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Challenges and opportunities in modeling pharmaceutical manufacturing processes

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ABSTRACT

The pharmaceutical industry currently faces economic and regulatory challenges associated with process development. Process modeling tools can play a role in developing robust and economically efficient manufacturing processes. However pharmaceutical companies have lagged behind other specialty chemical manufacturers in the adoption of these tools. This is in part due to the challenges associated with modeling solids-based processes. However recent advances in the modeling of particulate processes have created opportunities to apply process modeling tools, including flowsheet modeling, to pharmaceutical manufacturing processes. This work will provide an overview of the challenges associated with modeling particulate processes and discuss recent developments in pharmaceutical process modeling. In addition, a case study involving a continuous feeding and blending process will be presented where many of the modeling approaches discussed in this work are applied.

1. Introduction

The pharmaceutical industry currently faces a number of non-trivial challenges associated with the development and implementation of manufacturing processes. Regulatory agencies worldwide are adopting the Quality by Design (QbD) paradigm for process development, introduced by ICH guidance Q8 (ICH, 2009). QbD advocates a science-based approach to ensuring product quality through process understanding. Within this framework, it is necessary to collect sufficient process information to clearly establish the relationship between process performance and product quality. It is necessary to demonstrate that developed manufacturing processes are not only feasible, but also robust (Yu, 2008). Meanwhile companies face economic pressure from increased global competition, particularly with manufacturers of generics (Suresh, 2008). The limited competition-free life span of drugs due to patent expiration means that process development must be expedited in order to ensure profitability (Shah, 2004). For both economic and regulatory reasons it is necessary for pharmaceutical manufacturing processes to be robust, efficient and sufficiently understood to ensure product quality. In this context, modeling and optimization tools have an important role to play in pharmaceutical process development (Gernaey et al., 2012). Process modeling tools can be used to supplement experimental studies in evaluating process sensitivity and operability (Boukouvala et al., 2012; Saltelli et al., 2000). This in turn is beneficial in conducting quality risk assessment, identifying critical process parameters and evaluating process design space (Boukouvala et al., 2010a; Rogers et al., 2014). Modeling tools can also be used to evaluate the relative costs of batch and continuous manufacturing processes, thereby making a business case for the selection of one manufacturing route over another for a particular product (Schaber et al., 2011). Despite the potential benefits of implementing flowsheet models in a process development context, these tools remain relatively underutilized in the pharmaceutical industry as compared to other fine and specialty chemical applications. This is particularly true of drug product manufacturing processes, wherein active pharmaceutical ingredients (API) are formulated into a final dosage form to be administered to patients. The underutilization of process modeling tools can be attributed in part to the difficulties associated with modeling solids-based processes (Muir Wood, 2008; Muzzio et al., 2002).

This paper is meant to provide an overview of recent advances in pharmaceutical process modeling, while acknowledging ongoing challenges associated with modeling solids-based processes. An emphasis will be placed on continuous manufacturing of oral-solid dosage forms (tablets and capsules), as these represent approximately 80% of products in the US domestic market (Muzzio et al., 2002). Section 2 will focus on challenges associated with modeling solids processes. Recent advances in solids process modeling, particularly flowsheet modeling and reduced-order modeling,

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Table 1
Symbols used in this work.

Symbol	Definition
z	Time delay domain
y_d	Feed rate set point
y^{delayed}	Delayed feed rate
ω	Feeder screw rotation rate
ν	Feeder noise parameter
K	Feed factor
m_{out}	Powder feed rate
θ	Feeder mean residence time
τ	Feeder time constant
n	Bin index
i	Component index
$\bar{u}_x^n$	Mean axial velocity in bin n
L	Blender length
τ_n	Residence time in bin n
X_n^n	Weight fraction of material entering bin n
$\dot{F}_n^{i,\text{in}}$	Mass flow rate of component i entering bin n
$\dot{F}_{\text{total}}^{i,\text{in}}$	Total mass flow rate of component i entering bin n
ω_b	Blender agitator rotation rate
$\dot{F}_n^{i,\text{delayed}}$	Delayed flow rate of component i in bin n
$\dot{F}_n^{i,\text{out}}$	Flow rate of component i exiting blender from bin n
m	Mass holdup in blender
N	Number of bins
RSD	Relative standard deviation
C_i	Concentration of component A in bin i
$\bar{C}$	Average concentration of component A

will be discussed as they relate to solids-based pharmaceutical processes in Section 3. An example of a flowsheet model that incorporates reduced-order models will be shown in Section 4. Results and discussion of the case study will be provided in Section 5. Section 6 will summarize conclusions and discuss areas for future work. Table 1 defines symbols and that will be used throughout this work.

2. Challenges in pharmaceutical process modeling

The challenges associated with modeling of solids-based processes can be attributed in part to the so-called continuum duality of particulate materials. This is the notion that the bulk behavior of particulate flows is influenced by particle level phenomena. Thus it is difficult to develop constitutive models to describe the response of granular flows to applied stresses and strains (Muir Wood, 2008). Discrete element method (DEM) simulations can accurately represent these particle level phenomena, as these simulations evaluate Newton's equations of motion for all particles in a system over short time scales to ensure accuracy of particle movement trajectories (Zhu et al., 2007). However this causes DEM simulations to be computationally expensive to evaluate. For this reason it is not practical to use DEM in applications requiring numerous calls to the process model such as sensitivity analysis or optimization.

Within the pharmaceutical industry, the challenges associated with modeling particulate processes are exacerbated by stringent process constraints. When setting specifications for raw materials or establishing the design space for a process, it is important to be conservative relative to the boundaries of failure for the process (Yu, 2008). Thus the quality and predictive ability of models used in process design space evaluation is an important consideration in pharmaceutical applications. Pharmaceutical process models may even need to be validated at manufacturing scale if these models are to play a critical role in development of control strategies for product quality (Chatterjee, 2008).

Determining the relationship between raw material physical properties and process performance is also challenging for solids-based processes. Measurements for raw material properties tend to by multivariate in nature, and it may not be straightforward to determine which properties influence process performance most significantly (García-Muñoz, 2009). In addition, a wide range of properties may be observed in different active pharmaceutical ingredients (APIs). The powders used in pharmaceutical manufacturing vary significantly in size, morphology, physical, chemical and electrical properties. As such, the behavior of these materials is difficult to generalize (McKenzie et al., 2006).

For all of the aforementioned reasons it is difficult to model the operations used in the manufacture of oral solid dosage forms. However, advances in solids-based process modeling have resulted in increasing applications for pharmaceutical development in recent years. Some of these will be discussed in the following sections.

3. Advances in solids process modeling

3.1. Discrete element method (DEM)

As previously mentioned, discrete element method (DEM) simulations can provide detailed representations of particulate processes, considering all particle-particle and particle-geometry interactions. DEM has been used to model pharmaceutical processes including powder conveying, blending, powder flow into dies and compaction of powders into tablets (Ketterhagen et al., 2009). These models are sufficiently detailed to represent phenomena including dispersion, segregation, particle packing and bed densification (Zhu et al., 2008). While DEM simulations can provide high-fidelity representations of particulate processes, they also incur significant computational expense as the number of particles considered increases. For this reason it is not practical to implement DEM simulations directly in a flowsheet modeling environment. However, information from DEM models can be incorporated into flowsheet simulations through the use of certain types of reduced-order models, which will be discussed in Section 3.5.

3.2. Population balance modeling

Population balance models (PBM) are less detailed representations than DEM, but still consider the influence of particle-level properties on bulk material behavior. PBM describe the evolution of particle distributions with respect to internal and external coordinates over time. Internal coordinates include particle size (length, volume or mass) and granule composition (liquid, solid and vapor content), while axial and radial position within a piece of processing equipment are examples of external coordinates. Given their ability to represent size-dependent phenomena, PBM are useful in modeling processes involving size and/or composition change, such as crystallization, granulation, milling, continuous mixing and drying (Gernaey et al., 2012). Solving PBM can be numerically intensive, especially for higher-order models like those representing wet granulation processes. However hierarchal strategies can expedite the solution of PBM. In addition, order-reduction techniques can be used to address three and four dimensional population balance models (Barasso and Ramachandran, 2012).

3.3. Semi-empirical models

Although constitutive models for particulate processes are not widely available, there are certain unit operations that have been well characterized using semi-empirical models. These include equations that are based on fundamental process understanding, coupled with empirical parameters that are function of equipment and material properties. The parameters can be estimated using experimental data collected for a specific piece of equipment and material of interest. Examples of such models include Johanson's theory of rolling granular solids (Johanson, 1965), which has