used to calculate the strain.

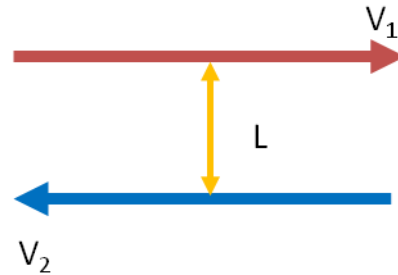


Figure 2.22 Shearing of two moving surfaces.

In all coating processes examined here, the velocity used is the radius of the process multiplied by the angular velocity which is

$$V = r\omega$$

Such that the strain rate can be estimated as

$$\text{Strain Rate} = \frac{r\omega}{L}$$

And ω can be calculated two different ways, either by using the RPM or in terms of the frequency as follows

$$\omega = \frac{RPM}{60} \times 2\pi = \text{Frequency} \times 2\pi$$

From here, the strain rate of each coating process can be calculated.

2.7.1 MAIC

There were several assumptions made to calculate a range of the best estimate of strain rate. The speed of the magnets has been previously estimated at 500-1000Hz. The size range of the magnets is from 700 microns to 1400 microns, which gives an average magnet size of 1050 microns, or 1.05mm. The effective shear zone of the magnets can be estimated based on the number of magnets used and the volume of the jar. The jar is 2.25 inches in diameter and 2 inches in effective height, thus the volume is estimated as

128466 mm³. Another student's work indicates that there are approximately 460 magnets in a gram. If there is 20 grams of sample, using the optimized ratio of 0.5:1 magnets to sample, there would be 10 grams of magnets for approximately 4600 magnets. Dividing the overall volume of the jar by the number of magnets and taking the cube root gives the effective two dimensional shear zone of 3.03 mm for each magnet.

To set up a range of the strain rate, a low and a high magnet velocity is chosen, ie., 500 Hz and 1000Hz. Using these two speeds, the angular velocity, ω is estimated as 1000π and 2000π , respectively. Multiplying each of the angular velocities by the average radius of the magnet (1.05mm) gives the velocities as 1050π and 2100π , respectively.

$$V = r\omega = 1.05\text{mm} \times 500\text{Hz} \times 2\pi = 1050\pi \frac{\text{rad} \cdot \text{mm}}{\text{s}}$$

From there, the strain rate can be calculated by dividing these velocities by the shear length, in this case estimated as 3.03mm.

$$\text{Strain Rate} = \frac{1050\pi \frac{\text{rad} \cdot \text{mm}}{\text{s}}}{3.03\text{mm}} = 346.5\pi \frac{\text{rad}}{\text{s}}$$

Thus the strain rate for the MAIC can be estimated as 346.5π to 693.1π .

2.7.2 Comil

Using the same basic calculations as shown above, a strain rate range can be set up for the Comil. The comil was operated at a low rate of impeller speed of approximately 798 RPM and at a higher speed of 1300 RPM. The radius of the impeller, which is imparting the shear, is 4 cm. Thus the velocity can be calculated as follows

$$V = r\omega = 4\text{cm} \times \frac{798\text{RPM}}{60} \times 2\pi = 106.4\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}$$

The velocity ranged from 106.4π to 173.3π . The shear distance, which in this case is the clearance between the impeller and the screen is estimated as 0.05 cm. The strain rate can be calculated as follows

$$\text{Strain Rate} = \frac{106.4\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}}{0.05\text{cm}} = 2128\pi \frac{\text{rad}}{\text{s}}$$

The calculated strain rate ranged from 2128π to 3466.6π , depending on the velocity of the impeller.

2.7.3 V-blender

There are 2 moving parts to the v-blender, working independently and the strain rate for each will be estimated. The shell operates at a slower speed of about 25 RPM and has a radius of about 15.25 cm while the agitator bar operates at 500RPM, has 3 tines and has a radius of approximately 4 cm.

The velocity of the agitator bar can be calculated as follows

$$V = 3 \times r\omega = 3 \times 4\text{cm} \times \frac{500\text{RPM}}{60} \times 2\pi = 200\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}$$

The shear zone for the agitator bar is estimated as 10 cm such that the strain rate can be calculated as

$$\text{Strain Rate} = \frac{200\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}}{10\text{cm}} = 20\pi \frac{\text{rad}}{\text{s}}$$

The velocity of the shell can be calculated as follows

$$V = r\omega = 15.25\text{cm} \times \frac{25\text{RPM}}{60} \times 2\pi = 12.7\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}$$

The shear zone for the shell is estimated as 12.7cm such that the strain rate can be calculated as

$$\text{Strain Rate} = \frac{12.7\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}}{12.7\text{cm}} = \pi \frac{\text{rad}}{\text{s}}$$

2.7.4 Cyclomix

Another dry coating device commonly used but not shown here is the Hosokawa Cyclomix. It is a 3 paddle system; the paddles are different sizes, 3.5 cm, 5.0 cm and 6.3 cm. The system operates at 1600 RPM. Using the largest paddle, which should have the highest shear, the velocity can be calculated as

$$V = r\omega = 6.3\text{cm} \times \frac{1600\text{RPM}}{60} \times 2\pi = 336\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}$$

The effective shear zone is estimated as 0.5 cm so that the strain rate can be calculated as

$$\text{Strain Rate} = \frac{336\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}}{0.5\text{cm}} = 6720\pi \frac{\text{rad}}{\text{s}}$$

2.7.5 Mechanofusion

Another dry coating device commonly used but not shown here is the Hosokawa Cyclomix. It is an inner piece that is stationary while a cylinder is rotating and creating a shear zone between the inner piece and the cylinder. The radius of the cylinder is estimated as 10 cm. The system operates at approximately 800 RPM. The velocity can be calculated as

$$V = r\omega = 10\text{cm} \times \frac{800\text{RPM}}{60} \times 2\pi = 266.7\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}$$

The effective shear zone is estimated as 0.2 cm so that the strain rate can be calculated as

$$\text{Strain Rate} = \frac{266.7\pi \frac{\text{rad} \cdot \text{cm}}{\text{s}}}{0.2\text{cm}} = 1333.3\pi \frac{\text{rad}}{\text{s}}$$

2.7.6 Overall Summary

The strain rate for each coating device is shown in Table 2.2.

Table 2.2 Summary of Strain Rates for Various Coating Devices

Device	Strain Rate
MAIC	
<i>Low Speed</i>	345.6π
<i>High Speed</i>	693.1π
Comil	
<i>Low Speed</i>	2128π
<i>High Speed</i>	3466.6π
V-blender	
<i>Agitator</i>	20π
<i>Shell</i>	π
Cyclomix	6720π
Mechanofusion	1333.3π

2.8 Comparison of Strain Rates

From prior work, excellent coating is seen in the MAIC for 10 minutes. Knowing the strain rate of each coating device, the time to achieve the same strain and thus the same coating as the MAIC can be calculated.

The strain is calculated as the strain rate multiplied by time. For the MAIC running at the low speed for 10 minutes, the strain is calculated as

$$\text{Strain} = \text{Strain Rate} \times \text{Time} = 346.5\pi \frac{\text{rad}}{\text{s}} \times 10\text{min} \times \frac{60\text{s}}{1\text{min}} = 207900\pi \text{ rad}$$

Similarly for the high speed for 10 minutes, the strain is calculated as

$$\text{Strain} = \text{Strain Rate} \times \text{Time} = 693.1\pi \frac{\text{rad}}{\text{s}} \times 10\text{min} \times \frac{60\text{s}}{1\text{min}} = 415860\pi \text{ rad}$$

To achieve the same strain, the time to run each of the other coating devices can be calculated as

$$\text{Strain Rate of other device} \frac{\text{rad}}{\text{s}} \times X \text{ seconds} = 207900\pi \text{ rad}$$

Then, solve for time. As an example, for the Comil running at the low speed compared to the low speed of the MAIC, the time is calculated from the following

$$2128\pi \frac{\text{rad}}{\text{s}} \times X \text{ seconds} = 207900\pi \text{ rad}$$

Where X in seconds is 97.69 which is 1.62 minutes. The overall running time for each coating device are shown in Table 2.3. Each dry coating device is compared to the MAIC running at both a low and high speed for 10 minutes.

Table 2.3 Processing Time Necessary to Achieve Same Strain as MAIC

Process	Low Speed MAIC	High Speed MAIC
Comil		
Low Speed	1.62 min	3.25 min
High Speed	.999 min	1.999 min
V-blender		
Agitator	2.88 hrs	5.78hrs
Shell	57.75 hrs	115.51 hrs
Cyclomix	.55 min	1.11 min
Mechanofusion	2.59 min	5.19 min

This table indicates that the v-blender takes significantly longer time than any other processing device even when using the agitator bar. This is a similar result to what has been seen in experimental practice. The comil, cyclomix and mechanofusion take less time than the 10 minutes required for the MAIC, which indicates these are potential candidates to do dry coating in a shorter amount of time.

2.9 Conclusions

Surface modification has proved to be a worthwhile method to reduce the van der Waals forces between cohesive pharmaceutical powder particles. Using silica is an acceptable powder as it is generally regarded as safe by the FDA when used in amounts less than 1%. Silica comes in various different nanosized forms including hydrophobic and hydrophilic. Coating can be done continuously using the comil for batches as small as lab scale and as large as manufacturing full scale. Other methods including MAIC and hybridizer can be used as screening tools to test for coatability potential and make smaller batches on a batch by batch basis. All of the surface modification processing techniques have been either previously optimized or optimized as a result of this work.

CHAPTER 3

POWDER CHARACTERIZATION

3.1 Introduction: Need For Characterization

The flow behavior of granular materials can be broadly classified into four different flow regimes: plastic behavior, inertial flow, fluidized flow and entrained flow, determined by particle size, density and gas flow [8]. In the plastic behavior range, stresses inside the granular material are supported by the contacts between the particles and the velocities of particles are zero or very small. Also, the stresses are independent of velocities of particles. In inertial flow, the stresses are supported by the collisions between the particles. In this case, the velocities of particles are large but smaller than the terminal velocities in the interstitial fluid. In fluidized flow, the stresses are supported by the interstitial fluid. The velocities of the particles must be comparable to their terminal velocity in the interstitial fluid. In the case of entrained flow, particles are isolated in the interstitial fluid. However, a single physical model is not capable of explaining the behavior of granular material in all four dynamic regimes. Likewise, a single flow characterization instrument cannot assess the flow behavior in all four regimes. Therefore, it is imperative that before proceeding for the testing, the dynamical flow region of the granular material first needs to be identified. Cohesive powders are particularly more challenging and cannot be tested by a single testing device since it is very difficult to quantify and predict the cohesive powder behavior [19]. In order to understand the flow behavior of cohesive (*poor flow*) powders and surface modified (*good flow*) powders various techniques including quantitative, direct and indirect method of measurements are employed. Direct techniques measure the adhesion force

directly; and indirect techniques provide other relevant parameters, e.g., Carr's Index, Hausner ratio, Flow Index, Angle of Repose and tensile stress. A point score is awarded based on the individual predetermined scale based on its angle of repose (AoR), compressibility, angle of spatula and the uniformity/cohesion index. Cohesiveness is estimated in terms of the flow index based on the total score. As the functionalized (surface modified) powders exhibit a fluid-like behavior, such conventional flow measurements suffer from the limitations to characterize these powders and thus alternate methods of characterization need be explored [6, 20-21]. However, in spite of these existing techniques, there is no in-line method available in the literature that can measure the flow properties of powders in a relevant, dynamic flow regime. In other words, there is no single method that can provide a complete picture of flowability of powders. Therefore, it is necessary to develop innovative methods that can measure the flowability of powders by in-line technique.

3.2 Defining Granular Materials

Granular materials exhibit several regimes of behavior: solidlike, inertial, fluidlike, and suspension, but not all materials can pass through all of these states. The concern is with the criteria that determine the transition from one regime to another and with the boundaries to the various flow regimes that these criteria define. Experimentally we have focused on fine, cohesive powders, where the interparticle cohesive force dominates over gravitational force and where entrained air can cause moving powder to become fluidized. Particle size, particle density, cohesiveness, gas-solid interaction and kinetic energy determine which of these types of behavior should be expected. [34]

Granular materials can display four different dynamical regimes:

Solid like or plastic flow is a behavior where the stresses inside the material are supported by contacts between particles. The velocities of the particles are zero or very small. Stresses are independent of velocities.

Inertial flow is a regime where the stresses inside the material are supported by the collisions between the particles. The velocities of the particles are large, but much smaller than their terminal velocity in the interstitial fluid. Stresses depend on velocities. Spacing between particles is much less than their size and the stresses are due transport of moment by interparticle collisions.

Fluidization is the third regime, where the stresses inside the material are supported in its greater part by the interstitial fluid. The velocities of the particles must be comparable to their terminal velocity in the interstitial fluid. The spacing between particles is of the same order of particle size and the interstitial fluid velocity determines the stresses.

Suspension is the final regime. The particles are isolated in the interstitial fluid and the spacing between particles is much greater than the particle size. The interaction between particles is negligible. [35]

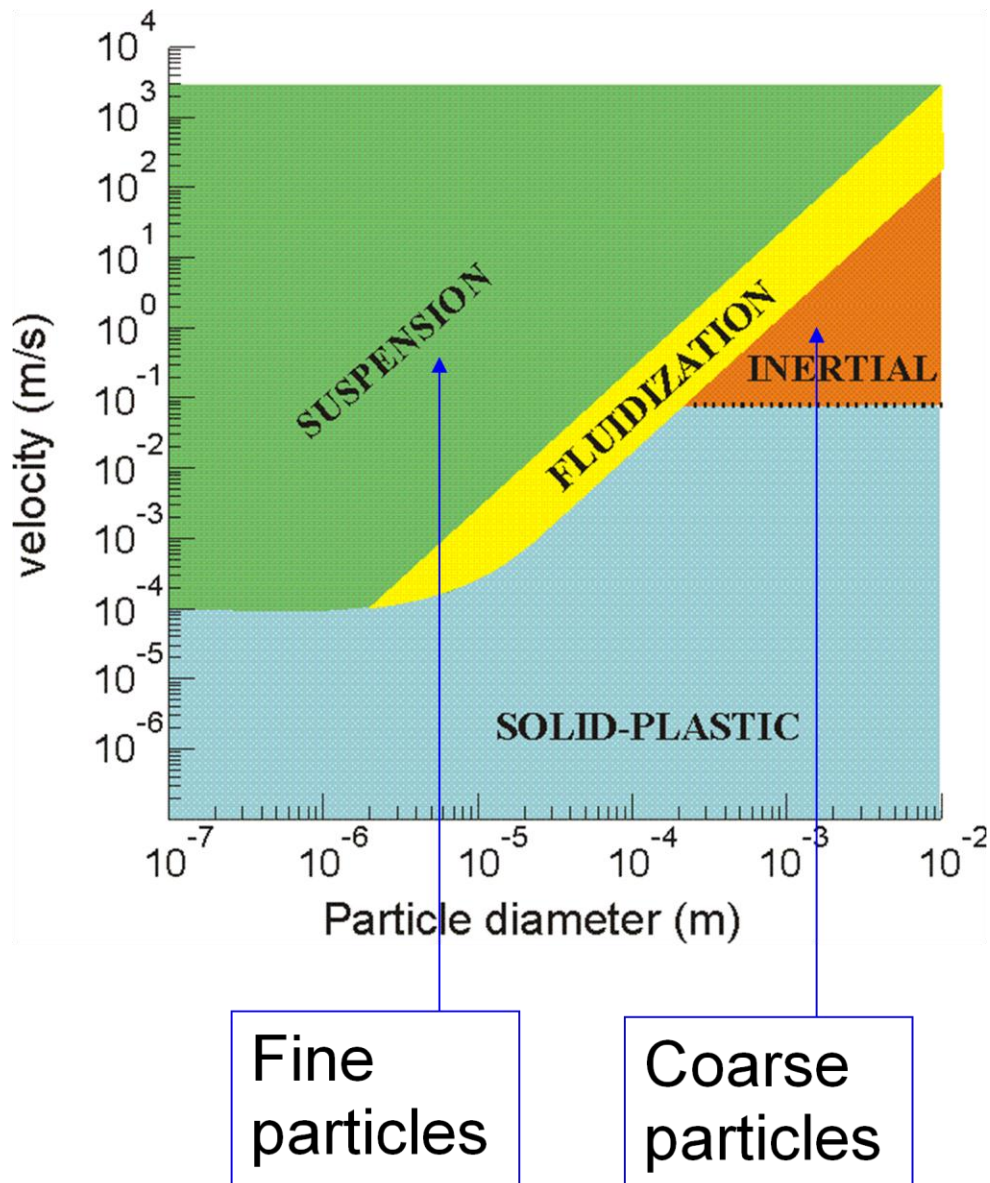


Figure 3.1 Flow regime diagram.

The flow regime diagram (Figure 3.1) provides a useful way of interpreting the flow properties of both fine, cohesive powders and coarse granular materials. In general the motion of coarse granular material is characterized by transition from plastic to inertial flow, whereas fine particle motion at atmospheric pressure is characterized by the transition from plastic to fluidized flow. Fluidized flow, however, requires an ambient gas and at low gas pressure the fluidization process is suppressed. [35]

There is not a single physical model capable of explaining the behavior of a granular material in the four dynamical regimes and a single testing device can not give meaningful results for the flowability of a powder all the four regimes. Before committing time for testing, the dynamical regime of the powder in the plant process needs to be identified. A testing device in which the powder is in the same dynamical regime as in the plant process must be selected. Bulk measurements (bulk density, tensile strength, etc.) are needed to predict the behavior of a particular powder. [34]

3.3 Types of Testers

3.3.1 Shear Tests

In these tests the stresses applied to the powder are controlled to ensure the velocities of the particles are small and the powder is always in the plastic regime. Shear tests are the only tests backed by a well established physical theory. There is quite a large number of shear testers, depending on how the shear to the sample is applied. The diagram below in Figure 3.2 shows the various testers and the types of shear applied.

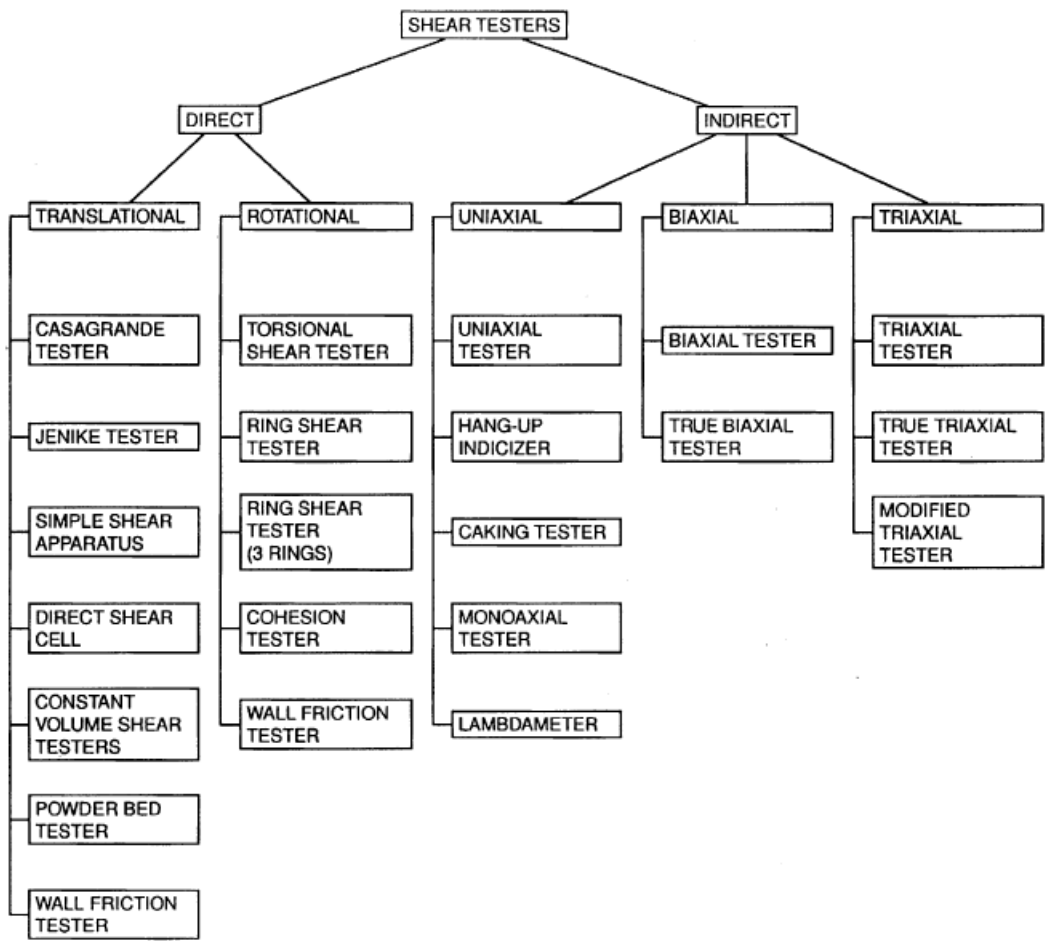


Figure 3.2 Summary of available shear testers. [24]

Theory of granular plastic flow provides the basis for the shear tests. This theory is based on the assumptions that the mechanical behavior of granular materials is elasto-plastic and a granular material yields plastically when state of stress is located on a yield surface, which is a function of the stresses and the solid fraction of the material. [24]

The operation of shear testers is aimed at determining the position of the yield surface. The diagram in Figure 3.3 below shows the theoretical yield surface for the states of stress.

Example: Theoretical yield surface for bidimensional states of stress

- σ : consolidation stress
- τ : shear stress
- e : porosity

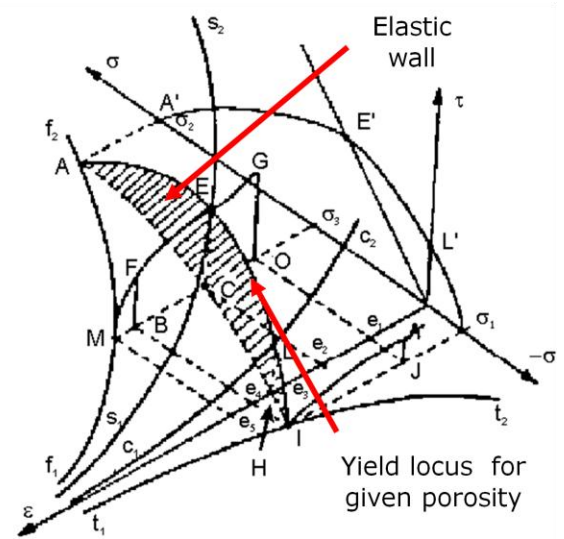


Figure 3.3 Theoretical yield surface for the states of stress. [9]

Biaxial shear testers measure slices of the yield surface known as a yield locus. The sample is initialized by shearing it under a given consolidation σ_{sf} until the shear stress reaches a constant value $\tau_{s,f}$. Next, the consolidation stress is decreased to a value σ_i and the sample is sheared. The maximum shear stress τ_i is recorded. A yield locus is obtained joining the points (σ_i, τ_i) and (σ_{sf}, τ_{sf}) . One yield locus is obtained for each consolidation σ_{sf} as shown below in Figure 3.4.

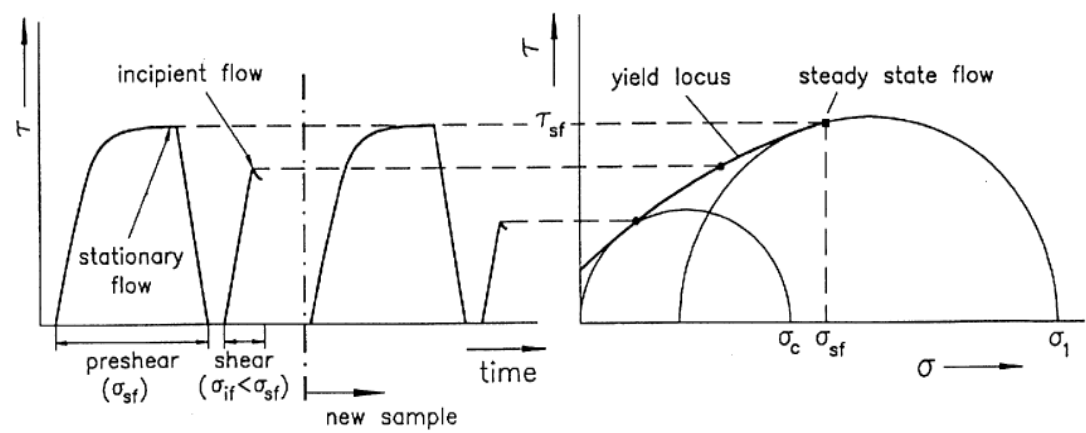


Figure 3.4 Yield locus analysis using Mohr circles. [24]

Characterization of the cohesivity can be done using shear tests. Knowledge of the whole yield surface of the powder is not needed if the aim is to compare the flowability of different powders. To simplify the picture, the quantity that is used for comparisons is the unconfined yield stress σ_c , which is a function of the maximum consolidation stress σ_1 acting on the sample. The unconfined yield stress is the compressive stress that needs to be applied parallel to the free surface of a granular material in order to make the material flow. The Mohr circle analysis is shown as follows:

σ_c is found drawing a circle tangent to the yield locus and passing through the origin
 σ_1 is found from the largest circle that can be drawn tangent to the yield locus

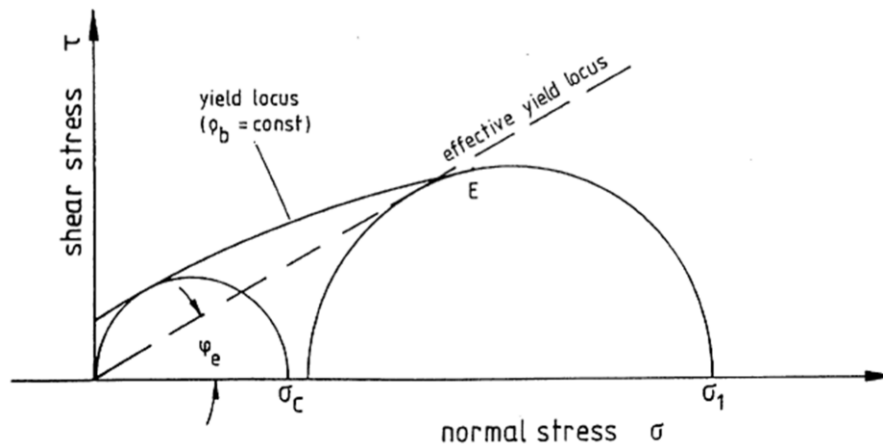


Figure 3.5 Mohr Circle analysis to determine unconfined yield stress and consolidation stress. [24]

The Flow Function is another variable determined using a shear test. The flow function is a plot of the unconfined yield stress σ_c versus the maximum compressive stress σ_1 . Sample flow functions are shown below for non-flowing, very cohesive, cohesive, easy flowing and free flowing powders.

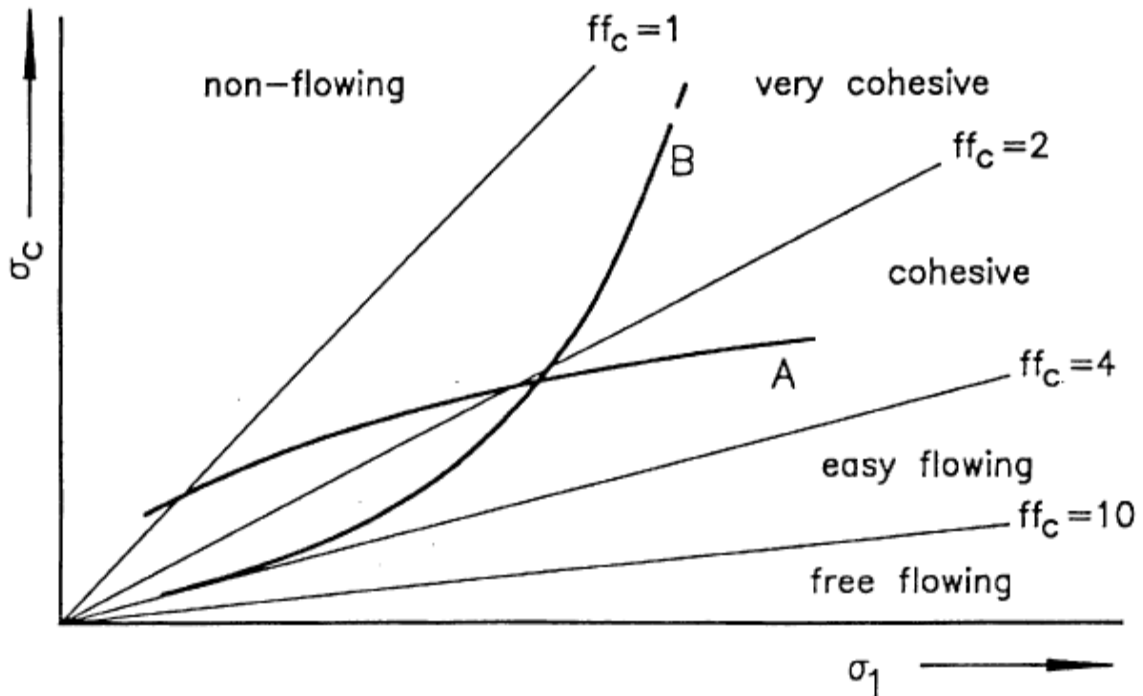


Figure 3.6 Sample flow functions for various types of powders. [24]

The plot (σ_c, σ_1) is divided into regions corresponding to different cohesivity by straight lines through the origin. The inverse of the slope of those lines is called the flow factor ff_c . The values of the flow factor that separate regions of different cohesivity are chosen on the basis of experience. The higher the flow factor, the better the material will flow in the plastic regime. [24]

Comparisons between Shear Testers can be made, however in general, not all the volume below the yield surface in the stress space is accessible to a shear tester. The accessible volume depends on the details of the construction of the tester and therefore, even following correct experimental procedures, different shear testers may yield different results for the same material.

3.3.2 Rheometers

Rheometers borrow methods and ideas developed for fluid testing, but they lack the backing of a physical theory because the fluid mechanics does not directly apply to powders. Rheometers characterize the powder flowability by measuring the force, torque or powder needed to maintain the movement of a impeller in the powder. [36]

3.3.3 Tests Based on Mechanical Stability

In these tests the stresses applied to the powder are not controlled. Therefore, the powder may experiment transitions from the plastic regime to the granular or the fluidized regime. In this type of tests the stresses inside granular material are driven to the yield condition in an uncontrolled way and it is allowed to flow until the stresses are relaxed and the flow stops. Because the initiation of the flow is determined by the plastic yield condition, the results of these tests is influenced by the flowability of the powder in the plastic regime. However, since the velocities attained in the flow are not controlled, it may happen that the material enters the inertial or fluidization regimes. Hence, the flowability of the powder in these regimes may affect the results of the test. There are two types of this test: tests based on avalanches and tests based on the angle of repose. [9]

The tests based on the angle of repose characterize the flowability of a powder by the angle of the free surface of the material when the granular flow stops under different configurations. When the unconfined yield strength of the material is not negligible, the stability of the free surface depends on the consolidation stresses acting on the surface. Since the consolidation stresses depend on the geometry and scale of the test, for cohesive materials these tests show scale and geometry dependence. A smaller angle of

repose generally implies better flow characteristics. Angle of repose as a measure of flowability is most useful (only) for free flowing powders. Hiestand states that “for pharmaceutical materials the angle of repose [as a flowability measure] is satisfactory only with powders whose flow characteristics are so good that one seldom needs the measurement.” [9] Additionally, the United States Pharmacopeia issued a procedure and guidance for the AOR measurement in USP <1174> and it is used widely throughout the pharmaceutical industry to quickly quantify the flow of a powder. USP<1174> gives the powder a rating according to Table 3.1 below.

Table 3.1: AOR Classification

Angle of Repose (Degrees)	Flow Property
25-30	Excellent
31-35	Good
36-40	Fair, aid not needed
41-45	Passable, may hang up
46-55	Poor, must agitate/vibrate
56-65	Very poor
>66	Very very poor

Results of Angle of Repose testing are shown in section 3.5.

3.3.4 Tests Based on the Solid Fraction

Tests that measure the density are based on the fact that in cohesive powders, the attractive forces between particles can stabilize arrangements of particles with solid fractions smaller than those found in non-cohesive powders. Because of this, if a cohesive powder is gently poured in a container, its solid fraction ϕ_{loose} would be on the

lower end of the range attainable for that powder. If the container is tapped, the acceleration on the taps causes a consolidation stress on the powder that rearranges the particles into a larger solid fraction ϕ_{tapped} .

The result of the test is usually given in terms of the tapped solid fraction ϕ_{tapped} , the ratio $\phi_{\text{tapped}}/\phi_{\text{loose}}$ (Hausner ratio) or $(\phi_{\text{tapped}} - \phi_{\text{loose}})/\phi_{\text{tapped}} \times 100$ (Carr index). Typically, the higher $\phi_{\text{tapped}}/\phi_{\text{loose}}$ and the lower ϕ_{tapped} the poorer is the flowability of the powder. [1]

Vibrated Packing density is a novel packed density device that works well with powders that cannot be fluidized well. Hence a new approach is required for measuring packed density that can work over all regimes. This novel characterization test is useful as a test of flowability improvement. Under the same consolidation stress, a more flowable powder will have a higher solid fraction upon packing and similarly under the same consolidation stress, a less flowable powder will have a lower solid fraction than another. Testing has been done varying the API, the amount of silica additive and the percentage of API in a blend. The setup and procedure are shown in more detail in Chapter 4.

At the beginning of the test, material is fluidized to initialize and clear history of the powder. The material is given time to randomly settle. The frequency of the system is set to 60 Hz and the acceleration velocity ranged from 0.5 to 4g in 0.5g increments. Time cumulatively increased by a minute for each test as the acceleration velocity is increased. Ultrasound measures the height of the powder and is translated into solid fraction based on the weight of the powder. As additive amount increases, solid fraction increases for each consolidation stress

3.3.5 Tests Based in Fluidization

These tests determine the properties of the sample in the fluidized regime.

3.4 Results of Angle of Repose Testing

In this work, a Hosokawa powder tester is used to determine the angle of repose. The Hosokawa is shown in Figure 3.7.

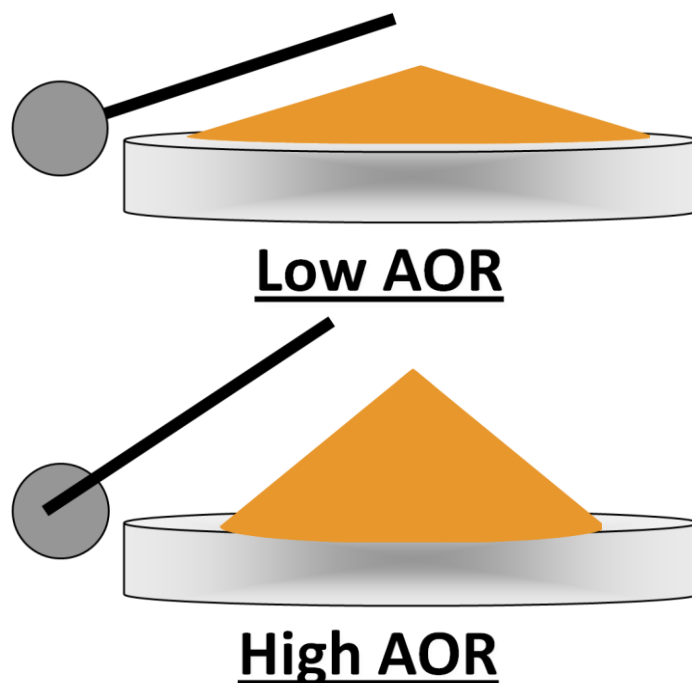


Figure 3.7 Hosokawa Powder Tester set-up.

The Hosokawa Powder Tester is normally used to determine the Carr indices and Hausner ratio, but it can be inconclusive for free flowing powders due to the nature of the testing methods, especially for the tapped density test. However, for the angle of repose, the Hosokawa is a good, reliable instrument that is somewhat automated to reduce variability. It gives repeatable results and the equipment is designed with ASTM

standards. Additionally, using the Hosokawa allows testing over all 4 flow regimes, as a vibratory mechanism is used to feed the powder.

In general, a lower angle of repose indicates better powder flow and a lower powder cohesivity. Examples of a low and high AOR are shown in figures 3.8a and 3.8b.



Figures 3.8a and 3.8b Examples indicating a high or low AOR.

The AOR can be measured quickly to get a quantitative view of the powder flow, and in this case can easily show the difference in powder flow when comparing an uncoated powder to the processed, coated powder.

3.4.1 Testing of API Powders

Powders are tested initially when received and then after the processing for dry coating takes place. Using the AOR can indicate which dry coating process produces better coating and which guest material shows a more marked flow improvement. Figures 3.9

and 3.10 show AOR results for various coatings of Semi-micronized acetaminophen and Ibuprofen, respectively.

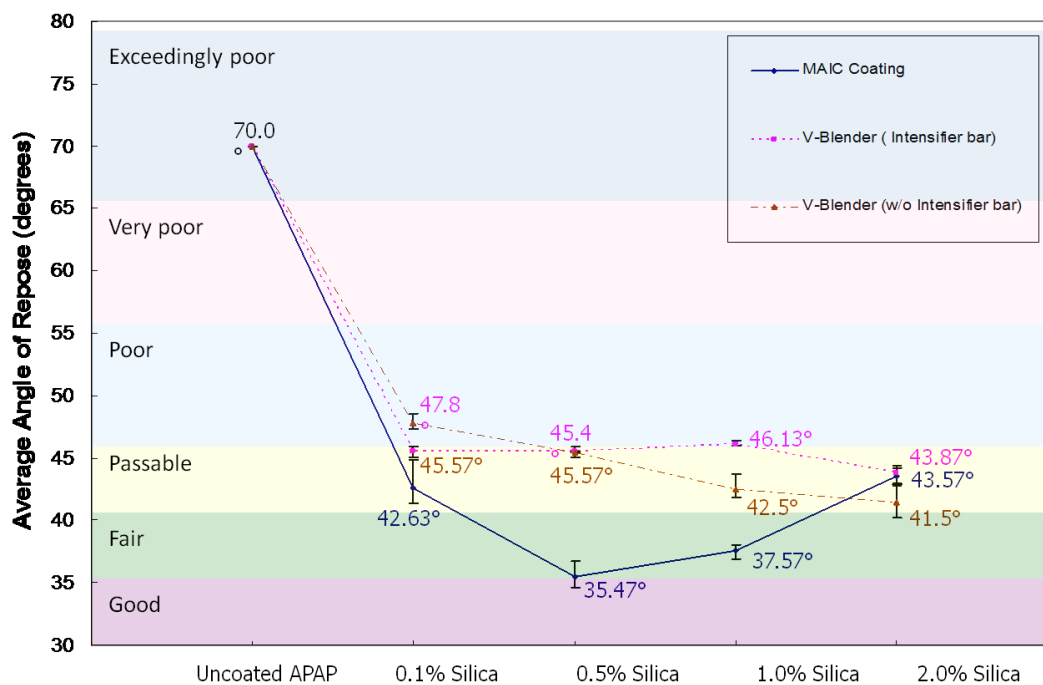


Figure 3.9 Averaged angle of repose for the coating of semi-micronized acetaminophen with different percentages of R972 silica processed in MAIC and v-blender (with and without intensifier bar).

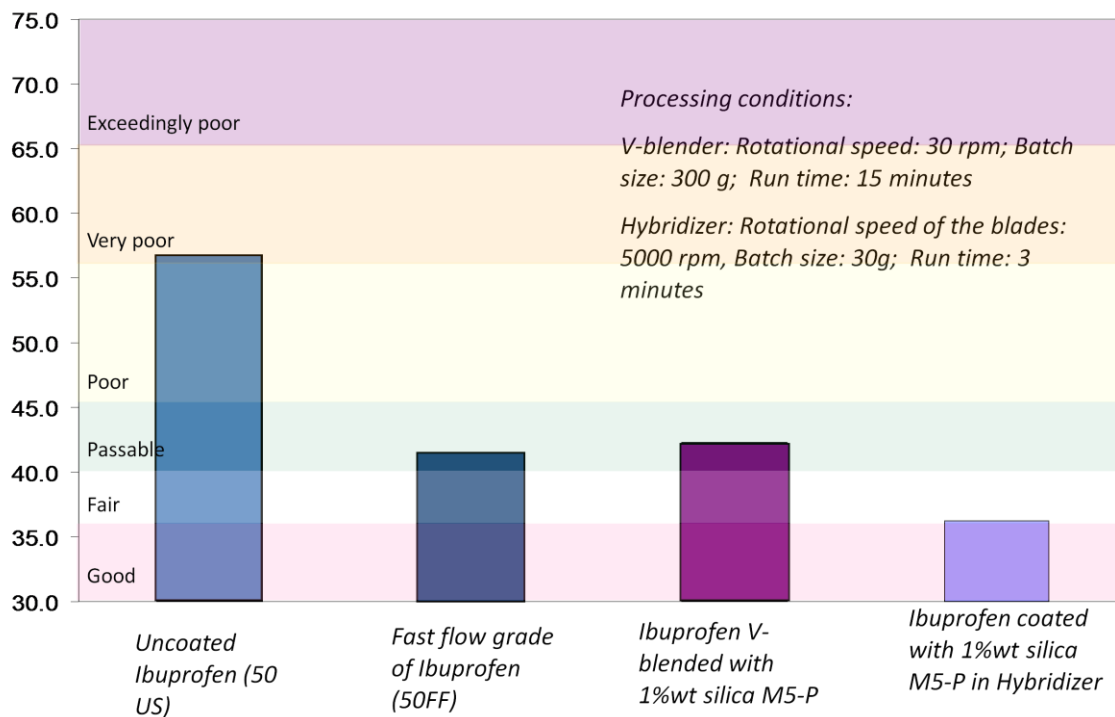


Figure 3.10 Angle of repose of various grades of uncoated ibuprofen 50 and ibuprofen 50 coated with silica M5P.

Semi-micronized acetaminophen is coated in the MAIC and in the v-blender, both with and without the intensifier bar. It is also coated with varying levels of R972 silica. The lowest angle of repose, ie the powder with the best flow, is the Semi-micronized acetaminophen processed in the MAIC with 0.5% R972 silica. This falls in the good range of powder flow. After the silica percentage is increased past that point, the AOR starts to increase. This is because there is more than 100% surface area coverage and there is excess silica.

Ibuprofen is coated with 1% M5P silica in both the v-blender and the hybridizer. The lowest angle of repose was attained when coating with the hybridizer and this showed the coating brought the powder from having very poor flow to having good flow. Important to note in Figure 3.9 is that the AOR of a commercially available fast flow Ibuprofen 50 grade is plotted. This commercially available grade is co-processed with

silica during the crystallization process. Using a dry coating process showed significant flow improvement as shown by the AOR when compared to this commercially available grade. Thus the coating process is more effective here.

3.4.2 Testing of API Blends

API powders on their own are not usually encountered during formulation and manufacturing processes in the pharmaceutical industry; they are often in blends with other inactive ingredients, the excipients. The excipients are often filler materials that serve other purposes such as tablet disintegration and tableting lubricant. Excipients are used to aid mostly in manufacturing processes and often add no value or use to the tablet or drug product except to aid in manufacturing and to make the API into an elegant dosage form.

Semi-micronized acetaminophen was coated with both 0.5% and 1% R972 Silica in the MAIC. The coated powders were then combined with lactose in a v-blender to form simple binary blends. Drug loading percentages were varied to show the effect of coating in low loading and high loading blends. Results are shown in Figure 3.11.

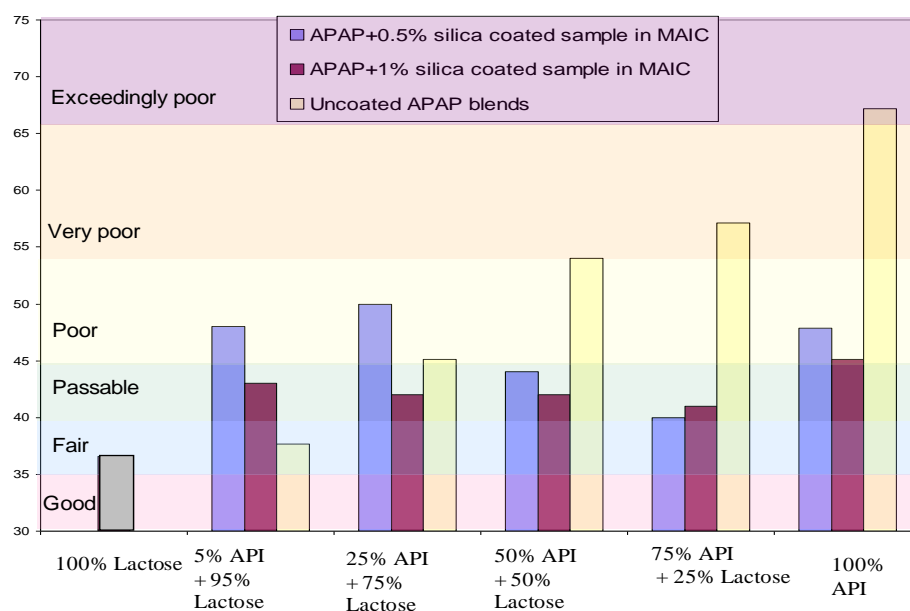


Figure 3.11 Averaged angle of repose of pre-dry coated semi-micronized acetaminophen blended with fast flo lactose in v-blender without intensifier bar for 8 minutes.

This shows that as the drug loading increases, the AOR of the coated powder blends is much lower than those of the uncoated powder blends. In blends of less than 50% API, the excipient, in this case fast flow lactose, is the main contributor to the flow. In blends of more than 50% API, the API becomes the main contributor, and using the coated API makes a significant difference in the flow properties. Different types of silica coated powders are shown in Figure 3.12.

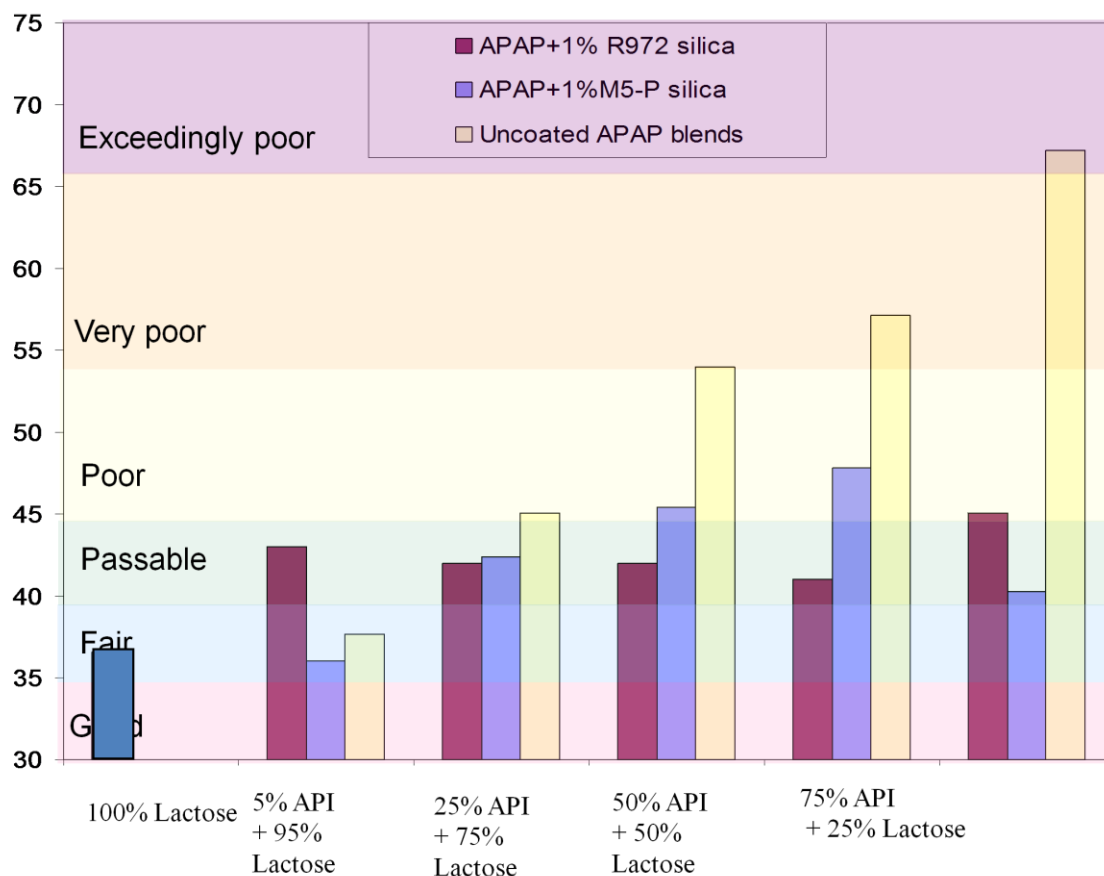


Figure 3.12 Averaged angle of repose for blends of semi micronized acetaminophen that was coated with different types of coating materials (blends made with fast flo lactose in v-blender without intensifier bar for 8 minutes).

M5P and R972 silica were used at 1% by weight of the API and coated in the MAIC and again mixed with lactose. In general, coating with the R972 silica produces a more significant improvement in flow than coating with the M5P and this is shown in the blends.

AOR of Ibuprofen 110 blends are shown in Figure 3.13. The ibuprofen was first coated with 0.5% and 1% silica R972 in the hybridizer and then again blended with lactose to make blends with varying drug content.

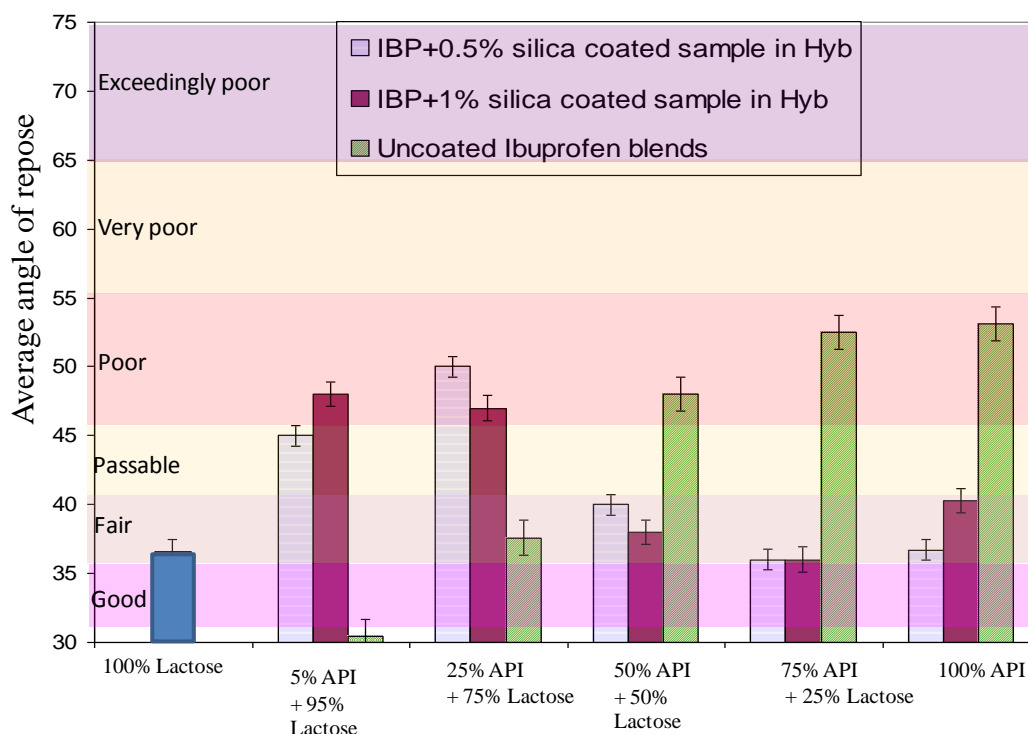


Figure 3.13 Angle of Repose of dry-coated Ibuprofen 110 blended with Lactose in V-blender.

Again, at low loadings of drug, the fast flow lactose is the main contributor in flow but at over 50% loading, the blends made with the dry coated powders have significantly better flow than the blends made with the uncoated powders. To note, at this point in time, particle size was not being tested to assure no attrition. It is believed that using the hybridizer for these powders created significant particle size reduction, which lead to the poor flow with the low loading blends due to segregation issues. More importantly, even with the particle size reduction, these powders still possessed very good flow, as shown in the higher loading blends.

An overall summary of both the semi-micronized acetaminophen and ibuprofen blends with coated and uncoated powders is shown in Figure 3.14.

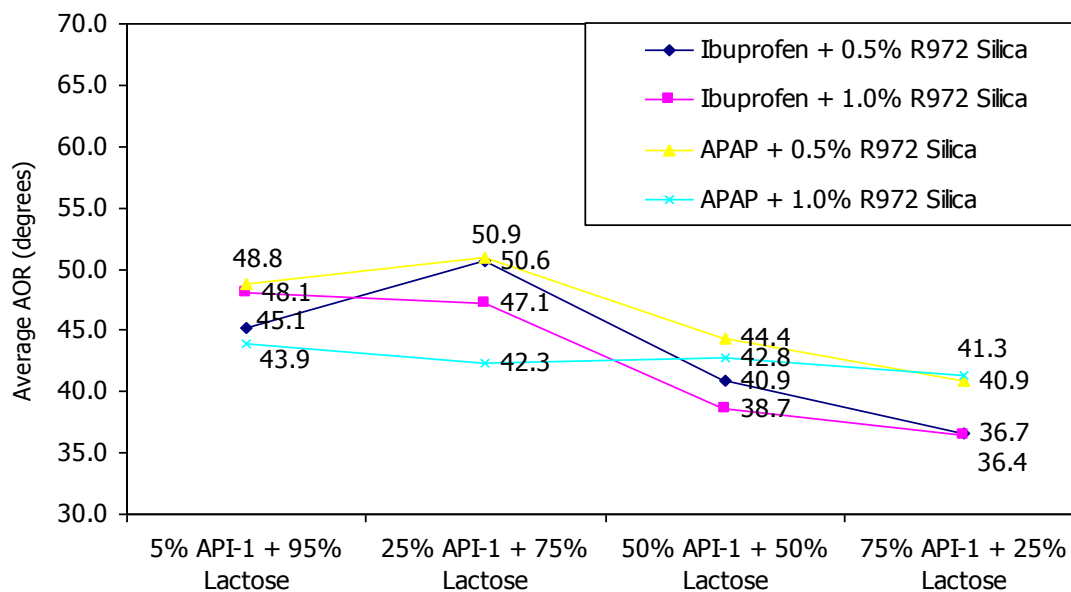


Figure 3.14 Overall view of angle of repose of dry-coated APIs blended with lactose in v-blender.

3.5 Conclusions

Due to the complex nature of granular solids and specifically pharmaceutical powders, it is extremely important to understand the behavior of the powder at both the particle and bulk level. After surface modification, the powder often changes from one regime to the other, so characterization methods need to be developed that can accurately describe the behavior of the powder at multiple, if not all states. Additionally, characterization methods need to be correlated to determine the relationship between them. This will add a more in depth understanding of both the powder and the characterization method.

CHAPTER 4

NOVEL PACKED DENSITY DEVICE

4.1 Introduction

In particle technology it is a well known fact that particles with good flow properties tend to form dense packings, with solid fractions close to the solid fraction of the close random packing ϕ_{RCP} , whose theoretical value for spherical particles is $\phi_{RCP} = 0.647$ [37], although values attained in experiments and numerical simulations are closer to $\phi_{RCP} = 0.636$ [38-39]. Particles with non-spherical shape may form even denser packings as it is the case when the particles are roughly disc-shaped [40]. On the contrary, particles with poor flow properties can form loose packings, with solid fractions much smaller than the close random packing of spheres [41-42]. In extreme cases found when working with nanopowders, solid fractions close to 0.05 or less are not uncommon [43].

The solid fraction alone cannot be taken as a reliable indicator of the flow properties of a powder, since the loose packings formed by poorly flowing particles can be densified by the action of consolidation stresses [44]. Since the consolidation process is not reversible, the solid fraction of a powder depends on the previous history of the powder, rendering the solid fraction of a powder “as received” totally useless as an indicator of flow quality.

On the other hand, it is possible to have some indication of the cohesiveness of a powder by comparing its solid fraction under different consolidations. The reason for this is that poorly flow particles often owe their behavior to the existence of strong interparticle attractive forces, which in turn make loose packings possible [45]. When

this is the case, it is said that the powder formed by those particles is cohesive. An increase in the solid fraction of a powder implies a rearrangement of the particles into a denser structure. Therefore some contacts in the initial structure must yield either by friction or rolling. In this case, dry coating of a host particle with a nano sized guest particle drastically reduces the cohesive forces and eliminates the larger agglomerates of the host powder. Reducing the cohesive forces allows the particles to pack better. [1] Theoretically, the stronger the attractive adhesive forces acting in a contact, the harder it is to cause failure of the contact either by friction or rolling [46-48]. In consequence, a reduction in the adhesive forces between particles causes a reduction in the consolidation stress that is needed to achieve a given value of the solid fraction of the powder [4, 34]. Thus, a possible procedure to determine which of two powders A and B has better flow properties would be to subject them to an uniaxial compression up to a given solid fraction: the powder requiring the smaller consolidation stress will be the one with better flow properties. [21, 49]

The idea outlined in the previous paragraph is exploited in the Hausner ratio to measure the flow properties of a powder [50]. Typically, the powder to be tested was gently poured in a container and its solid fraction, ϕ_{loose} was measured. Then a number of taps was applied to the container, the powder was compressed by the consolidation stress acting as a consequence of the deceleration experienced in each tap and the resulting solid fraction, ϕ_{tapped} was measured. The Hausner ratio was defined as $HR = \phi_{\text{tapped}}/\phi_{\text{loose}}$. Because the particles of powders with low cohesiveness will pack efficiently even under the small stresses applied when being poured in the container, the solid fraction ϕ_{loose} will be close to ϕ_{tapped} and HR will be low. Highly cohesive powders will require large

stresses to pack efficiently, and therefore, ϕ_{loose} will be much smaller than ϕ_{tapped} , provided the taps were energetic enough to compress the powder and that the previous history of the powder was properly erased in the pouring procedure. These two requirements are difficult to meet, making the Hausner ratio only a coarse “quick test” method [1].

However, given the simplicity of a test in which the powder is tapped or shaken and the small amount of time needed to perform it, it is worthwhile to consider if the significance of such a type of test may be improved by the knowledge of the consolidation stress acting on the powder. By comparing the tapped density and the consolidation acting during the taps, this type of test may provide similar information. In this work measurements are presented to try the validity of these ideas.

4.2 Shortcomings of United States Pharmacopeia Tapped Density Test

Bulk and tapped density tests are used widely in pharmaceutical industry. It is a relatively easy measurement and gives valuable information about the powder with respect to flowability. The tapped density test may also indicate some information regarding compressibility of the powder and give an insight into its handling properties. In general, a higher tapped density indicates less cohesive forces between the powders and thus the powder is more flowable than one that possesses a lower packing density. The United States Pharmacopeia has a chapter which defines the method and procedure for measuring both bulk and tapped density; it is USP <616>.

The USP test can be difficult to use for functionalized (liquid-like) pharmaceutical powders, specifically those that are modified by the previously defined dry coating processes. The test can be too jarring, which may dislodge powder from the

vessel and lose the powder, which may lead to results that are not meaningful. The test also only gives one discrete value for both the bulk and tapped density.

Using the novel vibrated packed density set up, a more comprehensive view of the powder can be given. Consolidation is not applied in the form of a tap, but rather using constant vibration at a certain frequency and set acceleration amplitude which can be varied using a control loop. The test is a continuous test; the solid fraction (i.e., tapped density) is measured over time to give a better overall view of the powder behavior. Measuring the solid fraction over time gives an idea how quickly the powder rearranges and packs and then how quickly the powder reaches its equilibrium solid fraction (the final solid fraction) and thus this novel test gives more useful information than the USP test. At this time, work is being done to relate the solid fraction to a compressibility measurement to simulate a tableting process, adding further benefit to running this test in comparison to the USP method.

4.3 Experimental set-up

4.3.1 Materials

As materials, we have used various host particles including Cornstarch, with a diameter of approximately 15 μm and a density of 1.55 g/cm^3 , and a few other selected pharmaceutical ingredients such as acetaminophen and Celphere. The guest particles were hydrophobic silica R972 with a diameter of 16 nm and a density of 2.55 g/cm^3 and vegetable grade magnesium stearate. Powders used in the experiment are processed in Magnetic Assisted Impaction Coater (MAIC).

4.3.2 Experimental Set-up: Tapped Density

The tapped density of the powder has been measured using a Labworks Inc. Model ET-127 Electrodynamic Shaker. A cylindrical fluidization cell is placed in the plate of the shaker. The internal diameter of the cell is 5.08 cm, and its height is 19.2 cm. The distributor is made out of Mott Corp sintered porous stainless steel, with 5 μm pore size and 3.2 mm in thickness. When it is desired, a flow of dry nitrogen can be supplied to the cell, the flow rate being controlled with a rotameter. On top of the cell a Senix Ultra-U ultrasound sensor connected to a computer measures the height of the powder. The vertical acceleration of the cell is measured using a piezoelectric accelerometer placed on the upper part of the cell. The acceleration amplitude is maintained by operating the shaker in closed loop configuration using a Labworks Inc. Vibelab Model VL-144 vibration controller and a Labworks Inc. model PA-141 power amplifier. The setup is shown in Figure 4.1.

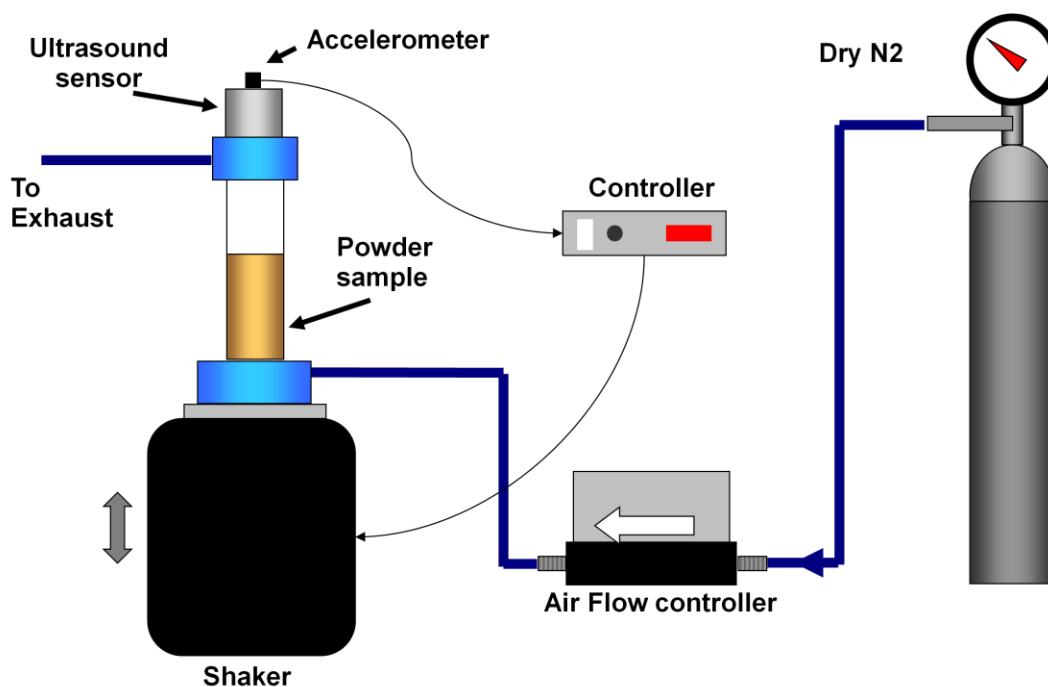


Figure 4.1 Overall schematic of novel packed density device.

To measure the tapped density a given mass of powder is placed in the cell. To initialize the powder the powder is fluidized using dry nitrogen. A close up of the powder cell is shown in Figure 4.2.

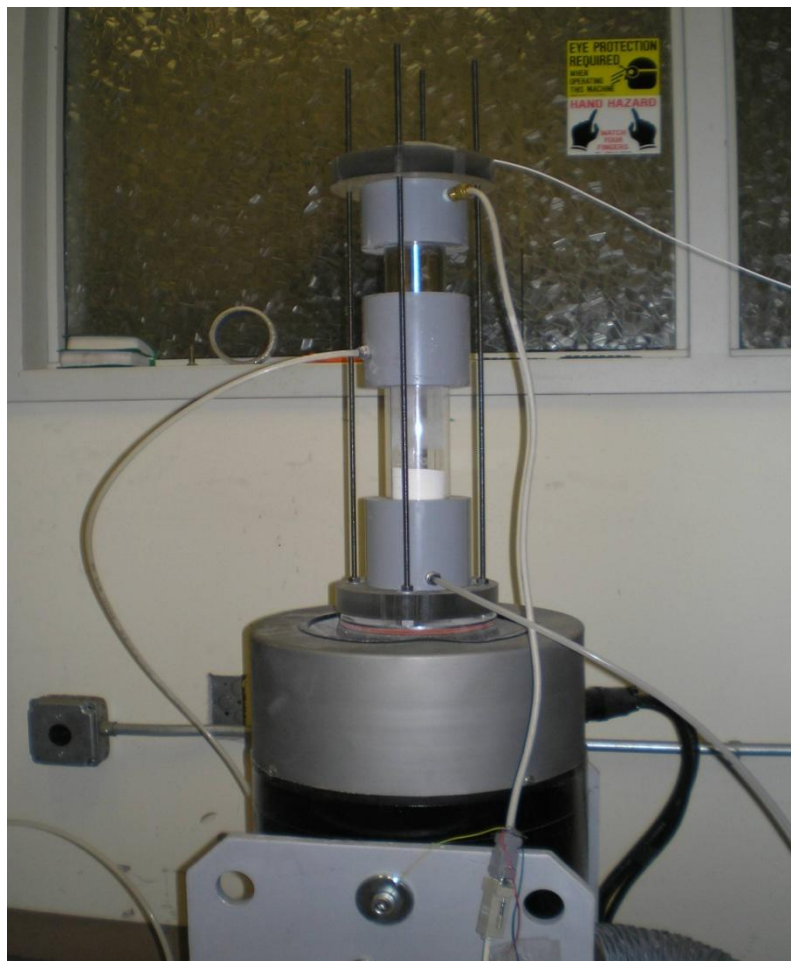


Figure 4.2 View of cell with sensor and shaker of novel packed density device.

The gas flow is increased while the bed height is monitored. Once the bed height reaches its maximum value, marking the onset of the bubbling instability [51], the gas flow rate is maintained for approximately 30 seconds. During the initial stages of this initialization process, it may be necessary to shake the powder gently if the powder initially lifts as a plug. This gentle shake is applied using the shaker and it is intended to break any bonds that may have formed between particles if the powder has become

consolidated, either by its own weight when placed in the cell or by the vibration in previous runs. Once the fluidized bed is fully expanded, the gas flow is shut off and the powder is allowed to collapse undisturbed under its own powder and weight until the height of the bed reaches its final, constant value. In this way, the initial solid fraction obtained for each sample can be reproduced after the sample has been packed by the vibrations.

The next step is to apply the vibrations and record the height of the bed as a function of time. The frequency ν of the vibrations is fixed at $\nu = 60$ Hz. The desired acceleration amplitude is not instantly achieved, but it takes a few seconds to be established. The time needed to reach the desired acceleration amplitude has been minimized by increasing the gain of the power amplifier as much as practically possible. The time it takes to reach the desired vibration amplitude is small compared to the duration of each run. While the powder is shaken in this way, the height of the powder is recorded by the ultrasound sensor at a rate of 20 Hz.

The consolidation stress is taken as the maximum apparent weight per unit area of the sample in the cell that the powder experiences as a consequence of the vibrations, that is:

$$\sigma_c = W_N \left(1 + \frac{4\pi^2 \nu^2 A}{g} \right)$$

Where W is the weight per unit area of the powder in the final step N , g is the gravity acceleration, ν is the frequency of the vibrations and A is the amplitude of the vibrations. While the frequency ν of the vibrations is fixed at 3600 vibrations per minute ($\nu = 60$ Hz), the amplitude A can be adjusted between 0 and 2.5 mm. The amplitude of

the vibrations has not be measured at this time, however a linear relationship is assumed between the scale (in arbitrary units) of the amplitude control of the sieve shaker and the amplitude in mm, with the higher end of the amplitude control corresponding to an amplitude of 2.5 mm. Each powder has been tested under different amplitudes to find the dependence of ϕ_{tapped} with the consolidation stress σ_c .

4.4 Results

4.4.1 Cornstarch

Initially, cornstarch was chosen to test the set up shortly after it was constructed. Cornstarch had been widely used prior for both coating and characterization and its behavior was well understood. The testing method for the packed density setup was determined using cornstarch. Initially, the powder is fluidized to erase history, then the vibration begins. The frequency is set constant at 60Hz and the acceleration amplitude is varied from 0.5g to 4g in 0.5g increments. At 0.5g, the vibration is set for 5 min. As the acceleration amplitude is increased, a minute is added at each increment such that at 4g, the test is run for 12 min. This is to allow the powder to rearrange as much as possible, reaching its equilibrated solid fraction. Figure 4.3 shows the raw data as it is recorded by the ultrasonic sensor, with the height translated to solid fraction simply using the geometric dimensions of the cell.

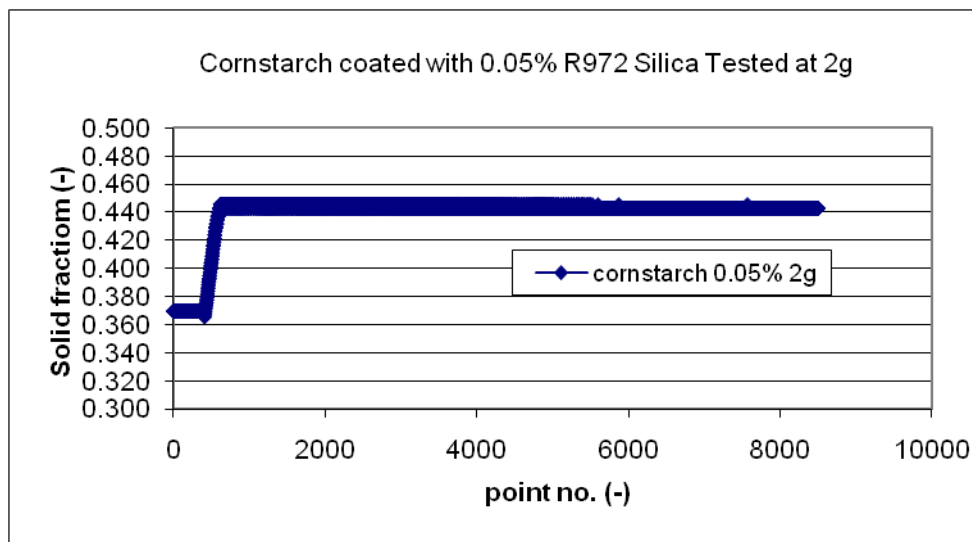


Figure 4.3 Raw data as received from sensor.

The equilibrium solid fraction is chosen as the final solid fraction of the powder achieved during testing, which should be its highest solid fraction attainable due to the packing under vibration. This is repeated at each acceleration amplitude. The results are shown in Figure 4.4, plotted with increasing acceleration amplitude and with different levels of silica used to coat.

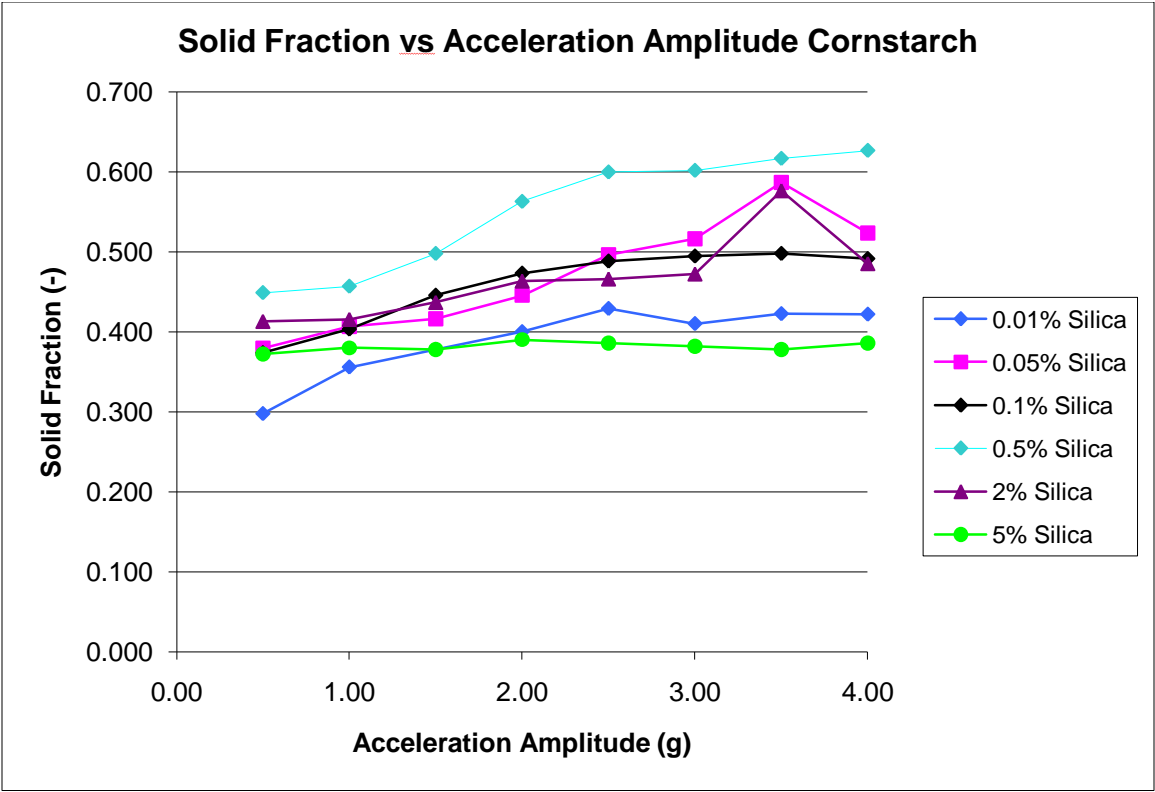


Figure 4.4 Cornstarch solid fraction with changing amplitude and coating level.

The uncoated cornstarch is not shown because it is not able to be fluidized, even under slight vibration. Thus, its packing history cannot be erased and the test results are not useful. It is important to note that even with the lowest level of silica coating, the cornstarch can be fluidized. The cornstarch coated with 0.5% silica almost reaches the solid fraction of the known close packing spheres value. This shows that after coating, the packing density is almost as good as theoretically possible. Figure 4.5 shows the solid fraction as a function of the weight per unit area, which is a good indicator of the consolidation.

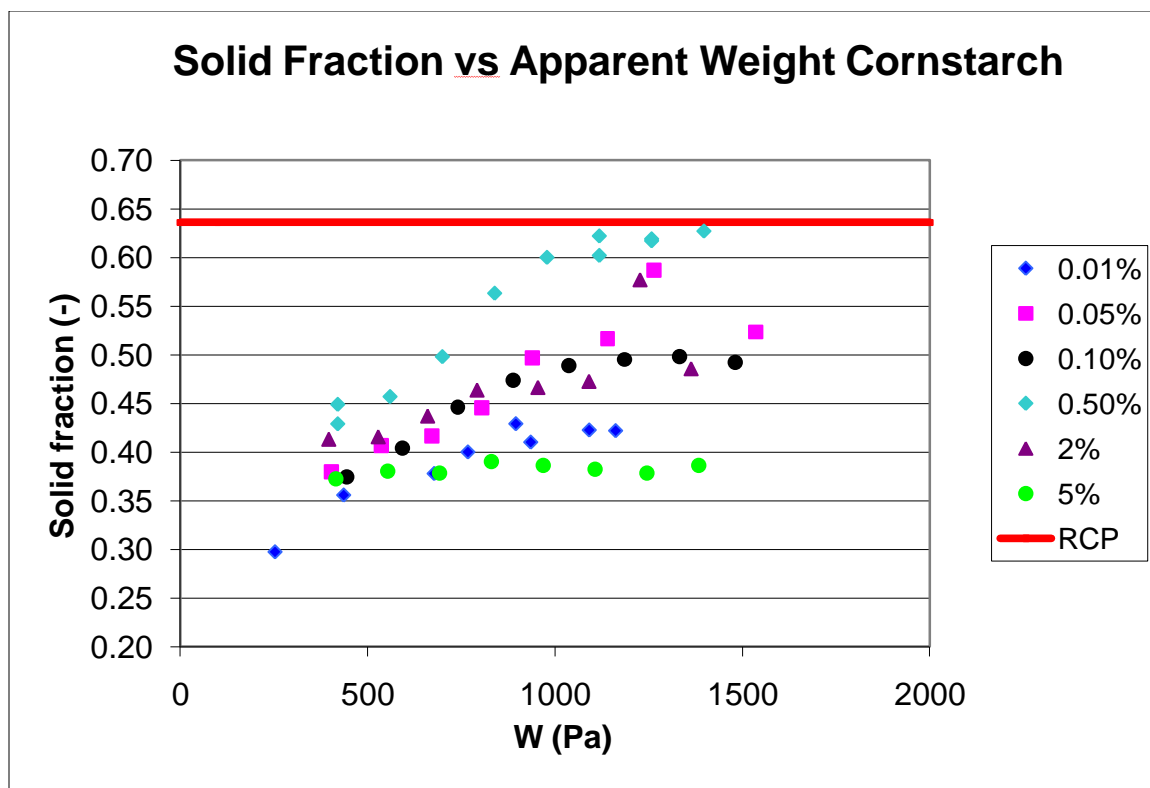


Figure 4.5 Cornstarch apparent weight with changing amplitude and coating level.

The data shows that with an increasing consolidation, the solid fraction increases, which is to be expected.

4.4.2 Active Pharmaceutical Ingredients and Excipients

After developing a procedure and seeing repeatable and intuitive results with the cornstarch powders, API powders were tested to see if the same trends seen as results with the AOR could be seen with powders that are inherently more difficult to handle and harder to coat. Figure 4.6 shows solid fraction results of two different pharmaceutical powders, semi-micronized acetaminophen coated with varying levels of silica R972 and Celphere coated with varying levels of magnesium stearate. Both were coated in the MAIC.

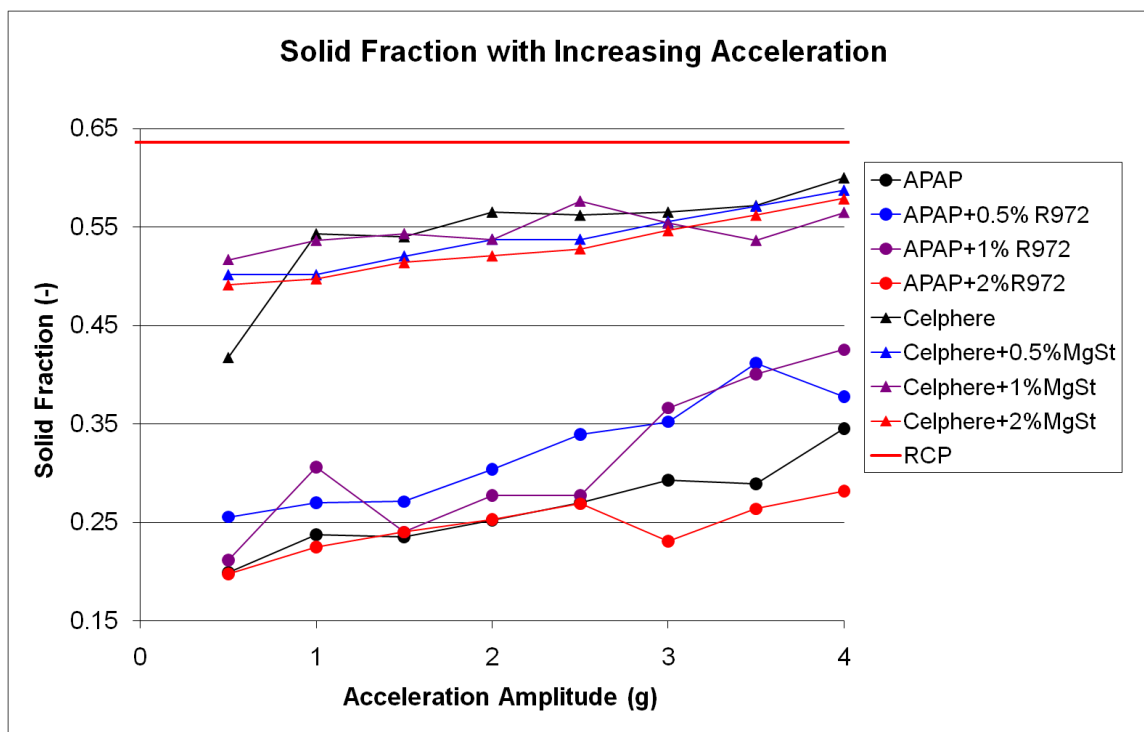


Figure 4.6 Coated and uncoated acetaminophen and Celphere solid fraction with changing amplitude and coating level.

The results for Celphere did not indicate much of a change in flowability, which was not unexpected. Celphere was coated with magnesium stearate to create a precision lubricant for tableting. The results for semi-micronized acetaminophen did show a trend of improving flowability when silica was added. Semi-micronized acetaminophen coated with 0.1% and 0.5% silica showed significantly higher solid fractions than the uncoated powders under the same consolidation. This indicated that the flow would be improved, which was confirmed using AOR as shown in Chapter 3. Semi-micronized acetaminophen coated with coated with 2% R972 silica showed a decrease in solid fraction, which would also translate to a decrease in flow. This is due to the over 100% surface area coverage in the coating, therefore excess silica is present to interfere with the flow. This is also shown in Chapter 3 with the AOR results.

The solid fraction was also shown as a function of weight per unit area for both semi-micronized acetaminophen and Celphere in Figure 4.7.

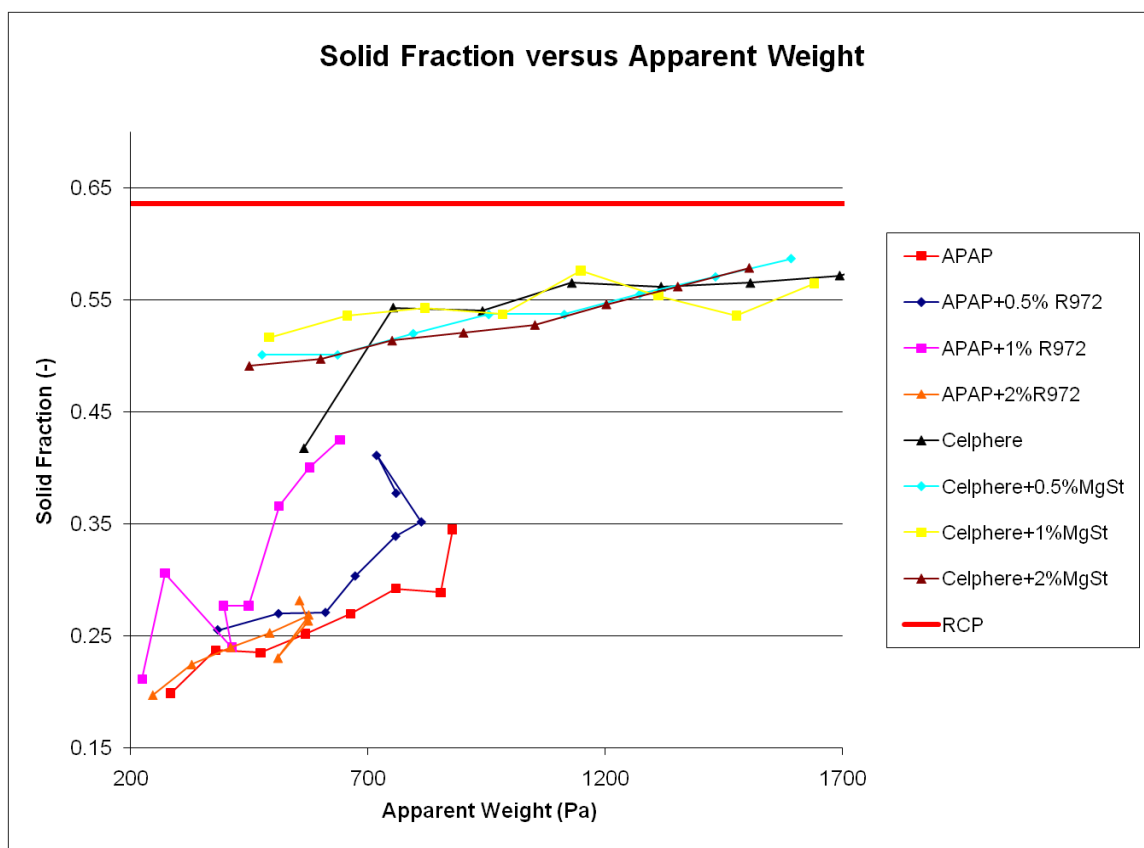


Figure 4.7 Coated and uncoated acetaminophen and Celphere apparent weight with changing amplitude and coating level.

The results are not as linear as with the cornstarch, but overall these powders are much worse behaved in general which contributes to difficult in testing and in getting repeatable results. With that said, there is still an overall trend of increasing solid fraction with increasing acceleration amplitude.

More investigation was done for the semi-micronized acetaminophen, as this was coated for improved flow. Angle of repose results had previously been done (See Chapter 3) and a linear correlation was shown with increasing silica fraction and it was hoped that the vibrated packed density could correlate that as well. Figure 4.8 shows the results plotted with linear correlations.

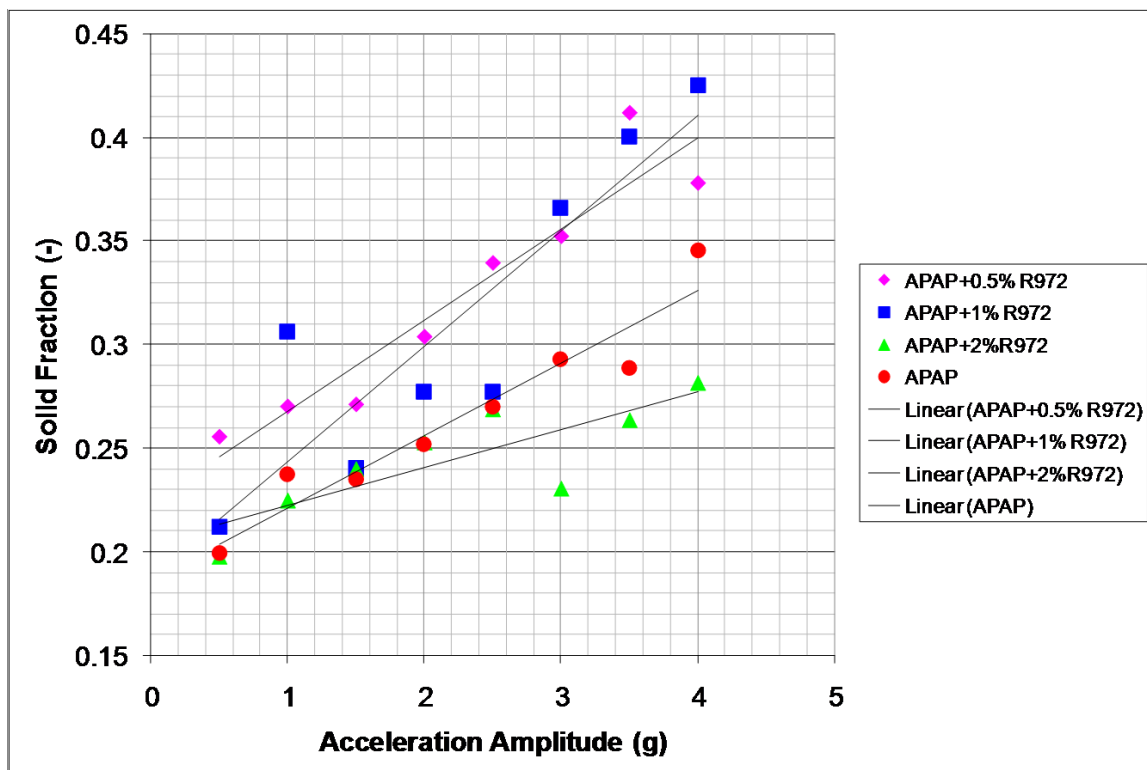


Figure 4.8 Acetaminophen solid fraction results with linear correlations.

These linear correlations show that the vibrated packed density device could give the same rank order as with the AOR, but with more information generated, such as the packing density under certain consolidations and packing density determined over time. This would overall offer up more in depth information than the more widely used powder tests, especially in terms of behaviors relevant to tablets and the tableting process. Additionally, there was a linear correlation observed with the equilibrium solid fractions with increasing amplitude for each coating level of silica.

4.4.3 Semi-micronized Acetaminophen Blends

After testing semi-micronized acetaminophen coated in the MAIC using various coating levels of silica, blends were made with the powders coated with 1% silica and lactose, creating a binary blend. The purpose was to see if the vibrated packed density setup

could discern changes in flow in blends and discern changes in blends of uncoated powders versus coated powders. 5%, 25% 50% and 75% drug loadings were chosen and the corresponding AOR results were seen in Chapter 3. At the lowest drug loading of 5%, Figure 4.9 shows that the vibrated packed density setup shows a slight improvement in flow at some acceleration amplitudes when using the coated powders.

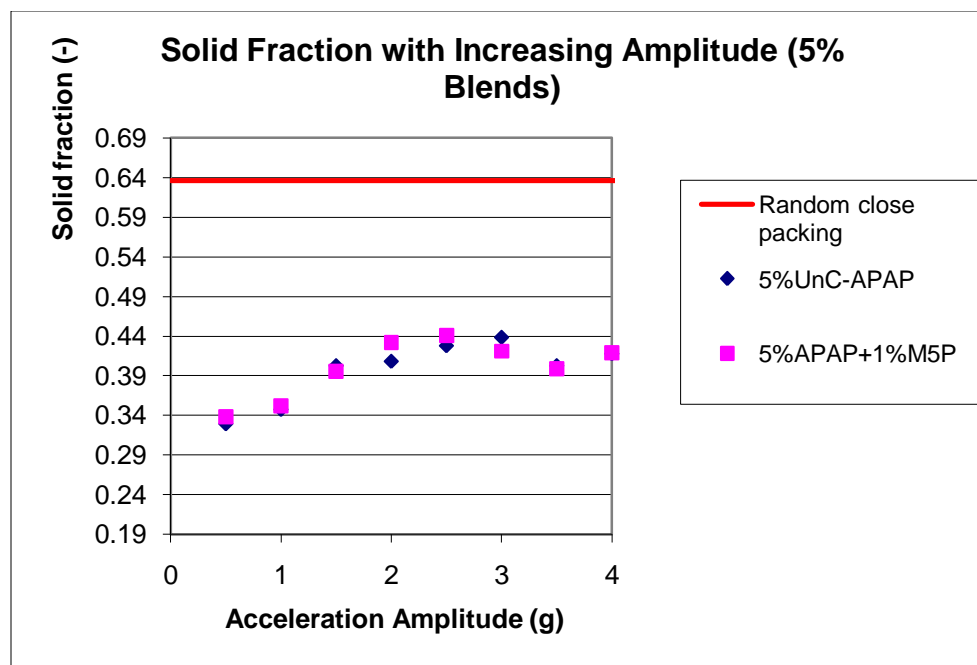


Figure 4.9 Packing density of blends with 5% coated and uncoated acetaminophen.

As the drug loading is increased to 25%, 50% and 75%, Figures 4.10, 4.11 and 4.12 show, respectively that as the drug loading is increased, there is a larger improvement in solid fraction and thus flow of the coated powder blends when compared to the uncoated powder blends. It is especially prevalent when the drug loading is highest, at 50% and 75% drug loading.

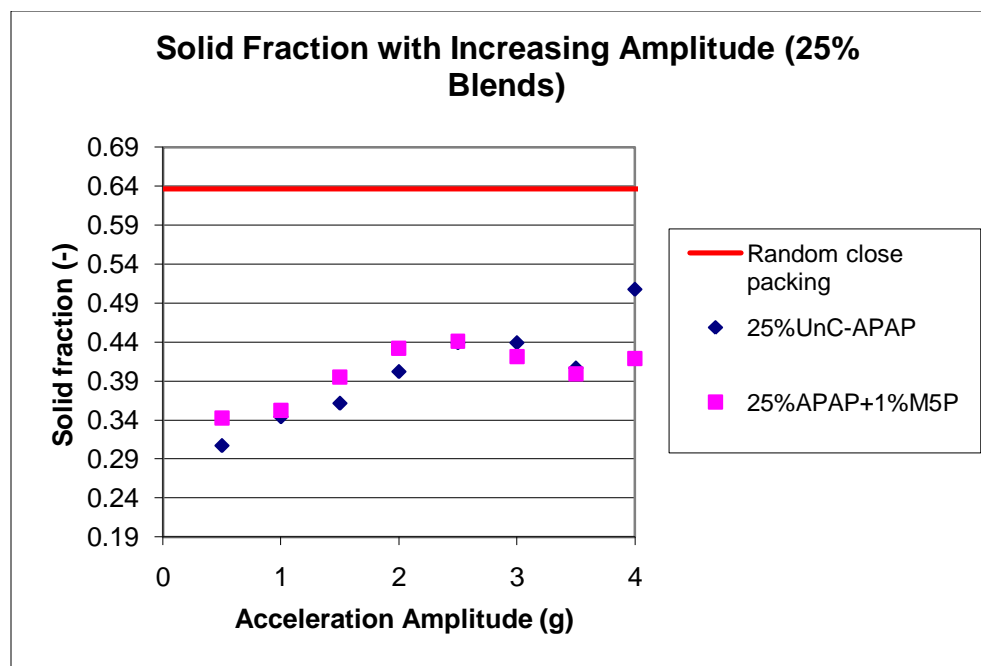


Figure 4.10 Packing density of blends with 25% coated and uncoated acetaminophen.

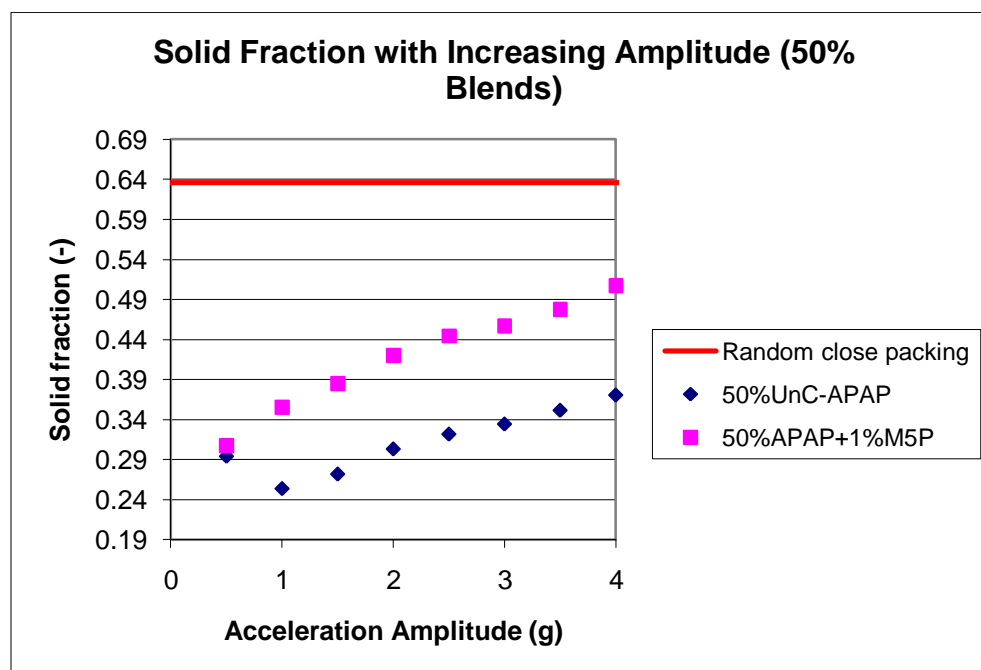


Figure 4.11 Packing density of blends with 50% coated and uncoated acetaminophen.

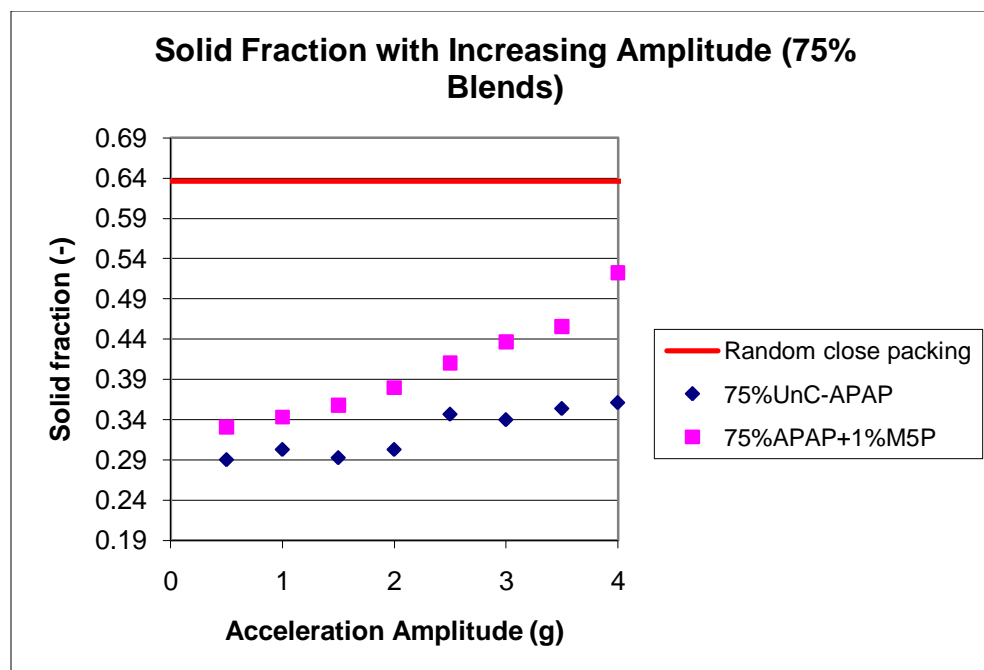


Figure 4.12 Packing density of blends with 75% coated and uncoated acetaminophen.

At 5% drug loading, the excipient, in this cast fast flow lactose, is the major contributor to the flow while at drug loadings of over 50%, the drug is the major contributor to the flow as seen with the AOR results in Chapter 3 and shown again here using the packed density setup. Thus, the vibrated packed density setup can be used to characterize blends and can differentiate between coated and uncoated powders, even within the blends.

4.5 Conclusions

Flowability of fine powders is strongly dependent on memory effects such as the effect of previous consolidation stresses on the packing density of the powder. In this work we present Measurements of the particle packing density of fine cohesive powders as a function of the consolidation stress previously applied on the sample. The particle volume fraction is derived from the height of the bed, which is measured by a high-accuracy sensor placed on top of the vessel. It is observed that powders with lower

amounts of coated additive have larger cohesion and form larger agglomerate structures and hence show lower packing densities. As amount of coated additive increases, cohesion is reduced and smaller agglomerates are formed which pack better in both fluidized and non-fluidized states. The effect of low consolidation stresses are also examined on the packing density.

CHAPTER 5

DYNAMIC POWDER FLOW

5.1 Introduction

Powder flow characterization has been an active field for decades, most notable contributions are those from Jenike (theory based on incipient failure of powders) and Carr (set of indices, now part of ASTM standard D6393 – 08). [52] Over the past 20 years, numerous powder testing devices have been introduced and promoted (e.g., variety of shear testers, Avalanche tester, Freeman rheometer), making the task even more complicated due to the difficulty in testing, interpreting and correlating the results from various devices. In general, the powder flow is dependent on three important, related state variables; consolidation, σ , shear τ , and solid fraction ϕ . Most powder testers attempt to gain some knowledge of their inter-dependence, and may provide part of the yield surface shown in 3-D in Figure 3.3. Shear testers are frequently used for powder flow testing; Schewedes has classified them according to the way the shear plane is formed. [24]

The overall powder testing approach examined selection of testers depending on the regime (amongst four listed in Chapter 3) of the powder process in mind. For example, a shear tester is most suitable in design of a hopper, Freeman FT4 or equivalent rheometer may be suitable in examining the flow from a screw feeder. In cases where the scrutiny focuses on the influence of added ingredients such as flow-aids, or lubricants, multiple devices may be necessary and there is a need for correlating within those measurements and with other properties, such as surface energy, hydrophobicity or electrostatic properties. When powders are very fine, devices based on fluidization are

also very suitable (e.g., Sevilla Powder Tester- SPT) and there is need for a better packed density measurement device (e.g., novel vibrated packed density measurement, see Chapter 4).

Qualitatively examining the changes in powder behavior after dry coating processing is very important to understand the improvement and change in powder flow performance. Quantitative observations are made as well. In this case, an improvement in powder flow is the desired effect from the dry coating process. With that said, it is important to get as much information as possible about the powder to construct a comprehensive overview of its behavior. From there, the dry coating can be optimized and better defined and more efficient formulation and manufacturing is possible.

Testing that covers more than one powder regime is very important and will allow for as much comparison as possible between powders. Often after dry coating, powders are in a different regime than they were originally. Hence, it is very important to use or devise a test that is valid and useful over multiple regimes. Additionally, having tests that offer up more than one piece of information about the powder is also desirable to minimize work involved and form the most comprehensive picture of the powder.

“Measuring dynamic, bulk, and shear properties of powders allow identification of the parameters that best define product performance, both during processing and in final application.” [53] This knowledge gives way to fast, successful formulation development and effective process control.

In addition to the flow properties, it is critical to look at the handling properties of the powders, i.e., how these powders respond to the unit operations and movement they encounter during both formulation and manufacturing processes. Handling of powders

creates a history to the powder. The history is one or more properties the powder comes to possess that it did not originally have due to consolidation or interaction with itself or an additional powder or equipment.

Dynamic testing is testing that is done that simulates some kind of handling or operation that the powder will encounter. This type of testing is crucial for gaining an overall understanding of the powder, specifically the powder as its being used.

“Predicting flow performance of powders through a given process is of great importance in industry where the flow properties of powders change, which can result in manufacturing difficulties and out of specification products. The need is for reliable prediction of flow performance which requires reliable information on the bulk, flowability and processability characteristics of the powders concerned. No definition or units exist to describe the dynamic flow of powders and no ideal way of measuring these complex materials exists.” [53]

In this work, testing has been done using angle of repose, bulk tapped and packing density, powder rheometry, positron emission particle tracking, near infrared spectroscopy, particle size and ring shear tester. Some of these tests are not useful for certain regimes of powder and hence is why so many tests have been used.

5.2 Freeman FT4 Powder Rheometer

The dynamic powder flow behavior of each powder sample was examined using a Freeman FT4 powder rheometer. The stability and variable flow rate method was used to evaluate each powder (seven cycles at a fixed speed, four cycles at different test speeds) in a 25cm³ split cell using a 23.5 mm impeller [30]. Each powder was conditioned in a closed environment at $20 \pm 2^{\circ}\text{C}$ and $50 \pm 2\%$ relative humidity for 16 to 24 hours prior to

testing to minimize the effects of moisture uptake. The results from this test were not clear and therefore a discussion is not included here and a proper interpretation will be investigated at a later time as part of ongoing work with Freeman Technology.

5.2.1 Benefits of using the FT4 Powder Rheometer

FT4 performs 11 various tests to get a whole “big picture” overview of the powder. The rheometer does shear testing to determine flow properties, but also can investigate the stability of the powder in addition to the compressibility, aeratability and permeability among others. The FT4 powder rheometers can provide fast, repeatable, sensitive measurements with a high degree of automation. [53]

5.2.2 Limitations of using the FT4 Powder Rheometer

FT4 performs at its best with certain types of powder. Free flowing or extremely cohesive powders can lead to mixed results with poor repeatability. Specifically with the shear test, the unconfined yield strength and to a lesser extent the cohesion can be determined with reasonable accuracy for the cohesive powders but not for the non-cohesive powders due to errors from extrapolating the yield loci close to zero when doing the Mohr circle analysis. In this case, bulk density, compressibility, permeability and adhesion measurements are more useful for helping to interpret flow behavior. [53] Additionally, more repeatable and accurate results are generally attained using the largest of the powder cells, which requires a significant amount of powder which may not always be available.

5.3 Schulze Shear Cell

The powder flow behavior of each sample was determined using a Schulze annular-type ring shear tester model RST-XS. Each sample was equilibrated in a closed environment at $20 \pm 2^\circ\text{C}$ and $50 \pm 2\%$ relative humidity for 16 to 24 hours prior to testing to minimize the effects of moisture uptake. The steady state shear stress of each powder was measured as it was subjected to a series of applied normal loads ranging from 1 to 2.6 kPa. Prior to each load, the powder was pre-sheared to steady state at 4kPa, which helped create a consistent initial powder bed condition, i.e. bulk density. From the yield locus plot, the ratio of the principle consolidation stress (σ_1) to the unconfined yield strength (FC) was used to calculate the FFC value. FFC values typically range from 1 to 10 and powders with FFC values less than 4 are considered cohesive and poor flowing. [30]

5.3.1 Benefits of Using the Schulze Ring Shear Tester

The idea of the shear cell was originally developed to assist in design of hoppers and silos. It has subsequently been used to characterize powder behavior in consolidated state. From a series of shear tests, the opening of the hopper, the wall material, the angle of hopper and other design parameters can be determined. It also does not have some of the inherent limitations that FT4 does in that it can test a variety of powders in different flow regimes and can test a much smaller sample with greater repeatability. Additionally, the Schulze Ring Shear Tester is totally automated and does not require changing/moving parts.

5.3.2 Limitations of Using the Schulze Ring Shear Tester

The Schulze Ring Shear tester is only capable of performing a single test, the shear test. The pre-shear stress can be changed along with the applied loads throughout the test to get as much information as possible over a wide range of stresses; however that is an inherent limitation to this particular setup.

5.4 Results

After dry coating with a comil, the powders exhibited a considerable and in some cases outstanding improvement in flow performance and bulk density.

5.4.1 Ibuprofen

Initially, two grades of ibuprofen (50 and 110) were coated in the MAIC, both with 1% R972. According to previous results of both SEM and AOR, both grades coat well and a significant flow improvement was noted. After coating, particle size was tested to assure there was no attrition during the coating process. The powders were then conditioned and tested in the RST. The results are shown in Figure 5.1.

Powder Description	Particle Size μm D[4,3]	Effective angle of internal friction (degrees)	Angle of internal friction (degrees)	Flow Function Coefficient	Cohesion (Pa)	Consolidated bulk density (kg/m ³)	AOR (degrees)	Flodex (mm)
Ibuprofen 50	77.05	43	33.5	2.95	711.5	551.5	41.8	20
Ibuprofen 50 blended with 1% R972 Pharma	88.35	48	43.5	5.2	431	525		
Ibuprofen 50 coated with 1% R972 in MAIC	79.85	40	39	23	96.5	568		
Ibuprofen 110	138	31	26	5.05	400	599.5		
Ibuprofen 110 coated with 1% R972 in MAIC	127.67	41	41	30.67	75.67	617		

Figure 5.1 Ibuprofen characterization with consolidation using a shear cell.

Important to note is that a simple blend of ibuprofen and silica was tested for an accurate comparison to what is currently used in the pharmaceutical industry to improve flow. With the simple blend, the flow function coefficient does improve from the uncoated, from 2.95 to 5.2, however, when the same amount of silica is precisely dry coated onto the same ibuprofen, the flow function coefficient goes from 2.95 to 23 which is a much more significant change and the powder becomes completely free throwing. This significant increase is also shown for the other grade of ibuprofen, the 110 in this case. Also important to look at is cohesion and the effective angle of internal friction. In the case of the ibuprofen 50, with the coated powders, both the cohesion and the angle of internal friction are reduced. The simple blend decreases cohesion but there is an increase in the effective angle of internal friction, which may be due to the silica freely in the blend. In the case of the ibuprofen 110, the cohesion is cut down significantly but the effective angle of internal friction has increased. This may be due to the change in particle size.

The cohesion and the flow function coefficient are shown to have an inverse relationship. As the flow function is increased, the cohesion is decreased. This relationship is shown in graphical form in Figure 5.2.

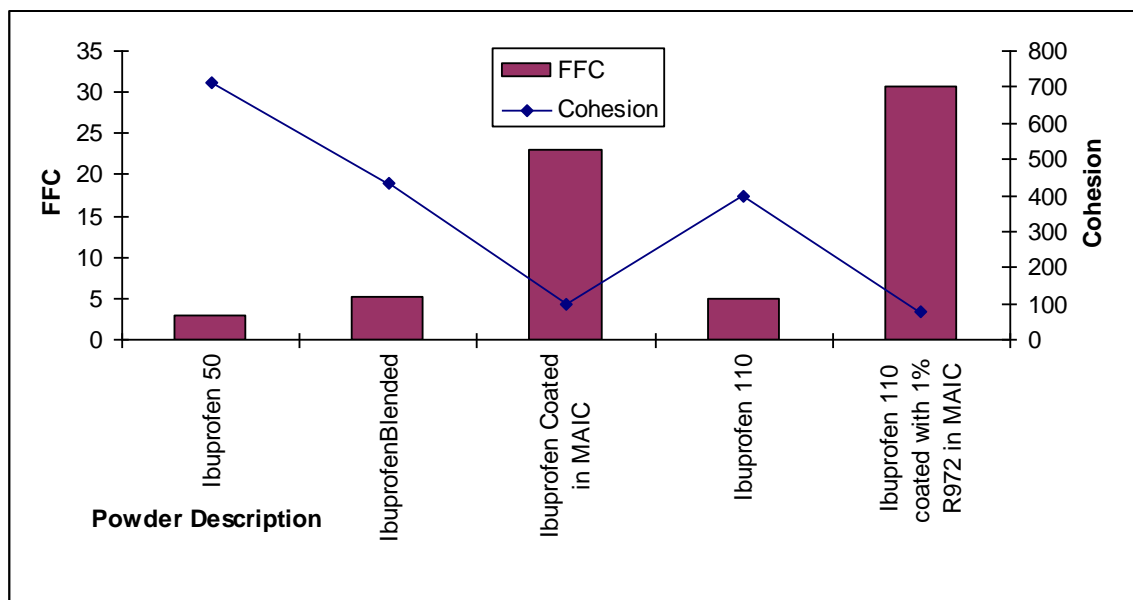


Figure 5.2 Flow function and Cohesion of Ibuprofen powders with and without coatings.

Again, the simple blend of the Ibuprofen shows that its flow is improved with the addition of the silica, but when the silica is actually dry coated precisely on the surface, a much more significant improvement in flow is seen.

5.4.2 Acetaminophen

After testing was completed with the ibuprofen, two grades of acetaminophen (micronized and coarse) were coated in the MAIC, both with 1% R972. According to previous results of both SEM and AOR, both grades coat well and a significant flow improvement was noted. After coating, particle size was tested to assure there was no attrition during the coating process. The powders were then conditioned and tested in the RST. The results are shown in Figure 5.3.

Powder Description	Particle Size μm D[4,3]	Effective angle of internal friction (degrees)	Angle of internal friction (degrees)	Flow Function Coefficient	Cohesion (Pa)	Consolidated bulk density (kg/m ³)	AOR (degrees)	Flodex (mm)
Micronized APAP	15.5	79	41.5	1.055	2072	307.5		
Micronized APAP coated with 1% R972 in MAIC	13.2	52	44	2.9	760	469.5	41.2	9
Coarse APAP	62.9	58	43	1.75	1425	519.5		
Coarse APAP coated with 1% R972 in MAIC	61.2	43.5	38.5	4.55	462.5	743.5		

Figure 5.3 Acetaminophen characterization with consolidation using a shear cell.

Both grades of acetaminophen are very poor flowing as received, falling in the poor to no flow range as shown with both AOR results and with the flow function coefficient. After coating, the powders transitioned to a cohesive but flowing state. For each grade, the flow function coefficient doubled with the application of a dry coating. Additionally, the effective angle of internal friction dropped significantly and the cohesion went down by an order of magnitude. A graphical representation of the change in flow function coefficient and cohesion is shown in Figure 5.4.

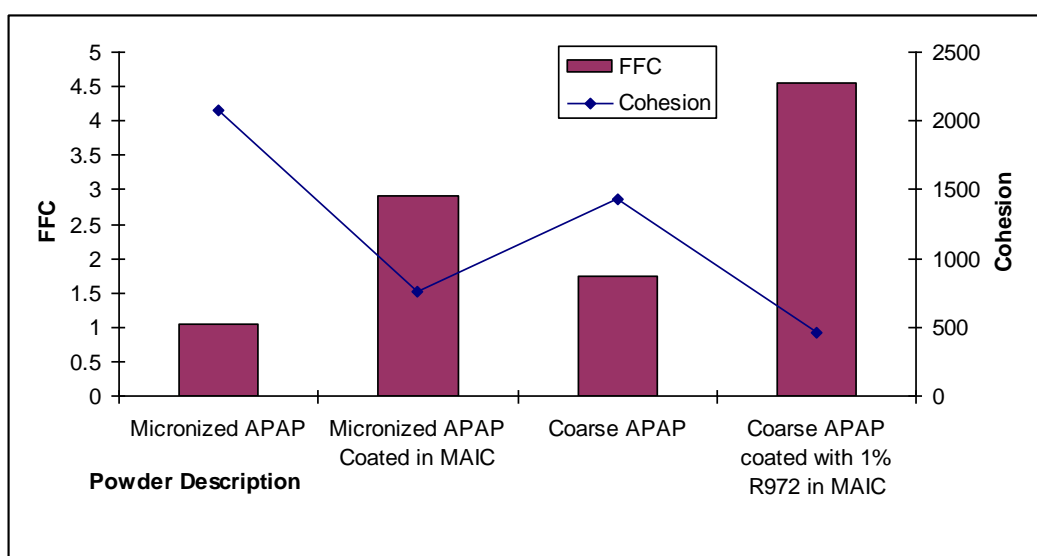


Figure 5.4 Flow function and Cohesion of APAP powders with and without coatings.

With the application of dry coating, the flow properties of both grades of acetaminophen are drastically improved.

5.4.3 Scale up of Continuous Coating Device

The Comil coating device and process was initially developed using a lab scale U3 Comil. After initial optimization was done, the continuous Comil coating process was successfully scaled from the laboratory to pilot scale with similar improvements in flow. The process was scaled using the same screen size for the Comil 193 as for the U3 and the tip speed was scaled up accordingly. The RST was used to confirm that the scale up was successful. Figure 5.5 shows a plot of flow function coefficient and cohesion for the uncoated ibuprofen 50, a simple blend of ibuprofen 50 and silica, the lab scale comil and the pilot scale comil.

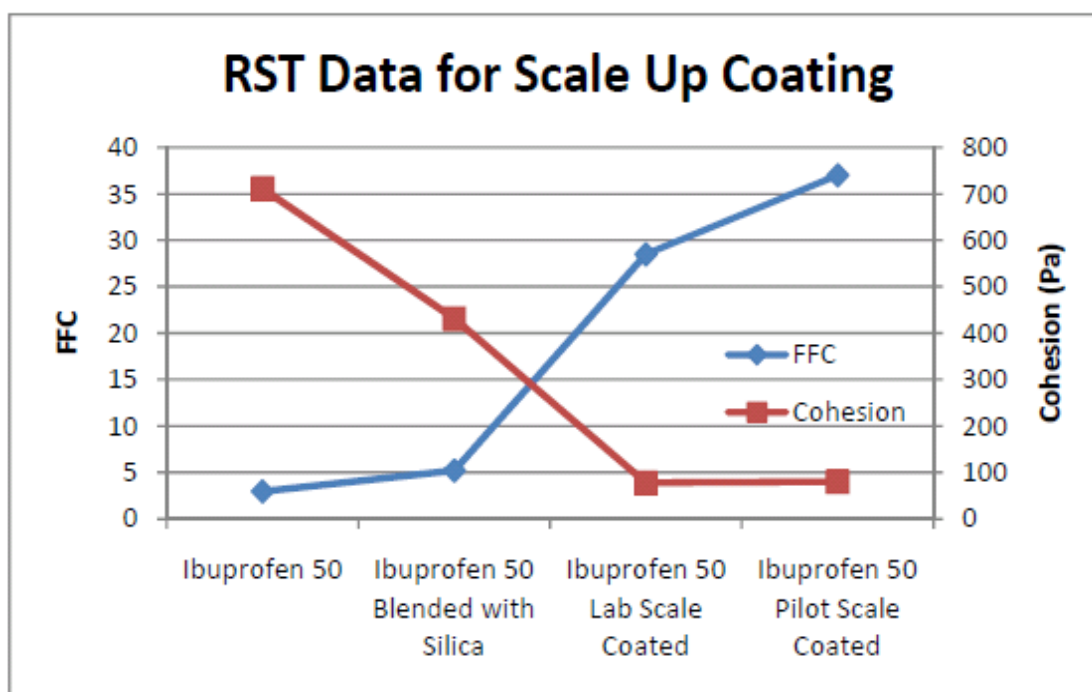


Figure 5.5 Ensuring scale up methodology has worked when going from lab scale to pilot scale.

The figure shows that the scale up was successful, with the pilot scale 193 Comil performing as well and better than the lab scale U3 Comil.

5.4.4 API Blends

After all the uncoated and the coated APIs were tested, various drug loading blends were made from these APIs. Initially blends were made with the ibuprofen 50, since there were promising results for the powder itself. Blends were made with various excipients at different drug loadings of 10%, 30%, 60% and 100%. The blends were constructed with the uncoated powders and the coated powders and with silica added to the powders to simulate the normal industrial practice. Figure 5.6 shows the results of the RST testing, specifically the flow function coefficient plotted with increasing drug loading.

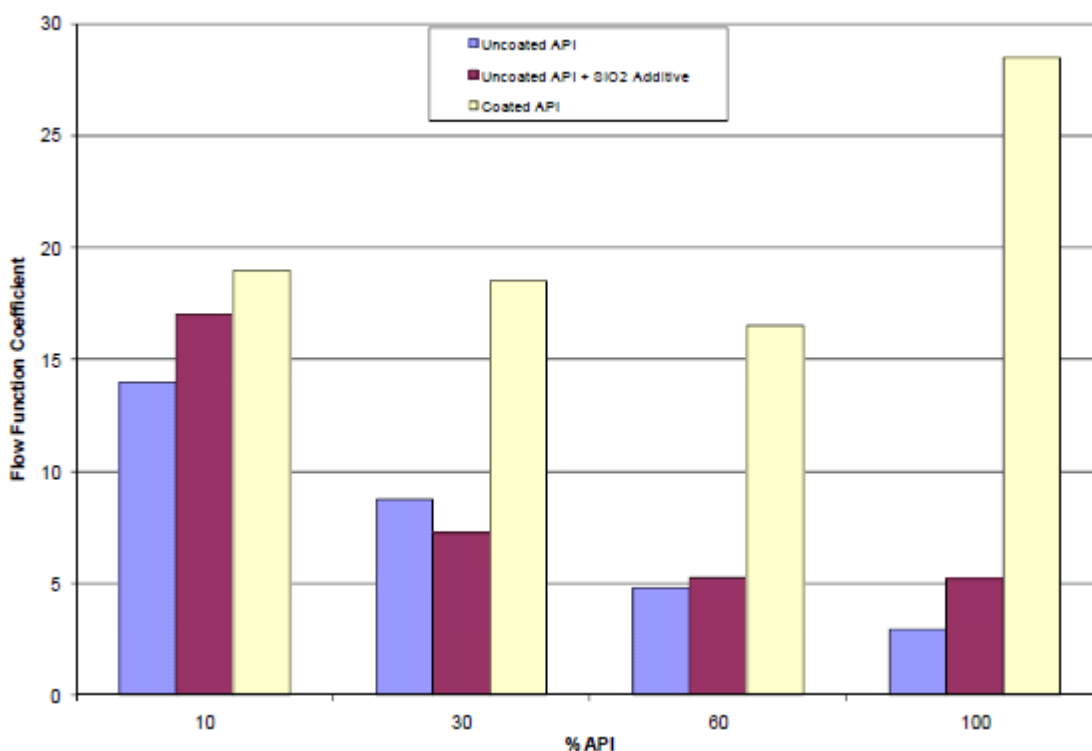


Figure 5.6 Flow Function Coefficient of increasing drug loaded blends of ibuprofen 50.

These results indicate that even at the lowest drug loading of 10%, the coated powders had better flow performance than those made of either the uncoated or the blends with silica additive. As the drug loading is increased, the difference in flow between the uncoated and coated blends gets larger. The flow function coefficient increases for the coated powders as the drug loading is increased while for the uncoated and silica additive blends the flow function coefficient decreases. The dry coated material consistently out performs the uncoated and the silica additive blends at every drug loading. The superior performance translated to subsequent formulated blends, demonstrating the benefit of using dry coated powders over uncoated powders. [30]

5.5 Influence of Unconfined Yield Strength on FFC

A more in depth statistical analysis of the ring shear tester data is necessary to understand completely the information that the testing gives. There are two facets to look at, the measurement variability (from multiple runs of the same sample) and the process variability (variability within different runs of one process and from process to process). The main focus will be on the measurement sensitivity and determining how accurate and precise is the RST data and the variability from one powder to the next, including determining the error. Also to be determined is the sensitivity of the flow function coefficient and determine where the major contribution is coming from.

5.5.1 Measurement Variability

Typically two different repetitions of the same sample are tested in the RST. There is one large amount sampled from the batch, and then it is divided in half for two separate tests. It is important for these measurements to match, as the sample is the same. In

general, two different shear cells of the same size are used for the testing and the variability is reduced by one person preparing the sample. Taking a look at the relative standard deviation (RSD) between the samples should give a good idea of the variability between measurements. Figure 5.7 shows the relative standard deviations between the two tests for each sample of ibuprofen.

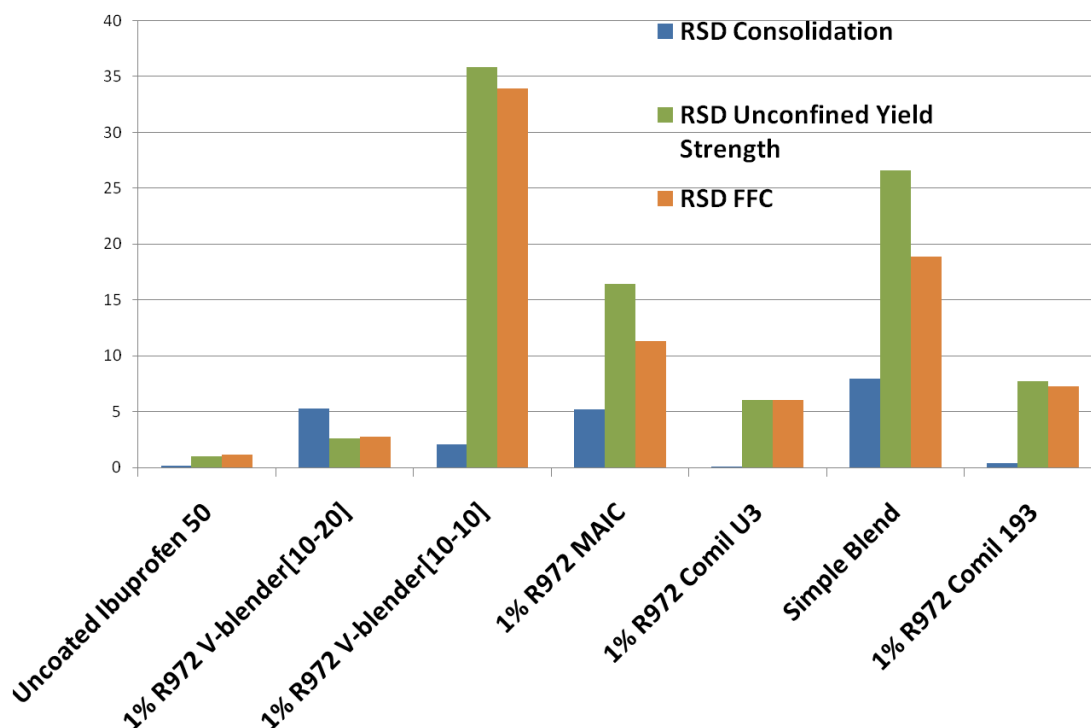


Figure 5.7 Relative standard deviations of RST measurements for various coating processes.

Uncoated is shown as well as ibuprofen coated in the v-blender (10 minutes with agitator bar and 20 minutes with agitator bar only for 10 minutes) coated in the MAIC, coated in the Comil U3 and coated in the Comil 193.

Figure 5.7 shows that the RSD of the consolidation remains relatively low in each case, however the RSD of the unconfined yield strength is quite high. The RSD of the flow function coefficient is also high, and Figure 5.7 shows that the variability of the flow function coefficient is due to the variability in the unconfined yield strength. It was

also expected that the coated powders would have a lower RSD than the uncoated powders because overall the coated powders behave better than the uncoated powders. However, the RSD analysis shows the opposite, that the uncoated powders had the lowest RSD. This is somewhat surprising and may warrant more investigation.

5.5.2 Sensitivity of the Flow Function Coefficient

The flow function coefficient is really a ratio of two values found from the yield locus analysis. The flow function coefficient is the ratio of the consolidation stress to the unconfined yield strength. As the analysis is done to show the difference in the flow properties between uncoated and coated powders, it is important to see which variable, the consolidation stress or the unconfined yield strength, is affected or if they are both affected and to which extent.

Percent change for each coating process was calculated. The change in each variable (the consolidation stress and the unconfined yield strength) was examined between uncoated and coated. That is, each coating method was compared to the uncoated powder and seeing how each variable changes under the effect of the coating. Table 5.1 shows the percent change from uncoated to coated.

Table 5.1 Percent Change of Shear Test from Uncoated to Coated

% Change from Uncoated			
Coating Method	SIGMA 1	FC	FFC
Coated (1% R972 V-blender[10-20])	20.49	-85.53	732.3
Coated (1% R972 V-blender[10-10])	11.96	-83.89	640
Coated (1% R972 MAIC)	15.92	-84.81	670.5
Coated (1% R972 Comil U3)	18.67	-87.63	861.3
Simple Blend	29.66	-24.36	75.82
Coated (1% R972 Comil 193)	14.4	-88.27	878.2

Overall, the unconfined yield strength (FC) is the contributing factor to the flow function coefficient, especially when comparing how the coated powder changes when compared to the uncoated. The consolidation stress (SIGMA 1 or σ_1) does change as well, just not to the extent that the unconfined yield strength does. Additionally, the percent change in the flow function coefficient is also shown. The larger the percent change the better the improvement in flow.

5.6 Bulk Density

After completing all the RST testing, a powerful correlation emerged. As the flow function increased as an effect of the dry coating, the bulk density also increased and a linear correlation could be formed. It was shown that dry coating APIs with the silica significantly improves powder bulk density and while flow function is an indicator of the powder flow performance, bulk density can be predictive of the tableting processes and altering the bulk density can enable direct compression formulations, leaving out processes such as wet and dry granulation which are costly and often troublesome.

After the results of RST testing with the ibuprofen blends, additional pharmaceutical material blends were tested. Three additional proprietary Pfizer APIs were dry coated using the comil and various types of silica and coating level of silica. Hydrophobic silica R972 and hydrophilic silica A200 were both used in levels of 1% or 3% by weight of the API. Blends were made with a 30% drug loading and the bulk density was tested initially. When used in direct compression drug products, the formulations using the coated powders continued to have higher bulk density. The percent increase of bulk density when compared to the uncoated blends is shown in Figure 5.8.

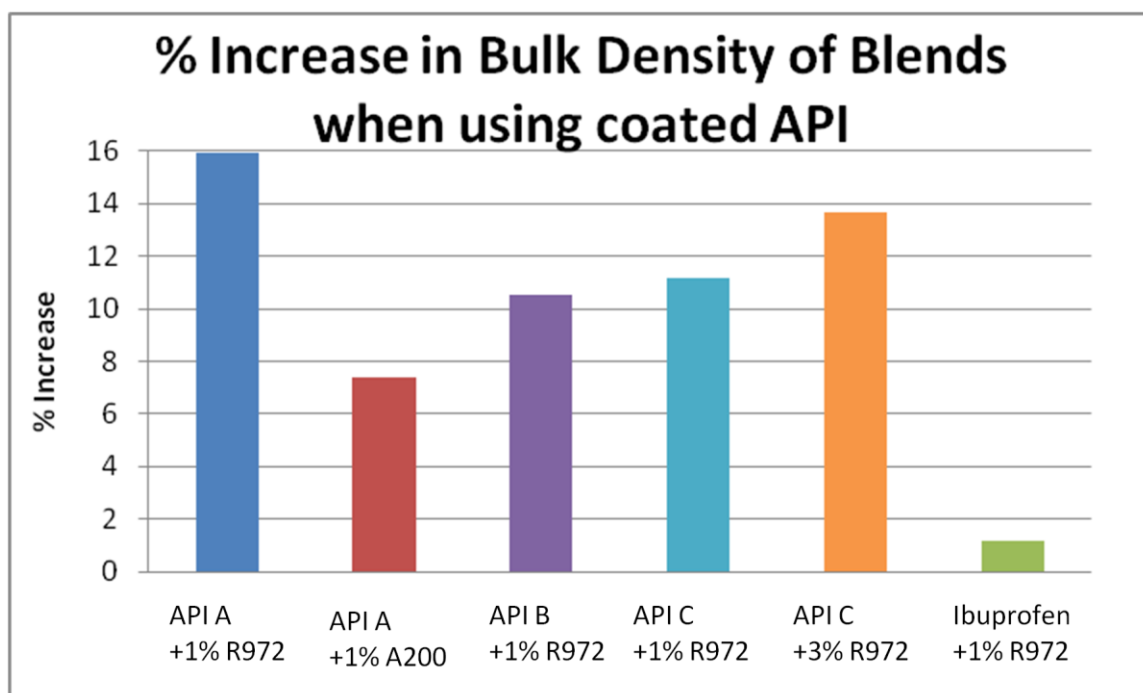


Figure 5.8 30% drug loaded blends characterized for change in bulk density when powders are coated.

After doing this bulk density testing, it was hard not to notice that the bulk density increased along with the flow function coefficient. Using this correlation helped to determine the optimum coating material and percentage of coating material. Figure 5.9

shows various APIs and excipients as the guest materials and two different coating materials, A200 and R972 in 3 different percentages, 0.5%, 1% and 3%.

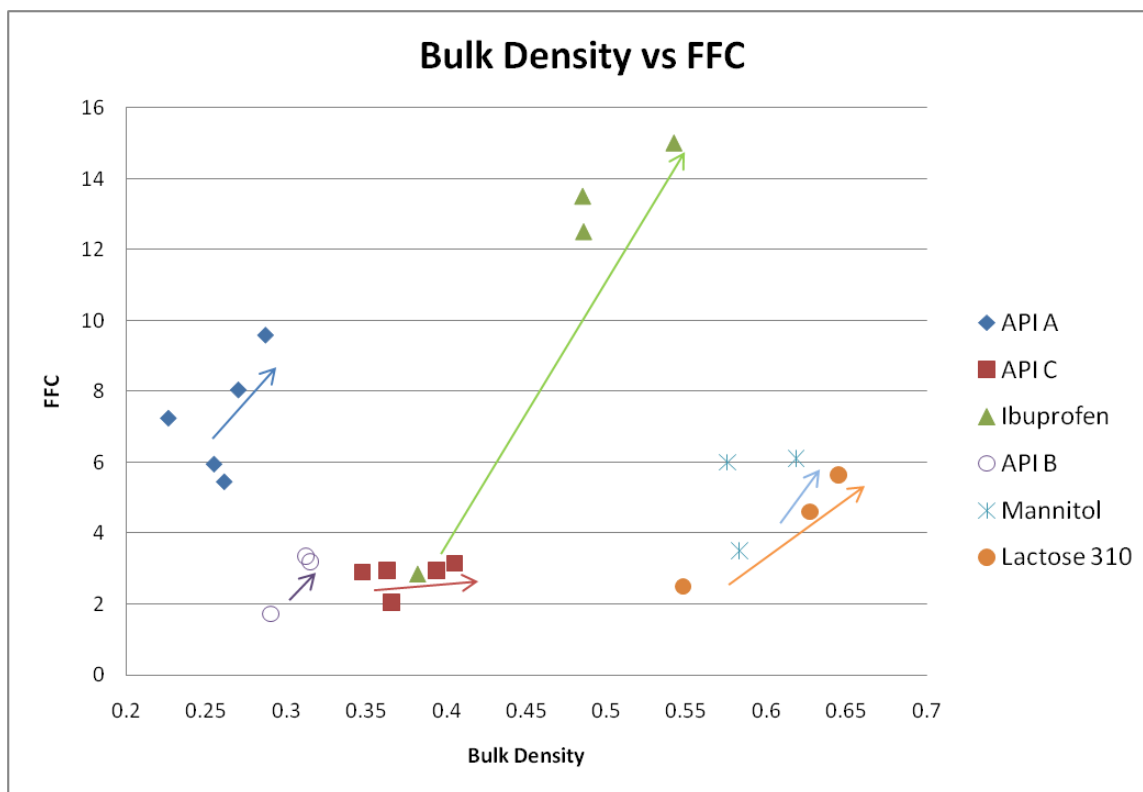


Figure 5.9 APIs and excipients characterized for change in bulk density when powders are coated with different percentages and grades of materials.

After seeing this, the optimum coating material and coating percentage was chosen. Figure 5.10 shows the optimum coating material and percentage (1% R972) and also shows the linear tendency of the relationship.

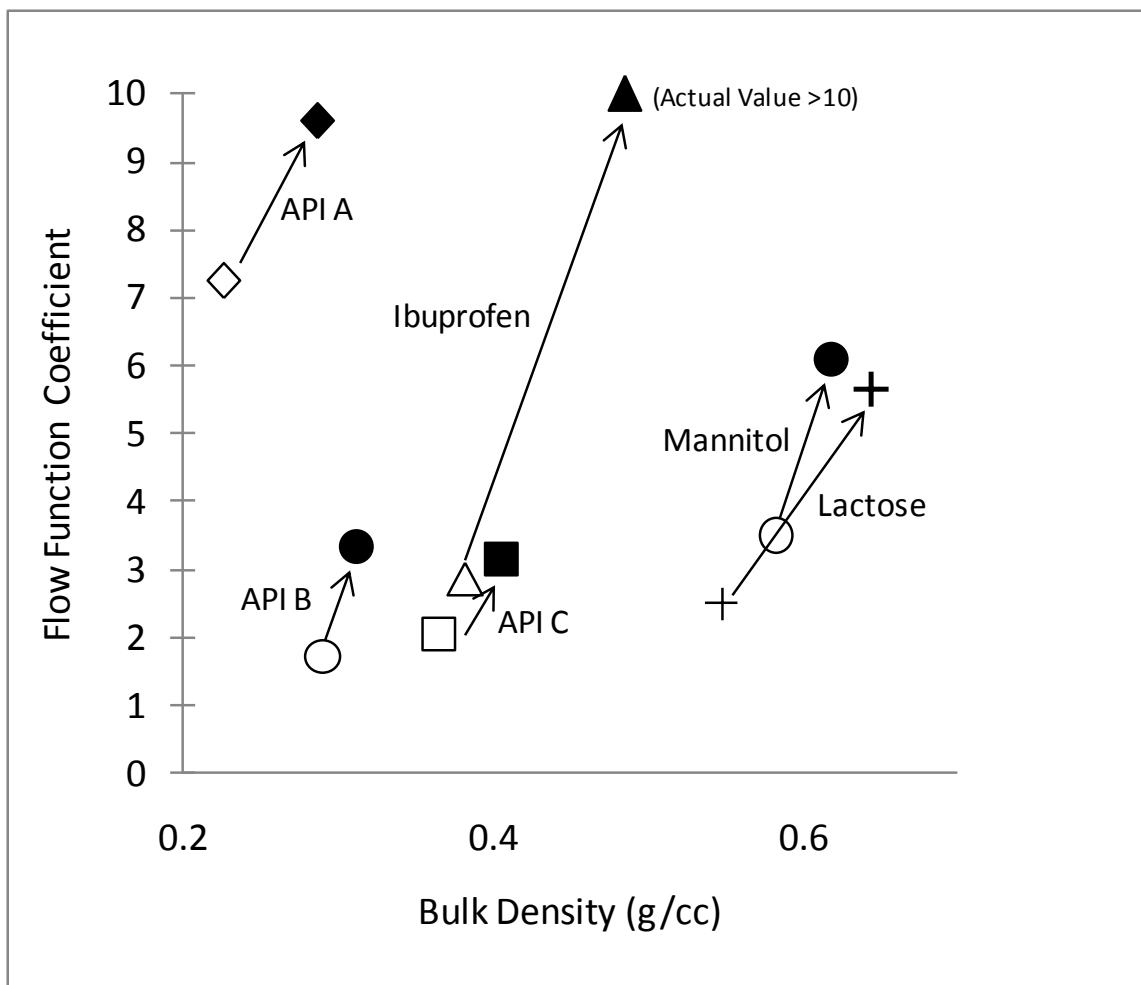


Figure 5.10 Bulk density of optimized processing conditions using the phase map.

Overall, this relationship shows that better flowing and higher density APIs can enable higher drug loadings in direct compression drug products and that bulk density appears to be a rapid and useful surrogate for assessing changes in powder flow performance.

5.7 Conclusions

Powder flowability is still a very long way from being an exact science and yet the need for industry to be able to predict flow performance is more important than ever. The typical industrial challenge is to identify differences between very similar powders.

Therefore the highest achievable levels of sensitivity and repeatability of measurement are required over the widest range of test methods, including both shear and dynamic flow techniques. [52] Shear strength is a complex function of many physical and environmental properties. Flowability is even more complex being dependant upon shear strength, compressibility, air content, the rate of flow and other factors. In particular the high transmissibility of flow forces in consolidated, noncohesive powders, resulted in high flow energy, even though these materials have relatively low shear strength and are free flowing when not confined. [52]

CHAPTER 6

INLINE MONITORING AND PAT

6.1 Introduction

In pharmaceutical manufacturing, it is necessary to understand the factors that affect the flow behavior of powders. Powders are important in pharmaceutical mixing, tablet manufacturing, and encapsulation as processes such as granulation, drying, milling, and die filling depend on powder flow. The transfer of powders in pharmaceutical and other industries involves flow in hoppers, pipes, and chutes in different unit operations. Experimental measurements must also be identified to evaluate powders and guide in the selection of process conditions [54]. The characterization of powder flowability is often restricted by test methods that require relatively large amounts of powders, a requirement that becomes a significant difficulty in the early stages of drug development; moreover, the available methods are generally not suitable for in-line testing [54].

Most drug powders used in pharmaceutical industries have very poor flowability, which affects manufacturing and other operations like blending and tableting and leads to problems such as lack of content uniformity resulting in significant loss of revenue. The flow behavior is mainly dependant on the powder cohesiveness due to strong van der Waal's forces and plays a very important role in development of powder formulation, manufacturing processes, and handling procedures [29]. For example, in the case of tableting, cohesiveness of powder mixture affects the die filling and the uniformity of the mass of the tablets [29]. The cohesiveness of powders could also make the subsequent powder handling and processing operations very difficult as reported in In case of pharmaceutical powders, they often consist of nonuniform size and include significant

amount of fine powders which further exaggerates the flow-related problems [29]. In addition, due to the poor solubility of many new drug molecules, there is an increased need for improving the bioavailability; one of the ways to do so is to reduce the particle size [29]. One major bottleneck in incorporating particles with smaller size in tablet formulation is increasingly poor flowability as particles become finer. In addition, poor flowing powders significantly agglomerate and result in nonuniform API content. Hence, improved flow for fine powders is very desirable. In addition, many pharmaceutical powders even in size range of 50–100 μm have poor flow behavior which requires special efforts during manufacturing [29]. Besides utilizing aeration and vibration, addition of a flow agent is an effective way to improve the flowability of cohesive particles, as discussed in the pioneering work of Molerus and other researchers [29]. One of the most effective methods to improve the flowability of highly cohesive powders is surface modification, which usually involves particle coating to alter the surface properties of micron to nano-size particles/powders. It is typically carried out by wet-coating techniques (e.g., pan coater, fluidized bed coaters, wet chemistry techniques, etc.). However, these methods are not suitable for very fine powders; the main disadvantages include cost of drying and solvent removal, caking and agglomeration after drying, added steps such as milling and sieving, solvent residues, and potential environmental impact. Dry-particle coating is a promising alternative approach to coat fine size particles with the nano-size particles by the application of mechanical forces [29]. In dry-particle coating, nano or submicron size “Guest” particles are brought in contact with relatively larger micron size “Host” particles by means of mechanical forces. Due to the high number of collisions between the host particles and the walls, guest particles are coated

on the surface of host particles as the Van der Waal's forces are dominant in creating a strong cohesive bond between the host and guest particles. Since there are multiple collisions that take place, there is a possibility of attrition, in particular if magnet to powder ratio is high and/or processing times are greater than 10 min. It has been shown that such surface modification allows for modifying and controlling properties such as cohesion, flow, sinterability (coated material can be made to sinter at a lower or higher temperature than normal), etc. [29]. It was also shown that dry coating is more effective than simple addition of nano silica to the cohesive powder [29]. There are many other factors besides Van der Waal's forces, which can influence powder flow and cohesivity, e.g., particle size, surface area, amount of fines, roughness, absorbed moisture, etc. In general, these properties are very difficult to control once an API form and manufacturing process are specified. Therefore, dry-powder coating is an attractive approach to engineering the API particles and customizing them for dosage form and manufacturing requirements.

Several methods have been developed to predict powder flow and applied to pharmaceutical processes. Jenike shear tests evaluate the angle of internal friction of highly consolidated granular materials [54]. The ratio of bulk and tap density has been used as a flow index based on packing geometry and describes percent compressibility [54]. Rheometers have been used to characterize the powder flowability by measuring the force or torque needed to maintain the movement of an impeller in the powder [54]. The angle of repose describes the flowability of a powder by the angle of the free surface of the material when the granular flow stops under different configurations [54]. Jenike shear tests, rheological measurements, and angle of repose are static measurements that

take into account different properties of the particle to predict dynamic powder behavior. However, there are several particle properties that are considered responsible for powder flow properties. In some cases, the friction between the particles is the most critical factor, and in other cases, the friction with the wall or recipient vessel determines the flow.

6.2 Approach

Powder flow properties may also be evaluated on the basis of dynamic flow characterization measurements. The critical orifice method measures the flowability of a powder when it is discharged from funnels with different orifice diameters [54]. The critical diameter is the size of the smallest orifice through which powders flow. Flow rate may also be estimated by measuring the time to empty a hopper at various valve openings [54]. The tests based on avalanches characterize the flowability of a powder by measuring the time interval between avalanches in a rotating drum, where shorter times between avalanches are indicative of better flowability [54]. The combination of static and dynamic measurements is another possibility as demonstrated by Taylor et al. who proposed a composite index of flowability [54]. This composite index used principal component analysis to generate a single score or representation for each material, based on angle of repose, percent compressibility, and critical orifice number.

However, there is no in-line method available in the literature that can measure the flow properties of powders in a relevant, dynamic flow regime. Therefore, it is necessary to develop methods that can measure the flowability of powders by in-line technique. Near-infrared (NIR) spectroscopy is introduced as an innovative technique to characterize the flow properties of powders [29]. It was observed that powders that flow

well provide spectra with less noise, and powders that flow poorly have greater changes in baseline and noise. A flow intensity index, which is based on the inverse of the noise spectra, was developed to evaluate the consistency of powder flow.

In this work, powder flow is quantified by recording the in-line spectra of powder being discharged from a container and further utilized as a tool for distinguishing the difference in flow behavior between the cohesive and surface modified or dry coated powders. The setup is shown in Figure 6.1.

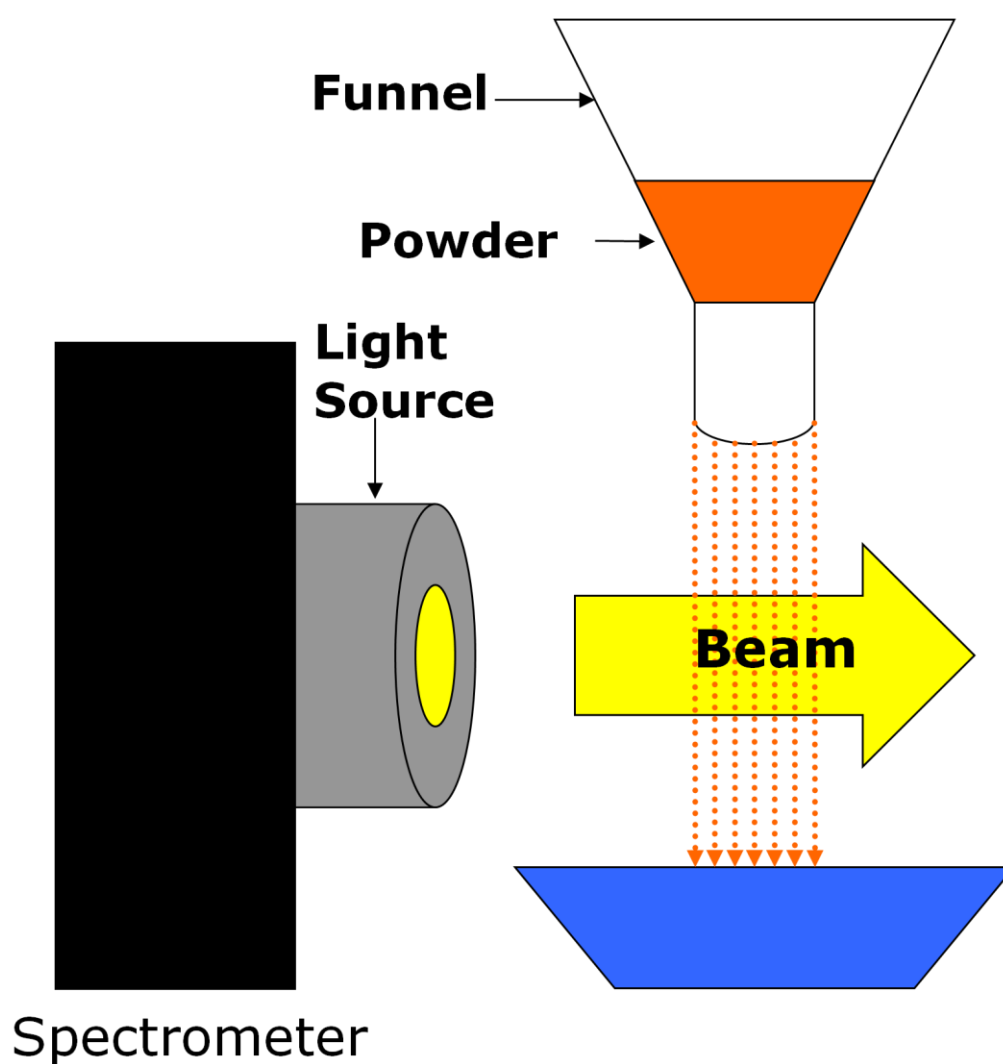


Figure 6.1 NIR in line measurement of flow setup.

The concentration and the homogeneity of the powder are also important. A recently published method described the use of near-infrared spectroscopy (NIR) to measure the concentration of flowing ibuprofen powder mixtures emptied from a hopper [54]. Previous efforts have also shown that NIR spectroscopy may be used to obtain physical information from flowing blends. Barajas showed that NIR can detect differences in particle size of pharmaceutical powders during voiding and observed particle size segregation as a result of air resistance to the movement of the pharmaceutical particles [54]. This study reports a novel use of NIR spectroscopy, as an in-line characterization method of powder flow behavior. The spectra of flowing powders were used to measure the flow, continuity, and interruption of powder flow and evaluate the chemical homogeneity of pharmaceutical powders. Two similar dynamic indices of powder flow were developed using the noise or the change in baseline of NIR spectra. The method is based on the observation of large changes in baseline and increases in noise for powders that flow poorly. The method described may be used to understand the flow behavior of powders but may also be used with already implemented NIR applications such as blend uniformity. The same NIR spectra that provide blend uniformity information may also be used to understand the flow behavior of powders. Thus, NIR spectra from a blend uniformity application or any application involving flowing powders will yield information on the flow properties of the powders.

It is shown that NIR may be used to obtain information on the flow properties of powders and increase process knowledge in addition to the already developed pharmaceutical applications that include blend uniformity analysis, drug concentration in tablets, and evaluation of moisture in drying granulations [29]. The NIR method

complements previous efforts based on powder avalanching and NIR spectroscopy [29]. The use of the NIR is also beneficial from the standpoint of incorporating the quality by design (QbD) in pharmaceutical manufacturing. The QbD of a pharmaceutical formulation needs to consider the properties of materials (excipients and API) in the formulation. In the case of a highly cohesive and poorly flowing powder, QbD could involve the surface modification of the drug particles to improve its flow properties. This work describes methods to improve flow properties and the use of near-infrared spectroscopy to evaluate these improvements in-line. [29] Consequently, the main purpose of this work is to demonstrate that NIR may be used in-line to detect the flow uniformity, which in general depends on the flowability of the powder.

In order to corroborate the observations from the in-line NIR signals of the powder sample being discharged, a simple independent method to characterize the powder flowability based on the angle of repose (ASTM standard ASTM D6393-99) is employed. Results of the angle of repose, which is not an in-line method, are expected to provide a supporting evidence of the powder behavior based on the extent of surface modification. Overall, the purpose of the work is to investigate: (a) whether NIR may be used via the inverse of the noise signal to obtain the flow intensity as well as the indication of flow uniformity through the relative standard deviation (RSD) of flow intensity; (b) if the dry coating improves the flow and flow uniformity of otherwise cohesive pharmaceutical powders and NIR provides the rank order of flow improvement; (c) whether the flow improvement measured during voiding via in-line NIR spectroscopy generally corresponds with the flowability improvement as measured via off-line means such as the angle of repose.

6.3 Methods and Materials

Highly cohesive and poorly flowable APIs such as acetaminophen (micronized grade with primary mean size 20 μm , supplied by Mallinckrodt, Inc., Hazelwood, MO, USA) and ibuprofen (70 grade USP/BP/EP, mean size 70 μm , supplied by Albemarle, Baton Rouge, LA, USA) are used for the characterization of the enhanced flowability by utilizing an in-line measurement technique, in this case NIR spectroscopy. Hydrophobic fumed silica (R972 grade supplied by Evonik Degussa, particle size 16 nm) is used for the surface modification of these APIs carried out by the various routes such as the dry coating, sieve mixing, and preblending method discussed below in details. R972 is hydrophobic due to the surface treatment by dimethyldichlorosilane, as per the information supplied by Degussa. All particle sizes reported are from the manufacturer, although SEM imaging confirmed the specified size range. Powder blends for the characterization of flow properties were prepared with the excipient, spray dried lactose monohydrate (Pharmatose DCL-11, DMW International, Veghel, The Netherlands).

Surface modification of APIs by coating with silica is carried out in dry-coating equipment as illustrated in Chapter 2. Dry coating was carried out for acetaminophen in MAIC and ibuprofen in the Hybridizer, as preliminary studies had indicated the best results using these configurations. In addition to the dry coating devices, V-blender (Patterson-Kelley, BlendMaster, East Stroudsburg, PA, USA), the most commonly employed blending device in the pharmaceutical industries, is used for preparing the blends of nano-size silica-coated APIs and the excipients. Acetaminophen and ibuprofen were coated with 0.5% and 1.0% w/w hydrophobic fumed silica, respectively, in the dry coating device.

For the initial flow measurements, blends of 0%, 5%, 15%, 25%, 50%, 75%, and 100% w/w of each of the active ingredient with the excipient, in this case, spray dried lactose monohydrate, were prepared by mixing in a V-blender for 4 min at 15 rpm. The amount of silica by percent is that of the API amount and not the total blend. Prior to blending, all materials were sieved in a (US standard test sieve 25, 750 μm mesh size) wire sieve and the materials were initially combined together before placing in the blender for 4 min. A similar procedure was repeated for the uncoated acetaminophen and ibuprofen powders. A typical batch size of 150 g was used for the processing of blends and charged to about 50% level. The performance of the blends prepared by dry coating method was compared with the blends that included appropriate amount of silica, but prepared by adopting two conventional approaches followed in the industry, the sieve mixing and preblending methods. Those methods are described in the following sections.

6.3.1 Sieve Mixing Method

In this method, the API was placed on a US standard wire mesh test sieve (25, 750 μm mesh size). Hydrophobic fumed silica (0.5% and 1.0% w/w of API) was placed on the top of API. The remaining 90% w/w of the API was placed on top of the silica layer, and the powders were sieve mixed into a collection container. The mixing method is shown in Figure 6.2.

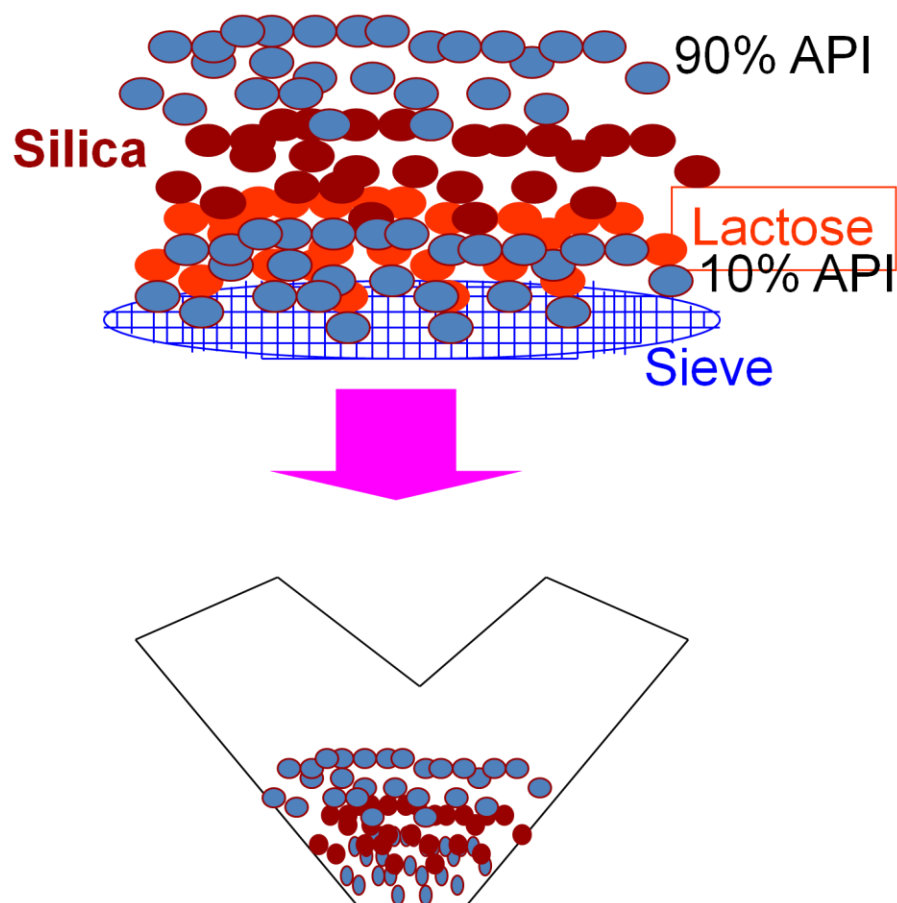


Figure 6.2 Sieve blending method.

The sieve mixed material was then combined with the excipient and blended in a Vblender for 4 min at 15 rpm.

6.3.2 Preblend (V-Blender) Method

The preblending method was also used in conjunction with the V-blender. In this approach, initially, 10% w/w of API was placed in a plastic container. Hydrophobic fumed silica was weighed in the required proportions (0.5% and 1.0% w/w of the API) and placed inside the container, which was then sealed and shaken vigorously by hand for 1 min. The remaining 90% of the API was added to the container and then the entire

contents were added to the V-blender and mixed for 2 min at 15 rpm. The mixing process is shown in Figure 6.3.

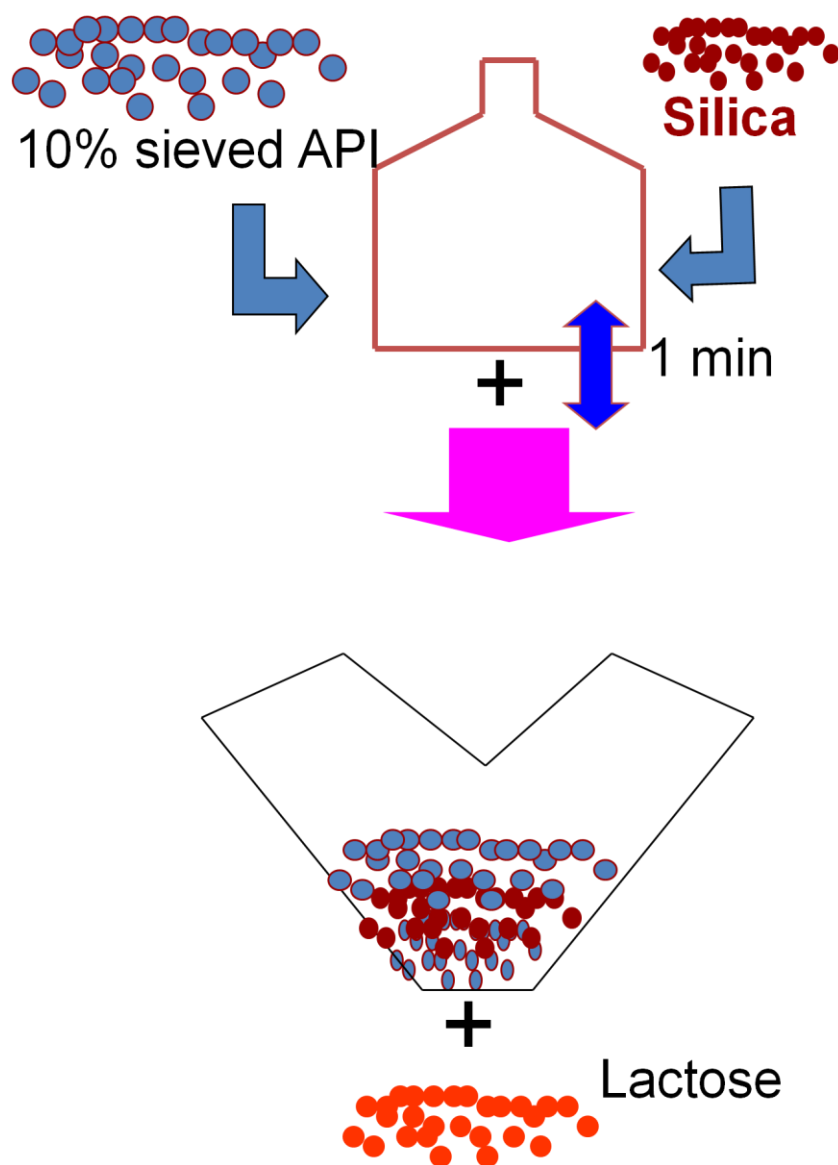


Figure 6.3 Pre-blending method.

The excipient was then added and the contents were mixed for additional 4 min. Flow rates of blends using uncoated, coated, sieve-prepared, and preblended APIs were compared.

6.4 Analysis

The objective of this work was to utilize the novel method based on the use of NIR spectroscopy, described in detail in [54], for the purpose of quantitatively understanding the effect of dry-particle coating on the flow properties of APIs. This also allows for evaluating the effectiveness of the different techniques for the preparation of powder blends (APIs with or without flow aids).

A CDI (Control Development, Inc., South Bend, IN, USA) NIR spectrometer was used to obtain the spectra of the voiding powders from the funnel, as described in [54]. The powder samples were discharged from the glass funnel, and diffuse reflectance NIR spectra were collected with the spectrometer positioned at 10 mm from the powder flow. The spectrometer was placed without any physical barrier or separation from the voiding powder flow. In this work, spectral noise was estimated by measuring the standard deviation throughout the 1,050–1,070 nm regions, where the powders do not have absorbance bands. This noise was observed to be minimal for a continuous flow, increasing when the flow is interrupted, and particles do not reflect the NIR radiation. The noise was found to be inversely proportional to powder flow, thus the inverse of noise can be considered a measure of flow intensity. The variation in the flow intensity indicates whether the flow is continuous or interrupted, and hence the standard deviation in the inverse of the noise can be considered as an index for flow uniformity.

The most important feature of NIR spectroscopy for flow monitoring is its use for real time evaluation of powder flow. As discussed in [54] the inverse of noise signal provides information regarding the strength of the flow, which is termed flow intensity. In addition, the standard deviation of the continuously acquired data on flow intensity

also gives an indication of the flow uniformity. A more rudimentary use of those signals may be to compute the average flow rate during the voiding experiment because the spectra give clear indication of the beginning and end of the voiding process, which can be automated via use of the software. It is noted that just obtaining the average flow rate can also be easily done by use of a stop watch, but in this case, the NIR signals provide additional information, including chemical and physical properties, such as the average flow rate.

6.5 Results

6.5.1 Flow Rate

The flow rate was based on the mass of powder voided and the time of voiding computed from the intensity of the inverse of the noise spectra (also called the flow intensity) of the NIR signals. In each case, a minimum of three replicates were done.

Fig. 6.4 illustrates the averaged flow rates of ibuprofen blends for either no coating (listed as 0% w/w) or two different levels of silica coatings (0.5% and 1% w/w). The blends, as discussed earlier, were prepared in the v-blender by mixing the excipient with previously dry-coated ibuprofen in 5%, 25%, 50%, 75%, and 100% w/w proportions.

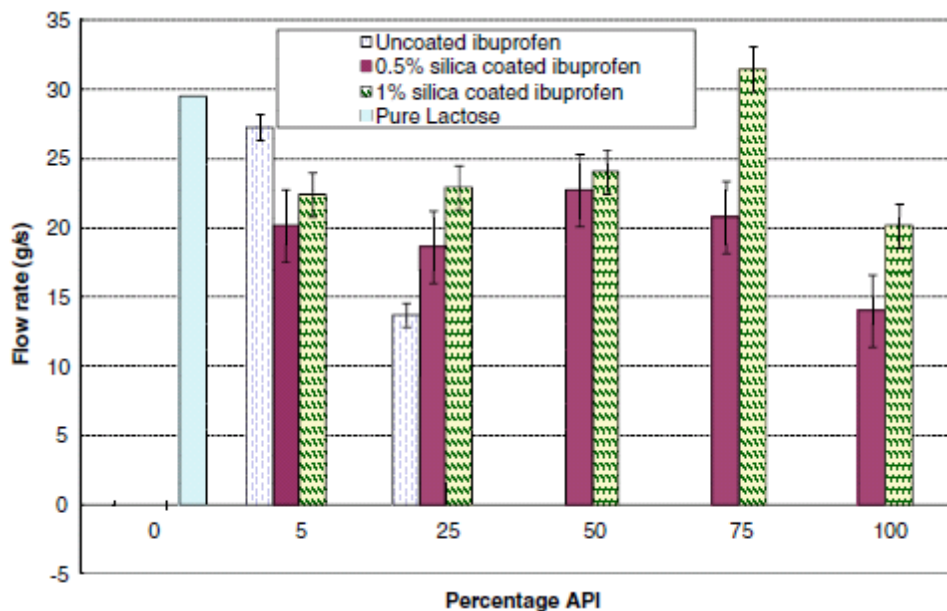


Figure 6.4 The averaged flow rates of uncoated ibuprofen blends with blends of two different levels of dry-coated silica; note 0 % w/w API blend is composed of fast flow lactose only. Also note that no flow was observed for uncoated blend beyond 25% w/w API.

The general trend of better (or higher) flow rate was observed for 1% w/w nano-coated blend of ibuprofen as compared to 0.5% w/w coated blend for all the different compositions of blends. For the blends prepared from uncoated ibuprofen, an uninterrupted flow was observed for the 5% w/w of ibuprofen concentration only. However, flow with increasing level of interruptions was observed for the blend with uncoated ibuprofen concentration of 25%, 50%, and 75% w/w, while there was little or no flow for pure ibuprofen (i.e., 100% w/w). On the other hand, significantly improved flow rates were observed for the coated ibuprofen blends for the similar blend compositions. The flow rate was found to increase for higher proportions of coated ibuprofen blends till 75% w/w, which is exactly the opposite trend as compared to uncoated ibuprofen blends. Without any addition of excipient (100% ibuprofen-coated sample) resulted into lesser flow rate as compared to the other compositions with 5%, 25%, 50%, and 75% w/w ibuprofen concentrations for the same coating levels of silica.

The standard deviation in the flow rates was found to be low for the lesser concentrations of uncoated as well as coated ibuprofen in the blends and increased gradually as the concentration of ibuprofen in the blends increased from 5% to 100% w/w. These results indicated that dry-particle coating of ibuprofen improved flow for the pure API as well as its blends. The most improved flow rates were observed for the blends with higher loading of 75% ibuprofen concentration in the blend of (1% silica coated) ibuprofen. It is noted that for 5% API blends, uncoated ibuprofen blend had a better flow rate than the dry coated ones. This may be attributed to the fact that there was appreciable size reduction for the coated ibuprofen due to the dry coating process and the reduced size leads to higher cohesion of the blend despite having surface modification. The results show that with a significant concentration of well-flowing excipient in the blend, there is no need to employ dry coating. However, the results shown in Figure 6.4 clearly indicate that dry coating is necessary when the API amount in the blend is 25% w/w or higher.

6.5.2 Flow Intensity

The time to void, and hence the average flow rate alone does not adequately characterize the flow. During the tests, it was observed that many discharge experiments had interruptions, unevenness of the flow, or no flow without the gentle tapping of the funnel. The visual observation of the blends indicated better smoothness of flow for the dry coated samples. For the purpose of quantification, information from NIR measurements was extracted by computing the inverse of the noise as described [54]. This measurement has been called the flow intensity index, with the higher values obtained for continuous flow and the lower values observed when the flow was less. The results for uncoated,

sieveblended, preblended, and dry-coated flow of ibuprofen 50% w/w blends are illustrated in Figures 6.5a, b, c and d, respectively.

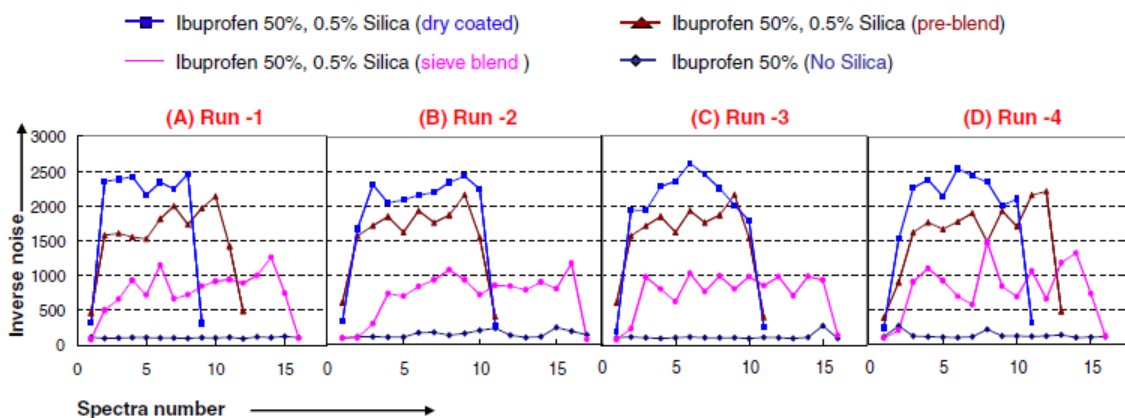


Figure 6.5 a, b, c and d Signal to noise ratio for ibuprofen processed using various methods. Higher signal indicates higher flow intensity, and lesser fluctuations indicate the flow smoothness.

As shown in Figure 6.4, uncoated ibuprofen (50% w/w concentration) blend did not flow, which is clear from the very low value of the inverse noise signal. Figure 6.5 shows that the flow intensity was highest for the dry-coated blends, followed by the preblended, and then sieve-blended.

6.5.3 Flow Uniformity

In addition to computing the flow intensity, the NIR signals are used to understand flow uniformity because higher fluctuations for flow intensity (evaluated via taking a RSD) indicate higher fluctuations in the flow of the powder. Thus, the RSD of flow intensity can be used to quantify and assess the consistency in the powder flow, and it may be then called the flow uniformity index. Therefore, in addition to the flow intensity plots during the voiding experiment, their average value as well as RSD were computed. These are illustrated in Figure 6.6 for the ibuprofen blends, clearly indicating that the flow performance of dry-coated blends is the best, since the average flow intensity is highest

while the RSD, i.e., the flow uniformity index, is the lowest, indicating the flow smoothness.

Inverse noise measurement represents the flow intensity and thus the RSD of the inverse noise shows the uniformity of the flow. Note that as shown in Figure 6.6, the sieve coated and pre-blended methods have lower inverse noise measurements and thus less flow than that of the dry coated case. Also note that the dry coated case has the lowest RSD of the three cases and has the most uniform flow of the three.

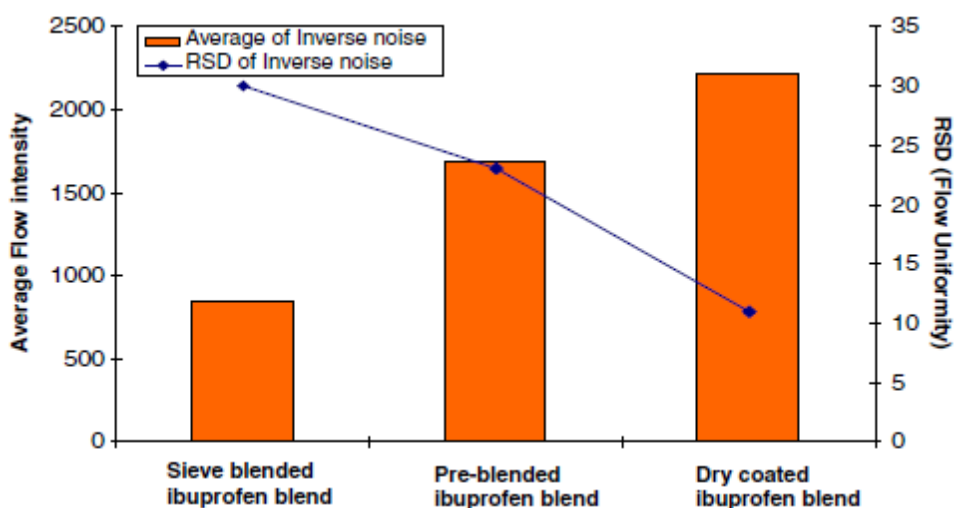


Figure 6.6 Average values and relative standard deviations for the inverse noise for ibuprofen blends prepared using different methods.

The average flow intensity values obtained from the sieve mixed and preblended methods are significantly lower than the dry-coated blends and thus indicate poor flow compared with the dry-coated case. Moreover, the dry-coated blends have the lowest RSD of the three cases and hence have the most uniform flow.

6.6 Conclusions

Through characterization done via the novel application of in-line NIR spectroscopy, dry coating is shown to be very effective in powder flow enhancement and results in

significantly improved flow uniformity during the voiding of blends of API powders. It is shown that the blends prepared from dry-coated APIs, ibuprofen and acetaminophen, had better flow intensity and uniformity as compared to the uncoated API blends. The NIR method clearly shows that the surface modification of API powders via the dry coating method results in improved flow properties when compared with addition of flow aid done through industry standard methods. For both APIs, the dry-coated blends with higher API content showed much better flow properties as compared to the uncoated or silica-added API blends. This is a significant result because most formulators need capability of handling higher API loadings for number of APIs having higher dosage requirement.

CHAPTER 7

IMPACT OF SURFACE MODIFICATION ON THE PRODUCT

7.1 Introduction

This research focused on developing techniques and novel applications of functionalization and coating by and of nano-particles for enhancement of pharmaceutical materials. Pharmaceutical materials are generally very difficult to work with due to their inherent cohesive properties. The cohesiveness impacts many aspects of manufacturing and formulation including feeding, mixing, tableting and dissolution.

Currently, work was done using dry coating of various pharmaceutical excipients and active ingredients using nano-particles to alter properties such as flow, electrostaticity, hydrophilicity, compressibility, packing, glidant, lubricative, and other. Also, the effect of coating on downstream processes was examined.

After the powders were coated with various types of nano-silica, both hydrophilic and hydrophobic, the powders were characterized using several techniques as outlined in previous chapters. Once initial characterization was complete, both uncoated and coated powders were formulated into blends to simulate a more industrial perspective. Again, these blends were characterized using all the same characterization techniques that were aforementioned. Even in the blends, very positive results in terms of flowability improvement were seen. The dry coating process improved the flowability of the initial powders themselves, but also improved the flowability of the powder blends.

To further investigate, the prepared blends were then pressed into tablets. It is important to study of the influence of API and excipient property modification on properties of subsequent products. It is possible that the coating may affect many of the

important downstream processing parameters, as this can affect the final product, the tablet, in terms of the pharmaceutical industry. Tablets were pressed of both the uncoated API blends and of the coated API blends.

Tablets were examined for hardness, friability, weight uniformity, content uniformity and tablet thickness. Additionally, tablet dissolution will also be examined for the drug release profile and disintegration time.

7.2 Tableting Conditions

Two different sets of tablets were made. One set was pressed by hand in the labs at NJIT and the second set was pressed using a tablet simulator at Pfizer Global Research and Development.

Tablets at NJIT were pressed using a Carver platen press. The tablets were pressed at approximately 10,000 lbs-force using a 13mm die. The tablets were comprised of 50% API with the rest a lactose, multocrystalline cellulose mix. The API in this case was semi-micronized acetaminophen. It was coated in the MAIC with 1% Silica M5P.

Tablets at Pfizer were compressed into 200mgW tablets using a compaction simulator with a Fette 2090 profile and 150ms dwell time. The tablets were comprised of 30% API with the rest a lactose, multocrystalline cellulose and magnesium stearate mix. The APIs in this case were Pfizer APIs A, B, C and ibuprofen 50. They were all coated with 1% R972 silica in the continuous Comil coating process.

7.3 Results

7.3.1 Tablet Integrity Testing

The tablets made at NJIT were tested only for tablet hardness. The results are shown in Figure 7.1.

COATED APAP (50% APAP + 1% M5P Silica +Pharmatose/Avicel 102)		UNCOATED APAP (50% APAP +Pharmatose/Avicel 102)	
AVERAGE HARDNESS	14.6 N	AVERAGE HARDNESS	12.5N
Standard Dev	3.39	Standard Dev	3.37

Figure 7.1 Hardness testing of tablets of 50% coated and uncoated Acetaminophen blends made using the Carver hand press.

These results show that the hardness of the tablets made with the coated powders possessed a slightly higher hardness than those made with the uncoated powders.

The tablets made at Pfizer were tested for tablet tensile strength, friability, and disintegration. The tablet tensile strength results are shown in Figure 7.2.

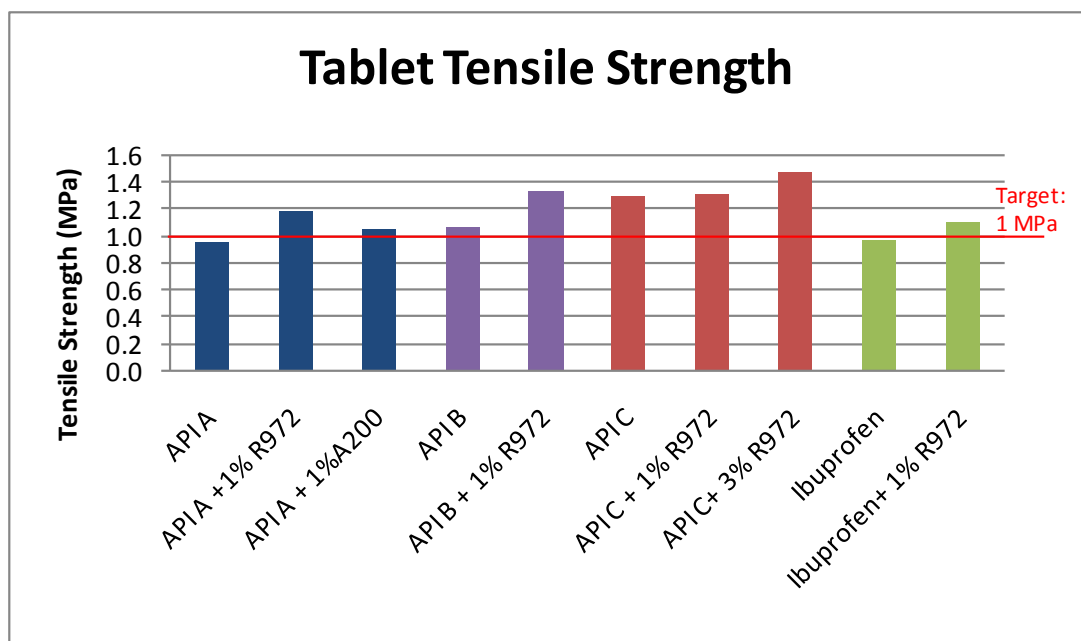


Figure 7.2 Tablets made from 30% drug loading blends tested for hardness/tensile strength.

These results indicate that in every API tested, the tablets made with the coated powders possess a higher hardness than those made of the uncoated powders, and in some cases using coated powders brought the tablets into the acceptable range of Tensile Strength > 1MPa. The tablet friability results are shown in Figure 7.3.

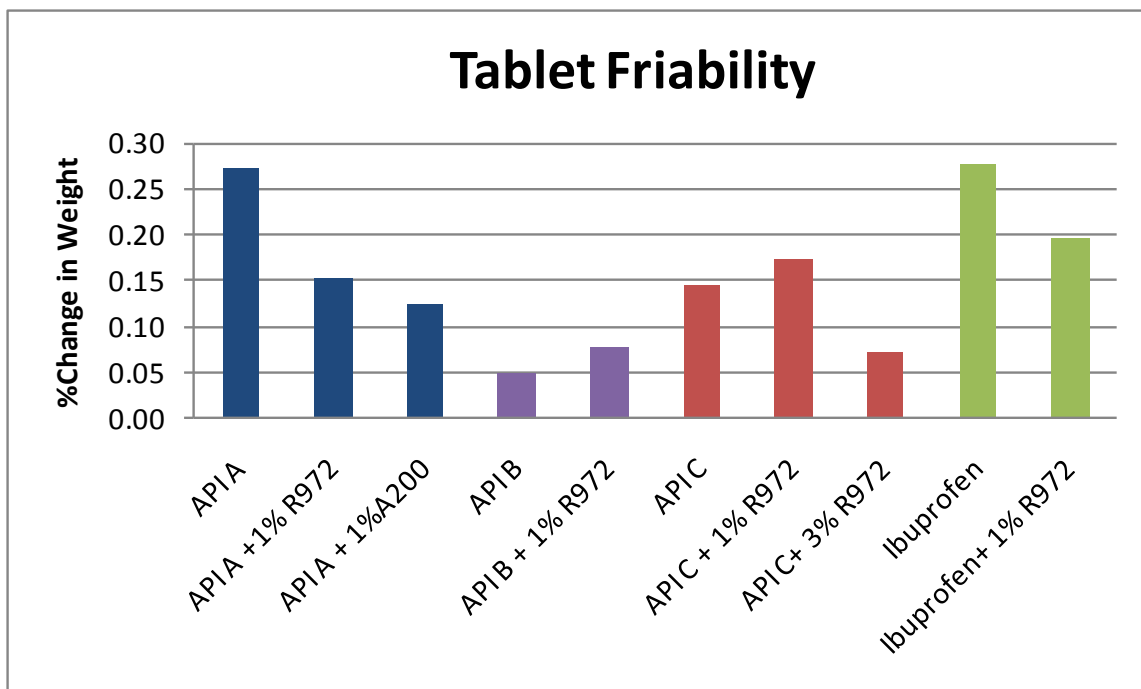


Figure 7.3 Tablets made from 30% drug loading blends tested for friability.

The friability is a measure of the loss in weight of the tablets when subjected to handling. A lower friability indicates a more robust tablet that is less susceptible to handling conditions. In each case the tablets made with the coated tablets had either very similar friability to their uncoated counterpart or they had improved friability. In general, the friability should be $\ll 1\%$. Lastly, the tablet disintegration results are shown in Figure 7.4.

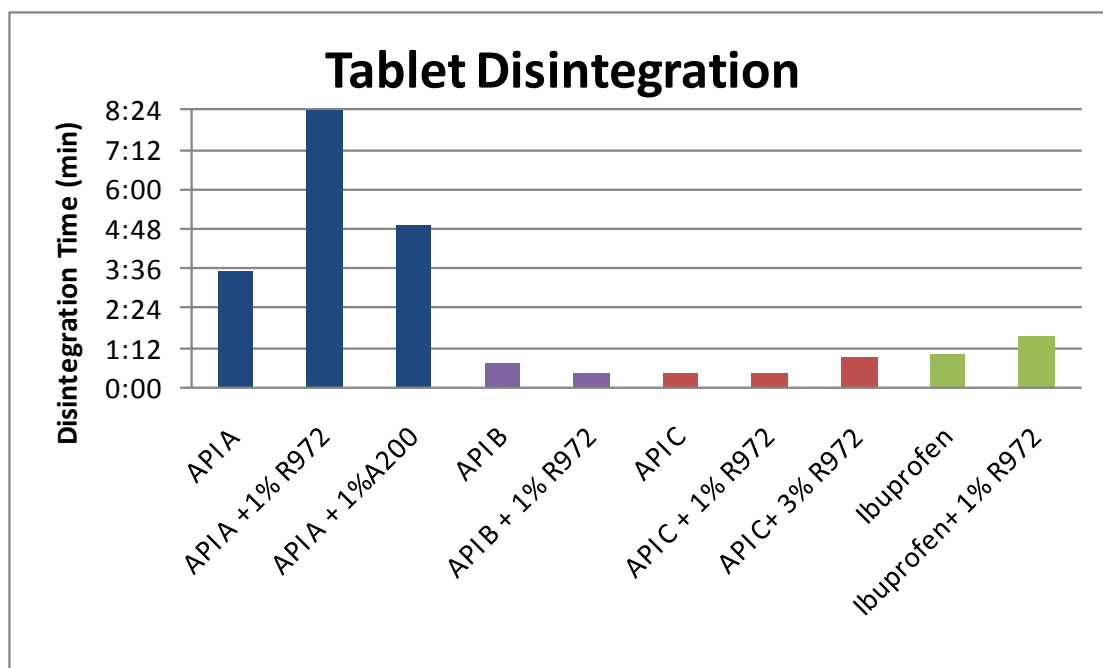


Figure 7.4 Tablets made from 30% drug loading blends tested for disintegration.

All of the tablet formulations with coated powders achieved acceptable disintegration time which is considered <15 minutes. In some cases, the use of hydrophobic silica may lengthen disintegration time for poor wetting or low solubility APIs (e.g. API A) but overall, the tablets made with the coated powders had similar disintegration times to those made of the uncoated powders.

7.3.2 Tablet Dissolution Testing

Tablets made at NJIT were graciously tested at Wyeth with the help of Dr. Michael Huang. The dissolution is shown in Figure 7.5.

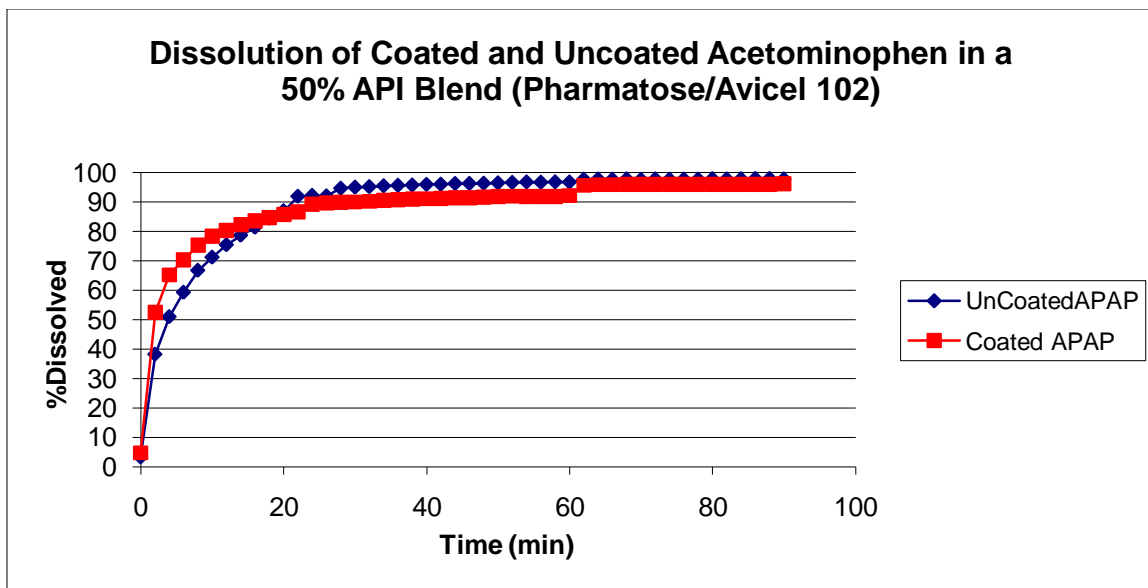


Figure 7.5 Dissolution results of tablets of 50% coated and uncoated acetaminophen blends made using the Carver hand press.

The tablets made with the coated powders dissolved faster than those made of the uncoated powders and reached the same level of dissolution at the end of the test.

Tablets made at Pfizer were tested at Pfizer with the help of Todd Hatajik who is gratefully acknowledged. These results are shown in Figure 7.6.

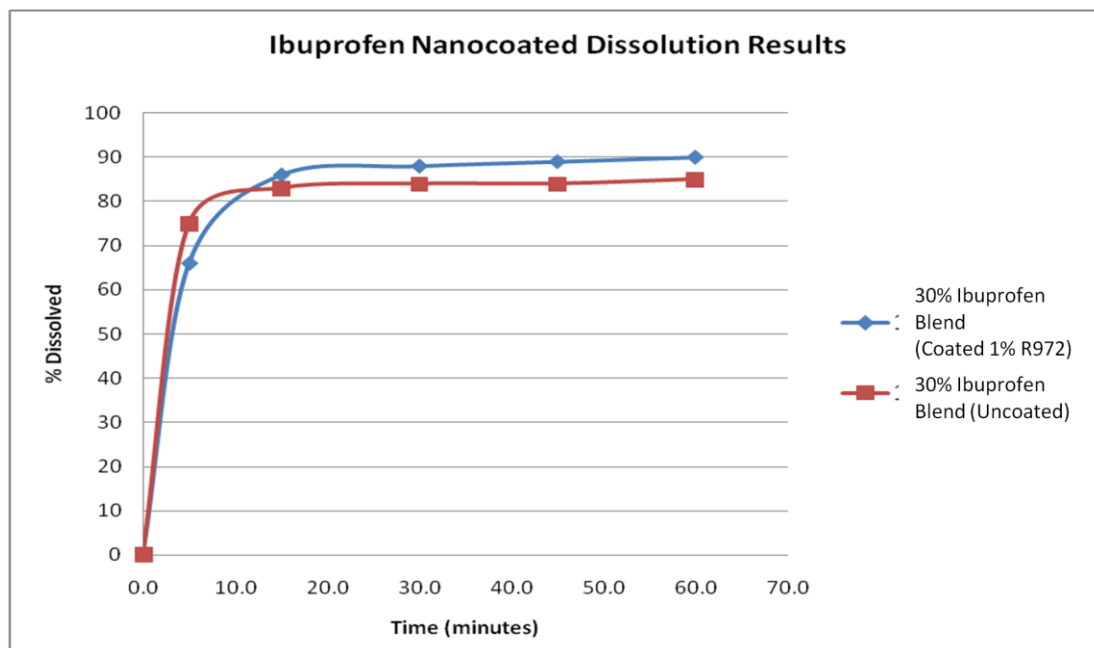


Figure 7.6 Dissolution results of tablets of 30% coated and uncoated ibuprofen blends made using the compaction simulator.

After 60 minutes, the tablets made with the dry coated powder had a slightly higher amount of the API dissolved compared to the tablets made with uncoated powders, however, overall the dissolution curves for both lots were very similar.

7.4 Conclusions

At the beginning of the testing of the drug products (i.e. the tablets), the desired outcome was to have the same exact properties for the uncoated tablets as for the ones made of the coated powders. It was a pleasant surprise that in many cases, the tablets made with the coated powders significantly outperformed the tablets made with the uncoated powders. This is a milestone result for this research. Not only was there no undesirable affect when using the coated powders, in some cases, these were better drug products overall. The overall conclusion is that using dry coating the tablets can be made with more ease. Less material is needed as well as less processing steps. Additionally, higher drug loading tablets can be made and due to the increase in bulk density the tablets can be made using a direct compression tableting mechanism.

CHAPTER 8

CONCLUSIONS

8.1 Overall Summary

In this work, dry coating based particle engineering techniques have been applied to pharmaceutical powders for improving API and excipient properties. Use of dry coating was motivated by previous work showing that the MAIC and hybridizer are useful tools for dry coating to improve powder flow [6]. In contrast to previous studies that only employed angle of repose to evaluate flow improvement, in this work various quantitative flow characterization techniques have been used to assess the changes in flow properties. In addition to use of MAIC and hybridizer which are batch devices, this work also included development of continuous dry coating methodology which is based on a typical pharmaceutical powder processing device, namely comil. The comil is found to be fast and efficient, as it is a continuous process with little loss of material. The comil has also been scaled up to pilot scale, indicating that it could easily be implemented in existing formulation and manufacturing processes. This work also clearly illustrated that the pharmaceutical materials undergo significant attrition if the dry coating devices are not optimized.

Powders were characterized using various methodologies to assess the improvement due to coating, begin with characterization via scanning electron microscopy to confirm the coating of nano-particles. The thesis also presented preliminary evaluation of improved particle mobility due to dry coating through use of Positron Emission Particle Tracking (PEPT) method. In terms of guest materials, both hydrophilic and hydrophobic silicas, as well as other materials such as magnesium

stearate were utilized and shown to promote flow. Various flow testing methods, starting with the AoR were employed. The coated and uncoated powders were tested both under consolidation and with no consolidation to better assess flow improvement under various subsequent process conditions. This work also included development of two novel methods, one for testing powder density under small consolidations done via vibrated packed density measurements, and second for analyzing improved discharge using Near-IR imaging, which is a collaborative work with the group of Prof. Rodolfo Romanach of University of Puerto Rico at Mayaguez.

In all cases, the coated powder performed significantly better in terms of flow than the uncoated powder. Cohesion is cut down immensely and the coated powder begins to operate in a new free flowing regime. Lastly, the uncoated and coated APIs have been formulated into drug product blends and then tableted. The tablets are tested for friability, disintegration, dissolution and stability. At this point, there is no adverse affect from the coating and in some cases and parameters, the dry coated powder tablets actually performed better than the original.

It is hoped based on all of testing and experimentation work presented here that the coated powders can significantly improve the manufacturing and formulation processes in the pharmaceutical industry by improving the flow of both the powder itself and within a blend. This can be done without compromising the compressibility of the tablets or the dissolution profile and thus does not change the drug's overall profile.

8.2 Future Directions

Phase maps developed using shear test data showing flow function coefficient and bulk density are very useful tools to quantify flow improvement. Additionally, these phase

maps can help optimize or develop coating devices. Using the phase map may also help to develop formulation guidelines based on results of the powder testing and ease or improve manufacturing processes. Other variables from the shear test aside from FFC, such as unconfined yield strength may also be used to create additional phase maps to establish other guidelines.

The dry coating process is somewhat understood at this point and key variables that impact the coating and thus the final product such as type and percentage of guest particles as well as shear intensity and screen size have been identified. There is a need to further investigate material and surface properties such as particle size, particle shape, crystal structure and surface energy to examine how that may affect the coating.

More systematic work is necessary with APIs or excipients that fall out of the range that generally coats best. Alternate choices in coating material and percentages may be explored. Additionally more shear may be necessary to coat smaller particles.

Determining the critical shear rate i.e., the threshold for coating, for each coating apparatus is in progress through use of modeling and some experimental work and this will help identify key parameters that affect the shear and allow for better comparison between coating methods.

At the beginning of this work, there was very little knowledge of powder surface modification applied in the pharmaceutical industry. Currently, powder deficiencies can be addressed using particle engineering, specifically dry coating and through systematic work, this is now an active field of science. There is still a need to develop fundamental understanding using particle scale measurements, inter-particle adhesion models, and device level simulations. This will allow designing of the materials and processes that

will help develop simpler formulations and improve manufacturing process. Dry coating based surface modification has the potential to become a routine tool for use in pharmaceutical industry to enable better formulations and aid in manufacturing, especially for APIs that are difficult to work with.

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