The Design of Nanostructures from the Blending of Flowing
Agents Influencing Critical Properties of a Pharmaceutical
Formulation

Casey F. Kick

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THE DESIGN OF NANOSTRUCTURES FROM THE BLENDING OF FLOWING AGENTS INFLUENCING CRITICAL PROPERTIES OF A PHARMACEUTICAL FORMULATION

by

Casey F. Kick

A thesis submitted to the Graduate College in partial fulfillment of the requirements for the degree of Master of Science in Engineering (Chemical) Chemical and Paper Engineering Western Michigan University August 2015

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Brian Young, Ph.D.
Raja Aravamuthan, Ph.D.
James Springstead, Ph.D.
In the pharmaceutical manufacturing process, it is well known that flowing agents such as MgSt and Cab-O-Sil widely affect critical flow properties that influence the finished product performance of oral dosage tablets. Though the effects of flowing agents are beneficial to some extent, the sensitivity of the pharmaceutical formulation to process shearing of flowing agents during blending can be catastrophic which often results in product and batch failures. Hence it is essential to study the concentration of flowing agents and chemical nature of active pharmaceutical ingredients (API) with respect to applied process shear on formulations. Previous studies have shown that new nanostructures form as a result of mechanical stress, which alter the intermediate powder properties such as hydrophobicity, powder flow, and electrostatics. These in turn influence critical properties such as the tablet hardness, friability, and drug release. While the robust nature of formulation is determined by its ability to match standard processing speeds during compression, defects and batch failures are often mistakenly linked to a lack of a particular flowing agent in the blend. The greatest unknown during the processing of pharmaceutical powders is how the uniformity, extent, and amount of nanostructures formed at contact surfaces on the API and carrier particles influence critical properties. The primary aim is to address this gap in a systematic fashion by focusing on the shear and scale dependence of lubrication and its impact critical blend performance. In the first stage of the research, the investigation sought to understand whether the formation of nanostructures was due to applied process shear. In the second stage, the incorporation of nanocharacterization techniques to characterize whether the change in flowing agent concentration affected the rate of formation of new nanostructures. Subsequently in the third stage, the focus sought to correlate how nanodeposits influence powder density, particle porosity, and flow. Statistical analysis of the identified process input variables in correlation to key responses measured by pharmaceutical companies, in terms of product performance validation. This analysis was used to identify significant interactions and effects that may help scientists better understand the mechanistic rate behind the formation of nanosmears at contact particle surfaces during blending of pharmaceutical ingredients with flowing agents.
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Casey F. Kick
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# ABBREVIATIONS AND SYMBOLS

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>AOI</td>
<td>Area of Interest</td>
</tr>
<tr>
<td>APAP</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulation</td>
</tr>
<tr>
<td>cGMP</td>
<td>Current Good Manufacturing Practices</td>
</tr>
<tr>
<td>CS</td>
<td>Cab-O-Sil, or Silica Oxide</td>
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<tr>
<td>EDS</td>
<td>Electron Dispersive Spectroscopy</td>
</tr>
<tr>
<td>ESEM</td>
<td>Environmental Scanning Electron Microscopy</td>
</tr>
<tr>
<td>FA</td>
<td>Flowing Agent</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GDR</td>
<td>Gravitational Displacement Rheometer</td>
</tr>
<tr>
<td>ICPMS</td>
<td>Inductively Coupled Plasma Mass Spectroscopy</td>
</tr>
<tr>
<td>MgSt</td>
<td>Magnesium Sterate</td>
</tr>
<tr>
<td>MO</td>
<td>Mixing Order</td>
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<tr>
<td>RSD</td>
<td>Relative Standard Deviation</td>
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<table>
<thead>
<tr>
<th>Symbol</th>
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<tbody>
<tr>
<td>µm</td>
<td>micrometer</td>
</tr>
<tr>
<td>cc</td>
<td>cubic centimeter</td>
</tr>
<tr>
<td>gm</td>
<td>gram</td>
</tr>
<tr>
<td>kN</td>
<td>kilonewton</td>
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<tr>
<td>mg</td>
<td>milligram</td>
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<tr>
<td>mm</td>
<td>millimeter</td>
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<tr>
<td>ng</td>
<td>nanogram</td>
</tr>
<tr>
<td>ppb</td>
<td>parts per billion</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>rpm</td>
<td>revolutions per minute</td>
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<td>wt</td>
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1. INTRODUCTION

Tablets are the desired means of drug delivery compared to other delivery mechanisms; such as aerosol, edible film, transdermal, and intravenous delivery. Compared to the other methods for drug delivery, tablets are less costly to manufacture, simple to administer, and can deliver a precise dosage to the intended recipient. Roughly 80% of the pharmaceutical products produced come in tablets or capsules that have been blended from bulk powder materials (Boukouvala et al., 2012). However, the drawback to tablets is that the activation and drug release is more prolonged, ultimately affecting the bioavailability of the therapeutic drug.

Today, the pharmaceutical industry relies heavily on batch modified processes to produce solid pharmaceutical drugs. This is due to the need to ensure production is fast, cost effective, and quality controlled. Utilizing batch driven processing to ensure quality control provides pharmaceutical companies with the necessary reassurance to comply with strict regulatory standards set forth by various governmental agencies. Batch driven processing can ensure quality control is maintained throughout the various processing steps. A few of these steps include raw material handling, dispensing, milling, mixing, compression, coating, and packaging. However, what’s often a troublesome case with batch processes is the number of potential problems that arise from scale up implementation of unit operations from the laboratory to the full scale processing plant; the difficulties to produce a homogeneous and fluidized powder; and the lack of understanding from how the nature of the Carrier and API interaction influences critical properties relating to product performance (Plumb, 2005). Because of the above problems incurred in the batch processing of pharmaceutical materials, pharmaceutical manufacturing produces products that often have a large amount of variability and unaccountability of how minuet process characteristics can result in the acceptance or rejection
of a batch of product (Boukouvala et al., 2012). Even high shear mixing curtailed to a specific mixing order has created prolonged product development issues as there is a significant lack of knowledge of how critical material attributes can lead to large scale batch failures (McKenzie et al., 2006). In this context, the complexity of physical phenomena during high shear mixing affecting such large scale batch failures is poorly understood in the most recent years. Furthermore, new products are pulled out of production if the product fails to conform to quality standards on the manufacturing order filed with the FDA. Since the change control process with the FDA to fix processing issues through formulation modification can take years for product recertification, there is significant interest to understand how minute adjustments in blending or compression can bring a formulation back to quality conformance. Despite the recent advancements in studying the powder behavior (A. Mehrotra et al., 2007a; Shah et al., 1977), lack of fully developed quantitative techniques to address the impact of nanoscopic phenomena points to a strong need to enhance the Quality by Design of pharmaceuticals. The development of new novel techniques that can characterize deviations in the pharmaceutical blend, which can be reconciled early on in the pharmaceutical manufacturing process to correct critical factors influencing product performance variability, is the foundation of this thesis.

1.1 Project Definition

1.2 Project Objectives and Scope

Previous work has shown that new nanostructures formed as a result of mechanical stress alter the intermediate critical blend properties which scale up to drastically to impact tablet performance properties. To date, the uniformity and extent of nanostructures have been poorly understood. Furthermore, the question of whether or not the nanostructures interact with carrier
particles, either affecting cohesion or stability degradation, is not completely understood. To address this gap, the work will explore the scale dependence of lubrication and its impact on critical blend properties. To tackle this gap, the work is divided amongst three different milestones.

The first task is to assess whether the rate of formation of nanostructures is due to applied process shear on the powders during mixing. In the second stage, an investigation assessed the scale dependence of flowing agents added to the blends, to see if chemical composition influences the rate of formation of nanostructures. This stage evaluates how mixing order and maintained strain on flowing agent components affect nanostructure smearing and composition. Subsequently in the third stage, the work evaluates characterized nanodeposits assessed with conventional microscopy techniques to understand how the granular structure influences nanostructures, powder density, and flow. Addressing the question of scale up influences from nanosmear formation is a complicated study for future work. An instance of the influence on nanosmear formation as it imparts key drug performance parameters will be demonstrated through two commonly measured tablet critical quality parameters (CQP): dissolution and hardness. Additionally investigating how characterized nanostructure formations influence microstructure, mesostructure, nanostructure, thickness, and density of tablets will be studied.

The primary goal of this work is to provide a scientific mechanistic understanding to describe the formation and variation of nanostructures in pharmaceutical powders that will emphasize their need for consideration in processing and handling of pharmaceutical powders.

Multiple pharmaceutical formulations of both lubricated and un-lubricated blends will be prepared and mixed in a v-blender under variable shear and fixed strain conditions to characterize the formation of microstructures and nanostructures on excipient particles within a
pharmaceutical blend. The changes in powder properties and surface topography throughout the various blends can be attributed to these formations of nanostructures, which is the focus of this study. These nanostructures will be characterized using Scanning Electron Microscopy (SEM) with Electron Dispersive Spectroscopy (EDS) mapping. While the uniformity and extent of coverage on the API particle interface controls the powder flowability, only a fraction of the MgSt lubricant used in the flowing agent formulation coats the API surface and forms the nanostructure. The powder flowability of the blends will be quantified in a gravitational displacement rheometer (GDR). Past work has shown that the extent of coating for the Cab-O-Sil was non-uniformly distributed on the API and much weaker than MgSt, which can be attributed to the interaction between the coating and the API particle surface. The variations in uniformity, extent of coating, and characteristic nanostructure formation in the powders are key parameters that will influence tablet performance and bioavailability, which has wide applications for enhancing the quality by design in pharmaceutical manufacturing.

1.3 Background

1.3.1 Pharmaceutical Ingredients Comprising a Blend

Raw material handling is an essential operation in the manufacture of pharmaceutical products. The ingredients comprising the blend have to be carefully considered when determining which route to take in the processing of the pharmaceutical material to the finished product. Of the different unit operation pathways available in the processing of pharmaceuticals, the three major pathways are identified as Direct Compression, Wet Granulation, and Dry Granulation. While granulation of ingredients before blending and compression is well understood to improve powder flow properties, blend uniformity, and reduce solid dosage form
defects, the scope of this thesis will focus on the materials and ingredients necessary for direct
compression of the blend. The necessity of choosing the right combination of ingredients for the
pharmaceutical dosage form is to ensure that the pharmaceutical formulation doesn’t stick,
doesn’t cap in the press, runs to the speed of the press, has less than 2% RSD, and provides
hardness and dissolution conforming to quality standards. The goal in blending ingredients is to
process the pharmaceutical powder in as few steps as possible. Powders that do not flow,
compress, eject, or dissolve will require more unit operations to process the final product.
Limiting deviations in densification, flow, compressibility, and ejection are therefore
accomplished by understanding the nature, mixing, and scale dependency of the raw materials
used in the formulation.

A pharmaceutical powder is ideally blended to achieve uniform distribution of the drug
amongst the bulk carrier, which will effectively control the delivery of the drug to the patient.
Since the processing of pharmaceutical ingredients requires transfer from totes, feeder hoppers,
conical mills, and ejection from the press, flowing agents for a pharmaceutical powder are
required to ensure the blend uniformly distributes the active ingredient in the end product to
control dosage. More importantly, the active pharmaceutical ingredient (API) does not satisfy
the consumer’s sense of taste, which is why a carrier helps to reduce direct contact of the API
with the consumer’s senses. Furthermore, a formulation typically only requires milligrams of the
API in the design of a solid dosage form, so the carrier makes the transport the pharmaceutical
into the GI tract more manageable. The primary components comprising the pharmaceutical
blend are therefore the API and excipient. Under the excipient, there are different classes, which
include the binder, filler, compression aid, color, sweetener, coating, disintegrant, lubricant, and
glidant.
The active ingredient is the most important component of a tablet’s formulation responsible for treating or alleviating a symptom of concern in the recipient. For this research, the API chosen for the study is an Acetaminophen blend found in Tylenol™. Acetaminophen is known to be a mild pain reliever, fever reducer, and headache remedy used in the Tylenol™ drug. The active ingredient dosage is typically specific to the recipient’s physical characteristics and not necessarily a person’s biological immune system, which will alter the bioavailability of the active ingredient for treatment.

Excipients comprise the majority of a tablet’s formulation and include vastly comprise the carrier and binder for the active ingredient. Filler agents, carriers, and binders help form the complex matrix that enables controlled release to be possible. Lubricants make up between 0.25% to 1% of the pharmaceutical blend, but never more than 1% of the formulation. Increasing the lubricant concentration is known to increase the hydrophobicity of the both the blend and tablet which result in irreversible performance validation consequences. Specifically, one consequence is prolonged drug release in tablet dissolution, which ultimately limits the bioavailability of the API for therapeutic treatment. When a pharmaceutical product fails to meet targets for drug release or extended release specifications on the manufacturing card, the batch is often destroyed, resulting in a waste of manpower, machine time, materials, and money. Lubricants are primarily used in the formulation to reduce adhesion forces and friction between the wall and dye during tableting manufacture. Lubricants therefore influence both the physical properties of a powder and the physiochemical properties of the tablet, making them an important factor of study in understanding tribological behavior in different pharmaceutical blends.
The lubricant associated with this blend is Magnesium Stearate, which has the ability to coat particles and decrease adhesive particle interaction, making it a very effective lubricant. Specifically, lubricants are intended to help with the speed and quality by which pharmaceutical powders are processed through the turrets on a rotary press. Without lubricants, pharmaceutical powders experience very high ejection forces coming out of the ejection cams, which leads to quality defects including capping, lamination, picking, and shearing. Glidants on the other hand are responsible for reducing the electrostatic forces that arise from friction out of particle-particle or particle-wall interactions. Most powder particles exhibit a great degree of polarity which inhibits mixing efficiency due to static buildup. The choice of an appropriate glidant is to mitigate this polarity and improve uniformity during mixing. The chosen glidant for this work will be Cab-O-Sil, which is a fine granular silica based ingredient with a large particle surface area to help reduce charge accumulation in the powders. A large unknown in oral dosage drug delivery is how the glidants, carriers, and lubricants interact with the active ingredient to impact drug release. Lubricants and glidants are hydrophobic in nature, and can slow drug dissolution and diffusion controlled mass transfer of the active ingredient into the liquid phase. The compressive force applied to these tablets during their manufacture can impact properties of tablet porosity, hardness, and surface energy characteristics, which will also influence the rate of the diffusion of the solid dosage into the liquid phase.

1.3.2 The Fundamentals of Nanosmearing

Nanosmearing refers to the phenomena of material deposition to a particle surface during varying degrees of mixing. The rate at which material becomes transferred to either a larger carrier or API particle is dependent on the shear of ingredients during blend lubrication. In
Figure 1, the fundamental of nanosmearing occurs when low yield strength particles come in contact with a larger particle surface. At the moment of contact, interparticle friction results in the transfer of mass from the particle of lower yield strength to the more rigid material. In the case of nanosmears observed in this research, nanosmears formed from Magnesium Stearate and Cab-O-Sil create different structures on the larger particle surface to influence Van der Waals and Electrostatic properties. Even localized clusters of nanosmears form different characteristic structures with different orders of mixing of the flowing agents. The different size distributions of nanosmears being formed on the particle surface provide evidence that surface characteristics of the nanosmear govern the growth, distribution, and development of the nanosmear layer during mixing. The physical structure of the nanosmear created when flowing agents are deposited to the carrier and API particle surfaces is influenced therefore by the size and yield strength of the flowing agent during mixing.
Two different characteristic structures are formed when the excipients Cab-O-Sil and Magnesium Stearate are added to the blend. The flowing agent Cab-O-Sil is an agglomeration of nanoparticles with low yield strength that deposits a cluster of the agglomeration during contact friction with the carrier particle surface. These can be viewed under an SEM as very small, spherical particles covering the larger particle surface. The lubricant MgSt is a highly friable platelet with low yield strength that transfers a portion of its mass to the thin-film nanolayer when contact friction with the excipient particle surface is experienced. Under an SEM, MgSt forms a smear on the particle surface, conforming to the shape definition of its host particle. The strength of these layers has shown that CS forms a much stronger layer to the particle surface, while the thin-film nanolayer of MgSt forms a very weak and friable smear which can be broken away with enough particle shear friction.

These shear induced nanosmears hold to the particle surface from Van der Waals attraction between the large particle surface and the smaller flowing agent smear. Since the force of attraction is a magnitude larger than the mass of the nanosmear, a very strong bond between the smear and the particle surface has been known to form (Yu et al., 2003). In the opposite sense, a cluster of hydrophobic smears on the contact particle surface can significantly influence interparticle forces. These forces originate from the cluster of smears, where Electrostatic repulsion forces can keep carrier and API particles from closing to a distance where Van der Waals forces will take hold to impart better powder bulk density. In this sense, the control of shear induced nanosmears becomes pivotal towards reducing macro-scale drug performance variability.
2. LITERATURE REVIEW

2.1 Scale Dependence of Mixing Order and Lubrication in the Blend

In the pharmaceutical manufacturing process, it is well known that lubricants and glidants, such as MgSt and Cab-O-Sil, widely affect critical blend properties, such as the flow indices, hydrophobicity, bulk density, and drug release of the oral dosage tablets (Amit Mehrotra et al., 2007b; K. Pingali et al., 2011b; Vasilenko et al., 2011). Though the effects of flowing agents are beneficial for two reasons, limiting the cohesion of the granules to the tooling and improving granular flow properties to some extent (Moody et al., 1981), sensitivity to shear of flowing agents can be catastrophic to product performance, resulting in product and batch failures. Understanding the relationship between scale dependence, mixing order, and sensitivity to shear of the lubricant are essential to filling in the gap, formed from the scale-up, between the laboratory development of a drug and its full-scale manufacture.

Mixing of pharmaceutical flowing agents has long been suspected to coat the individual API and excipient particles in the blend (Shah et al., 1977). Preconditioning excipient and API powders by mixing independently has shown alterations in surface structure that influence cohesion at contact surfaces (Podczeck, 1998). Mixing of flowing agents into the pharmaceutical preblend, comprising the API and carrier(s), has long been performed by a trial and error approach to determine the optimum mixing order (Wang et al., 2010), duration (Kikuta et al., 1994), and intensity (Kushner et al., 2010). Increases in blending time, lubricant concentration, and intensity of mixing of pharmaceutical ingredients has been shown to impact physical performance properties of manufactured tablets, such as reductions in hardness (Mitrevej et al., 1982). While a trial and error approach of optimizing the mixing of pharmaceutical ingredients with flowing agents has proved successful to an extent, the mechanistic formation of these
surface coatings, known to be nanosmears, is not well understood. During scale up implementation from lab mixers to pilot scale blenders, evidence has shown that lubricants coat pharmaceutical particles to a greater extent in large scale batch mixers than laboratory mixers at similar operational parameters (Otsuka et al., 2009). A thorough understanding of surface interactions from the structural arrangement of nanodeposited flowing agents on contact particle surfaces in the pharmaceutical blend is therefore essential to prevent over lubrication of blends in large scale mixers and provide optimal tribological tablet performance.

### 2.2 Effect of Shear on Tablet Properties and Drug Performance

A review of the literature does support that the order of mixing of glidants and lubricants in the pharmaceutical pre-blend do influence the formation of nanostructures that affect critical and tablet properties (Llusa et al., 2013). Not only is the mixing order and scale dependence of lubricant dependent on the critical blend properties, but equally significant is the influence of shear and strain during the blending of the pharmaceutical formulation. In this sense, common laboratory simulation of shear during the blending of pharmaceuticals has been performed in either a Couette Shear Rheometer or traditional V-blender with an intensifier bar. While the instruments to characterize flowability of sheared powders can vary, Vasilenko et al compared the flowability of different sheared powders assessed using a FT4 Powder Remoter by Freeman Tech (Malvern, Worcestershire, UK) in comparison to a Gravitational Displacement Rheometer (GDR) (Vasilenko et al., 2011). The results from Vasilenko’s experimentation showed that the both instruments ranked the 14 pharmaceutical blends with varying shear and strain conditions in the same order of flowability. However, with the FT4, the powders exhibited a higher degree of compressibility and high RSD at low shear. (Vasilenko et al., 2011).
Mehrotra et al performed a comparison study between a MCC Couette Shear Rheometer, which provides uniform shear conditions between two concentric plates, and a V-blender. The disadvantage to the Couette is that it provides poor axial mixing of the powders, thus requiring a very uniformly mixed preblend prior to the experimentation. The experimentation assessed the influence of shear rate at 1, 10, 40, 80, 160, and 245 rpm at different shear conditions from 267 to 400 shear units for blends containing 0% to 2% lubrication. Mehrotra et al’s results indicate that improved homogeneity of the blend was achieved at low RSD with increased shear. From the testing, Mehrotra discovered that the shear rate has a smaller effect on lubricated blend’s RSD than total strain. (Amit Mehrotra et al., 2007b).

2.3 Incorporating Nanotechnological Characterizations into Pharmaceuticals

With a large growth in demand of pharmaceuticals, the application of nanotechnology into pharmaceutical systems has seen a growing interest in the study of microparticles, nanoparticles, nanofibers, nanoemulsions, solid lipid nanoparticles, nanocarriers, and more. In particular, the synthesis of pharmaceutical drugs into crystalline nanosuspensions has revitalized many of the promising pharmaceuticals born from the drug discovery programs that were rejected due to their poor water solubility and limited bioavailability (Rabinow, 2004). However, in today’s pharmaceutical processing, API are formulated into crystalline structures to provide increased surface area to volume ratio and stability (Wu et al., 2011). This provides enhanced drug effectiveness through increased in-vitro and in-vivo bioavailability.

With the development of any novel drug or delivery method, there are systematic gaps in the capabilities of producing therapeutic delivery to the target site, the stability of the drug particles at the target site, and the understanding of the biological affects the drug particles will
have on the surrounding tissues and organs (Gaumet et al., 2008). To explain the phenomena of the unknown interactions taking place on the nanoscale, there is a high demand to develop novel technologies and methods to characterize the performance and behavior of nanostructures that influence particle to particle interactions. Therefore, the establishment of techniques and equipment to characterize nanostructures as a measure of deviation troubleshooting at the batch production scale is seeing a considerable increase in demand. The promise provided by these highly analytical tools and techniques allows manufacturing of pharmaceuticals to overcome common issues arising from drug design, synthesis, stability, scale-up, and performance (Qiu et al., 2008). The advent of developing the pharmaceutical manufacturing into a highly technological enterprise does stem from the Federal Drug Administration (FDA) to increase productivity Overall, the need for pharmaceutical processes to become more efficient, reliable, and productive has become more apparent with the onset of Quality by Design (QbD) and Process Analytical Technology (PAT) (Muzzio et al., 2002). These practices are driving the development of efficient manufacturing practices and reliable manufacturing processes in the industry today.

To meet the criteria of QbD, the implementation of multi-scale process modeling has focused on treating the powder at three different scales of quantification: particle, powder, and dosage form (tablet, capsule, etc.). The growth of multi-scale process modeling arose from the lack of a mechanistic understanding to incorporate experimental design, optimization, and multivariate data analysis in a manner that would connect process parameters and material properties to product quality attributes (Boukouvala et al., 2012; Hamad et al., 2010). The application of predictive modeling allows properties of the active pharmaceutical ingredient and the excipients to be assessed at the particle, powder, and dosage scales. At the particle level, the
primary focuses for characterizations are with solubility, dissolution rate, hydrophobicity, and
degree of crystallinity. At the powder scale, the primary characterizations focus on powder flow,
bulk density, and compressibility. At the final level, the dosage form, the critical process
parameters involve the dissolution rate, hardness, and weight variability. (Hamad et al., 2010).

To generate these multi-scale process models, understanding how nanosmears influence
the performance parameters between the particle, powder, and dosage scale are critical for
successful predictions. To date, product recalls of pharmaceutical products occur due to three
reasons: the lack of API uniformity in the dosage form, inconsistent or undesired rate of drug
release, or too high of an impurity level creating undesired side effects to the general population.
All these reasons are flaws from a methodological and scientific lack of understanding of the
change in property parameters with pharmaceutical processing (Hamad et al., 2010).

### 2.4 Surface Modification of Powders to Improve Critical Properties

Surface modifications to API and excipient components comprising the pharmaceutical
blend have been studied to improve flowability (Ghoroi et al., 2013a), bulk density (Han et al.,
2013; Jallo et al., 2012), tablet compaction (van Veen et al., 2005), and blend compressibility
critical properties (More et al., 2013). Surface modified powders during the pre-processing of
API and excipients using Magnetically Assisted Impaction Coating (MAIC) and Fluid Energy
Milling (FEM) have shown that coating the particle surface increases fluidization of the bulk
powder from the reduction of interparticle forces that govern particle instability and performance
behavior after compaction (Ghoroi et al., 2013b; Han et al., 2013; Jallo et al., 2012).

In previous work, the order of mixing of glidants and lubricants in the pharmaceutical
preblend was found to influence the formation of nanostructures that affect critical blend and
tablet properties (K. Pingali et al., 2013b). Three factors that are critical to the blend properties were found to be the mixing order, scale of lubricant/glidant, and level of shear and strain applied during the blending. Between shear and strain however, it was reported that applied shear has a smaller influence on the lubricated blend’s RSD than total strain (Amit Mehrotra et al., 2007b). Previously, it was shown that varying the addition of flowing agents while maintaining consistent strain conditions during the mixing of pharmaceutical powders had a significant influence on tablet properties (K. Pingali et al., 2011a, 2011b). It is intuitive to argue that the changes in tribological powder behavior and tablet performance previously seen were significantly due to the formation of different nanosmeared structures created by different orders of mixing flowing agents with the pharmaceutical ingredients.

Previous work has also shown that new nanostructures formed as a result of mechanical stress alter the intermediate critical blend properties which in turn affect tablet performance properties (K. Pingali et al., 2013b). Until recently, the uniformity, extent of nanostructures, and their composition have been poorly understood. How nanostructures interact with excipient particles that can affect the blend’s cohesion tendencies or stability is not completely understood. To address this gap, this thesis explores whether the physical and chemical nature of nanosmears formed on excipient and API particles influences physiochemical properties of the blend and solid dosage form performance. Subsequently, the work also focuses on the characterization of nanodeposits affecting the granular nanostructure, powder density, and flow. The purpose of this work is to provide a scientific mechanistic understanding to describe the formation of nanostructure during different orders of mixing that influence critical blend and tablet properties. Subsequently, we investigate how the formation of nanostructure from different orders of mixing influences hardness, porosity, and drug release in tablets.
3. EXPERIMENTAL METHODOLOGY

Multiple pharmaceutical formulations of both lubricated and un-lubricated blends were prepared and mixed in a v-blender under variable shear conditions at a constant strain to characterize the formation of microstructures and nanostructures on the API and Carrier surfaces. The shear conditions applied to the pharmaceutical blends was varied by adjusting the level of the intensifier bar during the blending cycle for the pharmaceutical formulation. The chosen levels of intensifier bar intensity provided varying levels of shear to the powders at two chosen levels of significance for this study. A low shear condition of 500rpm and a higher shear condition of 1000rpm was chosen for the experimental design. The changes in powder properties and surface topography throughout the various blends can be attributed to formations of nanostructures as a response to the input variable mix conditions. Nanostructures formed during the blending of ingredients will be characterized using techniques of Inductively Coupled Plasma Mass Spectroscopy (ICPMS), Gravitational Displacement Rheology (GDR), and Scanning Electron Microscopy (SEM). The uniformity and extent of coverage of coating on the particle interface then controls the responses of powder flowability and powder dilation.

Utilizing Electron Dispersive Spectroscopy (EDS) equipped on a Variable Pressure SEM, this research focused on qualitatively characterizing the smearing area of the metallic elemental components of the lubricant (Mg) and glidant (Si) measured across scanned particle surfaces. The total concentration of these elements in the nanosmears, which have been developed across a known amount of sample can then be measured using an ICPMS. The powder flowability and dilation responses were then assessed in GDR. A concept map depicting this methodology is given in Figure 2.
Figure 2: Concept Map for Experimental Design
4. EXPERIMENTAL TECHNIQUES

4.1 Materials and Sample Preparation

4.1.1 Batch Preparation of the Pharmaceutical Powders

Assessment of nanosmear formation among varying mixing orders was studied using an Acetaminophen (APAP) formulation for the production of tablets. In the formulation used, the preblend for all conditions comprised a single excipient, microcrystalline cellulose (MCC) (FMC – Avicel PH102, particle size 100 µm nom.), and 9 wt% of the active pharmaceutical ingredient (API), Acetaminophen (Mallinckrodt particle size – 38 µm). Flowing agents added to the preblend included a lubricant, magnesium stearate (MgSt, Hyqual, particle size 35 µm) and a glidant, fumed colloidal silica (CS, CABOT Cab-O-Sil grade M5-P, particle size 0.2-0.3 µm). For this study, the powders were mixed under consistent shear and mechanical strain while mixing order (M.O.) of the blends was varied. The goal of this study was to experimentally study the significance mixing order of pharmaceutical ingredients has on nanostructure formation.

Pharmaceutical blends were prepared in a Patterson-Kelly Model B V-Blender where conditions of intensifier setting, drum revolution, and shear strain will be carefully maintained for the experimental conditions. Using predetermined calibrations for intensifier speed and shell speed, experimental parameters will be established that maintain constant shell speed of 12 rpm. Experimental conditions will then comprise adjusting the intensifier setting between shearing intensities of 500rpm and 1000rpm. These mixing conditions will then be applied to four categories of batches, where mixing order will be the independent variable of study. For the experimentation, the effect of mixing order of pharmaceutical ingredients will be studied where (M.O.1) lubricant and
Glidant is added to preblend formulation together [B1 and B4], (M.O.2) glidant is mixed with the preblend followed by the lubricant [B5 and B8], (M.O.3) lubricant is mixed with the preblend followed by the glidant [B9 and B12], and (M.O.4) only lubricant is mixed with the preblend [B15 and B16]. The control for the experiments will be B17, which contained the preblend formulation (Avicel and APAP) only. The breakdown of compositions of each ingredient comprising the pharmaceutical blend is referenced in Table 1. In a separate parameter of study, the scale dependency of the flowing agents will be assessed by a homogeneous decrease in flowing ingredient.

### Table 1: Experimental Conditions

<table>
<thead>
<tr>
<th>Intensifier Bar [rev]</th>
<th>COND</th>
<th>Mixing Order</th>
<th>Avicel [g]</th>
<th>APAP [g]</th>
<th>Cab-O-Sil [g]</th>
<th>MgSt [g]</th>
<th>Avicel [%]</th>
<th>APAP [%]</th>
<th>Cab-O-Sil [%]</th>
<th>MgSt [%]</th>
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<td>B1</td>
<td>Preblend + (Cab-O-Sil + MgSt) (Together)</td>
<td>2256.25</td>
<td>225</td>
<td>6.25</td>
<td>12.5</td>
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<td>9</td>
<td>0.25</td>
<td>0.5</td>
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<td>Preblend + (Cab-O-Sil + MgSt) (Together)</td>
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<td>225</td>
<td>12.5</td>
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<td>89.5</td>
<td>9</td>
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<tr>
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<td>225</td>
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<td>12.5</td>
<td>25</td>
<td>89.5</td>
<td>9</td>
<td>0.5</td>
<td>1</td>
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<td></td>
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<td>Preblend + MgSt (First) + Cab-O-Sil</td>
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<td>9</td>
<td>0.5</td>
<td>0.25</td>
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<tr>
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<td>Preblend + MgSt (First) + Cab-O-Sil</td>
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<td>225</td>
<td>25</td>
<td>12.5</td>
<td>89.5</td>
<td>9</td>
<td>1</td>
<td>0.5</td>
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<tr>
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<td>Preblend + Cab-O-Sil</td>
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<td>225</td>
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<td>0</td>
<td>90.5</td>
<td>9</td>
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<tr>
<td></td>
<td>B16</td>
<td>Preblend + MgSt</td>
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<td>225</td>
<td>0</td>
<td>25</td>
<td>90</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>225</td>
<td>0</td>
<td>0</td>
<td>91</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1000</td>
<td>B1</td>
<td>Preblend + (Cab-O-Sil + MgSt) (Together)</td>
<td>2256.25</td>
<td>225</td>
<td>6.25</td>
<td>12.5</td>
<td>90.25</td>
<td>9</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>B4</td>
<td>Preblend + (Cab-O-Sil + MgSt) (Together)</td>
<td>2237.5</td>
<td>225</td>
<td>12.5</td>
<td>25</td>
<td>89.5</td>
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<td>Preblend + Cab-O-Sil (First) + MgSt</td>
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<td>6.25</td>
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<td>0.25</td>
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<tr>
<td></td>
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<td>12.5</td>
<td>25</td>
<td>89.5</td>
<td>9</td>
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<td>B9</td>
<td>Preblend + MgSt (First) + Cab-O-Sil</td>
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<tr>
<td></td>
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<td>Preblend + Cab-O-Sil</td>
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<td>225</td>
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<td>90.5</td>
<td>9</td>
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<td></td>
<td>B16</td>
<td>Preblend + MgSt</td>
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<td>225</td>
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<td>90</td>
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<tr>
<td></td>
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<td>0</td>
<td>91</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The past work (K. Pingali et al., 2013b), has shown that homogeneity of the nanosmearing layer was best seen in the blends where the concentration of flowing ingredients will be increased together rather than pronominelly increasing one flowing agent’s concentration over the other. In the present work, the studies will test the effect of nanosmearing from high concentrations of flowing agents in the pharmaceutical blend consisting of 0.5 wt% CS and 1 wt% MgSt, with the exception of blends B1, B5, B9, and
B15 where the concentration of flowing ingredients was maintained at 0.25 wt% CS and 0.5 wt% MgSt.

The manner at which flowing agents are added to the preblend is important. In the industry, typically ingredients are dry milled to a uniform particle size prior to blending. Since a lack of dry milling equipment was available, hand milling the ingredients consisted of passing ingredients through a 20 mesh stainless steel screen to filter out agglomerates of a particular flowing agent in the mix. This ensures a uniform blend in the final mix. Strain conditions were controlled in 10 minute intervals. The preblend formulation comprising the API and carrier was allotted 10 minutes for initial blending. Flowing agents were added to the preblend formulation. In instances where one flowing agent was added first, a 10 minute strain period was given at high shear to allow the flowing agent subsequent time to mix with the preblend. The second flowing agent according to the design of experiments was then added subsequently for another 10 minute strain period to allow enough time for mixing. In instances where two flowing agents were added simultaneously to the preblend, a 20 minute strain period was given. The total mixing time, including the preblend, across all formulations was no more than 30 minutes.

4.1.2 Preparation of Pharmaceutical Powders for ICPMS

Samples of pharmaceutical blends collected from the above mixing conditions were prepared for Inductively Coupled Plasma Mass Spectroscopy (ICPMS) analysis by dissolving the metallic ions from the thin film nanolayer into a nitric acid and hydrogen peroxide solution with a refined microwave digestion protocol. While APAP is readily
soluble, its carrier Microcrystalline Cellulose (MCC) is not. Since 90% of the formulation used in this study is comprised of a carrier, MCC has to be broken down to release the metallic ions present in its nanosmeared layer. The ions of interest are Magnesium, decomposed from the Magnesium Stearate, and Silica, decomposed from Cab-O-Sil in the nanosmear layer. Samples were completely dissolved in a nitric acid matrix, then further diluted with millipore purified water to a target solution concentration of 100ppm for the analysis through the ICP. Internal standards of Lithium, Scandium, Yttrium, and Indium were added to each sample to check for consistency and correct for drifts in the analysis of the Magnesium and Silicon ion concentrations. Since ICPMS relies on comparing the count of a particular ion with a calibration of counts achieved from known concentrations of a pure element, standards of Magnesium and Silica were prepared at target concentrations of 1000ppm, 500ppm, 250ppm, 125ppm, 62.5ppm, 31.25ppm, 15.625ppm, 7.8125ppm, and 3.90625ppm in a nitric acid matrix with internal standards above. Figure 3 below shows the preparation of samples for analysis during the setup of the developed Microwave digestion protocol.

Figure 3: ICP Sample Prep
4.2 Methods

4.2.1 Qualitative Identification of Nanosmear Distributions

The modification of the Scanning Electron Microscope (SEM) has allowed for the advancement in characterization tools necessary to study nanoparticles and their interactions. To analyze the pharmaceutical particles and characterize their nanosmears, Environmental Scanning Electroscopy (ESEM) coupled with Energy-Dispersive X-ray Electroscopy Spectroscopy (EDS) was employed.

Distributions of the MgSt and CS components will be qualitatively assessed by electron density mapping regions of identified elemental detection on top of an acquired ESEM image. Mappings of the individual elemental components representing the MgSt and Si will be acquired with an AOI encompassing 100+ Excipient and API particles. Combining these overlays with the ESEM image, AOI will be calculated with NIH ImageJ Histograms. Highlights of elemental distributions across the particle surfaces, representing the presence of the primary elemental component of the nanosmear, will be counted and compared against ImageJ histograms to provide representative smearing data across numerous particles of varying shape and size. An example of the ImageJ capability is shown in Figure 4.

4.2.2 Quantification of Nanosmear Chemical Composition

Inductively Coupled Plasma Mass Spectroscopy (ICPMS) was used to provide quantitative analysis of the concentration of nanostructures present on primarily the excipient particles. The ICPMS equipment takes a collected sample and generates an aerosol of the sample which is then introduced into argon plasma to dissociate the
molecules. The instrument removes an electron from the metallic elements and counts the frequency of a specific ion/isotope. This count is then compared to a developed calibration curve from known concentrations of the trace elements of interest and reported in terms of a ppb concentration. A few elemental isotopes for the magnesium ion and silicon ions were measured in the created standard solutions. Of those isotopes measure, shown in Figure 5 through Figure 8, the best calibration curves showing the greatest accuracy at lower concentrations of standard solution were isotopes 26 of Mg, and 28 of Si. During the experimentations, the ThermoFisher Scientific software accompanying the instrument automatically applied the chosen calibrations to the ion
count measured in the samples. This provided a measurement reported in parts per billion of concentration for detected ions of Magnesium and Silicon.

**Figure 5: ICPMS – 24Mg Ion Concentration Calibration**

![Graph showing 24Mg concentration calibration](image)

Intercept CFS=33.222264 Intercept Conc=0.462221
Sensitivity=71.675315 Correlation Coeff=0.999946

**Figure 6: ICPMS – 26Mg Ion Concentration Calibration**

![Graph showing 26Mg concentration calibration](image)

Intercept CFS=7.444448 Intercept Conc=0.452006
Sensitivity=61.469315 Correlation Coeff=0.999970

**Figure 7: ICPMS – 28Si Isotope Concentration Calibration**

![Graph showing 28Si concentration calibration](image)

Intercept CFS=431.780035 Intercept Conc=44.39453
Sensitivity=9.736149 Correlation Coeff=0.999799
The trace analysis provided by the ICP measured concentration was converted into a weighted average using stoichiometry and average physical properties of an Avicel particle. Since analysis of the Cab-O-Sil coating layer requires detection of Silicon, which presents multiple mass interferences in the sample analysis, the Collision Cell Technology (CCT) operation of the ICPMS provided improved accuracy and quantification of the Silica component on the Avicel particles. Figure 9 showcases the Thermofisher X-Series ICPMS, rented for use through the cooperation of the QBIC group and Dr. Keith MacRenaris at Northwestern University.
4.2.3 **Gravitational Displacement Rheology**

Characteristics of the flow properties for each prepared blend will be measured by two techniques associated with the Gravitational Displacement Rheometer (GDR): the powder flow index under dynamic changes in powder density and dilation of the packed powder bed in a simple drum tumbler. The validation and operation of these methods have been detailed extensively in previous publications (Faqih *et al.*, 2006; K. C. Pingali *et al.*, 2009). The pharmaceutical powder is loaded into a drum to 50% capacity for the analysis. The powder is then compacted on the drum’s horizontal axis in an AutoTap Tap Density Analyzer for 1000 taps. The compacted powder is placed on the GDR and rotated at a constant speed of 15 rpm. The expansion of the compacted powder bed was captured by an IR Camera, where the change in expansion by the powder was recorded for every half rotation and calculated by the software. Since the Dilation of the powder was uniform across the length of the drum, the software assesses the dilation of the bulk powder as that seen at the front end of the cylindrical drum. The Flow Index for each powder will be assessed by rotating the powder at rotational drum speeds of 5, 10, 15, 20, and 25 rpm. At different rotational speeds, the drum placed on a calibrated load cell picks up fluctuations in the moment of inertia of the powder bed caused the avalanche force of the bulk powder. The changes in avalanching pattern and load variability on the load cell increase when high cohesion from powder agglomerates are predominant in the powder. When cohesion tendencies of the bulk powder are less predominant, the variability of force on the load cell is less predominant. A more detailed explanation of the experimental setup and methodology is described in detail by Alexander *et al*.
(Alexander et al., 2006). The setup to measure powder flowability and dilation is shown below in Figure 10.

![GDR Setup for Powder Flowability and Dilation](image)

Figure 10: GDR Setup for Powder Flowability and Dilation

4.2.4 **Mercury Porosimetry of Tablets**

Porosimetry was assessed on select samples using an Hg Porosimeter. This test compares the intrusion volume of mercury into a sample at low and then high pressure to calculate the average pore size distribution of different poor structures based on forcing a non-wetting fluid, mercury, into a restricted pore volume on the sample surface. Incremental Intrusion of a non-wetting agent into the porous network of compressed grains comprising the tablet will provide the distribution of micropores and nanopores in the sample. This network of pores results from existence of varying levels of molecular and electrostatic forces generated from the domination of confined zones or smearing area of MgSt on the particle surface. Mercury Porosimetry correlates incremental change in intrusion volume of Mercury with applied pressure utilizing Washburn’s Theory to
estimate equivalent pore diameter (Westermarck, 2000). The results from this assessment will allow for the understanding of changes in microstructure with smearing of flowing agents.

4.2.5 Dissolution of Tablets

Prior to performing the Dissolution testing, the UV-Vis Spectrophotometer required a calibration curve to correlate measured UV absorbance to a known concentration of APAP in the required buffer for the Dissolution of APAP Tablets protocol. A line scan of a solution of APAP dissolved in a Phosphate Buffer of PH of 5.8 was performed to determine the peak absorbance concentration of APAP. The peak absorbance of APAP was measured to be at a wavelength of 243.5nm, which corresponds closely to absorbance values documented in the literature. Once the peak absorbance was found, several diluted concentrations of APAP in a phosphate buffer ranging from 0.52 ppb to 33.33 ppb were measured for their UV absorbance values at a peak absorbance wavelength of 243.5nm. The line scans of wavelength versus UV absorbance are shown below in Figure 11.

Figure 11: APAP Standardization Curves – Scanning Multiple Wavelengths for Peak APAP Absorbance
Using software provided by Agilent, the peak absorbance values measured at the wavelength of 243.5nm were correlated to the known concentrations of the various solutions of APAP used in the calibration. A linear relationship, as shown in Figure 12, correlating the absorbance value to the known calibration standards was then used to calculate the concentration of APAP during the dissolution of tablet over the testing interval.

![Calibration of APAP at Peak absorbance - 243.5nm](image)

**Figure 12: APAP Standardization of UV Absorbance with Concentration**

Pharmaceutical blends were prepared in the V-Blender, compacted with an MCC MP-10 Tablet Press under compression forces of 8kN and 12kN, and tested for drug release using a USP configured DS708 Dissolution Apparatus from Agilent. The purpose of producing tablets was to provide a preliminary proof of concept to associate changes in
product performance with altercations in nanosmear attributes across particle surfaces in select blends. Dissolution of Acetaminophen tablets was performed according to USP Monographs in a phosphate buffer solution of pH 5.8 for 90 minutes (Pharmacopeia, 2007). Drug release profiles of the active ingredient Acetaminophen from 6 tablets were simultaneously measured using a Cary 60 UV-Vis Spectrophotometer from Agilent. Dissolution rate of the Acetaminophen tablets in the six vessels was calculated from absorbance information collected from the individual vessels compared against the blank and saturated solutions. A depiction of the equipment used to perform the Dissolution testing is shown in Figure 13.

![Dissolution Testing Equipment](image)

Figure 13: USP Agilent 708 UV-VIS Dissolution Apparatus

### 4.2.6 Design of Experiments Statistical Analysis

To assess the statistical correlation and relationships between parameters of mixing order, shear intensity, and glidant/lubricant scale, the experiments are arranged in a random $2^k$ factorial design, as shown in Table 2, which can be assessed for statistical
significance of factor interactions in ANOVA. However, since not every factor can be appropriately represented in our DOE, the choice to utilize a two level fractional factorial based design was chosen. This would allow the variations in uniformity, extent of coating, and characteristic nanostructure formation in the powders to be studied as multi-variant parameters which hypothetically have significant interactions on tablet performance and bioavailability. The support of statistical design to validate the significance and interaction with the factors discussed in this DOE has wide applications for quality control and product performance validation in bio-medicine manufacturing.

Providing statistical validation and direction as to which combination of effects has the most significant influence on product quality forms will help Pharmaceutical Manufacturing optimize current inefficiencies and improve their overall Quality by Design.

Table 2: Statistical DOE

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<th>Run</th>
<th>Order of Mixing</th>
<th>Lubricant Conc</th>
<th>Shear</th>
<th>Compression</th>
<th>Hardness</th>
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<th>Dissolution</th>
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5. RESULTS

5.1 Nanosmearing Layer Characteristics Due to Mixing Order of Ingredients

The formation of nanosmears at the contact particle surface formed during shear of flowing agents in the pharmaceutical blend create an unique understanding in the application of addressing scale up variables in the processing of pharmaceutical powders. In Figure 14, localized clusters of nanosmears form different characteristic structures with different orders of mixing. The different size distributions of nanosmears being formed on the particle surface provide evidence that surface characteristics of the nanosmear govern the growth, distribution, and development of the nanosmear layer during mixing. The physical structure of the nanosmear created when flowing agents are deposited to the excipient particle surface is influenced by the size and yield strength of the flowing agent during mixing. The flowing agent Cab-O-Sil is an agglomeration of nanoparticles with low yield strength that deposit a cluster of the agglomeration during contact friction with the excipient particle surface. The lubricant MgSt is a highly friable platelet with low yield strength that transfers a portion of its mass to the thin-film nanolayer when contact friction with the excipient particle surface is experienced. The strength of these layers has shown that CS formed a much stronger layer to the particle surfaces, while the thin-film nanolayer of MgSt is very weak and friable to shear friction.
When the mixing order of flowing agents was altered during the experimentation, different characteristic developments in nanosmear size were seen, as shown in Figure 15. The histograms shown relate two cases: (Figure 15a) blends mixed with a low concentration of flowing agents (0.25 wt% CS and 0.5 wt% MgSt) and (Figure 15b) blends mixed with a high concentration of flowing agents (0.5 wt% CS and 1.0% MgSt). In cases where the flowing agents were added simultaneously during mixing (B1 & B4), nanosmears showed a greater distribution in size across the excipient surface. Increasing the flowing agent concentration in the blend during mixings indicates that the presence of these additional ingredients increase the size of the smear formed on the excipient surface and their distribution in smear size. In the batches where CS was mixed with the preblend first (B5 & B8), nanosmears were observed to have a rougher surface texture on the excipient particle surfaces, mostly due to the deposits of CS nano-agglomerates.
These particular nanosmears were bigger in size and shape on the excipient surface, having a size distribution between 0.5-1000 µm². Increasing the concentration narrowed the distribution of observed smear size slightly, but the average smear size was more or less the same with an increase in flowing agent concentration in the blend. A very interesting observation in nanosmear size distribution was seen in the blends where CS
was added after the addition of MgSt to the preblend (B9 & B12). More predominate clusters of CS agglomerates were seen to have bound to the base MgSt nanolayer, creating smaller nanosmears, but with a smaller distribution in smear size. The increase of flowing agent concentration was seen to significantly reduce the size distribution of the measured smears, indicating the predominance of similar size and shape smears across the particle surface. It is reasonable to conclude that this order of mixing creates potentially a more porous smeared layer, as smears formed from this mixing order were less frequently overlapping and covering large areas of the excipient surface. When only MgSt was added to the preblend during mixing (B15 & B16), the base thin film nanolayer was observed to be uniform, showing smeared deposits of MgSt across the excipient particle surface.

Interestingly, it is clearly evident when only MgSt is added to the blend, the smear size distribution remains more or less the same. While the average smear size was seen to increase slightly with an increase in MgSt concentration, the distribution of nanosmear size on the excipient surface is not dependent on concentration. This outlines a critical interaction that the flowing agent Cab-O-Sil plays in the rearrangement and structure of the nanosmear layer during mixing, which will be explored in future works. Additional applications for enhancing the understanding of nanosmear formations are the influence that concentration has on the formation of nanosmears. Controlling concentration was seen to control the distribution in smear size on the excipient particle surface. This presents an interesting key towards understanding the necessity of controlling nanosmear size distributions for a promising application of optimizing physiochemical performance of pharmaceutical blends and tablets.
Stepping backward to the macro scale, particles of the ingredients comprising the pharmaceutical blend will interact to form different distributions and densities of nanosmears. Analysis of multiple particles under an ESEM with the X-Ray Mapping, as shown in Figure 16, highlights noticeable differences in electron density distributions. These differences in flowing agent density amongst the scanned particles underline unique frequency distributions arising from the mixing of ingredients. Different orders of mixing have shown a buildup of agglomerates and areas of non-uniform distribution in the electron density for certain conditions in the maps, emphasizing the need to characterize the significant differences in nanostructures formed from flowing agent coating of the Preblend. Non-uniform distributions of flowing agents across the excipient and API particle surfaces are greatly seen in M.O.3, where MgSt was mixed with the preblend first. For M.O.2, where CS was mixed with the preblend first, agglomerates of CS on the particle surface created cluster zones where MgSt would also cluster in the nanolayer. It is believed that these clusters are very hydrophobic in nature, which can possibly attribute to high impediments in drug release characteristics seen in the compressed tablets for that particular mixing order. While the present work is not sufficient to explain why scale up issues and product batch failures from improper mixing occur, these regions of high concentration of one flowing agent over the other create predominant interparticle interactions that catastrophically affect blend cohesion and tablet tribological behavior, which will be explained further.
Singular particle analysis is useful for understanding the characteristics of nanostructures, but the variability of particle shape and size distributions will create different levels of nanosmearing on other particle surfaces. In this context, the technique to correlate area distribution of nanosmears on multiple particles from their electronic...
patterns obtained through EDS micrographs were developed. EDS micrographs were
masked to confined particle boundaries obtained from the ESEM image. Using NIH
image histograms, localized clusters and confined pixels identified from the EDS
mapping were counted and compared against the total area for each particle. This
comparison was then used to collect an average of the extent of nanosmears for CS and
MgSt across the particles outlined from the ESEM image. The results of smearing area of
CS and MgSt for different blends are shown in Table 3.

Table 3: Results of ICP and ESEM-EDS Nanosmear Quantification

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<tr>
<th>Group</th>
<th>mg MgSt / gm Avicel</th>
<th>ICP MgSt StDev</th>
<th>mg MgSt / particle Avicel</th>
<th>mg CS / gm Avicel</th>
<th>ICP CS StDev</th>
<th>ng CS / particle Avicel</th>
<th>Smear Area %MgSt</th>
<th>MgSt Error</th>
<th>MS RSD</th>
<th>Smear Area %CS</th>
<th>CS Error</th>
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<th>Flow Index</th>
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5.3 Weight of Characteristic Nanosmears

The amount of nanosmear was measured using ICPMS technique previously
discussed to identify the elemental concentrations of Mg and Si in the nanolayer. This
technique helps illustrate the scale dependency of nanosmear formations as they impact
macro scale physiochemical characteristics in the solid dosage form. From Table 3, it
was seen previously in M.O.3, where MgSt was added to the preblend first during
mixing, that the extent of nanosmears from processing created the greatest coverage of
both following ingredients on pharmaceutical particle surfaces. However, the ICPMS
analysis indicates that the concentration of ingredients in the thin film nanolayer is the
least, providing insight into the strength and stability of the nanolayer formed from
M.O.3. When all flowing agents were mixed together (M.O.1) and when CS was added to the preblend first (M.O.2), the greatest concentrations of flowing agents was present in the thin film nanolayer. The relationship between the extent of smearing and the concentration of nanosmears on particle surfaces emphasizes a critical link to the design of solid dosage forms that will be experimentally supported and explained in future sections.

5.4 Critical Blend Properties

Flowability and dilation testing has shown that applied mechanical strain from varying the mixing order of flowing agents with the preblend formulation was a dominant factor in changing the physical behavior of the bulk powder (K. Pingali et al., 2013a). Flowability and dilation assessments of the bulk powder were measured using a GDR apparatus detailed in the experimental section above. The analysis performed highlights differences in the flowability of the blend when varying mixing orders of the ingredients were prepared with flowing agent concentrations of 0.25 wt% CS & 0.5 wt% MgSt (Figure 17a) and 0.5 wt% CS & 1.0 wt% MgSt (Figure 17b). Assessment of the flow index by characterizations of the variation in avalanching force is a proven tool to understand cohesive properties of the pharmaceutical blend (Alexander et al., 2006). In this context, the greatest cohesive properties of the blends was ranked in blends B1, B4, B5, and B9. The blends exhibiting the least cohesive properties in order of decreasing cohesive properties was seen in blends B8, B15, B12, and B16. It is interesting to note that mixing flowing agents together simultaneously created powders exhibiting the
greatest cohesive properties. Only blends that were mixed with the lubricant, MgSt, exhibited low cohesive properties to provide better powder flowability.

The measure of dilation as a tool to characterize the powder’s elastic recovery from a compacted state was used to understand the material response capabilities of the powder. Dilation of each powder was measured for blends containing a low concentration of flowing agents (Figure 17c) and a high concentration of flowing agents (Figure 17d). Given the two concentrations of flowing agents used in the preparation of the powders, the ranking of material response due to mixing order showcases that batches mixed according to the M.O.1 and M.O.3 schemes had the least and greatest potentials for bed elastic recovery, respectively. The dilation response of powders is a critical factor in maintaining blend uniformity during the processing of pharmaceutical powders, which will be discussed in the subsequent sections.

Figure 17: Flowability and Dilation of the Powders
5.5 Compacted Tablet Physicochemical Properties

Unique nanosmears formed during mixing created different microstructure arrangements in the porous tablet matrix (Figure 18a and Figure 18b). While ESEM images are not shown, compaction of the powders rearranged the excipient and API particles in a matrix best suiting the intermolecular stability of the system. Increasing the compression force to 12kN in the powders was seen to migrate nanoparticulate remainders of the flowing agents to the surface of the solid dosage form, thereby creating localized clusters to impart tablet porosity and drug release. At low compression forces, the pharmaceutical tablets showed a greater porous network when CS was added to the preblend first (M.O.2). A large microporous network is also seen in blend B16 (M.O.4) with just MgSt in the nanosmear layer. When compacted, the materials were rearranged to form tighter nanoporous structures, with the exception of the B16 where MgSt nanosmears predominate the surface of the particles. The distribution of pore diameters in the tablet matrix for blend B16 was confined to the micropore region, even after increasing tablet compaction, indicating that the glidant is responsible for particle interactions and rearrangement of tablet microstructure.

The rearrangement of tablet microstructure will essentially control the kinetics for release of the active ingredient from the tablet matrix (Figure 18c and Figure 18d). Amongst two different levels of tablet compaction force, drug release was least hindered for blends where the flowing agents were mixed together simultaneously. The rate of release of APAP into the buffer solution was hindered the greatest in formulations B8 and B12 where flowing agents were mixed individually into the blend. Amongst all both conditions, the ranking of the kinetics for drug release for two levels of compaction force
remained the same. The association of both porosimetry and dissolution assessments with characterized formations of nanosmears provide a unique insight into tablet physiochemical behavior, which will be discussed in greater detail.

Figure 18: Effect of Mixing Order on the Physiochemical Properties of Compressed Tablets
6. DISCUSSION

6.1 Extent of Nanosmearing by Area Distribution

Nanosmearing forms unique nanoparticulate surface structures that alter the distribution of flowing ingredients and surface characteristics of the particles. Therefore, the extent of nanosmearing is not only dependent on mixing order but potentially on the concentration of the formulation. Past work has shown that increasing the concentration of one flowing agent over another in the pharmaceutical blend has shown clusters of nanosmears that create the non-even distribution of flowing agents in the nanolayer (K. Pingali et al., 2013b). During smearing, no particle can be 100% smeared by a flowing agent due to the friability of ingredients, porous characteristics, and physical morphology at the particle surface. Since excipient particles are known to have varying shape and size distributions, no two excipient particles will smear the same. The same can be said for varying size distributions of the API particles as well. Therefore, refinement of techniques to interpret the extent of smearing and amount of smearing amongst multiple particles that govern a pharmaceutical formulation’s tribological behavior is a necessary endeavor for future works.

The largely quantitative differences in smearing extent previously shown from the variation in processing mixing order of flowing agents supports a few important conclusions. First, it is supported that the evenness of distribution of flowing agents is the best when flowing agents are added together simultaneously in the mixing process. Second, the flowing agent CS, which is known to interact with the flowing agent MgSt, is most effective in increasing particle smearing when it is added after MgSt has been mixed with the Preblend. While MgSt is highly friable with shear to coat the particles,
given the lesser extent of smearing when it is the sole ingredient (M.O.4), it is evident that CS creates stronger bonds to MgSt and the particle surface that hold against interparticle shearing friction during mixing. The results suggest that the extent of smearing is dependent on a possible reorientation of nanostructures in the nanolayer from changes in the mixing order. Reorientation of nanostructures allow for different spatial configurations of particles during packing, giving compressed powders unique categories of void volumes which would affect tablet performance properties, such as hardness and dissolution. If this true, the phenomenon of nanosmear structural reconfiguration, which is not completely understood, could be a key mechanism to controlling surface properties that spark interparticle interactions. An enhanced improvement in methodology would be needed to interpret particle interactions in a physically reasonable way. Whether smearing of flowing agents during mixing creates singular layers or a multi-layers on the particle surface, and whether the thickness of these layers across varying particles is similar, is not yet known. However, it is intuitive to argue that the surface density of the nanosmeared layer plays an important role in the stability of the thin-film nanolayer against particle collisions and friction.

6.2 Quantification by the Weight of Nanosmearing

The extent of nanosmearing on the particle surface for various blends provides an insight into the variability of nanosmears across pharmaceutical particles. However, the amount of nanosmear ingredients MgSt and CS is equally important to visualize the thickness of nanosmear deposits on the particle surfaces. These results previously shown in Table 3 stress that the formation of nanosmeared structures are time dependent during
the mixing process, which underline the importance of shear strain on the formation of these nanosmears with varying mixing conditions. Surprisingly, different mixing orders have shown that increased coverage of the nanosmear does not increase the amount of nanosmear on the particle surface. In this sense, we experimentally demonstrate that nanosmear structures change as a function of the extent of distribution on particle surfaces.

The extent of nanosmear coverage with respect to their measured mass in the nanolayer is shown in Figure 19a. There exists a clear correlation between the weight of the nanosmear and its coverage in the thin-film nanolayer. Interestingly, the weight of the nanosmear flowing agent deposited on the particle surface is inversely related to the extent of particle coverage by the correlating nanosmear component. Larger weights of nanosmear are seen to provide less coverage of the particle surface, indicating that higher concentrations of the flowing agents preside in the nanolayer but do not necessarily create an extensive particle coating.

Figure 19: Relationship between Smeared Area vs Smear Layer Composition
Although M.O.3 showed electron density regions of heavily clustered agglomerates of CS with a far greater extent coverage in the nanolayer, the lack of flowing agent presence in the nanolayer from the ICPMS support that the bonding of MgSt to particle surfaces is very weak and most likely wears away, decreasing the nanolayer thickness, due to particle friction during mixing. Amongst the different smears formed, MgSt nanosmears were seen to cover less of the particle surface with a greater mass in the nanolayer. The smears formed by CS on the other hand had a greater extent of coverage on the particle surface with less mass given the size and structure characteristics of the smear they form. For the two concentrations of flowing agents used in this study, increasing the flowing agent concentration was seen to systematically increase smear coverage and weight on the particle surfaces. In this context, it is necessary to control the concentration of flowing agents in the processing of pharmaceutical powders. It is important to note for future discussion that smearing that exceeds roughly 33% of the particle surface has severe consequences to the tribological performance of manufactured tablets. While this article doesn’t propose an effective means to chemically control the formation of nanosmears and their distribution in particle surfaces, it is evident that the first step to controlling nanosmearing on particles can be achieved by controlling the order and concentration by which flowing agents are blended.

Controlling the rate of nanosmear formation is a missing link and an underestimated consideration in the processing of pharmaceutical powders for the manufacture of solid dosage forms. What is a greater unknown is the mechanism by which particles of different shapes and sizes can effectively contain consistent smears of flowing agents in their coating. The variability in the extent of nanosmears was seen to be significant from
blend to blend, and the mixing order of flowing agents was a factor on the variation of smearing. An increase in nanosmear weight on the particle surfaces was found to increase the relative standard deviation in the extent of nanosmears across multiple particle surfaces in Figure 19b. It is intuitive to argue that smear weight directly influences nanosmear layer stability. As a larger variance in smear area is seen with higher masses of nanosmears on the particle surfaces, this particularly presents the case that nanosmears grow in the nanolayer to a certain extent before they break off the particle surface from particle collisions arising during mixing to create gaps in the thin-film nanosmear layer. However, the problem of characterizing indirect deformations to the thin film nanolayer due to ordered mixing has not been solved and will be addressed in future works.

6.3 Bulk Powder Property Response Due to the Mixing Order of Ingredients

Material response properties of the powders are dependent on interparticle interactions taking place at the particle surface, so it is intuitive to conclude that changes in particle surface chemistry will impart different responses to the macro scale. An incremental increase in cohesive properties from simultaneous mixing of flowing agents versus improved flowability through individual mixing of flowing agents reflects the apparent change in interparticle behavior. This arises from physiochemical changes brought about by unique nanosmear characteristics at the particle surface. Experimental analysis of the bulk powders in the GDR reveal that the flowability of the powders, characterized by a Flow Index, show higher cohesive physical tendencies when different nanostructures were formed. When flowing agents were mixed together (M.O.1), an
even distribution of the nanosmears and limited extent of nanosmearing showed higher cohesive tendencies in the GDR, indicated through a higher flow index. The lowest cohesion in the blend, characterized by a low flow index, was seen when only MgSt was mixed in the blend where no CS nanosmears were present. When CS nanosmears formed in the nanolayer they created new nanostructures to alter tribological particle interactions. It was evident that when CS was mixed first in the blend (M.O.2), the blend exhibited low cohesion and a smaller smear area of CS. When CS was added after MgSt to the blend (M.O.3), nanosmears of CS forming on top of nanosmears of MgSt evidently increased the bulk powder’s interparticle cohesion, evident by a greater flow index. This marks an interesting phenomenon. Often, the pharmaceutical industry relates high cohesion of the bulk powder to processing as not having enough lubricant in the blend. If high cohesion by the development of pronounced nanosmears of CS results in greater interparticle bonding, then monitoring the level of CS in the pharmaceutical blend and its mixing are very important considerations during manufacturing. While M.O.3 had the greatest smearing of MgSt, nanosmears of CS predominating on the nanolayer create physicochemical changes to the response of the powders when compacted in the tablets, which will be discussed later in the evaluation of tablet performance.

The formation of nanosmears is seen to influence critical material response properties of the pharmaceutical blend. It is understood and supported above that increasing smearing improves bulk flow properties. However, the variability in smearing is dependent on a wide array of factors, such as different orders of mixing and flowing agent concentration, which is not easily predicted. In this manner, we experimentally show how the relative standard deviation of the extent of smearing from particle to
particle is related to the flowability of the powder (Figure 20a). A reduction in smearing variation from particle to particle is seen to enhance the flowability of the powder. The experimental results show that non-consistent smearing increases the cohesive properties of the blend. Therefore, choosing the correct concentration and appropriate mixing order of flowing agents are necessary for the control of the powder’s material response characteristics.

The elastic recovery of the pharmaceutical powder blend was found to be proportional to the extent of nanosmear formation across particle surfaces. (Figure 20b). Through Dilation experimentation performed on the GDR, the Dilation of the bulk powder is directly proportional to the smearing of MgSt on the particle surfaces. Higher smearing of MgSt altered contact mechanics between particles to significantly recover the powder to a less dense bulk state, than blends with less smearing of MgSt. Even with higher smears of CS on the particle surfaces, which have proven to increase cohesion of the blend, show that CS smear does not hinder the powder bed’s expansivity. This indicates that the predominance of electrostatic forces under softly compacted conditions exhibited by MgSt deter cohesion of the blend. The smearing of MgSt on the particle surfaces is expected to alter contact mechanics of adjacent particles which ultimately explain the change in powder bed porosity and volume. From this perspective, controlling the elastic recovery potential during the processing of the pharmaceutical powder to maintain blend homogeneity could potentially be controlled through the smearing applied to the particles.
The weight of the MgSt nanosmear formed from varying orders of mixing at contact particle surfaces influences the compactability and bulk density of the blend. Increasing nanosmears improved bulk and compaction densities to an extent, which can be attributed to the contact mechanics arising from interparticle forces strengthened by clusters of nanosmears on the particle surface (Figure 21). Increasing the amount of smearing on the particle surface is shown to improve properties of bulk density when low concentrations of flowing agent are mixed with the Preblend. Interestingly, an increase in flowing agent concentration during mixing is observed to significantly improve bulk and compact densities, but also highlights the critical inflection where excessive nanosmear weight on particle surfaces reduces properties of bulk density. Understanding this inflection where material properties begin to adversely change underlines the necessity to control flowing agent concentration in the pharmaceutical formulation. Changes in material response have been seen to affect the critical performance properties of the blends when they were compacted into tablets.
Figure 21: Relationship of Nanosmearing with Powder Response Properties

When compressed into tablets, the contact mechanics between particles change as a result of thermomechanical alterations to the microstructure in the form of material rearrangements and deformations, which will be discussed more in detail in the next section. Under high compaction forces, new physiochemical bonds and molecular reorientations will occur, thereby changing critical properties in performance of the solid dosage form. To understand the change in performance response due to variances in nanosmeared structures, it was important to assess the performance of solid dosage forms once the powders were compacted into tablets at a high and low compression forces (12kN and 8kN).
6.4 Influence of Nanosmearing on Tablet Porosity

The characterization of the powder microstructure after compaction provides a better insight as to the particle-particle behavior and rearrangements occurring in the tablet matrix. The increase in microporosity of the tablet is due to the electrostatic forces resisting particle interactions caused by the smearing of MgSt on the particle surface (Figure 22). When translating these porous distribution networks to characterize the bulk porosity of the tablet, it is evident that higher porosity characteristics were seen when the smearing of MgSt in the nanolayer increased. However, as one would expect, higher smears of CS in the nanolayer decreased porosity. This is most likely due to rearrangements in tablet microstructure from interparticle interactions enhanced by the development of CS nanosmears. Higher amounts of CS increased particle smearing of flowing agents, although this has been seen to directly hinder the release of the API from the excipient matrix.

![Effect of MgSt Smear on Tablet Porosity](image)

Figure 22: Relationship of Nanosmearing with Tablet Porosity
It is evident that increases in nanosmears, particularly the smearing MgSt across the particle surface, led to prolonged drug release and increased porosity in the tablets. This brings us to believe that mutual dependencies between the distribution and amount of CS and MgSt on particle surface can be critical in determining the product behavior. Results discussed previously highlight the influence of mixing order on the rate of release of the active ingredient from the excipient matrix. Previously, it was seen that flowing agents mixed simultaneously in the blend provide the fastest mechanism of release while flowing agents mixed separately into the blend create a more complex excipient matrix to hinder drug release. This phenomenon is most likely the result of excess lubricant migrating to the caps of the solid dosage form, which can prevent solubilization of the active ingredient into the buffer media. When drug release was assessed by characterizing the critical inflection point where release begins to slow, at approximately 21 minutes (Figure 23), it was evident that the relationship between smearing of MgSt on the particle surfaces and drug release highlights a critical equivalence point. This critical equivalence point is seen to be around 33% smearing of MgSt and supports that nanosmearing exceeding the critical equivalence point has significantly impeded drug release with increased smearing. This critical equivalence point is also evident from data collected from the Mercury Porosimetry testing that an increase in coverage of MgSt in the nanolayer increased the tortuosity ratio characterizing the distance traveled from pore to pore over the actual distance between pores (Figure 24). An increase in tortuosity in the tablet matrix slows the solvent penetration rate and increases the time of dissolution for the API. However, we cannot assume that dissolution is solely dependent on extent of lubricant covering the nanosmear layer. To provide a qualitative picture as to the greater impact of
nanosmears on bulk scale behavior, the thickness of the nanolayer, along with the extent area and amount of ingredient in the nanolayer all need to be completely understood.

The influence of nanosmeared distributions of MgSt on an excipient or API surface not only influence the chemical dependencies of the product behavior, but also influence physical attributes of the final product. In this case, we present a study to understand the impact of these nanosmears on the hardness characteristics of the tablet. It is well known that increases in concentration of MgSt can create friable tablets. In this respect, increasing smearing area of the lubricant can weaken the tablet matrix and affect solid dosage durability. In Figure 25, tablet hardness characteristics were seen to decrease with an increase in smear of MgSt across the particle surface. However, tablet hardness was regained at the end where MgSt coverage was the highest primarily due to interactions of CS nanosmears with the excipient and API to form a stronger matrix. These cases to correlate the order of mixing of pharmaceutical ingredients have shown that nanoscale deposits and interactions play critical factors in macro scale performance in both the critical blend and tablet properties which cannot be ignored.
Figure 23: Relationship of Nanosmearing with Tablet Tortuosity

Figure 24: Relationship of Nanosmearing Weight with Tablet Hardness
6.5 Response of Shear, Mixing Order, and Lubrication on Nanosmearing

From the work previously shown, limiting the nanosmearing of the lubricant MgSt in the final blended product is detrimental to the solubility, porosity, hardness of the final drug product. These attributes are a few of several that govern the release criteria for a drug product. Understanding the combination of effects to limit nanosmearing and optimize the final release attributes is essential in the formulation and manufacture of a drug product. In Figures 26A-26C, the extent of MgSt nanosmearing are increased by increasing lubrication amounts and intensifier shear. However, MgSt smearing was observed to decrease with increasing mixing time in the V-blender. This supports the notion that the smeared layer of MgSt is very friable and breaks from the particle surface with longer periods of mixing.
In Figures 26D-26F, the amount of MgSt nanosmearing on the particle surface is greatest when the lubrication quantity in the blend is the greatest and mixing time is minimal. Increasing the shear with the intensifier bar was seen to reduce the amount of nanosmearing on the particle surface, supporting this smeared layer is friable when subjected to high shear forces. Figure 27A supports that MgSt nanosmearing is
influenced by an interaction between intensifier shear and mixing time of MgSt, as well as an interaction between the intensifier shear and lubrication level. The main effects plots below show there is a statistical significant interaction between shear and mixing time that could be understood further with future studies into the effects of shear on nanosmearing.

Figure 27: Main Effects Influencing Nanosmearing
7. FUTURE WORKS

Understanding the influence of shear and the interaction of the CS nanosmeared layer with the nanosmearing phenomena of MgSt is necessary to fully understand the phenomena behind nanosmearing and its influences to blend properties and final drug product critical quality attributes. As shown in Figure 28, this work found an interaction between CS nanosmearing and the smearing potential of MgSt. In order to control the smearing of MgSt in the final blend, controlling the smearing of CS is also essential. To create the best formulation, minimizing the smearing of CS and MgSt would need to understand to develop better controls for nanosmearing during the blending of pharmaceutical ingredients. As shown in Figure 29 and Figure 30, further exploring the influence of shear on the extent of nanosmearing has shown that at a higher shear rate of the intensifier bar in the blender, a minimum level of MgSt and CS can be achieved. Understanding this minimum point of smearing to produce optimum critical quality attribute results in the final drug product will be the focus of future works.

Figure 28: Relationship between CS and MgSt Nanosmearing
Figure 29: Influence of Shear on MgSt Nanosmearing

Figure 30: Influence of Shear on CS Nanosmearing
8. CONCLUSIONS

From the work, it is evident that understanding the structural characteristics of nanosmearing development is crucial towards understanding the tribological behavior of bulk powders and critical tablet properties that affect the final product performance. While shear was maintained between two levels during the order of mixing in the preparation of the pharmaceutical blends, the results support that applied shear is a critical factor that cannot be ignored. Applied mechanical strain on the pharmaceutical ingredients and flowing agents changed the overall material response characteristics of the particles in terms of the alteration of cohesive tendencies in flowability, changes in bed expansion response in dilation, shifts in tablet matrix organization to offset porosity, and the migration of nanosmeared ingredients to impede drug release.

A detailed nanoscale investigation of the prepared pharmaceutical particles confirmed that the blending of lubricants and glidants form thin-film nanolayers on excipient and API particle surfaces. It was clearly evident that the shape and size distribution of the nanosmears formed on the excipient surface are influenced by both concentration of ingredients and their order of mixing. The distribution in size of nanosmears measured on the excipient particle surface were seen to be the greatest when only MgSt was mixed into the pharmaceutical preblend. When two flowing agents were mixed together at low concentrations, the greatest distribution in smear size was seen when CS was added to the preblend first, while the smallest distribution in smear size was evident when both CS and MgSt were added to the preblend together. Increasing the concentration of flowing agents in the blends indicated that the smear size formed on the excipient surface was the smallest and most consistent in size when MgSt was mixed to the preblend first.
The difference in size distributions in smear across the excipient particles highlight a significant importance that mixing order plays in flowing agent interaction to create structural reconfigurations in the nanosmear layer.

The orientation of these different nanosmears from the various mixing orders in turn affected physiochemical properties of the tablets, such as porosity, dissolution, and density. These structural configurations presented by the nanosmears in the coating layer provide unique insights that explain changes in product performance from mixing. As a result of mixing the pharmaceutical flowing agents in different orders, nanosmearing of MgSt was seen to increase when CS was mixed after the addition of MgSt to the formulation to form more nanosmears across the particle surfaces. Tablet porosity was seen to increase with an increase in MgSt nanosmearing across the particle surfaces to an extent where an increase in distribution of CS conformed to areas of the porous network to most likely fill in void volumes. The rate of release in the tablets was seen to have been hindered when the amount of MgSt nanosmearing exceeded an identified critical equivalence point of 33%. Tablet hardness also decreased with increasing amounts of MgSt nanosmearing across the nanolayer, but the tablets showed indications of strength recovery from friability when greater nanosmearing of CS was present across the nanolayer. Future work to enhance the understanding of nanosmears shows great promise, as nanosmear rearrangements during mixing orders are unique. This makes nanosmear classification and control a trivial influence in the processing and performance of all pharmaceuticals manufactured under existing standards and practices.
LITERATURE CITED


