Electrostatic Nanosmearing Architecture of Additive Functional Groups during High Shear Mixing of Pharmaceutical Blends

Sajan Kumar Chatarla

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ELECTROSTATIC NANOSMEARING ARCHITECTURE OF ADDITIVE FUNCTIONAL GROUPS DURING HIGH SHEAR MIXING OF PHARMACEUTICAL BLENDS

by

Sajan Kumar Chatarla

A thesis submitted to the Graduate College in partial fulfillment of the requirements for the degree of Master of Science in Engineering Chemical and Paper Engineering Western Michigan University December 2016

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The main objective of the research project is to detect and quantify the rate and extent of nanosmearing of hydrophobic functional groups of additives on multiple pharmaceutical particles during high shear mixing of formulations due to electrostatics affecting critical blend properties on the bulk scale. We accomplished this task by systematically detecting the electrostatics during powder flow and its consequence on the nanosmearing distribution of additives during mixing. In the first stage, the electrostatic behavior of particles was correlated to the powder flow. Secondly, its relative influence on nanosmearing of additives during mixing was determined by developing a methodology to quantify (a) rate and (b) extent of nanosmearing. In the third stage, the distribution and % extent of hydrophobic additive affecting the critical blend properties were investigated. For the first time in the field of particle technology, Raman Spectroscopy was employed to develop an innovative method to quantify the presence and % extent of nanosmears of hydrophobic additive (magnesium stearate). The results indicated that electrostatic charges are generated due to particle interaction during powder flow. A direct correlation between charge accumulation and dissipation to the forces acting on the load cell measurements were found. Applied process shear increased the % nanosmeared area on multiple particle surfaces which improved the overall powder flow. A direct correlation between nanosmearing with applied process shear, cohesion and electrostatics was found.
ACKNOWLEDGMENTS

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Sajan Kumar Chatarla
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<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>APAP</td>
<td>N-Acetyl-Para-Amino-Phenol</td>
</tr>
<tr>
<td>MgSt</td>
<td>Magnesium Stearate</td>
</tr>
<tr>
<td>CS</td>
<td>Colloidal Silica</td>
</tr>
<tr>
<td>GDR</td>
<td>Gravitational Displacement Rheometer</td>
</tr>
<tr>
<td>RSM</td>
<td>Raman Spectroscopy Mapping</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>BSM</td>
<td>Biological Stains Method</td>
</tr>
<tr>
<td>rpm</td>
<td>Revolutions Per Minute</td>
</tr>
<tr>
<td>FI</td>
<td>Flow Index</td>
</tr>
<tr>
<td>PDMPO</td>
<td>2-(4-Pyridyl)-5-((4-(2-Dimethylaminoethylaminocarbamoyl) Methoxy) Phenyl) Oxazole</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning Electron Microscopy</td>
</tr>
<tr>
<td>TEM</td>
<td>Transmission Electron Microscopy</td>
</tr>
<tr>
<td>EDS</td>
<td>Energy Dispersive X-ray Spectroscopy</td>
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<tr>
<td>DC</td>
<td>Direct Current</td>
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</tbody>
</table>
1 INTRODUCTION

Many industries, which involve the processing of granular particulate systems, experience various problems in unit operations, handling, controlling and quality of production due to problems related to cohesion, segregation, electrostatics etc. Pharmaceutical manufacturing, in particular, deals with numerous powder handling processes involving mixing, formulation, tablet making etc. that primarily require the free-flowing nature of the powders to minimize the problems related to mixing, segregation and drug distribution in the overall mixture or blend. Surface properties of particles during mixing and formulation in pharmaceutical industry are known to affect the particle interaction behavior [1-4]. Moreover, Active Pharmaceutical Ingredients (API) (drug materials) are very cohesive in nature whose flow properties must be enhanced for enhanced product formulation and API content uniformity. The process conditions of mixing determine the quality of blend in terms of its content uniformity and blend performance [5]. One of the process conditions such as the high shear particle mixing is a routine process to increase the uniformity of the API in the blend. However, such a condition is also known to affect the surface properties of the particles in the blend [6]. Particularly, pharmaceutical processes encounter the problems associated with over-lubrication or under-lubrication due to uneven distribution of nano-additives. Either of the two problems result in enormous product losses and batch failures. Amount of coating of nano additives onto surrounding powder particles is an intriguing field to be explored. Very little knowledge exists in literature so far to determine the exact amount of lubricant that is needed to coat the powder particles completely. In addition, we do not yet know if the powders will be entirely covered with coatings. An important information related to the amount of additive required to coat the powder particles completely is still lacking in theory and practice. Hence, there is a need to understand the surface properties of particles, their coating extent, uniformity of coating under the influence of shear conditions to determine the overall blend performance.
on a macroscopic scale in bulk manufacturing. It is also important to have an intrinsic understanding on the new structural changes caused on the surfaces due to various particle interactions and process or shear conditions, which not only affect the blend properties but also influence the finished product performance.

The improved flowability of the powder particulate systems not only enhances the process control performance by optimizing the overall production but also improves the finished product performance. Many methods and techniques were introduced to reduce the cohesive nature of the pharmaceutical formulations [7, 8] to an appreciable extent but the basic knowledge for understanding the particle-particle interactions at nanoscale and their subsequent multi-scale effects is poorly understood. Recent studies [9-11] have suggested that the flow and electrical properties of the powder blends have significant relation. However, extent of electrostatics leading to cohesive nature of powder blends continue to intrigue the scientists. Many pharmaceutical formulations consist of high cohesive API, which adversely affects the flow properties of the powder blend resulting in powder processing and handling problems, electrostatics issues and product failures.

Lubricants such as Magnesium Stearate (MgSt) and glidants such as Colloidal Silica (CS) are common flowing agents added to the blend to overcome such an effect of a cohesive API. The distribution of the API and its biopharmaceutical performance principally depends on the extent to which the API is coated. This depends on two factors: (a) shear exposure by which the additive or flowing agent coats on the API and (b) concentration of the additive in the overall blend. Our previous study [12] has shown that only 3% of the additive added to the blend is coated on the neighboring particles and 97% remains uncoated and flows along the particles in the blend. In this context, it is essential to understand the factors and conditions contributing to such a behavior of lubricant coating and its limitation that only 3% of the total additive added gets coated. From our previous results [12], it is imperative to think that the
particle coating ability is limited irrespective of the concentration of the additive in the blend. Hence, it is needed to understand the extent to which the particles can be coated under the determined process conditions. If not 100% coating, it is important to investigate the extent (in %) to which the particle surface area that is coated under the set operating parameters of particle mixing. To extend such study to the overall blend where numerous particles are present is a challenge, but is truly worth studying given the effect it has on blend and product performance. Therefore, in this work, we propose a systematic investigation of uniformity and extent of nanosmearing on particle surface and behavior of nanosmearing on the overall bulk particles in the pharmaceutical blend. We also propose the consequent effect of nanosmeared blends show on powder flow performance due to its hydrophobic nature of the blend. An experimental and mechanistic approach of detecting and mapping the phenomena of hydrophobic MgSt nanosmears causing such overall biopharmaceutical performance will be systematically studied. Finally, contribution of electrostatics in the distribution of nanosmears will also be investigated. As a result, this knowledge in nanoscience helps in optimizing the process parameters for product formulation. By using nano-additives, new efficient design processes involving nanoparticles in pharmaceutical systems can be developed for producing best desired products for societal needs in terms of enhanced quality medical products.

2 BACKGROUND

In pharmaceutical industries, additives like flowing agents, lubricants, glidants such as MgSt or CS have been added during the mixing process of pharmaceutical formulations in order to improve the flow properties of the powder mixture [13, 14]. In previous studies, it is shown that the addition of pharmaceutical lubricants and glidants modify the surface characteristics of the particles [15]. Surface properties of particles play a vital role in effecting the bulk properties of powder blend. Surface modification of particles during mixing in
heterogeneous systems can alter the functional properties of the components in the powder blend which in turn affects the behavior of the finished product properties [12]. Thin coatings on particle surfaces enhanced the flow properties of ibuprofen powder particles by altering the surfaces of the ibuprofen particles [16]. Previous studies and works have shown that addition of nanosized particles to pharmaceutical formulations improve the pharmaceutical cohesive powder flowability [17, 18]. However, the effect of coating uniformity, distribution and extent of surface coating on altering the particle-particle interactions in the blend mixture is to be further investigated. Previous works show that in the pharmaceutical blend mixture, approximately 35% area of particle surface gets coated with the additives and this coated area constitutes only about 3% weight of total additive used during blending process and the remaining 97% of total additive is unused [12]. It is interesting that only 3% of total additive added can influence and alter the microscopic blend properties and finished product properties. Hence, there is a technological need to understand the science involving the additives altering the surface characteristics of constituent particles, particle adhesions and particle interactions. Previous studies show that using single lubricant MgSt in pharmaceutical formulations, lubricant concentration and mixing time doesn’t always show considerable effect on drug release rate [19]. However, tablet hardness is found to be increased with the MgSt concentration [20]. In recent works, it is of scientific interest to study the interactions and the combined effects of lubricants (MgSt) and glidants (CS) when used together in the formulation. The mutual interactions of MgSt and CS have significant effect on the formation of MgSt and CS nanosmears in covering the excipient particles [21]. The interactions are depended on order of mixing and concentration of lubricants and glidants in the formulation [21]. The study of the surface topography on particles and the factors affecting the coatings at nanoscale is of high importance in particle processing. In previous studies, evaluation of physiochemical performance of coatings is done by determining hydrophilic or hydrophobic nature of the
coated material where the flow properties of the blend improved with hydrophobicity [22].

Among different coating methods to improve flowability, dry coating is an efficient method involving no binders or solvents. In dry coating, the uniformity of the coating of nanosized silica particles onto the surface of the API or excipient is comparatively better, reducing the cohesion between the particles and thus improving powder flowability [23, 24]. Dry coating of fine, cohesive API powders with fine excipient achieved improved blend properties and high-speed direct compaction tableting [25]. However, in most of the methods adopted for improving the flow properties, problems arise as they require coating uniformity and substantial contact of additives to have an effect on powder properties. The composition of the formulation, shear and strain history applied, and also the mixing order of additives play a critical role in influencing the blend and tablet product properties [26]. In addition to process shear applied, composition of lubricant in the blend mixture also have important role in effecting the blend hydrophobic nature which directly influence the tablet dissolution properties [27]. However, the interactions between the additives, API and excipient particles at nanoscale level is to be investigated. The interactions of additives with the host particles depending on the API and excipient chemistry are unknown. The applied shear environment is critical during the mixing process of pharmaceutical formulations which affects transformations of powder components, formation of smeared layers and the changes in tribological behavior [12]. During the high shear mixing process of pharmaceutical formulations, the lubricants and glidants get coated in the form of thin nanolayers on the surface of excipient and API [12]. The distribution of these nanolayer deposits alter the surface characteristics and particle-particle interactions affecting the material response of powder blend and tablet product performance [12]. The investigation on the rate of nanosmearing on the particle surfaces and studying its dependency on various factors gives a better understanding on the role of nanolayers in macroscopic particulate systems.
Previous studies showed that the adhesion between the particle surfaces depends on the properties of coating components [28] and the mechanical engagement of particles in the rough surfaces [29]. It was also shown that the distribution of coatings of MgSt and CS on particle surfaces and also their concentration has effect on tableting properties of pharmaceutical excipients [30, 31]. However, the effect of nanocoating uniformity on the blend behavior at macro scale is to be further investigated. Mostly all the pharmaceutical formulations require micronized drug particles which have large surface areas to increase bioavailability in the body. In general, micronized particles are greatly affected by electrostatic and Van der Waals forces [32] which in turn increases the cohesive nature of the drug particles. As a result, drug particles are prone to form agglomerates adversely affecting the content uniformity [33] and this causes difficulties in handling processes and in their application. In previous studies, product dissolution differences are caused mainly because of hydrophobicity of API and excipient material [34]. The type of shear mixer used for mixing process of formulation also affects the drug dissolution [35]. Depending on blend composition, shear conditions and also lubrication time have an effect on the drug dissolution [36]. During the powder handling processes, electrostatic charging of particles results in several problems such as unwanted agglomeration, segregation [37], increased drug-carrier adhesion [38], powder ignition [39] which severely affect the operations carried out mainly in pharmaceutical industries where sensitive and fine powders are dealt in processing. As a result, pharmaceutical blend homogeneity, content uniformity, free flowability would be difficult to achieve which give undesired and inconsistent product properties. Hence, the control of electrostatic charge generation in powder particles is of much needed area of scientific investigation. Using static eliminator, the flow properties of pharmaceutical powders can be improved without additives added [10]. In the presence of lubricants and glidants, static elimination for improving flow properties of the powder mixture is negligible [10]. Therefore, it is interesting to investigate the mechanism of additives involved
in improving the flow properties is either by reduction in friction between powder particles or mitigating the tribocharging between particles during flow. Using fine particles in mixture of materials effectively reduce the net charge produced during powder handling operations subsequently avoiding the particle agglomerations and segregations [40].

Hence, research work on quantifying the rate of nanosmearing, particulate level interactions, and surface chemistry at nanoscale is of acclaimed importance for the benefit of many pharmaceutical manufacturing processes. It is important to note that the adhesion properties between the additives, API and excipients have a major influence on tablet thickness, hardness and drug dissolution. Several studies [4, 14-17] are made on the surface chemistry of powder particles but the conceptual establishment of relation between the nanolayer coatings on particle surfaces and microscopic blend properties has to be developed. This knowledge of nanoscience is useful to design the best parameters for processing the formulations and helps to optimize the production process resulting in good yield and quality of products.

3 CONCEPT OF RESEARCH AND GENERAL IDEA

Depending upon the shear applied, compressive stresses and local chemistry, lubricants and glidants in the form of thin nanolayers were smeared onto the surface of the larger particles of API and excipient. This phenomenon of formation of thin nanolayers at particle level was termed as nanosmearing. In this study, the rate and % extent of nanosmearing of the pharmaceutical hydrophobic lubricant (MgSt) on microscopic API (APAP) particle surfaces were investigated with respect to electrostatics under high shear mixing conditions. The rate of formation of these nanosmears, extent of nanosmearing and distribution of nanosmears were quantified on multiple API particles with respect to the electrostatics and applied high shear conditions. In addition, the extent and orientations of hydrophobic functional groups of
lubricant smeared onto the API particle surfaces were investigated. Samples of pharmaceutical formulations consisting of API (Acetaminophen), excipient (Lactose) and lubricant (MgSt) were prepared and subjected to different high shear mixing conditions in a v-blender for a definite interval of time. The high sheared blend samples, collected from the v-blender, were initially tested using Gravitational Displacement Rheometer (GDR) and then tested under Raman Spectroscopy Mapping (RSM). Using GDR equipment, flow and electrical properties of the high sheared blends were calculated as the powder blend flows in the tumbling cylinder. Using RSM, the % extent and distribution of the nanosmeared areas of hydrophobic lubricant (MgSt) on multiple APAP particle surfaces were analyzed. With the help of RSM, the hydrophobic groups were detected and confirmed on the surface coating by which the physicochemical nature of the nanosmeared areas on the particle surfaces was identified. This gave a better understanding of the interactions of all the components with each other occurring at particle-scale level. With the help of Image-J Histogram analysis program, % nanosmeared areas of lubricant on particle surfaces were calculated using the Raman mapping images produced from RSM. With the proposed approach, the rate and % extent of nanosmearing were quantified with electrostatics and the process shear applied. Nanoscale properties like % extent of nanosmearing, their hydrophobic groups orientation in affecting the overall blend behavior, content uniformity and homogeneity of blend were quantified with respect to electrostatics and applied process shear. In our previous studies [12, 21, 26, 27], the rate of nanosmearing and the extent of nanosmearing with process shear was evaluated only on a few randomly selected particle surfaces. In the proposed research, the study was extended to investigate the nanosmearing averaging on multiple particle surfaces with process shear and electrostatics for better understanding of nanosmearing phenomena on bulk scale manufacturing of industrial pharmaceutical blends.
4 EXPERIMENTAL METHODOLOGY

4.1 Materials Required and Sample Preparation

In the first stage of experimental research, two sets of pharmaceutical blends were prepared by mixing fast flo lactose (Foremost Farms, particle size—90 μ) as excipient material, micronized acetaminophen (N-Acetyl-Para-Amino-Phenol (APAP), particle size—15 μ) as an Active Pharmaceutical Ingredient (API) and hydrophobic Magnesium Stearate (MgSt) (Mallenkrodt, particle size—38 μ) as a lubricant at two different shear mixing conditions in a v-blender. The resulting single pharmaceutical formulation preblend consists of 90% excipient, 9% APAP and 1% MgSt by weight. Using this preblend, two sets of blends B1 and B2 were prepared by varying the process shear conditions in the v-blender. The required pharmaceutical blends were mixed under high shear mixing conditions in a v-blender operating with same shell speed of 15 Revolutions Per Minute (rpm) and intensifier bar speed at 100 and 500 rpm respectively for B1 and B2 blends for a time duration of 20 minutes. Two blends exposed to two different process shear conditions were produced. Approximately 4 pounds of each sheared blend sample was prepared from the v-blender for sufficient sample quantity required to perform experimental tests analysis. In the second stage, the high sheared blend samples with different shear history, collected from the v-blender, were tested in Gravitational Displacement Rheometer (GDR) for their flow properties in terms of Flow Index (FI) and % dilation measured in a tumbling cylinder. The electrical properties in terms of electrostatic charge generation during mixing and flow of the blend samples inside the tumbling cylinder was also measured. Then the high sheared samples were tested under Raman Spectroscopy Mapping (RSM) for % extent and distributions of nanosmears and analyzed for physicochemical nature of the nanocoating microstructures of hydrophobic lubricant (MgSt) on multiple API particle surfaces with respect to applied process shear and electrostatics. RSM was used to investigate
the hydrophobic groups of lubricant (MgSt) and their orientations on the surface coating. Finally, a new methodology was developed to quantify the rate and extent of nanosmearing phenomena with respect to applied process shear and electrostatics on bulk scale.

4.2 Experimental Methods

4.2.1 Gravitational Displacement Rheometer

The flow properties of the high sheared pharmaceutical blends were measured in terms of Flow Index (FI) and % dilation under dynamic density conditions using the Gravitational Displacement Rheometer (GDR) [9, 41]. In this method, the powder blend collected from the v-blender was filled up to 40% volume of the cylinder which is rotated at speeds of 5, 10, 15, 20 and 25 rpm on a platform equipped with load cell and corresponding FI and % dilation were captured from the GDR screen as shown in Figure 1. In addition to flow properties, the powder blends were also tested for electrostatic charge generation during the flow of powder inside the tumbling cylinder. To detect electrostatic charge generations, the blend sample was filled to half of the cylinder volume and a thin long aluminium wire was inserted through the holes drilled at the center of the cylinder faces. One end of the wire facing the GDR camera was connected to the positive probe of the multimetre and the other end of the wire was left free. The negative probe of the multimetre was grounded and this instrument was used to record the Direct Current (DC) voltage variations as the powder flows in the tumbling cylinder. Cylinder half filled with the powder blend was rotated at speeds of 2, 4, 6 and 8 rpm for a duration of 20 minutes at each speed and then after 20 minutes correspondingly the multimetre DC voltage digital readings, FI and the load cell variations from the GDR screen were captured for a duration of 2 minutes. With this method, contribution of electrostatics for cohesion of the powder during flow and mixing were investigated. Finally, we intend to study the contributing
factors to the magnitude of force acting on the load cell and the role of electrostatic charge
distribution on the vertical force acting on the load cell.

![GDR equipment setup](image)

![Load cell reading](image)

![Flow index and dilation measurements](image)

![Powder bed flowing inside tumbling cylinder](image)

Figure 1. (a) GDR equipment setup (b) load cell reading (c) flow index and dilation
measurements (d) powder bed flowing inside tumbling cylinder

### 4.2.2 Raman Spectroscopy Mapping

Raman Spectroscopy Mapping (RSM) gives fingerprint likewise information about the
vibrational, rotational frequency modes of the system which is used as a means of identifying
different molecules. In this method, a small portion of the sheared blend sample was collected
and placed into the specimen press holder fitted with Barium Fluoride (BaF₂) window glass.
This window glass was used to create even and flat surface for the portion of the sample
exposed for scanning. All blend samples were analyzed using Renishaw inVia Raman
Microscope system. For experimentation, red laser of 633 nm edge excitation wavelength at a
grating of 1800 grooves/mm (visible) was used. A long working distance 20x microscope
objective lens, 5 mW of laser power and 10 seconds exposure time with 4 accumulations were
selected for all the experimental scans on APAP particle surfaces. Renishaw’s Windows-based
Raman Environment (WiRE) software was used to process and analyze the Raman data. After
observing the Raman spectral lines obtained for individual pure components in the blend, an optimum wave number range of 2800-3200 cm\(^{-1}\) was selected. The APAP particles in the blend sample were exposed to focused beam of red laser. The photons from the laser beam cause molecular vibrations and interacts with the chemical bonds of the molecule resulting in the emissions of inelastic scattered photons or radiations from the sample which are unique for respective molecules. The nanosmeared APAP particles in the blend sample when analyzed with RSM, the vibration frequencies of methyl groups (-CH\(_2\)-) of hydrophobic lubricant (MgSt) were captured. With the Raman spectral lines obtained as shown in Figure 2, molecular mapping of the MgSt nanosmears on sheared APAP particle surfaces was performed to determine and quantify the extent of hydrophobic groups and their orientations. With the Raman mapping images, using ImageJ Histogram, % nanosmeared area and distribution patterns of smeared nanolayers of MgSt on the surface of high sheared API particles were quantified as a function of applied process shear and electrostatics. Thus, a new methodology was developed to quantify the % nanosmeared areas of additives on multiple particle surfaces.

![Raman Spectroscopy Mapping](image)

Figure 2. Methodology of Raman Spectroscopy Mapping
5 OVERVIEW OF RESEARCH PROJECT WORK

The overview of the project work is shown in Figure 3 in the form of a flow chart. The objective of the research is to quantify the nanosmearing of additive functional groups on high sheared pharmaceutical blends with respect to applied process shear and electrostatics. A pharmaceutical formulation consisting of 9% Acetaminophen (API), 90% fast flow lactose (excipient) and 1% hydrophobic MgSt (lubricant) by weight was selected. Using this pharmaceutical formulation, two blends B1 and B2 were prepared by varying the applied process shear rate in the v-blender. Both the blends (B1 and B2) were mixed in the v-blender for a duration of 20 minutes at the same shell speed of 15 rpm and with intensifier bar speeds of 100 rpm for blend (B1) and 500 rpm for blend (B2). The high sheared blend samples, obtained from the v-blender, were tested using Gravitational Displacement Rheometer (GDR) for flow and electrical properties. The hydrophobic functional groups of MgSt on APAP particle surfaces were detected and confirmed using Raman Spectroscopy Mapping (RSM). Also, the nanosmeared MgSt image mapping on APAP particle surface was performed using RSM. The MgSt mapping images from Raman on multiple APAP particles were then analyzed using Image-J Histogram with ROI (Region of Interest) manager tool and % nanosmeared area of MgSt on multiple APAP particle surfaces was quantified with respect to applied process shear and electrostatics. From the obtained results, a direct correlation between powder electrostatics and the nanosmeared distributions was found. Also, the effect of applied process shear during mixing on the % extent of nanosmeared area and consequent effect on the powder flowability was determined. In the future work, pharmaceutical blends exposed to multiple shear mixing conditions along with varying order of mixing of additives and additives' concentration are to be tested. Finally, the interaction phenomena across multi-scales must be studied and addressed.
To quantify electrostatic nanosmearing of additive functional groups on high sheared pharmaceutical blends

**Pharmaceutical formulations:**
- API - APAP,
- Excipient - Cellulose/Lactose,
- Lubricant – MgSt, Glidant - CS

**API (9%) + Excipient (90%) + MgSt (1%)**

**Shear-1** 100 rpm

- Electrostatics
  - Multimetre

**Shear-2** 500 rpm

- Flow
  - GDR

- Detection of Functional Groups
  - RAMAN

- Mapping
  - RAMAN

- % Nanosmeared area
  - Image-J Histogram

**Future Work**

**Scientific Contribution**

**Conclusions**

Figure 3. Overview of research project work
6 RESULTS AND DISCUSSIONS

In the first stage of experimental protocol, electrostatic charge generation was captured as the powder flows in the tumbling cylinder during mixing. The GDR method described in section 4.2.1 was performed at three different conditions. Initially, the experiment was performed using the empty cylinder without including powder material. In the second condition, fast flo lactose powder (Foremost Farms, particle size–90 μ), filled to half of cylinder’s volume, was used for the experimental run. In the third condition, the experiment was done using cohesive micronized acetaminophen powder (N-Acetyl-Para-Amino-Phenol (APAP), particle size–15 μ) filled to half of cylinder’s volume. The experimental runs, to detect electrostatic charge generation, for all the three conditions were performed at low rotational speeds of 2, 4, 6 and 8 rpm.

6.1 Electrostatic Sensing Using Empty Cylinder

In the first stage, with empty cylinder, corresponding DC voltage fluctuations were captured from the multimetre instrument as shown in Figure 4. We observed that the DC voltage varied continuously in the region of –3 mV to +3 mV with time. The variations of the DC voltage readings were captured due to the interactions at the at the insertion points with the powder particles. In order to eliminate the element of vibrations caused due to the rotation of the cylinder, we had performed the experiments at very low speeds (below 10 rpm). A normal operation speed of the rheometer goes until 30 rpm. Since the mechanical forces are expected to be dominant at higher speeds, care was taken in this experiment to capture the DC voltage measurements due to charge generation at lower speeds. Figure 5 presents the variation of DC voltage peak intensity with time at different selected speeds of 2, 4, 6 and 8 rpm using an empty cylinder. From Figure 5, we can see that the DC voltage peak intensities increased with a
corresponding increase in cylinder rotational speed until 6 rpm and then remained stable beyond 6 rpm. This can be partially attributed to the increase of friction of powder particles and vibrations with the cylinder caused at these relative speeds of 6 and 8 rpm.

**Figure 4.** DC voltage fluctuations using empty cylinder at rotational speeds of 2, 4, 6 and 8 rpm in a time interval of 2 minutes

![DC Voltage Fluctuations](image)

**Figure 5.** DC voltage peak intensity using empty cylinder at rotational speeds of 2, 4, 6 and 8 rpm in a time interval of 2 minutes

![DC Voltage Peak Intensity](image)
6.2 Electrostatic Sensing Using Free Flo Lactose

In the second stage, GDR method described in section 4.2.1 was performed using cylinder filled, half to its volume, with fast flo lactose powder material. DC voltage fluctuations were observed in the multimetre as the powder flows in the tumbling cylinder as shown in Figure 6. Simultaneously the Flow Index (FI) and load cell variations were also captured at each rotational speed. From Figure 6, corresponding to the selected rotational cylinder speeds, we can see that DC voltage varies continuously in the region of –30 mV to +60 mV with time. It is interesting to observe that there is a considerable increase in the DC voltage amplitude obtained using lactose half-filled cylinder (Figure 6) compared with DC voltage amplitude obtained using empty cylinder (Figure 4). The results suggest that the electrostatic charge generated between the particles in the granular flow increased the DC voltage amplitude.

![DC voltage fluctuations using half-filled lactose cylinder at rotational speeds of 2, 4, 6 and 8 rpm in a time interval of 2 minutes](image)

From the data in Figure 7, it is interesting to note that the FI of the lactose powder decreased with speed till 6 rpm and then increased beyond 6 rpm.
Figure 7: Flow index using half-filled lactose cylinder at rotational speeds of 2, 4, 6 and 8 rpm.

**Figure 8** represents the variation of DC voltage peak intensities with time at different selected rotational speeds of 2, 4, 6 and 8 rpm using lactose half-filled cylinder in comparison with observations made using an empty cylinder. From **Figure 8**, we can see that the DC voltage peak intensity increased with increase in cylinder rotational speed in both cases of lactose half-filled and empty cylinder. Unlike the relatively low DC voltage readings observed using empty cylinder, which were solely dependent on wire friction with cylinder, various rotational vibrations and disturbances, it appears from the data that the relatively high DC voltage readings with lactose half-filled cylinder was mainly due to the particle interactions with the wire. This serves as a proof of concept for the detection of the electrostatic charge generation as the powder flows in the tumbling cylinder. A further improvement in the methodology to quantify the overall distribution of electrostatic charge accumulation and dissipation between the particles in the granular flow and mixing, is needed.
Figure 8. DC voltage peak intensity using half-filled lactose cylinder and empty cylinder at rotational speeds of 2, 4, 6 and 8 rpm in a time duration of 2 minutes

6.3 DC Voltage Peak Intensity and Voltage Spike Frequency

From the DC voltage data collected using lactose half-filled cylinder, we tried to further examine the effect of cylinder rotational speed on the observed DC voltage spikes. Figure 9 shows the relationship between the number of DC voltage spikes obtained and speeds of the rotating cylinder. Results show that the number of DC voltage spikes produced increased with an increase in the rotational speed of the cylinder. During the granular flow and mixing, the interparticle interactions due to multiple components and multiple geometries are expected to result in the electrostatic charge accumulation and dissipation within the powder bed. The results showed that with an increase in the rotational speed, the number of voltage spikes increased. Consequently, the increase in the frequency of voltage fluctuations can be attributed to the possible rapid increase in shear rate, which in turn increased inter-particle interactions.
Figure 9. Effect of rotational speed on the number of DC voltage spikes obtained using half-filled lactose cylinder in a time duration of 2 minutes.

Figure 10 shows the relation of the average DC voltage spike intensity with respect to the rotational speed of the tumbling cylinder. From Figure 10, it can be seen that the average DC voltage peak intensity increased with an increase in the rotational speed of the cylinder. The results indicated that the amount of electrostatic charge generation increased with an increase in speed of mixing. This can be related to the increase in powder flow and simultaneous interaction between powder particles resulting in increased charge generation and dissipation. However, such trend was observed at periodic intervals as the cylinder kept tumbling. It should be noted that the DC voltage fluctuations are significantly influenced by the speed of the rotation. It was observed that the above phenomenon continued as long as the powder flow was a function of rotational speed. Whether or not the charge accumulation continued as the powder was consolidated remained to be a point of interest and will be explored in our next stage of work.
Figure 10. Effect of rotational speed on average DC voltage spike intensity using half-filled lactose cylinder in a time duration of 2 minutes

6.4 Electrostatic Sensing Using Cohesive APAP

In the third stage, GDR method described in section 4.2.1 was performed using a cohesive APAP powder material, filled to half of cylinder’s volume. In this case, DC voltage peak intensities were recorded from the multimetre as the powder flows in the tumbling cylinder. Figure 11 represents the variation of DC voltage peak intensities with time at selected rotational speeds of 2, 4, 6 and 8 rpm using APAP half-filled cylinder in comparison with that of empty cylinder. From Figure 11, it is interesting to observe that the DC voltage peak intensity continuously decreased with increase in cylinder rotational speed whereas the opposite effect was observed in the case of free-flowing lactose powder as shown in Figure 8. This can be attributed to the sticking of APAP powder particles to the walls of the cylinder during the experimental run and as a result powder particles were inhibited to generate increasing electrostatic charges with increase in speed of cylinder. Due to high cohesive nature,
APAP powder particles also formed agglomerates of larger particles which then flowed as individual particles inside the tumbling cylinder and thus reducing the electrostatic charge generation with rotational speed. From the data in Figure 11, it was observed that the DC voltage peak intensities at 6 and 8 rpm are similar and stable without any significant difference. This can be possibly due to APAP powder reaching the consolidated state at faster rate beyond 6 rpm resulting in stable DC voltage peak intensity output.

![Figure 11](image-url)  
Figure 11. DC voltage peak intensity using half-filled APAP cylinder and empty cylinder at rotational speeds of 2, 4, 6 and 8 rpm in a time duration of 2 minutes

### 6.5 Comparison of Electrostatics Between Free Flo Lactose and Cohesive APAP

Figure 12 shows the comparison of variations in DC voltage peak intensity with time obtained using empty cylinder, half-filled lactose cylinder and half-filled APAP cylinder at the lowest rotational speed of 2 rpm. Comparing the results in Figure 12, it was observed that the DC voltage peak intensity was minimum in the case of empty cylinder indicating relatively
very small contribution of mechanical disturbances to electrostatic charge generation. At this rotational speed of 2 rpm, it was seen that the DC voltage peak intensity of cohesive APAP powder was significantly greater than that of free flowing lactose powder. This results showed that electrostatic charge generation had direct correlation with cohesion of powders.

![Figure 12](image)

Figure 12. Comparison of DC voltage peak intensity using empty cylinder, half-filled lactose and half-filled APAP cylinder at rotational speed of 2 rpm in a time duration of 2 minutes

Using the DC voltage peak intensity data collected using lactose half-filled cylinder and APAP half-filled cylinder, comparisons were made in terms of number of DC voltage spikes and average DC voltage peak intensity with the effect of rotational speed. Figure 13 shows a comparison of the number of DC voltage spikes obtained with increasing speeds of the rotating cylinder for free-flowing lactose and cohesive APAP powder. In both cases, it was observed that the number of DC voltage spikes increased with increase in rotational speed of the cylinder and also DC voltage spikes are relatively same in number at given rotational speed. From the results, it was evident that the increased number of interparticle interactions resulting
in increased DC voltage spike frequency is mainly dependent on the external shear applied in the form of rotational speed and least dependent on the type of powder material.

![Graph](image_url)

**Figure 13.** Comparison of number of DC voltage spikes using half-filled lactose and half-filled APAP cylinder in a time duration of 2 minutes

**Figure 14** shows a comparison of the average DC voltage spike intensity with increasing rotational speed of the cylinder for free-flowing lactose and cohesive APAP powder. From **Figure 14**, results show that with increase in rotational speed of the cylinder, the average DC voltage peak intensity was increased for free-flowing lactose but it was decreased for cohesive APAP. It should be noted that, in both cases, the DC voltage peak intensities are significantly influenced by the rotational speed of cylinder.

Further analysis was made to observe the change in the trend of DC voltage peak intensity with time considering a duration of 20 minutes. Using GDR cylinder, half-filled with cohesive APAP powder, the voltage peak intensities were captured, from the time the cylinder starts rotating to a time duration of 20 minutes, at a rotational speed of 4 rpm as shown in **Figure 15**.
Figure 14. Comparison of average DC voltage spike intensity using half-filled lactose and half-filled APAP cylinder in a time duration of 2 minutes.

From Figure 15, initially it was observed that the voltage peak intensity is very high of about 135 mV and then subsequently the voltage peak intensity dropped to nearly 60 mV with
time. After 15 minutes, voltage peak intensity further decreased to 40 mV and from then the variations in voltage peak intensities were minimum and stable indicating that the powder had reached consolidated state. At the starting stage, cohesive powder showed greater electrostatic charge generation. But the drop in voltage readings, with increasing time, was possibly due to the formation of agglomerates and powder particles sticking to the cylinder walls because of high cohesion resulting in the decrease of electrostatic charge generation. The results suggest that cohesion played a key role in affecting the electrostastics during powder flow and mixing.

6.6 Correlation of Electrostatics With Powder Flow

Figure 16 shows the variations of load cell readings captured from the GDR screen compared with the voltage fluctuations observed from the multimeter readings using the lactose half-filled cylinder at different speeds. The peaks in the load cell readings are relatively in synchronization with the voltage spikes obtained in multimeter readings at respective rotational speeds. It should be noted that the electrical output from the load cell is due to the vertical forces of powder particles acting on the load cell. From the trends observed in Figure 16 which were similar to the that of the load cell readings it appears that the electrostatic charge accumulation and dissipation during mixing can be one of the contributing factors to the magnitude of forces acting on the load cell. However, further investigation was carried out (described in the next section) to quantify the extent to which electrostatic distribution has an effect on the granular flow in terms of over-lubrication and under-lubrication affecting the overall powder flow. Since electrostatic charge is one of the principal factors in making the particles agglomerate, the resultant behavior of particle friction potentially caused due to rolling and static friction affecting the lubricant distribution on surrounding micro particles, is of interest in this study. In addition, such behavior is expected to adversely impact the content uniformity of active ingredient.
Figure 16. Load cell variations at (a) 2 (c) 4 (e) 6 (g) 8 rpm and the DC voltage variations using half-filled lactose cylinder at (b) 2 (d) 4 (f) 6 (h) 8 rpm in a time duration of 2 minutes.
Although lubricants and glidants are widely used to mitigate the problem due to charge generation, their role is surprisingly limited to the ability to coat the excipient or active ingredient particle surfaces. Electrostatic charge is one such phenomenon that is believed to affect the ability of the lubricant and glidant to coat on surrounding powder particles. Hence, in this study, we systematically investigated the principal cause of nanosmearing of lubricant on surrounding powder particles, with electrostatics of particles during mixing being one of the major contributing factors in determining surface energy of inter-particle interactions which in turn can determine the extent and rate of nanosmearing. The focus of this study therefore is to experimentally investigate the link between powder charge and its ability to determine the extent of rate of nanosmearing during high shear mixing of pharmaceutical blends.

6.7 Raman Mapping on APAP Particle Surface

In the second stage of the research, a new methodology was developed to quantify the rate and extent of nanosmearing distribution of hydrophobic functional groups of lubricant (MgSt) on multiple APAP particle surfaces. Complete accurate detection of the hydrophobic groups’ coating on a single particle surface was a difficult task and extending the study to investigate the distribution of nanosmears on multiple particle surfaces on bulk scale was challenging. Raman Spectroscopy Mapping (RSM) method was used to confirm and detect the presence of nanosmears of hydrophobic functional groups of MgSt on APAP particle surface and also made an attempt to quantify the % nanosmeared area distributions as a function of applied process shear.

RSM method described in section 4.2.2 was used to test and analyze the surface of APAP particles of two blends B1 and B2, described in section 4.1, for investigating the distribution of nanosmears of MgSt. Initially, the pure components (APAP, lactose and MgSt), used in the preparation of pharmaceutical blends, were tested under RSM method to obtain the
Raman spectral lines which were unique for respective individual pure components as shown in Figure 17. The peak intensities in the spectrum were due to the radiation emissions from molecular vibrations of respective component. From Figure 17, certain peak intensities of the pure component spectral lines were selected such that the peak of one component is distinctive from the rest of the peaks of other components. For APAP component, it was easy to select a distinctive peak but for MgSt component, the peaks were smaller and covered by the spectrum of APAP and lactose as shown in Figure 17. In the wave number range of 2800-3200 cm\(^{-1}\), distinctive peaks could be selected for all the components and this wave number range was selected for further analysis of overall blend particles.

![Figure 17. Raman spectral lines of pure components APAP, lactose and MgSt](image)

For MgSt and APAP components, peaks at wave numbers 2848 cm\(^{-1}\) and 3065 cm\(^{-1}\) were selected respectively. The APAP particle surface from the blend sample when tested under RSM, the resulting Raman spectrum, as shown in Figure 18, would be the combination of spectrums of all components (APAP, lactose and MgSt) present in the blend. The selected distinctive peaks of APAP and MgSt, at wave numbers 2848 cm\(^{-1}\) and 3065 cm\(^{-1}\) respectively, were unique for respective components and by detecting the respective peak of the selected component in the Raman spectrum of blend, we could confirm the presence of that component.
In this research, it is of interest to study the distribution of MgSt nanosmears on APAP particle surface and its consequent effect on the overall critical blend properties. The small portion of the blend sample, placed in the specimen press holder, was observed through Raman microscope system to visually identify the needle shaped APAP particles in the overall blend. It was difficult to visually identify and distinguish the lubricant (MgSt) coatings on the APAP particle surface. Initially, depending on the ‘needle shape’ of the particles, they were assumed to be APAP particles as shown in Figure 19 (a). The surface area of these identified APAP particles was scanned under RSM method, with the conditions described in section 4.2.2. With the help of Raman mapping tool, analysis was performed on the obtained spectral lines. The area under the selected peaks of respective components was calculated and corresponding component mapping was performed on the surface of APAP particles. APAP mapping was done as shown in Figure 19 (b), which is represented in green color. Using this RAMAN mapping and functional group confirmation on APAP particle, we could confirm the needle shaped particle as an APAP particle. In the next step, MgSt mapping was done as shown in Figure 19 (c), which is represented in red color. Thus, the obtained MgSt mapping confirmed the presence of MgSt nanosmears on the APAP particle surface.
Figure 19. Raman image mapping on APAP particle surface (a) APAP particle with no mapping (b) APAP mapping (c) MgSt mapping

6.8 Raman Mapping on Multiple APAP Particles as a Function of Process Shear

Using the Raman mapping image analysis, we extended the study to investigate the extent and distribution of MgSt nanosmears on multiple APAP particle surfaces with respect to process shear. Two blends B1 and B2, prepared at two different shear rates of 100 rpm and 500 rpm, were studied for the uniformity and % extent of nanosmearing of MgSt. From each blend, 20 APAP particles were randomly selected and then each APAP particle surface was scanned and analyzed under Raman mapping method. The Raman mapping images of multiple APAP particles of blend B1 and B2 are shown in Figures 20 and 21 respectively.

Figures 20 and 21 represent the Raman mapping images of MgSt nanosmears (in red color) on multiple APAP particle surfaces. In addition, APAP mapping was also done simultaneously on multiple individual particles (in green color) confirming that the selected particles were indeed APAP particles.
From Figures 20 and 21, it is evident that the distribution of MgSt nanosmears on APAP particle surfaces was non-uniform at both process shear rates of 100 rpm and 500 rpm. In addition, the extent of nanosmearing was not found to be constant on all APAP particles with respect to the shear condition. However, there was a significant change in extent of nanosmearing on APAP particles between the two blends B1 and B2, which were processed at two different shear conditions. The results showed that the applied process shear during mixing of pharmaceutical blends had a significant effect on the nanosmearing of additives. We can now definitively say that the applied process shear is a critical factor during mixing (cannot be ignored) with respect to the uniformity of coating. The most interesting finding in this study arises from the increase in nanosmeared coating area when the applied process shear rate was increased.

Figure 20. Raman image mapping of MgSt nanosmears on multiple APAP particles of the blend 1 at shear rate of 100 rpm
Figure 21. Raman image mapping of MgSt nanosmears on multiple APAP particles of the blend 2 at shear rate of 500 rpm

6.9 Image-J Histogram Analysis of Raman Images of MgSt Mapping on APAP Particles

In this section, Image-J Histogram was used to quantify the % nanosmeared area of MgSt on each APAP particle surface from Raman images. Due to irregular shape of APAP particle, the Raman image scanning performed on the APAP particle surface area also includes the surrounding area material in its vicinity. For accurate results, each Raman image of MgSt mapping was cropped exactly to the shape of APAP particle surface and processed in Image-J Histogram which enhances the quality of MgSt mapping image as shown in Figure 22. The Raman images of MgSt mapping on all APAP particles of both blends B1 and B2 were processed in Image-J Histogram. From Figure 22, the dark colored region was the uncoated
APAP particle surface and the red colored region was MgSt coated area on APAP particle surface. It was clearly observed that the extent of nanosmearing was significantly increased as the shear rate increased from 100 to 500 rpm. Also, the MgSt nanosmears were accumulated at certain regions on APAP particle surface instead of a uniform coating distribution.

Figure 22. Image-J Histogram images of MgSt mapping on APAP particles

6.10 Quantification of % Nanosmeared Area of MgSt on APAP Particle Surface

The MgSt mapping images from Image-J Histogram were analyzed with ROI (Region of Interest) manager tool to calculate the number of pixels of dark colored region (uncoated area of APAP particle) and red colored region (MgSt coated area on APAP particle) to determine the % nanosmeared area of MgSt on APAP particle as shown in Figures 23 and 24. For a selected single APAP particle in each blend, the % nanosmeared area of MgSt was 19.51% and 46.63% at shear rates 100 rpm and 500 rpm respectively. The results show that the % nanosmeared area increased with increase in applied shear in case of single APAP particle.
To study the nanosmearing phenomena on bulk scale, all 40 APAP particles with MgSt mapping from both blends B1 and B2 were analyzed using Image-J Histogram and the resulting % nanosmeared area of MgSt on multiple APAP particle surfaces were calculated as shown in Table 1 and Table 2 at shear rates 100 rpm and 500 rpm respectively.
Table 1. Quantification of % nanosmeared area of MgSt at shear 100 rpm

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<tr>
<th>Particle number</th>
<th>Total area of APAP particle (pixel count)</th>
<th>Uncoated area on APAP particle (pixel count)</th>
<th>Nanosmeared area of MgSt on APAP particle (pixel count)</th>
<th>% Nanosmeared area of MgSt on APAP particle</th>
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**Average % nanosmeared area of MgSt = 22.48**

From the results of Table 1, for the blend B1 at lower shear rate of 100 rpm, the average % nanosmeared area of MgSt on APAP particles was 22.48%. It can be observed that the maximum and minimum % nanosmeared area of MgSt on individual APAP particle was 37% and 13% respectively. Majority of the APAP particles showed % nanosmearing area in the range of 20 – 25%. These results suggest that the % extent of nanosmearing area on all APAP particles is not constant and varies on multiple particles indicating that the smeared coating is an uncontrolled phenomenon.
Table 2. Quantification of % nanosmeared area of MgSt at shear 500 rpm

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<th>Particle number</th>
<th>Total area of APAP particle (pixel count)</th>
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Average % nanosmeared area of MgSt = 41.02

From the results of Table 2, for the blend B2 at higher shear rate of 500 rpm, the average % nanosmeared area of MgSt on APAP particles was 41.02% which was significantly greater than that of 22.48% for blend B1 at 100 rpm. These results show that the applied process shear had significant effect on extent of nanosmearing on multiple particles. The maximum and minimum % nanosmeared area of MgSt on individual APAP particle was found to be 48% and 20% respectively. Majority of the APAP particles showed % nanosmeared area in the range of 43 – 48%.
The results from Table 1 and Table 2, show that the % extent of nanosmearing had direct correlation with the applied process shear. The two blends B1 (at shear rate 100 rpm) and B2 (at shear rate 500 rpm), were tested using the GDR method, described in section 4.2.1, for flow properties. All the results of % nanosmearing area averaging on multiple particles and the dilation of blends B1 and B2 at different shear rates (100 and 500 rpm) were represented in Figure 25.

![Figure 25. % area of nanosmearing and dilation with applied process shear rate](image)

Figure 25. % area of nanosmearing and dilation with applied process shear rate

It was evident that the % nanosmeared area of MgSt on multiple APAP particles increased from 22% to 41% with a simultaneous increase in applied process shear rate from 100 rpm to 500 rpm. The results from GDR showed that the dilation for blend B1 (at shear rate 100 rpm) is relatively greater than the dilation of blend B2 (at shear rate 500 rpm). This indicated that the overall powder flow was improved with an increase in the applied process shear. This can be attributed to the increase in % extent of nanosmearing, with increase in process shear, which in turn reduces the cohesion between particle interactions resulting in the improved blend flow properties. Also, powder electrostatics would be affected causing the
improved overall powder flow. This could be possibly related to the formation of nanosmearing distributions on particle surfaces. Thus, the powder electrostatics had direct correlation with nanosmearing of additives.

The results clearly showed the pattern of nanosmearing distribution on the particle surfaces, which are indeed dependent on the shear conditions. The results also indicate that the coatings cannot be uniform throughout the particle surface making some areas exposed to interact with the surrounding particles resulting in higher surface energies. This can be one of the reasons for the electrostatic charge accumulation due to friction at the uncoated regions. However, the higher the coating area, and more uniform the nanosmeared distribution, lower the electrostatic generation arising from the nanosmeared distribution. This leads to an interesting hypothesis that the thin nanosmeared layers coated on the particle surfaces play a critical role in determining the particle interactions, mainly with respect to the % extent and uniformity of coatings. The results also strongly suggest that no particles can be uniformly and 100% accurately coated. However, all particles are expected to reach a consolidation point during the interaction, and the nanocoatings will be subject to the limit beyond which the coating area is ineffective. It was observed that cohesive blends with higher dilation reached a consolidation stage beyond which the nanosmeared area was ineffective, possibly due to the formation of separate granules during the powder flow. A comprehensive and in-depth analysis on these interactions is a very complex phenomenon, and has to be widely studied, based on the fundamental information gathered from this study. At this point, we can confidently say that the present investigation so far, has established a base pointing the indicators in the direction to follow with respect to the multi-scale or bulk scale manufacturing. A systematic mechanistic approach can further be developed from the information gathered in this study, which not only advances the multi-scale integration of particles, but also minimizes the bulk manufacturing costs, particularly relating to over-lubrication and under-lubrication of MgSt.
A new methodology was developed to confirm and quantify the % nanosmeared area distributions of hydrophobic lubricant (MgSt) on multiple APAP particle surfaces using Raman spectroscopy mapping method. Multiple scanned analysis on several APAP particles of Raman images showed that the nanosmearing distributions on particle surfaces was non-uniform. The % nanosmeared area increased with simultaneous increase in the applied process shear during mixing. This increased % nanosmeared area had direct impact on powder flowability where the dilation of overall blend decreased, indicating improved overall powder blend flowability. We can conclude that the relation between shear rate and nanosmeared area will be helpful in advancing the field of granular mixing, especially involving multi-scale interactions. At the formulation level, optimizing the concentration of additives required to coat the material can be investigated. At bulk manufacturing level, the findings will be useful in developing mechanistic approaches to control over-lubrication and under-lubrication, which are principal causes of product or batch failures. Electrostatic charge accumulation and dissipation was found to be one of the contributing factors to the forces acting on the load cell measurements. The voltage peak intensity increased with increase in speed (shear rate) for free-flowing powders but decreased for cohesive powders. However, cohesive powders exhibited higher voltage peak intensities than free-flowing powders. In pure component powders, both voltage peak intensity and flow properties were found to be correlated. With the direct effect of nanosmeared area on powder flowability, as observed in the findings, it can be confirmed that the powder electrostatics had direct correlation with the nanosmeared distributions. Also, the nanosmearing decreased with increase in cohesion and electrostatics. For cohesive powders, the variations of voltage peak intensity declined and remained stable with increasing time. Thus, electrostatics had consolidated effect as a function of time during powder flow and mixing.
8 FUTURE WORK

Various sets of high sheared pharmaceutical blends of different formulations will be prepared in the v-blender by changing the concentration and order of mixing of MgSt and CS and also varying the API and excipient fraction. The pharmaceutical blends prepared will be categorized mainly into three groups depending on the components present in the blend. The first group will be prepared by mixing API and excipient with only MgSt. The second group will be prepared by mixing API and excipient with only CS. The third group will be prepared by mixing API and excipient with both MgSt and CS. In each group, the concentrations of MgSt and CS will be varied resulting in different formulations. Each pharmaceutical formulation of each group will be prepared by mixing the respective components in v-blender mixer operating at same shell speed of 15 rpm and at multiple different intensifier bar speeds ranging from 100 to 1000 rpm for a duration of definite interval of time. As a result, each formulation consists of additional sets of blends exposed to multiple high shear mixing conditions. The resulting sets of high sheared blend samples will be tested under Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Energy Dispersive X-ray Spectroscopy (EDS), Raman Spectroscopy Mapping (RSM), Biological Stains Method (BSM) and analyzed for nanosmearing distributions. In the next stage of experimental study, the high sheared blends will also be tested in GDR for their flow properties in terms of Flow Index (FI) and dilation measured in a tumbling cylinder. The electrical properties in terms of electrostatic charge generation during mixing and flow of the blend samples inside the tumbling cylinder will also be measured. In addition, the powder hydrophobicity of the sheared blend samples will be analyzed using the Washburn method.

Multiple sets of high sheared pharmaceutical blend samples collected from v-blender will be initially checked under SEM for surface morphology of nanocoated API and excipient particle surfaces with MgSt and CS nanosmears. The high-resolution SEM images of particle
surfaces will be used to analyze the microstructures of nanosmears on particle surfaces. We will then evaluate the size and distribution of the smeared nanolayers of MgSt and CS. From the SEM images, the structures of MgSt nanolayers and CS nanoparticles on the surface of multiple particles will be observed. With the analysis of the SEM images obtained in the future experimentation, the effect of electrostatics on the geometry, uniformity and homogeneity of nanocoatings will be investigated. Therefore, the relations between charge generation and extent of nanosmearing will be established. The high sheared blend samples will also be analyzed by EDS, which is generally coupled to SEM, to study the elemental distribution of nanosmears. EDS mapping of Magnesium (Mg) and Silicon (Si) elements on the surface of multiple particles will be performed by which we will separately identify the areas of MgSt and CS nanosmears on particle surfaces as a set of numerous green and blue colored spots respectively. From the respective EDS images of Mg and Si, we can differentiate the distribution of MgSt and CS components smeared on the surface of particles. Comparing the SEM and EDS images of the smeared surfaces of the particles will then provide the nanosmear distributions of MgSt identified as green regions and CS as blue regions. From these images, we will be able to determine the extent, uniformity and distribution of the surface coating of additives with respect to MgSt and CS.

The uniformity of green regions representing the Mg distribution zones is expected to affect the hydrophobic or hydrophilic nature of the particle surface. The even and uneven distributed Mg green zones result in more hydrophobic and hydrophilic particle nature respectively. The percentage area distribution of nanosmears of MgSt and CS on multiple particle surfaces at bulk scale will be evaluated and quantified as a function of process shear and electrostatics. With respect to the third group blend samples containing both MgSt and CS, nanosmear distributions will be analyzed with different mixing order of the additives along with high process shear. The future research plan is focused on developing the methodology to
study the surface mappings of nanosmearing and quantifying the extent of rate of nanosmearing of additives averaging on multiple high sheared API and excipient particle surfaces with respect to process shear and electrostatics. The objective is to establish the relation between the rate of nanosmearing and electrostatics. It is expected that with an increase in the intensity of process shear, the rate of nanosmearing on multiple particle surfaces will also be increased due to static charge generation. The principal goal of the study is to establish the role of electrostatics on extent of nanosmearing and to study this phenomenon on multiple powder particles which can represent the bulk scale rather than individual particles. The main focus of the future study is to extend the experimental protocol to represent multiple particles.

In our previous works, nanosmearing of MgSt and CS had two different distribution patterns where the smeared MgSt was seen in the form of flakes and smeared CS was seen in the form of independent nanoparticles [12]. The nanosmears of MgSt and CS are of different sizes due to which the surface roughness and adhesion forces between the particle surfaces varied significantly. The smeared areas on particle surface with MgSt nanolayers are smoother whereas the smeared areas with CS nanoparticles are rougher. Using the SEM images, it is difficult to investigate the surface smoothness or roughness. In the future research, we will further analyze the surface texture to understand the variation of nanosmearing geometry causing variation in interaction between particle surfaces due to nanosmearing phenomenon. We will use SEM imaging and EDS patterns together to analyze the surface texture and the distribution patterns of MgSt and CS on the surface of particles. From our previous results, the nanocoatings of additives on particle surfaces is uniform and also non-uniform [12]. Due to the non-uniform smeared areas, the surface energies across the surface area of particle may vary leading to different particle-particle interactions. The major area of interest in our proposed research is to investigate the contribution of electrostatics on nanosmearing of the flowing agents at particle contacts during particle mixing. Overall, with the quantification of
electrostatic charge generation, we propose to address its effect on the formation of nanosmears on API and excipient particle surfaces at bulk scale.

We will also investigate the extent of hydrophilic and hydrophobic groups and their orientations on the surface of high sheared API and excipient particles. Biological Stains Method (BSM) will be using for the first time in particle technology. The chemical compound PDMPO which is 2-(4-Pyridyl)-5-(4-(2-Dimethylaminoethylaminocarbamoyl)Methoxy)Phenyl)Oxazole is a fluorescent dye material which excites under the ultraviolet light with wavelength (\(\lambda\)) of 357 to 377 nm and has a dual emission fluorescence in the blue spectrum with wavelength (\(\lambda\)) of 417 to 483 nm and in the yellow/green spectrum with wavelength (\(\lambda\)) of 490 to 530 nm [42, 43]. PDMPO selectively binds to polymerizing silica and emits an intense fluorescence under ultraviolet light excitation at the depositions of silica [43]. PDMPO is an excellent probe for imaging newly deposited silica in living cells and has been in practice in various silica related disciplines, including biology of living organisms as diatoms, higher plants, clinical research, and chemistry and physics of materials research [43]. Phalloidin is a staining reagent which identifies the methyl groups of MgSt deposited areas on particle surface. In the proposed study, two color image mapping will be attempted using phalloidin for staining hydrophobic areas of MgSt deposits and PDMPO for selectively staining of nanosized silica deposited hydrophilic areas on the surface of high sheared API and excipient particles. With the visual mapping, we attempt to analyze and quantify the extent of the distribution of hydrophobic and hydrophilic areas on high sheared API and excipient particle surfaces with respect to electrostatics of powder particles.

BSM will be used mainly to identify the hydrophilic and hydrophobic areas on the particle surfaces using fluorescent dye materials. This staining method was previously performed on living biological cells and tissues for detection, labeling and tracing the required cell components. In the proposed study, it will be the first time to employ this staining method.
on powder particles to detect the hydrophobic and hydrophilic areas on nanocoated API and excipient particle surfaces. The hydrophobic areas of MgSt deposits will be stained using the staining reagent phalloidin and the hydrophilic areas of silica deposits will be stained using PDMPO fluorescent dye. Overall visual mapping of the distribution of hydrophobic stearate and hydrophilic silica areas on the surface of multiple particles will be obtained in terms of two color stained images. The resulting stained two color imaging will confirm the presence of additive components (MgSt and CS) in the nanosmeared areas and will be used to analyze the extent and uniformity of the distribution of the MgSt and silica nano-deposited areas on the surface of high sheared particles. The distribution of hydrophobic and hydrophilic areas will be quantified with electrostatics of powder particles in the blend. We attempt to study the nanosmearing phenomena and electrostatics affecting the hydrophobic or hydrophilic nature of the particle surfaces and its subsequent effect on the blend behavior and biopharmaceutical performance of finished product.

In the second stage of future research, the objective is to quantify the effect of nanosmearing on critical blend behavior like blend flow properties and electrical properties. The high sheared blend samples collected from the v-blender will be tested in GDR for their granular properties. The flow properties of each high sheared blend sample will be measured in terms of FI and dilation using GDR. The electrical properties in terms of electrostatic charge generation during the powder flow will also be measured. The nanosmears formed on the surface of particles would alter the surface properties and disrupt the particle interactions at contact points leading to the modification of blend properties. With the quantitative analysis of flow properties, the effect of nanocoatings in altering the blend behavior of microscopic particle systems will be confirmed. It is expected that the formation of nanolayers on the particle surfaces would enhance the flow properties of the overall blend resulting in low FI and low dilation measurements. The extent to which the nanosmearing has an enhanced effect on
blend behavior will be investigated to determine the limitations of various factors. Also for the first time, we propose to investigate the role of electrostatics in nanosmearing and address the issue of cohesion during the granular flow and mixing. Finally, we attempt to correlate the rate of nanosmearing phenomena with the critical blend flow properties at micro-scale and investigate the contribution of electrostatics on nanosmearing coating phenomena.

The future research will give us the better understanding of the particle interactions of additives with API and excipient at nanoscale level during the granular mixing processes. The purpose of the research is to establish scientific relation showing the effect of nanoscale properties on the micro-scale blend properties and product performance. The quantification of rate of nanosmearing with respect to electrostatics is of high technological importance to many pharmaceutical industries. This nanoscience knowledge is helpful in developing efficient design processes involving nanoparticles in product formulation and in optimizing the production process to manufacture best quality pharmaceutical products with enhanced biopharmaceutical performance for societal needs.

9 REFERENCES


