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Effects of powder flow properties and shear environment on the performance of continuous mixing of pharmaceutical powders ☆

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ABSTRACT

This paper focuses on two aspects of continuous powder mixing, namely characterizing the effects of material properties on the bulk powder flow behavior, and developing continuous blending strategies suitable for cohesive materials. The relative effects of process parameters and material properties on the bulk powder flow behavior were analyzed by performing a PLS analysis of the output parameters, including mean residence time, and axial dispersion coefficient as a function of input parameters (impeller speed, flow rate, bulk density and cohesion). The mean residence time was primarily affected by the bulk density and impeller speed, whereas the axial dispersion coefficient was affected by impeller speed and cohesion. Based on previously developed knowledge of mixing performance as a function of process parameters [1], a design rule to select the optimal number of impeller passes based on the bulk density was proposed. Impeller speed and cohesion showed a significant interacting effect on the output variable, the axial dispersion coefficient. Increase in cohesion leads to increase in the axial dispersion coefficient at higher impeller speeds, whereas a negligible effect of cohesion on the axial dispersion coefficient was observed at lower impeller speeds. In the second part of the paper, a continuous blending methodology for blending cohesive materials was demonstrated. Considering the feeding limitations of cohesive materials, and limitations in the application of shear in the bladed continuous mixer, a combination of high shear and low shear mixing with high-shear mixing as a first step exhibited an optimal mixing strategy.

1. Introduction

There are typically five routes for manufacturing solid dose pharmaceutical products, namely direct compression, dry granulation, wet granulation, capsule filling and hot-melt extrusion. Powder mixing is an essential process in all the aforementioned manufacturing routes. Since pharmaceutical processes are conventionally carried out in the batch mode, the available knowledge for the mixing of pharmaceutical powders pertains to batch processes and the necessary methods or design rules required to develop an equivalent continuous process are scarce within the literature. This paper focuses on two aspects of continuous powder mixing — developing a relationship between bulk material properties and the flow behavior in continuous mixing systems, and developing an integrated low and high shear continuous mixing processes suitable for mixing highly cohesive powders.

In recent years there have been quite a few papers published in the literature focusing on the characterization of continuous powder blending processes using either purely experimental approaches [1–4], or using computational modeling approaches such as the Discrete Element Method (DEM) [5]. In both approaches, typically the observed mixing behavior is related to the powder flow behavior in the mixer. In the DEM modeling approach, powder flow behavior is characterized by computing the velocity probability density functions (PDFs) and/or dispersion coefficients, whereas in the experimental approach PIV (Particle Image Velocimetry) or RTD (Residence Time Distribution) measurements are performed. The RTD approach is interesting because it can be used to build predictive models which predict powder concentration at the blender discharge as a function of incoming concentrations [6] and process parameters, which essentially makes it suitable for process control. In the literature, Fokker Plank Equations (FPEs) [7,8] have been widely used to model RTDs since the number of fitted parameters in the FPE is small compared to other modeling approaches such as Markov chains [9], tanks-in-series, or fractional tubularity models [10].

In our previous paper [11], FPEs were used to model RTDs from the Gericke GCM-250 mixer, and a mathematical model was developed to relate mixing performance with the incoming feed rate variability and process parameters (blender speed, flow rate). Typically such models are valid for a particular formulation and they are

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difficult to transfer for completely new formulations without prior experimental studies. The missing link in this case is the relationship between material properties and RTDs. In this paper, key material properties of commonly used pharmaceutical excipients were identified and correlated with the RTD parameters. The approach typically involves the measurement of RTD and fitting the model parameters such as the mean residence time and the axial dispersion coefficient.

The second part of this paper focuses on the development of alternative continuous mixing strategies for materials which tend to form agglomerates in powder blends. APIs (Active Pharmaceutical Ingredients) that have an average size of less than 20 μm in diameter are highly cohesive, and tend to form agglomerates because of the overwhelming Van der Waals forces. Cohesion in powder/granular systems is also caused by the capillary forces that exist due to the presence of moisture in the system; however in the present case of dry powders the primary source of cohesion is Van der Waals forces and/or electrostatic forces [12]. Powders that tend to agglomerate are typically mixed in a high shear rate environment such that the agglomerates are de-lumped and an, sometimes, an "ordered mixture" is created. High shear blending is typically performed using a V-blender with a high-speed intensifier bar, a convective mixer with a chopper, or by introducing a mill [13]. In this study, a Comil was selected as a suitable continuous de-lumping device. In order to qualify the feasibility of a Comil for the continuous process, its efficiency for mixing and de-lumping needs to be examined. In this paper, the effect of Comil process parameters on mixing performance and its position in the overall continuous processing scheme is examined.

This paper is organized as follows. In the second section, materials and methods are presented. In the third section, equipment used in this study is described. The fourth section focuses on results, which include the characterization of effects of material properties on RTD parameters, and the integrated design of mixing and de-lumping. Finally, conclusions are presented in the fifth section.

2. Materials and methods

2.1. Materials

The materials used in this study, their mean particle size and the supplier are listed in Table 1. In the first part of the paper, excipients including micro-crystalline cellulose (Avicel® PH-200, Avicel® PH-101), Fast Flo lactose, and dicalcium phosphate were used as the model materials to study the effect of material properties on the powder flow behavior in the mixer. Acetaminophen was used as a tracer material for measuring RTDs for micro-crystalline cellulose and lactose, whereas caffeine was used as a tracer for dicalcium phosphate. In the second part of this paper, Avicel® PH-200 was used as the model free-flowing powder and acetaminophen (micronized) was used as the model cohesive drug.

Table 1
Materials.

Material	Supplier	Particle size (μm) (d50)
Avicel® PH-200	FMC Biopolymer	230
Avicel® PH-101	FMC Biopolymer	90
Fast Flo lactose	Foremost Farms USA	120
Dicalcium phosphate	TLC Ingredients	186
Acetaminophen (APAP) (micronized)	Mallinckrodt	20
Caffeine	TLC Ingredients	36

2.2. Methods

2.2.1. NIR spectroscopy

Chemical composition of the powder samples were analyzed using NIR spectroscopy. Chemometric calibration models were built for individual tracer-excipient combinations. The general protocol for building calibration models includes the following steps. Calibration samples with known concentrations of tracer are prepared by accurately massing the individual components. Calibration samples are then scanned multiple times to acquire representative spectra. The NIR analyzer used was an Antaris system (Thermo Fisher). The Ominc software package was used to acquire the calibration spectra, and the TQ Analyst was used to build the chemometric model. A PLS algorithm was used to build calibration curves. Each calibration model was validated using a cross-validation program (which leaves one spectra out at a time); in each case, after careful selection of spectral pre-treatments, a robust calibration model was built. The calibration model used in the second part of this study for measuring APAP in APAP-Avicel® PH-200 mixtures is shown in Fig. 1. The calibration error (RMSEP) for this model was ~0.44.

2.2.2. Material properties

Material flow properties were characterized using two methods, namely the Carr Index (C.I.) and the dilation.

2.2.2.1. Carr Index. The Carr Index (C.I.) is an indicator of the compressibility of a powder. The higher the C.I. is, more compressible is the powder. The C.I. was calculated using Eq. (1) by measuring the bulk and tapped densities of a powder. C.I. measurements are listed in Table 2.

$$\text{C.I.} = 100 \times \left(1 - \frac{\rho_B}{\rho_T}\right) \tag{1}$$

2.2.2.2. Dilation. Dilation is a complementary measurement to the C.I. which is also an indicator of the compressibility of the powder. Dilation was measured using a device called a GDR (Gravitational Displacement Rheometer). Dilation is calculated as the percent change in volume of the powder bed as function of time. Details on the experimental set-up of dilation measurement can be found in Faqih et al. [14]. The procedure for dilation measurement can be briefly described as follows. Powder was filled up to 40% volume in a transparent acrylic cylinder, and then the cylinder was tapped on a tapping machine such that powder is compacted to its tapped density. The cylinder was then mounted on the GDR, which rotates the cylinder such that the powder tumbles inside the cylinder. The tumbling or avalanching motion of the powder is monitored in the cross-sectional direction using a camera. The images being captured using the camera are subsequently analyzed using an image analysis program to measure the

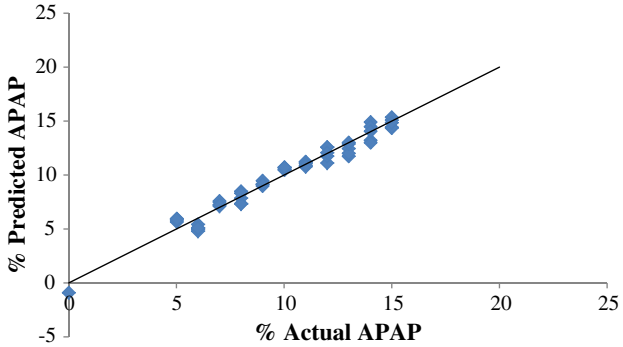

Fig. 1. Calibration model for APAP-Avicel® PH-200 mixture.