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Evaluation of strain-induced hydrophobicity of pharmaceutical blends and its effect on drug release rate under multiple compression conditions

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Abstract

Objective—The purpose of this study was to investigate the effect of mechanical shear on hydrophobicity of pharmaceutical powder blends as a function of composition and particle size, and to determine the impact on drug release from tablets.

Methods—Four powder formulations were subjected to three different shear strain conditions (40 rev, 160 rev, and 640 rev) in a controlled shear environment operating at a shear rate of 80 rpm. A total of 12 blends were tested for hydrophobicity. Subsequently, sheared blends were compressed into tablets at 8 kN and 12 kN in a rotary tablet press. During tablet compression, powder samples were collected after the feed frame and their hydrophobicity was again measured.

Results—Results indicated that increase in shear strain could significantly increase hydrophobicity, predominantly as an interacting function of blend composition. Blends with both colloidal silica and magnesium stearate (MgSt) were found to show higher hydrophobicity with shear than other blends. Additional shear applied by the tablet press feed frame was found to change the powder hydrophobicity only in the absence of MgSt.

Conclusions—Studies showed that the drug release rates dropped with shear more for the blends with both colloidal silica and MgSt than the other blends. Furthermore, the rate of drug release dropped with a decrease in particle size of the main excipient. Surprisingly, the relationship between the relative increase in hydrophobicity and a corresponding drop in the drug release rate was not found when either MgSt or colloidal silica was mixed alone in the blends.

Keywords

Colloidal silica; drug release; dissolution; hydrophobicity; shear

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Introduction

Physicochemical properties of powders are of interest to the pharmaceutical industry as they affect both manufacturability and critical quality attributes of finished products. An effective approach to formulate a drug product must consider both the physical properties of the raw materials and the effects of process conditions; some process variables, such as force during tableting, are obvious and well known, whereas others, such as the shear rate and the level of strain imposed on the blend, can be important, particularly because they are scale-dependent, but are less known^{1,2}. Increase in strain during the blending process has been shown to increase lubricant homogeneity³. However, uniform distribution of active drug and its bioavailability can depend greatly on the blend microstructure (i.e., its local degree of agglomeration, consolidation, and microscopic uniformity). How these blend attributes are affected by a given mixing protocol in the presence of glidants such as silica, which change flow properties significantly, is not completely understood. To optimize the dosage formulation, it is essential to develop a careful understanding of the effects of composition and shear conditions on materials properties such as blend hydrophobicity and on quality parameters such as drug release profile. However, for cohesive powders, blend microstructure, blend flow properties, and flow/mixing processes interact in complex ways that are not well understood.

The effect of shear conditions and levels of magnesium stearate (MgSt) on the hydrophobic behavior and drug release rate of solid dose products has been a subject of some debate. Hydrophobicity of silica layers was found to greatly depend upon the compression and expansion of particle layers⁴. Hydrophobicity was also known to increase with an increase in concentration of MgSt. However, high levels of MgSt do not always increase hydrophobicity. Interestingly, levels of MgSt and mixing time often have only a moderate effect on drug release characteristics⁵. On the contrary, some studies⁶⁻⁸ showed a strong influence of shear mixing on dissolution and physicochemical characteristics. Additional evidence in the literature suggests that in vitro dissolution is affected by the shear and stress applied on tablets^{9,10}. However, applied shear does not always slow down drug dissolution. Although high-shear granulation can be used to decrease the drug dissolution consistently¹¹, use of low shear force can also increase the dissolution time¹². In other words, depending on composition, both high shear and low shear can increase the dissolution time for different conditions. In addition to process shear conditions (i.e., shear rate), lubrication time (i.e., strain) also significantly affects the drug dissolution¹². In addition, high-shear blenders can result in uncontrolled particle size reduction if the applied shear is high. It is therefore required to optimize the shear conditions and lubricant composition to control particle size reduction and to achieve desired drug dissolution rate. Similarly, it is necessary to control the effect of these variables to maintain desired performance. Although this is largely an obvious statement, unfortunately this precept is often violated during process scale-up or process change.

Optimization of product shear history can often be achieved by selecting appropriate process conditions¹³. The overall goal is to achieve the product performance robustness by minimizing the dissolution differences caused by process conditions. In previous studies, dissolution differences were found to be largely related to the hydrophobicity of active

ingredients¹⁴ or main excipients. Interestingly, dissolution differences have been found to increase when multiple excipients are mixed with an active ingredient¹⁴. In addition, the type of shear mixer was also found to affect drug dissolution¹⁵. It is known that the desired dissolution profiles can also vary with a change in manufacturing process, composition, and formulation variables^{16–19}. Level of MgSt, impeller speed in the mixer, and composition of binders and fillers are some of the parameters that have been found to affect the desired drug release rates^{2,20}. Thus, understanding the significance of lubricant distribution at various shear conditions may help develop a better drug formulation.

The main purpose of this work is to explore the relevance of shear conditions to the lubricant distribution and drug release rate. We focus here on the shear treatments of multiple lubricated blends containing MgSt and colloidal silica. A systematic investigation of shear effect on hydrophobicity and its corresponding influence on drug release rate with respect to composition and particle size is presented.

Experimental

Sample preparation

Several sets of formulations of pharmaceutical powders containing Pharmatose® (DMV International, Veghel, Netherlands, 100 µm), microcrystalline cellulose (MCC; Avicel 102; FMC, Philadelphia, PA; 90 µm), micronized acetaminophen (APAP; Mallinckrodt Inc., Raleigh, NC 19 µm), magnesium stearate (MgSt; Mallinckrodt Inc., St Louis, MO 38 µm), talc (Barretts Minerals Inc., Dillion, MT), and colloidal silica (Cab-O-Sil; Grade: M-5P; Cabot Corporation, Tuscola, IL; 0.2–0.3 µm) were preblended in a 4-quart V-blender (Patterson Kelley Blendmaster, East Stroudsburg, PA) and later processed at different shear conditions in a modified Couette-controlled shear environment (MCC, East Hannover, NJ, USA). A more detailed discussion on this last piece of equipment can be found in our previous work²¹.

All blend compositions are summarized in Table 1. To obtain a homogeneous preblend of lubricant and excipients, all the powders were pre-mixed in a 3.8-liter V-blender for 10 minutes. The Couette cell cannot be used as a ‘macro-mixer’; it should be used to subject the pre-mixed powder samples to uniform shear conditions. A 50–50 mixture of Pharmatose and Avicel 102 was used as an excipient blend. Micronized acetaminophen (9%) (active pharmaceutical ingredient—API) was mixed with the excipient blend in all the samples. Talc and colloidal silica were used as additives whereas MgSt was used as a lubricant. The concentration of additives and lubricant in the blends was limited to 1% each.

Table 2 shows the experimental grid used to prepare sheared samples in the Couette cell, displaying the shear rates in rows (with the corresponding rotational speeds of the cylinder in rpm) and strain units (or shear time expressed as number of revolutions) in columns. A sparse block design is used to examine the effects of shear rates for similar amounts of strain, and the effect of strain at constant shear rates, for a wide range of treatment conditions. Every powder pre-mixed in the V-blender was processed in a shear cell processor at a shear rate of 80 rpm and shear strains of 40 rev, 160 rev, and 640 rev so that the powders were exposed to minimum, average, and maximum strain. The modified

Couette cylindrical cell consists of uniformly spaced pins that create a uniform shear environment. The shear cell processor can only treat a sample size of 300 g at a time. Because 500 g of powder from each sample was needed to prepare tablets, a larger sample for each formulation as shown in Table 1 was prepared. From our previous work, it is known that the pre-mixing procedure generates a sufficiently uniform mixture for the purposes of this study.

Sheared powder samples were compressed into tablets in an MTP-8 rotary tablet press. Approximately, a sample size of 500 g of powder was loaded in the feed hopper. Tablets were prepared at a compression force of 8 kN and 12 kN. While running the machine, punch speed and tablet thickness handwheel were adjusted by monitoring the pressure display. To avoid excessive tablet weight variance, tablets produced initially were discarded until the average pressure value displayed was stable. Finished tablets were kept inside a sealed bag to avoid excessive exposure to environmental moisture.

Experimental techniques

Powder hydrophobicity

The hydrophobicity measures the ability of a solution to move by capillarity through a column of powder²². The ‘overlubrication’ effect on hydrophobicity can be simply quantified by measuring the dynamics of capillary rise, which can be easily measured using the Washburn method²²; similar measurements for drop penetration of a powder bed are routinely used in the development of granulation processes. The Washburn equation, in terms of mass²³ that penetrates a horizontal column of powder, is given by

$$t = \frac{\eta}{C \rho^2 \gamma \cos \theta} m^2 \quad (1)$$

where t is the time, η is the liquid viscosity, C is a geometric factor (constant as long as the powder packing density and the particle size remain unchanged), ρ is the liquid density, γ is the surface tension of the liquid, θ is the contact angle between solid and liquid, and m is the mass of liquid that has penetrated the powder column by capillarity. The hydrophobicity is then defined as the slope of the line in Equation (1). To obtain a constant solution parameter, the same solution was used to compare the hydrophobicity values for different set of blends. In this way, the effect of change in powder properties was measured.

The apparatus for measuring the hydrophobicity comprised a glass cylinder with a glass filter and is shown in Figure 1. A saturated solution was prepared containing any soluble component of the blend. The saturated solution was prepared by adding 125 g of Pharmatose and 10 g of micronized acetaminophen. The solution was stirred overnight to dissolve the maximum amount of lactose and acetaminophen and to saturate the solution at room temperature. The solution was filtered to remove the excess amount of lactose. A limited quantity of 30 g of powder was used in the cylinder with a sintered glass filter. To compact the powder bed reproducibly, the cylinder was tapped 500 times in the Quantachrome Autotap density equipment (Quantachrome Instruments, Boynton Beach, Florida; Model Number: 2106-60-01). The cylinder, attached to a stand on a measuring scale, was then

submerged in the saturated solution previously prepared. The weight was tared immediately after the liquid level rising in the column touched the filter. The rise of liquid in the compacted powder bed was then measured as a function of time, as shown in Figure 1. Hydrophobicity was measured from the slope of the squared mass versus time. The procedure was repeated three times on every sample and the average value of the slope of hydrophobicity was recorded.

Tablet dissolution

The dissolution apparatus used in this study consists of two paddles that run at 50 rpm. A 900 mL of phosphate buffer solution with a pH of 5.8 was used in each measurement. The equipment was operated at 37°C for 90 minutes. The operating time can be changed depending on the tablet performance. In the first step, the buffer solution was set up in each vessel with a fixed height of the paddles. After evaporation covers were put in place, buffer was allowed to preheat to 37°C by running the baffles at 100 rpm for 30 minutes. Tablet thickness and weight were recorded for each vessel.

In the second step, the samples were tested for UV dissolution. A modified USP method was used for dissolution testing of acetaminophen tablets. The tests were done on a Vankel VK7010 USP II apparatus (Vankel, 1300 Weston Parkway, Cary, NC 27513-2228) with online reading in a flow cell Cary 50 spectrophotometer (Varian Industries, 2700 Mitchell Drive, Walnut Creek, CA 94598, USA). A total test time of 90 minutes was used to monitor the full release profile of slower dissolving tablets. Tablets were simultaneously dropped in all eight vessels and the absorbance was automatically read every 2 minutes. Paddles were rotated at 50 rpm for the duration of the test, with an infinity time point final spin of 250 rpm for 5 minutes. Sampling probes were fitted with 10- μ m filter tips. Absorbance readings were read at 243 nm in 5.0-mm flow cell cuvettes. A five-point calibration curve was developed to convert absorbance into concentration, which resulted in a linear extinction coefficient of $\varepsilon = 65.353 \text{ mL/mg/cm}$ with $r^2 = 1$. For each tablet blend/shear sample, eight tablets were tested simultaneously. The weight and thickness of each tablet were recorded before measurement. The weight was used with the percentage active concentration of the formulation and the amount released at each time point to derive a percentage release profile. The standard deviation for each time point is shown as error bars on the release profile.

Results and discussion

Influence of shear on hydrophobicity of powder

The four blends from Table 1 were tested to measure the effect of colloidal silica and MgSt on hydrophobicity. The formulations are as follows: (a) MCC, Pharmatose, and API; (b) MCC, Pharmatose, API, and Cab-O-Sil; (c) MCC, Pharmatose, API, and MgSt; and (d) MCC, Pharmatose, API, Cab-O-Sil, and MgSt. The Washburn method described above was used to measure the powder hydrophobicity.

Figure 2 shows the relation between the square mass of liquid moving by capillarity as a function of time. The results show that the shear applied to the material increased powder

hydrophobicity for all the blends. Cab-O-Sil, by itself, caused only a small effect, whereas MgSt, acting alone, contributed a very large effect. However, the largest effect was observed in the presence of both lubricant (MgSt) and colloidal silica. For the blend containing both ingredients, the observed effects were very large; when strain increased from 40 rev to 160 rev, hydrophobicity increased 4.2 times; a further increase in strain from 160 rev to 640 rev caused an extremely large, 280-fold increase in hydrophobicity of the powder. This suggests that at higher applied strain, the effect of strain in the presence of both Cab-O-Sil and MgSt becomes nonlinear and possibly reflects an interaction between these ingredients. This is interesting when considering that the presence of Cab-O-Sil alone in the blend did not significantly change the hydrophobicity as a function of strain.

Influence of shear in the feed frame on hydrophobicity of powder

To evaluate the effect of the additional strain applied in the feed frame of the tablet press, two upper punches of the tablet press were removed. The powder was collected from the empty dies and tested for hydrophobicity. Figure 3 shows that a moderate further increment in the hydrophobicity indeed occurs for the blend with both Cab-O-Sil and MgSt. For this blend, the hydrophobicity at 160 rev increases by a factor of 1.7 relative to the hydrophobicity of the powder before passing through the feed frame. For the blend strained for 640 rev, hydrophobicity was found to increase only slightly. This can probably be explained by the fact that the powder strained in the shear cell for 640 rev is already highly hydrophobic, that is, it is already extensively overlubricated, and the additional strain in the feed frame only has a small additional effect.

In a previous study²¹, we showed that powder flow properties are also significantly affected by application of strain. In fact, changes in powder cohesion can affect both the measured hydrophobicity and the outcomes of the compression process through the same mechanism: powders with different cohesivities pack differently, whether in the glass vial or in the tablet press die, leading to different porosity and impacting fluid penetration. Thus, in addition to the measured hydrophobicity, other factors are also important in affecting drug dissolution. This issue is evaluated in the next section.

Influence of shear on dissolution properties of tablets

Sheared powders were compressed at 8 kN and 12 kN and their dissolution properties were investigated. It is evident from Figure 4 that the presence of Cab-O-Sil in the powders affected the dissolution rate of the API. In addition, mixing of talc (Figure 4) did not change the dissolution rate. The following two major observations were listed from the drug release profiles seen in Figure 5:

- a. The rate of drug release decreased with the increase in the shear strain from 40 rev to 640 rev.
- b. The effect of shear on dissolution was much higher in the lubricated blend containing both MgSt and Cab-O-Sil than in the blend with MgSt but without Cab-O-Sil.

These results can be correlated to the flow behavior of powders. Our previous work²¹ showed that the flow properties of powders improved (i.e., cohesion decreased) with an

increase in shear strain from 40 rev to 640 rev. However, decrease in cohesion, by itself, is not the only cause. In our previous work²¹, we showed that Cab-O-Sil has the maximum effect on cohesion. However, Cab-O-Sil alone does not have a large effect on hydrophobicity whereas MgSt alone does show a moderate effect on hydrophobicity (Figure 2). However, when both MgSt and Cab-O-Sil are present, the effect on hydrophobicity and dissolution are maximized (Figures 2 and 6). The proposition that large decreases in rate of drug release require both lower cohesion and higher hydrophobicity is further demonstrated by the fact that an increase in concentration of MgSt from 0.5% to 2% did not change the drug release rate¹⁷, but a large variation in drug release rate was found with the changes in the porosity caused by the changes in compaction pressure²⁴. Accordingly, in this study, the results strongly suggest possible changes in cohesion (and packing) and, therefore, in resulting porosity, as the blend is strained in the presence of *both* Cab-O-Sil and MgSt. For this blend, our results showed that the applied shear increased hydrophobicity and slowed the drug release rate.

Figure 6 suggests that shear history and composition of formulation are both critical factors governing the drug release properties of compressed tablets. It was found that the presence of lubricants and glidants affected the drug release behavior of the tablets only at high-shear strain conditions (160 rev and 640 rev). This can be attributed to the increase in tablet compaction in the presence of lubricants and additives. Whereas most of the drug was released within 60 minutes for the blends consisting of only MgSt or a combination of MgSt and talc, when Cab-O-Sil was added in the blend, the time taken for drug release dramatically increased. However, this phenomenon was only observed *at high-strain conditions* as the rate of drug release was almost the same for all the blends at low shear strain (40 rev). Again, as discussed in previous section, the difference in dissolution rates was more evident (a) in the blends containing both Cab-O-Sil and MgSt and (b) under high-strain conditions. The results clearly show a strong influence of the combination of silica with lubricant on dissolution profile. Although a further increase in the amount of MgSt in the blend did not alter the dissolution rates¹⁷, interestingly, our current investigation showed that the dissolution rates can be significantly altered if MgSt was used in combination with Cab-O-Sil at high-strain conditions.

Because the amount of strain experienced by a blend is both equipment-dependent and scale-dependent, these results strongly suggest that to optimize the drug release profile in direct compression formulations, formulators and process engineers need to perform a multivariate analysis considering blend composition, strain history, and compression parameters. This is typically not the case in current practice, where systematic analysis of strain history across scales is seldom performed.

Influence of tablet compression force on dissolution

The effect of compression force (8 kN and 12 kN) on the tablet dissolution is clearly evident in Figure 7 but only (a) at high-strain conditions (160 rev and 640 rev) and (b) in the presence of both Cab-O-Sil and MgSt. Results in Figure 7 show that at the low-strain conditions of 40 rev, the compression force did not change the drug release behavior of API. As shown in Figure 7, the time taken for 100% drug release was 15 minutes at 40 rev, 40

minutes at 160 rev, and 90 minutes at 640 rev. This strongly suggests a possible increase in compaction of tablets with increase in strain. The explanation for this phenomenon is rather simple: As shown in our previous work²¹, higher strain causes more uniform distribution of Cab-O-Sil and lower blend cohesion. This improves powder packing in the tablet press die and reduces the microporosity of the tablets, thereby increasing the dissolution time. However, once again, this trend was not observed at a low shear of 40 rev, highlighting the impact of strain on flow properties and emphasizing the critical need to ensure that all excipients are appropriately micro-mixed in the blend.

Influence of excipient particle size on table dissolution

Figure 8 shows the effect of excipient particle size on the dissolution properties of tablets. In this test, blends with MgSt and Cab-O-Sil were prepared with excipients of two different particle sizes (Avicel 102–100 μm ; Avicel 200–190 μm). Tablets were prepared and tested for dissolution. Interestingly, the effect of shear was much more predominant in the tablets prepared with small particle size, which exhibited a much longer time for 100% drug release. These results confirm those shown in the previous sections; in this case, the decrease in the drug release rate can be attributed to a decrease in the pore size because of the use of smaller excipients particles, and the larger effect of strain is due to the fact that when the excipients particles are smaller, there is more surface to cover with MgSt and Cab-O-Sil, thus requiring more strain. This is similar to the findings discussed in the previous section, where increase in compaction because of shear decreased the rate of drug release. Although a decrease in drug release rate with a decrease in excipient particle size was expected, it was interesting to notice the clear difference in dissolution profiles for various strain levels.

Overall, the results clearly show that in addition to excipient particle size, mixing time (shear strain) can significantly impact the tablet strength and dissolution. Therefore, appropriate shear conditions and particle size are needed to optimize the overall drug release rate and tablet quality.

Conclusions

The most immediate conclusion of this article is to reinforce the notion that processing conditions in general, and strain in particular, can have significant impact on dissolution characteristics. Our results showed a strong influence of strain on blend hydrophobicity and on drug release rate from tablets. The following conclusions can be drawn from this study.

- Hydrophobicity of lubricated powders increased with applied strain. The effect of strain on powder hydrophobicity was larger in the presence of *both* Cab-O-Sil and MgSt, indicating previously unknown interactions between these two common excipients.
- Powders without MgSt became less hydrophobic after passing through the feed frame.

- Drug release rate decreased with an increase in strain. The effect of strain on drug release rate was more evident at high-strain conditions in the blends containing both MgSt and Cab-O-Sil.
- Increase in compression force slowed down the drug release rate only for powders that had experienced large amounts of strain. This effect was not observed for powders that had experienced low levels of strain.
- Effect of shear was predominant in the tablets prepared with smaller particle size for the main excipients.

Overall, the main conclusion is that the effects of blend composition, particle size, strain history, and compression parameters interact strongly. Dissolution rate and possibly other critical quality attributes (CQA) are multivariate functions of this large parametric domain. To achieve and maintain the desired results, QbD programs need to examine all of these variables simultaneously.

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Figure 1. Apparatus for measuring hydrophobicity, which was measured from the slope of the squared mass versus time.

Figure 2.

Effect of shear on hydrophobicity. Hydrophobicity increased with shear strain. The effect was dominant in the presence of lubricant and colloidal silica. With increase in strain, Cab-O-Sil alone did not alter the hydrophobicity. However, shearing the powders with MgSt alone and in combination with Cab-O-Sil increased the hydrophobicity.

Figure 3. Effect of feed frame on powder hydrophobicity. Although a slight decrease in hydrophobicity was found at low shear strain, feed frame was found to be ineffective in altering the hydrophobic behavior of powder.

Figure 4.
Effect of shear strain on the drug release. Drug release slowed down at highshear conditions in the presence of Cab-O-Sil.

Figure 5. Effect of mixing talc in the blends on the dissolution profiles of tablets. Addition of talc did not change the dissolution behavior for two sets of blends shown in (a) and (b).

Figure 6. Effect of compression force on the dissolution of API. Higher compressive force slowed down the drug release only at the high-shear strain conditions.

Figure 7.

Effect of shear strain and composition on dissolution of tablets. Drug release slowed down only at high-shear strain conditions (160 rev and 640 rev) in the presence of Cab-O-Sil. At the same time, addition of talc to the blends did not show any change in dissolution rates of the API in the tablets.

Figure 8.

Effect of particle size on the dissolution. Although drug release slowed down with shear for both the blends, the release was slower for the tablets prepared with smaller particle size of excipient.

Table 1

Formulations of pharmaceutical blends prepared for measuring shear effects on hydrophobicity and dissolution of tablets.

Blends	Composition
B1	9% Mic. acetaminophen + 45% Avicel 102 + 45% Pharmatose + 1% MgSt
B2	9% Mic. acetaminophen + 44.5% Avicel 102 + 44.5% Pharmatose + 1% MgSt + 1% talc
B2	9% Mic. acetaminophen + 44.5% Avicel 102 + 44.5% Pharmatose + 1% MgSt + 1% Cab-O-Sil
B4	9% Mic. acetaminophen + 44% Avicel 102 + 44% Pharmatose + 1% MgSt + 1% Cab-O-Sil + 1% talc

Table 2

Experimental design of the shear conditions.

	40 rev	160 rev	640 rev
5 rpm			
20 rpm			
80 rpm			