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Influence of shear intensity and total shear on properties of blends and tablets of lactose and cellulose lubricated with magnesium stearate

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Abstract

A new technique to quantify the effects of shear intensity and total shear on the homogeneity, flowability and bulk density of a lubricated free-flowing pharmaceutical blend and on properties of resulting tablets is presented. A modified Couette cylindrical cell with uniformly spaced pins is used to create a uniform shear environment. The range of lubricant concentrations explored is 0–2% (on a mass basis). Sheared blends are used to produce tablets in the Presster™ (a simulator of an actual tablet press), allowing us to correlate the shear history of the blend (shear intensity and total shear) with the crushing hardness of tablets. The results show that the larger the total shear, the more homogeneous the blend. Bulk density increases with total shear until reaching a distinctive plateau. Results also indicate that high total shear affects the blend flow properties. For tablets, crushing hardness decreases as concentration of lubricant and total shear increase. Interestingly, and unexpectedly, under constant total shear, shear intensity affects the crushing hardness of tablets only slightly.

Keywords: Powder flow; Cohesion; Shear; Shear rate; Tablet hardness; Bulk density; Content uniformity; Flowability

1. Introduction and background

Lubrication is a process of high importance in the pharmaceutical industry. Lubricants are added to tablet formulations for two reasons: (a) to prevent of sticking of granules to the tooling—anti-adherent; (b) to improve granule flow properties—glidant (Moodya et al., 1984). As anti-adherents, they reduce the friction between the die wall and granules as the tablet is formed and ejected (Moodya et al., 1984). As glidants, they can enhance the blending of an active and decrease processing problems and weight variability during compaction (Mackin et al., 2002). There are numerous examples of the effects of lubrication on densification and compactability of mixtures (Vromans and Lerk, 1988; van Veen et al., 2005; Ebba et al., 2001) and also on tablet properties such as tensile strength, friability and disintegration time (Johansson, 1984; de Lourdes Garzón Serra and Robles, 2003). Capsule filling performance of powders can also be modified by adding a lubricant such as magnesium stearate (Podczeck and Michael Newton, 2000). It is also reported that filling properties are better at lower magnesium stearate concentrations, whereas the machine performance improves with an increase in magnesium stearate. It is widely known that blend flowability and tablet properties will depend on the extent the blend has been exposed to shear. Typically, dissolution (Fukui et al., 2001) and hardness (Aoshima et al., 2005) are adversely affected by excessive shear. This phenomenon is known as over-lubrication.

The bulk density of a powder is an important parameter which is deeply affected by total amount of applied shear. Since processing equipment has fixed volume, density directly affects batch size and capacity (and productivity). For cohesive powders, density also affects effective flow properties (Abdullah and Geldart, 1999). Harnby et al. (1987a,b) mentioned that relative changes in bulk density can be very sensitive indicators of changes in the structural strength of a loosely compacted powder and hence of its flow characteristics in many process operations. Finally, and most critically, density and flowability directly impact weight and dosage reproducibility of tablets and filled capsules, and affects the compression force applied in tablet

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Table 1
Materials used in the experiment

Name	Size (D50) and morphology	Vendor, City, State
Fast-flo lactose	100 μm, spherical	Foremost farms, Newark, NJ
Avicel PH 102 microcrystalline cellulose	90 μm, needle like	FMC, Rothschild, WI
Magnesium stearate	20 μm, irregular	Mallinckrodt, St. Louis, MO

Table 2
Mixtures studied in this paper

Preblend	Magnesium stearate (%)	Fast-flo lactose (%)	Avicel 102 (%)
Mixture 1	0	60	40
Mixture 2	1	59	40
Mixture 3	2	58	40

presses, having an impact on hardness, porosity, dissolution and frequent problems such as sticking and capping.

Two variables are important to the lubrication process: concentration of lubricant and exposure to shear. Some studies have correlated the performance of a lubrication process with mixing time (Ragnarsson et al., 1979) and with the scale and operating conditions of the blender (van der Watt and de Villiers, 1997) rather than with shear itself, presumably due to a lack of quantitative knowledge about the shear conditions existent in blenders. The Couette shear cell described here provides an excellent environment of nearly uniform shear conditions, facilitating the correlation of exposure to shear to observed blend properties. There have been multiple geometries considered for dense granular flows, but the most common ones have been parallel plates (Babic et al., 1990; Thompson and Grest, 1991; Zhang and Campbell, 1992; Aharonov and Sparks, 1999), rough inclined planes (Drake, 1990; Ancey et al., 1996; Pouliquen and Renaut, 1996), flow on a pile (Khakhar et al., 2001; Andreotti and Douady, 2001) and coaxial cylinders (Veje et al., 1999; Mueth, 2001; Mueth et al., 2000; Miller et al., 1996). We consider granular Couette flow in this study as it is suitable for fundamental research because of its simplicity.

Section 2 in the paper describes the materials used in the study and the geometry and working of the instrument. It also presents the experimental grid, and the methodology used for preparing and analyzing samples. Subsequently, in Section 3, results are described for content uniformity, bulk density, flowability and tablet hardness, respectively. Finally, Section 4 is devoted to summary and conclusions.

2. Materials and methods

2.1. Materials and preblend method

The materials used in our experiments are presented in Table 1. Magnesium stearate is used as a lubricant. Three preblends with different levels of magnesium stearate (Table 2) are studied comprehensively to investigate the effect of shear rates and total shear on bulk density, flow behavior and mixing properties of lubricated pharmaceutical blends. These materials are some of the most common pharmaceutical excipients and in the interest of brevity their SEM images are not included in this paper but can be found in "Handbook of Pharmaceutical excipients" (Rowe et al., 2003).

Prior to using the modified Couette shear cell, a preblend of all ingredients must be prepared. The practice of using a preblend is adopted because the Couette cell is not a good axial mixer. Dispersion is the main axial macro-mixing mechanism in the device; convection along the axis of rotation is very slow. When the cell is loaded with the excipients and lubricant in a stratified manner, it takes a long time to achieve lubricant homogeneity throughout the cell. For lubrication studies, gross homogeneity is critical because if ingredients are not preblended, some parts of the blend will have a high concentration of lubricant and others will have a low concentration of lubricant while being sheared, making the lubrication process uneven; unless this is avoided results could be misleading. Thus, a grossly homogeneous preblend of the lubricant or APT and the excipients is prepared as explained in previous section. To minimize uncontrolled exposure to shear prior to the shear cell experiment, the mixing time used for preblending is short (50 revolutions), the rotational speed moderate (10 rpm) and the mixer is small (4 qt). The shear cell is loaded to full capacity (1.8 l) with preblend and one of the experimental conditions indicated in Table 3 is used.

Samples are prepared by first mixing fast-flo lactose and Avicel 102 in a 4-quart V-blender. Powders are loaded in the V-blender from the bottom to make sure that equal amounts are added on both shells for faster mixing. The loading pattern is top-bottom as shown in Fig. 1 and is mixed at 10 rpm for 50 revolutions only in order to minimize shear. Mixing is characterized using NIR spectroscopy and it is found that the mixture is

Table 3
Grid showing the shear environments under which the experiments were performed

rpm (shear rate)	Total no. of revolutions (total shear units)							
	10 (267)	40 (1068)	80 (2136)	160 (4272)	320 (8544)	490 (13,083)	980 (26,166)	2000 (53,400)
1 rpm (0.45 s^{-1})	X	X	X					
10 rpm (4.45 s^{-1})	X	X	X					
40 rpm (17.8 s^{-1})			X	X	X			
80 rpm (35.6 s^{-1})			X	X	X			
160 rpm (71.2 s^{-1})			X	X	X	X	X	X
245 rpm (109.03 s^{-1})					X	X	X	X

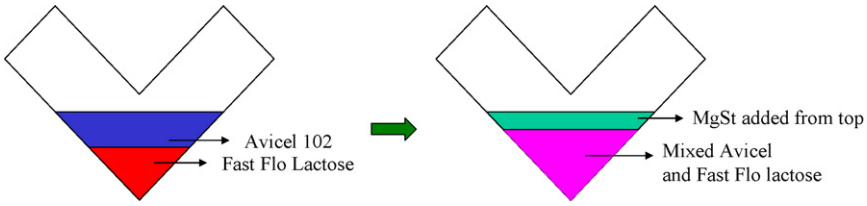

Fig. 1. Illustration of the preblending process for the high shear experiments.

well mixed with RSD of the order of 2%. Magnesium stearate is then added from the top and it is further mixed for 50 additional revolutions at 10 rpm. The magnesium stearate is sifted with a 20 mesh screen before addition to the powder mixture.

2.2. Instrument: modified Couette shear cell

The modified Couette shear cell geometry is based on an annular Couette rheometer used for liquids. The internal cylinder has a diameter of 6.5 in. (16.51 cm) and the gap between concentric cylinders is 0.75 in. (1.9 cm). The height of the cell is 7.5 in., which allows a volume of powder of about 1.8 l. Fig. 2 shows the actual picture of the shear cell with schematics. The internal geometry of cylinder with pins and top view of the cell showing the gap between the cylinders is shown in Fig. 3.

The internal cylinder can rotate at any speed in the range of 1–245 rpm whereas the external cylinder is stationary. Both cylinders are made of aluminum. Other modified Couette shear cells have been used for powders (Harnby et al., 1987a,b). The shear cell is designed to expose the entire powder sample to a flow and shear environment as uniform as possible. In this study, the existing Couette cylinder has been modified to have equidistant interlocking pins so as to provide a uniform shear environment in the whole cell. As shown in Fig. 3 both cylinders are supplemented with equally spaced interlocking pins that create a homogeneous shear field in the flow region. The modified Couette shear cell has a lid and a seal that permits to work with an unconfined or a confined powder bed under a known amount of applied normal stress.

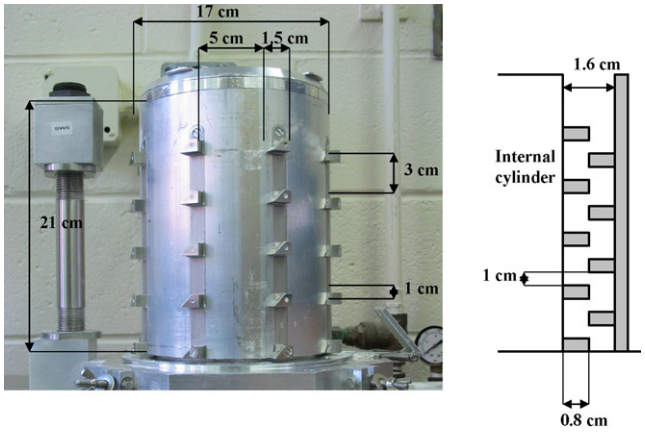

Fig. 2. The figure shows the schematic and actual picture of the new instrument. The inner cylinder rotates at a constant speed transmitting shear to the blend in a controlled and uniform fashion. The panel displays the total torque, rotation speed and can be attached to a computer to get continuous data.

2.3. Near infrared spectroscopy

Magnesium stearate homogeneity was quantified using near infrared spectroscopy. It has been reported in literature that near infrared can be used as useful tool to characterize magnesium stearate (Roggo et al., 2005; Ebube et al., 1999). The Rapid Content Analyzer instrument (Silver Spring, MD) manufactured by FOSS NIR Systems and Vision software (Version 2.1) is used for the analysis. The method begins by selecting a calibration sample set according to the lubricant concentration. Samples are prepared by keeping the ratio of Avicel to lactose randomized in order to minimize effects of imperfect blending of excipients during the experiments. The samples are prepared by weighing 1 g of mixture into separate optical scintillation vials (Kimble Glass Inc., Vineland, NJ) using a balance with an accuracy of ±0.01 mg. Near-IR spectra are collected by scanning in the range 1116–2482 nm in the reflectance mode. The vials are rotated in a vortex (Genie 2^{TM}) manufactured by Fisher for 5 min to ensure homogeneity of the calibration set samples. Partial least square (PLS) regression is used in calibration model development using the second derivative mathematical pretreatment to minimize the particle size effects. Excellent agreement is achieved between the calibrated and predicted values. The standard error of calibration (SEC) is 0.0315 and the multiple correlation coefficient (R^2) 0.9963, indicating the spectral data fits well the constituent values.

2.4. Experimental conditions: shear rates and total shear

As already mentioned, the main variables that are expected to affect the outcome of a lubrication process are concentration of lubricant, shear rates, and total shear. In previous studies, because of the lack of means to assess shear rates in a blender and therefore estimate the exposure to total shear, mixing time has been the only variable correlated in the literature with blend and tablet properties. The main advantage of the modified Couette shear cell presented here is that it provides a nearly uniform shear field and known shear rates in the range 0.45 s^{-1} (at 1 rpm) to 109.03 s^{-1} (at 245 rpm). The duration of the process (shear time) can be used to estimate the total imposed dimensionless shear units. In the experiments reported here, total shear units vary over two orders of magnitude from ∼270 to ∼53,000 shear units. This range can be shown to comprise total shear values typical of most industrial application, including tumblers with and without intensifier bars and "high shear" mixer-granulators.

Table 3 presents the experimental grid used here, displaying the shear rates in rows (with the corresponding rotational speeds of the cylinder in rpm) and total shear units (or shear

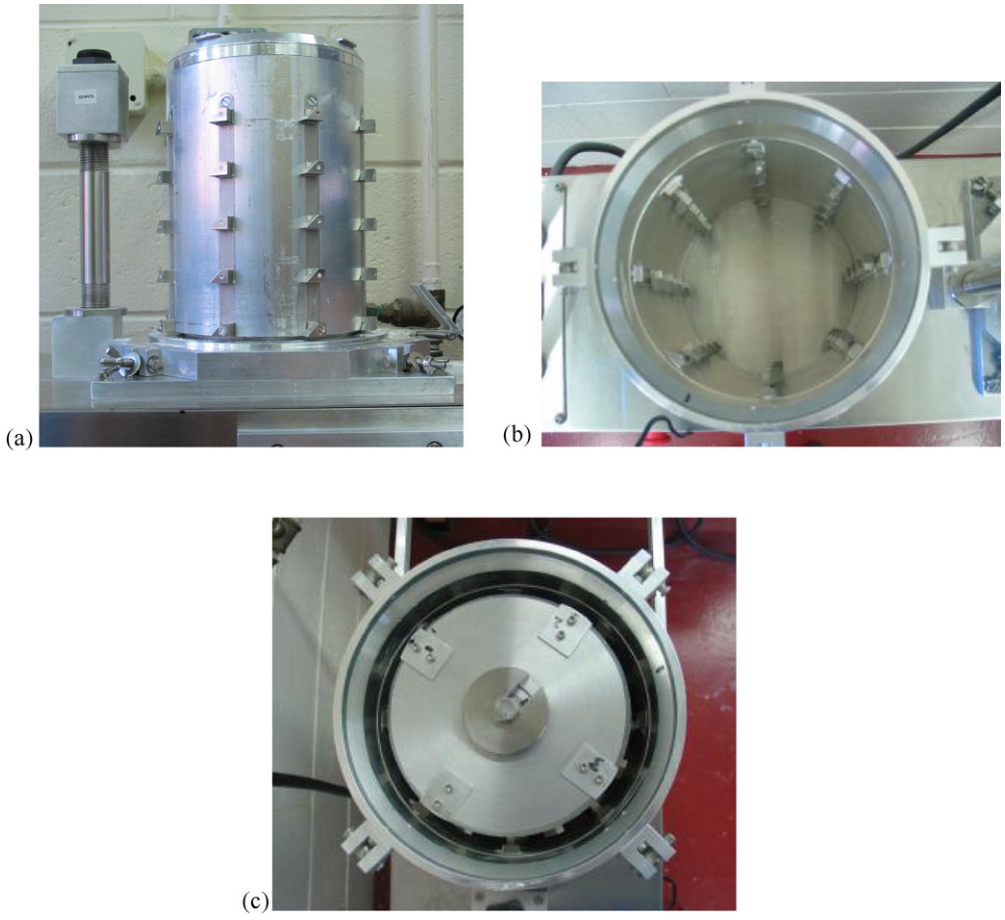

Fig. 3. The figure shows the modified Couette shear cell: (a) shows the pins on the inner cylinder; (b) shows the pins on the outer cylinder; (c) shows the top view of the assembly.

time expressed as number of revolutions) in columns. The combination of values used in our experiments is marked with 'X'. A sparse block design is used to examine the effects of shear rates for similar amounts of total shear and the effect of total shear at a constant shear rate for a wide range of treatment conditions. All the experiments were randomized in order to minimize effects due to extraneous factors.

3. Results

After conducting the experiments, the rheometer is emptied through the discharge port. The blend is collected in a beaker and it is analyzed for homogeneity, flowability and bulk density. Tablets are subsequently made out of these lubricated blends using a Presster^{TM} to simulate the effects of tablet press brand and model, speed, and force/displacement settings. Tablet crushing hardness is then measured. Herein we discuss the results.

3.1. Lubricant homogeneity

As mentioned earlier, the homogeneity of the blend is assessed by collecting a group of 20 samples of 1 g each. The homogeneity index used is the RSD, where C is the concentration of each individual sample, $\bar{C}$ the average concentration of all samples and n is the total number of samples:

$$\text{RSD} = \frac{s}{\bar{C}}$$

where

$$s = \sqrt{\frac{n\sum C^2 - \left(\sum C\right)^2}{n(n-1)}}$$

The results show a general trend to improved homogeneity index (lower RSD) with increased shear imparted to the system. Homogeneity is checked for both 1% and 2% magnesium stearate concentration for blends sheared under the conditions stated in Table 3. Figs. 4 and 5 show the resulting magnesium stearate RSD as a function of total number of revolutions and rotation rate in the device for the two different lubricant concentrations, respectively. For 1% magnesium stearate, as the total shear increases, there is an exponential decay in the magnesium stearate RSD. The plot shows a typical behavior of mixing curves with a steep decay in RSD values at short mixing times followed by a slow exponential decay in the RSD value at long times. *Contrary to intuition, shear rate appears to have a much smaller effect than total strain*. For 2% magnesium stearate, RSD decreases with total applied shear for all shear rates. Fig. 5 shows that total shear has a larger effect on RSD values as compared

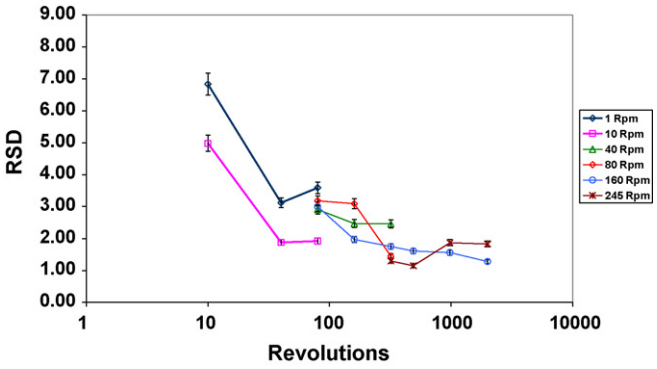

Fig. 4. RSD curves representing content uniformity for preblends with 1% lubricant concentration sheared under different environments as in Table 3. Error bars corresponding to the variability associated to the measurement technique (of <5%) are including in the figure.

to shear rate. It is also observed that lubricant homogenization at higher concentrations is a difficult process. No clean plateau is observed within the range of shear values examined, but no values smaller than 1% RSD are observed either.

3.2. Bulk density

Density is calculated here by accurately weighing a known volume of powder. Five samples are taken from the blend discharged directly from the rheometer. They are collected in two different beakers of volume 155 and 285 ml and the mass is accurately is measured. Results show that the presence of magnesium stearate strongly affects the bulk density of the sheared powders. Fig. 6 shows the effect of shear on the density of unlubricated sample (mixture 1). It can be observed that even at high shear rates and high total shear, the bulk density remains nearly unchanged. The bulk density at extreme shear conditions fluctuates only by a maximum of about 3% from that of the preblend.

However, blends with a small amount of magnesium stearate exhibit a substantial change in the bulk density of the material when exposed to shear. Figs. 7 and 8 show a large increase

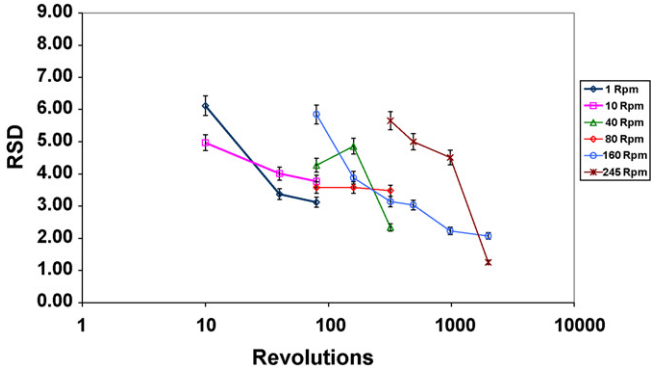

Fig. 5. RSD curves representing content uniformity for preblends with 2% lubricant concentration sheared under different environments as in Table 3. Error bars corresponding to the variability associated to the measurement technique (of <5%) are including in the figure.

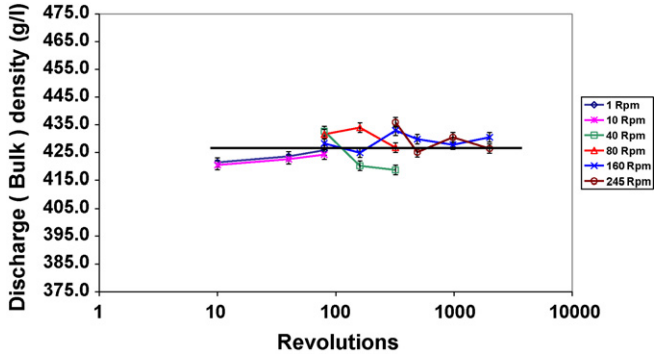

Fig. 6. Density of sheared preblends with no lubrication. Error bars corresponding to the variability associated to the measurement technique (of ∼0.4%) are including in the figure.

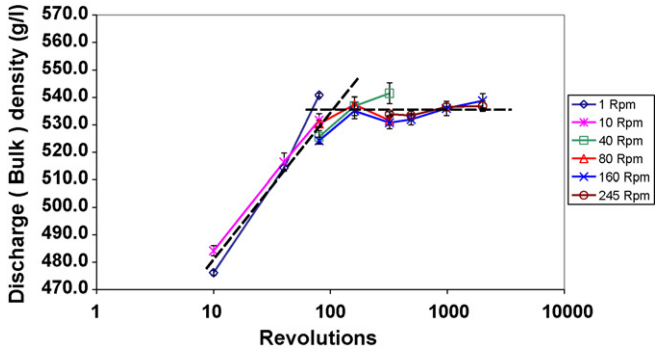

Fig. 7. Density of sheared preblends with 1% magnesium stearate as lubricant. Error bars are computed using $n = 5$ measurements, all values found are smaller than 0.70%.

in bulk density of mixture 2 and mixture 3, respectively. The initial density for mixture 2 (preblend) is 480 g/1 and that of mixture 3 (preblend) is 490 g/1. Results show that the bulk density increases by about ∼13% and then reaches a distinctive plateau, suggesting the existence of two regimes, one where density depends on shear, and another where a substantial degree of lubrication-driven densification has been "achieved". The existence of two regimes qualitatively agrees with the two regimes for RSD decrease observed in Figs. 5 and 6.

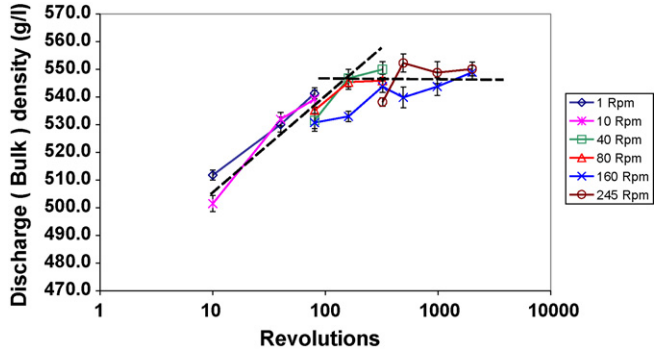

Fig. 8. Density of sheared preblends with 2% magnesium stearate as lubricant. Error bars are computed using $n = 5$ measurements, all values found are smaller than 0.75%.

3.3. Flowability

A lubricant often also works as a glidant, directly affecting the flow properties of the blend. Exposing the lubricant to extensive shear is known to strongly affect powder flow properties. The purpose of this section is to determine the shear-rate and the total-shear effects on flow properties.

The flowability of blends is measured using a technique denominated GDR (gravitational displacement rheometer). In this novel instrument developed at Rutgers, the mixture flow properties are characterized in terms of the size of the avalanches. The GDR is based on a simple concept: powder is loaded on 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 bed caused by powder avalanches. The RSD measurement of the GDR which has been shown to be proportional to cohesive inter-particle forces is an easy and convenient method for characterizing the flow behavior.

Flow properties of prepared samples were strongly affected by total shear. It was observed that flow properties of unlubricated blends become worse when exposed to large amounts of shear, possibly indicating electrostatic effects. Fig. 9a shows that flow properties of the preblend lies between those of fast-flo lactose and Avicel 102. However, when the preblend is exposed to increasing amounts of total shear, it is observed that the standard deviation of the GDR signal increases substantially indicating worsening of flow properties that can could be caused by the electrostatic charging of the preblend when subjected to high shear environments for a long period of time. Even though the shear cell is made of metal, the tested materials are poor conductors, and electrostatic charging of the powder under high shear conditions could be visually observed (increase in asperity).

Flow properties of lubricated blends were also measured as a function of total shear applied. As shown in Fig. 9b, it was observed that flow for blends lubricated with 1% magnesium stearate under different shear environments is better than the preblend, which is contrary to un-lubricated blends. However, there is no marked difference in flow properties for different levels of total shear (high (2000 revolutions, 245 rpm), medium (160 revolutions, 80 rpm) and low (10 revolutions, 1 rpm)). It is important to notice that the improvement in flow properties occurs simultaneously with an increasing density, indicating a decrease in the cohesion of the blend.

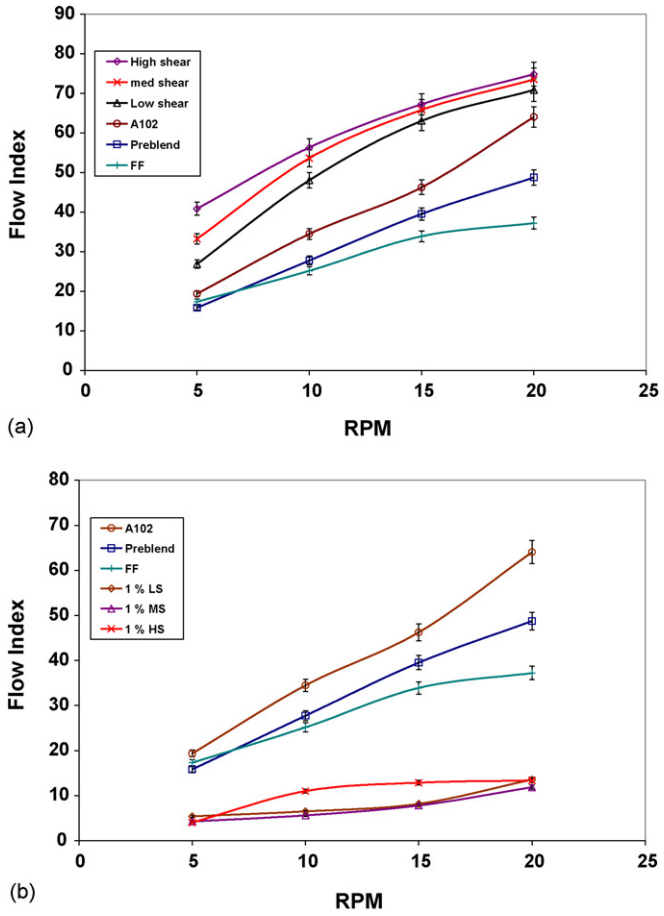

Fig. 9. (a) Standard deviation of GDR signal for powders and preblends when exposed to controlled shear environments. Higher RSD values correspond to worse flowability. Error bars corresponding to the variability associated to the measurement technique (of <4%) are included in the figure. (b) Standard deviation of GDR signal for powders and lubricated preblends when exposed to controlled shear environments. Higher RSD values correspond to worse flowability. Error bars corresponding to the variability associated to the measurement technique (of <4%) are included in the figure.

3.4. Tablet hardness

Perhaps most importantly, it is quantitatively shown that tablet hardness is consistently and reproducibly affected by the total amount of shear imposed on the blend. Figs. 10 and 11a and b demonstrate how the hardness of tablets made by MCC's Presster™ (MCC, East Hanover, NJ), strongly depends not only on the magnesium stearate concentration (as expected) but also on the amount of total shear. The Presster™ is a tablet press replicator designed to match compression force and dwell time of any press. It is a high-speed single station tablet press with

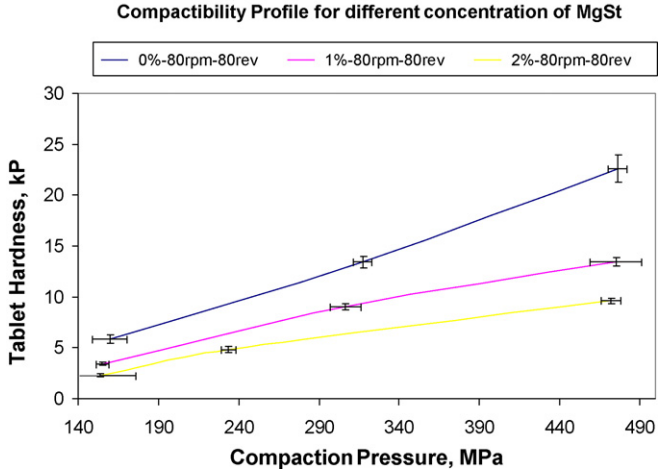

Fig. 10. Effect of lubricant concentration on tablet hardness.

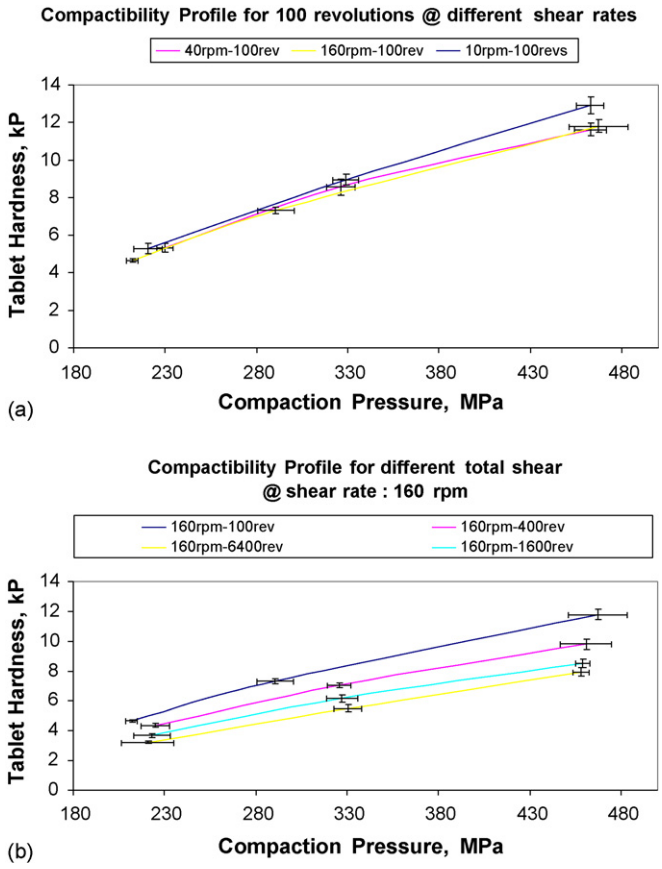

Fig. 11. (a) Effect of shear rate on tablet hardness. (b) Effect of total amount of shear on tablet hardness.

standard tooling. The Presster™ is operated simulating Fette PT 3090 61 station press at 60 rpm (dwell time: 6 ms).

Table 4 shows the treatment conditions under which preblend is sheared and then tablets are made and tested for crushing hardness. For each blend, five tablets are compressed under low, medium and high compaction forces. Tablet crushing hardness is measured for each individual tablet in a standard tablet tester (Dr. Schleuniger, Pharmatron, model 6D). The software that comes with the Presster™ records the values of compaction pressure and tablet hardness and estimates a 95% confidence interval for these two variables. Figs. 10 and 11, which consist of tablet hardness versus compaction forces, represent the CI intervals with error bars. These plots are utilized to analyze the effects of concentration of lubricant, shear intensity and total shear on tablet hardness.

Fig. 10 shows the effect of lubricant concentration on the crushing hardness of tablets. Three blends with varying amounts of magnesium stearate (0–2%) are sheared under the same conditions and subsequently, tablets are made and tested for hardness. It was observed that as magnesium stearate concentration increases, tablet hardness decreases. Fig. 11a and b demonstrates the effect of shear rate and total amount of shear on tablet hardness. Tablets from three blends sheared under rates varying from 4.45 to 71.2 s^{-1} are tested for hardness. Against expectation, in Fig. 11a, it can be observed that shear rate has no effect on tablet hardness.

However, when tablet hardness is plotted as a function of total amount of shear and is found that as the total shear imparted to the system increases, the corresponding tablet hardness decreases subsequently. As shown in Fig. 11b as the total shear is increased from 2670 to 170,890 shear units, the corresponding crushing hardness decreases by 50%.

Table 4
Grid showing the shear environments from which tablets are made and tested for hardness

Shear rates (rpm)	Revolutions				
	25	100	400	1600	6400
10	X	X	X	X	
40		X	X	X	
160		X	X	X	X

4. Conclusions

The results presented here demonstrate the feasibility of the proposed method for characterizing shear effects, and provide an excellent starting point for a systematic study of the effect of shear on critical blend properties (particle size and shape, bulk density, flow properties, and level of cohesion) and tablet properties (hardness, dissolution, friability, and weight variability). The controlled shear cell described here can be used as a formulation tool, to optimize the amount of excipients and additives used in a given product, or as a process development tool, to determine the optimum shear rate and the total shear for a given product.

It was found that the larger the total shear, the more homogeneous the blend. Surprisingly, shear rate appears to have a much smaller effect than total shear. Results show that density of lubricated blend was also affected by total shear. Bulk density increases by about ∼13% and then reaches a plateau, suggesting the existence of two regimes, one where density depends on shear and another where a maximum degree of lubrication-driven densification has been achieved. However, the density of unlubricated blend remains unaffected by total shear.

Unlike lubricated blends, flowability of unlubricated preblends become worse when exposed to increasing amounts of total shear. Finally, as the total shear imparted to the system was increased, the corresponding tablet hardness decreased. However, again there was no effect of shear rate on tablet hardness.

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References

Abdullah, E.C., Geldart, D., 1999. The use of bulk density measurements as flowability indicators. Powder Technol. 102, 151–165.

Aharonov, E., Sparks, D., 1999. On phase transition and self-organized critical state in granular packings. Phys. Rev. E 60, 6890.

Ancey, C., Coussot, P., Evesque, P., 1996. Examination of the possibility of a fluid-mechanics treatment of dense granular flows. Mech. Cohes. Frict. Mater. 1, 385–403.

Andreotti, B., Douady, S.S., 2001. Selection of velocity profile and flow depth in granular flow. Phys. Rev. E 63, 031305.

Aoshima, H., Miyagisnima, A., Nozawa, Y., Sadzuka, Y., Sonobe, T., 2005. Glycerin fatty acid esters as a new lubricant of tablets. Int. J. Pharm. 293, 25–34.

Babic, M., Shen, H.H., Shen, H.T., 1990. The stress tensor in granular shear flows of uniform, deformable discs at high solid concentrations. J. Fluid Mech. 219, 81–118.

de Lourdes Garzón Serra, M., Robles, L.V., 2003. Compatibility of agglomerated mixtures of calcium carbonate and microcrystalline cellulose. Int. J. Pharm. 258, 153–163.

Drake, T.G., 1990. Structural features in granular flows. J. Geophys. Res. 95, 8681–8696.

Ebba, F., Piccerelle, P., Prinderre, P., Opota, D., Joachim, J., 2001. Stress relaxation studies of granules as a function of different lubricants. Eur. J. Pharm. Biopharm. 52, 211–220.

Ebube, N.K., Thosar, S.S., Roberts, R.A., Kemper, M.S., Rubinovitz, R., Martin, D.L., Reier, G.E., Wheatley, T.A., Shukla, A.J., 1999. Application of near-infrared spectroscopy for nondestructive analysis of Avicel powders and tablets. Pharm. Dev. Technol. 4, 19–26.

Fukui, E., Miyamura, N., Kobayashi, M., 2001. Effect of magnesium stearate or calcium stearate as additives on dissolution profiles of diltiazem hydrochloride from press-coated tablets with hydroxypropylmethylcellulose acetate succinate in the outer shell. Int. J. Pharm. 216, 137–146.

Harnby, N., Hawkins, A.E., Vandame, D., 1987a. The use of bulk density determination as a means of typifying the flow characteristics of loosely compacted powders under conditions of variable relative humidity. Chem. Eng. Sci. 42, 879–888.

Harnby, N., Hawkins, A.E., Vandame, D., 1987b. Chem. Eng. Sci. 42, 879–888.

Johansson, M.E., 1984. Granular magnesium stearate as a lubricant in tablet formulations. Int. J. Pharm. 21, 307–315.

Khakhar, D.V., Orpe, A.V., Andersen, P., Ottino, J.M., 2001. Surface flow of granular materials: model and experiments in heap formation. J. Fluid Mech. 441, 255–264.

Mackin, L., Sartnurak, S., Thomas, I., Moore, S., 2002. The impact of low levels of amorphous material (<5%) on the blending characteristics of a direct compression formulation. Int. J. Pharm. 23, 213–226.

Miller, B., O'Hem, C., Behringer, R.P., 1996. Stress fluctuations for continuously sheared granular materials. Phys. Rev. Lett. 77, 3110–3113.

Moodya, G., Rubinstein, M.H., FitzSimmons, R.A., 1984. Tablet lubricants. I. Theory and modes of action. Int. J. Pharm. 9, 75–184 (review article).

Mueth, D.M., 2001. Measurements of particle dynamics in slow, dense granular Couette flow, cond-mat/0103557.

Mueth, D.M., Debregeas, G.F., Karczmar, G.S., Eng, P.J., Nagel, S.R., Jaeger, H.M., 2000. Signatures of granular microstructure in dense shear flows. Nature 406, 385–389.

Podczeck, F., Michael Newton, J., 2000. Powder and capsule filling properties of lubricated granulated cellulose powder. Eur. J. Pharm. Biopharm. 50, 373–377.

Pouliquen, O., Renaut, N., 1996. Onset of granular flows on an inclined rough surface: dilatancy effects. J. Phys. II 6, 923–935.

Ragnarsson, G., Hölzer, A.W., Sjögren, J., 1979. The influence of mixing time and colloidal silica on the lubricating properties of magnesium stearate. Int. J. Pharm. 3, 127–131.

Roggo, Y., Jent, N., Edmond, A., Chalus, P., Ulmschneider, M., 2005. Characterizing process effects on pharmaceutical solid forms using near-infrared spectroscopy and infrared imaging. Eur. J. Pharm. Biopharm. 61, 100–110.

Rowe, R., Sheskey, P., Weller, P., 2003. Handbook of Pharmaceutical excipients, 4th ed. APhA Publications, New York.

Thompson, P.A., Grest, G.S., 1991. Granular flow and the dilatancy transition. Phys. Rev. Lett. 67, 1751–1754.

van der Watt, J.G., de Villiers, M.M., 1997. The effect of V-mixer scale-up on the mixing of magnesium stearate with direct compression microcrystalline cellulose. Eur. J. Pharm. Biopharm. 43, 91–94.

van Veen, B., Bolhuis, G.K., Wu, Y.S., Zuurman, K., Frijlink, H.W., 2005. Compaction mechanism and tablet strength of unlubricated and lubricated (silicified) microcrystalline cellulose. Eur. J. Pharm. Biopharm. 59, 133–138.

Veje, C.T., Howell, D.W., Behringer, R.P., 1999. Kinematics of a two-dimensional granular Couette experiment at the transition to shearing. Phys. Rev. E 59, 739–745.

Vromans, H., Lerk, C.F., 1988. Densification properties and compatibility of mixtures of pharmaceutical excipients with and without magnesium stearate. Int. J. Pharm. 46, 183–192.

Zhang, Y., Campbell, C.S., 1992. The interface between fluid-like and solid-like behaviour in two-dimensional granular flows. J. Fluid Mech. 237, 541–568.