Powder Technology 241 (2013) 85–97

Contents lists available at SciVerse ScienceDirect

Powder Technology

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

Multi-component population balance modeling of continuous granulation processes: A parametric study and comparison with experimental trends

Dana Barrasso [a], Samjit Walia [b], Rohit Ramachandran [a,*]

[a] Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA
[b] Department of Chemical Engineering, The Cooper Union, New York, NY 10003, USA

ARTICLE INFO

Article history:
Received 16 August 2012
Received in revised form 25 January 2013
Accepted 1 March 2013
Available online 13 March 2013

Keywords:
Continuous granulation
Population balance modeling
Twin-screw
Multi-component
Liquid distribution

ABSTRACT

In the recent few years, continuous processing has been considered as a promising process alternative to batch processing in pharmaceutical manufacturing. Via a novel population balance model framework, a multi-dimensional multi-component model for a continuous granulation process was developed, describing time evolutions of distributions with respect to granule size, liquid distribution and granule composition. A parametric study was performed to analyze the effects of various process and design parameters, including granulator size and configuration, liquid spray rate and particle velocity, on evolutions and distributions of key granule properties. Simulation results capture experimentally observed sensitivities and trends thus demonstrating the use of a model-based framework for granulation process design, control and optimization to enable QbD in drug product development.

1. Introduction

Granulation is a particle design process in which fine powder particles agglomerate to form larger granules with improved properties, such as flowability, reduced dust formation, and composition uniformity. In wet granulation processes, aggregation is facilitated with the addition of a liquid binder. Wet granulation is governed by three rate processes; wetting and nucleation, consolidation and aggregation, and attrition and breakage [1,2].

Granulation processes are utilized in various process industries, such as food, pharmaceuticals, and fertilizers [1]. Because a narrow size distribution is often desired, industrial granulation processes are typically inefficient, with large recycle ratios of up to 6:1 [3]. As a result, design, scale up, and control of granulation processes are usually based on heuristic experimentation. Particularly in the pharmaceutical industry, granule composition, in addition to other granule properties such as liquid content and porosity, must be controlled to ensure product uniformity that meets strict regulatory guidelines [4].

Pharmaceutical manufacturing processes are almost exclusively operated in batch configurations. However, continuous processing has gained recent attention due to its numerous potential advantages over batch processes [5–7,4,8]. For instance Schaber et al. [8] predicted substantial economic benefits of continuous manufacturing. However, Vervaet and Remon [4] caution against the common misconceptions surrounding continuous processing in the pharmaceutical industry, such as the idea that continuous processes on their own cannot always consistently meet the quality requirements of the highly regulated industry. Instead, they argue that real-time monitoring using in-line process analytical techniques (PAT) would result in better process control, higher efficiencies, and less destruction of product due to failed specifications.

In order to successfully transition to continuous processing, significant process understanding must be developed. A model-based approach to design and control of continuous powder processes has been proposed to tackle this challenge [9,3]. This approach can be used to define a design space, and if the process variables are kept within the design space, the product will be of acceptable quality, a concept known as Quality by Design (QbD). For instance, Glaser et al. [10] and Ramachandran et al. [11,12] have demonstrated model-based control methods for continuous granulation using population balance modeling. Additionally, Boukouvala et al. [13–15] have developed data-driven models for continuous powder processes.

1.1. Continuous granulation

A typical continuous horizontal granulator is divided into three zones. The first zone is the premixing zone, where dry powder particles are fed and mixed to achieve blend homogeneity. The particles then move into the spray zone, where liquid binder is sprayed onto the particles, and they begin to nucleate and aggregate to form larger granules. After the spray zone, the particles pass through a wet-massing zone, where they continue to aggregate and consolidate due to residual liquid and collisions, forming larger and denser granules. Other mechanisms

* Corresponding author. Fax: +1 732 445 2581.
E-mail address: rohit.r@rutgers.edu (R. Ramachandran).

0032-5910/$ – see front matter
http://dx.doi.org/10.1016/j.powtec.2013.03.001

such as breakage and layering may also occur concurrently in the spray and wet massing zone.

Continuous wet granulation processes can be categorized into four types: fluidized bed, twin screw, high shear, and drum granulation. Horizontal fluidized bed granulators are often used in industries with high product volumes, such as the food industry [4]. These machines can include dryers, removing the need for a separate drying step.

In twin screw granulation, two screws transport the particles through an extruder, mixing them in the process. This technique has been widely studied for pharmaceutical applications [16,4,17], particularly because it is suitable for various capacities [4]. However, a separate drying step is necessary to produce dry granules. Additionally, the screw configuration can become an important design parameter.

A high shear mixer can also be used for granulation with the addition of sprayers. This process is similar to twin screw granulation, using an impeller to transport the particles instead of screws. High shear granulation also produces wet granules, and it often is operated at a higher capacity than twin screw granulation [4].

Finally, a continuous drum granulator consists of a rotating cylinder, operating at a lower shear rate than high shear granulation. The cylinder is slightly inclined to transport the material. Continuous drum granulation is commonly used in the fertilizer industry [18].

1.2. Population balance models

The population balance model (PBM) framework tracks the number of particles with a given set of properties (e.g. size) as they are subject to rate processes, such as aggregation, nucleation, and breakage. PBMs are often used to model powder processes, such as crystallization, mixing, milling, and granulation. The general population balance equation is given in Eq. (1) [19].

$$\frac{\partial F(\mathbf{x},t)}{\partial t} + \sum \frac{\partial}{\partial \mathbf{x}}\left[F(\mathbf{x},t)\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t}(\mathbf{x},t)\right] = \Re_{\text{formation}}(\mathbf{x},t) - \Re_{\text{depletion}}(\mathbf{x},t). \quad (1)$$

Here, F is the number of particles or particle density with the set of properties described by the vector $\mathbf{x}$. This vector $\mathbf{x}$ is often composed of the internal coordinates of solid, liquid, and gas volumes. The first term of this equation describes the rate of change of particle density, and the second term accounts for changes along one internal coordinate, such as liquid addition, consolidation, or layering. The formation and depletion rates, $\Re_{\text{formation}}$ and $\Re_{\text{depletion}}$, account for net changes due to aggregation, nucleation, and breakage.

A three-dimensional (3-D) PBM has also been employed to model granulation processes [20–25]. As shown in Eq. (2), this model accounts for simultaneous distributions of solid, liquid, and gas volumes.

$$\frac{\partial}{\partial t}F(s,l,g,t) + \frac{\partial}{\partial s}\left[F(s,l,g,t)\frac{\mathrm{d}s}{\mathrm{d}t}\right] + \frac{\partial}{\partial l}\left[F(s,l,g,t)\frac{\mathrm{d}l}{\mathrm{d}t}\right] + \frac{\partial}{\partial g}\left[F(s,l,g,t)\frac{dg}{\mathrm{d}t}\right] = \Re_{\text{nuc}} + \Re_{\text{agg}} + \Re_{\text{break}}. \quad (2)$$

This model includes terms for solid layering $\left(\frac{\mathrm{d}s}{\mathrm{d}t}\right)$, liquid addition $\left(\frac{\mathrm{d}l}{\mathrm{d}t}\right)$, gas consolidation $\left(\frac{\mathrm{d}g}{\mathrm{d}t}\right)$, net rates of nucleation $(\Re_{\text{nuc}})$, aggregation $(\Re_{\text{agg}})$, and breakage $(\Re_{\text{break}})$. To fully model multi-component granulation, a fourth dimension must be added for the second solid component. However, higher-order PBMs are computationally expensive, and a four-dimensional PBM can take days or weeks to solve [26]. Higher-order PBMs can be reduced by assuming that one or more properties that are less significant are lumped within the other distributions [26].

The PBM can be extended to include spatial coordinates to model non-uniform batch processes and continuous processes [19]. As shown in Eq. (3), a vector of external coordinates ($\mathbf{z}$) is added, accounting for spatial distributions in particle frequencies and properties.

$$\frac{\partial F(\mathbf{x},\mathbf{z},t)}{\partial t} + \frac{\partial}{\partial \mathbf{x}}\left[F(\mathbf{x},\mathbf{z},t)\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t}(\mathbf{x},\mathbf{z},t)\right] + \frac{\partial}{\partial \mathbf{z}}\left[F(\mathbf{x},\mathbf{z},t)\frac{\mathrm{d}\mathbf{z}}{\mathrm{d}t}(\mathbf{x},\mathbf{z},t)\right] = \Re_{\text{formation}}(\mathbf{x},\mathbf{z},t) - \Re_{\text{depletion}}(\mathbf{x},\mathbf{z},t) + \dot{F}_{\text{in}}(\mathbf{x},\mathbf{z},t) - \dot{F}_{\text{out}}(\mathbf{x},\mathbf{z},t). \quad (3)$$

The term $\frac{\mathrm{d}\mathbf{z}}{\mathrm{d}t}$ represents the particle velocity, and $\dot{F}_{\text{in}}$ and $\dot{F}_{\text{out}}$ are the inflow and outflow rates.

1.3. Previous applications of PBMs

One-dimensional (1-D) PBMs are most commonly used for batch and continuous modeling because they are easy to solve and computationally inexpensive [27,28,26]. These models account for distributions with respect to one particle property, usually size. For granulation processes, this assumption has been found to be inefficient since other particle properties such as liquid content and porosity can significantly affect aggregation rates [27,29,26]. Additionally, 1-D PBMs cannot represent distributions of key product quality attributes such as granule composition.

Most previous multi-dimensional PBM studies of wet granulation have involved batch processes [23,21,30]. These PBMs often focus on distributions in size, porosity, and liquid content, without simulating multiple solid components. However, Matsoukas and Marshall [31] have developed a solid composition-dependent aggregation rate kernel. Marshall et al. [32] presented a multi-component PBM for batch granulation to analyze the effects of binder content distribution, and Lee et al. [33] have investigated segregation of solid components in batch granulation. In a previous study, Barrasso and Ramachandran [26] presented a four-dimensional model for batch granulation, considering size, porosity, liquid content, and composition.

Fewer models of continuous granulation have been developed. Heinrich et al. [34,35] presented a dynamic 1-D PBM of continuous fluidized bed granulation, which did not include spatial coordinates. Further, Vreman et al. developed dynamic and steady state 1-D models for fluid bed granulation. Wang and Cameron [3] reviewed the progress in modeling continuous drum granulation for control applications. Although these 1-D models are useful for design and optimization, they cannot capture inhomogeneities and spatial effects. For use in a control study, Ramachandran and Chaudhury [11] have developed a 3-D PBM of continuous drum granulation that models spatial coordinates in three compartments. PBMs have also been used to model other continuous powder processes, such as crystallization and mixing [36,37]. No studies were found that use a PBM to simulate a twin-screw granulation process.

In this study, a 3-D continuous PBM for multi-component twin-screw granulation processes will be presented, accounting for distributions in size, liquid content, and solid composition that vary throughout the granulator.

1.4. Objectives

The purpose of this study is to propose a multi-dimensional model for continuous granulation processes. In particular, the following objectives will be addressed:

- Develop a dynamic 3-D PBM for multi-component, continuous granulation with two spatial dimensions, accounting for the rate processes of aggregation, breakage, liquid addition, and consolidation.
- Demonstrate this model's ability to capture experimental trends and observations based on using data from a twin-screw granulator.
- Perform a parametric study to analyze the effects of various input parameters on steady-state product distributions and start-up dynamics.