

The Effects of Shear on the Flow Properties of Multiple Pharmaceutical Blends

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Abstract

Although most pharmaceutical blends contain some form of lubricant to reduce friction, the adhesive material buildup can cause processing problems. Excessive lubricant can cause the blend to form masses of substance that are difficult for the body to break down. Thus, many attempts have been made to improve the flow of the blend by other means. One such mean is the amount of shear in the process to which the particles are exposed to. Multiple pharmaceutical blends were prepared in a v-blender at different levels of shear strain and shear rate in order to find the optimal combination of these two factors and further determine the effect of shear on the flow properties of pharmaceutical blends. Lubricants and glidants were added to test what percentage of each was necessary to optimize the flow properties of the blends. We performed tests to determine the flow index, bed expansion due to dilation, charge density, and adhered mass of each of the blends. Each test determines the strength of the electrostatic forces that affect the flow properties of the blends and results of these tests were used to find a correlation between these properties and the flow of each of the blends. Through these tests, we found that an increase in the average charge density brought about a corresponding increase in the average dilation of the blend. Differing shear strain and rate led to differing charge density and powder bed expansion. The greater the charge density, the more electrostatic forces are found between powders, the less efficiently it flows. Effects of lubrication are positive and improved flow of the blends. Further research is being conducted at Rutgers to determine the full effect of shear on these blends.

1. Introduction

Throughout the years pharmaceutical developments have enabled everything from large scale victories such as creating a polio vaccine to smaller but equally as important innovations like discovering antibiotics and how to cure a common cold. As time progresses so does the pharmaceutical industry's methods for healing the public. Plants are no longer the primary source of medicine. Top pharmaceutical companies such as Pfizer, Novartis, Wyeth, GlaxoSmith Kline, and Merck manufacture tablets and capsules that serve the same purpose and are easier to digest. Tablets have become a prominent and popular form of medicine. Most people are familiar with the pain relievers, Tylenol and Aspirin, which are

composed of active drug components which are initially prepared as powders. The pharmaceutical industry's main purpose for using powder is due to its ability to flow freely; however, powder may not always flow so easily. This creates a problem for the pharmaceutical industry and therefore more additives go into the blend in order to serve as an aid. Efficiency is crucial in the pharmaceutical industry because it is what enables the latest drugs to become marketable. Therefore the flow properties of powders has become an increasingly popular area of interest in the past several years due to the implications the flow of powders hold in the agricultural, industrial, commercial, and especially in the pharmaceutical. In the chemical industry shear plays an important role in developing dugs that can flow efficiently and not

cause extensive buildup in machines and in the body. In the pharmaceutical industry, the search of new beneficial drugs and their optimization are equally important to drug designers. Adhesive material buildup could lead to severe processing problems. Numerous attempts have been made to enhance the mixing efficiency of the powders in industrial manufacturing and formulations.

2. Background

In the industrial and pharmaceutical processes, extensive inter-particle electrostatic charges have shown to pose a problem in powder transport. Friction between powder and the walls of the equipment being used may lead to agglomeration of the powders. Agglomerates are clumping of the powder into larger particles of the blend, or may be described as non-uniform distribution of the powder. The aim of most drug manufacturers is to maintain content uniformity in the drugs. These agglomerates may later grow larger to cause a severe interference with drug processing. In the context of increased electrostatic forces triboelectrification causes serious problems including explosions in the apparatus being used. It has been studied that static electrification causes charge accumulation in the powders. Parameters leading to these charge accumulations are being studied and shear is amongst the factors that impact the amount of pharmaceutical powders accumulate during their blending. The effects of shear on the pharmaceutical blends will show the impact frictional forces will have in the flow properties of the powders[6]. The goal is to find the powder with the most efficient flow properties. Along with varying amounts of shear applied to the powders, we tested whether the percentage of lubricant used in the blend affected the flow properties. Magnesium stearate acted as the lubricant in the blends prepared. A lubricant acts to cover individual particles in the mixture to decrease the inter-granular friction between particles when they flow past each other. In addition to the lubricants, glidants were used to cover the blends as a whole. They work to serve a similar purpose as to that of the lubricant. Shear is the stress applied parallel or tangential to the side of the particles. To find the optimum

shear that must be used on the pharmaceutical blend, several combinations of shear rate and shear strain are used. Shear rate is the gradient of velocity on flowing powder, or the rate at which shear is applied. In the experiment, shear rate is controlled by the number of revolutions per minute made by the V-blender. Shear strain acts parallel to the face of the particle it is acting on, as compared to the normal force which is applied perpendicularly. It is controlled by the minutes the blends are kept in the blender. The gravitational displacement rheometer is used to measure the flow index of the powder samples. Flow index is the ease at which the powders flow through a system. The GDR (described below) measures the flow index by measuring the change in the center of gravity on the load cell that is used in conjunction with the GDR. A standard for the flow index is set to describe the efficiency of flow in the powders. Other quantities measured in this experiment include charge density, adhered mass, and dilation. The charge density measures the current that passes through each of the blends. Adhered mass measures the charge of the blend which reflects the electrostatic forces present. The greater the electrostatic forces, the greater the density of the blend, which causes cohesiveness to prevent smooth flow in the powders. Through experimentation with multiple blends, we seek to find the best flowing powder.

3. Experimental Setup

Materials

A number of commercially available powders were used to form the two pharmaceutical blends tested. These include acetaminophen (APAP), Avicel 102, Pharmatose, and magnesium stearate. APAP is a typical pharmaceutical ingredient that can be found in drugs such as Tylenol, Panadol, and Liquiprin. It is used as a common analgesic and antipyretic, as a pain relieving and fever reducer. Acetaminophen appears as a white crystalline powder which has a bitter taste. It is soluble in boiling water and in alcohol. Pharmatose is a white, odorless crystalline powder used in tablet production. Avicel 102 is powder that is used to direct compression of the pharmaceutical tablet. This type is specifically used to improve the

flow, compaction, and disintegration properties of the pharmaceutical blends and since it is less sensitive to lubrication it will not work against the activity of the magnesium stearate added to the blend. Magnesium stearate, also known as stearic acid or magnesium octadecanoate acts as the lubricating the system. It reduces the cohesiveness between powder particles by surrounding individual powder particles, although its total effects are dependent upon the concentration of it in the blend. Therefore two sets of blends; each with a different compositional percentage of the lubricant is tested.

- The two sets of experiments are as follows: 3% APAP, 48.7% Avicel 102, 48.7% Pharmatose, and 0.5% MgSt
- 3% APAP, 48.5% Avicel 102, 48.5% Pharmatose, and 1% MgSt

See Figure 1 for their chemical and physical properties. SEM images of the materials not found in this paper may be found in the *Handbook of Pharmaceutical Excipients*.

Similarly, glidants used included Cab-O-Sil and talc. Cab-O-Sil and talc act as anti-adhesive agents and surround the entire blend, not individual particles as does the lubricant.

	Chemical Name	Chemical Formula	Particle Size	Mol. Weight (g/mol)
APAP (acetaminophen)	N-(4-Hydroxyphenyl)acetamide	C ₈ H ₉ NO ₂		151.2
Pharmatose	Lactose monohydrate	C ₁₂ H ₂₂ O ₁₁	100-µm	50.0
Avicel 102	Microcrystalline cellulose		90-µm	200.0
Magnesium Stearate	Magnesium octadecanoate	C ₃₆ H ₇₀ MgO ₄	38-µm	591.3
Carb-O-Sil				
Talc				

Figure 1: List of materials used and their characteristic physical and chemical properties

3% APAP + 45.5% Avicel 102 + 45.5% Pharmatose + 1% MgSt									
Shear Strain (min)	5			10			20		
Shear Rate (rpm)	25	525	1000	25	525	1000	25	525	1000
	S10	S11	S12	S13	S14	S15	S16	S17	S18
<i>Bulk Density</i>									
<i>Tap Density</i>									
<i>Flow Index</i>									
<i>Dilation</i>									
<i>Dynamic Density</i>									
<i>Charge Density</i>									

Figure 2: Data table for blends S10-S18 with their corresponding shear strain and rate applied.

Equipment and Apparatus

The powders were blended in a v-blender as shown in the diagram in Figure 3. Each blend made with a different shear rate and strain was labeled as a powder from S10 through S18. (Figure 2.)

A number of laboratory equipment is used to test the flow properties of the pharmaceutical blends and measure the electrostatic forces between internal molecules. First the gravitational displacement rheometer (GDR) measures the flow index of the powders, or how easily it flows. The GDR works on the basis that when

cohesive powders are tumbled in blenders they exhibit the property of “avalanching flow.” The particles of the powders due to the electrostatic forces between them refuse to separate and flow completely. On the contrary, they may form “slumps”, or localized failures of the powder to flow in an area. A correlation can be made as to the magnitude and frequency of these avalanches and the flow efficiency of the powder. The GDR works on the basis of these avalanches. It is made of a cylinder that is 8 inches in diameter and 10 inches deep made of Plexiglas that allows for the observation of the

avalanching flow (figure 4). The cylinder and its drive mechanism are mounted on a pivoted framework that holds the load cell. The load cell measures the shift in the center of gravity as powder rotates in the cylinder. As rpm (rotations per minute) increase, the size of avalanches also increases due to centrifugal forces. (See figure 3)

For the dilation experiment, a cylinder 8 inches in diameter and 10 inches deep is used, in conjunction with dilation rollers (Lab Mill 3000). A camcorder was used to film the dilation process.

An electrometer was used with a feeder tray to determine the charge density.

Experiments are conducted at room temperature and a constant relative humidity.

4. Method

To measure the flow index, the gravitational displacement rheometer was filled 40%. The cylinder was rotated for five minutes to allow the powder to reach a steady state. Otherwise, the tensile cracking phenomenon exhibited by the powders in the initial stages of the rotation would lead to a discrepancy in the result. Thus high and low frequency noises are cancelled out. The digital output given by the GDR is then converted into

vertical into



Figure 4: Diagram of the V-blender

First, bulk and tap density were measured. Mass and volume were recorded in a 250 mL graduated cylinder. With these data, the bulk density was calculated. Afterward, the powder was tapped on the AutoTap, which significantly reduces the volume of the powder. The tap density was then recorded from this data.

The charge density was then measured. Approximately 100 grams of the pharmaceutical blends were added to the feeder tray, which

a relative flow index number in terms of the standard deviation of the weight signal recorded by the load cell.

The pharmaceutical blends that were tested in this experiment were created by adding the excipients, lubricants, and additives together in a v-blender. Nine blends were created while varying the shear rate (rpm): 25, 525, 1000; the shear strain was set to 5, 10, or 20 minutes.

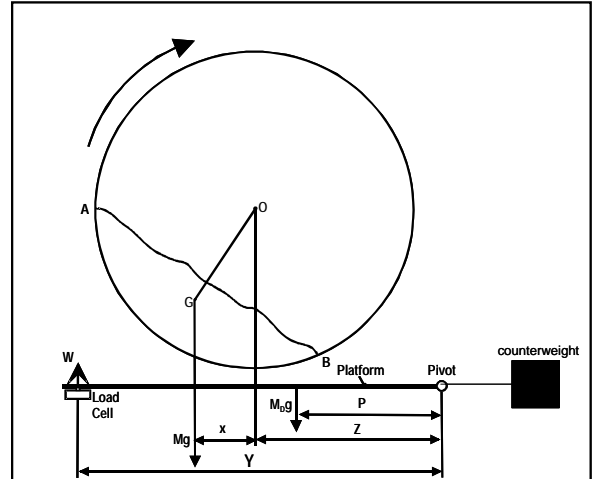


Figure 3: Schematic diagram of how the GDR works.

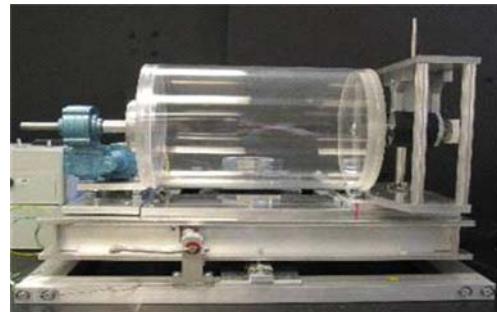


Figure 5: Picture of GDR

allowed the powder to flow into a collecting container. As the powder flowed, the charge of the powder in coulombs was recorded every 5 grams until 100 grams from the electrometer. This process was repeated three times for each blend.



Figure 6: Picture of the charge density apparatus.

The powder was then tested for bed expansion of the powder in the dilation measurement. Equipment, such as the cylinder and measurement tools, was vacuumed clean prior to use in the dilation, to prevent interfering residue of other powders. The blend was massed before placing it into a cylinder. Before putting the cylinder on the dilation roller, an auto-tapper was used to tap the cylinder 500 times obtain its maximum compaction. The cylinder was placed horizontally onto the auto-tapper, and the taps were evenly distributed. The cylinder was then placed on Lab Mill 3000. The rollers and

cylinder were both slightly wiped with water before the cylinder was placed on to reduce the friction between both. A video camcorder was set up to record the dilation trials. Each blend underwent 15 revolutions on the dilation roller. The dilation results were then analyzed in the Adobe Premiere and DilationMeasurer program. The former saves stills from the movie of the dilation (figure 5), which are then transferred over to the later program to compute the volume of the powder bed after every revolution. This can later be compared to the volume of the initial powder bed to determine percentage of bed volume increase:

$$\% \text{ increase in Bed Volume} = \frac{\text{Volume}_{\text{new}} - \text{Volume}_{\text{initial}}}{\text{Volume}_{\text{initial}}}$$

Each experiment was repeated for verification of results.

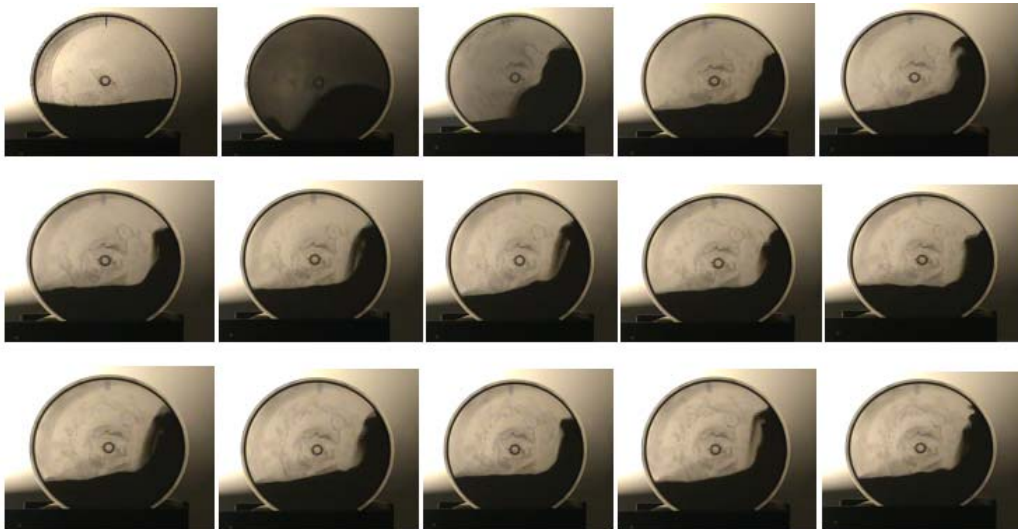


Figure 7: Stills captured from Adobe Premiere after every full revolution. These stills were later analyzed using the Dilation Measurer program to calculate bed expansion.



Figure 8: Rendered images from the DilationMeasurer program.

5. Results

After the results were conducted, it was found that the charge density increased in the first few grams of the powder and later stabilized as shown in figure 7. S16, which corresponds to the powder blended at a shear strain of 5 minutes and at a shear rate of 25 rpm had the highest charge density. The lowest charge density was that of S18 which was blended for 20 minutes at an rpm of 1000. S15 was a blend that also corresponds with a 1000 rpm had a lower charge density. S11 and S17 which have the same rpm of 525 rotations per minute also have similar charge density. From these results it can be analyzed that the charge density of the pharmaceutical blend correlates with the shear rate.

Similarly for the results of the dilation, powders S11 and S17 had similar results and induced the highest dilation results (figure 6). The powder blended at a shear strain of 20 minutes and at a shear rate of 25 rpm (powder S16) and the powder with a shear strain of 5 minutes and 25 rpm (powder 10) had a very similar charge density. Once again the S18 had the most minimal dilation of the group corresponding

with the best flow. For the powders the most minimum average dilation value was 20.24% bed expansion. The highest average dilation value was 28.56% expansion of the S11 sample. The efficiency of the flow as determined by the flow index of the powders showed that the easiest flowing powder was the S18 powder which had a flow index of 28.45. This matches our data obtained from the charge density and dilation results. The plot of average dilation values versus average charge density values in coulombs per gram show a positive correlation if not a linear trend as found in figure 8. Although tap density results were expected to correlate with the dilation data, they did not do so. We expected that as the tap density increased (better compaction of powders, and fewer gaps between particles) the easier the powder flow would be there would not be electrostatic friction creating pores in the powder bed.

Although our correlations were not perfect in the sense we expected them to be, the slightly positive correlation and stabilization of most graphs comes quite close to the expected results for the effect of shear to have some impact on flow properties, i.e. dilation, flow index, and charge density.

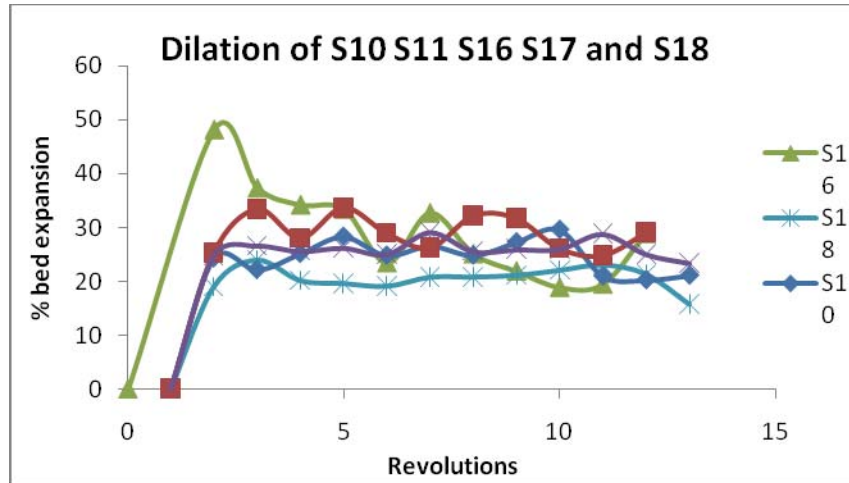


Figure 9: This graph shows the charge density for the S10 through S18 blends.

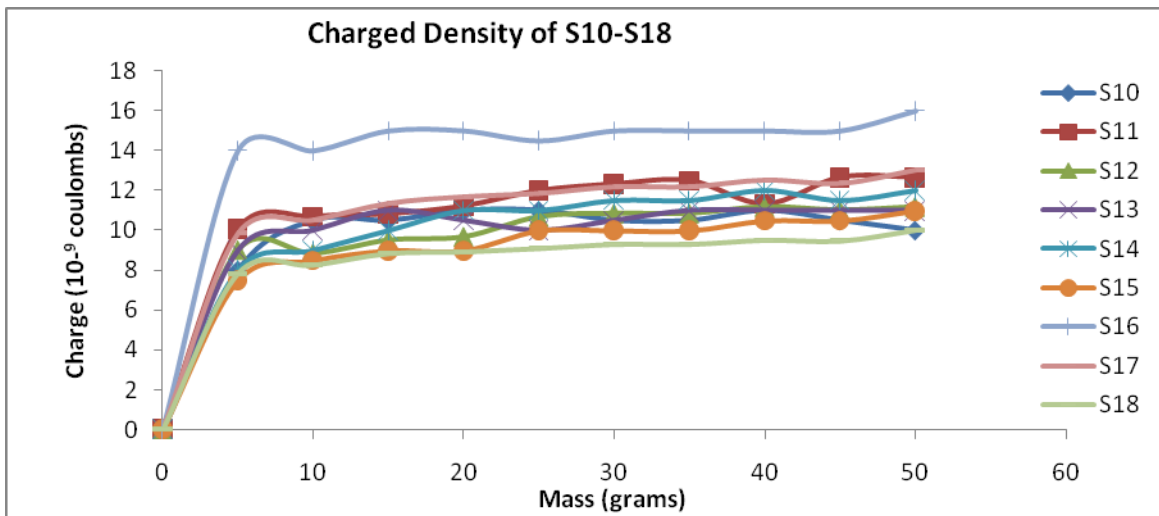


Figure 10: This graph shows the Dilation Results for the S10, S11, S16, S17, and S18 Blends

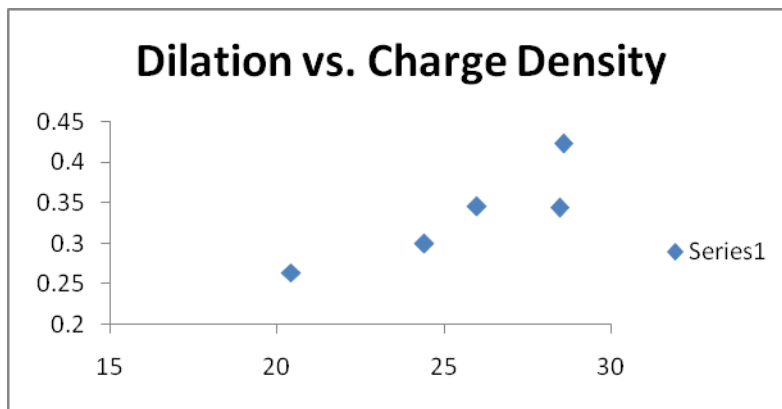


Figure 11: This graph shows a relationship between the dilation results and charge density results.

6. Discussion

In this section, the effects of shear and its role on cohesion properties and other powder properties will be discussed.

6.1 Effects of Shear Rate and Strain on Cohesiveness

The amount of shear is regulated through shear strain and shear rate. This impacts the amount of friction between the wall of the apparatus and the surface of the particles, and also between particles themselves. It was found that the shear rate had more of an impact on the results of the experiments. It was found that the greater the shear rate in rotations per minute the less the

dilation and charge density. Because the particles are moving at such a high speed through the v-blender, their contact with another single particle may be minimal. In the speed in which the individual particles are coming into contact a great enough deformation cannot occur to deform the particle, shift its center of electrostatic forces and change the particle's degree of cohesion. The greater the shear that is applied to the powder particles the less free-flowing they become, and the force applied causes the powder to agglomerate.

6.2 Dilation and Cohesion: A Direct Relation

Cohesion plays a great role in dilation

mechanics. Particles flow as individual grains, continuously down a cascading surface in the absence of cohesion. Therefore dilation is minimal. For the powders used in the experiment, each had a varying degree of cohesiveness due to the amount of shear applied to it. Therefore each varied in the size of the avalanches and expansion of bed volume. Static friction between particles and the dynamic friction of the shear causes the deformation of the particles increasing the porosity of the powder bed, thus volume expansion. Agglomerates may also cause a discrepancy in the dilation results. The interstitial volume between agglomerates is much greater compared to the individual particles due to the greater surface area of the group of particles, causing the bed porosity to increase. As degree of cohesiveness increases so does dilation of that powder.

6.3 Charge Density Shows Direct Correlation with Cohesion

Charge density increases in the powder due to an increase of the electrostatic forces we wish to minimize. Since the electrostatic forces such as Van der Waals forces and dipole-dipole interactions increase, so does the cohesion between particles. These forces cause the particles of the powder to be pushed farther apart. The graphs show that the best flowing powder, the one sheared for 20 minutes at 1000 revolutions per minute had a relatively low charge density.

6.4 Effects of the Initial Deformation of the Powder on Dilation

The powder was allowed 2 revolutions to reach a steady state. A steady state is required because the maximum dilation occurs in the first few revolutions and this may affect the results and calculations in the bed expansion. Powders in this early state may undergo the tensile cracking phenomenon, where powder avalanches continue to grow due to extensive cohesion and then experience a big fall of avalanche where the powder bed seems to crack. In the still, the powder bed takes up a great area, thus should not be considered in the result. The greater the cohesive forces between the particles the more severe the phenomenon. [2]

6.5 Effects of Agglomeration

Agglomeration had an impact on the charge density and the dilation results. Due to the fact that the particles in a several powder blends carried some forms of agglomeration, or little clumps of powder, the charge density and dilation results would come out greater. The powder in these cases were already agglomerated thus they had more electrostatic forces between them, which the electrometer picked up, perhaps skewing the results. On the dilation experiment agglomerates have a greater surface area and are close to spherical in shape therefore they create large pores in the powder bed. Also because they have more electrostatic forces, dilation of the powder bed is greater. Thus this may produce a greater average of the powders.

6.6 Effects of Lubricant and Glidants

Increased concentration of magnesium stearate leads to decreased cohesion of the powder causing them to flow with greater ease and without much resistance. The lubricant magnesium Stearate coats each individual particle. By doing so it smoothes the surface, thus reducing the friction between it and surrounding particles into which it comes into contact with. The addition of the lubricant reduced the number of agglomerates formed in the powder. The glidants, Cab-O-Sil and Talc added to the blend in minimum quantities helps the blend flow through the blender by coating the entire surface of the blend rather than individual particles of powder. This also increases the efficiency of flow in the powder and serves to reduce cohesion. At a greater shear rate and strain, the lubricant can be blended most efficiently.

7. Conclusion

After analyzing the data, we found that an increase in charge density corresponds with an increase in dilation. The greater the charge in the powder, the less efficiently the powder will flow. The aim of this experiment was to find the optimal blend to create an efficiently flowing powder. To do this, we would need to minimize the electrostatic forces between particles of the powder. Changing the shear rate and shear strain

impacts the amount of static friction generated between the particles. Finding the best rate and strain at which the blends can be blended is essential to remove the electrostatic forces and create the best flowing powder. The charge density represented by the electrostatic forces between particles contributes to agglomeration, thus increased the pores in the powder bed, which after some time may lead to extensive buildup in the equipment processing the drug. The shear impacted the particle-particle interactions and the particle-wall interactions, thus deforming the molecules and increasing porosity in the bed. A decrease in charge density and minimal dilation was best to create a better flowing powder. This will help to reduce the greater buildup of small area of the apparatus used to manufacture drugs and decrease the number and size of agglomerates found. The simplicity of the process used to measure dilation, flow index, and charge density shows promising hopes for future progress in this area of research.

8. Related Work

A major part of the work conducted in this area of research has been conducted by the Chemical and Biochemical Engineering sector at Rutgers University, as a subsidiary of pharmaceutical companies such as AstraZeneca and Pfizer, as well as by the Institute of Technology and Engineering at Massey University in New Zealand. It is focused on improving cohesive powder flow through the use of lubricants. Work is being conducted on the computational analysis of determining cohesive powder flow, dilation of cohesive powders, and on the specific properties of avalanches in powder.

In the Avalanching flow of cohesive powders experiment, Fast-Flo lactose, Avicel 102, Avicel 101, and regular lactose were used as powders due to their varied cohesion. Each powder was placed into a cylinder mounted on a load cell. Avalanches occurred as the cylinder began to rotate and the powder bed experienced a shift in the center of gravity. The load cell used the shift in the center of gravity in order to determine its size and displacement. By calculating the percent increase in powder bed volume, it was determined that as dilation

increases, cohesion increases. The results proved that as cohesion increases, the avalanching flow also increases. [1]

The Flow- Induced Dilation of Cohesive Granular Materials experiment further examined the relationship between cohesion and dilation. The same powders used in the previous experiment were placed in a Gravitational Displacement Rheometer, which determined the flow index. The results produced by the GDR corresponded with the Avalanching flow experiment, proving that dilation occurs because of cohesion. The experiment also examined the inefficiency in the flow properties of powders by demonstrating that more cohesive force will produce large pores in the powder bed that affect both uniformity and quality. [2]

A Gravitational Displacement Rheometer was also used in the Experimental/computational approach for examining unconfined cohesive powder flow experiment. In addition to using an actual device to examine flow properties, a computational model was developed to estimate the relationship between inter-particle cohesive strength. By using both the GDR and Simulations, it was determined that increased flow index makes it difficult for powders to flow. [3]

9. Future Work

It should be emphasized that a better understanding of the role of shear in process design and scale-up is long overdue. A fundamental limitation is the lack of well-defined experimental systems for which samples are sheared uniformly at a controlled rate to allow systematic quantification of the effects of shear on blend and tablet properties. The development of such a system is actively under way at various institutions, including Rutgers University. Promising results have been obtained and are currently being checked for reproducibility.

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