Quality by Design in Twin Screw Granulation

Granulation is often used as a size enlargement unit operation in various solid handling and powder processing industries such as pharmaceuticals, foods, detergents, catalysts, and particulate chemicals. Granulation helps to mitigate issues related to poor flowability, dust hazards, and powder segregation. Traditionally, granulation has been performed in the batch mode of operation. More recently, the United States Food and Drug Administration is encouraging manufacturers to adopt continuous processing due its several advantages over batch manufacturing. Twin screw granulation is therefore becoming increasingly relevant due to its compact size, continuous and robust mode of operation, flexible and customizable design, and flexible production capacity.

Wet granule breakage is reported to be a key rate process in twin screw granulation and is also the main mechanism for controlling granule size within the granulator. This dissertation is the first study to explicitly measure the influence of material properties, process conditions, and screw element geometry on the breakage process in the twin screw granulator (TSG). Novel breakage isolating experiments were performed at various screw speeds and powder feed rates using model granules having a wide range of material dynamic yield strengths (DYSs) in conveying and distributive mixing element screw configurations. The process parameter dependence was quantified using the dimensionless powder feed number. Daughter size distributions and survivor pellet shape visualization was used to infer that the breakage mechanism in conveying elements (CE) is primarily edge chipping whereas in distributive mixing elements (DME), breakage is a combination of chipping and crushing. The maximum size of granule that could remain unbroken (3.49 mm for CE and 3.18 mm for DME) was determined by the largest available gap size in the element as measured by an analysis of the screw elements' open volume geometry. Below the maximum size, breakage probability varied inversely with granule strength up to 9 kPa, and directly with the powder feed number. For granules stronger than 9 kPa DYS, breakage characteristics are independent of formulation properties and process conditions, and depend only on screw element geometry. This helps explain why twin screw granulation is more robust with respect to formulation changes compared to high shear wet granulation.

Implications for using the results for both optimizing screw element design and calculating kinetic parameters for population balance modeling are discussed. Preliminary breakage rate process models

were formulated based on the experimental data obtained from the breakage isolating experiments. A modified Weibull breakage kernel was used to fit the breakage probability data for the 3 mm pellet breakage in CEs and 3 mm and 2 mm pellet breakage in DMEs. Consequently, a piecewise breakage probability model as a function of granule size is proposed for conveying and distributive mixing elements. The daughter size distribution data was fitted by using a one parameter power law model for both CEs and DMEs.

The conclusions from the breakage isolating experiments were validated by performing wet granulation experiments using industrially relevant powder formulations. The influence of pharmaceutical formulation characteristics on granule properties formed using CEs and DMEs in twin screw granulation were examined. High and low drug dose formulations with three different active pharmaceutical ingredients (APIs) were considered. The type and concentration of the API in the formulation significantly affected the dry blend particle size distribution and the wet blend dynamic yield strength. However, despite the differences in blend properties, the granule size distributions in DMEs were not significantly affected by the type of API used. The granule size distributions in DMEs were solely functions of the liquid-to-solid ratio and the screw element geometry. However, the granule porosities were observed to be dependent on both the liquid-to-solid ratio and the dynamic yield strength of the blends.

The granule size distributions in CEs were a strong function of the liquid-to-solid ratio, screw element geometry, and material DYS. A CAD geometry analysis of the free volume in the granulator revealed that there is a direct quantitative correlation between the screw geometry and the maximum size and aspect ratio of the granules obtained using conveying elements. Conveying element geometries with different pitch lengths were 3D printed to generate cost-effective prototypes of the designs. Wet granulation experiments were performed using the 3D printed designs to test the hypothesis that the correlation between the granule shape and maximum granule size and the screw element geometry is predictable a priori. The feasibility of 3D printing method for fabricating new screw element designs is examined. Quality-by-Design strategies and scale-up criteria for twin screw granulation are discussed.

The influence of differences in formulation wettability for CEs and DMEs were studied. High drug dose formulations with and without a hydrophobic additive were considered for wet granulation in the two screw geometries. It was observed that the low shear CEs do not cause significant liquid redistribution, and differences in powder wettability are reflected in the granule properties. However, DMEs cause significant granule breakage resulting in efficient liquid redistribution, and no differences were observed in the granule properties for hydrophilic and hydrophobic formulations. These results suggest that breakage mechanisms strongly influence the effect of the raw material properties on the final critical quality attributes of granules.

The work in this dissertation highlights the importance of rate-process specific fundamental experiments and relevance to real powder formulation behavior in twin screw granulation.