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RESEARCH ARTICLE

Population Balance Model Validation and Prediction of CQAs for Continuous Milling Processes: toward QbD in Pharmaceutical Drug Product Manufacturing

Dana Barrasso · Sarang Oka · Ariel Muliadi · James D. Litster · Carl Wassgren · Rohit Ramachandran

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Abstract Continuous tablet manufacturing has been investigated for its potential advantages (e.g., cost, efficiency, and controllability) over more conventional batch processes. One avenue for tablet manufacturing involves roller compaction followed by milling to form compactible granules. A better understanding of these powder processes is needed to implement Quality by Design in pharmaceutical manufacturing. In this study, ribbons of microcrystalline cellulose were produced by roller compaction and milled in a conical screen mill. A full factorial experiment was performed to evaluate the effects of ribbon density, screen size, and impeller speed on the product size distribution and steady-state mass holdup of the mill. A population balance model was developed to simulate the milling process, and a parameter estimation technique was used to calibrate the model with a subset of experimental data. The calibrated model was then simulated at other processing conditions and compared with additional unused experimental data. Statistical analyses of the results showed good agreement, demonstrating the model's predictive capability in quantifying milled product critical quality attributes within the experimental design space. This approach can be used to optimize the design space of the process, enabling Quality by Design.

Keywords Conical screen mill · Population balance modeling · Parameter estimation · Continuous milling · Quality by Design

D. Barrasso · S. Oka · R. Ramachandran (✉)
Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ, USA
e-mail: rohit.r@rutgers.edu

A. Muliadi · J. D. Litster
School of Chemical Engineering, Purdue University, West Lafayette, IN, USA

J. D. Litster · C. Wassgren
Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN, USA

C. Wassgren
School of Mechanical Engineering, Purdue University, West Lafayette, IN, USA

Introduction

Manufacturing of solid dosage therapeutics has traditionally been dominated by batch operations, so much so that even continuous and semicontinuous processes like milling, spray drying, and tablet compaction are modified to fit into the batch schematic [17]. A part of this is attributed to historical reasons. The other important factor has been regulation which requires a process to run unperturbed for its entire lifetime.

Historically, manufacturing cost contributed little to the overall cost of bringing the product to the market. However, due to rising research and development expenditures, rising manufacturing costs, expiration of patented drugs, and competition from generics, the industry has recognized the need to change its manufacturing practices and is looking for avenues to alleviate costs.

Coinciding with the above factors is the willingness of regulatory agencies to allow innovators to develop processes that advance understating of underlying physical phenomenon which would allow them to build quality into their products. The mission statement of the FDA initiative called Quality by Design (QbD) is that quality should be