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Model-based analysis of a twin-screw wet granulation system for continuous solid dosage manufacturing

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ABSTRACT

Implementation of twin-screw granulation in a continuous from-powder-to-tablet manufacturing line requires process knowledge development. This is often pursued by application of mechanistic models incorporating the underlying mechanisms. In this study, granulation mechanisms considered to be dominant in the kneading element regions of the granulator i.e., aggregation and breakage, were included in a one-dimensional population balance model. The model was calibrated using the experimentally determined inflow granule size distribution, and the mean residence time was used as additional input to predict the outflow granule size distribution. After wetting, the first kneading block caused an increase in the aggregation rate which was reduced afterwards. The opposite was observed in case of the breakage rate. The successive kneading blocks lead to a granulation regime separation inside the granulator under certain process conditions. Such a physical separation between the granulation regimes is promising for future design and advanced control of the continuous granulation process.

1. Introduction

Granulation in the pharmaceutical industry aims at enlarging powder particles, which can be advantageous during the formulation of solid dosage forms [9]. The size enlargement results in gravity forces exceeding the van der Waals forces, thereby contributing to better flow properties required for improved processability and accurate dosing in further downstream processing [21]. Especially in the pharmaceutical industry, where often highly potent drugs are processed, the amount of dust generated by powder handling is reduced by granulation, resulting in improved safety. Also, segregation (demixing) can be minimized along with the improved downstream processing characteristics of the granules.

In the last decade, continuous manufacturing of pharmaceutical solid dosage forms has received great interest due to several process and economic benefits associated with it [10]. A continuous production process can conceptually eliminate scale-up requirements and intermediate storage. With this in mind, twin-screw granulation has emerged as promising method which can be embedded in a continuous manufacturing line which also includes dryer, screening unit and tabletting machine making continuous powder-to-tablet production possible. Moreover, the screws used in the granulator have a modular structure (interchangeable transport and kneading elements) providing flexibility towards adaptation in equipment and process variables depending upon feed characteristics to achieve the required product characteristics.

The available studies have primarily focused on the effect of process variables (such as screw configuration, material throughput, screw speed, etc.) [28,5,25] and formulation properties [8,6] on granule properties at the outlet of the twin-screw granulator

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(TSG) due to the opacity of the multi-phase system in the granulator. Thus, little is known about the effect of these variables on the evolution and kinetics of granule formation in the TSG and the resulting granule structure. In a recent study, granule size distribution (GSD) evolution along the TSG screw was experimentally mapped in order to understand the dominant constitutive mechanisms of a granulation system such as growth, aggregation and breakage [14]. However, such measurements merely provide a semi-quantitative insight regarding the GSD at discrete time steps, making it difficult to apply in process design applications. Population balance equations (PBEs) are a frequently used mathematical tool to describe particulate processes such as wet granulation [13] and drying of the wet granules [18]. An extensive review of the applications of such equations to particulate systems in engineering is given by Ramkrishna [22]. Barrasso et al. [4] used a multi-component population balance model (PBM) for tracking the liquid content and porosity of each particle size class during the twin-screw granulation. The experimental data reported by El Hagrasy et al. [8] was used in the study of Barrasso et al. [4]. The data originated from samples collected from the granulator outlet, and therefore a lumped-parameter approach was adopted for the development of the model. Furthermore, Barrasso et al. [3] applied bi-directional coupling between a particle scale discrete element method (DEM) and PBM for a more mechanistic description of a twin-screw wet granulation process. The model showed sensitivities to the screw configuration, process parameters such as screw speed, liquid-to-solid ratio as well as material properties such as binder viscosity and pore saturation. Although, the bi-directional coupling between DEM and PBM to evaluate collision frequencies and liquid distribution was an excellent proof-of-concept of mechanistic modelling of granulation processes, it is computationally very expensive and requires many particle-scale assumptions, which demand further validation. Due to this, there is still very little understanding regarding the primary driving mechanisms and function of screw components in the twin-screw wet granulation.

In this study, the principal constitutive mechanisms of a granulation system such as growth, aggregation and breakage were included in a PBM framework to track particle size evolution in the different individual screw blocks of a continuous TSG. Based on an experimentally determined inflow GSD [14] and mean residence time (MRT) [15] of the granulator, predictions of the outflow GSD were made. The experimental data was used for calibrating the model for individual screw modules in the TSG at different process conditions. The results from the calibrated model were used to understand the role of mixing zones and their locations in the screw under different process conditions.

2. Materials and methods

2.1. Continuous wet-granulation using TSG

Granulation experiments were performed using a 25 mm diameter co-rotating TSG with option to open the barrel, which is the granulation module of the ConsiGma-1 unit (GEA Pharma Systems, Collette™, Wommelgem, Belgium). The TSG consists of a barrel enclosing two co-rotating self-wiping screws. The granulator screws had a length-to-diameter ratio of 20:1. The screw configuration with 6 kneading elements (Length = Diameter/4 for each kneading disc) were composed of one kneading block. For the screw configuration with 12 kneading elements, two kneading blocks each consisting of 6 kneading elements were used (Fig. 1). Both kneading zones were separated by a conveying screw block (Length = 1.5 Diameter). The stagger angle of the kneading elements was fixed at 60°. An extra conveying element (Length = 1.5 Diameter) was implemented after the second kneading block together with 2 narrow kneading elements (Length = Diameter/6 for each kneading disc) in order to reduce the amount of oversized agglomerates, as reported by Van Melkebeke et al. [26]. The barrel jacket temperature was set at 25 °C. During processing, the powder premix was gravimetrically fed into the feed segment of the granulator by using a twin-screw feeder with agitator (DDW-MD2-DDSR20, Brabender, Duisburg, Germany). Distilled water as granulation liquid was pumped into the screw chamber using a peristaltic pump (Watson Marlow, Comwall, UK) using silicon tubings connected to two 1.6 mm nozzles, one for each screw, before the material reaches the mixing zone which contained kneading elements (Fig. 1). The powder was hence wetted by the granulation liquid in this region. Further down, since the granulation occurs by a combination of capillary and viscous forces binding particles in the wet state, the wetted material was distributed, compacted and elongated by the kneading elements of the mixing zones, changing the particle morphology from small (microstructure) to large (macrostructure). It is believed that the material is mixed, compacted and chopped to form irregular and porous granules by the succeeding transport elements and kneading blocks [27]. The rotation of the screws conveys the material in axial direction through the different zones of the TSG by the drag and flow-induced displacement forces and thus causing mixing and granulation. The rheological behaviour of the material also changes based on liquid-to-solid ratio (L/S) [1].

2.2. Population balance model for TSG

A TSG consists of a wetting zone and several mixing zones containing a finite number of kneading elements, which significantly drive the solid–liquid mixing and hence the granulation process. For the mathematical description of a TSG with two mixing blocks, the compartmentalisation into two well-mixed zones for simulation solved the challenge of inhomogeneous distribution of particle properties along the TSG length. This inhomogeneity exists due to the geometry of the screw as well as the position of the liquid addition ports. The application of compartmentalisation for modelling the inhomogeneity by partitioning the fluidized bed into two different zones was recently presented by Hussain et al. [12]. Introducing an external coordinate can be another possibility to model this inhomogeneity, but that will require implementation of the DEM together with population balances which is computationally more demanding. In order to model the change in GSD across the individual mixing zones, these mixing zones were assumed to be well-mixed systems. The granulation rate processes which are considered to be dominant in the kneading element regions of the granulator, i.e. aggregation and breakage, were included in a PBM framework [13], which can be represented as:

$$\begin{aligned}\frac{\partial n(t,x)}{\partial t} &= \frac{Q_{in}}{V} n_{in}(x) - \frac{Q_{out}}{V} n_{out}(x) \\ &\quad + \frac{1}{2}\int_0^x \beta(t, x-\varepsilon, \varepsilon)\, n(t, x-\varepsilon)\, n(t,\varepsilon)\, d\varepsilon - n(t,x) \\ &\quad \times \int_0^\infty \beta(t,x,\varepsilon)\, n(t,\varepsilon)\, d\varepsilon \\ &\quad + \int_0^\infty b(x,\varepsilon) S(\varepsilon) n(t,\varepsilon)\, d\varepsilon - S(x) n(x,t) \qquad (1)\end{aligned}$$

where, $n(t, x)$ is the number density function of particle size x as the internal coordinate at time t. Here particle size refers to the particle volume. Q_{in} and Q_{out} were inflow and outflow of the material based on throughput and V was the volume of the mixing zone. Assuming the material transport across the mixing zone to occur at a steady state, inflow and outflow can be eliminated from Eq. (1). Moreover, the GSD of the inflow to the second mixing/transport zone was