

# Computer-Aided Flowsheet Simulation of a Pharmaceutical Tablet Manufacturing Process Incorporating Wet Granulation

Fani Boukouvala · Anwesha Chaudhury ·  
Maitraye Sen · Ruijie Zhou · Lukasz Mioduszewski ·  
Marianthi G. Ierapetritou · Rohit Ramachandran

Published online: 18 January 2013  
© Springer Science+Business Media New York 2013

**Abstract** In this work, a dynamic flowsheet model for the production of pharmaceutical tablets through a continuous wet granulation process is developed. The unit operation models which are integrated to compose the process line form a hybrid configuration which is comprised of a combination of mechanistic models, population balance models, and empirical correlations, based on the currently available process knowledge for each individual component. The main objective of this study is to provide guidance in terms of the necessary steps which are required in order to move from the unit operation level to the simulation of an integrated continuous plant operation. Through this approach, not only significant process conditions for each individual process are identified but also crucial interconnecting parameters which affect critical material properties of the processed powder stream are distinguished. Through the integration of the dynamic flowsheet with a final component of tablet dissolution, the connection of the processing history of a set of powders which undergo wet granulation and are contained in each produced tablet to the release rate of the pharmaceutical ingredient is enabled. The developed flowsheet is used for the simulation of different operating scenarios and disturbances which are often encountered during operation for the assessment of their effects towards critical material attributes, product properties, and the operation of further downstream processes. Simulation results demonstrate that granulation and milling which control the particle size distribution of the processed powder mixture highly affect the hardness and dissolution of the produced tablets.

**Keywords** Pharmaceutical manufacturing ·  
Wet granulation · Flowsheet simulation ·  
Population balance modeling

## Introduction and Objectives

The pharmaceutical industry is a tightly regulated industry where all production must comply with good manufacturing practices and quality requirements should be strictly satisfied. Historically, manufacturing in the pharmaceutical industry has been carried out in batch mode which potentially results in expensive, inefficient, and poorly controlled processes [18, 26]. Recently, both pharmaceutical industries and regulatory authorities have recognized that continuous manufacturing has a significant potential to improve product quality and reduce manufacturing cost [1, 2, 14, 27, 28, 34, 38, 49, 55, 61, 62]. Moreover, environmental, health, and safety issues are driving the industry towards more efficient and more predictive manufacturing. Therefore, a great opportunity arises for developing a generic continuous manufacturing platform that will benefit from state-of-the-art strategies, modeling tools, and enabling technologies to implement this transition. In this work, we focus on the manufacturing of oral solid dosage drugs which consist of approximately 85 % of the entire pharmaceutical production. A typical manufacturing process for a powder-based product (e.g., tablets and most capsules) involves multiple processing steps, of which the most common are powder feeding, blending, granulation, and tableting or capsule filling.

Dynamic flowsheet modeling and simulation is a prerequisite for the design, analysis, control, and optimization of an integrated process. While several integrated modeling and simulation tools (commercial and noncommercial)

F. Boukouvala · A. Chaudhury · M. Sen · R. Zhou ·  
L. Mioduszewski · M. G. Ierapetritou · R. Ramachandran (✉)  
Rutgers, The State University, Piscataway, NJ, USA  
e-mail: rohit.r@rutgers.edu