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Detailed modeling and process design of an advanced continuous powder mixer

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ABSTRACT

A vertical in-line continuous powder mixing device (CMT – Continuous Mixing Technology) has been modelled with the discrete element method (DEM) utilizing a calibrated cohesive contact model. The vertical design of the mixing device allows independent control of mean residence time (MRT) and shear rate. The hold-up mass and outlet flow are controlled by an exit valve, located at the bottom of the in-line mixer. A virtual design of experiments (DoE) of DEM simulations has been performed and parameters such as particle velocities, powder bed shape, residence time distribution (RTD), travel distance, and mixing quality are evaluated for the complete operating space. The RTD of the DEM model has been validated with tracer experiments. The resulting RTD has been fitted with an analytical form (generalized cascade of n continuous stirred tank reactors) and utilized to study the downstream response of the continuous mixing device to upstream fluctuations in the inlet material stream. The results indicate a high mixing quality and good filtering properties across the operating space. However, the combination of low hold-up mass and high impeller speeds leads to a reduced filtering capability and wider exit valve openings, indicating a less desirable operating point.

1. Introduction

The pharmaceutical industry is undergoing a transformation from batch to continuous production, which has successfully been used in chemical, petrochemical and food industries. Continuous manufacturing has many general advantages (e.g., smaller footprints, better control of process parameters and product quality and less down-time compared to batch processing). Specific advantages for the pharmaceutical industry include the straightforward scale-up by extension of time. In contrast, batch processes are time-dependent and cannot be scaled up easily. However, continuous manufacturing also presents several challenges, such as continuous powder mixing which is an important unit operation in the pharmaceutical industry for the manufacturing of solid dosage forms (e.g., tablets, capsules, and granules). In order to obtain a high product quality, a good understanding of powder mixing behavior and a correct control strategy during the process have to be established.

Capabilities, feasibility, monitoring and process control techniques in continuous manufacturing/mixing have been investigated by several research groups (e.g., Plumb, 2005; Berthiaux et al., 2008; Pernenkil et al., 2006; Portillo et al., 2008; Vanarase et al., 2010; Vanarase and Muzzio, 2011; Gao et al., 2013; Martíne et al., 2013; Ammarcha et al., 2017; Laske et al., 2017; Van Snick et al., 2017) addressing a wide range of continuous pharmaceutical unit operations. For powder blending, two basic mixer designs can be used, as shown in Fig. 1.

The first type is a horizontal (or slightly inclined) mixer, in which the powder is horizontally transported and simultaneously mixed by a rotating screw. In this mixer, the RTD varies with rotational speed. As reported by Vanarase and Muzzio (2011), a higher mixer speed comes at the expense of a shorter residence time. Because residence time and

Abbreviations: CMT, Continuous Mixing Technology; CSTR, Continuous Stirred Tank Reactor; DEM, Discrete Element Method; DoE, Design of Experiments; GPU, Graphics Processing Unit; MEPA, Macro Elasto-Plastic-Adhesive; MRT, Mean Residence Time; MTD, Mean Travel Distance; n-CSTR, cascade of n Continuous Stirred Tank Reactors in series; NIR, Near Infra-Red; PAT, Process Analytical Technology; PFR, Plug-Flow Reactor; RTD, Residence Time Distribution; VRR, Variance Reduction Ratio; XPS, Extended Particle System

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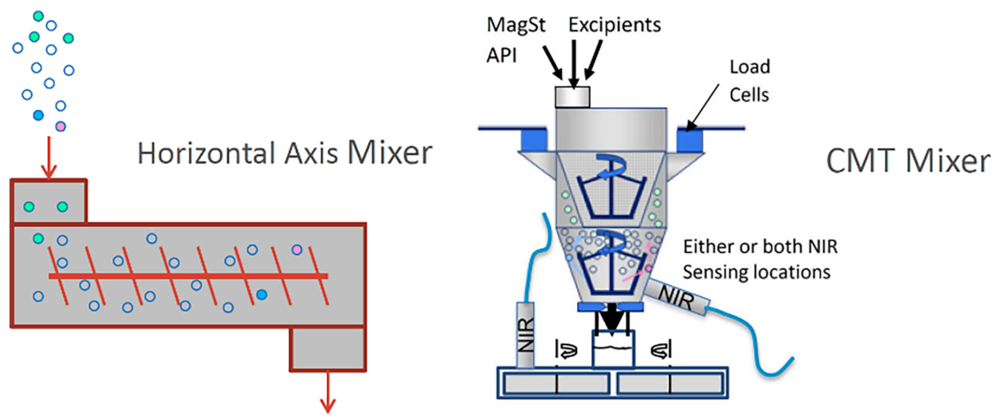

Fig. 1. Horizontal and vertical continuous powder mixers, Blackwood (2015).

screw speed are competing factors, a maximum number of blade passes occurs at moderate speeds (Blackwood, 2015; Ketterhagen et al., 2015). The second type is a vertical mixer, also termed CMT, in which the powder's vertical transport is accomplished via gravity and mixing is performed by a rotating impeller. The hold-up mass and the throughput are controlled by an exit valve. The advantage over the horizontal axis mixer is that for the same RTD, lower and higher shear rates (impeller speeds) can be applied. Furthermore, hold-up mass can be adjusted independently from overall mass throughput and the shear rate and impeller speed, respectively (Dubey et al., 2011). The particles traverse complex trajectories in pre-dominantly spiraling paths along with the vertical gravity-driven downward movement. There is a high likelihood of intermixing between the particles with long residence times and the newly-entering particles. Thus, a CMT mixer results in a consistent, Continuous Stirred Tank Reactor (CSTR)-like RTD under a range of process conditions.

The computational DEM commonly applied to analyze granular flows in a wide range of devices, including continuous blenders. Sarkar and Wassgren (2009) performed DEM parametric studies using non-cohesive particles in a periodic slice of a horizontal continuous in-line mixer. The fill level and screw rotation speed were simultaneously varied to cover a wide range of operating conditions. Sarkar and Wassgren (2010) expanded their research by considering mixing of cohesive powders. The effect of inter-particle cohesion at various screw speeds and fill levels was investigated. In both of these works, a periodic slice of a horizontal axis mixer has been used to reduce the computational time by decreasing the number of particles in the considered domain. An averaged particle diameter of 4 mm was used in their work. Sen et al. (2013) carried out DEM simulations to study mixing in a horizontal mixer and developed a multidimensional Population Balance Model (PBM), which can be applied to analyze a continuous powder mixing/blending process. They used a particle diameter of 2 mm in the DEM simulations. Tamrakara et al. (2016) analyzed the same mixer using a particle diameter of 1 mm in the simulations. Pantaleev et al. (2017) studied the predictive capabilities of the DEM method in a laboratory-scale paddle blade mixer. They used the scaling method for a cohesive material developed by Thakur et al. (2016) and applied a particle aspect ratio of 1.25, actually 3.125:2.5 mm, which led to a significant increase in the flow energy compared to spherical particles. The material used in their simulations was synthetic zeolite powder, with a measured D50 of about 3 μm. Ketterhagen et al. (2015) conducted DEM simulations for the CMT mixer and examined various impeller speeds and their influence on the RTD. An averaged particle diameter of 1.4 mm was applied in this work. Simulations were run for up to 100 s of mixing time, which was, however, insufficient for calculating the total RTD. However, the DEM simulation results could be compared with tracer studies and showed a reasonable agreement.

In this work, DEM was used to analyze the RTD, particle velocity, particle mass fraction within the mixing zone, the exit valve position and the general mixing behavior in the CMT mixer under various operating conditions. In contrast to Ketterhagen et al. (2015), a macro-elasto-plastic adhesive model is used to define inter-particle cohesion. To reduce the number of particles and the computational time, the particle diameter was scaled: the original range of particle diameter was 10–250 μm and the scaled one was 400–700 μm. First, the DEM model parameters were calibrated (Section 3.2). For this purpose, two experimental tests were performed on the powder blend to be simulated: the compressibility test and the shear-cell test. The exact experimental procedure was replicated in DEM simulations. The contact model parameters have been adjusted to match the results from the blend characterization experiments.

After estimating the model input parameters for the given blend, a DoE was created to investigate mixing in the CMT mixer under various operating conditions. In order to predict the entire RTD curve, computation for more than the duration of 500 s of process time was necessary (depending on the operating conditions). However, this long process time requires large computational resources and is a limiting factor for all DEM simulations. To overcome this obstacle and to obtain simulation results in a shorter time, a hybrid model was developed that considers the DEM data and an n-CSTR RTD exponential function (Eq. (25) in Section 3.3). As a result, predictions of the entire RTD curve using the DEM data for only one mean residence time (MRT) of the process time were achievable (Section 4.3). Good agreement between the experimental tracer studies and the hybrid model confirms the applicability and accuracy of the RTD curve prediction (Section 4.4). Based on the estimated RTD curves under various operating conditions, the dampening capability of the CMT mixer against feeder fluctuation was investigated. Finally, compiled an analysis of the simulation results and the various operating conditions was compiled by plotting the obtained results in the operating contour maps (Sections 4.5 and 4.6).

2. CMT design and operating space

The CMT mixer has a cylindrical shape and tapers conically towards the bottom. There are two impellers connected via a shaft-in-shaft arrangement, which allows for variable rotational speed and direction of rotation for the upper and lower impellers independently. The top region of the CMT device is separated from the bottom region by a screen that de-lumps agglomerates, which may be present in the raw materials or formed during previous processing steps (e.g., feeders). The actual mixing occurs in the bottom region, where the particles spend most of their time. A control system continuously adjusts the exit valve, located below the bottom impeller, which opens to create a flexible sized cross sectional area through which the blend can flow out of the CMT. If the measured hold-up mass (via load cells) is above/below set point, the cross sectional opening of the exit valve is gradually increased/