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An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process

Fani Boukouvala, Vasilios Niotis, Rohit Ramachandran, Fernando J. Muzzio, Marianthi G. Ierapetritou*

Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ 08854, United States

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ABSTRACT

Manufacturing of powder-based products is a focus of increasing research in the recent years. The main reason is the lack of predictive process models connecting process parameters and material properties to product quality attributes. Moreover, the trend towards continuous manufacturing for the production of multiple pharmaceutical products increases the need for model-based process and product design. This work aims to identify the challenges in flowsheet model development and simulation for solid-based pharmaceutical processes and show its application and advantages for the integrated simulation and sensitivity analysis of two tablet manufacturing case studies: direct compaction and dry granulation. The developed flowsheet system involves a combination of hybrid, population balance and data-based models. Results show that feeder refill fluctuations propagate downstream and cause fluctuations in the mixing uniformity of the blend as well as the tablet composition. However, this effect can be mitigated through recycling. Dynamic sensitivity analysis performed on the developed flowsheet, classifies the most significant sources of variability, which are material properties such as mean particle size and bulk density of powders.

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1. Introduction

Historically, the pharmaceutical industry has been very innovative and successful in the field of new drug discovery and development. However, this has drawn the focus away from the development of efficient manufacturing methods and process understanding (Gernaey & Gani, 2010; Huang et al., 2009; Klatt & Marquardt, 2009; McKenzie, Kiang, Tom, Rubin, & Futran, 2006). In addition, one of the fears that the industry is facing today is the significant decrease in profit due to the expiration of important patents and the difficulty of the development of new drugs to replace them. This fact drives the focus towards efficient manufacturing strategies, which would significantly make products competitive in a market where generic manufacturers are also involved.

Due to the lack of knowledge of how critical material attributes and process parameters affect end-point product attributes, combined with ineffective control strategies, pharmaceutical manufacturing processes generate products that are often characterized by a relatively large amount of variability that would not be tolerated in other process industries (e.g. petrochemicals or foods) (McKenzie et al., 2006). One additional challenge for the establishment of efficient, controlled, and automated manufacturing methods is the considerable variability in new raw material properties, since any new formulation has unique molecular structure, physico-chemical and biological properties. In addition, the majority of pharmaceutical products (~80%) are in a solid based form of tablets or capsules, composed from bulk powder materials, which are far more complex and challenging to handle than liquid or gas phase materials. Even though significant progress has been made recently in particle technology research, there is a gap between fundamental science and applied engineering due to the need for integration of multiscale knowledge (Ng, 2002). All of the above reasons have been the source of consensus and legacy based heuristic production strategies, conducted overwhelmingly in batch mode; with product quality being traditionally verified offline through acceptance sampling. This approach has lead to additional sources of variability, which are the effects of the analytical method, and the human factor, since it is common for operators to regulate the process based on their individual knowledge and experience.

Recently, the Food and Drug Administration (FDA) has recognized the need for modernizing pharmaceutical manufacturing and

* Corresponding author. Tel.: +1 732 445 2971; fax: +1 732 445 2581.
E-mail addresses: marianth@soemail.rutgers.edu, marianth@rutgers.edu (M.G. Ierapetritou).

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Nomenclature

Symbol

A	surface area (m^2)
C_{API}	API concentration (−)
d_{50}	mean particle size (m)
F	PBM density function (particles)
H	height (m)
h_0	half of ribbon thickness (m)
m	mass flow (kg)
P	compaction pressure (MPa)
R	radius (m)
RSD	Relative Standard Deviation (−)
RT	residence time (s)
u	feed speed (m/s)
W	width (m)
α	nip angle (rad)
δ	effective angle of friction (rad)
ε	porosity (−)
θ_{in}	inlet angle (rad)
ρ_{bulk}	powder bulk density (kg/m^3)
σ	material stress (MPa)
$\Re$	rate (particles/s)
ω	rotation rate (rpm)
a_h	heckel parameter
b_i ($i = 1, 2, 3, 4$)	feed frame response surface parameters
C_1^{rc}	stress-angle empirical parameter
k_{break}	breakage kernel
k_g	process gain
k_h	heckel parameter
K^{rc}	stress-angle empirical parameter
θ	delay
τ	time constant

Domain

g	gas
n	component
r	particle size
s_1	API
s_2	excipient
z	time delay
z_1	axial
z_2	radial

Subscript

in	inlet stream
out	outlet stream
P	pressure
sp	set point
u	speed
ω	rotation rate

Superscript

delayed	delayed
disc	feed frame disc
f	feeder
ff	feed frame
m	mixer
mil	mill
rc	roller compactor
rib	ribbon
rol	roller compactor roll
tablets	tablets
tp	tablet press

has launched an initiative for enhancing process understanding through Quality by Design (QbD) and Process Analytical Technology (PAT) tools (Garcia, Cook, & Nosal, 2008; Lionberger, Lee, Lee, Raw, & Yu, 2008; Nosal & Schultz, 2008; Yu, 2008). The major goals of these efforts include the development of scientific mechanistic understanding of a wide range of processes; harmonization of processes and equipment; development of technologies to perform online measurements of critical material properties during processing; performance of real-time control and optimization; minimization of the need for empirical experimentation and finally, exploration of process flexibility or design space (Lepore & Spavins, 2008). To achieve these goals, the industry needs the modeling tools and databases for measuring, controlling and predicting quality and performance.

In the last five years, one of the main approaches for modernizing pharmaceutical manufacturing, transition of production from batch to continuous mode, is becoming increasingly more appealing to the industry and regulatory authorities (Betz, Junker-Bürgin, & Leuenberger, 2003; Gonnissen, Gonçalves, De Geest, Remon, & Vervaet, 2008; Leuenberger, 2001; Plumb, 2005). The advantages of this change have been proven very beneficial in many aspects when applied in other fields, such as petrochemicals and specialty chemicals (Gorsek & Glavic, 1997). Firstly, continuous manufacturing allows the use of the same equipment for the production of smaller and larger quantities, which minimizes the need for scale-up studies and the time-to-market significantly (Leuenberger, 2001). At the present time, processes developed in small-scale equipment used for initial clinical studies must be scaled-up (empirically) and subsequently validated experimentally and further optimized, since their operation is always potentially different at the larger scale. This leads to another advantage of continuous integrated manufacturing, which is the minimization of the plant footprint, since the entire continuous process typically fits inside a much smaller space. A well controlled continuous process involves the handling of small aliquots of material throughout the unit operations, increasing the ability to monitor a significant fraction of the process streams, which is impossible in a large-scale batch process. In addition, continuous operations can produce higher throughputs under better control, which implies the optimal use of the invested capital (space, raw materials and equipment), as well as the reduction of waste (Plumb, 2005). Also, in a continuous setting, the human factor is significantly decreased through automation of operation and thus labor costs can be reduced. Finally, risks associated with material handling, such as contamination and undesired segregation and agglomeration are reduced since less time is necessary for filling, emptying and cleaning equipment. A detailed economical analysis and comparison of batch versus continuous operating mode for the production of pharmaceuticals has been performed by Schaber et al. (2011), demonstrating the possibilities and advantages of the latter.

However, a switch from the already established batch to continuous operation involves many challenges, and could lead to failure if not performed correctly. Firstly, pharmaceutical substances are highly sensitive to environmental conditions, such as humidity and temperature and a possible larger residence time than required can cause significant material degradation. This can cause dangerous product contaminations and should be avoided. In a batch setting, the residence time is more easily controlled whereas in a continuous setting this is more challenging. Subsequently, in a continuous production, the process does not reach steady state from the beginning, and this may cause off-specification product to be produced during a particular time interval. However, because regulatory authorities require detailed and time-consuming documentation for the establishment of a manufacturing strategy, and