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Mixing order of glidant and lubricant – Influence on powder and tablet properties

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ABSTRACT

The main objective of the present work was to study the effect of mixing order of Cab-O-Sil (CS) and magnesium stearate (MgSt) and microlayers during mixing on blend and tablet properties. A first set of pharmaceutical blend containing Avicel PH200, Pharmatose and micronized acetaminophen was prepared with three mixing orders (mixing order-1: CS added first; mixing order-2: MgSt added first; mixing order-3: CS and MgSt added together). All the blends were subjected to a shear rate of 80 rpm and strain of 40, 160 and 640 revolutions in a controlled shear environment resulting in nine different blends. A second set of nine blends was prepared by replacing Avicel PH200 with Avicel PH102. A total of eighteen blends thus prepared were tested for powder hydrophobicity, powder flow, tablet weight, tablet hardness and tablet dissolution. Results indicated that powder hydrophobicity increased significantly for mixing order-1. Intermediate hydrophobic behavior was found for mixing order-3. Additionally, mixing order 1 resulted in improved powder flow properties, low weight variability, higher average tablet weight and slow drug release rates. Dissolution profiles obtained were found to be strongly dependent not only on the mixing order of flowing agents, but also on the strain and the resulting hydrophobicity.

1. Introduction

Flowing agents, lubricants, and anti-sticking agents such as Cab-O-Sil (CS), magnesium stearate (MgSt) and talc have been widely used in pharmaceutical formulations in order to enhance the flowability of powder mixtures (Johansson and Nicklasson, 1986; Hussain et al., 1988). Optimal concentrations of these excipients are critical factors for flow enhancement for reducing die friction and improving tabletability. It has been reported that powder mixtures containing 1% (or sometimes much less) colloidal silica displayed greatly improved flow properties (Chowhan and Yang, 1983). However, when multiple flowing agents were used in powder mixtures, they display interactions among each other which are modulated by the shear history of the blend (Pingali et al., 2010, in press). Moreover, all of these ingredients potentially affect both processing performance and finished product quality attributes. Interaction between these multi-component flowing agents and the shear history during processing influences the powder flowability, content uniformity, tableting performance and drug release characteristics. Thus, the development of an optimized formulation/process requires multivariate analysis of the joint effects of formulation parameters and processing conditions on multiple system responses.

Shear histories of a blend are not only scale dependent but also equipment dependent. Therefore, they are affected by process changes which often occur during the life cycle of a product. Since any blend can be (and to some extent is) subjected to infinitely many shear histories, the determination of the optimum combination of excipients and shear history to optimize multiple material responses, both during processing and in finished products, is a complex task. While the pharmaceutical manufacturing community is aware of the fact that excessive shear can adversely affect product properties in lubricated blends, many issues are only starting to be examined. For example, the impact on blend and product physical characteristics caused by the addition and mixing of multiple flowing agents at different times or all at once time is relatively unknown. Other than some data showing that high uniformity of MgSt is undesirable, the desirable degree of uniformity of excipients is unclear. Clearly, given the large number of interacting variables involved, some mechanistic understanding that could provide *a priori* guidance regarding order of addition and selection of shear protocols is highly desirable.

In the present study we investigated the effect of the order of addition of two commonly used excipients, CS, a commonly used glidant, and MgSt, a universally used lubricant that also has glidant properties. The role of glidants and lubricants on tablet properties

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Table 1
Formulations and blend compositions prepared with various shear conditions (40, 160 and 640 revolutions) at a shear rate of 80 rpm.

	Formulations	Shear conditions		
		40 (revolutions)	160 (revolutions)	640 (revolutions)
Mixing protocol-1 (CS added first) (M1)				
B1	9% Mic.acetaminophen + 44.5% Avicel PH200 + 44.5% Pharmatose + 1% CS (first addition) + 1% MgSt.	S1	S2	S3
B2	9% Mic.acetaminophen + 44.5% Avicel PH102 + 44.5% Pharmatose + 1% CS (first addition) + 1% MgSt.	S4	S5	S6
Mixing protocol-2 (MgSt added first) (M2)				
B3	9% Mic.acetaminophen + 44.5% Avicel PH200 + 44.5% Pharmatose + 1% MgSt (first addition) + 1% CS.	S7	S8	S9
B4	9% Mic.acetaminophen + 44.5% Avicel PH102 + 44.5% Pharmatose + 1% MgSt (first addition) + 1% CS.	S10	S11	S12
Mixing protocol-3 (CS and MgSt added together) (M3)				
B5	9% Mic.acetaminophen + 44.5% Avicel PH200 + 44.5% Pharmatose + [1% CS + 1% MgSt] [together].	S13	S14	S15
B6	9% Mic.acetaminophen + 44.5% Avicel PH102 + 44.5% Pharmatose + [1% CS + 1% MgSt] [together].	S16	S17	S18

has been explored in recent years. Combined usage of a glidant and lubricant in a formulation was found to improve powder flow properties (Lindberg et al., 2002). The influence of binders and lubricants affecting the mechanical strength of tablets has been widely reported (Chowhan, 1980; Sheskey and Robb, 1995). Previous findings showed that when MgSt alone was used in the formulation, level of MgSt in the powder mix did not always change the rate or the amount of drug released (Sheskey and Robb, 1995). Moreover, crushing strength sometimes was found to increase with an increase in the MgSt level (0.2–2%). However, increase in the mixing time of MgSt is known to decrease the tablet hardness (Kikuta and Kitamori, 1994). Therefore, it is interesting to investigate the effect of MgSt when used along with other flowing agents like talc and CS, and to examine the interactions between composition and strain history.

It has been previously reported that cohesion of the mix increased when the mixing ratio of fine solid flow additives such as talc, MgSt and CS was above 0.5 (Wakiyama et al., 1994). Interestingly, binary and ternary mixtures of MgSt, talc and CS were found to act as dissolution retardants in powder mixtures (El-Shabouri, 2003). In addition, increase in hydrophobicity strongly correlated to reductions in tablet hardness when silica and MgSt were used in the powder blend (Ohta et al., 2003a,b). Therefore, along with MgSt, CS was also known to have a significant role in altering physical characteristics of powder blends. CS was found to increase the tablet hardness obtained when using lubricated blends (Van Veen et al., 2005) and decrease adhesion of MgSt to the punch tip (Roberts et al., 2004). Furthermore, concentration of CS was found to affect the lubrication efficiency of the blend (Sabir et al., 2001). More importantly, mixing CS with the powder blend prior to lubrication with MgSt was found to maintain the lubrication efficiency of MgSt (Sabir et al., 2001). The drug release profile of the blend containing both MgSt and CS was found to be similar to the blend containing MgSt alone (Lee et al., 1999). Our previous study showed that the tablets containing MgSt and CS have slower drug release rate than the tablets containing only MgSt (Pingali et al., 2010, in press). Porosity of flowing agents (Ohta et al., 2003a,b), lubricant–glidant ratio (Khan et al., 1995) and grades of glidant (Kucera et al., 2008) were found to affect the drug release rates.

In addition to flowing agents, drug to excipient ratio (Pather et al., 1998) and type of lubricant (Bastos et al., 2008) in the powder mix were also found to influence physicochemical characteristics of tablets (Bastos et al., 2008). For example, formulations prepared with stearic acid showed higher hardness and higher percentage of drug release compared to a formulation prepared with MgSt (Bastos et al., 2008). Another study showed that use of excipients such as lactose and microcrystalline cellulose in formulations increased the rate of drug release (Levina and Rajabi-Siahboomi, 2004). Until now, there have been many studies on the drug release behavior in the presence of lubricant alone and glidant alone or in combination of both. However, there has been no study to show the impact on drug release behavior when CS and MgSt were added at different times during the process. Moreover, the changes in physical parameters affecting the drug release profiles due to mixing conditions and mixing order of CS and MgSt are not understood. Several studies were done on lubricant sensitivity, interactive mixtures and order of mixing related to their bonding properties (Bolhuis et al., 1987, 2003; Bolhuis and Holzer, 1996; Louey et al., 2003; Louey and Stewart, 2002; Sundell-Bredenberg and Nystrom, 2001). Although interactive mixtures were studied, formation of microstructures due to interaction of lubricant and glidant with excipient and active drug ingredient by varying the mixing order was not investigated in the aforementioned prior literature in reference to finished product properties. The formation of microlayers during the process of mixing which in turn affected the product properties was poorly understood and is the primary focus of our research work.

The main purpose of the study reported here was to explore the influence of mixing order of CS and MgSt and formation of microlayers during mixing on blend hydrophobicity, blend flow properties and tablet dissolution. Two sets of pharmaceutical blends comprising of four formulations each were prepared and exposed to different strain histories. In the first set, CS was added at the beginning and MgSt was added midpoint through the mixing process. In the second set, MgSt was added first and CS was added at the midpoint. Subsequent to mixing, all blends were exposed to three levels of strain following the completion of the blending process. Both sets of blends were tested for blend hydrophobicity and blend flow properties. Tablets were pressed from these blends and were tested for their dissolution properties.

2. Materials and methods

2.1. Materials and sample preparation

Powder blends were prepared by mixing Pharmatose (Foremost Farms, mean particle size 100 μm) and either Avicel PH102 (FMC, mean particle size 90 μm) or Avicel PH200 (FMC, mean particle size 190 μm) as excipient materials, micronized acetaminophen (APAP; Mallinckrodt Inc., mean particle size 19 μm) as an active ingredient, MgSt (Mallinckrodt, mean particle size: 38 μm) as a lubricant, and CS (Cabot, mean particle size: 15 nm) as a glidant. The formulation contains 50–50% Pharmatose–Avicel (44.5% Pharmatose (w/w) and 44.5% Avicel (w/w) in total formulation), 9% acetaminophen, 1% MgSt and 1% CS. Two sets of blends with three mixing protocols and

three shear conditions each (a total of 18 blends) were prepared by varying the mixing order of CS and MgSt.

2.1.1. Samples preparation

2.1.1.1. Mixing order 1. In the preparation of the first mixing protocol (M1), API–Avicel–Pharmatose mixture was gently mixed in a V-blender at a shell speed of 15 rpm for 5 min. CS was first added to the excipients/acetaminophen preblend in a V-blender and was mixed with a shell speed of 15 rpm for 5 min (75 revolutions). Subsequently, MgSt was added to the blend and the blender was operated for another 5 min/75 revolutions. Care was taken such that the mixing time prior to adding MgSt was 75 revolutions and after adding MgSt was 75 revolutions each with a total mixing action not exceeding 150 revolutions. The intensifier bar was not operated in order to mix the powders with minimum shear in the V-blender. The blended powder was then unloaded from the V-blender and was split into three sets. These three samples were subjected to a controlled shear environment in a modified Couette cell equipped with equidistant baffles (Mehrotra et al., 2007). The shear rate for all the samples was 80 rpm, i.e., only strain was varied while keeping the shear rate constant. The first sample was subjected to a strain level of 40 revolutions, the second sample was subjected to a strain level of 160 revolutions, and third sample was subjected to a strain level of 640 revolutions, respectively.

2.1.1.2. Mixing order 2. The second mixing protocol (M2) was prepared by adding MgSt at the beginning, mixing for 75 revolutions at 15 rpm, and later adding CS and mixing for an additional 75 revolutions at 15 rpm. Except for the order of addition, the same mixing process and composition as mentioned above for M1 was also repeated for M2.

2.1.1.3. Mixing order 3. In the third mixing protocol (M3), MgSt and CS were added together to the excipient/acetaminophen preblend. The blend is mixed in the V-blender for 150 revolutions at 15 rpm and then was subjected to three different shear conditions as mentioned above. Therefore, a total number of nine samples were collected by operating both the blends M1, M2 and M3 at three different strain levels in the Couette controlled shear environment. The blends and formulations are listed in Table 1. Another nine sets of samples were prepared by replacing Avicel PH200 (mean particle size: 190 μm) with Avicel PH102 (mean particle size: 90 μm). Mixing orders-1–3 were repeated for the formulation containing Avicel PH102. In conclusion, nine samples (three each from mixing orders 1–3) were prepared with the formulation containing Avicel PH200 (stage 1) and another nine samples (three each from mixing orders 1–3) with the formulation containing Avicel PH102 (stage 2).

3. Methods

A small quantity of (30 g) each sample was analyzed for hydrophobicity. Adsorption of water through a column of powder was analyzed in this method using Washburn (1921) technique. The equipment consists of a glass column and a glass filter. In order to pack the powder reproducibly, the column was tapped 500 times in a tap density meter. The column was then fixed to a stand and submerged into a solution saturated with all soluble components in the mixture. The rise of water through the powder bed was measured by recording the change in weight of the powder bed as a function of time. A detailed experimental procedure of measuring powder hydrophobicity was discussed in our previous work (Pingali et al., 2010, in press).

Flow index and dilation measurements were carried out to characterize the flow properties of powder blends. A quantity of 2 kg

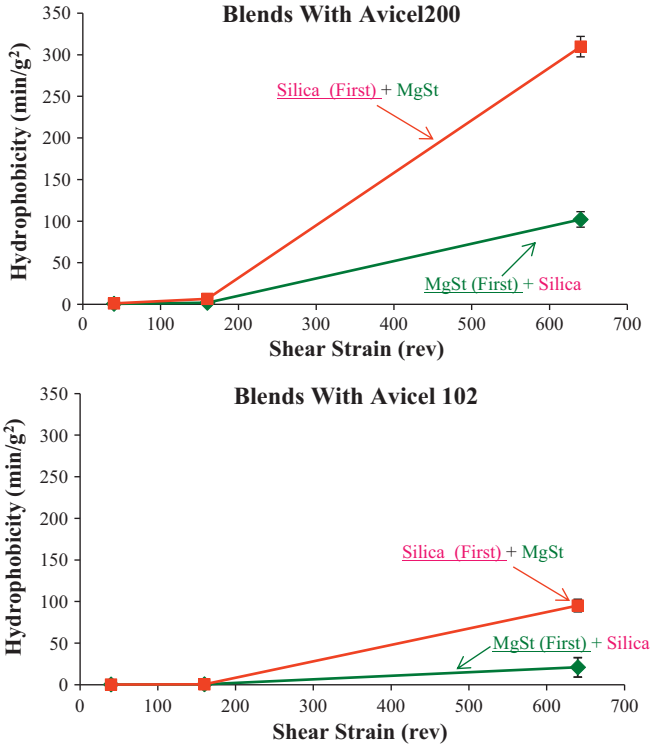

Fig. 1. Effect of mixing order of flowing agents (CS and MgSt) on powder hydrophobicity. In all cases, hydrophobicity increased more whenever CS was added to the blend first, prior to mixing with MgSt. First addition of silica in the blends increased hydrophobicity more for the blends containing Avicel PH200 than the blends containing Avicel PH102.

from each sample was used in these measurements. The gravitational displacement rheometer (GDR) was used to measure flow index. The equipment consists of a rotating cylinder with powder, mounted on a pivoted table supported by a load cell. The variability on the force acting on the load cell caused by the avalanches of the powder movement at various rotational speeds was recorded. In this method, the more cohesive the powder is, the larger the avalanches are, and correspondingly, the larger the fluctuations in the force experienced by the load cell. These force measurements were used to compute the standard deviation of the position of the center of mass of the powder bed. The average of this standard deviation for four rotational speeds (5, 10, 15, and 20 rpm) is the flow index. In the dilation technique, flow is generated from a consolidated bed condition, and the percentage change in powder bed volume was measured as a function of time. A video capturing the powder movement through the cylinder's transparent side wall was converted into still images and the bed volume in each still was measured by digital imaging. A detailed description of these techniques was provided elsewhere (Faqih et al., 2006; Pingali et al., 2009).

Tablets were pressed in a rotary tablet press (MTP-8) at a constant compression force of 12 kN. A sample size of 0.5 kg of sheared powder was loaded into the feed hopper. During the operation of the tablet press, tablet thickness and punch speed handwheels were adjusted by simultaneously monitoring the pressure display of the tablet compression step on the computer interface. Tablet weight variability was minimized by discarding the initial tablets until the compression force stabilized. The speed of the feed frame was 30 rpm and the die diameter was 10 mm. A total of 100 tablets were collected from each sample loaded in the feed hopper. Tablet weight and tablet hardness were recorded for all the tablets manually. A crushing hardness tester (Pharmatron Dr. Schleuniger Tablet Hardness Tester) was used to measure the tablet hardness. The

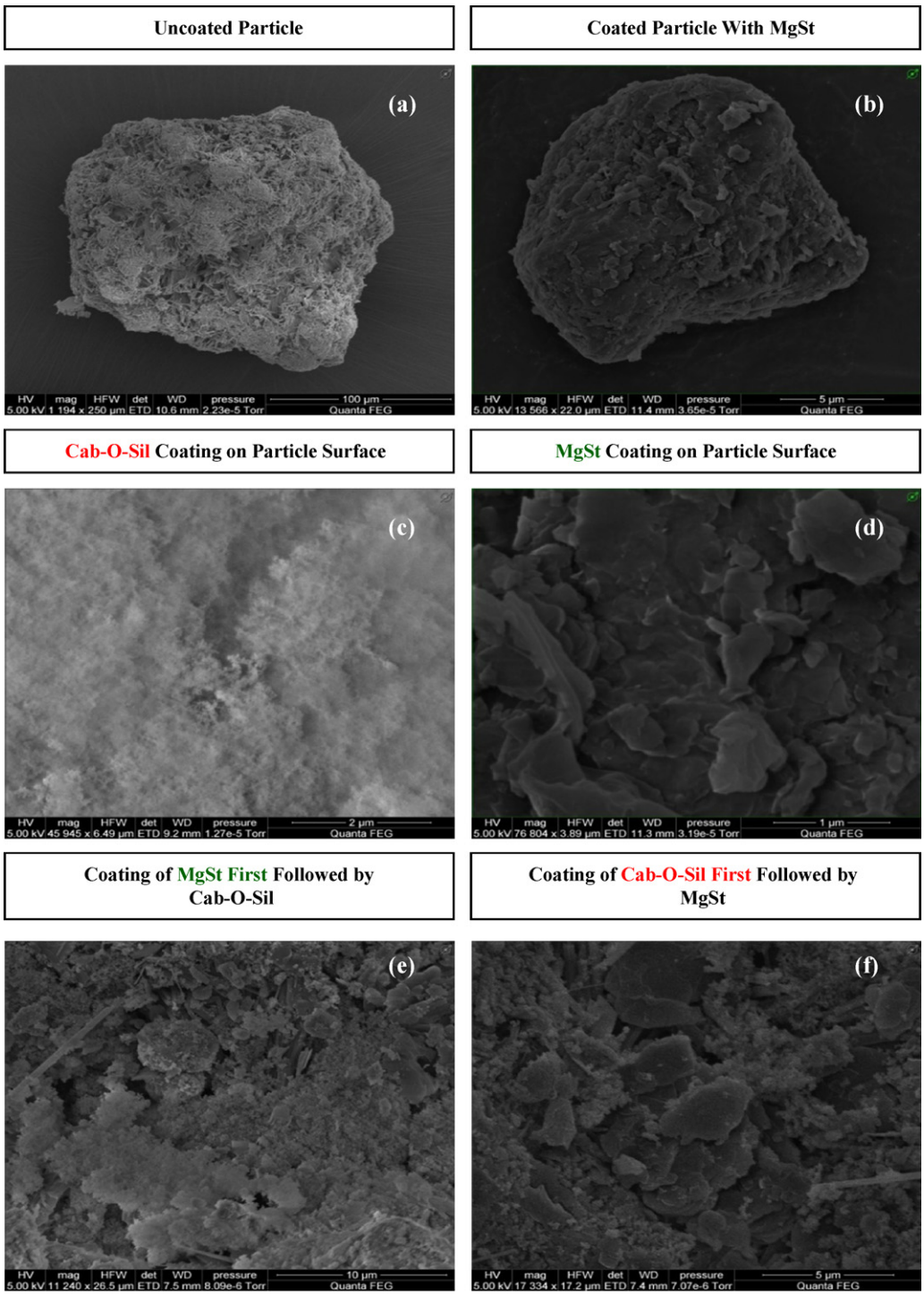

Fig. 2. SEM images of coating of MgSt and CS on particle surface. MgSt formed flakes on particle surface whereas CS was deposited as tiny spherical particles. The coatings of one over the other forming layer over layer can be seen.

digital display of force at which the tablets were broken was recorded for 100 tablets and their average and standard deviation values were recorded for every sample.

Finally, dissolution tests were performed on the tablets pressed from each sample using a modified USP method (USP II apparatus, Vankel VK7010). Eight tablets from each tablet/blend sample were used in this study. A full release profile of the dissolving tablets was monitored for 90 min. Absorbance was read every 2 min. The weight of tablet during dissolution recorded was used with the percentage active concentration of the formulation to derive a percentage drug release profile. A detailed discussion of this measuring technique can be found in our previous work (Pingali et al., 2010, in press).

4. Results and discussion

4.1. Effect of mixing order of silica and MgSt on powder hydrophobicity

Results of hydrophobicity of all sheared blends show that blends sheared with MgSt and CS exhibit significant increases in the time required for moisture uptake (Fig. 1). To some extent,

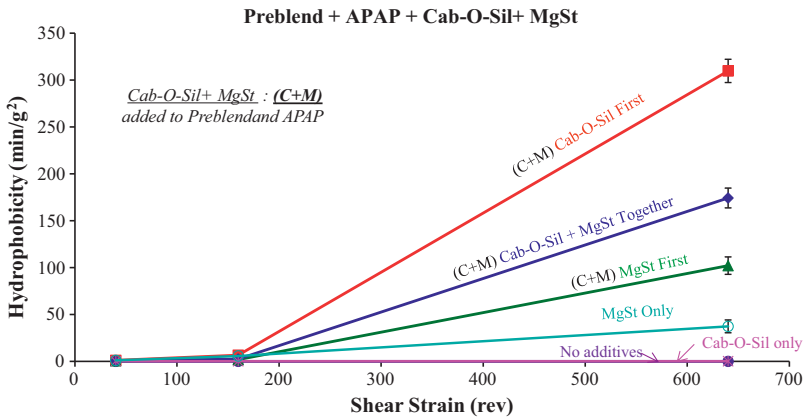

Fig. 3. Comparison of ordered mixing and combined mixing of CS and MgSt. Interestingly, when both the lubricant and glidant are added together, hydrophobicity was found to exhibit intermediate behavior. It is evident that blends exposed to high shear environment showed high hydrophobicity.

this is expected, since all the blends contain MgSt, a hydrophobic component. However, what is completely unexpected is that hydrophobicity increases much more when CS is added to the blend first. This is contrary to expectations because under this blending condition, MgSt experiences slightly less shear (since it is added last) yet the result is higher hydrophobicity.

One possible explanation for the results in Fig. 1, which have been reproduced three times, is that an ordered mixture could be created during blending (Hersey, 1975). In this model; as CS and MgSt are added to the blend, they would cover the major portions of excipients and API, forming an onion-like structure. Such a structure, as shown in Fig. 2, would survive the subsequent application of shear, perhaps consolidating by normal stress during particle collisions. In this model, whichever ingredient is added last would be on the outside of these composite particles. Thus, when CS is added first, MgSt would end up in the outer layer of the composite particles, and the resulting blend would be more hydrophobic.

The coating morphology of CS and MgSt on an excipient particle surface as a result of applied shear was examined by FESEM. The images showed that the resultant coating of CS on a larger particle surface displayed a "cloudy" agglomeration of nanoparticles (Fig. 2(c)) whereas MgSt coating displayed hard aggregates of thin irregularly shaped flakes (Fig. 2(d)). The individual coated particles of excipient either with MgSt or CS clearly exhibited different surface structures regardless of the shear intensity. This can be attributed to the particle size, shape and density of CS and MgSt. The nanosized particles of CS tend to form an inhomogeneous porous layer on the particle surface. On the other hand, since MgSt is a wax-like substance, exposure of particles to high shear is expected to cause a continuous attrition of MgSt particle, in which a layer-by-layer is removed by shear intensity. Such a phenomenon is expected to deposit irregular shaped MgSt layers on excipient particle surfaces as seen in Fig. 2(d). The uniformity of coating, however, depends upon the time of exposure to applied shear (shear strain). To better visualize the structure of coating, the surfaces of coated particles with either CS or MgSt only were compared with the structure of particles surfaces coated with both MgSt and CS, but using different mixing orders. Major differences can be observed in Fig. 2(e) and (f) for different mixing orders. Deposition of CS particles on top of MgSt deposits can be observed in Fig. 2(e) where the blends were mixed first with MgSt. In comparison, when CS was first mixed in the blend, followed by MgSt, an irregular shaped layer of MgSt deposition was seen on top of CS particles (Fig. 2(f)). Overall, the interactions between MgSt and CS and with excipient particle surface play a vital role in understanding the onion-like structures of nanocoatings formed under shear environment.

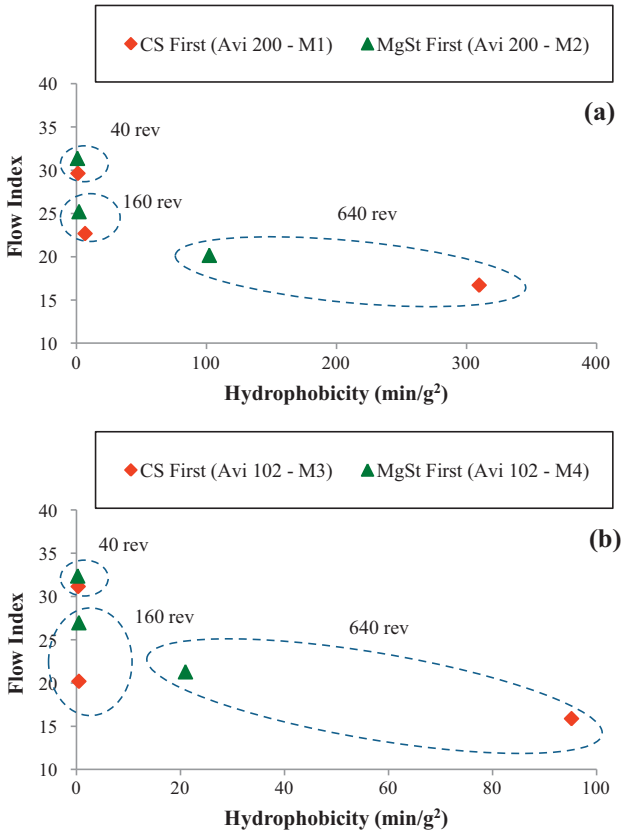

Fig. 4. Relation between hydrophobicity and powder flow. Blends of mixing order-1 (CS first) have shown low flow index (improved powder flow). An increase in powder hydrophobicity was associated with a corresponding decrease in flow index for the blends mixed first with CS. The drop in flow index with an increase in hydrophobicity was more evident for the blend with Avicel PH102 as an excipient. Powder flow improved with shear more for Avicel PH102 blends than Avicel PH200 blends.

Interestingly, the effect of mixing order on hydrophobicity was strain dependent. For blends containing Avicel PH200, the effect is moderate at 40 revolutions and reaches full bloom at 640 revolutions; results at 160 revolutions are almost identical to those at 40 revolutions. On the other hand, the blend containing Avicel PH102 as excipient material shows almost no effect at low and intermediate strains, but at 640 revolutions it shows a fully developed effect, similar to the blends containing Avicel PH200 but lower in magnitude. This indicates that the measured effect is affected by the particle size of excipients. For Avicel PH200, which has larger

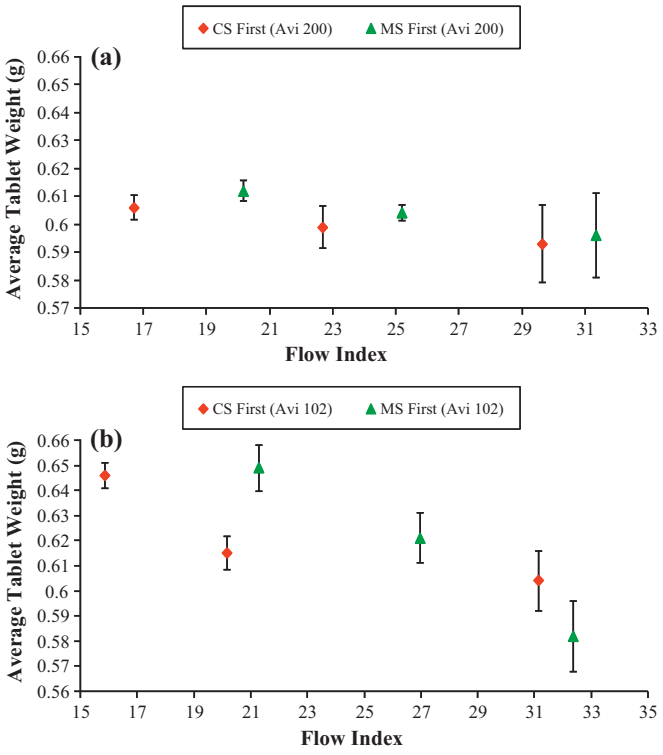

Fig. 5. Influence of mixing order and shear on tablet weight and powder flow. In all the cases, tablet weight decreased with an increase in flow index (worsening powder flow). (a) Mixing order was least effective for the blends mixed with Avicel PH200. Average tablet weight remained unchanged by changing the mixing order of flowing agents (CS and MgSt). (b) Mixing order was effective for the blends mixed with Avicel PH102. A slight drop in tablet weight at low shear and increase at high shear was found. Compaction increased at high shear.

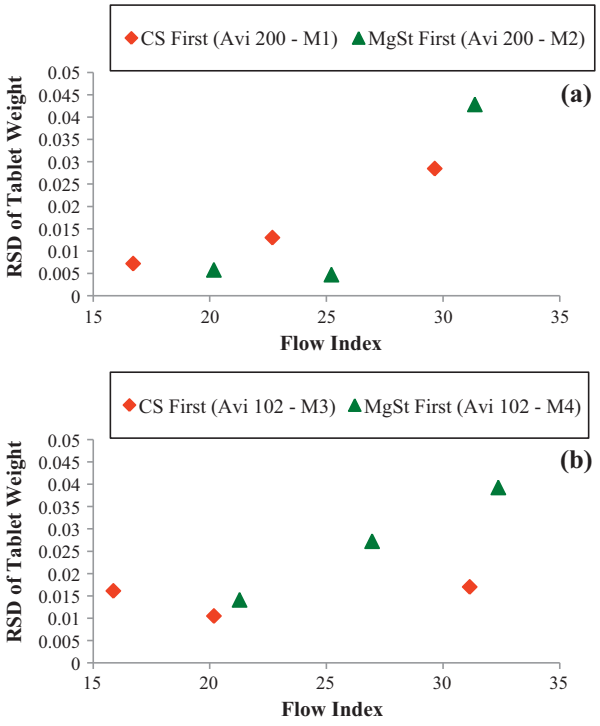

Fig. 6. Influence of mixing order and shear on tablet weight variability and powder flow. RSD of tablet weight increased with an increase in flow index (worsening powder flow). (a) Mixing order was not effective for blends with Avicel PH200 (larger particle size excipient). (b) Mixing order was effective in the case of blends mixed with Avicel PH102. First addition of CS showed low tablet weight variability.

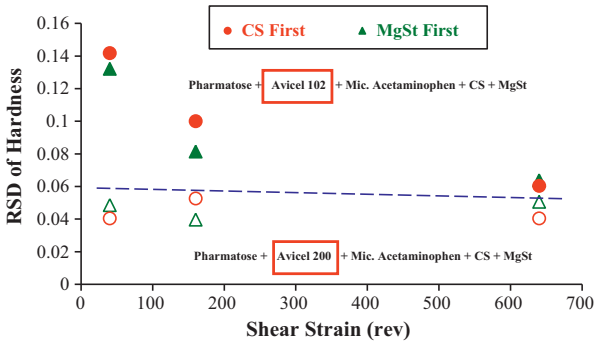

Fig. 7. Influence of mixing order on tablet hardness. The variability in tablet hardness due to change in mixing order can be attributed to the variation in powder flow properties.

particles (190 μm), there is less surface to cover, and the effects are detected at lower strain levels, while for Avicel PH102 (90 μm), which has about four times more surface area, more mechanical work is required to provide extensive enough coating and affect the rate of water uptake (Yang et al., 2005; Zhang et al., 2009).

To further examine the combined effect of CS and MgSt on blend hydrophobicity, another set of blends was prepared by adding both the flowing agents together at the same time during the mixing process for the blends containing Avicel PH200. Fig. 3 shows the hydrophobic behavior of powder blends at three strain conditions. Interestingly, the slope of the water uptake curve for these blends was found to be in between the blends prepared with conditions of mixing orders 1 and 2. Again, effects were strain dependent; an intermediate hydrophobic behavior was clearly observed at high strain conditions of 640 revolutions but not at 40 revolutions and 160 revolutions. The combined effects of shear and mixing order on powder hydrophobicity can be seen in Fig. 3. It is evident that powder hydrophobicity increased when the blends were exposed to high shear environment.

It should be mentioned here that during the mixing process, blends prepared by adding CS first and later added with MgSt showed very few agglomerates and enhanced blend homogeneity. One way to interpret our results is to indicate that lubrication efficiency is enhanced in the presence of CS. Although particle interaction in the presence of multiple ingredients is not fully understood, we hypothesize a possible change in the intensity of particle interaction energy. In such cases, decrease in adhesion force of MgSt particles can be expected when a glidant was mixed first in the blend.

4.2. Effect of mixing order of CS and MgSt on powder flow

The anti-correlation between powder flow properties and hydrophobicity is evident in Fig. 4. The results reveal two findings. First, irrespective of mixing order of flowing agents, flow measurements of multiple sheared blends show that as strain increases, powders become less cohesive powders (i.e., they display a lower flow index) and become more hydrophobic. This is consistent with the usual expectation regarding overlubrication: as strain increases and MgSt gets "smeared", powders should flow better but also become hydrophobic. The second observation, however, argues with the common wisdom: both of these effects are more pronounced when CS is added first to the mixture, even though for these blends MgSt experiences less strain during mixing.

Again, ordered mixing helps explain these observations. When MgSt is added last, it would deposit itself on the outside of the multilayer particles, making them as hydrophobic as possible. These

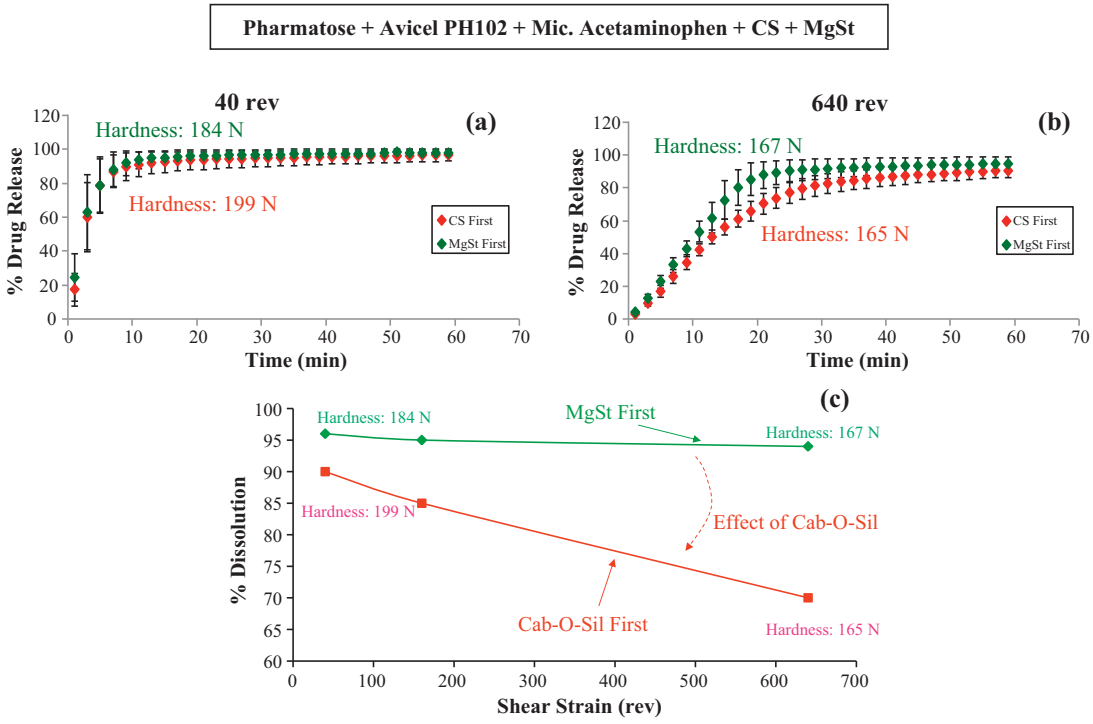

Fig. 8. Influence of mixing order and shear on dissolution and tablet hardness. Increase in shear decreased the tablet hardness for both the mixing orders. Although not much difference was seen in the tablet hardness, a phenomenal change in dissolution was observed when CS was added first. Decrease in the dissolution rate for mixing order-1 (CS first) was more evident at high shear conditions.

results were in agreement with our previous findings that cohesion of lubricated powders decreases with an increase in strain (Pingali et al., 2010, in press). In the current study, we believe that increase in strain also contributed to increase in lubricant distribution, thus increasing hydrophobicity.

4.3. *Effect of mixing order of CS and MgSt on tablet properties*

Tablets pressed from sheared powder blends were tested for tablet weight and tablet hardness. The relationship between tablet weight and flow index is shown in Fig. 5. Results show that average tablet weights were different for two sets of blends; heavier (denser) tablets are obtained under the same compression conditions for Avicel PH102 than for Avicel PH200, except at higher flow index where the difference between the tablet weights (0.582 g and 0596 g) is only 0.014 g that can be attributed to the poor flowability of the powder. This is counterintuitive, since even if flow properties are similar, it would be expected that finer particles would pack less densely than larger ones. The blends mixed first with CS (mixing order-1) had superior flow properties than the blends mixed first with MgSt (mixing order-2). This would be expected to have a positive effect on fluidity and compaction. Indeed, direct compression of tablets increased the average weight of tablets made of mixing order-1 (M.O.-1) and decreased for mixing order-2. Although the presence of CS and MgSt in both the sets of blends had acceptable powder flowability for direct compression, the average tablet weights were slightly higher for the tablets of M.O.-1. Such tablets also exhibited less weight variability, as seen in Fig. 6.

It is immediately apparent from the data that as the blends become less cohesive with applied strain (displaying smaller values of the flow index), tablet weight increases. This is perhaps the most obvious observation and it is in line with expectations. Results are also affected by mixing order. The blends mixed first with CS (mixing order-1) are less cohesive, and therefore had lower flow index (better flow properties) than the blends mixed first with MgSt (mixing order-2). In agreement, tablets made using mixing order-1 are denser than those prepared using mixing order-2, although this effect is moderate. Interesting trends are observed in the weight variability results, which are displayed in Fig. 6. The blends made with Avicel PH200 or Avicel PH102 span similar ranges of flow index, and they also show almost identical 10-fold increase in weight variability. Consistently, the blends prepared using mixing order 1 exhibit lower weight variability, and the dependence of weight variability on flow index (or, perhaps, on applied strain, reflected through the covariant effect on flow index) is magnified when the blends are prepared by adding MgSt first (mixing order 2). Thus, results indicate that when mixing order 1 is used, adding CS prior to mixing with MgSt, the tablets obtained under the same compression conditions are both heavier and show less variability. Correspondingly as well, during the pressing of tablets, we observed significantly more variation in compression force for blends mixed using mixing order 2. Also, as would be expected from Figs. 5 and 6, the compression force showed significantly more variability for blends exposed to low strain (40 revolutions) than for those exposed to moderate or high strain (160 and 640 revolutions).

An important additional comment concerns the relevance of the results displayed in Figs. 5 and 6 to commercial scale tablet presses. Modern manufacturing machines monitor the compression force as a means to control weight variability, and thus can achieve very uniform weight by dynamically adjusting the position of rolls driving the tooling. However, this narrower weight control is often achieved at the expense of two other important attributes: process yield (which is adversely affected when low weight or high weigh tablets are discarded) and size variability (which increases when the position of rollers is varied to minimize weight variability). In addition to affecting dissolution rate, in some applications (such as when tablets are packaged in blisters), size variability can be problematic on itself. Thus, there is value in understanding how to achieve uniform flow and reduce all forms of variability.

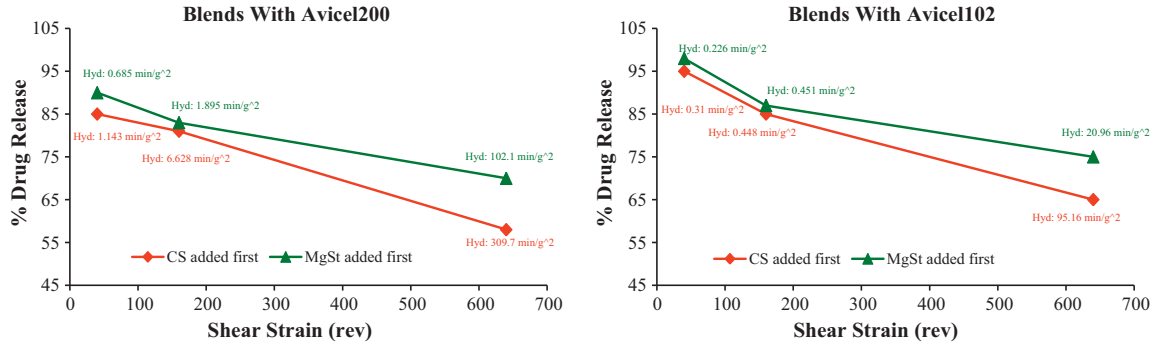

Fig. 9. Repeated study with new blends to show the effect of shear, mixing order and hydrophobicity on tablet dissolution. In both the cases, drug release rate decreased whenever CS was first added to the mix. It has to be noted that increase in shear strain increased the dissolution time and decreased drug release rate. Mixing order-1 (CS first) increased hydrophobicity and dissolution time.

The effect of flow properties and mixing order on tablet hardness is shown in Fig. 7. The RSD of the tablet hardness was higher for blends mixed with Avicel PH102 than the blends mixed with Avicel PH200 (in agreement with their higher density). Irrespective of the mixing order, an increase in strain decreased the tablet hardness for the Avicel PH102 blends.

4.4. Influence of mixing order of CS and MgSt on dissolution properties of tablets

Drug release from tablets prepared using different compositions, strain levels, and mixing orders was examined by measuring dissolution profiles (Fig. 8). An average drug release rate from eight tablets from each sample was determined from these measurements. It is evident from the data that as strain was applied, the tablet hardness decreased, and the drug release rate decreased substantially. Both of these effects are usually related to "overlubrication", which is a collection of symptoms observed for some (but not all) lubricated blends that have experienced "excessive" shear. The hardness of the samples mixed with MgSt first, did not correlate to the dissolution. This is probably due to the inhomogeneity of the blends in this condition of mixing order. Interestingly, while the mixing order did not affect tablet hardness within a strain level, it had a major effect on drug release rate at high strains. As shown in Fig. 8b for blends strained for 640 revolutions, the rate of dissolution is considerably slower when CS is added first to the mixture. Consequently, dissolution times increased for all the tablets prepared from highly strained blends (640 revolutions) (drug release rate was slower). In other words, the effect of mixing order of CS and MgSt on drug release rate was found to strongly depend on strain conditions.

It is generally accepted that smaller particles compact more than larger particles. Our results showed that the tablet hardness was higher for powder containing Avicel PH102 than Avicel PH200. In the results shown in Fig. 5, tablets made using Avicel PH102 were denser than those made from Avicel PH200, and all other things being equal, one would expect that the tablets made from Avicel PH200 would have larger pores and would disintegrate and dissolve faster than those made from Avicel PH102. This expectation is confirmed in Fig. 9. However, as shown in Fig. 9, hydrophobicity is also critically important. As hydrophobicity increases (due to the application of higher levels of strain) tablet dissolution becomes slower, and the effect is slightly more pronounced for the blends made from Avicel PH102 than those made using Avicel PH200. Moreover, Fig. 9 also shows that the mixing order-1 (CS first) also affects the dissolution rate, especially at high strain (640 revolutions) conditions. In fact, as shown in the figure, the effect of strain is larger than that of particle size of the excipients. The results presented above indicate that order of addition is indeed important and leads to significant effects on blends and tablets. Surprisingly, the application of strain after blending not only preserves the effect of the order of addition, it actually exacerbates it. This evidence strongly suggests the creation of an ordered mixture during blending that is unexpectedly made stronger during application of shear.

5. Conclusions

This study highlighted the importance of strain and excipient mixing order (for CS and MgSt) on blend and tablet and powder properties. First we showed that hydrophobicity of blends increased with strain, and increased more whenever CS was mixed in the blend prior to adding MgSt. The effect of mixing order was more evident in the case of blends mixed with Avicel PH102 than the blends mixed with Avicel PH200. Intermediate hydrophobic behavior was found when both MgSt and CS were added together. In all cases, the effect was strongly dependent on strain level. As strain applied increased, increases in hydrophobicity correlated to improvements in powder flow properties. Once again, these effects were larger for blends mixed first with CS.

Tablets compressed from these blends readily showed significant effects. Average tablet weights were different for two sets of blends mixed with CS and MgSt. Tablet weight increased, but weight variability decreased, when CS was first added to the blends. Hardness decreased significantly as strain increased, although this property seems indifferent to mixing order. However, the most important property, dissolution, exhibited significant effects of both strain and mixing order. Tablets prepared from blends which were mixed first with CS showed longer dissolution times and decreased drug release rate, but these effects were, once again, strain dependent.

Overall, it is critical to realize that composition, strain history, and even mixing order have significant, multivariate impact on blend and tablet properties. Most of the observations reported here can be qualitatively explained by postulating the creation of onion-like ordered mixtures where the order of addition of excipients has an impact on microstructures created during the mixing process. However, much more work is needed before such a conceptual model can be validated.

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