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Effect of moisture and magnesium stearate concentration on flow properties of cohesive granular materials

Abdul Mobeen N. Faqih [a], Amit Mehrotra [a], Stephen V. Hammond [b], Fernando J. Muzzio [a,*]

[a] *Department of Chemical and Biochemical Engineering, Rutgers University, United States*
[b] *Pfizer Inc., United States*

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Abstract

In this article the gravitational displacement rheometer (GDR) is used to characterize the effects of formulation composition and environmental conditions (moisture) on flow properties of cohesive pharmaceutical powders under unconfined conditions. The amount of moisture in the sample often has important effects on the physical and chemical properties of pharmaceutical solids. Properties such as flow, compaction, disintegration, dissolution, hardness and chemical stability are all influenced by moisture. In the case of lactose, as moisture content increases in the powder bed, the flowability becomes poorer as the moisture condenses on the surface and increases cohesion. The celluloses show opposite effect as compared to lactose. Here, as moisture content increases, the flow properties improve dramatically. The GDR also captures the effect of lubricant concentration on the cohesion of powders. The presence of lubricant does not play any significant impact for free flowing powders, but as powder cohesion increases, the lubricants allow for improved flowability of powders. The GDR was also used for a case study of real drug formulation. The methodology was able to evaluate the impact of humidity and lubricant concentration on the flow properties of the formulation.

Keywords: Powder flow; Cohesion; Powder avalanche; Moisture content; Lubricants

1. Introduction and background

Reliable flow of powders from storage devices and through feeding systems is of prime concern, among others, in agrochemical, ceramic, food, mineral and pharmaceutical industries. Knowledge of powder flow properties is important when developing powder processes and handling procedures such as flow from hoppers and silos, transportation, mixing, compression and packaging (Knowlton et al., 1994; Peleg, 1978). Granular flows can be extremely complex and in general are not well understood (Muzzio et al., 2002).

Powder flow characteristics are often investigated using a variety of methods. The most common method is the shear test, in which the force required to shear a powder is measured under well-defined conditions. The method was pioneered by (Jenike, 1964) who also developed the theoretical framework. Besides the Jenike tester, some other commonly used devices include ring shear testers (Schulze, 1994), the Johanson Indicizers (Johanson, 1992, 1993), uniaxial, biaxial, and triaxial testers (Maltby and Enstad, 1993), and Jenike and Johanson's quality control tester. The compressibility of a powder is a commonly used indicator of flowability and is often expressed using the Hausner ratio, which is the ratio between the tapped and the loose-packed bulk densities of the powder (Hausner, 1967). The higher the Hausner ratio, the more difficult it is for the powder to flow. Compressibility is also one of the tests proposed by (Carr, 1965) for the assessment of powder properties and is again a function of bulk to tap density. Another commonly used flow indicator is the time it takes for powder to flow out of a funnel with a well-defined orifice (Staniforth, 2002).

The amount of moisture in the sample often has important effects on the physical and chemical properties of pharmaceutical solids. Properties such as flow, compaction, disintegration, dissolution, hardness and chemical stability are deeply influenced by amount of moisture present. The amount of water present in the powder or tablet, where it is located and how

* Corresponding author.
E-mail address: fjmuzzio@yahoo.com (F.J. Muzzio).

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it is associated with the solid are all important issues that must be addressed to be able to predict and control the behavior of a solid powder during processing.

There are a number of studies in the literature investigating the effects of moisture content on powder flow behavior. These include measuring the angle of repose (Carr, 1965), the sticking point (Downton et al., 1982), the compressibility (Moreya and Peleg, 1981), the cohesion (Heng and Staniforth, 1988), and the powder flow function (Schulze, 1994) at various moisture contents. Jenike and Walker (Walker, 1967) showed that flowability of powders first decreased with moisture content until a critical water content, above which it increased, but the critical moisture content is dependant on the powder. Tomas and Schubert (1982) showed that the flow function of insoluble bulk materials depended primarily on the moisture content and particle size distribution.

Most pharmaceutical formulations also include a certain amount of lubricant to improve its flowability and prevent it from sticking to the surfaces of processing equipment. Lubricants also allow compression at lower pressure and reduce heat generation during tablet compression. Magnesium stearate is the additive most frequently used as a lubricant. It has been proposed that magnesium stearate reduces the adhesion due to long-range Van der Waals forces between the particles in a powder bed (Gold et al., 1968). The hydrophobic nature of magnesium stearate reduces the capillary forces significantly (Zimon, 1982; Deryaguin et al., 1978). It is hypothesized that magnesium stearate forms a film around the surface of larger excipients or the API to reduce internal powder friction. In the case of die filling, lubricants interpose a similar film of low shear strength material between the tablet mass and the die wall.

In this study we will utilize a recently developed methodology to characterize flow properties of cohesive granular materials (Faqih et al., 2006). The gravitational displacement rheometer (GDR) developed for characterization of flow properties of cohesive granular materials will be used to examine mixtures of excipients and the effect it has on flow when combined with the API. The GDR will also be used to evaluate the effect of moisture on cohesion of pharmaceutical powders on flow properties, to analyze the effect of magnesium stearate, and to improve flowability of pharmaceutical materials.

2. Materials

Commercially available, well-characterized powders were used to create a family of "standard" systems of varying cohesion. Sugar and other typical pharmaceutical excipients were used, both as pure and in mixtures. In addition, glass beads were used to establish baseline behavior. Particle sizes for these materials are: Fast-Flo lactose (the least cohesive) 100 μm, Avicel 102 (90 μm), Avicel 101 (60 μm), regular lactose (the most cohesive) 50 μm. The lubricant used for this study is magnesium stearate (30 μm). These materials are some of the most common pharmaceutical excipients. In the interest of brevity their SEM images are not included in this paper but can be found in the "Handbook of Pharmaceutical Excipients" (Raymond et al., 2005).

In addition, this paper includes a case study using a commercial drug '**A**' from Pfizer Inc., pure dibasic calcium phosphate, pure sodium starch glycolate, three excipient blends without drug, unlubricated pre-blend, and final blend with four different levels of lubricant (0.25%, 0.5%, 1.0%, 2.0% by weight), each one measured at four different levels of RH (20%, 30%, 40% and 50%).

2.1. Experimental method

A new device, called the gravitational displacement rheometer (GDR) was developed to quantitatively measure the flow characteristics of cohesive powders in a rotating drum. The GDR as shown in Fig. 1 is based on a simple concept. Powder is loaded into a rotating drum mounted on a hinged table that is supported by a load cell. As the drum rotates, the load cell measures the change in moment of inertia of the powder as it avalanches. The drum is a cylinder, measuring 8 in. in diameter and 10 in. deep. The entire cylinder is constructed of transparent Plexiglas^{TM}, which allows for observation of the flow dynamics within the drum, even though transparency is not necessary for data acquisition. Furthermore, video imaging may be used to directly relate the data output to specific movements of the powder within the vessel and to quantify powder density. The drive train is a 130 V dc motor by Glas-col (Terre Haute, IN, in USA) with a maximum speed of 2500 rpm and an output of 190 W. This motor is connected to the system using a flexible drive shaft, and the cylinder is held in place by spring-loaded pins (not shown).

Data is acquired for speeds from 5 to 30 rpm to capture the relevant dynamics of flow. The load cell used in this work was a 5 lb subminiature compression load cell, type 13/2443-06 by Sensotec, Ohio, USA. The range of the load cell determines the sensitivity of the experiment. The deadweight of the drive assembly and framework can be reduced to any required level by an adjustable counterweight. This allows the absolute range

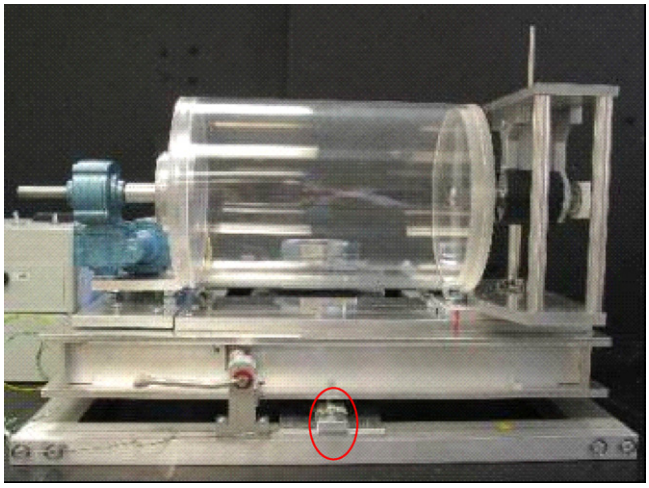

Fig. 1. Picture of the apparatus showing the vessel, drive and load cell. The drive is connected to the motor away from the vessel. The load cell is placed below the center (red circle). The load cell is supported by a counter-weight. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

of the load cell to be significantly lowered, increasing the overall sensitivity of the instrument. For the scale used here, a 5 lb load cell provides optimal conditions to detect the change in center of mass across the cylinder.

In all experiments, the cylinder was loaded with powder to approximately 40% by volume and rotated at the selected speed, and the load cell sampled at a frequency of 2000 Hz for 100 s (the data collection begins approximately 5 min after the cylinder is first started in order to get the steady-state flow data and ignore the initial transient phase in which avalanches are noticeably larger). The high frequency allows in eliminating noise caused due to vibrations by external sources. Considerable effort was devoted on the development of the data analysis tools, aimed at minimizing noise in the system (Faqih et al., 2006).

3. Results and discussion

Typical results for the pure excipients are shown in Fig. 2. The figure shows the R.S.D. of the weight signal as a function of drum RPM for four materials (Fast-Flo lactose, Avicel 101, Avicel 102, micronized lactose). As RPM increases, the size of avalanches also increases (due to centrifugal forces) resulting in increase of the flow index with increasing powder cohesion. In the case of Avicel 101, after 25 rpm, the avalanches overlap, thereby resulting in a drop of the R.S.D. of the weight signal. A similar but more pronounced trend is observed for regular lactose, the most cohesive powder, where the maximum R.S.D. occurs at a lower rotation rate.

Analysis of the data obtained from the GDR along with discrete element method (DEM) simulations allowed us to determine a flow index, which is based on powder cohesion. The flow index is easily and conveniently defined as the average R.S.D. of the load cell signal in the low (5–20) RPM range. Since the R.S.D. was measured at standard vessel speeds of 5, 10, 15, and 20 RPM, for practicality the index is defined as

$$\mathrm{IND} = \frac{\mathrm{RSD}_{5\mathrm{RPM}} + \mathrm{RSD}_{10\mathrm{RPM}} + \mathrm{RSD}_{15\mathrm{RPM}} + \mathrm{RSD}_{20\mathrm{RPM}}}{4}$$

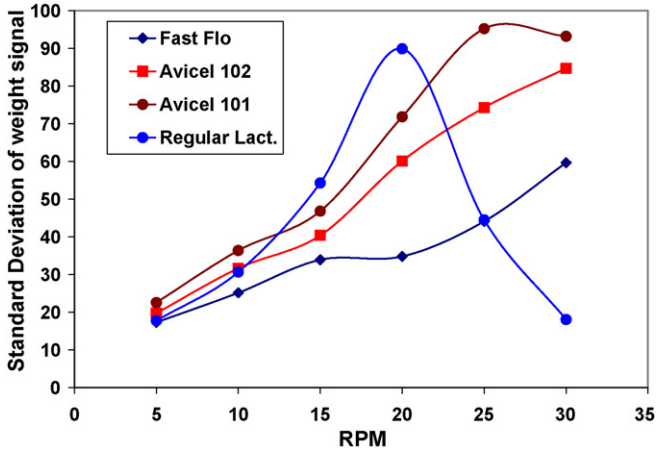

Fig. 2. Standard deviation as a function of the vessel speed. As dry cohesion increases the standard deviation of the weight signal increases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

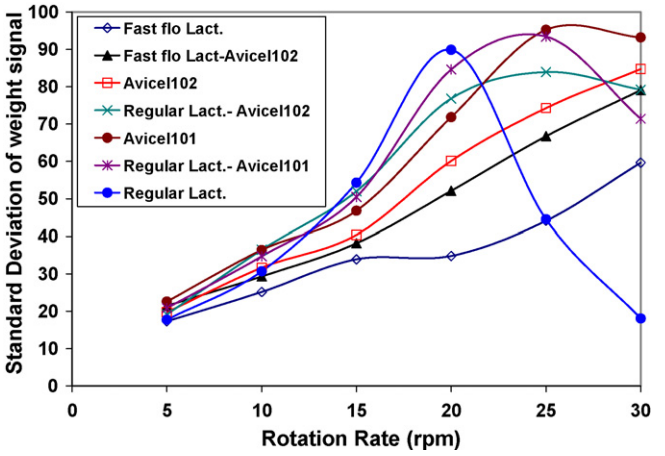

Fig. 3. The GDR captures the weight signal of mixtures. Plot for mixture 1 (Fast-Flo lactose and Avicel 102) lies in between the pure components. Mixtures 2 and 3 follow the same trend. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

In this section, we extend the capabilities of the GDR and evaluate the flow index of mixtures of the four pharmaceutical excipients. The method is used to examine critical variables (moisture and MgSt concentration) and the effect it has on flowability. A pharmaceutical formulation consists of a mixture of powders such as excipients, glidants, lubricants and most importantly the API. It is important to realize how various additives physically interact with the API as well as interact with external variables such as moisture and impacted by temperature to change the flow properties of the formulation. In order to understand this, we look into a 'real' drug formulation from Pfizer Inc. and analyze how the individual powders behave and eventually how they behave in the formulation. The most critical aspect of it is the effect that moisture and MgSt concentration has on the formulation as it can affect various pharmaceutical processes and cause variability in tablet weight, and possibly, tablet hardness, friability, porosity, and dissolution.

3.1. Extension to mixtures

Experiments were conducted for three mixtures. Mixture 1 consists of 50% Fast-Flo lactose and 50% Avicel 102. Mixture 2 consists of 50% Avicel 102 and regular lactose. Finally, mixture 3 consists of 50% Avicel 101 and regular lactose. Fig. 3 shows that the trend observed for three mixtures resembles the pure powders, where mixture 1 falls in between Fast-Flo lactose and Avicel 102, mixture 2 between regular lactose and Avicel 102, and mixture 3 lies between regular lactose and Avicel 101. Thus, for bulk materials having similar particle size, the GDR captures changes in flow behavior for mixtures of higher cohesion.

Further experiments were carried out for the three mixtures, each at three different compositions. The goals were both to examine the behavior of flow properties for combinations of commonly used materials, and to generate a repertoire of standard materials with different (well-characterized) flow properties that could be used to examine the impact of flow properties on relevant processes. In total, nine mixtures were examined. Mixtures displayed flow properties that were consistent with

Table 1
Flow index database of excipients as a function of composition

	100–0%	75–25%	50–50%	25–75%	0–100%
Fast-Flo–A102	27.8	32.6	35.2	35.8	38
A102–regular lactose.	38	44.5	46.1	47.9	48.2
A101–regular lactose	44.4	46.9	47.7	48.1	48.2

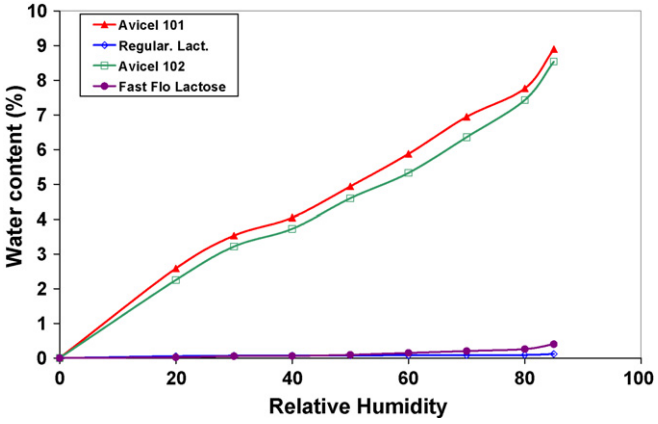

Fig. 4. Equilibrium isotherm for different pharmaceutical powders. In the case of Avicel 102 and Avicel 101 there is a uniform increase in water content as function of relative humidity. For the lactose's (inset), there is a jump in water content after 80% RH. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

those of the pure ingredients from which they were formed. Flow index values of the nine mixtures are shown in Table 1.

3.2. Effect of moisture on powder cohesion

To examine the effect of moisture on the flow properties of pharmaceutical powders, fast-flow lactose, regular lactose, Avicel 101, and Avicel 102 were exposed to a pre-determined value of relative humidity (20–85%) and temperature (25 °C) for 24 h until they reached equilibrium. Moisture uptake was monitored by recording the weight change of the powder bed as a function of time. In all four cases, weight reached a constant value well before 24 h. For both lactoses, the weight change was fairly low at lower RH values, whereas for the Avicels, the weight change was substantial throughout the range of RH values. The isotherms plotted in Fig. 4 show that for the Avicels the increase in water content is linearly correlated to the relative humidity. However, for the lactose, there is an insignificant change in the water content at lower humidity followed by a dramatic jump at higher humidity (above 80%).

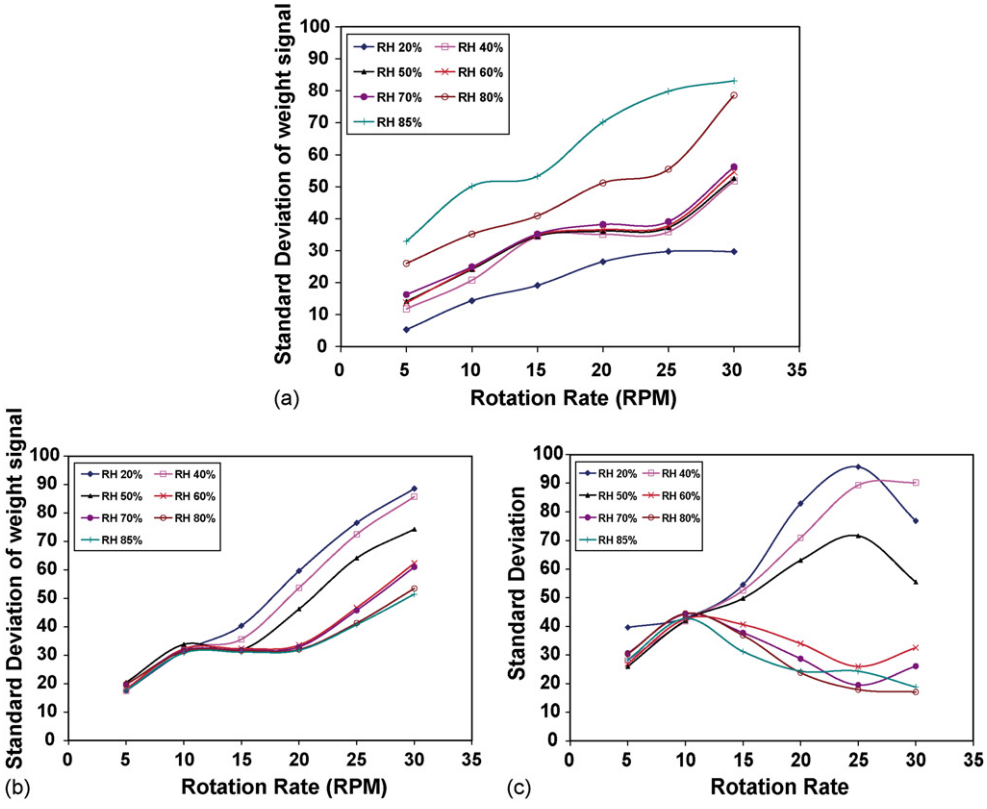

Fig. 5. In (a) as moisture content increases in Fast-Flo lactose, the standard deviation increases indicating poor flowability, whereas in (b) A102 and (c) A101, an increase in water content improves flowability. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

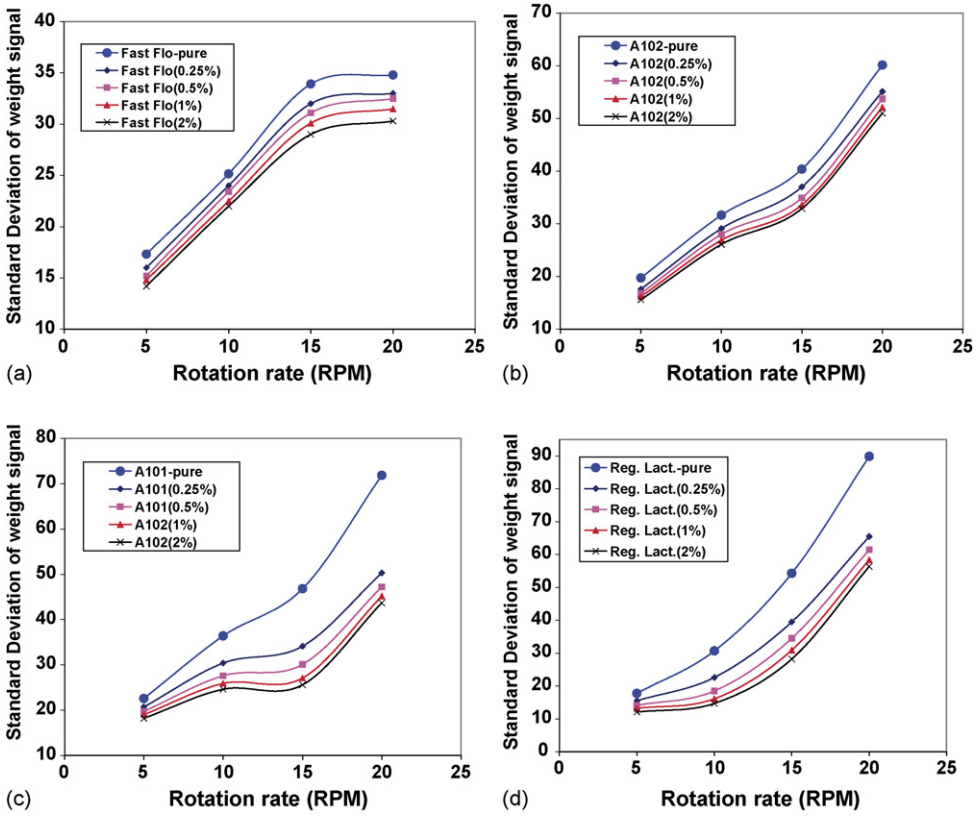

Fig. 6. For fast-flow lactose and A102 (a and b), the least and mildly cohesive powder, MgSt concentration does not have a significant impact on flow behavior, whereas for A101 and regular lactose (c and d), lubricant concentration improves flowability considerably. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

Fig. 5a illustrates the effect of moisture on flow behavior of Fast-Flo lactose. At lower RH, and up to 70% RH, little change is noted. However, for higher humidity, there is a drastic increase in the R.S.D. of the weight signal, indicating much larger avalanches. This is also indicative of the jump in weight as shown in the inset of Fig. 4. The hypothesis is that for low humidity, moisture is bound within the lactose granules and does not have a significant effect on flow. At higher humidity, we believe that moisture condensates on the external surface of lactose particles and acts as a binder, resulting in an increase in cohesion.

While the behavior of lactose is somewhat expected, Avicel 102 (Fig. 5b) and 101 (Fig. 5c) showed completely different behavior: avalanche size decreased, and flow properties improved dramatically as RH increased. Visually, Avicel becomes "clingy" as RH decreases, so the working hypothesis is that at low RH avalanche size increases due to electrostatic forces. At higher RH, these forces are dissipated as the air becomes more conductive. Another possible reason could be that the celluloses are hydrophobic; the water acts as a lubricant in the form of "free water" leading to an improvement in flowability. This is still a work in progress and much more needs to be done to completely understand the phenomenon of this behavior.

3.3. Effect of lubricant concentration on powder cohesion

Experiments were carried out by blending the least cohesive powder (Fast-Flo lactose), the two celluloses, and the most cohesive powder (Regular lactose) with varying amounts of magnesium stearate concentration (0.25–2.0% by weight). As seen in Fig. 6a, the lubricant does not have a significant effect on flow properties for Fast-Flo lactose. However, the effect of lubricant becomes more pronounced as cohesion increases. As shown in Fig. 6d, a small amount of lubricant in the blend (0.25%) leads to a significant change in the R.S.D. of the weight signal of regular lactose (the most cohesive material). For Avicel 102 (Fig. 6b), and Avicel 101 (Fig. 6c), increase in lubricant concentration shows similar behavior to that of lactose. The celluloses, Avicel 102 and Avicel 101, fall in between the two grades of lactose. The trend is similar to that seen when moisture is added to the system. The lubricant in the case of cellulose serves the same purpose as water and improves flowability.

The sensitivity of the GDR methodology to capture the effect of moisture and lubricants for different excipients makes it a viable tool to analyze and optimize drug formulations. One such case study will be discussed in the next section for a real drug formulation.

3.3.1. Case study: effect of moisture and lubricant on 'real' drug formulations

The pure drug substance used in this study has a strong tendency to agglomerate during flow and when stored for a few weeks. The drug needed to be milled in a Comill in order to bring it back to its "delumped" state. The results obtained are

Table 2
Flow properties of drug, pure components and mixtures

Pure component	S.D. (5–20 RPM)
Drug A (Batch 1)	40.8
Drug A (Batch 2)	40.7
Drug A (long term)	66.6
Drug A (long term)	67.2
DiBas. Cal. Phos.	29.5
Sod. Sta. Gly.	61.9
Avicel 102	38
Unlubricated mixtures	
A102–DCP	32.8
A102–DCP–SSG	57.1
A102–DCP–SSG–drug	58

similar to those of Avicel 101, where there is an initial increase in the R.S.D. yielding a flow index of 40.8 (Table 2) followed by a gradual decrease (black curve, Fig. 7). Over short times, results were highly reproducible (pink curve, Fig. 7). When the pure drug was rotated for a long time, the powder agglomerated extensively, resulting in much bigger avalanches (red curve, Fig. 7). This led to a dramatic rise in the R.S.D. as indicated in the figure, and resulted in a flow index of 66.6 (Table 2). Subsequently, the drug was milled again, recovering its initial flow properties (blue curve, Fig. 7). However, a few minutes later, agglomerates were present again, large avalanches were again observed, and the R.S.D. increased again very significantly (green curve, Fig. 7), showing the agglomeration process to be highly reproducible.

Subsequently, the flow properties of ingredient blends were examined. First, we examined the flow properties of the remaining excipients. Dibasic calcium phosphate showed good flow properties and a flow index of 29.5, while sodium starch glycolate showed very poor flow properties and an index of 61.9 (Table 2). Mixtures of these ingredients behaved as expected. The blend of Avicel 102 and dibasic calcium phosphate showed good flow properties and a flow index of 32.8. However, flow properties worsened substantially when the sodium starch glycolate was added, showing a flow index of 57.1, and remained unchanged when the API was included.

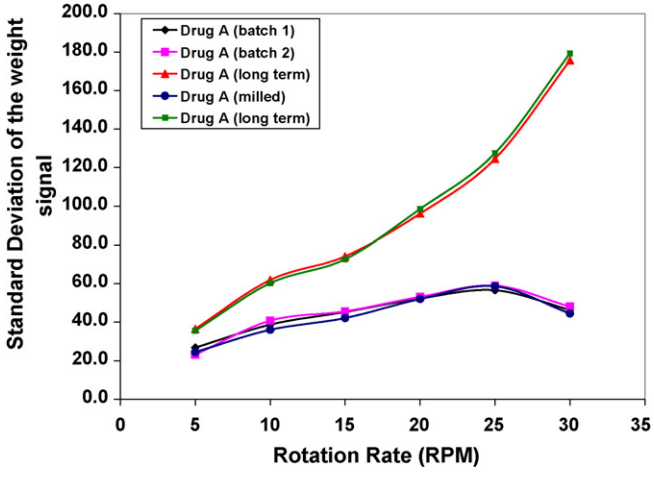

Fig. 7. As agglomerates are formed, the drugs flowability is impacted drastically (red curve). Milling brings it back to its original structure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

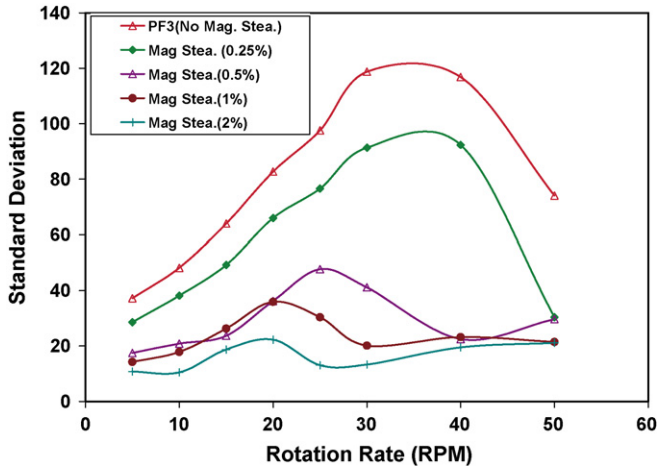

Fig. 8. Effect of MgSt concentration on flow behavior of the formulation ranging from 0.25% to 2%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

Materials that can coat other ingredients can have dramatic effects on flow properties even when present only in small quantities. The most dramatic impact on the blend was due to addition of magnesium stearate (MgSt). Fig. 8 shows the flow properties of the entire formulation as a function of MgSt composition, measured at 45% RH. Without MgSt, the formulation flows poorly (dark blue curve, Fig. 8) and has a flow index of 58. As levels of MgSt increase and reach standard values, flow properties improve dramatically. For example, for 1% MgSt (red curve, Fig. 8) the flow index is 23.6. At 2% MgSt, an extremely flowable material is generated, having a flow index of only 15.6.

These results correlate with interesting visual observations. For low levels of MgSt (0.25% or less) the formulation becomes coarse after a few minutes of flow, revealing fast agglomeration, likely driven by electrostatics. At higher levels of MgSt, the powder remains smooth, suggesting that MgSt actually prevents the development of agglomerates in the system. These observations clearly indicate that MgSt homogeneity can play a critical role in minimizing intra-batch variability. If MgSt concentration is non-homogeneous, different portions of the formulation might have very different flow properties, which in turn might cause other undesirable effects, including weight variability, inconsistency in hardness, and deviations in dissolution properties. The issue is particularly important in view of the fact that MgSt homogeneity is rarely validated during development. In most processes, it is not really known how much variability in MgSt composition is actually present, and therefore, how robust is the process with respect to effects such as those mentioned here. A number of additional issues immediately come to mind, including: mechanism for the observed phenomenon, reproducibility, effect of scale, effect of the source of MgSt, and role of moisture.

In order to begin to examine the effect of moisture, flow properties of the entire formulations were characterized at various moisture levels. Fig. 9a shows the effect of RH (30%, 40%, and

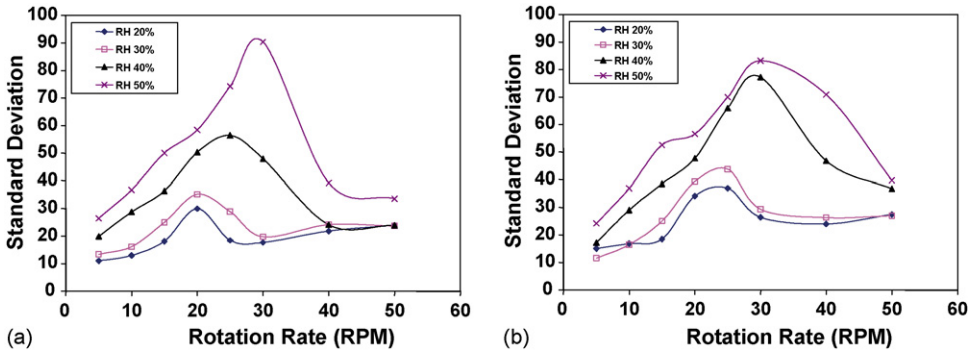

Fig. 9. (a and b) The effect of moisture on the formulation containing 1% and 0.5% MgSt concentration, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

50%) for the formulation containing the nominal amount (1%) of MgSt. As shown in the figure, flow properties of the entire formulation show substantial dependence with RH, in particular between 30% and 40%. Fig. 9b shows similar results for 0.5% MgSt concentration; in this case, the largest variation of flow properties occurs between 40% and 50% RH. Comparison of the two figures highlights the multi-variate nature of flow properties and the interaction between RH and MgSt concentration. The net observation, once again, is that MgSt homogeneity and RH can cause both intra- and inter-batch variability in powder flow properties, resulting in variability in tablet weight, and possibly, tablet hardness, friability, porosity, and dissolution. While it is possible to argue that process validation attempts to address these sources of variability, in practice, the lubrication process is rarely validated directly, and the specification for RH (no more than 45%) leaves the process vulnerable to RH levels below the specification.

4. Conclusion

The gravitational displacement rheometer is used to characterize flow behavior of common pharmaceutical powders both pure and mixtures. The results for mixtures are as expected and lie in between the pure components. The GDR also captures the effect of two crucial variables, moisture content and lubricant concentration. In the case of lactose, as moisture content increases in the powder bed, the flowability becomes poorer as the moisture condensates on the surface and increases cohesion. The celluloses show opposite effect as compared to lactose. Here, as moisture content increases, the flow properties improve dramatically. At low RH value, the powder is visually clingy due to the electrostatic forces. These forces are a major concern in the pharmaceutical industry as they lead to flow problems during processing conditions. In the case of some powders, an increase in moisture content allows the charge to dissipate as the air becomes more conductive. The working hypothesis is that cellulose being hydrophobic in nature enables the water to remain on the surface of the particle as 'free water' making it act as lubricant. It has been hypothesized that the presence of lubricant can also help in dissipating the electrostatic forces in cohesive powders. The methodology captures this behavior, where the presence of lubricant does not play any significant impact for free flowing powders, but as powder cohesion increases, the lubricants allow for improved flowability of powders. The most exciting extension is to develop predictive correlations between GDR measurements and the performance of processes that are sensitive to powder flow properties, such as flow in hoppers and feeders, blender design and scale-up, and the filling of dies and capsules. This method can be used to set meaningful ingredient specifications, optimize flow properties of pharmaceutical formulations, identify critical variables such as moisture and lubricant concentration and set useful process specifications.

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