Drug Development and Industrial Pharmacy, 2009; 35(12): 1460–1469

informa
healthcare

ORIGINAL ARTICLE

Practical methods for improving flow properties of active pharmaceutical ingredients

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Abstract

Objective: The essential aim of this article is to develop effective methods for improving the flow properties of active pharmaceutical ingredients (APIs) without requiring particle size or shape modification. *Methods*: The 'formulation' approach used here focuses on enhancing flow properties of three chemically different drug powders (micronized acetaminophen, levalbuterol tartrate, and didesmethylsibutramine tartrate) by using small amounts of lubricants, glidants, and other additives, both individually and in combination. Additives are intimately mixed using a laboratory-scale V-blender with an intensifier bar. Flow index, dilation, and electrical impedance were measured for a total of 24 blends. *Results*: The flow behavior of all three APIs improved with the addition of these additives. Relative effectiveness of different additive combinations displayed remarkable consistency for all three APIs. Simultaneous presence of SiO_2, MgSt, and talc led to substantial decreases in cohesiveness, causing major improvements in flowability of powder. All three properties showed a very tight correlation. *Conclusions*: Drug powders with improved flow were found to exhibit low dilation and low impedance values. A common linear correlation between flow index and impedance and also between dilation and impedance was observed for all three APIs, indicating that electric properties play a substantial role in the cohesivity of all three APIs, and suggesting the presence of a common mechanism for the emergence (and mitigation) of cohesive phenomena.

Key words: *Cohesion; dilation; drug; flow index; impedance; powder flow*

Introduction

Achieving good flowability of drug powders is an important component of pharmaceutical product development. Poor flow properties affect adversely our ability to process such materials, for example, by hindering the mixing process and potentially affecting process performance[1]. In some cases, such as inhalables, capsules, and tablets containing large amounts of active pharmaceutical ingredient (API), poor flow properties must be overcome before reliable manufacturing is possible. However, the problem is far from simple, because both the amount of excipients and the size of drug particle can influence pharmacokinetic properties[2].

Another common source of trouble is encountered in oral formulations when drugs need to be micronized, typically because large amounts of surface area are needed to enhance bioavailability. Micronized particles experience large electrostatic, capillary, and Van der Waals cohesive forces[3–5], which play a critical role in powder flow, affecting our ability to dry, transfer, and blend such materials. In these and in other systems, cohesion has large impact on finished product properties. Micronized materials also tend to agglomerate, potentially causing content uniformity problems[6,7]. Apparent density, porosity, and hardness are all affected by the flow properties of mixtures of drug powders[8]. In addition, in recent years, substantial interest has emerged in continuous manufacturing of pharmaceutical products, and it has been shown that powder flow properties play a controlling role on the homogeneity of continuously mixed blends[9,10]. Because of these and other reasons, pharmaceutical scientists often struggle to improve flow properties of APIs.

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(Received 23 Jun 2008; accepted 6 May 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639040903025830

Effects of drug particle size have extensively studied in recent years[11,12]. However, the emphasis has been to improve the flow properties of the final blend, not the API. Physical properties of drug substances such as bulk density, angle of repose, moisture content, and surface area have been examined to understand drug agglomeration[13,14]. Dispersion of the drug in the blend has been related to bulk flow behavior[15]. Concentration of drug in the blend is usually a critical variable[16]. A number of studies have also examined the effect of lubricants on blend flow properties[17–20]. Lubricant mixing time, which is often scale-dependant, is widely known to be a critical factor in many formulations[21]. However, optimization of the amount of lubricant and the effect of processing conditions remain poorly understood. In addition, the study of flowability of nearly pure drug powder under the influence of multiple lubricants and additives has received little attention in the literature[2,22]. Thus, this study focuses on improving the flow properties of the APIs before they are blended with the bulk excipients.

Our focus is to examine whether common additives and lubricants, alone and in combination, are effective for improving flowability of pure drug powders. We further extend our work to study the electrical properties of drug powders and examine the existence of a possible correlation between flow and electrical properties. The approach adopted here is predicated on two simple observations:

1. Most cohesive phenomena in APIs seem to be strongly related to either electrostatic forces or to the formation of capillary bridges.
2. Many of the additives known to affect flow properties of powders are loose agglomerates of very small particles that are known to coat other materials, affecting the hydrophobicity of the coated particle and the electric conductivity of the overall blend.

In this study, we demonstrate that the sources of cohesive behavior of APIs can be disrupted by using the same materials that are known to improve flow of final blends. The remainder of this article is organized as follows: In Section 2, we introduce the full list of materials and blends examined in this study. In Section 3, we discuss the methods used to characterize flow and electric properties of API blends. In Section 4, we present and discuss results, and the last section is devoted to conclusions.

Materials and methods

Materials

The materials used in this study were acetaminophen (APAP; semifine, 37 μm; fine, 28 μm; micronized, 19 μm; Mallinckrodt Inc., Raleigh, NC, USA), didesmethylsibutramine tartarate (DDMS; Sepracor Inc., Marlborough, MA, USA), levalbuterol tartrate (LEV; Sepracor Inc.), colloidal silica (Cab-O-Sil; Grade: M-5P; Cabot Corporation, Tuscola, IL, USA), talc (Barretts Minerals Inc., Dillon, MT, USA), and magnesium stearate (Mallinckrodt Inc., St. Louis, MO, USA). The powder formulations consisted of active ingredients, additives, and lubricants.

Methods

Blending

Three API powders (micronized APAP, LEV, and DDMS) were blended with several additives and lubricants in a V-blender. The effects on flow and impedance of magnesium stearate (MgSt), colloidal silica (SiO_2), and talc were examined. These three additives are widely known to improve flow properties of many formulations and are commonly used in a majority of oral dose formulations. When pure, all the three APIs were substantially cohesive powders. These powders were blended with the additives under 'high shear' conditions, using a 16 qt V-blender operated at 30 rpm with an intensifier bar rotated at 350 rpm. In each case, a sample size of 5 lb from each blend was prepared to test their flow properties. The same procedure was repeated for all the three drug materials. Samples collected after blending, milling, and tapping were stored in airtight containers to prevent the powders from exposure to moisture.

The entire list of blends prepared for each API is shown in Tables 1–3. Whenever an additive was used, it was added at a fixed concentration of 3%. Thus, the maximum total concentration of additives in the blends was limited to 9% when all the three were present. While these amounts may seem large, as the drug is typically a small fraction of the entire formulation, these concentrations of additives are smaller (and in some cases, much smaller) than those used in final blends.

Blends of APIs mixed with several combinations of additives were tested for their flow and electrical properties. The methods for measuring flow index, dilation, and impedance were discussed in detail in our previous work[23]. Figure 1 shows the equipment for measuring flow index, dilation, and impedance.

Flow index

As in our previous work, flow index was measured using the gravitational displacement rheometer (GDR)[24], which, different from other methods such as shear cells, characterizes powder flow behavior in the fully dilated state. The powder was loaded to fill 40% of the volume in a rotating drum mounted on a hinged table that was

Table 1. Lubricated blends of micronized acetaminophen tested for flow and electrical properties.

Blends	Composition	Flow index	Dilation (%)	Adjusted flow index	Impedance (MΩ)
1	Mic. APAP (pure drug)	16.68	36	60.82	19.26
2	Mic. APAP+SiO_2	12.43	21	50.27	11.36
3	Mic. APAP+MgSt	13.70	26	54.57	15.60
4	Mic. APAP+talc	14.30	30	57.64	16.72
5	Mic. APAP+SiO_2+MgSt	11.86	18	51.37	9.97
6	Mic. APAP+SiO_2+Talc	12.79	23	54.00	12.90
7	Mic. APAP+MgSt+talc	13.77	28	54.68	15.62
8	Mic. APAP+SiO_2+MgSt+talc	11.64	15	47.91	7.26

Table 2. Lubricated blends of LEV tested for flow and electrical properties.

Blends	Composition	Flow index	Dilation (%)	Adjusted flow index	Impedance (MΩ)
1	LEV (pure drug)	7.95	56	81.60	28.20
2	LEV+SiO_2	6.67	34	61.66	20.22
3	LEV+MgSt	6.81	38	62.58	20.40
4	LEV+talc	6.97	41	63.89	20.00
5	LEV+SiO_2+MgSt	6.08	22	54.78	14.01
6	LEV+SiO_2+talc	6.36	28	56.47	14.31
7	LEV+MgSt+talc	6.43	31	58.61	16.71
8	LEV+SiO_2+MgSt+talc	5.78	17	51.28	11.26

Table 3. Lubricated blends of DDMS tested for flow and electrical properties.

Blends	Composition	Dilation (%)	Impedance (MΩ)
1	DDMS (pure drug)	40	27.27
2	DDMS+SiO_2	24	14.77
3	DDMS+MgSt	30	21.22
4	DDMS+talc	33	22.67
5	DDMS+SiO_2+MgSt	25	15.46
6	DDMS+SiO_2+talc	27	17.63
8	DDMS+SiO_2+MgSt+talc	15	10.91

supported by a load cell. Variation in the moment of inertia of the powder bed was measured from the load cell during the rotation of cylinder as a function of time and rotational speed. For slow rotational speeds (under 20 rpm), cohesive powders display flow in the form of discrete avalanches. The basic assumption of the GDR method is that for increasingly cohesive powders, avalanche size increases, and the standard deviation of the force signal measured by the load cell (the basic GDR measurement) also increases, which provides a convenient method for characterizing the effect of cohesion on flow behavior under unconfined conditions (i.e., where the only normal stress applied to the powder is its own weight). The load cell output was digitally sampled as a continuous analog signal through a personal computer interface and was further processed to generate flow index, which as in our previous work, is defined as the standard deviation of the output of the load cell, averaged for four speeds (5,10,15, and 20 rpm). As the examined powders vary widely in dynamic bulk density, an adjusted flow index was also computed by dividing the flow index by the bulk dynamic density of the powder bed (described next).

Dilation

The expansion of the powder bed during the course of rotation of cylinder was measured in order to measure the dynamic density of the flowing powder. The powder was filled to 40% in a rotating cylinder at 15 rpm. The bulk powder movement was captured using a digital camera that recorded the powder flow through a transparent side window of the rotating drum. Video captures were later converted to digital stills. Each still was processed digitally using image analysis to determine the bed volume. As the powder expanded to its minimum density, the percentage change in bed volume was measured and then used to compute the average dilation as a function of time. Once dilation acquired a stable value (after, typically, 5–10 rotations of the drum), the dynamic density was computed by using the digital images to determine the total volume occupied by the powder bed. A dilation index was then computed as the ratio of the dynamic density to the tapped density. Measured values of flow index, percent dilation adjusted flow index, and impedance are listed in Table 1 for each blend.

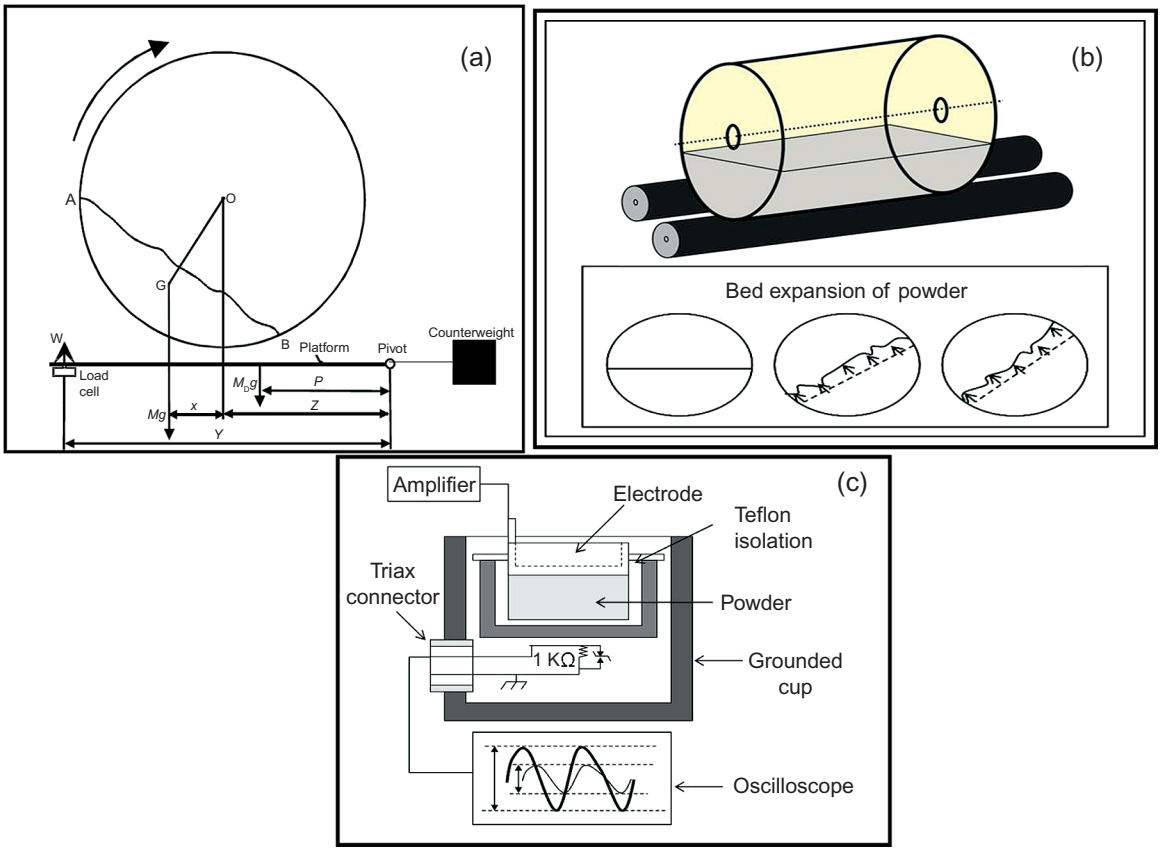

Figure 1. Laboratory equipment for the measurement of flow and electrical properties of pharmaceutical powders (a) gravitational displacement rheometer (GDR) to measure flow index[40]. (b) Dilation rollers with cylinder filled to 40% powder for measuring bed expansion. (c) Impedance measurement using oscilloscope, Faraday cup, and amplifier.

Impedance

Impedance was measured by supplying voltage to a Faraday cup containing powder at a frequency range of 10 Hz to 100 kHz. A 40-g sample was placed in the cup, the electrical signal was passed through the powder, and the output signal was recorded using an oscilloscope. A signal generator (model 105-2001; Global Specialties, Wallingford, CI, USA) and a TREK amplifier (610 E) were used to convert the supplied frequency into output voltage of up to 1000 V. Peak-to-peak voltage and current readings were recorded using oscilloscope, and impedance was measured as the modular ratio of the amplitudes of the applied voltage and the resulting current.

Results and discussion

Flow characteristics and impedance of micronized acetaminophen blends

Among the three types of APAP (semifine, fine, and micronized) that are commercially available, micronized APAP was chosen because of its greater cohesion than the other two types of drug materials (semifine and fine). As shown in Figure 2, micronized APAP is more cohesive (larger flow index and dilation) than the other two drug powders.

The experimental results of multiple formulations thus prepared in this study clearly demonstrate that the flow of pure drug powders can be enormously enhanced by adding small amounts of additives. However, the effectiveness of combined additives did not always improve the flow characteristics, indicating the need to study in more detail the effects of additive concentration ratio. This can be seen from the flow index and dilation values for micronized APAP blends in Table 1. Individually, all the three additives improved the flow (decreased flow index and dilation) of micronized APAP. However, their effectiveness was widely different, with silica being highly effective, MgSt being slightly less effective, and talc having a much more moderate effect. When used in pairs, talc in combination with other additives acted as a retardant. The silica–MgSt was by far the most effective binary combination, followed by silica–talc, and the most moderate effects were observed for MgSt–talc. In other words, flow properties

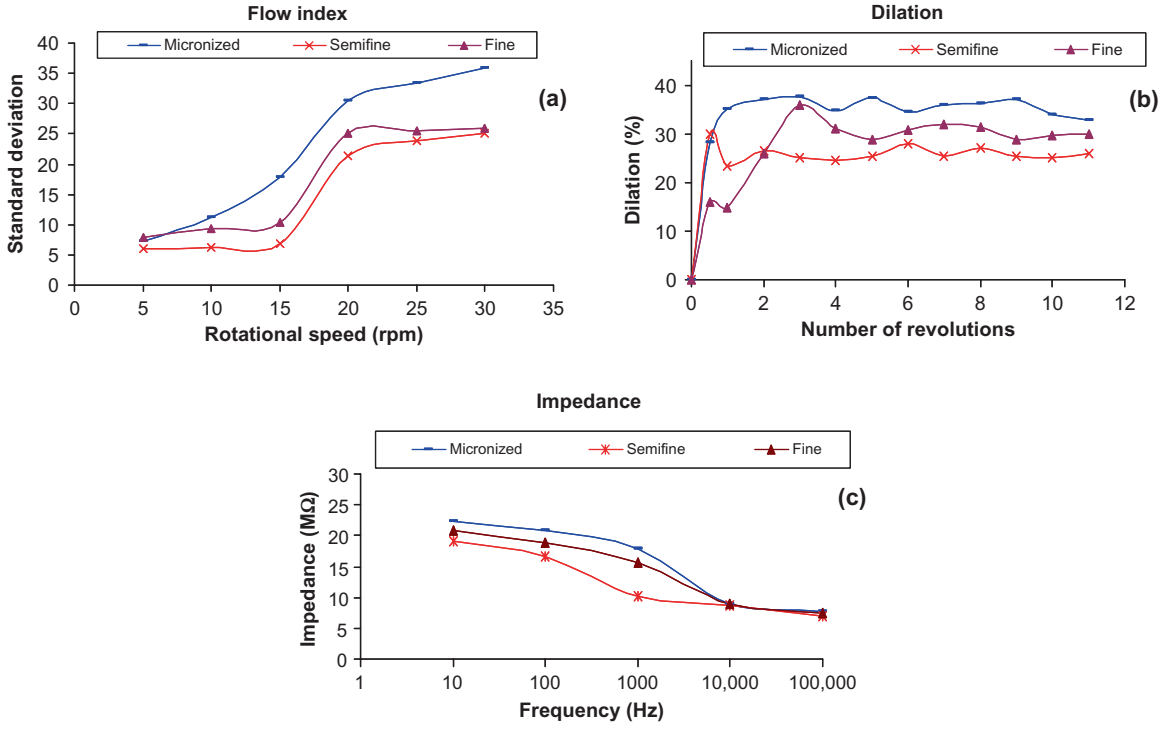

Figure 2. Flow index, dilation, and impedance curves for three grades of acetaminophen powder (micronized, semifine, and fine). Micronized acetaminophen had shown higher cohesion than the other powders.

of APAP improved to a greater degree when additives were used alone without talc. Interestingly, the largest decrease (best overall improvement) in flow index and dilation was observed when all the three additives were used simultaneously. Flow index decreased from 16.68 for pure drug to 11.64 for the drug with all the three additives. Dilation (relative to initial bed volume) decreased from a maximum of 36% for the pure drug, which corresponds to a poorly flowing material, to a minimum of 15% for the drug with all the three additives, suggesting a decrease in cohesion (decrease in bed expansion) and corresponding improvement in flow properties[24].

Electrical properties (impedance) of APAP blends were measured. Electrical conductivity has been observed to change in presence of various lubricant concentrations[25,26]. In our experiments, as additives were added individually, in pairs, and, finally, all three simultaneously, impedance decreased remarkably, from a maximum of 19.26 MΩ for the pure drug to a minimum of 7.26 MΩ for the drug with all the three additives. Moreover, as additives were added, impedance values decreased in approximately the same order as what was observed for flow index and dilation. This observation is in agreement with our previous work, where we have shown the existence of a high degree of correlation between flow properties and impedance of pharmaceutical blends[27].

The relationship between flow, density, and impedance has been explored in a previous article by our group, where we proposed that the relationship exists for two reasons: (i) More cohesive powders, having lower density, have less frequent particle–particle contacts, leading to lower electric conductivity (higher impedance) and (ii) powders with higher impedance are either less conductive or more capacitive (or both) and thus more easily acquiring electrostatic charge while they flow, leading to greater cohesive effects. As demonstrated below, results communicated in this study show that the correlation between flow index, dilation, and impedance is robust and applies as well to mixtures that are primarily API and contain small amounts of flow-enhancing additives.

Flow characteristics and impedance of LEV blends

The same procedures as described above for APAP were used to test the flow, dilation, and impedance of LEV blends. It has to be noted that the nonlubricated LEV powder was very cohesive and had shown very poor flow behavior. In addition, the density of powder was low and highly ‘staticky’, which was readily observed. For example, pure API particles were readily observed

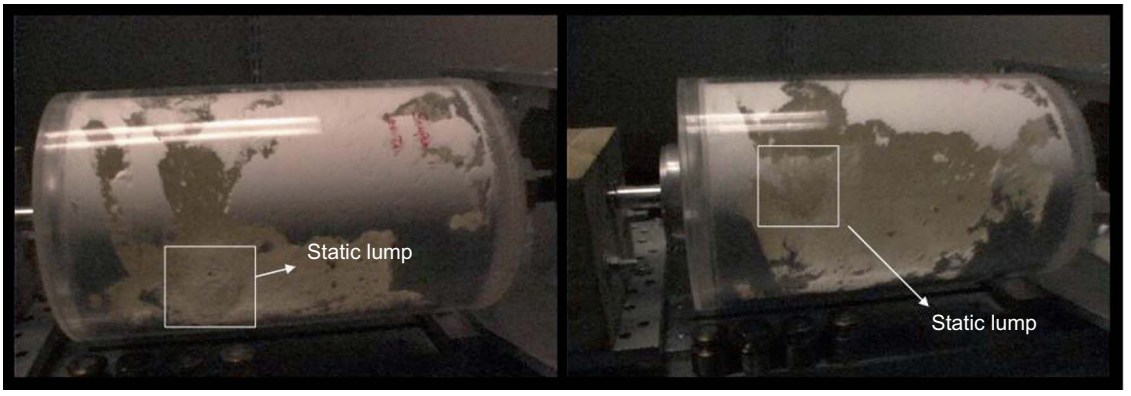

Figure 3. Formation of static lump during the rotation of cylinder while measuring flow index of pure LEV in the GDR.

'floating' in the rotating cylinder. As shown in Figure 3, while measuring the flow index, nonlubricated LEV powder spontaneously formed a large ball in the powder bed. In addition, attachment of powder particles to the walls of the cylinder was also readily observed, complicating the flow and density measurement technique. Such typically 'staticky' behaviors were found to decrease with the addition of additives, suggesting that electrostatic forces play a large role in the flow behavior of the drug. Over the years, lubricants and glidants have been used in blend mixing to achieve blends with desired flow properties and to facilitate ejection of tablets from rotary press dies[28–30]. In our experiments, the aforementioned formation of static lumps and the sticking of powder to the walls of the cylinder rapidly decreased when the powders were blended with multiple additives.

The effect of additives on the flow index of LEV blends can be seen in Table 2. When talc alone was added, results followed very closely the trends already observed for APAP. The improvement in flow properties was also similar when both silica and MgSt were added together. Again, the same order of improvement was observed for both Flow Index and dilation. Silica was the most effective single additive, followed by MgSt and talc, and silica–MgSt was the most effective pair. Both for flow index and dilation, talc was the least effective additive in decreasing the cohesiveness of the drug powder.

Overall, flow index decreased from a maximum of 7.95 for the pure drug to a minimum of 5.78 for the drug with all the three additives. Even more dramatically, the dilation of the powder bed, relative to its initial volume, decreased from 56% for the pure drug (a value typical of very poorly flowing powders) to a low value of 17%, which is typical of a good flow material such as Avicel 102[24].

It is evident from the impedance results for LEV blends shown in Table 2 that impedance was greater for more cohesive powders and decreased as the additives were added. Once again, the same rank order was followed for flow properties and impedance measurements. A remarkable decrease in impedance was recorded, from a maximum of 28.20 MΩ for pure LEV to a minimum of 11.26 MΩ, for the blend containing all the three flow additives.

Flow characteristics and impedance of DDMS blends

The flow behavior of the DDMS blends was analyzed using only dilation experiments. Flow index measurements were not performed for these blends because of the health risks involved with handling this particular powder. However, as shown later in this study, the strong correlation between flow index and dilation makes it possible to characterize flow properties based entirely on dilation behavior.

As shown in Table 3, the bed dilation, relative to its initial volume, decreased from a maximum of 40% for the pure drug to a minimum of 15% for the drug with all the three additives, indicating a substantial decrease in cohesion and, consequently, a marked improvement in flow properties. Once again, silica was the most effective single additive, silica–MgSt was the most effective pair, and the largest decreases in dilation were observed when all the three additives were used simultaneously. Once again, talc was found to retard the action of silica, as previously seen in the case of APAP.

As observed in the previous two cases, impedance for all the blends of DDMS decreased in the same order as dilation, from a maximum of 27.27 MΩ for the pure API powder to a minimum of 10.91 MΩ for API blended will all the three additives. It is evident from the impedance results shown in Table 3 that impedance decreased more for blends containing silica than for blends containing the other two additives. Once again, the largest decreases were observed when all the three additives were used simultaneously. Unfortunately, the blend containing

the binary pair of MgSt and talc could not be tested because of a lack of available API powder.

A comparison of dilation and impedance values for all three API

When all the three additives were added, direct comparison of dilation values for three API blends readily shows that the decreases in dilation are of similar order of magnitude. The similarity in rank order of flow behavior was also observed when talc alone was added to all three pure APIs. The maximum degree of dilation, observed for pure LEV powder (56%), is substantially larger than that of micronized APAP (36%) and DDMS (40%). Remarkably, all three materials exhibited nearly identical dilation behavior when mixed with all the three additives.

Consistency in the decrease of impedance can also be observed in the results. While impedance values were generally lower for APAP than for the other two APIs, the same relative degree of decrease of impedance with respect to dilation was observed for all the three APIs (63% for APAP, 60.07% for LEV, and 59.99% for DDMS).

Moreover, the order of improvement in flow index and dilation, and the order of decrease in impedance, was the same for all the three APIs. These observations suggest two potentially important hypotheses:

1. The correlation between flow index, dilation, and impedance, previously observed for pharmaceutical blends containing small amounts of APIs, could be generalized to blends that are mostly APIs.
2. A general relationship might exist between these material responses.

In the next section, we explore both of these hypotheses.

Relationship between flow and electrical properties of drug powders

Let us start this section by focusing on the first hypothesis. One of the most significant observations from the data in Table 1 is that for both APAP and LEV, flow index and dilation exhibit precisely the same rank order. In previous publications, we showed that the flow index and the dilation of pharmaceutical powder blends are directly proportional to each other and exhibit a linear correlation. As shown in Figure 4, this nearly linear direct correlation between flow index and dilation is extended for both micronized APAP and LEV blends. This relationship, first observed by Carr[31], has been confirmed by the more sensitive methods used here and reported in previous publications by our

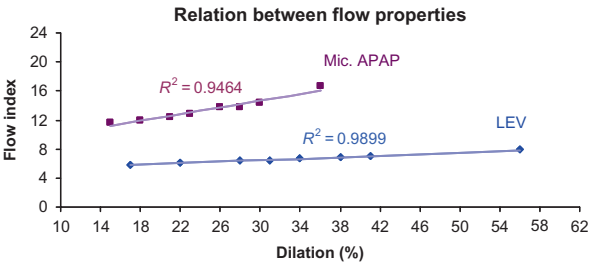

Figure 4. Direct nearly linear correlation between flow index and dilation for the two types of API blends (micronized acetaminophen and LEV).

group[24]. In addition, work done by Lindberg et al.[32] showed that flow characterizations of formulations measured with different techniques had the same rank order.

The reason for the existence of this direct correlation is actually quite simple. As discussed in a previous paper[27], when challenged with a certain stress level, a powder must dilate to the point where its configurational strength (characterized by the smaller of either its yield strength or its tensile strength) is sufficiently weakened to allow shear or tensile failure. Dilation weakens the bulk strength of the powder by decreasing the density of interparticle contacts[24]. The stronger those contacts are (the higher the particle-based cohesivity), the lower the density must be to allow flow for a given applied stress. As a result, the larger the cohesive forces, the larger also the geometric size of avalanches. The reason, here, is subtle: gravity, which drives the flow, is a volume force, while ''cohesion'' (yield strength) is a surface force. Thus, as the intensity of surface forces increases, a larger volume of powder is needed in the avalanche to overcome them.

Also very striking is the direct and nearly linear correlation between flow index and impedance, shown in Figure 5a, and between dilation and impedance, shown in Figure 5b, for APAP blends. The existence of both of these linear correlations is also confirmed for LEV and DDMS blends. This correlation of both flow index and dilation with impedance was originally communicated in a previous paper focusing on blends that were primarily composed of excipients, and it is confirmed here for much more cohesive blends that are mostly composed of API.

This study confirms that higher impedance blends produce more cohesive beds, which flow in larger 'chunks' (i.e., produce higher flow indices), and dilate more. Impedance is related to dilation by at least two direct mechanisms: (i) for materials with larger capacitance, capacitive charge storage increases the strength of interparticle forces, leading to increases in flow index and dilation and (ii) for more cohesive materials, decreases in density (increases in dilation) decrease

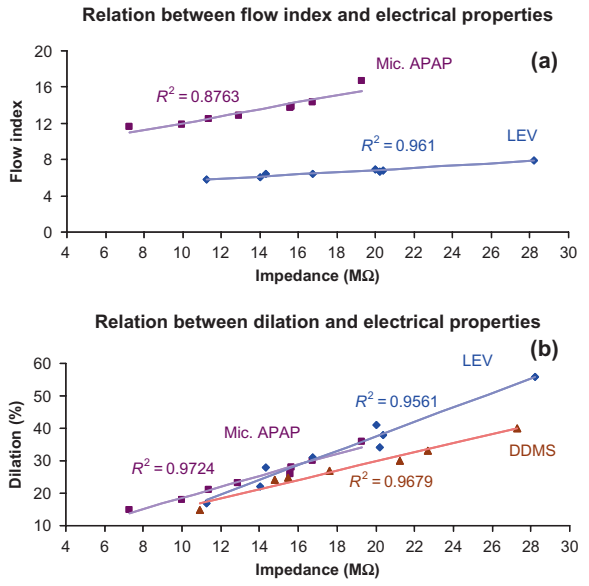

Figure 5. Direct nearly linear correlation between flow and electrical properties of pharmaceutical drug blends.

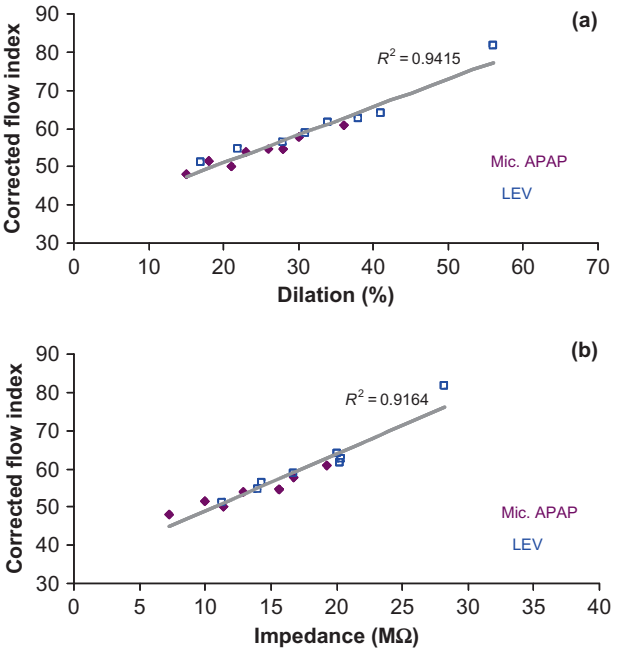

Figure 6. Normalization of flow properties of pharmaceutical blends. A common relationship is exhibited for both sets of API blends when results are plotted as corrected flow index versus dilation.

electric conductivity, correspondingly increasing electric resistance and thus impedance. Such adverse effect on powder flow can be caused due to charge acquisition in the powder blends[33–35]. Charge density in the powders, which is influenced by particle size, humidity, tribielectrification, impact angle, and impact velocity[36–39], is also proportional to impedance. Consequently, our results suggest that 'powder flow' might be characterized by measuring electrical impedance. This is highly advantageous when compared with shear cells or with the GDR, as it requires less work, less time, and fewer samples, and contributes to a mechanistic understanding of powder cohesive phenomena.

The preceding discussion provides a suitable entry point for addressing the second hypothesis made at the end of the previous section: that a general relationship exists between flow index, dilation, and impedance. In our previous papers, all the powders tested were within a relatively narrow range of bulk densities. Under such conditions, a single correlation was able to capture many different blends. However, the much more cohesive powders tested here exhibit much lower dynamic densities and smaller values of flow index. This happens not because the avalanches are smaller, but because they are lighter. A consequence of this effect is shown in Figure 4, which displays together the flow index-dilation plane for both APAP and LEV blends. Having very different dynamic densities, the two families of blends lay along entirely different lines. For a given pharmaceutical product, a correlation could be established that would facilitate optimization and control of flow properties. However, a remarkable result is shown in Figure 6a: If an 'adjusted flow index' is defined by dividing each value of the flow index in Figure 4 by its corresponding value of the dynamic density, then both families of results align themselves along a single common curve. This suggests that the 'adjusted flow index' is a smooth property that might be amenable to a 'mixing rule' useful for characterizing and optimizing material response. As should be expected, a similar relation was observed when the flow index was correlated to the impedance. Figure 5a shows that the linear correlation between impedance and flow index is different for blends of APAP or LEV. However, once again, all results fall along a common line when results are plotted as adjusted flow index versus impedance as shown in Figure 6b.

Conclusions

Two sets of conclusions emanate from the results presented here. The first set of comments pertains to the fact that flow properties of APIs can indeed be massively improved simply by mixing them with some of the same excipients that would be included in typical pharmaceutical blends. This is a major observation, which opens a practical approach for improving performance of troublesome materials without resorting to expensive major process changes such as crystallization and dry or wet granulation. Two important comments need to be repeated: (i) as our results show that the different

additives interact, and because at least one of them (MgSt) is known to be shear sensitive, the approach introduced here needs to be optimized. (ii) While we acknowledge that the proposed approach might impact other critical quality attributes such as hardness and dissolution, we believe that such adverse effects can be managed by a thorough exploration of the response surface.

At this point, we can simply conclude by stating that the additives were effective in improving the flow of cohesive drugs. The second set of observations relates to the emerging use of dynamic density and impedance as an approach for characterizing powder flow, optimizing formulation performance and manufacturability, and providing a potentially useful process control point. As previously discussed in our previous publications, and confirmed here, dynamic density (the density of the unconfined flowing powder) appears to contain critical information about intrinsic flow properties. The direct correlation between flow index and dilation, now generalized for API blends, indicates that density can be a useful surrogate for flowability. Given that density is clearly more easily measured, particularly for online systems, this observation is likely to prove useful in the future.

Declaration of interest: The authors report no conflicts of interest.

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