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Multi-scale modeling of granulation processes: Bi-directional coupling of PBM with DEM via collision frequencies

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ABSTRACT

Wet granulation is a complex particle design process often operated inefficiently in industrial applications. Enhanced process understanding is required to facilitate design, control, and optimization. In this study, a hybrid multi-scale model is presented using a bi-directional coupling approach between DEM and PBM. The hybrid model takes into account particle collision frequencies and liquid distribution, providing a framework suitable for the complex sub-processes in wet granulation. The effect of particle size distribution on the collision frequency function was demonstrated, indicating the need for a multi-scale model. Results of the hybrid model show an increase in particle size over time from an average diameter of 0.98 mm to 2.5 mm, which qualitatively agrees with experimental trends observed during the liquid addition and wet massing stages. Two-dimensional distributions in particle size and liquid fraction are also presented incorporating the key effect of liquid distribution on the evolution of granule PSD.

Keywords: Granulation; Population balance modeling; Discrete element modeling; Multi-scale model; Aggregation; Collision rate

1. Introduction

Granulation is a particle design process used to create larger granules from fine powder, improving flowability, compactibility, and homogeneity while reducing dust formation. Although it is widely used in the food, pharmaceutical, detergent, and fertilizer industries, it is often operated inefficiently, with high recycle ratios in continuous processes and high rejection rates in batch processes (Wang and Cameron, 2002). The design and control of granulation processes is primarily performed via heuristic experimentation, and a more mechanistic approach is required to improve operational efficiency (Cameron et al., 2005).

The wet granulation process is highly complex, governed by the rate processes of wetting and nucleation, aggregation and consolidation, and breakage and attrition (Iveson et al., 2001). In wetting and nucleation, the fine powder comes into contact with the liquid binder and forms granule nuclei. When wet particles collide, they can form liquid bridges, resulting in aggregation. Collisions with vessel walls and/or impellers also result in consolidation, leading to a reduction in the porosity of a granule. Breakage and attrition occur when large particles are subjected to shear, compressive, and tensile forces and break to form fragments.

Based on these sub-processes, a single granule can be described by three internal properties. The size, related to the solid volume, is a critical product attribute. The liquid content, related to the amount of liquid within and on the surface of a particle, affects the aggregation rate. The porosity, related to the air volume, affects the surface liquid and as it decreases, liquid is forced out of the pores and onto the particles, further affecting aggregation rates (Cameron et al., 2005). The product porosity also affects the compactibility of the granules, which is critical to tablet manufacturing (Vervaet and

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Remon, 2005). In multi-component granulation processes, the composition of each granule is also important, and segregation can occur, affecting the final product (Vervaet and Remon, 2005).

In the pharmaceutical industry, recent efforts focus on implementing Quality by Design (QbD). QbD involves developing a strong process understanding and defining a design space, a set of operating parameters that will result in a quality product Yu (2008). In contrast, a Quality by Testing (QbT) approach involves sampling the products of empirically designed processes and rejecting batches that do not meet specifications, often wasting expensive active ingredients. Current research and development efforts aim to shift from batch to continuous processing in tablet manufacturing in order to improve controllability, scalability, and profitability. In order to successfully transition to continuous processing, a QbD approach is desired, and a more mechanistic understanding of powder processes is needed.

To meet these challenges, a model-based approach has been proposed, where empirical and mechanistic models are developed and validated using experimental data (Glaser et al., 2009; Ramachandran and Chaudhury, 2012). Validated models can then be used as predictive tools to aid in design, model-based control, and optimization. Various modeling approaches have been employed for granulation. Data-driven models include response surface methodology (RSM) and artificial neural networks (ANN) (Ranjbarian and Farhadi, 2013; Behzadi et al., 2005). These models use data from existing or experimental processes, and have limited ability to predicting process behavior beyond the experimental space. Population balance models (PBMs) provide a more fundamental framework for tracking changes in particle properties over time, though they require rate expressions and empirical parameters that cannot easily be measured. Discrete element modeling (DEM) is more mechanistic, tracking particles as they move through space and collide. However, DEM by itself does not account for aggregation or other rate processes involved in wet granulation. Further, computational fluid dynamics (CFD) can also be used to determine drag forces resulting from fluid flow, which are significant in fluid bed granulation processes. Along with DEM, these forces can be used to determine particle fluxes.

In this study, a multi-scale model is presented, solving a two-dimensional PBM within a DEM simulation, focusing on systems such as high-shear, twin-screw, and drum granulation, which do not incorporate an air flow stream (such as in fluid bed granulation). As a result, CFD aspects can be neglected.

1.1. *Objectives*

The purpose of this study is to develop a coupled PBM–DEM model for wet granulation processes, with the following objectives:

- Demonstrate the limitations of PBM and DEM when used independently to model granulation processes.
- Present a hybrid PBM–DEM model using two-way coupling to transfer data related to collision frequencies and size and liquid distribution.
- Propose a framework for future work to incorporate additional sub-processes and complexities within the hybrid model.

2. Background

The PBM groups particles into classes based on properties such as size and wetness and tracks the change in the number of particles in each class over time. In contrast, DEM tracks each individual particle as it moves through space and collides with other objects. Both modeling techniques have been applied extensively to granulation processes.

2.1. *Population balance modeling*

The PBM is a class of integro-differential equations that describe the change in the number of particles within each class over time as the particles are subjected to rate processes, such as liquid addition, consolidation, aggregation, and breakage. A general form of the population balance equation is given in Eq. (1) (Ramkrishna, 2000).

$$\frac{dF(\mathbf{x},t)}{dt} + \frac{\partial}{\partial \mathbf{x}}\left[F(\mathbf{x},t)\frac{d\mathbf{x}}{dt}(\mathbf{x},t)\right] = \Re_{formation}(\mathbf{x},t) - \Re_{depletion}(\mathbf{x},t) \tag{1}$$

Here, F represents the number of particles or particle density as a function of particle class and time. The set of particle properties can include size, wetness, porosity, and composition, as well as spatial coordinates. This vector is represented by $\mathbf{x}$. The first term in Eq. (1) is the temporal component, representing changes over time. The second term accounts for changes in each property, such as an increase in liquid volume due to liquid addition or a decrease in porosity due to consolidation. This term can also account for particle fluxes when the property is a spatial coordinate. The source terms $\Re_{formation}$ and $\Re_{depletion}$ represent the change in particles within each class from aggregation, breakage, or nucleation.

PBMs have been used to model various powder processes, such as crystallization (Gerstlauer et al., 2002), powder mixing (Sen and Ramachandran, 2013), and milling (Bilgili and Scarlett, 2005), and wet granulation (Cameron et al., 2005; Verkoeijen et al., 2002). Most PBMs found in the literature are one-dimensional; they only consider distributions with respect to one particle property, typically size. Because wet granulation is a complex process facilitated by a liquid binder, 1-D PBMs have limited accuracy in representing real processes (Iveson, 2002). As a consequence, multi-dimensional PBMs have been developed using three internal coordinates: solid, liquid, and gas volume (Poon et al., 2008). Some studies have also used multiple internal coordinates to model two solid components, which may result in inhomogeneous distributions (Matsoukas and Marshall, 2010; Matsoukas et al., 2009; Marshall et al., 2011, 2012). Although these models can simulate more complex behavior, they are more computationally expensive and require many empirical expressions and parameters (Barrasso and Ramachandran, 2012). These models may be unsuitable for iterative calculations, such as parameter estimation and optimization. Reduced order modeling has been proposed as an alternative, representing one or more particle properties as a lumped parameter within the remaining internal coordinate system to reduce the dimensionality of the problem (Barrasso and Ramachandran, 2012; Hounslow et al., 2001; Biggs et al., 2003). This technique drastically reduces the computational time, but it may result in a loss of information and fail to represent wide distributions in lumped properties (Barrasso and Ramachandran, 2012).

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