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Effect of material properties and design parameters on the final blend uniformity using experimental and simulation results

Miguel Florian-Algarin, Rafael Méndez *

Chemical Engineering Department, University of Puerto Rico, Call Box 9000, Mayagüez 00681, Puerto Rico

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ABSTRACT

One of the most important operations in the food, chemical, and pharmaceutical industries is powder mixing. In the pharmaceutical industry this operation is currently performed mainly in batch mode. However, the Food and Drug Administration (FDA), using the Process Analytical Technology (PAT) initiative, has been working on the promotion of the application of continuous processes in the pharmaceutical industry. The main goal of this study was to understand the powder phenomena inside the mixer and monitor mixing uniformity using experiments and simulations by Discrete Elements Methods (DEM). The experimental results showed highest relative standard deviation (RSD) using the lowest active pharmaceutical ingredient (API) concentration (2.5%), and after using image analysis part of this effect was attributed to the position of the feed inlet. The two experiments with the highest RSD (50 and 70 RPM) were replicated using a new feeding position (25°). The RSD values for the new feeding position demonstrated an improvement in mixing uniformity. The new feed position was studied in more detail using DEM by performing a simulations set that included simulations at two mixer speeds (50 and 70 RPM), three concentrations (2.5%, 10.5%, and 50%), and two different material properties (with and without cohesion). Values of hold-up, velocity profile, mean residence time (MRT), and mixing uniformity were compared for both feed positions. Also the blend uniformities inside the tumble, at each tumble exit, and at the final exit of the system were compared. The results show a positive effect of the angle in the uniformity inside the mixer, in the exit points, and at the exit of the system. Additionally, a relationship between RSD and concentration was found.

1. Introduction

Powder mixing studies have increased in the last year, especially in batch and continuous systems, due to the fact that the granular material mixing is a major step in diverse industries such as: cosmetics, military, food processing, cement, chemical, petrochemical, and pharmaceutical. In pharmaceutical industries, one of the principal reasons to reject a batch process is the low blend uniformity after the mixing process, due to the sampling methodology and the small amount of sample used to determine the blend uniformity. Continuous mixing process reduces these difficulties and improves the manufacturing process. Continuous mixing processes of pharmaceutical materials are affected by operating conditions and the properties of the raw material. Different authors, primarily focused on the mixer speed, blade rotation, blade design, blade configuration, inlet flow rate, and powder properties, have previously studied the effect of the operating conditions. The effect of the material properties on the final uniformity has also been studied, paying special attention to the effect of cohesion on the final blend uniformity. The cohesion of a material is directly related to its flow properties; the higher the cohesion the lower is the expected flow property. Cohesion has an effect on the flow of the material through the mixer and on the mixing time.

1.1. Experimental mixing process

The principal continuous mixers in the actuality use screws and blades [1,2] that apply shear to the raw material affecting the material properties. The blade speed has been the most studied operating parameter in the continuous powder blending. Portillo et al. [3] used a continuous system with different formulations to study powder mixing behavior and the results show that the rotation rate and the processing angle affect the RTD, the total strain applied, and the blend uniformity. These operating parameters are related to the RTD and the final blend uniformity. An increase in the rotation rate of the blades of the mixer produces a decrease in the Mean Residence Time (MRT) of the material [4]. This relation was studied by Marikh et al. [5] finding that the blend homogeneity was a contribution of the residence time and the number of blade passes. RTD has been used to determine the effects of operating conditions (two feed rates) and the mixer configuration (two blade configurations and four blade speeds) in the mixing uniformity [6]. The

* Corresponding author. Tel.: +1 787 832 4040x3585; fax: +1 787 834 3655.
E-mail address: rafael.mendez1@upr.edu (R. Méndez).

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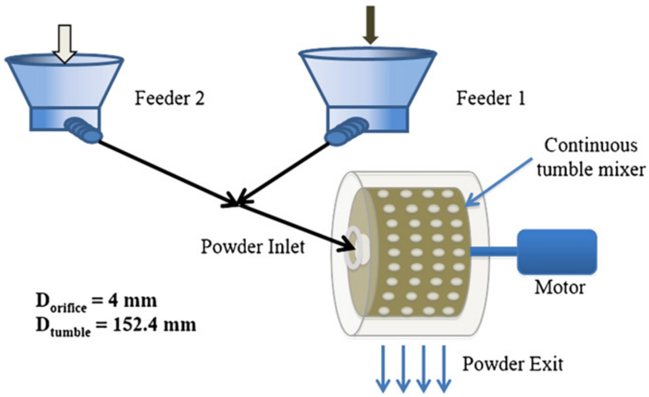

Fig. 1. Setup of the experimental continuous tumble mixer.

results showed that the use of a moderately low speed improves the mixing and that the change of feed rate doesn't have a significant influence on the overall output variance. The effect of the blade angle was also studied by Marikh et al. [7] to compare two different mixers (Mixer A with blades and a continuous screw and Mixer B with just paddles) using two different blends: a binary and a pharmaceutical mix. The results showed that the mixer with the blade A was more efficient than the mixer with blade B. In both cases a relatively high rotation velocity caused a loss in blend uniformity.

1.2. Simulation mixing process

Particulate material mixing processes, both batch and continuous, have also been studied using simulations software [8–11]. This method produces results similar to the experimental behavior of the particulate material [12–14]. A batch study of a tote blender using mono and bi-disperse particles in size was reported. The results show that the geometry of this system is sensitive to the initial loading and that the intensity and the mixing rate increase when the fill level is low [15]. When compared to the experimental part the results show an agreement between experiments and simulation of mono-dispersed particles.

For continuous mixing processes of particulate materials the main researches are related to the understanding of the effect of operational parameters such as mixer speed, blade speed, shape of the blades, fill level, and flow rate on the final mixing uniformity. An optimal combination of these parameters produces the most favorable uniformity for powder mixing processes [16,17]. A high mixer speed was also demonstrated to be an important factor in the improvement of the mixing performance [10].

Using computational processes it is possible to study the effect of the material properties in the final blend uniformity, and previous investigations showed that the cohesion is an important parameter that affects the mixing processes. Lower cohesion values improve the final homogeneity [8,9,18] and this effect is notable for batch and continuous processes [19].

The main goals of this work include the understanding of the powder phenomena inside the mixer [20] and monitoring mixing uniformity using the feeding angle as a design parameter, which was evaluated using experiments and simulations by DEM. The system responses such as mass hold up, RTD, flow regime, and velocity profiles were measured and their effects on the final mixing uniformity were studied.

Table 1
Material characterization.

Material	Median particle size (μm)	Bulk density (g/cm^3)	Tap density (g/cm^3)	Carr index (CI)	Flow function (FFC)	Cohesion
Lactose 70	125.0	0.55	0.68	19.11	11.9	0.32
Pre-blend	125.0	0.75	0.83	9.64	10.40	0.36
API	28.8	0.41	0.54	24.07	5.01	0.91

Table 2
Simulation parameters.

Simulation parameters	Values
Poison radius	0.5
Shear modulus (Pa)	2.00E + 06
Coefficient of restitution	0.05
Coefficient of static friction	0.5
Coefficient of rolling friction	0.005
Generation rate (kg/s)	0.018
Mass (g)	0.00073
Density (g/cm^3)	1.4
Standard deviation	0
Diameter (mm)	1

2. Experimental section

2.1. Low shear continuous tumble mixer description

The experimental system (Fig. 1) used in this work includes a two loss-in-weight feeders and the continuous tumble mixer, which was described in our previous work [20]. The mixer is comprised of two concentric cylinders that are both made of acrylic to allow the visual monitoring of the powder mixing behavior inside. The inner cylinder works as the mixer and has an internal diameter of 152.4 mm with multiple orifices in the radial wall. Each orifice is 4 mm in diameter and 6.35 mm in depth. The depth of the mixer cylinder is 50.5 mm. The mixer is closed at both ends, with one end connected to the shaft of a variable speed motor to control the speed. The other end has a hole in the center to permit the entrance of the materials; these materials enter the mixer through a 25.4 mm internal diameter acrylic tube. The mixer rotates counterclockwise to allow the powder particles to slide or form an avalanche while simultaneously exiting through the orifices due to the centrifugal force [20]. The simulated system was developed using Autocad software® with exactly the same dimensions of the experimental mixer [21].

2.2. Materials

The materials used for the experimental part include (1) naproxen sodium (Zhejiang Tianxin Pharmaceutical Co.) with a median particle size of 28 μm as active pharmaceutical ingredient (API), and (2) Tablettose 70 agglomerated monohydrate lactose Ph. EUR/USP-NF/JP (Malkerei Meggle Wasserburg GmbH & Co.) with a median particle size of 125 μm and Ligamed MF-2-K Magnesium Stearate (Peter Greven) with a median particle size < 10 μm.

Table 3
Experimental design.

Simulation	RPM	Cohesion	Angle	Particle concentration
1	50			50.0%
2	50		x	50.0%
3	70			50.0%
4	70		x	50.0%
5	70			10.0%
6	70		x	10.0%
7	70	x		10.0%
8	70	x	x	10.0%
9	70	x		2.5%
10	70	x	x	2.5%