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Application of Powder Rheometer to Determine Powder Flow Properties and Lubrication Efficiency of Pharmaceutical Particulate Systems

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ABSTRACT

The objective of this study was to understand the behavior of particulate systems under different conditions of shear dynamics before and after granulation and to investigate the efficiency of powder lubrication. Three drug powders, metronidazole, colloidal bismuth citrate, and tetracycline hydrochloride, were chosen as model drugs representing noncohesive and cohesive powder systems. Each powder was individually granulated with microcrystalline cellulose and 5%PVP as a binder. One portion from each granulation was lubricated with different levels of magnesium stearate for 5 minutes. The powder characterization was performed on the plain powders, nonlubricated and lubricated granules using powder rheometer equipped with a helical blade rotating and moving under experimentally fixed set of parameters. The profiles of interaction during the force-distance measurements indicate that powder compresses, expands, and shears many times in a test cycle. Test profiles also clearly reveal existence of significant differences between cohesive and noncohesive powders. In all cases lubrication normalized the overall interactive nature of the powder by reducing peaks and valleys as observed from the profiles and reduced the frictional effect. The developed methods are easy to perform and will allow formulation scientists to better understand powder behavior and help in predicting potential impact of processing factors on particulate systems.

KEYWORDS: Powder characterization, powder rheometer, lubrication efficiency, force-distance profile, particulate system.

INTRODUCTION

In pharmaceutical solid dosage forms particulate systems are frequently described as heterogeneous systems with different physical and/or chemical compositions and having a range of particle sizes from a few μm to about a mm. The behavior of such particulate systems, their mixing, flowability, and compression properties are of critical importance during blending, transportation, and scale-up operations. An optimum flow of powder must be achieved to ensure uniform feed from bulk storage containers or hoppers into dies and for achieving reproducible tablets and capsules with acceptable content uniformity, weight variation, and physical consistency. While powders are among the most frequently used materials throughout the pharmaceutical industry, they are the most difficult systems to be characterized. Due to their inherent heterogeneity and segregation tendencies during processing and handling, it is difficult to predict their behavior. Although a huge amount of experience and traditional methods are available, stoppages and problems with quality and processing of powders are still commonplace.

Powder flow characterization by rheological methods such as shear cell has been widely used to measure and predict powder flowability.[1] Conventional indices like bulk density measurements have also been used to this end.[2] In the recent past, many novel and innovative methods of characterization of powders such as avalanching behavior,[3,4] cohesivity determination,[5] dielectric imaging,[6] atomic force microscopy,[7] and application of artificial neural networks,[8] to name a few, have been introduced. These methods have numerous limitations including reproducibility, performance conditions, and predictability. Thus, an easy, reliable, and practical approach for characterizing powders and their flow properties would be valuable in assessing and predicting their performance during handling and scale-up operations.

The study of the rheology of powders by the application of empirical methods to analyze the torque and/or force encountered inside a powder bed has been reported. For example in one study, the resistance to rotation of a propeller stirrer used as a modified viscometer inside a predetermined quantity of a powder bed has been described by Cole[9] as a means to determine cohesivity of powders used in capsule filling. Podczeck and Newton[10] and Podczeck[11] investigated the capsule-filling properties of lubricated cellulose granules by the use of a powder rheometer and concluded that it was possible to discern and identify suitable concentrations of lubricant needed to augment the flowability of the fill material. Freeman[12,13] described several parameters that could serve as specific indices of powder

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flowability derived from a series of experiments using a powder rheometer.

In this study, a modified texture analyzer having a rotating probe for torque measurements was used to study the flow properties of drug powders' granules before and after controlled lubrication. Textural analysis is a technique that has found widespread applications in pharmacy.[14-17]

The texture analyzer-powder rheometer assembly provides for the detection of force and thereby torque by means of a sensitive moving probe in a given sample of powder system as shown in Figures 1, 2 and 3. The force detected versus the distance traveled by the probe, rotating at a predetermined angle into the given powder bed, depicts the work involved in getting the powder to flow around the geometry of the probe. The integration of the area under the force-distance curve for each particulate system based on the cohesivity or other properties can be used for comparative analysis.

The objective of this work was 2-fold: first, to understand and evaluate the behavior of 3 different powders before and after granulation and lubrication, and secondy to apply the proposed method to determine lubrication efficiency of various powders.

MATERIALS AND METHODS

Materials

Three drug powders, bismuth citrate (MCP, CT), metronidazole (Farchemia, Italy), and tetracycline hydrochloride (Sichuan Pharmaceutical Co Ltd, Chengdu, China) were selected as model drugs representing cohesive and noncohesive powders illustrating different ranges of flowability. Microcrystalline cellulose (Avicel PH 101, FMC Corp, Philadelphia, PA), PVP (Plasdone K-25, ISP Technologies Inc, Texas City, TX), and croscarmellose sodium (Ac-Di-Sol , FMC Corp) were used as excipients.

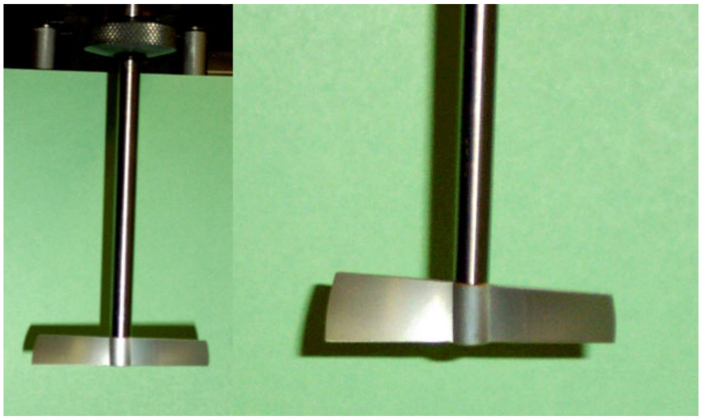

Figure 1. Powder probe of the texture analyzer and the zoomed-in view of the probe showing the blade that describes a true helix as it moves through the powder bed.

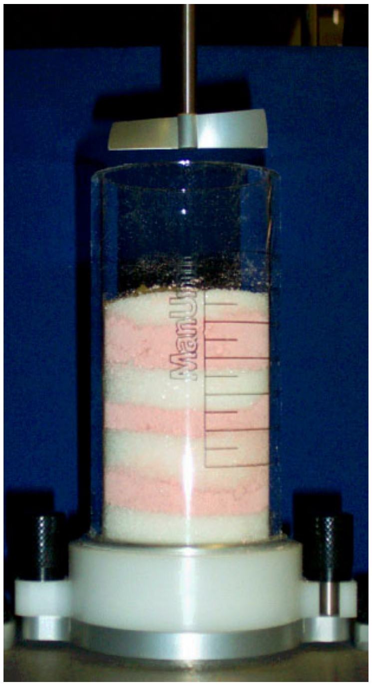

Figure 2. Layers of granulated sugar and calamine are placed in the cylinder to illustrate the helical movement of the probe (as demonstrated in Figure 3).

Methods

Wet granulation

For preparing granules, each powder was individually mixed with microcrystalline cellulose and granulated with 5% wt/vol PVP in deionized water and passed through an oscillating granulator (Erweka Wet Granulator Type FGS, Ottostrasse, Germany) fitted with #20 mesh screen and tray-dried in a convection hot-air oven. After resieving

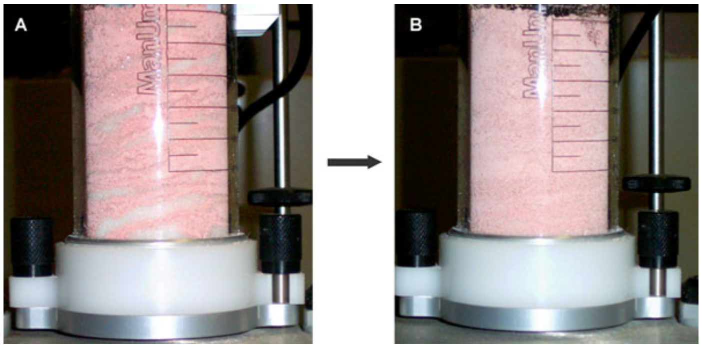

Figure 3. The helical path taken by the probe inside the powder column is shown in (a) and the end result after the probe retreats to its original position is shown in (b).

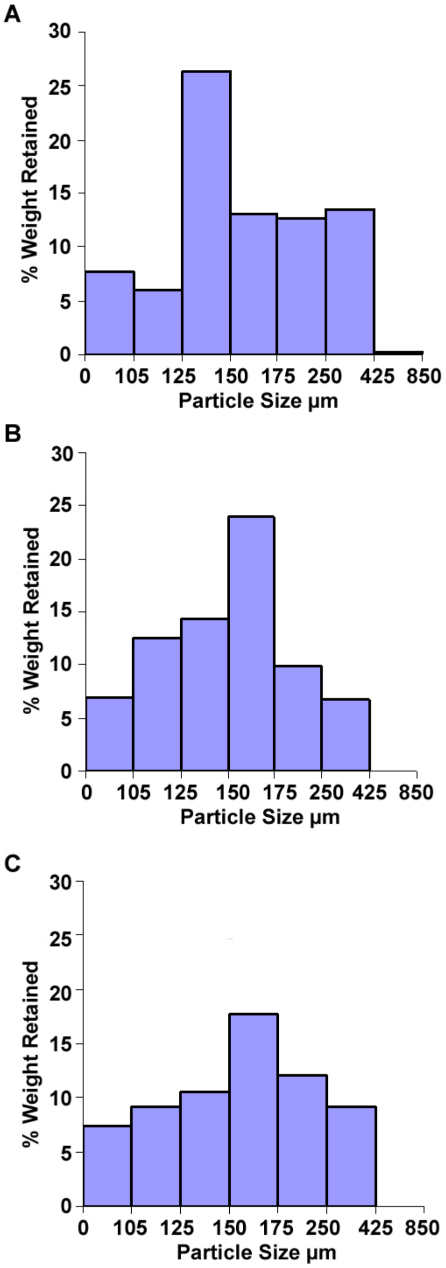

Figure 4. Relationship between percent weight and range of particle sizes for (a) bismuth citrate granules, (b) metronidazole granules, and (c) tetracycline granules.

using #20 mesh screen, the granules were blended with 2% croscarmellose sodium for 5 minutes, using a V-blender. One portion from each granulation was lubricated with 0.5% wt/wt magnesium stearate USP in the V-blender for another 5 minutes.

Sieve Analysis

The particle size distribution of each granulated drug powder was characterized by sieve analysis. A weighed quantity of the granules was passed through a set of nested sieves consisting of United States standard sieves #18, 20, 40, 80, 100, 120, and 140 corresponding to opening sizes of 0.850, 0.425, 0.250, 0.175, 0.150, 0.125, and 0.105 mm. The bottom of the nested assembly was fitted with a collection pan, mounted on a sieve shaker (Derrick Mfg Co, Buffalo, NY) for 5 minutes and the weight retained over each sieve was then determined.

Powder Flow Characterization

The powder characterization was performed on the plain powders as received, nonlubricated and lubricated granules using the ManUmit Powder Rheometer in conjunction with the TA.XT2*i* Texture Analyzer (Texture Technologies Corp, Scarsdale, NY). The instrument was initially calibrated for force, torque, and distance measurements. A cylindrical vessel with a capacity of 200 mL was partly filled with each powder and set on the platform of the texture analyzer. A specific probe capable of describing a true helix pattern as it moves into the powder bed was used to probe and detect various forces of cohesion and adhesion inside the powder bed (Figures 1 and 2). This feature has been illustrated by running a test on a powder bed consisting of layers of granulated sugar and calamine powder (Figures 2 and 3). The helical blade naturally cuts through the bed of powder being tested and the overall force/torque relationship with distance is integrated.

During a typical test the probe rotates and travels downward (ie, compression mode) at an angle of 45° and at a speed of 10 mm/s into the effective powder bed zone followed by an upward movement (ie, lifting mode) at an angle of 175° and at a speed of 50 mm/s. Each powder bed was subjected to 4 runs.

The force-distance profile of the effective zone in the powder column (ie, the middle two thirds of the powder bed) between 33 and 63 mm of the distance that the probe traveled was integrated for the plain powder, unlubricated and lubricated granules. The effective zone was chosen in such a way that the probe was completely inside the powder bed and fully capable of interacting with the bulk of the powder. Prior to actual data collection, the powder bed was subjected to a full cycle of probe movement as described above to normalize the potential variabilities in the powder bed, which might have occurred during powder filling.

Lubrication Efficiency

By systematically varying the percentage of lubricant added the efficiency of lubrication was studied by comparing the mean force that was detected inside the powder bed. Each

Table 1. Summary of the Salient Parameters Determined for Each Test Material (each value is mean of 4 data points ± SD)*

Materials	Total Work Done† J (Mean Â ± SD)	Gradient† N/m	Mean Force† N	Count of Positive Peaks†	Count of Negative Peaks†	% Reduction in Work Done for Lubricated Granules Relative to Unlubricated Granules
Bismuth citrate						
Plain powder	0.023 ± 0.001	50.45 ± 1.59	0.76 ± 0.02	1.00 ± 1.16	1.00 ± 1.16	
Unlubricated granules	0.094 ± 0.007	209.05 ± 20.43	3.14 ± 0.22	18.75 ± 3.20	18.25 ± 3.59	
Lubricated granules	0.023 ± 0.002	39.76 ± 4.79	0.76 ± 0.07	4.25 ± 1.26	3.50 ± 1.73	75.69
Metronidazole						
Plain powder	0.045 ± 0.001	37.43 ± 4.11	1.49 ± 0.05	4.75 ± 0.96	4.25 ± 1.26	
Unlubricated granules	0.042 ± 0.003	18.12 ± 3.63	1.41 ± 0.09	9.00 ± 2.45	9.25 ± 2.22	
Lubricated granules	0.026 ± 0.000	34.42 ± 8.13	0.88 ± 0.01	7.00 ± 0.00	7.00 ± 0.00	37.49
Tetracycline						
Plain powder	0.134 ± 0.006	181.12 ± 27.05	4.48 ± 0.19	18.00 ± 1.41	17.50 ± 1.92	
Unlubricated granules	0.062 ± 0.005	105.38 ± 14.38	2.08 ± 0.17	18.50 ± 1.73	18.50 ± 1.73	
Lubricated granules	0.025 ± 0.002	32.04 ± 6.08	0.82 ± 0.06	8.75 ± 0.96	8.25 ± 0.50	60.38

* Lubricated granules refer to 0.5% wt/wt magnesium stearate.

† For definition of each parameter please refer to Figure 5.

type of granules was lubricated for 5 minutes at increasing levels of magnesium stearate, namely 0.5, 1, and 1.5% wt/wt of the total weight of the granule. Each powder bed was subjected to 4 runs.

RESULTS AND DISCUSSION

Particle Size Distribution

The percentage weight retained over each sieve was plotted as a bar chart depicting the particle size distribution for each of the granules as shown in Figure 4. Bismuth citrate granules showed an uneven distribution of particle sizes, which could be an indicator of a poorly granulated and consequently poorly flowing powder. It should be noted that this powder is in colloidal form and therefore highly fluffy. With the exclusion of powder collected in pan, metronidazole and tetracycline granules showed a very similar distribution, which is generally expected of the granulation method. The nature of the flow for each of the granulates was different when force-distance behavior was analyzed (see data in Table 1).

Furthermore, variations in particle size distribution and the physicochemical nature of the materials have clearly substantiated the poor flow properties of the cohesive bismuth citrate, moderate flow properties of the less-cohesive metronidazole, and the noncohesive flow properties of tetracycline granules. In all cases lubrication normalized the overall interactive nature of the powders according to the shearing conditions and work done (see Table 1), and significantly reduced the frictional effect. It is also shown that when powders have comparable profiles (force-distance) their flow behavior might be more predictable, which may be translated into greater content uniformity and weight uniformity as long as powder composition is representative of the bulk from which it is removed and analyzed. This observation is consistent with recently published work.[18]

Powder Flow Characterization Results

As probe movement is controlled and set by the rheometer, powders that flow freely will exhibit very little resistance (shear) in force or torque sensed through the powder bed in either a downward or an upward direction. Conversely, poorly flowing powders (cohesive) exhibit substantial amount of resistance in force or torque in either direction. As the probe travels through the powder bed in both compression (downward) and lifting (upward) modes, powders resist the moving and rotating blade. Powders that cake will resist the blade's downward progress and will exhibit greater force and fluctuations in peaks and valleys. Cohesive powders that form relatively stronger physical contacts under pressure generally show caking. Powders that do not cake exhibit very little force as the blade progresses through the sample. In the context of this work and specifically pharmaceutical particulate systems, the total work done might be related to cohesiveness. However, under circumstances where powders may contain large amounts of entrapped air or having coarse characteristics, this generalization might not be true.

Powders that flow easily will freely cascade over and around the blade, generating a smooth force-distance profile. If the powder momentarily bridges, arches, forms cohesive bonds, or, in the case of granules, if the particles nestle, the moving blade will break these occurrences. The observed force or torque increases as the bonds are made and stressed followed immediately by a drop in force or torque as the bonds fail. The peaks and valleys of the force-distance profiles lucidly illustrate this concept. Figure 5 describes the useful parameters that are determined by this analysis on a typical powder bed.

Figure 6 illustrates the force-distance profiles of the typical compression (downward movement) and lifting (upward movement of the probe) patterns for unlubricated granules of bismuth citrate, metronidazole, and tetracycline hydrochloride, respectively. Powder flowability can be quantified from the curves by integrating the area under

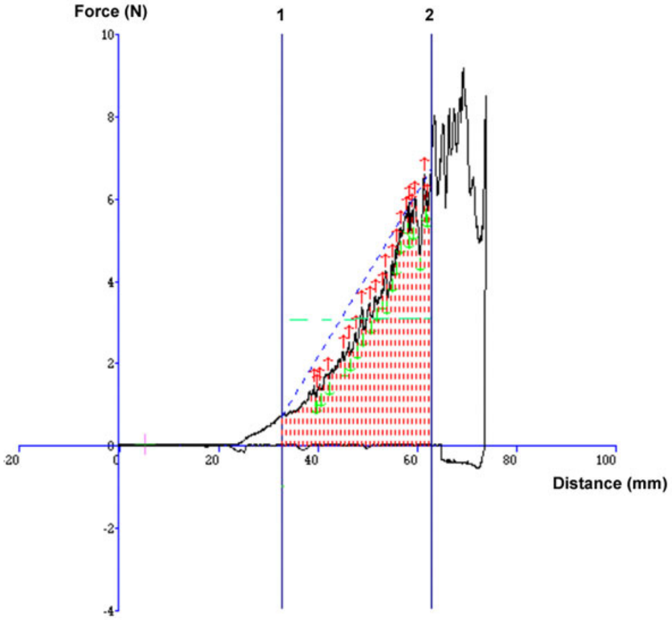

Figure 5. Typical force distance profile for a particulate system. The effective zone of interest is enclosed by the 2 anchors 1 and 2 and the various parameters that are determined from the textural analysis are • AUC – area under the curve representing integrated force-distance profile between the anchors 1 and 2 (Joules) • Gradient – the slope of the curve between anchors 1 and 2 (N/m) • Mean force – the mid-point value of force between the anchors 1 and 2 (N) • Positive peaks – force peaks on the curve between the anchors 1 and 2 shown by upward arrows • Negative peaks – force troughs on the curve between the anchors 1 and 2 shown by downward arrows.

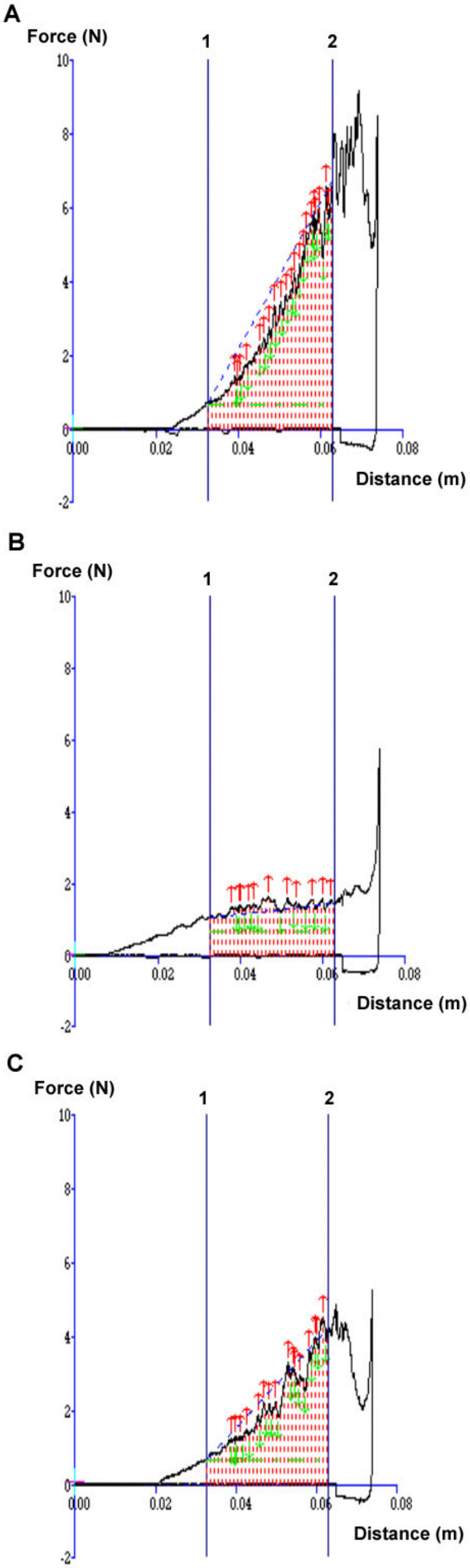

Figure 6. Force-distance profiles of unlubricated granules of (a) bismuth citrate, (b) metronidazole, (c) tetracycline hydrochloride (n = 4 for each unlubricated granules).

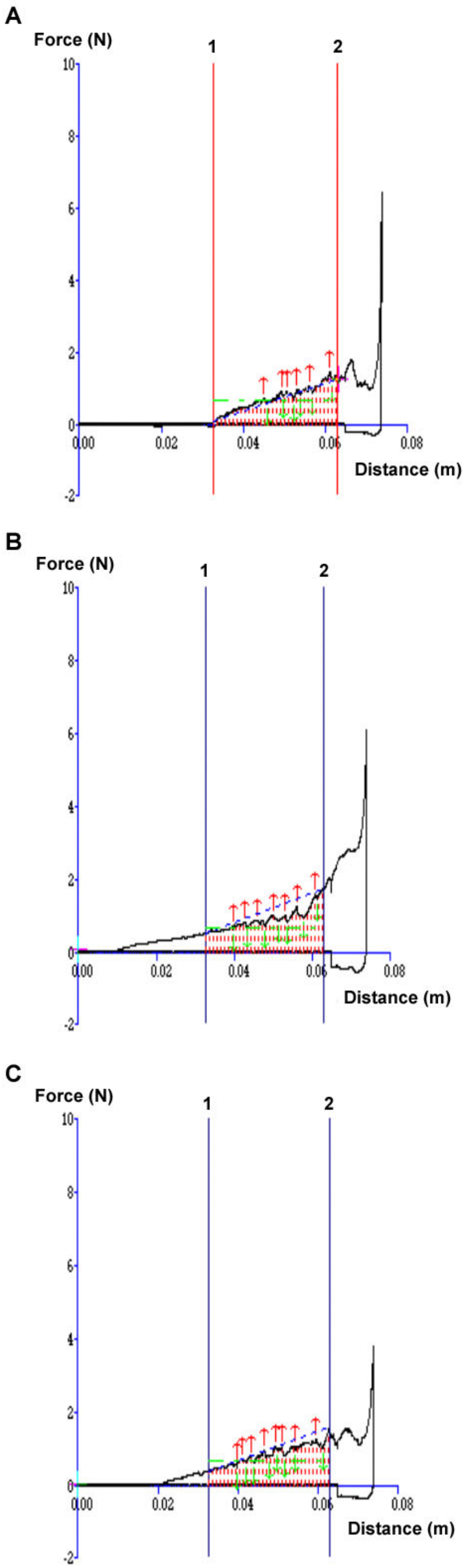

Figure 7. Force-distance profiles of lubricated granules of (a) bismuth citrate, (b) metronidazole, (c) tetracycline hydrochloride (n = 4 for each lubricated granules).

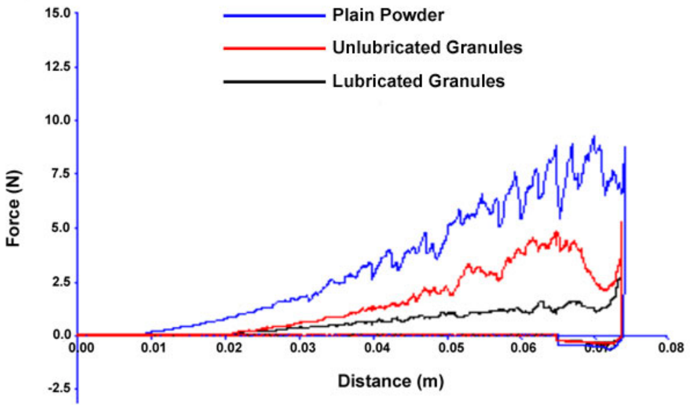

Figure 8. Typical F-D profiles of plain powder, unlubricated granules and lubricated granules of tetracycline showing reduction in AUC or work and smoothening of the profile.

the force-distance profiles, which will represent the energy or work done by the blade to break the resistances to movement of the blade within the powder bed for a given powder sample. As can be seen from Figure 7 the areas under the curves for identical but lubricated granules is significantly reduced relative to the curves of unlubricated granules (see Figure 6). It is also evident that lubrication tends to smooth the force-distance curve resulting in overall reduction in various peaks and valleys that are often observed in the measurements within the effective zone.

Figure 8 depicts the typical force-distance profile obtained for tetracycline hydrochloride powder as received as well as the lubricated and unlubricated granules. The force detected and shear resistance on the lubricated granules was significantly lower as compared with the unlubricated granules or the plain powders; therefore in properly granulated powders magnesium stearate could also improve the flowability of the system by reducing particle-particle friction in addition to its main role in facilitating tablet consolidation and ejection. The computed results of area and other salient parameters of the tests are summarized in Table 1.

Efficiency of Lubrication

To study the efficiency of lubrication, the mean force detected inside the effective zone of the powder column was determined for granules lubricated with 0.5, 1 and 1.5% wt/wt magnesium stearate. The results obtained are shown in Figure 9. It is evident that 0.5% w/w magnesium stearate brings about the greatest reduction in the mean force detected within the powder bed by the helical probe, when compared with 1% and 1.5% wt/wt. Further lubrication beyond 0.5% wt/wt only partially improved the powder flow and the overall frictional resistances within the zone of interest.

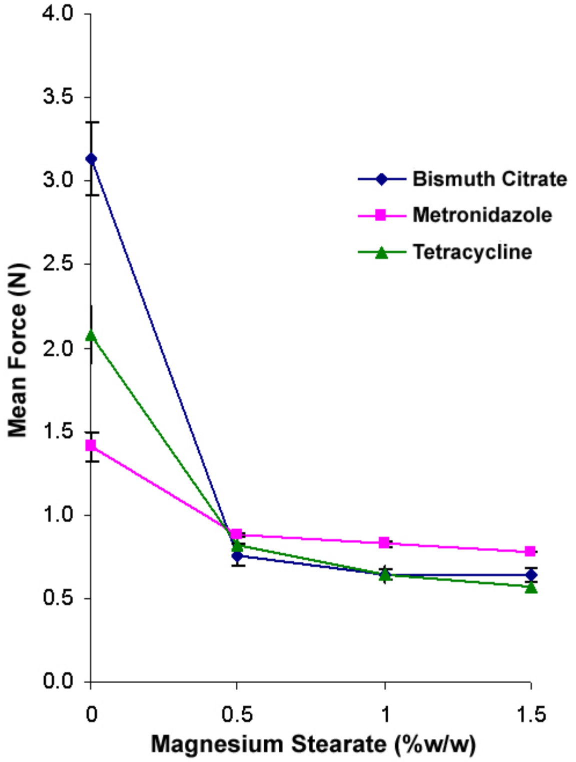

Figure 9. Lubrication efficiency for each type of granules when lubricated for 5 minutes with 0.5, 1, and 1.5% wt/wt of magnesium stearate (n = 4).

Results also show that total work done by the probe on 0.5% wt/tw lubricated granules relative to unlubricated granules was reduced by 75.69%, 37.49%, and 60.38% for bismuth citrate, metronidazole, and tetracycline hydrochloride granules respectively (see Table 1). Based on the observation, it may be suggested that 0.5% wt/wt magnesium stearate may be regarded as optimum and most conducive to the enhancement of powder flow and lubrication with the least adverse effect on tablet hardness and consolidation process.

CONCLUSIONS

The profiles of simultaneous interaction of a helical blade due to shear stress, strain, and powder heterogeneity during the force-distance movement indicate that powder compresses, expands, and shears many times in a test cycle. The applied test is capable of differentiating between properties of cohesive, noncohesive, granulated, or plain powders. The detection reliability and reproducibility is partly due to the manner in which the rheometer conditions the powders to exactly the same work history and the precise imposition of controlled forces onto the powders with subsequent force detection. The method also lends itself to predictable and easy characterization of powder properties and system dynamics before and after transportation, mechanical vibration, and aeration.

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