

Preventing Pharmaceutical Explosions Through Powder Lubrication: The Effect of Magnesium Stearate on the Flow Properties of Lactose

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Abstract

The pharmaceutical industry requires the use of lubricants to prevent static electric buildup in the cohesive powders that are processed in manufacturing plants. In this report we examine the effects of common lubricant magnesium stearate on two flow properties, flow index and dynamic dilation, of lactose. We conducted two experiments using a gravitational displacement rheometer and a dynamic dilation cylinder. In order to expedite dilation data analysis, we developed an automated program to evaluate the dilation stills. Both experiments showed that increased concentrations of magnesium stearate lead to decreased cohesion of the powder blends.

1. Introduction

Each year millions of tablets, pills, capsules, and other solid forms of medicine are manufactured, packaged, and marketed to the public. Even after years of drug study and development, careful research must be done on the part of pharmaceutical manufacturers to ensure a safe, streamlined process of pill development. Each tablet is composed of several powdered compounds that must not only be mixed in specific concentrations but also must be uniformly distributed throughout each tablet. In addition to the active ingredient, excipients, compounds that act as carrier molecules for the drug molecules, are added to medicinal blends.

Due to the high demand for powders for medicinal use, it is essential that the pharmaceutical industry develop methods of mass-producing powders in an efficient manner. In the manufacturing plants, powder flows through pipes before being blended and pressed into tablets. Some of the most important factors that influence these processes are the flow properties of the powdered mixtures.

One of the main properties of concern to manufacturers is the cohesiveness of the

powder. Within a blended powder, the various compounds demonstrate different levels of intermolecular attraction, ranging from hydrogen bonding to van der Waal forces. These intermolecular forces cause the powders to stick together, and excess amounts of such cohesion can have adverse effects on manufacturing. If a powder is too cohesive, it can clump together as it travels through the pipe. As it flows through the metal pipes, these clumps acquire a static charge. When this clump of powder grows too large, the accumulation of charge can cause an explosion, severely damaging the plant and halting production [9].

For instance, in a resin factory in Taiwan, the friction between dipropyl phenol powder and the storage bag led to a high static electric charge and caused a substantial dust explosion and fire [8].

To prevent incidents of this nature, lubricant excipients are added to powder blends. Lubricants are mixed in to prevent the powders from sticking to the machinery walls. In addition, they decrease the amount of friction between the powders flowing through the pipes. However, a balance must be struck since too much lubricant will increase cohesion between particles and cause over-

compaction and cracking during tablet formation. Different types of lubricants are utilized depending on the particular mixture.

Also of importance to manufacturers is the distribution of compounds within a powder mixture. Since the powder is separated into distinct tablets to be consumed separately, it is essential that each of the tablets have the same relative concentrations of active ingredient, filler, and lubricant. This means that the powder must be thoroughly blended before tablet production can begin.

NIR spectroscopy is often used to test component distribution within a powder blend. It utilizes the different molecular overtones and combination vibrations of bonds within a compound or mixture. When light waves of the same frequency as bond vibrations are shot at each bond, the light is absorbed and little light is transmitted. Since each bond has a different range of vibration frequencies, the types and amounts of bonds present can be determined based on the amount of light that is transmitted through the compound. This allows researchers to ascertain the concentration of various components within a mixture.

Most research in this area is focused on determining to what extent a particular powder mixture requires lubricant to enhance its flow properties. These results can lead to an optimal proportionality between ingredients for product efficacy and streamlined production.

2. Experimental Data Analysis

We examined the effect of the lubricant magnesium stearate on the flow properties of lactose, a common component in pharmaceutical powders. Magnesium stearate is a common lubricant used in the pharmaceutical industry to reduce cohesion between powder particles. However, the effectiveness of the magnesium stearate

depends both on the material it is blended with and on its concentration within the total blend.

We created and analyzed two blends of powders; one was two percent magnesium stearate in lactose; the other was eight percent magnesium stearate in lactose. We tested the distribution of the magnesium stearate in each blend using NIR spectroscopy, and we tested and compared two flow properties: flow index and dynamic dilation.

2.1. Creation of Powder

The first step in determining the optimum amount of lubricant is to create multiple samples of powder with variable compositions. It is also essential that the ingredients of each sample be evenly distributed. In order to evenly mix powders, we used a v-blender, a type of tumbling mixer. This blender consists of a V-shaped container rotating about a horizontal axis, in which gravity helps mix the sample. In order to optimize particle flow, the blender is generally filled to less than forty percent. To this effect, we mixed four pounds of each of the two samples we were studying. Since the shape of the blender aided the mixing of the substance, a relatively low rotational speed was chosen (20 rpm), and the mixtures were only mixed for fifteen minutes each.

Some experimental error may have been introduced in this stage due to problems with the v-blender used. The blender was cracked in several places, and despite our best efforts to tape up the cracks and cover the loading holes with Para film under the lids, slight amounts of powder still leaked out during the mixing process. Since thorough mixing is necessary to proper data analysis, error in this stage could be crucial in the later processes. However, large scale metal v-blenders are much more durable, and pharmaceutical manufacturers using such mixers should not experience any such problems.

Especially because of error introduced in blending, we deemed it necessary to test the distribution of lubricant in our samples before conducting further analysis. In order to do this, several phases of the blend were tested using NIR spectroscopy and compared to small mixtures of known lubricant concentrations to determine the composition of the large samples. This was important because even small changes in lubricant presence can make a large difference in powder flow and later in pill production.

2.2 Verification of Distribution

In order to make accurate comparisons, powder blends had to be tested at different lubricant concentrations. These samples were very small in order to prevent major mixing errors within a supposedly “known” sample. We created five gram samples of known concentrations, ranging from one to eighteen percent magnesium stearate. We massed the two powders and mixed them together in small glass vials. Each of these vials was placed on the rapidly vibrating surface of the vortex blender for at least thirty seconds to ensure thorough mixing of the calibration samples. The vortex blender prevented the powder inside the vial from separating by component and also from sticking to the sides of the vial, which can cloud the NIR recording. Ideally, the number of samples used to create a calibration model is near one hundred, but since the lubricant concentrations we were comparing were so far apart, we used fewer samples to formulate the method.

We used the diffuse reflection mode on Thermo Electron Corporation’s Nicolet Antaris Near-IR Analyzer to collect our data. The glass vial was placed directly above the light source, and software called TQ Analyst was used to graph the spectra we collected. Figure 2.2A shows the spectra for the samples we prepared. It is evident that the spectra

shifted slightly based on the concentration of magnesium stearate added to the lactose.

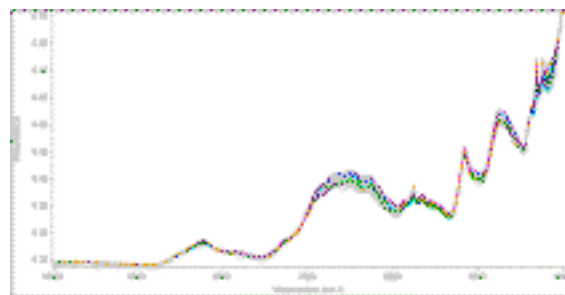


Figure 2.2A The graph shows the absorbance of the sample versus wavenumber of the projected light. Each of the peaks represents the bonds that vibrate at the frequency of the infra-red light shot at the sample. The spectra for various concentrations of magnesium stearate, represented by different colors, deviate slightly from each other at certain peaks.

After the spectral data points are collected, the data was compiled into a calibration model using a program called OMNIC. The program determined which part of the spectra changes with the different concentrations of lubricant. It then eliminated baseline drift in the spectra, using second derivatives of the spectra. A regression equation was then developed based on this data and the known concentrations of magnesium stearate in each sample [3]. Figure 2.2B shows the data points versus the linear regression equation can be seen below.

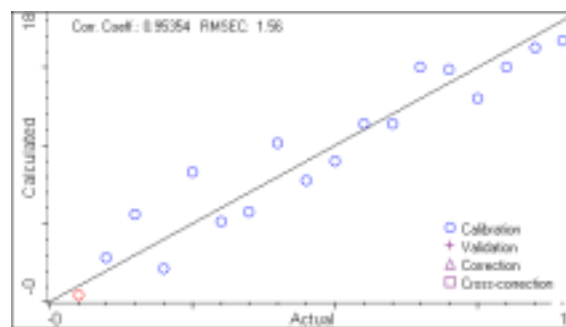


Figure 2.2B The graph shows the accuracy of the linear regression model. The y-axis values represent the calculated percent of magnesium stearate in each sample supposing the calibration model had been used; the x-axis shows the actual concentrations of magnesium stearate in the

samples.

To further validate the model, mixtures of known concentration that were not used in the calibration method were “predicted” using the model and compared to the known value [5]. The data was fairly accurate, so we proceeded to analyze the large 2% and 8% magnesium stearate blends using our calibration model.

Samples of our blends were then placed in the NIR spectroscope and the resulting spectra were plotted along the linear regression of the method. The concentration of magnesium stearate in each was determined using the calibration model. For the 2% sample, the predicted value of 2.02% was very accurate. For the 8% sample, the NIR reported an actual percentage of 5.90%. This difference could be accounted for by citing a faulty method or faulty blending. Since the method seemed accurate for the other tested samples, it is likely that the error induced by the v-blender decreased the concentration of magnesium stearate in the mixture or disturbed the distribution of mixture components. However, the calculated value of 5.90% was far enough away from that of the 2% sample that trends found in later data values can be still be correlated to a difference in lubricant concentrations.

2.3 Flow Index

To analyze the flow properties of the two powder blends, we began by taking data from a gravitational displacement rheometer. The GDR and the accompanying software was used to calculate the flow index of each powder blend and to compare increased concentration of magnesium stearate affected the flow index value. Flow index is a numerical value that corresponds to the amount of cohesion that the powder contains, with higher flow index values indicating more cohesion.

The GDR calculates the flow index by measuring the change in the center of mass of the powder when it is rotating. The rheometer consists of a rotating Plexiglas cylinder that is held in place by spring loaded pins. The weight of the motor and drive shaft are balanced by counterweights on the opposite side of the machine from the load cell, the most important part of data collection. The load cell registers the force caused by the avalanches of powder that cause a shift in the center of mass of the rotating powder. The magnitude and frequency of avalanches is recorded and graphed by the GDR software. The standard deviation of the weight signal for each speed tested is recorded, and the average of the standard deviations for revolution speeds from five rpm to twenty rpm becomes the flow index [2].

Powder from each prepared sample was added to the cylinder until it was about forty percent full. The cylinder was then rotated at five rpm until a steady state was reached. When each powder first began to spin at each new revolution speed, the avalanches were irregular and could not be reasonably assessed. At low speeds, it took the powder about five minutes to reach a steady state; at higher speeds this decreased to two to three minutes. The rotational speed of the cylinder was increased by increments of five rpm until it reached thirty rpm, with data being collected at each increment.

Once the load cell recorded the data from the rotating GDR at the six different speeds, we calculated the flow index of each of the two powder blends we had prepared. We found the standard deviation of the frequency of avalanches for each speed and took the average to output a single numerical value, the flow index. The values of the standard deviations and variances of the data can be seen in Table 2.3A and 2.3B below. The flow index for the 2% magnesium stearate powder was calculated to be 25.29403 and the flow index for the 8% magnesium stearate powder

was found to be 17.0951. This matched our qualitative observations that the 2% powder tended to have fewer and larger avalanches.

2% MgSt		
rpm	Var	SD
5	5.55E+02	23.56196228
10	2.64E+02	16.23986618
15	6.05E+02	24.58698953
20	1.35E+03	36.78731992
25	1.28E+03	35.70838969
30	9.74E+02	31.20940232
Flow Index		25.29403

Table 2.3A shows the standard deviation and variance of the weight signals for each of the revolution speeds and finally the flow index data for 2% magnesium stearate.

8% MgSt		
rpm	Var	SD
5	6.16E+02	24.82796785
10	1.06E+02	10.29906521
15	3.74E+01	6.112987727
20	7.37E+02	27.14038152
25	8.63E+02	29.37368631
30	7.49E+02	27.36879023
Flow Index		17.0951

Table 2.3B shows the standard deviate and variance of the weight signals for each of the revolution speeds and finally the flow index data for 8% magnesium stearate.

We then graphed (see Figure 2.3A) the respective standard deviations in order to better compare them. We found that at low revolutions (5 rpm) and at high revolutions (30 rpm), the standard deviations of the weight signals were fairly close, but in the middle, a large divide was evident. The 2% powder had much higher standard deviations. This makes sense with our early intuition; the 2% powder was less lubricated and thus more cohesive and less likely to flow smoothly as it rotated. It stuck more to itself and the sides of the cylinder until it finally sheared in a large clump that greatly disturbed the load cell. The 8% powder, in comparison, flowed much

more smoothly, so its effects on the load cell were more constant.

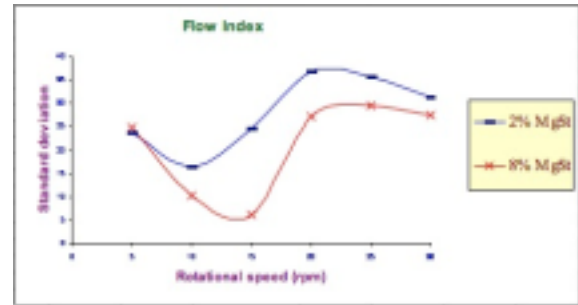


Figure 2.3A shows the graphs of the flow index of 2% magnesium stearate (blue) and 8% magnesium stearate (red).

2.4 Dynamic Dilation

To confirm the data obtained from the GDR, a technique known as dynamic dilation is used to once again measure the cohesiveness of the powder particles. In dynamic dilation, powder flow is induced inside a rotating drum and the expansion of the powder bed is measured. As the drum rotates, the powder inside must expand in order to flow. The flow of the powder can be visually noted based on the size of the avalanches that form when gravity overcomes the force of friction from the cylinder drawing the powder upwards.

The degree of dilation of the powder bed is highly dependent on the cohesion of the powder. Less cohesive powders reach an equilibrium state faster. As cohesion increases, the dilation of the bed also increases, and the dynamic density of the bed is much larger than the static density before it began to rotate. More cohesive powders also tend to have irregular dilation for the first few revolutions; the effects of initial conditions are more evident [1].

Dilation can be quantified by measuring the relative increase in the volume of a powder as the powder is disturbed. One method by which this disturbance can be implemented in

a controlled environment is by placing the powder in a rotating drum. This drum is caused to rotate at a constant rate by a motorized roller upon which it sits. The rate of rotation is controlled by a computer that regulates the voltage provided to the motor. When the powder bed reaches a stable state while rotating, its volume will be greater than in its initial state; in effect, its density will have decreased due to its flow against the rotation of the drum.

According to Faqih et al., the rotating drum method for evaluating dilation is "excellent" in its accuracy. In this study, quantitative computer simulations of the rotating drum, using a three-dimensional digital elevation model of the topography of the powder bed, were created for various drum sizes and rotation rates. In each resulting case, experimental results demonstrated "excellent" agreement with the simulations. Thus, with a relatively precise method of measuring the volume of the powder, we can compare the degree of dilation of different powders to measure their cohesiveness [1].

Because it can be assumed that any extruded cross-section of the powder bed will approximate the bed's volume, knowing the area of any cross-section at various times is enough to calculate the percent increase in volume. To accomplish this, a digital video is taken along the axis of rotation of the rotating drum. One frame of the pre-rotation state is extracted and used. Then, frames are extracted from the video a certain number of times per rotation.

2.41 Photoshop and MATLAB Analysis

The normal procedure by which the resulting photographic frames are analyzed involves various software programs and manual control of these programs. First, the motion picture is captured and frames are extracted using the program Adobe Premiere. The result of this step is shown in Figure 2.4A.

Next, these frames are imported into Microsoft PowerPoint for manual drawing of a red ellipse over the boundaries of the cylinder, to allow subsequent steps to distinguish between the interior of the cylinder and the exterior environment. The result of this is shown in Figure 2.4B. After this, the exported PowerPoint slides are imported into Adobe Photoshop, in which the Magic Wand tool is used to manually select the powder bed, the remainder of the interior, and the exterior environment; these regions are colored black, blue, and green respectively, as shown in Figure 2.4C.



Figure 2.4A shows the dilation cylinder unedited.

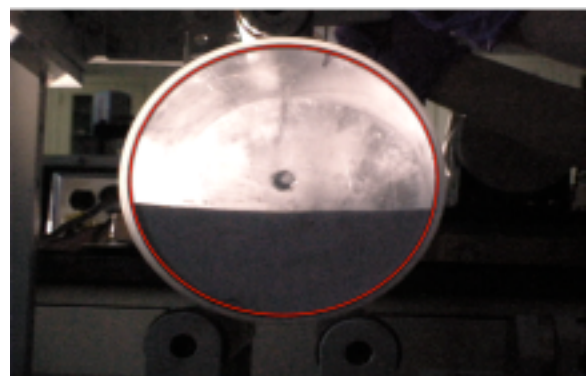


Figure 2.4B shows the dilation cylinder with the circle drawn in PowerPoint.



Figure 2.4C shows the dilation cylinder colored in Photoshop before MATLAB analysis.

Finally, the processed images saved from Photoshop are imported into a previously custom-designed pixel-counting program [4] for Matlab. This program translates images into the percentage of the interior of the cylinder taken up by the powder bed. Finally, the resulting list of numbers is pasted into a spreadsheet in Microsoft Excel, which calculates the percent differences between the value for the first frame and the values for subsequent frames. Calculating the average value of the differences for rotations after the system comes to equilibrium gives the degree of dilation.

2.42 Automated Programmatic Analysis

As a novel component of our research, we have developed a new custom program that attempts to automate and combine all steps of image analysis between, and not including, the steps in which Adobe Premiere and Microsoft Excel are used. This program, called DilationMeasurer, addresses certain inefficiencies in the manual procedure, such as the necessity of drawing red circles in multiple frames even though the cylinder's position and size do not change over time. Our program is written in Sun Microsystems' Java programming language and is thus relatively platform-independent. Its 1216-line source code will be released under the GNU General Public License, version 2. A screenshot of the

program is shown in Figure 2.4D.

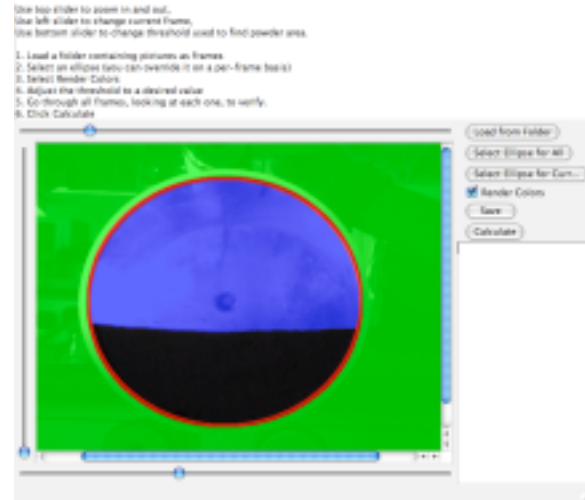


Figure 2.4D is a screenshot of the DilationMeasurer program we designed and used to analyze our data.

Once a folder of images is loaded, an ellipse can be specified for all frames at once. This can be very accurate thanks to zooming and scrolling features in the user interface. Next, a custom algorithm is used to colorize each frame, given a user-specified brightness threshold between the powder bed color and the empty interior color. This algorithm is based on the commonly used boundary-fill algorithm and is implemented using a linked queue, as opposed to a recursive function [4]. It efficiently iterates through the neighbors of a specified point, repeating with the neighbors of that point, until the current point is outside the boundary or is no longer dark. Upon modifying the threshold to a desired value, the user can, with a single click, calculate the percent of each frame's cylinder taken up by the powder bed. The results are then presented in both human-readable format and a list format that can be copied directly into the Excel spreadsheet for final analysis.

2.43 Dilation Results

For our experiment, we analyzed frames from 2% and 8% magnesium stearate powder samples using both the original manual

procedure and our custom program for each. The results between methods, shown in Table 2.4A, were quite similar, and they correspond to the qualitative observation that the increased concentration of magnesium stearate had a lower degree of dilation.

Method: Manual
Average Percent Dilation 2%: 26.3700%
Average Percent Dilation 8%: 22.3737%
Method: DilationMeasurer Program
Average Percent Dilation 2%: 27.9213%
Average Percent Dilation 8%: 20.6076%

Table 2.4A compares dilation results.

For final analysis, we decided to use the programmatically generated results. The program uses standardized thresholds and cylinder boundaries, so we felt that the data was more accurate than doing the Photoshop coloring manually. A graphical view of those results is shown in Figure 2.4E.

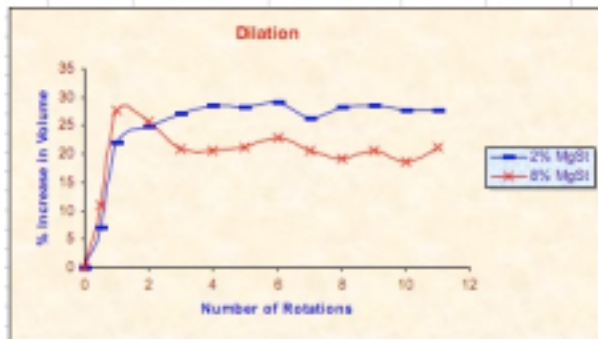


Figure 2.4E shows the percent increase in volume of the 2% magnesium stearate (blue) against the percent increase in volume of the 8% magnesium stearate (red).

3. Results Analysis

Table 3.0A below summarizes the results we collected. The flow index as measured by the GDR decreased between the 2% and 8% magnesium stearate powder samples. This indicated that the 8% powder was less cohesive than the 2% powder, since the avalanches after shearing were smaller and less stress was detected by the load cell. The

average dilation of the 2% powder was larger than the average dilation of the 8% powder. This indicated that the 8% powder maintained a steady state more readily than its 2% counterpart, and therefore flowed better. The dilation results confirmed what we had earlier discovered with the GDR.

Prepared Sample %	Measured Sample %	Flow Index	Avg. Dilation
2%	2.02%	25.294	27.921
8%	5.90%	17.095	20.607

Table 3.0A is a summary of our results.

Overall, the results demonstrated that the 8% magnesium stearate blend was much less cohesive than the 2% magnesium stearate blend. Magnesium stearate “lubricated” the lactose powder, interfering with the van der Waal forces that were causing the lactose grains to stick together. In the 8% blend, more magnesium stearate interfered with more of those intermolecular forces, causing the powder mixture to become even less cohesive. This is an important observation because it indicates that the presence of magnesium stearate can prevent static electric buildup that can lead to tragic explosions in pharmaceutical manufacturing.

4. Future Work

The nature of powder is unpredictable, so researchers and pharmaceutical companies must continue to experiment to find innovative ways to facilitate powder processing. Founder of Freeman Technologies, Reg Freeman describes, “Powder has the elastic properties of a solid, the compressibility properties of a gas, and can flow in all directions like a liquid” [7]. With these diverse qualities, one experiment is not enough to determine the final blend that will be manufactured in enormous quantities. Manufacturers must try their best to minimize the amount of lubricant in a batch while still

maintaining proper flow.

If we had blended more samples, it would have been possible to plot a chart of the flow indexes of more concentrations of lubricant within the powder blend, to see what the optimal concentration of magnesium stearate is for the lowest flow index and dilation results. It is likely that too much magnesium stearate would interfere too much with the intermolecular forces between the lactose molecules and hinder the tablet-making process that is the ultimate goal behind powder processing.

Another goal of future research would involve improvement of the DilationMeasurer program to make it a more robust, almost entirely automatic solution for dilation image processing. Currently, experimental errors such as static cling of powder to the cylinder walls and powder becoming trapped in a hole in the cylinder lid can decrease the accuracy of the program, and manual intervention is required for valid results. Possibly, the manual selection of the ellipse could also be made automatic. The program architecture allows for additional processing steps such as these to be easily added, and the open-source license will facilitate cooperation towards better algorithms. We hope that, with time and more development, the program will be highly accurate and widely used.

Research can also be directed towards finding new, more effective lubricants. Currently, magnesium stearate is one of the most widely used lubricants due to its ability to effectively aid powder flow and to decrease the probability of powder sticking to machinery. However, what the mixture gains in flow, it loses in hardness when it is made into a tablet, especially if the mixture is overblended [6]. The final goal is to create or discover a lubricant and concentration that are effective but do not harm the compaction of the tablet when the powder is compressed.

5. Conclusion

We ascertained through the two main experiments that we conducted that adding magnesium stearate as a lubricant can greatly increase the fluidity of lactose and decrease the cohesion that can lead to static buildup and potential explosion. This is an important fact for pharmaceutical industries that use naturally cohesive organic materials as ingredients in their tablet medicines. Chemical engineers conducting experiments like ours, though on a much larger and more exact scale, are therefore necessary to assist the pill manufacturing industry to improve and streamline production. Even the food industry turns to chemical engineers for powder analysis; the main components in common drinks such as Nestea are flavored powders.

Historically, the study of flow properties was limited to liquids, but in recent years the study has expanded to include the powdered products that are so common in our lives [1]. Using equipment like the gravitational displacement rheometer and the dilation cylinder, engineers can report back to companies on the various flow properties of the powders they are using and advise them on how best to combine materials to streamline production and prevent backed up pipes. Other engineers are working on discovering other materials with lubricating properties that may be more effective in smaller concentrations at assisting flow and decreasing cohesion.

Engineers are not only working, as we did, on analyzing the effects of lubricants on powders, but also on improving methods for data analysis. Changes to the GDR continue to be suggested and developed, and more accurate methods of dilation analysis (such as the software application we implemented) have yet to become widespread. With demand for the field becoming more widespread as pharmaceutical industries turn

in increasing numbers to chemical engineers to analyze their production processes, we confidently expect to see, and hopefully contribute to, great developments in powder analysis processes in the future.

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