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Model development and prediction of particle size distribution, density and friability of a comilling operation in a continuous pharmaceutical manufacturing process

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ABSTRACT

The comilling process plays an important role in solid oral dosage manufacturing. In this process, the granulated products are comminuted to the required size distribution through collisions created from a rotating impeller. In addition to predicting particle size distribution, there is a need to predict other critical quality attributes (CQAs) such as bulk density and tapped density, as these impact tablet compaction behavior. A comprehensive modeling approach to predict the CQAs is needed to aid continuous process modeling in order to simulate interaction with the tablet press operation. In the current work, a full factorial experiment design is implemented to understand the influence of granule strength, impeller speed and residual moisture content on the CQAs. A population balance modeling approach is applied to predict milled particle size distribution and a partial least squares modeling approach is used to predict bulk and tapped density of the milled granule product. Good agreement between predicted and experimental CQAs is achieved. An R^2 value of 0.9787 and 0.7633 is obtained when fitting the mean particle diameters of the milled product and the time required to mill the granulated material respectively.

1. Introduction

Solid oral dosage manufacturing is gradually shifting from batch to continuous processes. It is important for companies to devise ways to minimize time-to-market of product while maintaining product quality. In this environment, continuous manufacturing offers potential advantages in cost, efficiency and reduced time to market that translates to improved manufacturing efficiency. Regulatory agencies such as the US Food and Drug Administration (FDA) have introduced the Quality-by-design (QbD) approach (US Food and Drug Administration, 2009) that requires companies to demonstrate an understanding of the effect of variability in material properties and process conditions on the critical quality attributes (CQAs) of the drug product. Process systems engineering tools can play a significant role in the effective transition to continuous manufacturing and the successful implementation of QbD (Wang et al., 2017; Wang et al., 2017; Rogers et al., 2015).

Direct compaction (DC), dry granulation (DG), and wet granulation (WG) are the most common routes for continuous manufacturing and include numerous unit operations to process powder feeds and manufacture tablets as final product. In the DC route, the conical screen mill (comill) is typically used to delump cohesive powder feeds and enable their effective blending. In the DG and WG routes, comilling is used to break the compacted ribbons or granulated product to a required size distribution. Alternatively, a hammer mill may be used to break the ribbons and a comill is used for screening. The size distribution of the resulting granules is a Critical Quality Attribute (CQA) as it impacts the flow behavior and downstream product attributes. Non uniform flow of granules into a tablet press die could result in weight variability of the tablets. More significantly, the content uniformity of tablets is impacted which results in inconsistent drug dissolution profiles, an indicator of the drug bioavailability. In addition, the strength of tablet obtained from compaction is also impacted (Santl et al., 2012).

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Granule breakage in the comill occurs through weakening of pore structures within the agglomerate through stresses from a rotating impeller and collisions with equipment walls. The smaller sized granules thus obtained are discharged through a screen. Schenck et al. (2008) studied the fundamental breakdown behavior of granules in a comill and proposed impact attrition as the primary breakage mechanism. Milling experiments in the absence of a screen suggested that the screen acts only as a classifier and does not affect the breakage mechanism. Verheezen et al. (2004) modeled breakage in a comill through a size reduction ratio defined as the ratio of the median particle size of granules before and after breakage. The initial size of particles before granulation and the amount of binder used was found to have an effect on the breakage behavior. Samanta et al. (2012) presented detailed comilling experiments with compacted ribbons to study the effects of impeller shape, speed, screen type and concluded that the fines can be reduced considerably by choosing the correct impeller and screen type for the material milled. Whilst plenty of work has been published that studied the effects of various design and process variables for comilling, work published on modeling of the comilling operation to predict milled product CQAs is limited. Akkisetty et al. (2010) used an Artificial Neural Network (ANN) surrogate model to establish a relationship between mill operating conditions, material properties selection and breakage functions of a population balance model (PBM). However, the experiments used for this work did not consider the effect of granules exiting the mill as the screen holes were closed. Reynolds (2010) developed a PBM to predict the milled particle size distribution (PSD) through the use of a generalized daughter distribution function. A critical screen size ratio dependent on impeller speed was used to model the exit of granules. However, the d95 of the milled PSD was used, which limits the applicability of the model formulation as d95 is the required model output that is predicted and not a model input. In addition, the dynamics of the model i.e., flowrate of particles exiting the mill was not formulated, and as a result, the time required to mill the material could not be predicted. Barrasso et al. (2013) modeled the comilling of compacted ribbons through development of a PBM. A linear function was used to model the exit of particles from the mill through the screen which aided in predicting the dynamic holdup as well. However, the full effect of the impact of impeller speed on the model was not captured. In addition, the applicability of the model in simulating comminution of granules obtained from a wet granulation process was not established. Recent efforts have also focused on utilizing mechanistic models to simulate the comilling process. Deng et al. (2015) presented a discrete element method (DEM) simulation of the comilling process, where breakage of particles was not considered as the comill was used as a dry coating device. Capece et al. (2014a) established a bi-directional PBM-DEM framework utilizing a mechanistically motivated kernel formulation (Capece et al., 2014b). However, the framework was implemented for a ball milling process where particles were not considered to exit the mill. Metta et al. (2018) developed a multiscale framework to simulate a comilling process where material properties were explicitly incorporated and estimated. Literature published in the area of comminution focusses on predicting milled particle size distribution. Mentions of prediction of other CQAs such as bulk density, tapped density, friability etc., of the milled product are limited. It is important to note that these CQAs have an impact on the compaction behavior of granules and thus their effect on CQAs should be predicted.

In the current work, a hybrid modeling approach to predict particle size distribution and bulk density, tapped density, friability of the milled product is presented. Milled product particle size distribution is predicted through development of a population balance model. Prediction of other CQAs such as bulk density, tapped density and friability is pursued by using a Partial Least Squares (PLS) modeling approach which uses the milled product particle size distribution as one of the input variables. The approach presented is also calibrated and validated using experimental data generated from milling pharmaceutical material. The specific objectives of this work are:

- Analyze the effect of the influence of process parameters on milled product properties.
- Develop a PBM that predicts milled product particle size distribution as well as milling dynamics.
- Develop a PLS model that predicts milled product CQAs such as bulk density, tapped density and friability.
- Calibrate and validate the PBM as well as PLS models, present statistical significance of model parameters, where applicable.
- Present a comprehensive modeling approach for the milling process that aids in flowsheet modeling.

2. Materials and methods

The model formulation consisted of two Active pharmaceutical ingredients (APIs) and Maize starch, powdered cellulose, pregelatinised starch, sodium starch glycolate as excipients. The formulation was processed using demineralized water as granulation liquid.

2.1. Equipment details

The study has been conducted using the ConsiGma™-25 system (GEA Pharma systems, Collette, Wommelgem, Belgium), which is an oral solid dosage manufacturing line based on continuous wet granulation. This study involved three consecutive unit operations of the continuous system: the twin-screw granulator, fluid-bed dryer and Granule Conditioning Unit (GCU). The twin-screw granulator consists of two 25 mm diameter co-rotating screws with a length-to-diameter ratio of 20:1. The powder premix enters the granulator barrel using a gravimetric twin-screw loss-in-weight feeder (KT20, K-Tron Soder, Niederlenz, Switzerland). In a next step, the powder premix is moved forward using conveying elements. In this conveying compartment, prior to the first kneading compartment, granulation liquid is gravimetrically dosed into the screw chamber using two peristaltic pumps (Watson Marlow, Cornwall, UK) operating out of phase with silicon tubing (internal and external diameter of 1.6 and 4.8 mm, respectively) connected to 1.6 mm nozzles. The addition of granulation liquid takes place by injecting the liquid through two liquid feed ports located on the central top of each screw. The fixed screw configuration used in this study was composed of 2 kneading zones each consisting of 4 kneading elements (L = D/4 for each kneading element), staggered at an angle of 60 degrees. Both kneading zones were separated by a conveying element (L = 1.5D). An extra conveying element (L = 1.5D) was implemented after the second kneading block together with 2 narrow kneading elements (L = D/6 for each kneading element) in order to reduce the amount of oversized agglomerates.

In a next step, the produced wet granules are pneumatically transferred by means of a wet transfer line to the six-segmented fluid-bed dryer. This semi-continuous module uses a drying chamber which is divided in 6 identical cells, which are sequentially filled and discharged, hereby ensuring a continuous flow of incoming wet granules and exiting dried granules. After drying, the granules are pneumatically transported to the Granule Conditioning Unit (GCU). This module consists of a product control hopper (PCH) where the dried granules are collected. In a next step, the granulate material is gradually discharged to a conical mill using a metering valve, which ensures a consistent material flow. In this study, the conical mill is a U10 Quadro® Comil® (Quadro, Ontario, Canada) which is equipped with a grater style screen and a square bar impeller. The diameter of the screen holes is 1016 μm. After the milling step, the resulting product is assembled in a buffer reservoir where it is released for the next process step.

2.2. Design of experiments

An adequate Population Balance model calibration requires a