ABSTRACT

Sayin, Ridade. PhD, Purdue University, May 2016. Mechanistic Studies of Twin Screw Granulation. Major Professor: James Litster.

Traditionally, pharmaceutical industry has relied on batch processing. Over the last decade however, regulatory bodies such as Food and Drug Administration (FDA) have encouraged the pharmaceutical manufacturers to shift towards continuous processing due to its advantages over batch processing such as cost effectiveness, being amenable to implementation of process analytical technologies (PAT), and to eliminate certain scale-up challenges. Wet granulation is the process of forming agglomerates from fine powder with the addition of granulating liquid and agitation, forming liquid bridges to hold powder particles together. In solid dosage form production, continuous wet granulation is used to reduce dust formation and improve flowability, compactability, and content uniformity of the intermediate product and facilitate downstream handling. Twin screw granulation (TSG) has gained increasing interest in the pharmaceutical industry due to its design flexibility, wide range of throughputs and short residence times. However, although many experimental and some modeling studies have been performed on twin screw granulation, there’s little mechanistic understanding to be able to efficiently design and control such processes. This thesis aims at improving the mechanistic understanding of TSG first through characterization of the rate processes in a recently developed screw element, distributive mixing element (DME), section and secondly by elucidating the rate mechanisms taking place in the downstream conveying element (CE) section of the TSG. This understanding from experimental work was then combined with the population balance model (PBM) framework developed by Barrasso *et al.* to model TSG using a mechanistic compartment model, utilizing the regime-separated nature of TSG.

A placebo formulation composed mostly of α-lactose monohydrate was used for the experimental work. Aqueous solution (0.1%, wt.) of a black dye was used as the granulating liquid. The formulation was fed into a 16 mm granulator at 4kg/h and liquid was fed at such flow rates to achieve liquid to solid (L/S) ratios ranging from 0.15 to 0.35,

with 0.05 increments. A screw speed of 400 rpm was used in all the experiments. Four different DME configurations were used to investigate the effect of direction (forward *versus* reverse) and placement (adjacent *versus* spaced) on granule attributes at five L/S ratios. The granule samples were characterized for their size and liquid distributions (GSD and LD, respectively), porosity and shape through calculation of vertical aspect ratio. Additionally, residence time and flow visualization studies were performed to improve the understanding of flow inside the granulator. Overall, the adjacent-reverse (DME-AR) configuration gave superior granule attributes when compared to CE and several kneading element (KE) configurations. These include monomodal GSD without over-sized lumps even at the lowest L/S ratio, which will lower blend segregation potential; spherical granule shape, which will provide good flowability and drying uniformity in the downstream processes; and porous granules, which will have good compactability. The study showed that DME-AR is a promising configuration in optimizing the granule attributes in such a way to facilitate downstream processing.

To characterize the effects of presence and length of a downstream CE section on granule attributes, three different powder and liquid feed locations and five screw configurations were compared at four (five for RT1) L/S ratios measuring GSD, LD, and porosities of the resulting granules. Addition of downstream CEs was found to improve size and liquid distributions through breakage and layering mechanisms and decrease porosity to a certain level. The amount of over-sized lumps decreased with the addition of a short section of downstream CEs. The improvement in the liquid distribution however, was a lot more significant, resulting in almost homogeneous distribution of the liquid among granule size classes. Although addition of a certain amount of downstream CEs contributes as aforementioned, further addition of downstream CEs resulted in a less significant improvement in granule attributes.

To model the granulation process in TSG, a 2-D PBM was written using the framework developed by Barrasso *et al.*, tracking granule and liquid volumes, and taking into account nucleation, breakage, and layering rate processes. In this model, the section of the TSG used for granulation was divided into four compartments and a PBM is written for each compartment, utilizing the information on rate processes taking place in the specific screw element configurations present in each compartment. In this work, two screw configurations were used namely, CE and DME-AR, at five L/S ratios. Simple experiments were performed using test particles to estimate breakage critical size and probability for each screw configuration. The experimental data at the lowest L/S ratio was used to fit parameters, and the remaining data were utilized to test the ability of the model to predict the change in GSD with increasing L/S ratio. The compartmental PBM was able to predict the effect of L/S ratio on GSD with a small number of fitting parameters. The zero order breakage kernel estimated via simplified experiments was able to accurately reflect the behavior in CEs to predict size distributions and represent the trend in liquid distribution. However, to be able to predict the size and liquid distributions in DMEs accurately, more mechanistic studies are required to understand breakage rate and fragment distribution. This modeling approach can then be applied to all screw configurations and a database can be developed, which will enable optimization of screw configuration in TSG, as well as other design and process parameters of interest to obtain desired granule properties.