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Predicting flow behavior of pharmaceutical blends using shear cell methodology: A quality by design approach

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ABSTRACT

Purpose: The purpose of this study is to develop a model for predicting the flow properties of a four-component powder mixture.
Method: To build the model, 22 samples were prepared using an extreme vertices mixture design. The flow properties were characterized using rotational shear cell methodology. Two additional blends were tested for external validation to illustrate model applicability.
Results: Cohesion was shown to be in a linear relation with unconfined yield strength and a power relation with flow factor. The special cubic model was used to build a mathematical model. Normality test of residuals showed that the regression model was more robust to predict cohesion than to use flow factor.
Conclusion: This QbD approach is shown to be useful for predicting flow performance and finding design space during formulation development.

1. Introduction

The ability to understand, evaluate, and most importantly predict powder flow performance is critical for formulation development and process design of solid dosage forms in the pharmaceutical industry. During product development, flow properties are tested routinely to achieve desired manufacturability. This process often includes evaluation of the flow performance of APIs, blends, and sometimes even excipients. Poor flow performance can result in multiple problems during bulk solid processing, such as arching in hoppers, segregation and/or agglomeration after mixing, and content variability in final dosage forms [1]. Powders are complex materials. Flow measurement is more of a functional performance test than a physical test [2], and there have been many indices developed to indicate powder flow properties, such as angle of repose, compressibility index, Hausner ratio, flow through an orifice, and parameters from the shear cell tests. Another widely used dynamic test, the avalanching test, has been correlated to compressibility and shear cell results in a recent comparative study [3].

Among the various characterization techniques, one of the commonly used is the shear cell methodology, which was originally developed by Jenike for design of hoppers and silos [4,5]. A flow regime was proposed to describe the limit when powders jam and form an arch at the opening of a hopper. Useful information, such as cohesion, flow factor, unconfined yield strength and angle of internal friction, can be extracted from the test to guide process design. Jenike's mathematical analysis to determine hopper angle and opening size has become an engineering standard practice [6]. Shear cell testing has been therefore used extensively for flow property measurement. The effect of particle size, shape, and density on flow properties has been well studied using the shear cell methodology [7,8]. Effects of the storage time and environmental factors, such as relative humidity and temperature, have also been reported [9,10]. For example, Freeman showed repeatability in shear cell measurement [11], and examined the effect of consolidation on shear properties and normal stresses [12].

The quality by design initiative (QbD) of the U.S. Food and Drug Administration requires a process to be controllable and predictable [13]. Theories and methods to characterize powder flow have facilitated the implementation of QbD approaches to predict powder flow. Taylor et al. used principal component analysis based on five flow characterization methods to develop a method for material screening in early formulation development stage [14]. Both Niklas et al. and Yu et al. used principal component analysis and partial least square regression to predict powder flowability as a function of particle size and shape distribution [15,16]. Although attention has been paid to characterizing and predicting flow properties of a mixture, very few cases were presented to address the scenario during early formulation development when the amount of drug is limited and more than two ingredients are in the formulation.

The intention of this paper is to demonstrate a general QbD approach to quickly classify flow properties of a mixture during formulation development. Four ingredients, including one model drug and three excipients, were used to represent a realistic formulation design process.

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Table 1
Materials used and corresponding particle size.

Material	Mean (μm)	d10 (μm)	d50 (μm)	d90 (μm)
Semifine acetaminophen	48.9	5.6	32.6	122.7
MCC	141.2	34.0	120.8	244.1
FastFlo lactose	114.5	54.2	113.3	174.6
Regular lactose	71.9	10.3	63.5	157.7

This approach also addresses the challenge in using minimal materials during early formulation development. The remainder of this article is organized as follows: section II describes the materials, the experimental design, blend preparation and characterization methodologies used in our study; section III presents the prediction model based on experimental results and main findings; and finally section IV is devoted to the conclusions and the impact of future work.

2. Material and methods

2.1. Materials

The materials used in this study were: Semi-fine acetaminophen (Mallinckrodt, Raleigh, North Carolina, USA), microcrystalline cellulose (Avicel PH102, FMC Biopolymer, Newark Delaware, USA), FastFlo® lactose (Monohydrate N.F. modified-spray dried, Foremost Farms USA, Rothschild, Wisconsin, USA), and Regular lactose (Monohydrate, Foremost Farms USA, Rothschild, Wisconsin, USA). Particle size information of the reported materials is listed in Table 1. The particle size distribution of each ingredient was measured using a laser diffraction analyzer (LS-13320) with a Tornado Dry Powder System (Beckmann-Coulter, Brea, California, USA).

2.2. Design of experiment.

A mixture extreme vertices design was used to characterize flow properties of the four-component system [17]. Constraints for concentration of acetaminophen (APAP, x_1), MCC (x_2), FastFlo lactose (x_3) and regular lactose (x_4) are expressed as follows:

$$x_1 \le 0.45$$

$$x_2 \le 0.40$$

$$x_1 + x_2 + x_3 + x_4 = 1.0$$

The MINITAB® Release 16 (Minitab Inc.) software was used to aid the design and 18 conditions were generated. The four raw materials were also included to the design adding up to 22 conditions in the study. Fig. 1 shows the mixture design structure. Detailed formulation for each blend is listed in Table 2. Blends 13 and 14, 15 and 16, 17 and 18, 19 and 20 were four pairs of replications to evaluate experimental variations.

2.3. Blend preparation

To minimize amounts of materials used in the study (as is often the requirement in early formulation development), 100 g of each blend was prepared. Before blending, each material was passed through a no. 18 sieve (sieve size of 1.0 mm) to enhance blend homogeneity by breaking up agglomerates. Blends were prepared in a laboratory scale ResonantAcoutic® Mixer (RAM, Resodyn Acoustic Mixers, Butte, Montana, USA) which uses low frequency and high intensity acoustic energy to induce mixing and allows for sufficient mixing for small-scale blends [18,19].

2.4. Shear cell methodology

The flow properties of all blends were characterized using a rotational shear cell supplied as a component of the FT4 powder rheometer (Freeman Technology Inc., Worcestershire, UK), which is shown in Fig. 2. The testing procedure consisted of four steps: conditioning, consolidation, preshearing, and shearing. The powder was first filled into a glass cylinder. During conditioning, a helical blade moved downwards in a compressive motion, and then moved upwards in a lifting motion to

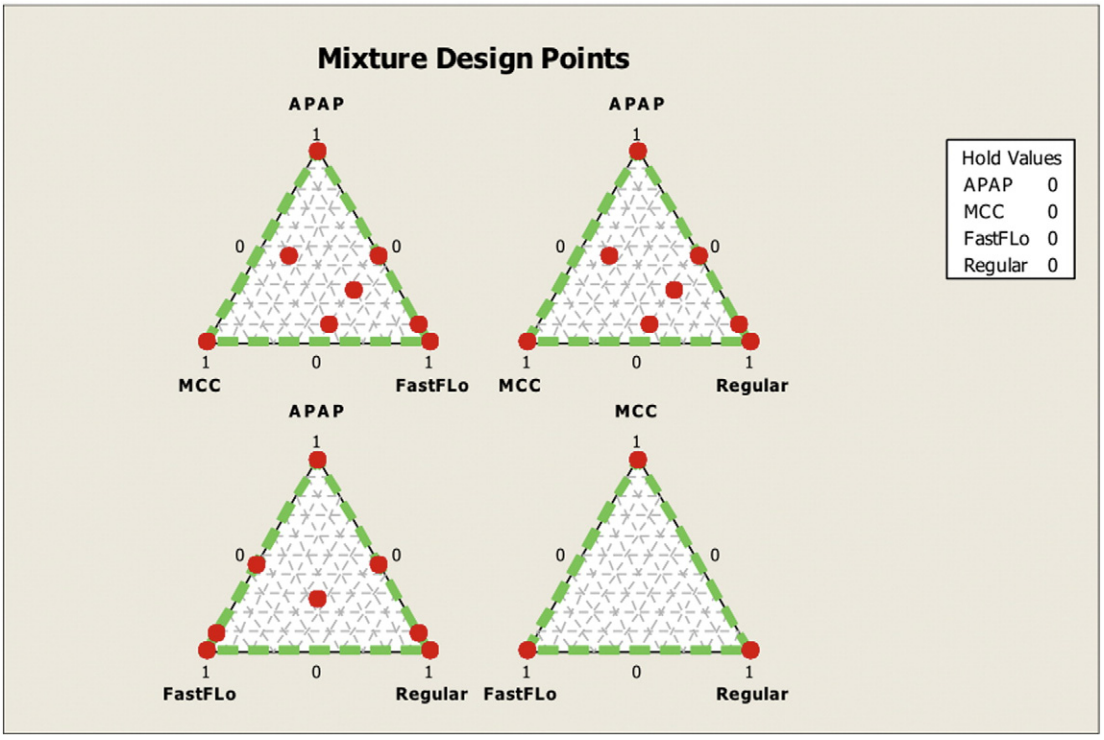

Fig. 1. Design of experiments. 18 blends were generated from extreme vertices design. 4 raw materials were also included adding up to 22 design points.