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Modeling continuous high-shear wet granulation with DEM-PB

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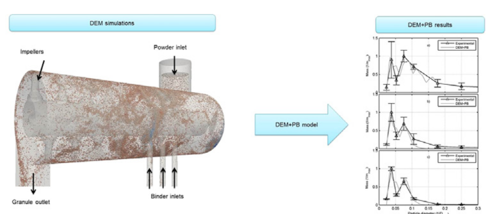
HIGHLIGHTS

- Coupling DEM and PB modeling methods in high-shear continuous granulation.
- DEM model validation with step responses.
- PB model construction based on the DEM simulations.
- Validating the developed DEM-PB model with experimental PSD.
- Shaft speed dependence effect on the granulator dynamics.

GRAPHICAL ABSTRACT



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ABSTRACT

A multiscale modeling procedure is introduced in this paper for modeling continuous high-shear wet granulation. Flow inside the granulator is accounted using the discrete element method (DEM) and particle-level interactions with population balance (PB). The developed DEM-PB model is validated against experiments, particle size distribution (PSD), and residence time distribution (RTD). It was observed that the model gave good correspondence to the experimental values. The developed methodology can be used when designing continuous granulation processes.

1. Introduction

Pharmaceutical granulation is an important phase of pharmaceutical tablet manufacturing line, which has traditionally been a batch process. The main advantage of the batch processes is accurate quality assurance since each batch can be accepted or rejected (Leuenberger, 2001; Suzzi et al., 2012). Their use is also motivated by regulatory requirements and small lot sizes. However, traditionally used batch wet granulation processes, such as high shear and fluidized bed granulation, suffer from the difficulty of scale-up and variability between batches (Leuenberger, 2001; Sochon et al., 2010; Järvinen et al., 2015). Additionally, several process-related factors as well as equipment and material parameters can have effect on the batch wet granulation processes making them difficult to control (Sochon et al., 2010; Faurea et al., 2001; Knight, 2004).

Continuous processes could be a viable choice to overcome these problems. However, continuous processing has not been favored in pharmaceutical industry due to the high production

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sizes, demands for daily changing product, product high quality standards, and delayed approval times for the product due to the skepticism of the regulatory authorities towards the process (Vervaet and Remon, 2005). For the pharmaceutical manufacturing, the main advantage of continuous processes is that they only need an extension of time to scale up while batch processes are time dependent and do not scale-up well (Vanarase et al., 2010). Secondly, waste is reduced as optimized continuous processes can operate in a much more efficient way than batch and are easy to control (Vanarase et al., 2010). Finally, expenditure on equipment, premises and operation especially for large volume products can be decreased (Schaber et al., 2011).

A candidate for continuous processing is a high-shear granulator, in which the powder is transported with the aid of impellers. Its most significant advantage over the widely studied twin-screw granulator (Barrasso et al., 2013; El Hagrasy and Litster, 2013) is higher production capacity. Nevertheless, high-shear granulation operating in continuous mode has not been widely studied previously for the pharmaceutical processing line compared to those operating in batch mode. To achieve the high quality demand and to meet the requirement for flexible production, effective process control is required. Moreover, understanding of the flow characteristics inside the granulator and of the dominant granulation sub-processes is needed. Both of these have a major effect on the evolution of particle characteristics during granulation.

In the modern picture, the granulation exhibits three rate processes: wetting and nucleation, consolidation and aggregation, and attrition and breakage (Iveson et al., 2001a). In wetting and nucleation, the binder droplet binds the powder into wet nuclei. In consolidation and aggregation, the nuclei exhibit collisions between each other and the granulator, which leads to granule densification and growth. In attrition and breakage, the wet granules break due to the impact between each other or the granulator. These microscale effects, together with macroscale phenomena, such as flows inside the granulator, determine important particle properties, such as size, porosity, and liquid saturation (Poon et al., 2008).

Discrete Element Modeling (DEM), originally proposed by Cundall and Strack (1979), is a widely used tool in pharmaceutical granulation to find out the flow properties of the particles in the system (Hassanpour et al., 2013; Remy et al., 2012). In this method, individual particles are tracked through the system, and their collisions with each other and with the system are taken into account. As a result, particle flow patterns and spatial distributions inside the granulator are obtained, which can be used to study the system behavior. Typically, a pharmaceutical granulation system contains millions of particles. Due to the computational effort of tracking all the particles in the system within the system operational timescale, simplifications to the DEM model must be made. The main simplifications include the size and number of particles, as well as interactions between particles and their disintegration.

In continuous granulation, population balance (PB) modeling has usually been used to study the characteristics of granule size, moisture, and porosity distribution of the granules. The disadvantage of PB modeling is the need for experimentally tunable parameters, which are unique for each experimental setup (Dosta et al., 2013; Chaudhury et al., 2014; Lee et al., 2015). To overcome this step, the flow field inside the granulator is first simulated, and then the results are utilized in the PB model development to predict the microstructure for the produced granules (Gantt et al., 2006). This way the process-dependent variables, which may not necessarily be accessible from experimental data, such as residence time distribution (RTD) in different parts of the granulator, can be diminished.

The RTD describes the time period a particle could spend in a certain part of a granulator. Since in non-ideal cases this time could vary, a probability distribution instead of a single value is used. In situations where particle flow or mixer heterogeneity is strongly tied to the particle population dynamics, particle motion must be accounted in the PB model (Freireich et al., 2011). This can be carried out by decomposing the vessel into a series of regions, and modeling each with its own PB equation and RTD. The resulting multi-zonal approach is called compartment model (CM). This methodology has been further utilized by Freireich et al. (2011), by combining DEM and PB with compartment modeling (CM) (Li et al., 2012; Chaudhury et al., 2015). In this work however, a DEM and 3D PBM model is used to study the continuous high-shear granulator, which is not much reported earlier in the literature.

Continuous mixer granulators are the most complicated ones for predicting the product attributes, because all three classes of rate processes (wetting and nucleation, consolidation and growth, and granule breakage) are present. Moreover, flow patterns are difficult to predict and a very wide range of shear rates and impact velocities occurs in the mixer (Litster and Ennis, 2010, pp. 226–230). This work shows that in this type of granulators, the RTD obtained from the simulations explains the granule particle size distribution (PSD) behavior observed in experimental measurements. Next, the method of utilizing the DEM results in the development of a microscale PB model is presented. The focus in this work is to study the effect of shaft speed on the flow patterns and on the resulting PSD. The model described in this paper makes use of the 3D population balance equation to describe the rate processes, and combines the information obtained from the DEM model to represent correct RTDs and flow patterns. Based on the DEM-PB model results, the varying residence times and recycling rates between the compartments have a significant effect on the end products.

2. Materials and methods

The DEM model was first used on the continuous high-shear granulator to obtain the flow structure, which was then applied in the development of the PB model. Finally, the results were verified with the experiments. Next, the process, applied models, and experiments are described.

2.1. Process description

Continuous horizontal granulators can be divided in the premixing, spray, and wet massing zones (Barrasso et al., 2013). In the current setup (see Fig. 1), the lengths of these are 17 cm, 15 cm, and 24 cm, respectively. The details of the setup are presented in Table 1. The experimental setup is described in Section 2.4.

In the premixing zone, the inserted powder is accelerated by the rotating impellers. The zone mainly acts as a feeding section to preblend the mixture to achieve the required homogeneity. From here, the powder is forwarded to the spray zone, where the binder is fed. The binder is assumed to be absorbed directly into the powder bed, which starts nucleation of the powder due to the liquid-powder interaction (Parkih, 1997, p. 440). New granules are formed from the liquid and fine powder feed, increasing both the mass and number of the granules. In addition to nucleation, aggregation plays the most significant role in this section. In this, a new granule is formed from the coalescence of two smaller granules, which does not change the total volume or mass of the granules (Litster and Ennis, 2010, p. 152). The formed granules enter the wet massing zone, where they are formed into their final shape and exit from the process (Parkih, 1997, p. 440). Additionally, aggregation is considered a dominant rate process in this zone (Barrasso et al., 2013). Large agglomerates are typical for the