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Examining the mechanics of granulation with a hot melt binder in a twin-screw extruder

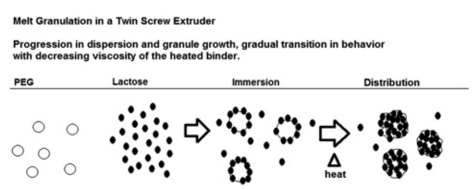
B. Mu, M.R. Thompson*

MMRI/CAPPA-D, Department of Chemical Engineering, McMaster University, Hamilton, ON, Canada L8S 4L7

HIGHLIGHTS

- ► Transitioning binder dispersion mechanism from immersion to distribution.
- ► Granule growth strongly related to screw design and binder concentration.
- ► Narrow residence time distribution indicating limited axial mixing.

GRAPHICAL ABSTRACT



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ABSTRACT

Hot melt granulation involves particle enlargement with a binder that is in its molten state during processing with accompanying solids. Fundamental studies of the technique have been presented for high shear mixers and fluidized bed systems in the literature but with the recent interest in twin screw extrusion machinery by the pharmaceutical industry for continuous granulation, further investigation was necessary to determine if similar mechanisms of wetting and growth were applicable to this new approach. Two different polyethylene glycols were used for the present study as model binders at 10–20% concentrations to melt granulate α-lactose monohydrate in a co-rotating intermeshing twin screw extruder for operating temperatures between 80 °C and 120 °C. Three different screw configurations were tested, primarily composed of conveying elements with an incremental number of kneading blocks included to vary the intensity of mixing as well as the residence time of particulates inside the extruder. Characterization of the granule size, granule strength and binder concentration in the final product was done to determine the mechanism, which appeared to be best described as an Immersion type.

1. Introduction

Hot melt granulation is a specialized form of wet granulation where the binding fluid used for bridging of particles exhibits differing viscosity depending on whether it is currently situated within the process or bound in the final product. Ideally, the binder is in its solid state at room temperature making handling of the final granules relatively simple, yet it softens and flows at an elevated temperature which should not thermally damage the other components in a formulation. The absence of water in the agglomeration process makes this approach quite valuable for moisture-sensitive ingredients as well as avoids the necessity for dryers or lengthy drying times prior to subsequent unit operations like milling during manufacture. The method has received notable attention in the past within processing equipment like high shear mixers and fluidized bed units (Abberger, 2001; Abberger et al., 2002; Kidokoro et al., 2002 , 2003; Knight et al., 1998; Passerini et al., 2010; Schaefer, 2001; Seo et al., 2002; Walker et al., 2006; Zhou et al., 1997). The research group of Schaefer (2001), Schaefer et al. (1992), Schaefer and Mathiesen (1996a, b, c) has provided considerable knowledge to the field with an analysis of processing variables in high shear mixers as well as the proposal of a mechanism for granule formation. Agglomerate nucleation has been described for both high shear mixers and fluidized beds as being initiated by either distribution or immersion mechanisms (or a combination of both). The mechanism that predominates depends on the binder viscosity,

Abbreviations: PEG, polyethylene glycol; DSC, differential scanning calorimeter; RPM, revolutions per minute; RTD, residence time distribution; PSD, particle size distribution

* Corresponding author. Tel.: +1 905 525 9140x23213.
E-mail address: mthomps@mcmaster.ca (M.R. Thompson).

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binder particle size, mechanical forces acting on the granules and the manner which the binder was introduced (i.e., as a solid or already melted) (Abberger et al., 2002; Schaefer, 2001).

Twin-screw extrusion machinery is an emerging platform for granulation, made interesting by its continuous operations, flexibility in user configurations, energy efficiency and consistency in product quality. Two Archimedean-type screws intermeshed side-by-side convey powders and liquids through a confined flow space, ensuring that all segments of the material mixture experience comparable residence time and mechanical action. Depending on the screw design, powders can experience a multitude of flow phenomena that include drag flow, tumbling, axial and/or tangential compression, stretching as well as grinding/chopping which control granule size, shape and porosity (Djuric and Kleinebudde, 2008; Shah, 2005; Thompson and Sun, 2010). Several research studies on wet granulation processes have been presented to describe the influence that variables like screw design, operating variables and formulation can have on product properties (Dhenge et al., 2010; Djuric and Kleinebudde, 2008; Keleb et al., 2002; Thompson and Sun, 2010; Vermeire et al., 2005). However, very little work has been done with hot melt binders despite one of the original functions of the extruder being the processing of molten polymers (Van Melkebeke et al., 2006; Vasanthavada et al., 2011). The flow mechanics and heat transfer within an extruder are significantly different from a high shear mixer or fluidized bed, much more localized and controlled, and so there was interest in determining how the mechanism of granule formation and growth compared.

The present work examines the agglomerate mechanism with hot melt binders in twin screw extrusion machinery. The study examined the influences of variables like screw design, binder content, binder molecular weight and process temperature, so as to investigate the impact of viscous and dispersive forces on granule development.

2. Materials and methods

2.1. Materials

The powder filler used for these trials was α-lactose monohydrate (Meggle Pharma FlowLac® 100; Mutchler Inc., NJ, USA), a spray-dried powder where all particles were less than 250 μm (based on mechanical sieving). The lactose had a measured moisture content of 0.28 wt% (wet basis, determined by a Mettler-Toledo HG63 moisture analyzer). Two relatively low melting polyethylene glycol (PEG) polymers with different molecular weights were used, either 3350 g/mol (PEG 3350; Spectrum Laboratory Products Inc., Gardena, CA) or 8000 g/mol (PEG 8000; EMD Chemical Inc.). The peak melting temperatures (and melting range) of the binders were 62 °C (47–73 °C) and 63 °C (52–73 °C) for PEG 3350 and PEG 8000, respectively as determined by a Q200 differential scanning calorimeter (TA Instruments; New Castle, DE, USA). Moisture content was similarly low for the binders, 0.70% for PEG 3350 and 0.46% for PEG 8000. The original particle sizes of all raw materials used in this study are summarized in Fig. 1. It should be noted that the binder powder was substantially larger in size than the lactose in this study, meaning that interpretations of particle enlargement must consider the PEG used in the formulation not only based on its viscosity but also incoming particle size to the extruder.

2.2. Methods

2.2.1. Hot melt granulation

Hot melt granulation was done in a 27 mm co-rotating intermeshing twin screw extruder (ZSE-27 HP, American Leistritz Extruder Corporation; Somerville, NJ, USA) with no die. To provide

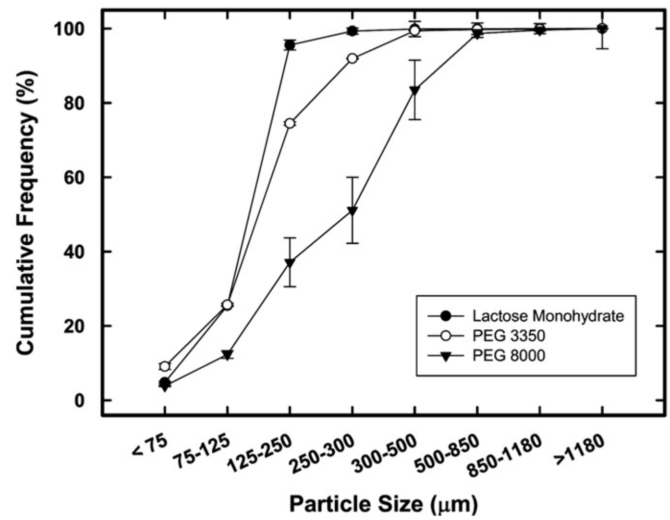

Fig. 1. Cumulative particle size distributions of the as-received materials.

adequate residence time to melt the binder and granulate the product, a barrel length of 40 L/D was used where L is the axial screw length of the machine and D is the inner bore diameter corresponding to one of the screws; the barrel was segregated into ten barrel zone with the first zone (Zone 0) being unheated where all powders were fed. The second zone was constantly set to 50 °C while the remaining eight zones were all heated to the same temperature of either 80 °C, 100 °C or 120 °C, depending on trial conditions. Heating to temperature took less than 20 min though the extruder was left to equilibrate for 60 min in total before trials began. The pre-weighed powders of lactose and PEG were tumble mixed for 5 min before use and then metered into the extruder by a T20 gravimetric feeder from Brabender Technologie (Brampton, ON, Canada). The concentration of binder was varied from 10 wt% to 20 wt% in the experiments. Powder feed rate and screw speed were kept constant at $Q=5$ Kg/h and $N=220$ RPM. The Q/N ratio dictates the degree to which the available volume of the screws were filled by powder and strongly influences both residence time of the process and the compressive/shear stresses applied to granules. Keeping the ratio fixed allowed the authors to interpret the granulation mechanism while minimizing multi-factor interactions. Samples were taken at the open end of the extruder once steady-state was reached for a trial condition, with 300 g batches collected in aluminum trays. Steady state was considered to correspond to an elapsed processing time that was approximately five times the determined mean residence time of a specific screw design when moving between different trial condition and a stable product temperature was confirmed over a span of 1 min before sampling occurred. Forced air cooling by an oscillating fan at 23 °C was used for 5 min to increase cooling of the sample taken in order to maintain agglomerate size without additional coalescence, though this was found to be largely unnecessary due to the rapid cooling rate of the particles based on their size. Samples were store at a relative humidity of $35 \pm 5\%$ RH for at least three days before characterization.

To understand the influence of mixing zones inside the extruder on binder dispersion and particle coalescence, three different screw designs were proposed for the study, as illustrated in Fig. 2. The screw designs were primarily composed of conveying elements of 30 mm and 40 mm pitch to maintain the highest available internal volume through which the powders could flow, minimizing the potential for flow blockage. A mixing zone in this study consisted of two consecutive 60° offset kneading blocks,