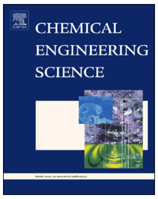
Chemical Engineering Science 123 (2015) 500–513

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces



A multi-scale, mechanistic model of a wet granulation process using a novel bi-directional PBM–DEM coupling algorithm

Dana Barrasso [a], Thomas Eppinger [b], Frances E. Pereira [c], Ravindra Aglave [d], Kristian Debus [e], Sean K. Bermingham [c], Rohit Ramachandran [a,*]

[a] Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA
[b] CD-adapco, Nordostpark 3-5, Nuremberg 90411, Germany
[c] Process Systems Enterprise Ltd., 26-28 Hammersmith Grove, London W6 7HA, UK
[d] CD-adapco, 11000 Richmond Ave, Houston, TX 77042, USA
[e] CD-adapco, California Office, CA, USA

HIGHLIGHTS

- A multi-scale, mechanistic model of a wet granulation process is developed.
- An efficient bi-directional coupling algorithm is implemented to exchange data between models.
- Particle-scale information from DEM simulations is used to evaluate rate expressions in the PBM.
- Sensitivities to process parameters, material properties, and equipment geometry are demonstrated.

ARTICLE INFO

Article history:
Received 19 August 2014
Received in revised form
21 October 2014
Accepted 3 November 2014
Available online 11 November 2014

Keywords:
Wet granulation
Population balance modeling
Discrete element methods
Multi-scale modeling
Quality-by-Design

ABSTRACT

In this study, a novel mechanistic model for a wet granulation process is presented, combining the techniques of population balance modeling and discrete element methods to predict critical quality attributes of the granule product, such as porosity and size distribution. When applied to a twin screw granulation process, the model shows sensitivities to the screw element type and geometry, as well as material properties (binder viscosity, pore saturation) and process parameters (screw speed, liquid-to-solid ratio). Predicted trends are consistent with experimental observations in the literature. Using this modeling framework, a model-based approach can be used to implement Quality by Design, establishing a design space to transition towards a quantitative mechanistic understanding of wet granulation processes.

1. Introduction

Over the past decade, Quality by Design (QbD) has gained importance in the pharmaceutical industry to manage risk, reduce costs, and satisfy regulatory requirements. In 2006, QbD was introduced in the ICH Q8 guidance document and later was defined as "a systematic evaluation, understanding and refining of the formulation and manufacturing process" (U.S. Food and Drug Administration, 2006, 2009). In contrast, the traditional approach of Quality by Testing (QbT) involves empirical design and operation of manufacturing processes and relies on testing and rejection of failed batches to assure quality, which can lead to sub-optimal product quality.

To implement QbD, predictive process understanding must be established to quantify the effects of process parameters and material properties on the critical quality attributes (CQAs) of the product. From this knowledge base, a design space can be identified, defining the multi-variate combination of process parameters and material properties that result in a product of acceptable quality. Experimental approaches to QbD often rely on large sets of experimental data and statistical models, but provide little insight beyond the experimental design space.

Alternatively, a model-based approach can be taken to describe the behavior of the process from a more scientific perspective. The underlying mechanisms driving the process are described mathematically, and a limited number of experiments are required to calibrate and validate the model (Kayrak-Talay et al., 2013). The development of truly predictive pharmaceutical process models is challenging because many of these processes involve powders. Powder processes are often operated empirically and inefficiently

---

[*] Corresponding author. Tel.: +1 848 445 6278; fax: +1 732 445 2581.
E-mail address: rohit.r@rutgers.edu (R. Ramachandran).

http://dx.doi.org/10.1016/j.ces.2014.11.011
0009-2509/

due to a poorer understanding of their behavior compared to that of liquid and gas processes. This paper focuses on the development of a more predictive model for a wet granulation process.

Wet granulation is a key unit operation in tablet manufacturing in which a liquid binder is added to fine powder particles to form larger granules, improving flowability and compactibility, while preventing segregation of the solid components. This complex process is driven by several interrelated subprocesses: wetting and nucleation, aggregation and consolidation, breakage and attrition, and layering (Iveson et al., 2001). As liquid is added, fine powders form porous nuclei that can coalesce, deform, and break. These particles can also take up additional liquid or fine powder particles, altering their behavior.

Various types of equipment can be used for wet granulation, including high shear mixers, fluidized beds, and twin screw extruders. This study focuses on twin-screw granulation (TSG), which has potential advantages in continuous pharmaceutical manufacturing because of its low throughput, flexible design, and short residence time (El Hagrasy et al., 2013). However, the multi-scale modeling approach presented in this study can be applied to the general class of wet granulation systems.

1.1. Powder process modeling

Traditionally, models of wet granulation processes fall into one of two categories: process models or particle-scale models. Population balance modeling (PBM) is a process modeling framework that groups particles into classes based on their sizes and other properties, tracking changes in the number of particles in each class as they undergo rate processes, such as aggregation and breakage. PBMs have been used extensively to simulate wet granulation processes (Cameron et al., 2005; Verkoeijen et al., 2002). Multi-dimensional PBMs are particularly useful in tracking distributions of multiple particle properties, such as size, liquid content, and porosity, which can affect the aggregation and breakage rates in the system (Immanuel and Doyle, 2005; Poon et al., 2008).

The development of accurate descriptions of aggregation and breakage rate expressions is an area of significant research. Many rate kernels are empirical and require estimation of unknown parameters from experimental data. Parameter estimation and validation have been performed for wet granulation processes, but these calibrated models have limited predictive capabilities outside of their experimental design spaces (Braumann et al., 2010; Ramachandran and Barton, 2010; Man et al., 2010; Chaudhury et al., 2014a; Barrasso et al., in press).

Mechanistic expressions have also been developed, describing aggregation (Darelius et al., 2005; Poon et al., 2008; Chaudhury et al., 2014b) and breakage (Ramachandran et al., 2009) rates. These expressions account for the effects of material properties, such as surface wetness, density, and yield strength. Since mechanistic expressions are based on particle-scale phenomena, such as individual collisions, they typically include terms for collision rates and particle velocities. This particle-scale information is not inherently known, and may depend on process parameters, equipment geometry, and material properties.

In contrast, discrete element modeling (DEM) is a particle-scale framework that tracks individual particles as they move through space and collide. Developed for soft spheres by Cundall and Strack (1979), this high-fidelity modeling tool provides the detailed particle-scale information that the PBM lacks, such as collision rates and velocity profiles, and is sensitive to process parameters, equipment geometry, and material properties. However, DEM does not inherently account for changes in particle size and other properties resulting from aggregation, breakage, consolidation, and liquid addition.

Because of the complementary advantages and limitations of each framework, efforts have been made to couple PBM and DEM. Ingram and Cameron (2005) discussed alternative multi-scale approaches for this problem, focusing on the information exchanged between the two frameworks and their integration. Most multi-scale studies involve one-directional coupling, where DEM data is collected and used within a PBM. Gantt et al. (2006) used DEM to evaluate mechanistic coalescence kernels for use in a PBM, and Bouffard et al. (2012) used DEM results to evaluate a spatial transfer in a compartmental PBM. Goldschmidt et al. (2003) used DEM simulations to solve a PBM, replacing small particles with larger ones as they successfully coalesce. Additionally, Reinhold and Briesen (2012) developed a coupled PBM–DEM model for wet granulation, using DEM simulations to evaluate a mechanistic aggregation rate kernel. Recently, Barrasso and Ramachandran (in press) implemented bi-directional coupling between PBM and DEM to evaluate collision frequencies and liquid distribution as a proof-of-concept, and Sen et al. (2014) combined this work with a computational fluid dynamics model to simulate fluidized bed granulation. Further, Barrasso et al. (2014) used DEM data to train an artificial neural network, which was then coupled with a PBM to capture collision rates as they depend on the impeller speed, particle size, and size distribution in the system.

In this study, a bi-directional coupling algorithm for PBM and DEM is presented and demonstrated for a twin-screw wet granulation process, developing a hybrid model to predict the effects of material properties, process parameters, and equipment geometry on the CQAs of the product.

1.2. Objectives

In order to predict the CQAs of a granulation process, a mechanistic process model is coupled to a particle-scale model. The purposes of this study are to:

- Present a mechanistic, two-dimensional PBM for a wet granulation process with sensitivities to material properties, process parameters, and particle-scale behavior.
- Develop an efficient bi-directional coupling algorithm, using DEM simulations to provide particle-scale data to the PBM.
- Determine the optimal settings for the model by characterizing the DEM simulation results.
- Apply the model to a twin-screw granulation process and demonstrate the model's sensitivity to equipment geometry, process parameters, and material properties on the CQAs of the product.

This work extends on previous models presented by Barrasso and Ramachandran (in press) and Sen et al. (2014), incorporating mechanistic expressions for aggregation, breakage, and consolidation and evaluating these rates using particle velocity and collision data from DEM. Variations in particle properties, such as porosity and liquid content, are also accounted for in DEM simulations using empirical correlations for coefficients of restitution and Young's moduli.

2. Model development

A bi-directionally coupled model was designed to use particle-scale information from DEM simulations within a mechanistic PBM, which tracked changes in the particle size distribution, liquid content, and porosity. The hybrid model captures sensitivities of the product CQAs with respect to material properties, process parameters, and equipment geometries. An overall schematic of the model is presented in Fig. 1. The model was applied to