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Investigating the flow behaviour of pharmaceutical blends using shear cell methodology

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ABSTRACT

Powder flow properties are critical bulk level features for the manufacturing of solid dosage forms. Small-scale powder flow measurements are also widely accepted as a tool for predicting large-scale production failure. The aim of this study is to explore the flow properties of a two-component powder mixture and investigate the effect of mixing two powders with different properties on the flow properties parameters. To achieve this aim, 12 blends were prepared using an acoustic mixer (Labram). The flow properties were studied using rotational shear cell methodology. The results showed that the addition of Micr APAP into the excipients with good flow properties significantly increased the flow resistance of the prepared blends and consequently reduced their flow properties. The main driving factor in determining the flow properties is the particle size of the blend's components. The results of this study suggest that it is very important to measure the flow properties of any pharmaceutical blends and not depend only on the flow properties of the original components before mixing.

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INTRODUCTION

Understanding, evaluating, and, most crucially, forecasting powder flow performance is a vital step for pharmaceutical formulation development and process design of solid dosage forms [1].

In the manufacturing of pharmaceutical dosage forms, Active Pharmaceutical (API) components are combined with an excipient and are processed for the production of the final medicinal product through a sequence of powder-based unit operations (for example, granulation, drying, compaction) [2–4].

The powder mixing step is also crucial in the manufacturing of other products such as cosmetics, catalysts, chemicals, petrochemicals and foodstuffs [5–7].

The Jenike shear cell has long been the preliminary point for determining a powder's flow properties, and many current procedures are still based on its principles [8–10]. While data from this technique is ideal for building silos and providing a firm basis for analyzing behavior during long-term storage, it does not necessarily indicate powder behavior in dynamic operations like filling and operating tablet machines. [11]

One of the most used powder flow characterization approaches is the shear cell methodology, [12]. It has long been standard practice in engineering to categorize and rank the flowability of various materials using the extracted flow function coefficient (ffc) [13].

Mohr circle analysis can be used to determine cohesion, unconfined yield strength, angle of internal friction, and other design characteristics. As a result, the shear cell test has been widely utilized to evaluate powder flow characteristics, and the influence of consolidation state on powder flow properties has been investigated [14].

In recent research, the powder flow characteristics of three commercially available shear cells were examined [15]. In addition, shear cell data and other flow indices have been analyzed using multivariate analysis. Principal component analysis, for example, was used to establish a strategy for developing early medicinal formulations [16].

The flow behavior of a powder is multifactoral and comes from the same material characteristics as the material handling, storage and/or processing equipment [17]. Different classification methods and indices were given in which the company introduced flow parameters for early development as flow screening technology [18–20].

However, individual powder flow indices like FF and basic flow energy (BFE) were employed for the evaluation of powder processing. There have also been noticed inconsistencies between several powder flow characteristics, which show that a single powder flow property might be inaccurate to forecast powder flow characteristics [21].

However, characterization of powder characteristics using only one classic single index approach, such as Carr's Index or flow through a funnel, is insufficient for excipient screening and powder in-process performance prediction [22]. Instead, a multi-method approach should be used, in which powders are evaluated using a variety of techniques, each of which evaluates distinct powder characteristics that are important to production [23].

A huge effort has been applied to study the effect of different factors on the shear cell results and many studies have been conducted to correlate these results with the experimental conditions using statistical tools. Also, all shear cell measurements have been done on the original components of any dosage forms [24, 25].

However, there are few reported works that have investigated the effects of mixing two components on rheological behaviors. Specifically, the effects of this mixing on some flow parameters such as (ff) values.

In addition, comparing flow properties measured from different blends is also needed. That is why it is of interest to investigate the flow properties of pharmaceutical blends and not only the single materials because, in the manufacturing of solid dosage forms, the flow properties of the blend determine the properties of the final dosage forms.

The purpose of this work is to explore the flow properties of different pharmaceutical blends using the shear cell technique to address the above issues. Measuring the shear properties of different pharmaceutical blends provides valuable information as to whether these blends will flow well through all manufacturing steps or whether flow problems arise during the manufacturing process.

To achieve this aim, five ingredients, including one model drug and four excipients, were used. The excipients and the model drug were mixed in various proportions in order to develop a binary mixture. As we mentioned early in this section, the flow properties of drugs and excipients play a crucial role in determining the properties of the final dosage forms; thus, it would be of interest to study the flow properties of a drug that mixed at different ratios with excipients that have different flow properties, and it would also be great to discuss the differences in the flow parameters among these blends.

MATERIALS AND METHODS

Acetaminophen USP/ Paracetamol Ph Europe micronized (Mallinckrodt- NC, USA) was selected as a drug model with very poor flow properties. It was mixed with four pharmaceutical excipients with different flow properties in this study, which are summarized in Table 1. All materials were used as received.

Preparation of Blends

Twelve sets of binary powder mixtures were prepared using micronized acetaminophen (Micro APAP) with each of (Avicel PH-200 (A200), Avicel PH-102 (A102), Regular Lactose monohydrate (LM), Lactose Fast Flow (FF), at three concentrations levels 75%, 50%, and 25% (weight/weight).

Blends were prepared using a laboratory-scale Resonant Acoustic® Mixer (RAM, Resodyn Acoustic Mixers, Butte, Montana, USA), which uses low frequency and high-intensity acoustic energy to induce mixing and allow for sufficient mixing for small-scale blends [26, 27]. 100 g of each blend was prepared at 40% intensity for 3 min vibration time.

Table 1: Summary of Materials

ID	Material name	Generic name	Provider
1	Avicel® PH-200 (A200)	Microcrystalline Cellulose	DuPont Nutrition USA, Inc - DE, USA
2	Avicel® PH-102 (A102)	Microcrystalline Cellulose	DuPont Nutrition USA, Inc - DE, USA
3	Lactose Monohydrate NF (LM)		Foremost Farms-Wisconsin, USA
4	Lactose Fastflow (LFF)		Foremost Farms-Wisconsin, USA
5	Micronized Acetaminophen (Micr APAP)	Paracetamol	Mallinckrodt- NC, USA

Shear cell methodology

The FT4 powder rheometer offers a wide range of powder testing procedures (Figure 1). Furthermore, within each of these approaches, numerous choices for tailoring the procedure to individual needs are accessible. For the shear and wall friction tests, four standard programs are provided with pre-consolidation levels of 3, 6, 9, or 15 kPa, i.e. the typical stress given to the bulk materials prior to testing. The device utilized in this study is a FT4 Powder Rheometer (Freeman Technology Ltd) that is comprehensively described in the previous literature [28]. Simply, powder samples were placed in a glass vessel. Blades, pistons, shear heads were used to induce a rotational and vertical movement in the powder bed.

To eliminate the influence of humidity variation on the samples, the humidity and temperature were recorded during the measurement. Generally, the humidity was between 60-70% and a temperature of 21°C.

Conditioning, consolidation, pre-shearing, and shearing were the four phases of the test procedure. The powder was first placed in a cylindrical glass container. To remove the entrapped air, a helical blade travelled down in a compressive motion while in a rising motion, evoking a homogeneous condition of reproduction. During consolidation, a vented piston applied a constant normal strain to the powder. Following that, the powder was recommended to create a steady-state flow with a constant sample bulk density. Shear stress, normal stress, and preventive stress were all measured. After the pre-shearing point was reached, normal stress was decreased and the sample was further sheared to generate a yield point. The combined pre-shear/shearing operation was done five times at varying normal stresses to achieve a yield locus [29]. In this work, all the experiments were done at 6 KPa normal applied stress and using a 25 mm * 10 ml split vessel.

Data analysis

The raw data was treated and analyzed using the FT4 Data Analysis software version 3.01.0057 (Freeman Technology Ltd., Tewkesbury, UK).

RESULTS

Shear Cell Curves

Powder flow characteristics should be studied during the manufacturing of solid dosage form to obtain acceptable properties for the medicinal product. The flow properties study of powders includes testing multiple excipients at varying concentrations and analyzing powder flow after each change until satisfactory results are reached. The number of blends and flow analyses that must be performed varies greatly depending on the properties of the materials in question, but the resources necessary to execute this work are frequently substantial. Furthermore, because the pharmaceutical industry frequently deals with tiny particles that have poor flowability or segregate, combining them properly can be difficult [30, 31].

Figure 2 a, b, c and d, illustrate the flow properties change for powder blends containing increasing concentrations of micronized APAP with A102, A200, LM, LFF, respectively when 6 KPa normal stress was applied. As the concentration of APAP was increased, the required shear stress increased as well.

Figure 2 a and b show that a high degree of shear stress is required as the concentration of Micr APAP increases in the blends. Under normally applied stress, pure A102 (non-cohesive in nature, its cohesion is 0.40 KPa) and pure A200 (non-cohesive in nature, its cohesion is 0.19 KPa) showed no trapping of air in the powder bed, which reorganized evenly

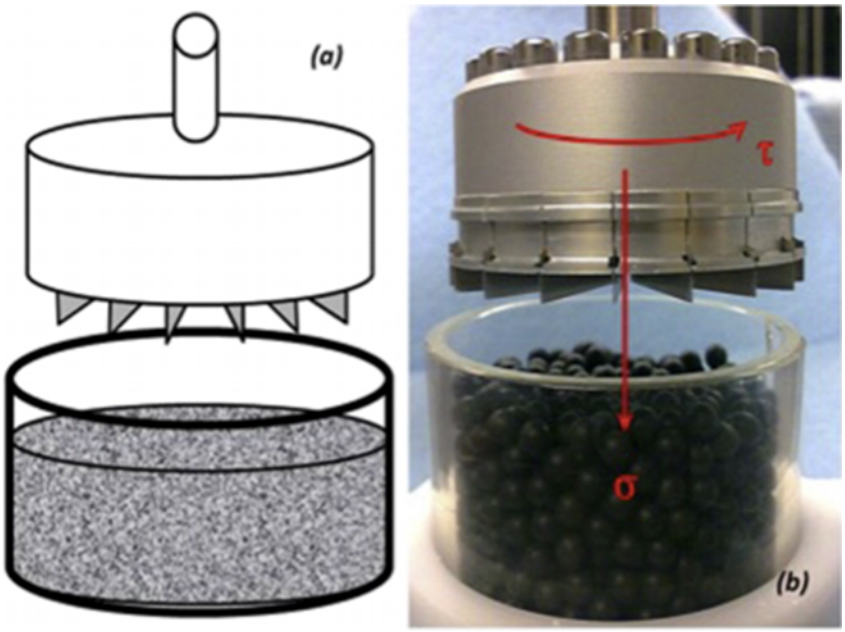

Figure 1: The schematic (a) and image (b) of the shear cell setup supplied with the FT4 powder rheometer. Picture source: A. Vasilenko, B. Glasser, Materials Science, 2011

due to the stiff nature of the particles and indicated a low degree of the required shear stress [32].

However, APAP (cohesive in nature, its cohesion is 1.64 KPa) needs a high degree of shear stress due to a large amount of entrapped air in the powder bed, which was gradually freed when stress was applied, resulting in a large change in volume. The powder mixes had the same cohesive character as pure APAP, in specific, at higher APAP concentrations.

In addition, when the amount of APAP added to the powder blend increased, the gap between the initial and final volume grew. In the same manner, the change in flow properties of both LM and LFF where an increase in the concentration of Micro APAP leads to an increase in the required shear stress to induce the flow, which means adding Micro APAP to the blends increases the flow resistance. This consequently leads to reduce the flow properties of both LM and LFF after adding Micro APAP as shown in Figure 2 c and d.

Figure 2, FT4, Shear Cell Results: Shear Stress versus increasing Normal Stress (in kPa) for increasing concentration of Micronized Acetaminophen (APAP) with a) Avicel PH 102 (A102), b) Avicel PH200 (A200), III) Lactose Monohydrate (LM), and IV) Lactose Fast Flow (LFF).

Comparison of the flow function coefficient (FF value) of all the prepared blends

Flow function coefficient (ffc) is a parameter that can be calculated as follows,

$$ff = \frac{Major\ Principle\ Stress\ (MPS)}{Unconfined\ Yield\ Strength\ (UYS)}$$

Where:

MPS is the greater of the two values at which the large Mohr Circle intercepts the x-axis (also known as σ_1).

UYS is the greater of the two values at which the smaller Mohr Circle intercepts the x-axis (also known as σ_c) Figure 3.

Consequently, in non-cohesive and free-flowing powder, the cohesion and UYS are low with a high ffc value, while cohesive and poor flow powder has a high level of cohesion and UYS and a low degree of ffc value. The ffc values for all the prepared blends at the same starting consolidation stress are presented in Table 2.

The ffc value of Micr APAP is low (ffc=2.077), which means that it has poor flow properties, while the ffc values of A200 (ffc=15.53) and LFF (ffc=20.22) are high (above 10, which means these materials have free flow properties.

Moreover, the ffc values of A102 (ffc=7.78) and LM (ffc=4.18) are moderate, which means that these materials have good flow properties. However, after the addition of the Micr APAP into these excipients, the ffc values significantly reduced to less than 3 in most cases except of adding a 25% Micr APAP to A102 and A200. These data indicated that most of the prepared blends have poor flow properties and

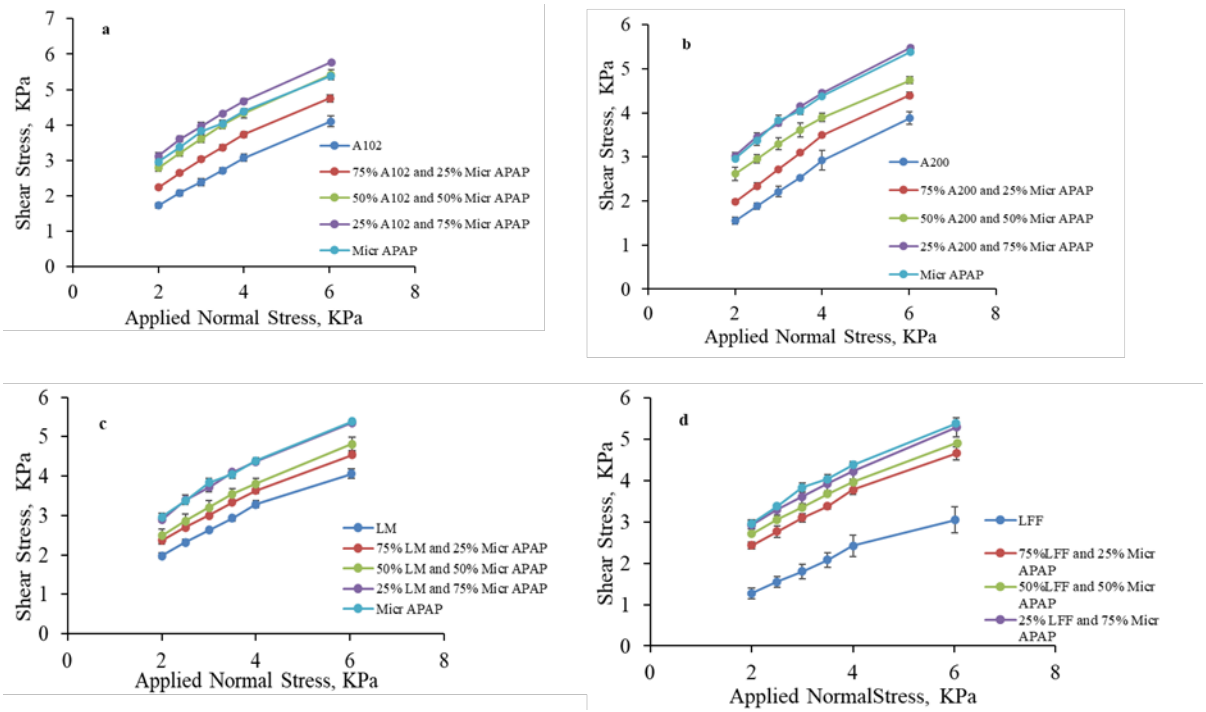

Figure 2: FT4, Shear Cell Results: Shear Stress versus increasing Normal Stress (in kPa) for increasing concentration of Micronized Acetaminophen (APAP) with (a) Avicel PH102 (A102) (b) Avicel PH200 (A200) (c) Lactose Monohydrate (LM), and (d) Lactose Fast Flow (LFF).

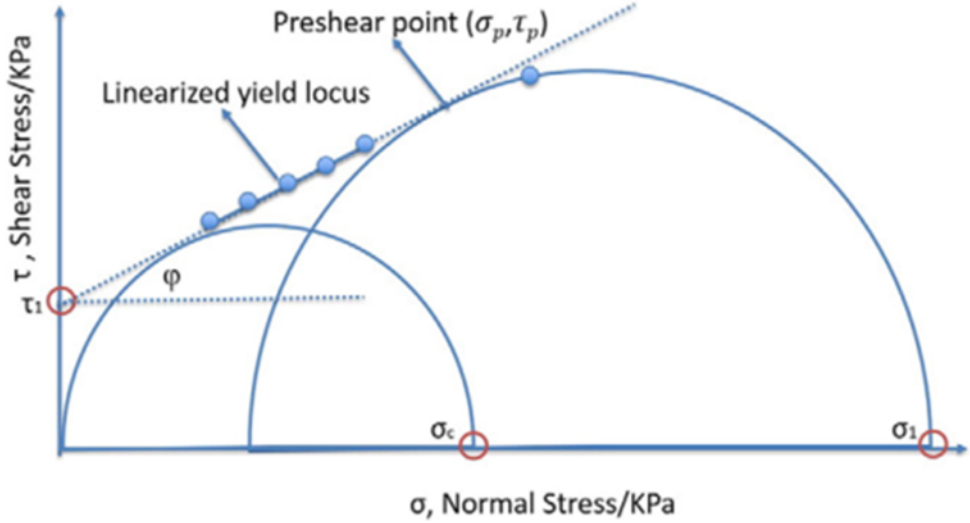

Figure 3: Graphical representation of shear cell data analysis (Adapted from Y. Wang et al. / Powder Technology 294, 2016, 105–112).

Table 2: ffc values for all the used materials and all the prepared blends

Material	As received	75% Excipient + 25% Micr APAP	50% Excipient + 50% Micr APAP	25% Excipient + 75% Micr APAP
A102	7.78	3.91	2.54	2.07
A200	15.53	6.37	2.40	2.09
LM	4.18	2.9	2.78	2.158
LFF	20.22	2.84	2.30	2.17
Micr APAP	2.07	-	-	-

Table 3: Particle size, D50(μm) for all the used materials

Excipients	D50 (μm)
A102	~120
A200	~ 140
LM	~ 63
LFF	~ 130
Micr APAP	~ 12

ffc values close to ffc of the pure Micr APAP. These results could suggest that Micr APAP addition (at 25%, 50% and 75%) has a significant effect on the flow properties of these blends by coating the excipient surfaces.

To elaborate on this proposed scenario, the particle sizes (D50) of all the used materials were presented in Table 3. As expected, Micr APAP has a very small particle size (D50=12 μm) while all the excipients have large particle sizes (D50 >100 μm). When Micr APAP is mixed with these excipients (even at a low concentration, 25%), APAP particles agglomerate the excipient particle surfaces. In this case, that the outer surface of the prepared blends is covered with Micr APAP, which has poor flow properties. Therefore, the ff values dramatically decreased by modification the excipient surfaces and increasing the frictional forces among the excipient particles; and thus, Micr APAP increases the resistance to shear stress and worsens the flowability of the blends.

DISCUSSION

The obtained data pointed out several interesting conclusive points.

1. A rotational shear cell is a quick, reproducible, and non-invasive technique to measure the flow properties of powders.The shear test can be conducted to study the flowability of blends after mixing two components at different concentrations. One key factor is the influence of adding drugs with poor flowability on the flow properties of two-components blends. The FT4 Powder Rheometer can measure the dynamic flow properties, which is very important to mimic the same conditions of pharmaceutical manufacturing in the industry.
2. The results of the shear cell study also suggest that increasing the concentration of Micr APAP in the blends means a higher degree of shear stress is required. This demonstrates that Micr APAP concentration has a significant effect on the blend flow properties.
3. The FF values were drastically decreased by adding the APAP to the blends. This could be explained based on the particle size differences between the Micr APAP and the used excipient. Micr APAP has a small particle size, while all the used excipients in the preparation of the pharmaceutical blends have large particle sizes. Therefore, the prepared blends have a flow property that resemble the flow properties of the pure Micr APAP because the outer surface of these blends are covered with APAP particles.

CONCLUSION

In this study, the flow characteristics of a powder combination based on a Two-component mixture system were measured using a rotational shear cell. The effect of the drug concentration on the flowability of the prepared blends was evaluated. This study confirms the generality and feasibility of using shear cells to study the flow properties of different pharmaceutical blends, which consist of a drug and different pharmaceutical excipients. This is very important in the pharmaceutical industry because different blends should be prepared and handled during the manufacturing of solid dosage forms. However, more work may be required to design a robust prediction model using advanced statistical tools. This model will enable pharmaceutical companies to use it as a reference in predicting the flow properties of any prepared blends with no need to measure these properties again. Also, further characterization studies, such as Scanning Electron Microscope (SEM), are required to confirm the coating or agglomeration of Micr APAP at excipients surfaces.

Conflict of Interest

The authors declare that they have no conflict of interest.

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