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Controlled shear system and resonant acoustic mixing: Effects on lubrication and flow properties of pharmaceutical blends

Yifan Wang [a], Juan G. Osorio [b], Tianyi Li [a], Fernando J. Muzzio [a,*]

[a] Rutgers University, 98 Brett Road, Piscataway, NJ 08854, United States
[b] Massachusetts Institute of Technology, 77 Massachusetts Avenue, E19-532, Cambridge, MA 02139, United States

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ABSTRACT

Purpose: Lubrication is critical in pharmaceutical manufacturing of solid dosage forms. The purpose of this paper is to systematically compare and correlate the lubrication effect of two devices, a controlled shear system and a Resonant Acoustic Mixer, on the flow properties of pharmaceutical blends.
Method: A model formulation was selected. Full factorial designs were conducted to examine the effect of the total strain (or total energy) and the shear rate (or power) on the powder blend flow properties. Analysis of variance (ANOVA) and effect size test using omega-squared statistics were performed.
Results: Lubrication significantly improved the blend flowability. Mixing without magnesium stearate, or insufficient strain, resulted in more cohesive blends. The statistical analysis suggests that the shear rate had a minimal effect on the blend flow properties. The experimental results also suggest that although the two devices had comparable lubrication effects on the overall blend flowability, the changes of the interparticle forces in the lubricated blends were not identical.
Conclusion: This study demonstrated a scientific approach to compare different lubrication processes in an objective and reproducible manner. The findings are useful for process design, development, and transfer between different equipment types and process scales.

1. Introduction

Achieving desired powder flowability is critical for powder handling and processing. In the pharmaceutical industry, the active pharmaceutical ingredient, which is often cohesive, is mixed with excipient materials through a series of unit operations before the delivery of final solid dosage forms [1]. Lubricants, such as magnesium stearate (MgSt), or glidants, such as colloidal silicon dioxide (SiO_2), are commonly used in pharmaceutical formulations. The main purposes of adding a lubricant are to facilitate tablet ejection, minimize sticking, and avoid stress concentration inside the tablet. Nevertheless, the lubricant can also interact with other materials during the lubrication process to improve the flowability of the blends, contributing to improved final product quality, acceptable weight variation and enhanced content uniformity [2,3]. The mechanism of lubrication has been explained by the formation of lubricant deposits on the large particles, reducing frictional and/or cohesive forces between particles [4,5]. Studies have shown that lubrication significantly affects the density, wettability, and compactability of blends [6,7]. Properties of the final solid dosage forms, such as tensile strength and in vitro drug release, are also heavily dependent on the lubrication process [8–10].

Controlling the extent of strain or its equivalent, the total mechanical energy per unit mass that the blend experiences during lubrication, is necessary to achieve the desired lubricity and flowability and to avoid over-lubrication [11]. Sufficient energy during mixing is necessary to homogenize cohesive ingredients by de-lumping agglomerates and redistributing them within the blend matrix. However, excessive energy can lead to electrostatic buildup and over-lubrication [12]. Studies have shown that tablet properties made from over-lubricated blends can be adversely affected [13–15]. Lubrication can take place in any unit operation that is intrinsically associated with shear mixing, such as blending, feeding, conveying, and passage though the feed frame of a tablet press [16]. Two process variables are important for lubrication: the total energy per unit mass and the rate of energy being applied. Although the rate is difficult to measure inside a blender, several studies have shown that these variables can be indirectly correlated to operating conditions, such as mixing time, fill level and rotation speed, and are used for process scale-up [17–19].

In recent studies, two laboratory scale devices have been used to investigate the effect of lubrication variables on blend and tablet properties: the controlled shear system and the Resonant Acoustic Mixer (RAM). The controlled shear system, also known as the modified Couette shear cell, provides a controlled and uniform shear

* Corresponding author at: Department of Chemical and Biochemical Engineering, Rutgers University, 98 Brett Road, Piscataway, NJ 08854, United States.
E-mail address: muzzio@sol.rutgers.edu (F.J. Muzzio).

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environment to the blends by equally spaced interlocking pins creating a relatively homogeneous shear field. Both strain, quantified by total revolutions, and shear rate, quantified by the rotational speed, can be controlled independently. The principles by which the controlled shear system works are explained in more detail elsewhere [11,20]. Studies show that increasing total strain improves the powder flowability and decreases tablet hardness. The shear rate was found to have smaller effect than total strain on the blend and tablet properties [12,20]. The RAM uses low frequency and high intensity acoustic energy to induce mixing and allows for sufficient mixing for small-scale blends [21]. The total energy during mixing can be easily assessed by controlling the energy input rate and the mixing time. Our previous work discussed the blending performance observed in a laboratory-scale Resonant Acoustic Mixer (LabRAM) and investigated the effect of process parameters on the material properties of blends and tablet performance. Studies suggest that improved flowability and increased wettability of the blend can be obtained with increasing energy input rate and blending time. The tableting performance and tablet properties were found to be correlated to the total energy [22,23].

The quality by design (QbD) initiative of the US Food and Drug Administration requires a process to be controllable and predictable, for which understanding the interactions between the process and materials is essential. Although both devices have been studied in previous work, to our knowledge there is no published work that systematically compares their performance. Based on our understanding of the shear mixing mechanism, it is expected that the observed lubrication trends using one device will generally agree with that from the other. However, questions that remain unanswered include: 1) is the lubrication process of the two devices, controlled by different operation parameters, processed at different scales and measured in different units, comparable? 2) Can final blends with the same flow properties be made using different device by adjusting process parameters? 3) More importantly, when comparing two devices that have different mixing principles, which properties can be correlated and which ones cannot? Considering how common and critical lubrication is, it is important to answer these questions using a systematic methodology [24].

The objective of this study is, in a QbD approach, to compare systematically the lubrication effects of the controlled shear system and the Resonant Acoustic Mixer on the flow properties of pharmaceutical blends. A model formulation consisting of a drug substance, a filler and a lubricant was used. Two factorial experimental designs were carried out to fully characterize the effect of the total strain in the controlled shear system and the total energy in the LabRAM. Shear rates were varied in both devices to examine their effect. Due to the complex nature of powders, many measurements have been developed to elucidate their flow properties. Powder flow properties in this study were characterized by density, compressibility and flow indices extracted from the shear cell test in the FT4 Freeman Technology system [25].

2. Materials and methods

2.1. Materials

The blend consisted of semi-fine acetaminophen (Mallinckrodt Inc., Raleigh, North Carolina) as the active pharmaceutical ingredient in the formulation, lactose monohydrate NF (Foremost Farms, Rothschild, Wisconsin) as the filler, and magnesium stearate NF (Mallinckrodt Inc. St. Louis, Missouri) as the lubricant. The particle size information of the materials is listed in Table 1. Particle size was determined using a laser-diffraction (LS-13320) analyzer with a Tornado Dry Powder System (Beckmann-Coulter, Brea, California).

2.2. Blending

The formulation in this study consisted of 90% w/w lactose, 9% w/w acetaminophen and 1% w/w magnesium stearate (MgSt). Prior to lubrication, 900 g of lactose and 90 g of semi-fine acetaminophen were gently mixed in a 1.87-L V-blender (Patterson Kelley, East Stroudsburg, Pennsylvania) at 15 rpm for 15 min. 10 g of MgSt was then added to the pre-blend and mixed further for 2 min also at 15 rpm. The blend with MgSt without further lubrication, either in the controlled shear system or in the LabRAM, is referred to as "0Rev" blend in this study. The above steps were repeated five times so that in total 5 kg of 0Rev blends were prepared for the lubrication experiments. The flow chart of the experiment methods is shown in Fig. 1.

Table 1
Particle size distribution of the raw materials used in the study.

Material	Mean (μm)	d10 (μm)	d50 (μm)	d90 (μm)
Lactose	71.9	10.3	63.5	157.7
Semifine acetaminophen	48.9	5.6	32.6	122.7
MgSt	8.8	2.1	7.8	16.6

To investigate the controlled shear system, a full factorial design covering three levels of shear rate and five levels of total strain was conducted. The variables to characterize the controlled shear system are listed in Table 2 (controlled shear system DOE). A total of 250 g of blend was prepared each condition. For the LabRAM study, a full factorial design including three levels of intensity and four levels of total energy was performed. The experimental design is listed in Table 3 (LabRAM DOE). A total of 100 g of blend was prepared for each condition.

In addition, a control group was prepared for each device, that is referred to as the "reference blend" and that does not contain MgSt. The reference blend was prepared by first mixing 90 g of acetaminophen and 900 g of lactose in the 1.87-L V-blender at 15 rpm for 17 min. The reference blends of the controlled shear system were then subjected to the five different strain levels from the experimental design (80, 160, 320, 640, and 1280 revolutions) at the 90 rpm shear rate. The reference blends for the LabRAM were subjected to the four different energy levels from the predefined experimental design (2000, 5000, 10,000, and 50,000 J/kg) at the 60% intensity (10.4 W).

2.3. Blend characterization

Bulk and tapped densities were measured using the standard procedure (ASTM Standard D7481-09) [26]. The bulk density was measured using a 100-mL graduated cylinder. The cylinder was filled at 60 mL and the mass was weighed. An automatic tapping machine (Model No. AT.4.110.60, Quantachrome Instruments, Boynton Beach, Florida) was used for the tap density measurement. Three replications were performed for each experimental condition.

The compressibility test and the shear cell test were measured using the FT4 Powder Rheometer (Freeman Technology Ltd., Worcestershire, UK) using the 25-mm × 25-ml split-vessel. Three measurement replications were conducted for each experimental condition. The compressibility test measures the change of powder density as a function of applied normal stress. The compressibility recorded in this study is the percentage change in volume after consolidation at normal stress of 15 kPa. Typically, a lower compressibility corresponds to a material with lower cohesion and better flowability [27].

The cohesion, flow function coefficient, and the angle of internal friction were extracted from the shear cell test based on the Mohr circle analysis [28]. The cohesion can be interpreted as the shear stress required in order to deform the powder when no normal stress is applied, and thus relates to the cohesive forces between particles. The angle of internal friction is a measure of the ease with which the powder particles will slide over one another [29]. The flow function coefficient (ff_c) can be used to characterize numerically the powder flowability. Larger ff_c indicates better flow performance based on the criterion by Schulze [30].