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RESEARCH ARTICLE

Population Balance Model-Based Hybrid Neural Network for a Pharmaceutical Milling Process

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Abstract
Introduction Population balances are generally used to predict the particle size distribution resulting from the processing of a particulate material in a milling unit. The key component of such a model is the breakage function. In this work we present an approach to model breakage functions that has utility for situations in which determination of the breakage function from first principles is difficult. Traditionally, heuristic models have been used in those situations but the unstructured nature of such models limits their applicability and reliability.
Methods To address this gap, we propose a semi-empirical hybrid model that integrates first principles knowledge with a data-driven methodology that takes into account the material properties, mill characteristics, and operating conditions. The hybrid model combines a discrete form of population balance model with a neural network model that predicts the milled particle size distribution given material and mill information.
Results We demonstrate the usefulness of this approach for compacted API ribbons milled in a lab scale Quadra conical mill for different materials and mill conditions. Comparisons are also given to the predictions obtained via a purely neural network model and a population balance model with a linear breakage kernel.

Keywords Milling · Modeling · Pharmaceutical processing · Breakage function · Neural net · Hybrid model · Population balance

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Introduction

Milling is one of the more common unit operations used in the pharmaceutical industry. For instance, it is usually the last step in the production of an active pharmaceutical ingredient (API) powder. Milling consists of the breakage of a dry feed into a powder product consisting of particles with a desired size distribution. The particle size distribution often plays an important role in determining the performance of the final product. Typically, particle size reduction is used to normalize particle size between different batches, narrow a size distribution for more predictable flow and handling properties, or match the particle size of API more closely with that of excipients to minimize the potential for segregation during blending [14]. The design of the milling step has generally been done by heuristics and trial-and-error. In this work, we present a model to predict the particle size distribution in a more quantitative manner.

The particle size distribution produced in milling is the result of a complex interplay between the material properties, the characteristics of the milling equipment, and mill-specific operating parameters, which jointly give rise to specific breakage mechanisms. Consequently, the prediction of breakage behavior becomes difficult in a generalized form. Population balance (PB) modeling [1] is the traditional approach for modeling the changes in particle size distribution that is the result of particulate processes such as milling. There are many forms of PB models in the literature to address a variety of types of processes. Linear time invariant equations, time dependent models, multi-dimensional population balance models (PBMs), etc. have been reported [1–4, 14]. The key requirement for the population balance model for the milling operation is the knowledge of the associated breakage functions. Briefly, breakage functions describe how