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Multi-dimensional population balance modeling and experimental validation of continuous powder mixing processes

Maitraye Sen, Ravendra Singh, Aditya Vanarase [1], Joyce John, Rohit Ramachandran *

Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA

HIGHLIGHTS

- We develop a novel multi-dimensional model to describe continuous mixing processes.
- We conduct both an experimental and computational study to verify our findings against each other.
- We quantitatively validate the developed model for further use in design and analysis.

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ABSTRACT

It has been recognized that the application of quality by design (QbD) to continuous processing in the pharmaceutical industry leads to better process control, improved product quality and mitigates scale-up issues (Schaber et al., 2011), whereby a component of QbD involves the development quantitative model-based representation of the process. In this work a population balance model (PBM) framework has been developed to model the dynamics of a continuous powder mixing process which is an important and complex unit operation used in a pharmaceutical tablet manufacturing process. Our previous studies have shown that PBM is effective in determining the various critical quality attributes (CQAs) (relative standard deviation (RSD), API composition and residence time distribution (RTD)) associated with mixing. It can also account for the key design and process parameters such as mixer RPM, processing angle, blender dimensions and number of radial and axial compartments. The developed PBM has been quantitatively validated by fitting experimentally obtained values of the above mentioned CQAs for different operating conditions. The model is dynamic and computationally tractable compared to traditional discrete element model (DEM) representations of mixing processes. This lends credence to the use of the model as an effective tool in control and optimization of blending process and can have future implementation in designing a Process Analytical Technology (PAT) system which will allow considerable improvements on the current manufacturing framework.

1. Introduction, background and objectives

In the pharmaceutical manufacturing industry, powder mixing or blending is a unit operation that is widely used but is nevertheless characterized by complex process dynamics. Powder mixing or blending is the act of bringing distinct bulk material into intimate contact with one another in order to produce a mixture of consistent quality. Blending is considered to be an important unit operation because the blend quality and content uniformity is primarily decided in this step and affects downstream unit operations such as roller compaction, wet granulation and tablet compaction. Mixing occurs because of the convective and diffusive velocity gradients produced when two or more bulk entities are brought into intimate contact with one another (Remy, 2010).

The unpredictability of the powder blending operation is attributed to the uniqueness of each drug formulation, which presents the challenge that no two blending processes can ever be identical. The randomness in the process urged engineers to try to describe the process in quantitative terms and not empirically such that the accuracy of the predictive model is increased. The pharmaceutical industry is tightly regulated wherein all the production must comply with the good manufacturing practices (GMPs) and the quality requirements are to be strictly satisfied (Reklaitis et al., 2010). It is due to inefficient control strategies (Gorsek and Glavic, 1997a; Leuenberger, 2001) and the non-predictive effects of process models that the final products obtained are often found to exhibit non-uniformity with a high degree of variability and do not meet the required specifications.

The behavior of powder processing units is still not as well predicted as compared to the fluid processing units mainly owing

* Corresponding author. Tel.: +1 732 789 4257; fax: +1 732 445 2581.
E-mail addresses: rohit.r@rutgers.edu, rohitrr@rci.rutgers.edu (R. Ramachandran).
[1] Current address: Bristol-Myers Squibb, New Brunswick, NJ, USA.

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to the absence of governing equations that can describe the granular flow in specified conditions. This renders the particle–particle interaction and particle–wall interaction difficult to understand and manage due to the model complexity. The bulk behavior of the powders is based on the micro-scale interactions among the particles which is highly chaotic, so most pharmaceutical manufacturers employ a univariate trial and error strategy in their process development. Significant strides have been made to improve the process understanding by coupling science and a holistic risk-based assessment of both the product and the process by employing the QbD (Quality by Design) approach and Process Analytical Technology (PAT) tools (Adam et al., 2011; Gracia et al., 2008; Lionberger et al., 2008; Nosal and Schultz, 2008; Yu, 2008; Singh et al., 2009, 2010a).

In chemical-based product manufacturing, as in pharmaceutical, food and agrochemical industries, efficient and consistent process monitoring and analysis systems (PAT systems) have a very important role. These PAT systems ensure that the chemical based product is manufactured with the specified end product qualities (Singh et al., 2010a). The United States Food and Drug Administration (FDA) defines Process Analytical Technology (PAT) as a mechanism to design, analyze, and control pharmaceutical manufacturing processes. It measures the Critical Process Parameters (CPPs) which affect Critical Quality Attributes (CQAs) of the final product. PAT aims at improving process understanding by defining their CPPs, and accordingly monitoring them in a timely manner (either on-line or in-line). This increases testing efficiency and also aids in time saving by avoiding unnecessary processing step, ensuring product consistency and reducing number of rejects (Singh et al., 2010a; Glassey et al., 2011). If a well formulated and validated model of the unit operation is available, it can significantly reduce the time and expenses towards design of an efficient PAT system.

Regulatory authorities and pharmaceutical manufacturers are lately recognizing the advantages a continuous manufacturing process has over the traditional batch configuration, in terms of cost-reduction, improved efficiency, better controlled processing and higher quality product (Plumb, 2005; Leuenberger, 2003; Leuenberger and Betz, 2007; Werani et al., 2004; Betz et al., 2003). Several other chemical industries such as refineries, food and petrochemicals have made this transition and are making use of state of the art techniques to satisfy the quality requirements of their products and improve process understanding (Gorsek and Glavic, 1997a). Among the batch processes, those that have multi-purpose equipment incorporated in them are more efficient in comparison with single-purpose equipment (Gorsek and Glavic, 1997b). But for higher production capacities continuous mode of operation is always favored. Continuous manufacturing processes reduce the overall operation cost, improve the product qualities, reduce risks associated with solid handing and non-predictive manufacturing and are suitable for easier scale-up. (Wilburn, 2010). Even though batch processing has its own disadvantages, but it is more flexible compared to a continuous process. Flexibility means that the same equipment can be used to fulfill more than one purpose. Efforts are being made in order to render significant flexibility to the continuous processes as well (Singh et al., 2010b).

A typical pharmaceutical manufacturing process for an oral solid dosage form involves multiple processing steps such as powder feeding, blending, milling, granulation, tableting and coating. It is important to have a sound understanding of each and every one of these unit operations in order to achieve the desired operation level. Considering the case-specificity of the product required, flexibility requires any characterization to be modular and characterization of a large number of unit operations. Flow sheet modeling of continuous processes can be performed which enables it to be accurately designed, optimized and can be used for simulating the functioning of a real plant (Ramachandran et al., 2011).

The reason behind inconsistency in pharmaceutical blending process that deals with fine cohesive powders is largely due to aggregation and segregation, which can occur within the blender, causing smaller particles to form agglomerates under the presence of cohesive forces. These phenomena trigger the segregation of particles due to differences in the mobility of the agglomerates (Remy, 2010). Segregation causes the separation of distinct particles within the blender leading to consistency and quality issues. A model-based approach can be an efficient way to understand the blender dynamics provided that the parameters lie within a well-defined design space. This can reduce both the time and cost of the process and product development and enable easier tracking of the final attributes of the product (Adam et al., 2011; Gernaey and Gani, 2010; Klatt and Marquardt, 2009; Boukoulava et al., 2010a). Various software packages and programming languages such as ASPEN (Aspen Technology), gPROMS (Process Systems Enterprise), GAMS (GAMS Development Corporation), EDEM (DEM Solutions), MATLAB (Mathworks) etc. are available which can be used for this purpose.

The various modeling approaches available and in-use today are the continuum and constitutive models (Sudah et al., 2002), statistical models (Boukoulava et al., 2010a; Wu et al., 2007; Portillo et al., 2006), the Monte-Carlo methods (Berthiaux et al., 2004), compartment models (Portillo et al., 2009, 2008), RTD models (Gao et al., 2010, 2011a,b; Vanarase et al., 2010), DEM (Ketterhagen et al., 2009) and hybrid models (Portillo et al., 2007; Freirich et al., 2011). Among the models mentioned above, DEM (discrete element modeling) is the most fundamental modeling approach that captures the particle level physics. Various authors have employed DEM as a tool for capturing the mixing dynamics (Sarkar and Wassgren, 2010, 2009; Bertrand et al., 2005; Dubey et al., 2011; Boukouvala et al., 2012; Remy et al., 2009, 2010b; Remy and Glasser, 2010; Hassanpour et al., 2011; Sen and Ramachandran, in press). DEM was coupled with computational fluid dynamics for describing particle–fluid interactions (Tsuji et al., 1993; Xu and Yu, 1997; Zhu et al., 2007) and continuum models (Zhu et al., 2007). Various rotational mixers (Moakher et al., 2000; Kuo et al., 2002; Lemieux et al., 2007; Sudah et al., 2005; Arratia et al., 2006), helical mixers (Endoh et al., 2000; Iwasaki et al., 2001; Hotta et al., 2001; Kano et al., 2001) and rotor type mixers (Schutyser et al., 2003; Stewart et al., 2001; Chaudhuri et al., 2006) have been studied with the help of DEM. Population balance models are an alternate model framework that can be used to describe particulate process dynamics and have been used in case of other particulate handling processes such as crystallization (Marchal et al., 1988; Puel et al., 2003; Gunawan et al., 2004; Ma et al., 2002) and granulation (Immanuel and Doyle, 2005; Poon et al., 2008, 2009; Ramachandran et al., 2009, 2012, 2008; Ramachandran and Barton, 2010; Stepanek et al., 2009; Ramachandran and Chaudhury, in press) but not for blending till date. The compartment modeling methodology developed by Portillo et al. (2008) discusses the significance of the flux terms and how these can be determined. We have tried to formulate a similar approach using population balance model. The blender has been divided into several compartments. The population balance equation has been formulated for each of these compartments. We have reinforced our work further with quantitative experimental validation and statistical analysis of the model.

In our past work (Sen and Ramachandran, in press; Sen et al., submitted for publication), a one-way coupling was performed in which a hybrid framework was created that coupled the Population Balance Model (PBM) with the Discrete Element Modeling (DEM). The blender was first simulated using DEM. The flux values obtained from DEM simulation were fed into the PBM as model inputs. The model was able to successfully incorporate the multi-scale