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Effects of processing parameters and blade patterns on continuous pharmaceutical powder mixing

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ABSTRACT

The present study summarizes the experimental characterization of a new continuous powder mixer (GCG-70 by Glatt®) using common pharmaceutical ingredients. The powder hold-up and residence time distribution were used to characterize the bulk behavior of the mixer as a function of impeller rotational speed, total throughput (mass flow rate) and blade configuration. The relative standard deviation (RSD), calculated from samples taken at the outlet of the blender, was used to characterize its mixing performance. The hold-up and the mean residence time decreased with increasing impeller rotational speed. The mean centered variance and the number of blade passes increased with increasing impeller rotational speed. The effect of the blade configuration on the mixing dynamics diminished as the rotation rate increased. The hold-up and mean residence time were sensitive enough to demonstrate the effects of blade configurations. The mixing performance, depending on the processing parameters, was found to be between 5% and 10% RSD for 5% w/w active pharmaceutical ingredient (API), and <3% for 30% w/w API. These results showed improvements in the mixing performance when compared to studies of other continuous mixers using similar materials and analytical techniques for quantification.

1. Introduction

Powder mixing is a critical manufacturing step in several industries, including pharmaceuticals, cosmetics, chemicals, food and minerals. Especially in the pharmaceutical industry, powder mixing is often carried out in batches. Therefore, batch powder mixing has been characterized more extensively than continuous powder mixing. In recent years, a strong initiative by the pharmaceutical industry and its regulatory agencies to understand, design and control more robust manufacturing processes, leading to high quality finished products, has led to growing interest in continuous processing [1].

Continuous processing offers several advantages over conventional batch processing [2,3]. These advantages include the opportunity for more meaningful implementation of process analytical technologies (PAT) and the use of modeling techniques for automated process control to maintain the required steady state and make finished products with sustained quality [4]. With continuous manufacturing, the same equipment used for process development can often be used in manufacturing. Therefore, the need for process scale up is reduced or eliminated, accelerating the introduction of new products to market. These advantages also include significant reductions in equipment size and the ability for integration with other continuous processes (e.g. tableting, capsule filling, roller compaction). Integration with an intrinsically continuous process would yield higher process efficiency and minimize segregation of the mixed materials. Moreover, because a continuous process can achieve a desired set point after a transient period of just a few minutes, entire sets of designed experiments can often be explored in a matter of just a few days, with great savings in materials, time and money. Overall, the advantages of continuous processing can significantly reduce costs during development and manufacturing of pharmaceuticals.

Continuous powder mixing equipment has been characterized both experimentally [5–11] and computationally [12–16] in the past few years. Such studies have described the mixing behavior and performance of continuous mixers as a function of design parameters, processing parameters and ingredient material properties. Design parameters include the impeller type and configuration [8,9,11], the outlet weir angle [8] and the mixer

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elevation angle [11]. Processing parameters include the impeller rotational speed and the total and individual flow rates (mass concentration) of the components [5,7–10]. However, only a few commercially available continuous powder mixers have been discussed in the literature. Marikh et al. studied and developed correlations for hold-up as a function of rotation rate for a continuous mixer (GCM-500 by Gericke with a length to diameter ratio (L:D) of 2.5) [10]. In a different study, using the same continuous mixer, Marikh et al. investigated the effect of impeller types on hold-up and mixing performance [9]. It was reported in both studies that mixing performance improved with increasing rotation rate and then worsened at higher rotation rates due to the change in mixing regimes (fluidization). Portillo et al. reported the characterization and comparison of two continuous mixers (GEA Buck Systems with L:Ds of 4.9 and 6.2) with the same design but different sizes [6,11]. In these studies, it was found that lower impeller rotation rates and a greater upward mixer elevation angle yielded enhanced mixing performance. Vanarase and Muzzio studied the effect of operating conditions and design parameters in a continuous powder mixer (GCM-250 by Gericke with an L:D of 3.0) [8]. It was found that the total strain that the powder experienced in the continuous mixer had a maximum at intermediate rotation rates also yielding better mixing efficiency. In our previous work, we examined the mixing behavior of the same continuous mixer (GC-250 by Gericke) using several pharmaceutical excipients differing in particle size and flow properties. It was found that although the material properties affected mixing behavior, the predominant variable was still the impeller rotation rate [7].

Most of the continuous powder mixers characterized and reported in the literature were not designed for pharmaceutical applications, but rather for food applications. In an effort to advance the understanding of continuous powder mixing and processing as a whole, a new commercial continuous powder mixer (Glatt GCG-70) – designed for pharmaceutical processing – was considered in this study. The main objective of this study was to characterize the mixing dynamics and performance of a Glatt GCG-70 using pharmaceutical powders. Contrary to liquid mixers such as stirred tanks, where dozens of impeller geometries have been studied, very few studies of the effects of impeller geometry on mixer performance have been reported for powder mixers. Thus, in this study, the effects of blade configurations on mixing dynamics and performance were studied as well.

2. Materials and methods

2.1. Materials

Materials used in these studies are listed in Table 1. Silicified microcrystalline cellulose (Prosolv HD 90) was used for the mixing dynamics and performance characterization, presented in Subsection 5.1. Microcrystalline cellulose (Avicel® PH 200) was used for the blade configuration studies, presented in Subsection 5.2. Magnesium stearate (MgSt) was used as the instantaneous pulse material to characterize residence time distributions. Semi-fine acetaminophen (APAP) was used to characterize the continuous mixing performance.

2.2. Continuous mixing

A new commercial continuous mixer (GCG-70, Glatt®), designed for pharmaceutical processing, was used in all the experiments presented in this article. The GCG-70 is 70 cm long and 8 cm in diameter (with an L:D of 8.75). The mixer and experimental set-up are shown in Fig. 1. Two gravimetric feeders (Model AP300, Schenck Accurate) were used to feed the raw materials using the configurations described in Table 2. The selection of the screw type and nozzle size was based on previous experience, and it was dependent on the required flow rates and the cohesion of the individual components used, to minimize feeding variability.

2.3. Sampling and near-infrared analysis

Stream sampling at the outlet of the continuous mixer was used. Samples were collected in 20-mL scintillation vials (Fisher Scientific) at different time intervals for the residence time distribution and blend uniformity measurements. Powder samples were analyzed in the vials using diffuse-reflectance near-infrared (NIR) spectroscopy. A Nicolet Antaris FT-NIR spectrometer (Thermo Electron) was used. The instrument measured the spectrum in the range of 4000 cm^{-1} to 10,000 cm^{-1} wave numbers. Spectral data was collected using the software "Omnic." Calibration samples were prepared in 20-mL scintillation vials in a vortex mixer (Fisher Scientific). The software "TQ Analyst" was used for calibration model development and quantification of the samples collected. Calibration samples were prepared by weighing 500 mg of mixture into the scintillation vials using an Ohaus Explorer analytical balance with an accuracy of ± 0.01 mg. In all cases, the regression method used was partial least squares (PLS). The description, including the materials of interest and the concentration ranges, of the NIR calibration models used is summarized in Table 3.

3. Mixing characterization

3.1. Hold-up

The powder hold-up (Eq. (1)) is the amount of mass accumulation in the continuous mixer. The hold-up was measured by monitoring the mass of the powder being fed to the mixer and the mass of powder collected at the outlet of the mixer. The difference between the amount of powder being fed and the amount of powder collected at the outlet of the blender after steady state flow through the mixer was reached determines the hold-up.

$$Hold - up = accumulation = mass_{in} - mass_{out} \quad (1)$$

3.2. Residence time distribution

The residence time distribution (RTD) and the calculated parameters from the RTD data describe the dispersion and the axial mixing behavior of continuous systems [17]. RTD in the continuous mixer was measured using the pulse experimental method. The

Table 1
Description of materials used.

Material	Type/Name	Vendor	Mean particle Size (μm)
Silicified Microcrystalline Cellulose	Prosolv HD 90	JRS Pharma	110
Microcrystalline Cellulose	Avicel PH 200	FMC Biopolymers	220
Magnesium Stearate	Magnesium Stearate	Mallinckrodt	10
Acetaminophen	Semi-fine	Mallinckrodt	45