TWIN SCREW WET AND DRY GRANULATION

TWIN SCREW WET AND DRY GRANULATION

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LAY ABSTRACT

Granulation is an important process to obtain a particular product known as “granules” which can be an intermediate between powder formulations and medical tablets in pharmaceutical industry. This thesis will further explore this granulation method by looking at screw configuration and the influence of heat from differing sources. Since screws can be configured with different components (screw elements), the study on functions of individual elements made up the first study in this thesis. The first section focused on twin-screw wet granulation where water is added during the process. The second body of work examined why particles were able to grow into granules by discussing the wetting ability of powders which affected by temperature. Because of disadvantages brought out by using water, a novel ‘twin-screw dry granulation’ technique was developed in this thesis using a similar screw configuration to twin-screw hot melt granulation. For this new technique, initial powder materials could be granulated directly without water addition. The last two sections in this thesis cover the new mechanism of granule growth by this technique, studying the influences of material and process parameters in order to provide guidance to the industry on its use and future research needed.

ABSTRACT

Twin screw granulation has gained wide interest by pharmaceutical manufacturing and the industry is still trying to expand its application. This thesis will further explore this technique and try to develop a new granulation strategy based on similar machinery setups.

This thesis is firstly focused on twin screw wet granulation by investigating the function of conveying elements upstream and downstream of the kneading blocks and the wetting behavior of ingredients, with immediate released and controlled released formulations, separately. Granular properties were found to be sensitive to the pitch of downstream conveying elements where larger and irregular shaped particles were found when higher pitch was used. Although these findings are consistent with the theories of granule growth proposed by earlier studies, chunks were prone to be produced when complicated formulations including hydroxypropyl methylcellulose (HPMC) were used but can be surprisingly diminished by higher barrel temperature. This is believed to relate to the wetting behavior of ingredients. Higher temperature was found to reduce water absorption capacity, particularly for HPMC due to the gel layer formation, which is proposed as the dominant bridging mechanism for particle growth at lower temperature. This water uptake as a function of temperature enables process modification to ensure equivalent wetting behavior amongst ingredients for proper particle size control.

Stimulated by the difficulties brought by the water addition as above and the needs from industry, a novel granulation strategy has been developed within a twin screw granulator by heat assistance which is significantly different from dry granulation in a roller compactor or conventional hot melt granulation. In twin screw dry granulation, particle combination is caused by the melting/softening of polymer binders which occurred exclusively in the kneading block driven by the heat generated from frictional, conductive and plastic dissipation. By limiting the heat exposure for formulations, this new method has advantages over hot melt granulation by protecting the ingredients from thermal degradation. For parameters, higher screw speed and lower feed rates enabled more of the feed particles to increase in temperature in the granulation zone and hence develop stronger and larger granules for a given screw pitch. Formulations including a polymer binder with lower molecular weight could be granulated at lower screw speed and binder content by comparing two grades of hydroxypropyl methylcellulose with different molecular weights, AFFINISOL^{TM} HPMC HME 100LV and 4M. In addition, formulations with a higher binder content were likely to granulate under a broader range of operating conditions and ingredients with extremely low coefficients of friction could retard the particle agglomeration by greatly reducing frictional heat generation.

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ABBREVIATIONS

ANDA	Abbreviated New Drug Application
APAP	Acetaminophen
API	Active Pharmaceutical Ingredient
CCEM	Canadian Centre of Electron Microscopy
COF	Internal Coefficient of Friction
CR	Extended/Controlled Release
DSC	Differential Scanning Calorimeter
HME	Hot Melt Extrusion
HMG	Hot Melt Granulation
HPLC	High-Performance Liquid Chromatography
HPMC	Hydroxypropyl Methylcellulose
IR	Immediate Release
L/S	Liquid-Solid Ratio
MADG	Moisture-Activated Dry Granulation
MCC	Microcrystalline Cellulose
MRT	Mean Residence Time
PSD	Particle Size Distribution
PXRD	Powder X-Ray Diffraction
RH	Relative Humidity
RTD	Residence Time Distribution

SEM	Scanning Electron Microscopy
SME	Screw Mixing Elements
T_g	Temperature of Glass Transition
TME	Tooth-Mixing-Elements
TSE	Twin Screw Extrusion
T_t	Transition Temperature

Chapter 1

INTRODUCTION AND OBJECTIVES

1.1 Introduction

The preference for continuous manufacturing in the pharmaceutical industry has encouraged the development of an emerging technology known as twin screw granulation (TSG) which is being extensively studied. Evolved from the machinery setup in the polymer compounding field, the twin screw extruder (TSE) has been used for hot melt granulation (HME) and wet granulation by removing its head die (Shah, 2005). Twin screw wet granulation is a more widely used method than twin screw melt granulation. With the use of water, the former technique enables initial particles to grow under milder

conditions whereas working at elevated temperatures and with molten binder in twin screw melt granulation increases the risk of ingredient damage.

The mechanism for granule growth during twin screw wet granulation has been widely accepted, proposing that the aqueous binder acts as a bridging agent to combine initial particles (Dhenge, Cartwright, Hounslow, & Salman, 2012) but this theory was originated from batch processes (Dhenge et al., 2012; Hapgood, Litster, & Smith, 2003; Litster & Ennis, 2013). Following this mechanism, several studies have focused on the impact of process parameters from different viewpoints such as flow rate (Dhenge, Cartwright, Doughty, Hounslow, & Salman, 2011; Djuric & Kleinebudde, 2010), screw configurations (Djuric & Kleinebudde, 2008; Vercruysse et al., 2015), screw speed (Thompson & Sun, 2010), formulations (El Hagrasy, Hennenkamp, Burke, Cartwright, & Litster, 2013; Saleh, Dhenge, Cartwright, Hounslow, & Salman, 2015; Thompson & O'Donnell, 2015) and wetting method (Thompson, Weatherley, Pukadyil, & Sheskey, 2012). While the irregular dimensions of screw elements and the varied screw configurations used in those studies make it tremendously difficult to conclusively determine the exact behavior of powder or particles along the screws, since barrel still seems like a 'black box' even though windows have been utilized for perspective (Thompson et al., 2012).

Effect of machinery setup on the granulation process has been investigated mostly by focusing on screw configurations (Barrasso, El Hagrasy, Litster, & Ramachandran, 2015; Kumar et al., 2016), while individual elements or the arrangement of adjacent

elements, has been rarely studied by researchers (Dhenge, Washino, Cartwright, Hounslow, & Salman, 2013). A crucial part to their functionality seems related to the redistribute of water and particles within; kneading block being the principal mixers in extrusion seem to have inevitable received the majority of discussions in previous literature. Granular strength is usually decided under the compaction behavior of the kneading block by reducing the available volume and minimizing the capacity of conveying powders. Since the kneading block can be stacked by discs, offset angle of the discs can be investigated as a factor (Djuric & Kleinebudde, 2008), while the effect of the offset angle rely on the fill level of the barrel (Thompson & Sun, 2010). At the same time, the function of the kneading block might interact with the neighbouring elements. More functions of the conveying elements therefore could be explored, instead of merely transporting or shearing the powder bed. This is also helpful to further reveal the profile of granule growth during twin screw wet granulation.

Lactose and microcrystalline cellulose (MCC) are frequently used as excipients for placebo formulations or immediate formulations (Dhenge et al., 2011; Dhenge et al., 2012; Dhenge et al., 2013; El Hagrasy & Litster, 2013; Sayin et al., 2015). These formulations enable granule growth to be simply explained by means of mixing and bridging due to the viscous and capillary forces, which have been widely accepted by regarding the initial particles as solid small balls. Chemical or bonding reaction between water and particles were commonly ignored. However, some preliminary experiments that initiated the work of this thesis indicated that other commonly used ingredients exhibit less predictable interactions with water when used and the granulation process

appears so unstable that chunks were prone to being produced. These chunks can be surprisingly diminished by elevated barrel temperature (Liu, Thompson, O'Donnell, & Grasman, 2016; Sayin et al., 2015). Capillary bridging mechanism seems incapable to explain this phenomenon since liquid bridge is not expected to be so sensitive to the temperature or so strong to produce chunks under higher shear environment within in a twin screw extruder.

Drying after wet granulation can be a time consuming procedure which increases the manufacturing cost, and potentially causes undesirable conversions like granule hardening (Chen, Alli, Igga, & Czeisler, 1990). Granulation with low water content or even without water is often more desirable to avoid these problems caused by high liquid/solid (L/S) ratios. Dry particles combined without water usually rely on their inherent cohesion to hold together when compressed with high pressure, according to dry granulation studies (Bultmann, 2002; Edge, Steele, Chen, Tobyn, & Staniforth, 2000; Salman, Hounslow, & Seville, 2007). Roller compactor and fluidized bed are commonly used for dry granulation. These two strategies are highly restrictive in the formulations and even still the granular product can exhibit insufficient strength because processes sometimes need to compress the powder many times to minimize the ungranulated powder, particularly for a fluidized bed dry granulation method named as pressure swing granulation (Bultmann, 2002; Salman et al., 2007; Shanmugam, 2015; Teng, Qiu, & Wen, 2009).

Hot melt granulation (HMG) is another granulation technology without water addition. For an extruder, the highest pressures are achieved in the kneading block (when no die is present) and yet such pressures are insignificant compared to roller compactor or the fluidized bed, but heat is well controlled and could be used to assist granulation process. As a result, hot melt granulation is commonly practiced in the twin screw extruder but there are no prior examples of dry granulation. Since researchers generally believed that lower temperature minimized drug damage, hot melt granulation sometimes was undesirable for pharmaceutical industry. A twin screw dry granulation would be highly desirable as a third approach though the granulation process is likely to be highly influenced by the properties of the binder.

1.2 Objectives and outline of the work

The discussion above identifies gaps in knowledge for this new field of twin screw granulation. A goal of this thesis was to address some of these gaps by further exploring the mechanism of granule growth for twin screw wet granulation, particularly how temperature affected granulation and that work naturally led to devising an alternative method which did not rely on the presence of water. The work involved the following major objectives:

1. To investigate the function of upstream and downstream conveying elements in wet granulation processes within a twin screw extruder (Liu, Thompson, & O'Donnell, 2015);

2. To examine the effect of temperature on the wetting behavior of hydroxypropyl methylcellulose for twin-screw wet granulation (Liu et al., 2016);
3. To develop a novel granulation method, heat assisted twin screw dry granulation, which capitalizes on the temperature control within the extruder (Liu, Thompson, O'Donnell, & Ali, 2017);
4. To further study the mechanism of twin screw dry granulation by examining the impact of non-binder ingredients and molecular weight of the polymer binder;

1.3 Thesis outline

The thesis is composed of three published papers and one manuscript to be submitted for publication to a refereed journal, constituting the four main chapters. The papers have been composed by the author of this thesis and subsequently approved by the coauthors and modified by following the reviewers' comments. The author conducted all major experiments and all analyses of the results. The work was supervised by Professor Michael Thompson, with technical guidance by Dr. Kevin O'Donnell from the Dow Chemical Company who also kindly helped with the HPLC analysis in latter chapters.

Chapter 1 introduces the motivation for the research and outlines a series of research objectives.

Chapter 2 reviews the literature of previous studies on twin screw wet granulation and briefly reviews dry granulation techniques and twin screw hot melt granulation.

Chapter 3 is a paper by Y. Liu, M.R. Thompson and K.P. O'Donnell published in *Powder Technology*, DOI: 10.1016/j.powtec.2015.07.011 (2015). This paper investigated the influence of conveying elements immediately before and after the kneading block on granulation processes by using a twin screw extruder.

Chapter 4 is a paper by Y. Liu, M.R. Thompson, K.P. O'Donnell and N.S. Grasman published in *Powder Technology*, DOI: 10.1016/j.powtec.2016.08.032 (2016). This paper examined the effect of temperature on the wetting behavior of hydroxypropyl methylcellulose in a twin-screw granulator.

Chapter 5 is a paper by Y. Liu, M.R. Thompson, and K.P. O'Donnell accepted by *AIChE Journal*, DOI: 10.1002/aic.15820 (2017). This paper developed the heat assisted twin screw dry granulation and proposed the basic regime of particle growth for this granulation strategy.

Chapter 6 is a manuscript to be submitted that elucidates the impact of molecular weight of polymer binder and non-binder ingredients on twin screw dry granulation. This granulation method is also compared with the corresponding hot melt granulation to evaluate differences between these two techniques.

Chapter 7 summaries the contributions and concluding remarks for this thesis followed by recommendations for future work.

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Chapter 2

LITERATURE REVIEW

2.1 Twin screw wet granulation

Twin screw wet granulation is a particle agglomeration process conducted in a twin screw extruder where counter-rotating and co-rotating twin screws are usually employed, the latter setup being more commonly reported. This emerging technology exhibits merit as a continuous process over the traditional batch granulation process and has received notable attention in past decades. Numerous studies has been adopted into the research related to: (1) the mechanism of granule growth, (2) characterization of granules, (3) impact of process variables, (4) formulations, and (5) process monitoring methods. Especially in recent years, twin screw wet granulation seems to be more attractive to the researchers in pharmaceutical manufacturing due to updated requirements of the FDA and renewed USP (Parikh, 2009). In most of these studies, understanding the details of particle agglomeration behaviors is preferred. Results from all earlier studies

implied that people are still struggling to seek fundamental theories that can explain and predict the results of granulation for most conditions (Keleb, Vermeire, Vervaet, & Remon, 2004; Thompson, 2015). The extrusion technique was proven as an option for wet granulation of paracetamol (Lindberg, Tufvesson, Holm, & Olbjer, 1988) in the 1980s but then nothing followed until Kleinebudde and Lindner (Kleinebudde & Lindner, 1993) made preliminary studies using materials of lactose and microcrystalline cellulose in 1993. The early studies focused on the general state of the process and differed from current methods due to the inclusion of a die. After 2007, work emerged more frequently focusing on the influence of process variables on the properties of granules and tablets, as well as monitoring method for the granulation process – now with no die attached. In 2012, a new liquid feed method was brought forward by Thompson et al. (Thompson, Weatherley, Pukadyil, & Sheskey, 2012) which brought up more variables to examine for the twin screw wet granulation area. After that, they employed controlled release formulations for the first time and reported ‘‘Rolling’’ phenomenon in the granulation process which is significantly different from results using traditional lactose and microcrystalline cellulose placebo formulations (Thompson & O’Donnell, 2015).

Whereas particle agglomeration principles in twin screw granulation are still not fully understood, an outline of particle growth has been proposed by Tu (Tu, Ingram, & Seville, 2013) and Dhenge (Dhenge, Cartwright, Hounslow, & Salman, 2012b; Dhenge, Washino, Cartwright, Hounslow, & Salman, 2013). The proposed mechanisms originated, in fact, from regime maps developed by Iveson and Litster (Iveson & Litster, 1998) for batch processes using drum or high shear granulators. Wetting and nucleation are widely

accepted as the route for granule growth, while the final enlargement size of particles is a balance of coalescence and breakup. Five states exist when powder is wetted: pendular, funicular, capillary, droplet and pseudo droplet state. By comparison of twin screw granulation and high shear mixer, Lee et al. (Lee, Ingram, & Rowson, 2013) concluded that immersion wetting is the main mechanism in twin screw extruder when binder fed is in a form of water solution. According this theory, a paste-like extrudate forms after the dry powder bed is immersed in a liquid binder, and then breaks up when pushed forward by conveying elements due to shear force. Since liquid-solid ratios of 0.8-1.2 were used in his research, which is surprisingly high compared to the most of other research, this unique situation seems more likely to happen only when high water content is applied. Vercruysse (Jurgen Vercruysse et al., 2014) and Fonteyne (Fonteyne et al., 2014) respectively prove that the bimodal particle size distribution is a result of inherent granulation mechanism by checking the homogenous distribution of binder.

Most of studies have tried to explain particle agglomeration in different independent aspects, while a uniform granule growth theory applicable to a broader range of states awaits development. Various formulations, equipment setup and production methods make a uniform granule growth theory extremely difficult to achieve. This also may be attributed to other factors. For one, most of authors have tried to understand the granule growth mechanism through macroscopic results by changing a few processing parameters, such as: liquid-solid ratio, formulations, screw configuration, screw speed and type of liquid. However, products obtained in these studies all look unique due to the limited conditions being use, let alone most researchers preferred to use modest

formulations to simplify the granular samples preparation. Thus it is no wonder why these theories usually have small ranges of application and hence poor compatibility among them. In addition, all growth theories are derived from traditional batch granulation technology, yet the machinery setup for twin screw wet granulation is highly different from the fluidized or high shear techniques. The free space of powder bed in the barrel for twin screw granulation is notably smaller than that in other granulation process; the shear force of screws is much more complex than that of the blades in high shear granulation. The manner that water is imbibed into the matrix of powder bed, the mechanism of consolidation of the particles and the force history that break up the solid-liquid matrix or lump into small pieces of granules are inevitable concerns when one proposes a mechanism of granule growth for the extruder.

2.2 Impact of process variables

Feed rate, liquid-solid ratio and liquid viscosity, screw configurations and formulation are the most significant factors to the properties of granules. Barrel temperature is another potential factor but researchers are usually cautious to change this variable in case of drug damage. Fonteyne et al. (Fonteyne et al., 2013) solely examined the influence of barrel temperature in a small range from 25 to 40 °C, with the increase in particle size seen at higher temperature explained by the higher lactose solubility in the water.

Feed rate are usually to the fill level within the extruder. High fill level result in high compaction and densification of powder bed, particularly in mixing element zone

such as comb mixer or kneading blocks where free space of particles is limited. Detection of the fill level has been reported in the literature though a post-granulation "screw pullout" technique introduced by Li et al. (H. Li, Thompson, & O'Donnell, 2014) has provided that information. With the screws extracted, the powder state could be directly observed, though the density of the powder bed along the screws was not measured in Li's study. In the same paper, the mean residence time of particles was found to be extended by lower feed rates. Direct assessment of the fill level is hard to obtain, but the impact of the feed rate and screw speed are still reflected by the properties of granular samples. Keleb evaluated the influences of feed rate, screw speed and liquid-solid ratio on the granules and subsequent tablets with a formulation of lactose (Keleb, Vermeire, Vervaet, & Remon, 2002) and concluded that none of these factors were significantly influential on the final product, which is contrast to later conclusions by other authors. Dhenge (Dhenge, Cartwright, Doughty, Hounslow, & Salman, 2011) conversely demonstrated that the density and strength of a granular product will increase with powder feed rate, and Djuric (Djuric, Van Melkebeke, Kleinebudde, Remon, & Vervaet, 2009) similarly found that particle size was increased by higher input rate.

Liquid is another factor investigated by multiple authors for twin screw wet granulation. Some research focused on the interaction between liquid and particles (Jurgen Vercruysse et al., 2014) and some concerned the properties of liquid (Dhenge et al., 2012b; Dhenge et al., 2013). All these authors were trying to discuss this interaction at a mechanism level and can be summarised by the trend that higher liquid content or higher viscosity will cause larger sizes and stronger granules. Compared to the high shear

mixer, a twin screw extruder actually has more shear and compression conditions to make it much more tolerant to the amount of liquid addition or viscosity of binder liquid. Yet, when controlled release formulations were employed by Thompson (Thompson & O'Donnell, 2015) and then followed by Vanhoorne (Vanhoorne et al., 2016), water addition was notably found to be a more critical variable and had to be optimized to avoid lumps being produced. In addition, Thompson et al. (Thompson, Mu, & Sheskey, 2012) examined the aspects of foamed binder addition and found that this liquid feed method allowed the liquid distribution to be more homogeneous by mechanical foaming, making a more robust process to variable changes.

Screw elements are always considered as a crucial parameter for twin screw wet granulation. Djuric assessed the influence of different screw element types on the wet granulation process (Djuric & Kleinebudde, 2008). The impact of screw elements has been investigated with differing formulations. Based on these results, various theories were brought forward by multiple authors (Dhenge, Cartwright, Hounslow, & Salman, 2012a; Djuric et al., 2009) but consistently, non-conveying elements are recognized as crucial components in determining the properties of granules (El Hagrasy & Litster, 2013; Thompson & Sun, 2010). A solid-liquid matrix of formulation is pushed forward at high speed by conveying elements, but delayed by mixing elements such that pressure will subsequently build up. Wet powder is compressed and sheared repeatedly in mixing elements region and thus the particulates and forming liquid bridges are dramatically redistributed. Non-conventional screw elements such as tooth-mixing-elements (TME), screw mixing elements (SME) and cutters were recently studied by Vercruysse (Jurgen

Vercruysse et al., 2015). Both conveying elements and non-conveying element were often examined for their dimensions such as pitch, offset and length. Djuric and Kleinebudde (Djuric & Kleinebudde, 2008) believed that larger particles were found at larger pitch due to the higher volume of screws. Vercruysse et al. (JCDD Vercruysse et al., 2012) found the offset angle of discs in a kneading block had no significant effect on granule size, which is similar to results from Van Melkebeke et al. (Van Melkebeke, Vervaet, & Remon, 2008) who found that angle only reduces oversized agglomerates but otherwise produces not change in the granule properties. Thompson and Sun (Thompson & Sun, 2010) found that properties of granules could be changed by the offset of kneading block, but only at high fill level. This was found again in the studies of Dhenge et al. that the effectiveness of conveying elements and mixing elements often depended on the degree of fill (Dhenge et al., 2011; Dhenge et al., 2010). Simultaneously, screw speed and feed rate will change the residence time distribution and shear stress, which change the mixing behavior and chances of granule breakup. Consequently, each variable change can result in a variety of influences on other factors so that the granule properties are determined by a complicated interaction of variables.

Formulation is essential for granulation, particularly in pharmaceutical industry. Formulation design not only impact the upstream process but also influence the downstream process. Limited by drug release and dry delivery qualities, formulation cannot be configured as freely as other process parameters. Thus, process setting are more commonly adjusted according to the given formulation rather than the reverse. Accordingly, the research on properties of the formulations themselves are instructive to

the material industry. Lactose and microcrystalline cellulose are favourite model excipients to researchers for immediate released formulations.

Changes in formulations can be considered at two scales, macroscopic and microscopic. From the macroscopic perspective, the formulation variables originate from the different excipients or their different ingredient ratios. The vast majority of work to date has been devoted to the formulation study at the macroscopic scale and mostly on immediate released formulations (Dhenge et al., 2011; Dhenge et al., 2012a; Dhenge et al., 2010; Lee, Ingram, & Rowson, 2012; Seem et al., 2015; Thompson, 2015). For example, Rocca et al. (Rocca, Weatherley, Sheskey, & Thompson, 2015) found higher microcrystalline cellulose will decrease the nucleation ratio (mass of nuclei/mass of binder). Thompson and O'Donnell (Thompson & O'Donnell, 2015) were the first to look at controlled released formulations in twin screw wet granulation and proved that different excipients will influence the granule process in many aspects. Particle size distribution, porosity, particle shape and strength of granules produced by control release formulations can be significantly different from that produced by immediate release formulations. Even the mechanism is potentially altered if the hydrophilic content was replaced by a hydrophobic ingredient due to the completely diverse wettability of these two kinds of powders (H. Li, Thompson, & O'Donnell, 2015). Ingredient ratio may also result in increased liquid need and thus creates disadvantage to the downstream process like drying procedure. Meanwhile, lubricating ingredients in the formulation might change the granule fracture strength, as well as the tablet strength due to a decrease in inter-particle friction.

From the microscopic perspective, different formulations do not necessarily mean excipients with different chemical structures, but also can be related to different particle size, particle shape, particle structure or molecular weight. Three formulations with three different grades of lactose were investigated by El Hagrasy et al. (El Hagrasy, Hennenkamp, Burke, Cartwright, & Litster, 2013) and the results showed that the granule growth behaviour displayed was similar. Although microscopic differences existed for the different particles, rare is it that researchers investigate this and it seems impossible for modeling studies to capture due to their complex physicochemical nature.

2.3 Granulation methods

Wet granulation and dry granulation are two main strategies covered in this thesis. Wet granulation is the most utilized granulation method by far for its robustness, even though the industry would rather avoid it for its costs. This traditional agglomeration method has not been eclipsed by the direct compression technology, although new raw materials have emerged over the past decades to make the latter easier. It can be attributed partially to the manufacturing reconstruction costs and habit of the industry (Salman, Hounslow, & Seville, 2007), and to a degree, due to the development of newer wet granulation systems (Thompson, Weatherley, et al., 2012). Wet granulation has high compatibility with the parameter settings and starting powder materials (Faure, York, & Rowe, 2001). In addition, water or other organic liquids can increase the flowability of the powder to make it more processable (Ullah et al., 2009). Better ingredient uniformity is another advantage of wet granulation (Faure et al., 2001). All of these enable wet

granulation to be widely applied and attract intensive research. However, the limits of wet granulation are obvious too when there is a need to process moisture-sensitive drug. Plus, drying is not only a time-consuming process but also leads to higher manufacturing costs (Christensen, Johansen, & Schaefer, 1994). Drying can also lead to "case hardening" during downstream processing (C.-M. Chen, Alli, Igga, & Czeisler, 1990) is a concern for the industry.

Dry granulation, which can include direct compression, is an infrequently considered technology. It has unique advantages over wet granulation for moisture-sensitive active pharmaceutical ingredient (API). And, costs or other downstream processing problems can be minimized by avoiding the drying process which is attractive to the pharmaceutical industry recently. However, the accomplishment of dry granulation relies highly on the properties of the dry powder (Teng, Qiu, & Wen, 2009), so its application is limited by the formulation to a certain extent. More dust and lower drug loading are two often named disadvantages of this technology (Shanmugam, 2015). For the roller compaction system, some of the granules will be recycled for recompression, leading to an increase in granular friability and porosity of the tablet (Bultmann, 2002). On the other hand, the hundreds of cycles under fluidized dry granulation (Salman et al., 2007) are time consumption, which is unfavorable to the pharmaceutical industry. Instead of liquid bridge, adhesion is believed to be the force that combines particles together in the dry granulation process (Bultmann, 2002; Edge, Steele, Chen, Tobyn, & Staniforth, 2000; Salman et al., 2007). Under high pressure, the air in the bulk is compressed out such that the contact area between the particles is increased and the distance among

particles is decreased. In this case, the attractive forces such as Van der Waals, polar and electrostatic are theoretically increased to combine the fine particles together (Bozic & Vrecer, 2008; Q. Li, Rudolph, Weigl, & Earl, 2004). In addition to the adhesion of the particles, the compressibility and the bulk density of the starting materials determine the quality of the product and even granulation feasibility.

To avoid the drying process and yet improve the feasibility of more formulations being granulated, moisture-activated dry granulation (MADG), also known as moist granulation, has been employed. A variant between conventional wet granulation and dry granulation, a very small amount of water (1-4% w/w) (Ullah et al., 2009) is added to activate the binder, followed by the addition of ingredients that naturally act as moisture absorbents. Dry microcrystalline cellulose (MCC) is most commonly used as the absorbent. Due to the moisture absorption of MCC to the extra moisture content the drying procedure is unnecessary for the downstream processing. The disadvantages of this technology is the lack of absorbent choices and low drug loading (Shanmugam, 2015). High shear batch mixers are usually used in this granulation method, which makes MADG not a continuous process.

The other granulation techniques reported in the pharmaceutical industry include melt granulation (Passerini, Albertini, González-Rodríguez, Cavallari, & Rodriguez, 2002; Van Melkebeke, Vermeulen, Vervaet, & Remon, 2006), spray drying (Broadhead, Edmond Rouan, & Rhodes, 1992), freeze granulation (Nyberg, Carlstrom, & Carlsson, 1991), thermal adhesion granulation (Y.-C. Chen, Ho, Chiou, & Sheu, 2014) and steam

granulation (Rodriguez et al., 2002). The latter two technologies are analogous to the MADG, by utilizing the addition of a small amount of granulation liquid. In the thermal adhesion granulation, liquid and solvent are used with the assistance of heat (30-130 °C). In the steam granulation process, a better diffusion coefficient of steam is easier to penetrate a wet matrix and homogeneously distribute into the bulk.

2.4 Polymorphism of ingredients

Many pharmaceutical solids can exist in different physical forms known as polymorphisms, which is not only possible for active pharmaceutical ingredients but also for excipients in formulations. This transition is an additional consideration, particularly for Abbreviated New Drug Application (ANDA) before submitted a drug application to FDA. The scientific identification of pharmaceutical solid polymorphism during processing is therefore critical for those drugs with potential polymorphic transitions.

Usually, polymorphism is taken into consideration when the compound exists in crystalline form, though the amorphous state does not preclude different polymorphic forms. During drug development, the crystalline polymorph with the lowest energy is usually chosen as the API because a polymorph with higher energy can be unstable (metastable) and readily lost. A typical case referred as an example is the HIV protease inhibitor ritonavir (Bauer et al., 2001). The stability between a pair of polymorphs can be categorized as either enantiotropy or monotropic. For an enantiotropy system, the relative stability of a pair of solid forms inverts at a transition temperature (T_t) below its melting point, whereas in a monotropic system, only one polymorph is stable throughout the

temperature range beneath the melting point. In addition to temperature, the polymorph most stable is determined by the processing environment, depending upon variables such as pressure and relative humidity (RH) (Zhang, Law, Schmitt, & Qiu, 2004). Therefore，polymorphs can be inverted in structure by heating, milling or even solvent-mediated processing (Byrn, Pfeiffer, Stephenson, Grant, & Gleason, 1994; Zhang et al., 2004) as demonstrated in Table 1 (Zhang et al., 2004). Bioavailability decreases or side effects may even arise with polymorphic transition. Researchers have found that drug-excipient interactions are also able to cause morph transitions (Airaksinen et al., 2005; Airaksinen et al., 2003; Guo et al., 2011).

Melt granulation is sometimes used by design for preparing amorphous solid dispersions by taking advantage of polymorphic transformation. However, more often polymorphs are formed unintentionally to create different solid phases having differing physical, chemical and mechanical properties such as density, crystal form, melting point and solubility (Guo et al., 2011), and even affect formulation processing. For instance, Yoshinari et al. induced (Yoshinari, Forbes, York, & Kawashima, 2002, 2003) a δ-mannitol form from its supplied β-form to produce a corresponding formulation that was more compactable due to its lower elastic recovery and lower die-wall friction (Burger et al., 2000). In addition, the dehydration of lactose monohydrate was also detected by Weatherley ea al. (Weatherley, Mu, Thompson, Sheskey, & O'Donnell, 2013) in hot melt granulation.

Polymorphism of drug salt could be decisive in pharmacology by altering efficacy and pharmacokinetics through its dissolution behavior. For example, different crystal forms of caffeine were recognized for different particle shape (Mazel et al., 2011) which potentially impacts the drug dissolution rate. During drug processing, polymorphism affects the quality of product. Therefore, polymorphic forms of the active pharmaceutical ingredient (API) are directly related to the control and optimization of process parameters for pharmaceutical manufacturing techniques. Polymorphic transition during granulation has been reported rarely though most research focuses on the result of simply mixing excipients and API, instead of influences of granulation parameters. For example, Guo et al. investigated polymorphic transformations during higher shear wet granulation (Guo et al., 2011); most research on polymorphic transformations are focused on hot melt extrusion (HME) instead of granulation (Liu et al., 2012; Nidhi, Indrajeet, Khushboo, Gauri, & Sen, 2011; Sarode, Sandhu, Shah, Malick, & Zia, 2013).

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Chapter 3

Function of upstream and downstream conveying elements in wet granulation processes within a twin screw extruder

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3.1 Abstract

Understanding the function of individual screw elements in twin screw wet granulation has become an area of intense study but has yet to contemplate the interactions of adjacent elements. The present work examines the influence of conveying

elements around the critical compression zone created by a kneading block. Granulated samples were prepared using nine different screw configurations with flight pitches of 20, 30 and 40 mm and tested at two different degrees of channel fill utilizing a placebo formulation of 20 wt% microcrystalline cellulose in α-lactose monohydrate. Samples were taken directly from the upstream and downstream conveying elements as well as the machine exit and analyzed for particle size, shape, apparent porosity and fracture strength. The results showed that the particle size, shape, and fracture strength of granules produced were significantly influenced by the pitch of downstream conveying elements while upstream conveying elements had no effect on exiting particles. Both zones were found to be insensitive to the degree of fill, though the variance in measurements decreased at higher fill. Similar results were observed when the formulation was adjusted to included 15% ibuprofen (though the ratio of lactose to microcrystalline cellulose remained constant).

3.2 Introduction

In the literature for twin screw granulation, kneading blocks and comb mixing elements are consistently recognized by researchers as providing significant functions in granulation, directly impacting the properties of granules as well as finished tablets [1–5]. For the kneading block, the disc offset angle design can notably increase the breakage of oversized particles while producing granules with lower friability and more spherical shape [1,4,6]. Additionally, the friability and density of produced granules are strongly influenced by the length of a kneading block, i.e. the number of discs in its set. Higher

numbers of discs or thicker discs lead to higher compaction of powders [4,6,7]. While these design features impact granulation and have been well researched, as mentioned above, a fundamental understanding of how screw elements both upstream and downstream of the kneading block impact granule properties does not currently exist. Furthermore, the degree of filling and extent of powder wetting can also contribute to the final granule properties. It is the purpose of this paper to better understand the influence of conveying elements that are normally adjacent to a kneading block.

A conveying element is principally defined by its number of flights and the pitch of those flights. The most common conveying element for co-rotating twin screw extruders is bilobal, meaning that two flights turn around the shaft at an offset of 180 degrees. The flight pitch (p), which refers to the axial distance between two adjacent flights along the length of the screw, is called 'square pitched' when it is equal to the inner diameter of the barrel (D), i.e. $p/D = 1$; the less commonly used term *flight lead* which refers to the axial distance corresponding to one turn of a flight will not be used in this paper. Being square pitched is considered a reference condition by screw designers, even in twin screw machines. A larger pitched conveying element (i.e. $p/D > 1$) has a larger volume that can accommodate more powder under normal starve fed operation; it is commonly used in zones where materials are being fed into the extruder or liquid binder is added. A smaller pitched conveying element (i.e. $p/D < 1$) has a smaller volume and is more readily pressurized; it is often considered to be better suited to push material into fully filled zones like a kneading block. The relevance of flight pitch for a conveying element on wet granulation has been studied for screws without a compression

zone (i.e. kneading block or comb mixing element) [6,8]. In those cases it was found that granule size and flowability were significantly influenced by pitch and flow rate. However, these finding may not extend to zones around a compression screw element like a kneading block. Findings by van Melkebeke and coworkers [4] have noted that conveying elements downstream of a kneading block were required to reduce the fraction of coarse granules (> 1 mm) exiting their process, thereby improving the granule yield. Their results imply a synergistic relationship with respect to the arrangement of screw elements beneficial to the particle size control generally attributed to a kneading block [3] however guidance to screw designers on how to use that understanding for twin screw granulation has not yet been provided.

This article examines the influence of flight pitch on the function of upstream and downstream conveying elements neighboring the compression zone of a screw design for wet granulation. Three values of flight pitch were employed (p/D = 0.67, 1, or 1.33) for the zones before and after the kneading block as well as two different degrees of screw channel fill based on changed flow rate for a fixed screw speed.

3.3 Materials and Methods

3.3.1 Materials

Two formulations were used in this work. The majority of trials utilized a placebo formulation containing 20 wt% microcrystalline cellulose (Avicel PH 101, FMC Biopolymers Corp; Philadelphia, PA) with α-lactose monohydrate (Meggle Pharma Flowlac 100, Mutchler Inc.; Harrington Park, NJ). In a small set of trials, a second

formulation containing 15 wt% ibuprofen USP (Spectrum Chemical; Gardena, CA), 68 wt% lactose monohydrate and 17% microcrystalline cellulose was used. The binder solution consisted of 4% hydroxypropyl methylcellulose (METHOCEL™ E3PLV Cellulose Ethers, The Dow Chemical Company; Midland, MI) in distilled water.

3.3.2 Twin screw granulator

Granular samples using the placebo formulation were prepared by a ZSE-HP 27 mm 40 L/D co-rotating intermeshing twin screw extruder (American Leistritz Extruder Corp.; Sommerville, NJ, USA) with nine different screw configurations. The general screw configuration, which closely resembled the design used in an earlier study of the kneading block [3], is shown as a schematic drawing in Fig. 1. The design consisted of conveying elements spanning the length of barrel zones Z0-Z8 which served the purposes of wetting, nucleation and early granular growth. A 10-disc 60° offset kneading block where its discs were bilobal and 5.6 mm thick. The last half of barrel zone Z8 and barrel zone Z9 show additional conveying elements at the end of the machine. The conveying zones under study and highlighted in the figure were 90 mm in length, placed immediately upstream and downstream of the kneading block and consisted of flight pitches of 20, 30 or 40 mm; note that the 30 mm pitch is considered square pitched for this machine. The length of each conveying zone (i.e. 3 L/D) was chosen such that it was long enough to exert its own influence on granule development yet not so long that the effect could not be reasonably ascribed to the compression taking place within the kneading block. The nine designs corresponded to a full factorial experimental design (3^2)

exploring the three flight pitches for the two zones. All collected samples were referenced in this study based on their 'flight pitch combination', for example '20–40' which denoted granules collected from screws with an upstream pitch of 20 mm and downstream pitch of 40 mm.

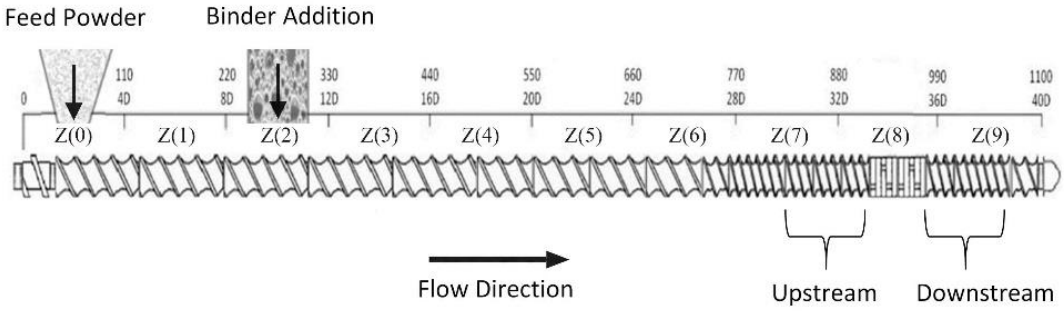

Figure 3-1: Extruder configuration

Each screw configuration was tested at two flow rates, 5 kg/h and 15 kg/h. The premixed powder formulation was fed into the feed zone (Z0) of the extruder by a T-20 gravimetric feeder (Brabender Technologie Ltd.; Mississauga, ON). The binder solution was fed as a foam (85% foam quality, [9]) into the second barrel zone (Z2) by means of a side stuffer. The site of liquid addition was set a considerable distance back from the kneading block in zone Z8 to ensure only uniformly wetted solids were under study; the uniform coloring of the powder by a dye included with the binding liquid was taken as evidence of uniform wetting in the zones of study. The mechanical foam generator was supplied by The Dow Chemical Company (Midland, MI), which consisted of separate liquid metering and gas flow rate controllers. The liquid-to-solids (L/S) ratio of 30% was selected to maximize the yield of particles in a desired size range of 0.5–2 mm. All

experiments were performed at a constant barrel temperature of 35 °C and at a constant screw speed of 300 RPM.

A smaller (2^2) experimental design was conducted with the formulation containing ibuprofen looking at the 20 mm and 40 mm pitch only, and only at 15 kg/h. A L/S = 38% was required to adequately granulate this formulation. This smaller study was completed to gain understanding of how the results would differ for a non-placebo formulation.

3.3.3 Granules collection

Granular samples were directly collected from both the upstream and downstream conveying elements of interest in this study as well as from the extruder exit, after 5 min of stable operations. The *Screw Pullout* method, described in an earlier paper [3], was employed for direct sampling of granular material from these two conveying zones as well as allowed direct observation of the granulation process. To prevent the screws from slowing down gradually, the granulation process was abruptly halted to preserve the state of granules inside. Screw pullouts were repeated 3–4 times for each trial condition to collect a reasonable sample size (~ 5 g) for particle size determination; this sample size showed comparable uncertainty to measurements at the exit of the machine. Samples were air dried at 35% relative humidity for two days and then sealed in bags prior to testing. Final moisture content was less than 1.8% for all samples, based on analysis using a Mettler-Toledo HG63 moisture analyzer.

3.3.4 Particle size analysis

The particle size distribution (PSD) was determined using a Ro-Tap RX-29 sieve shaker (W.S. Tyler Inc., Mentor, OH, USA) with nominal openings of 3350 μm, 2360 μm 1180 μm, 850 μm, 500 μm, 250 μm, 125 μm, as well as a bottom pan. The amount of sample used for PSD characterization was approximately 5 g for the upstream and downstream conveying elements and 100 g for the collected granules at the extruder exit. Each sample was sieved by mechanical agitation for 5 min which was found sufficient to separate granules weakly bound together by drying without influencing the state of granulation produced by the process.

3.3.5 Fracture strength characterization

The characteristic fracture strength of a granule was determined by confined uniaxial compression of a sample initially screened to consist of 1180–2360 μm particles. This fraction of particles involved substantial particle enlargement so it was felt to give proper resolution to the test as well as represents suitable material for tableting of solid oral dosage forms. A small quantity (0.60 g) of sample granules was introduced into an 11.05 mm diameter bore die. The die was closed with a close-fitting piston and then compressed to maximum load of 4200 N at a crosshead speed of 3.5 mm/min using an Instron 3366 benchtop universal mechanical testing system. The uncertainty in the determined fracture strength for exit samples corresponded to three repeats (n = 3). The strength value was calculated according to the equation below and method described by Adams [10]:

$$\ln(P) = \ln\left(\frac{\tau'}{\alpha'}\right) + \alpha'\varepsilon + \ln\left(1 - e^{-\alpha'\varepsilon}\right)$$

where P is the compressive pressure, α' is the lateral stress corrected pressure coefficient, τ' is the charactertic fracture strength of a granule, and ε is the natural strain. At large values of ε (> 20%), a plot of $\ln(P)$ as a function of ε was linear with a slope of α' and an intercept of $\ln(\tau'/\alpha')$, from which τ' was calculated.

3.3.6 Porosity measurement

Granules of 1180–2360 μm size were tested for their apparent porosity. For the large number of samples and their small quantities (at least those collected along the screws), mercury porosimetry was considered unrealistic. A technique known as kerosene displacement [11,12] was used to determine the apparent density of granules using a customized flask with narrow neck (approximate 4 mm of diameter) to improve the accuracy of the measurement. The true density of the sample was determined with a MVP-6 DC Multipycnometer (Quantachrome, Boynton Beach, FL, USA) using high purity nitrogen gas. The amount of sample used for a measurement was approximately 0.2 g. The uncertainty in the determined porosity was based on five repeats (n = 5).

3.3.7 Aspect ratio analysis

The aspect ratios of single granules were evaluated using the image analysis software, ImageJ (Version 1.48, U. S. National Institutes of Health, USA). The ratio was calculated based on the measured major axis over the measured minor axis for nine

particles randomly picked within an image. This number of particles was selected by considering both accuracy and the sample size. Errors for different sample size (generally caused by different collection position). The aspect ratio was calculated for classified sample found on the sieves with openings of 3350 μm, 2360 μm, 1180 μm, 850 μm, 500 μm, 250 μm, and 125 μm. Uncertainty was estimated by repeating one condition of 20-20 at 15 kg/h. The averaged standard deviations of all particle sizes were obtained from three repeats for upstream, downstream and exit zones along the screws separately, since the samples collected in these three zones generally were in different amount. The averaged standard deviations of these three zones are respectively 0.15, 0.28 and 0.32.

3.3.8 Statistical analysis

The significance of each experimental factor to measured responses was tested by Student's t-test (p-value) using the software package, JMP v10.0 (SAS Institute Inc.; Cary, NC). Factors were considered as statistically significant when $P < 0.1$. The significance criteria of 10% was chosen to ensure the model recognized apparent trends but the resolution of the model implied by this criteria reflects the difficulty in collecting sufficient quantities of samples for analysis. As the conclusions of these analyses were reflective of observations from the pharmaceutical industry, there was confidence that the significant criterion was adequate.

3.4 Results and Discussion

The majority of this discussion pertains to the placebo formulation exclusively. Results with the ibuprofen formulation will be highlighted in a specific section near the end of the discussion.

3.4.1 Particle size distribution

The particle size distributions for samples collected in the upstream conveying element, downstream conveying element, and at the exit of the machine are shown in Fig. 2 for both flow rates and all nine screw designs. It can be seen from the distributions that granules in the size range of 850–2360 μm were the main product for both flow rates of 5 kg/h and 15 kg/h with the selected wetting condition of 30% L/S. At 5 kg/h (i.e. lower degree of channel fill), the distributions for the upstream conveying zone were relatively broad and more likely to be mono-modal than downstream. The significant variance in particle size observed between screw configurations, even among those with the same pitch for the upstream zone, indicated considerable process sensitivity occurred before the compression zone at this lower flow rate. The variance is exemplified by plotting the d_{50} values in Fig. 3. At the higher flow rate of 15 kg/h the percent of screw channel volume filled by powder was increased significantly resulting in a reduction in the variance in granule size, as seen within the corresponding plots of both d_{50} and d_{90}/d_{10}values. The reduced variance was not only seen in the upstream conveying zone at 15 kg/h but also in the downstream zone and exit. Upstream of the kneading block, the particle size distributions of collected samples showed a more frequent bimodal

distribution at the higher flow rate than noted for 5 kg/h, while after the kneading block only bimodal distributions were found for both flow rates.

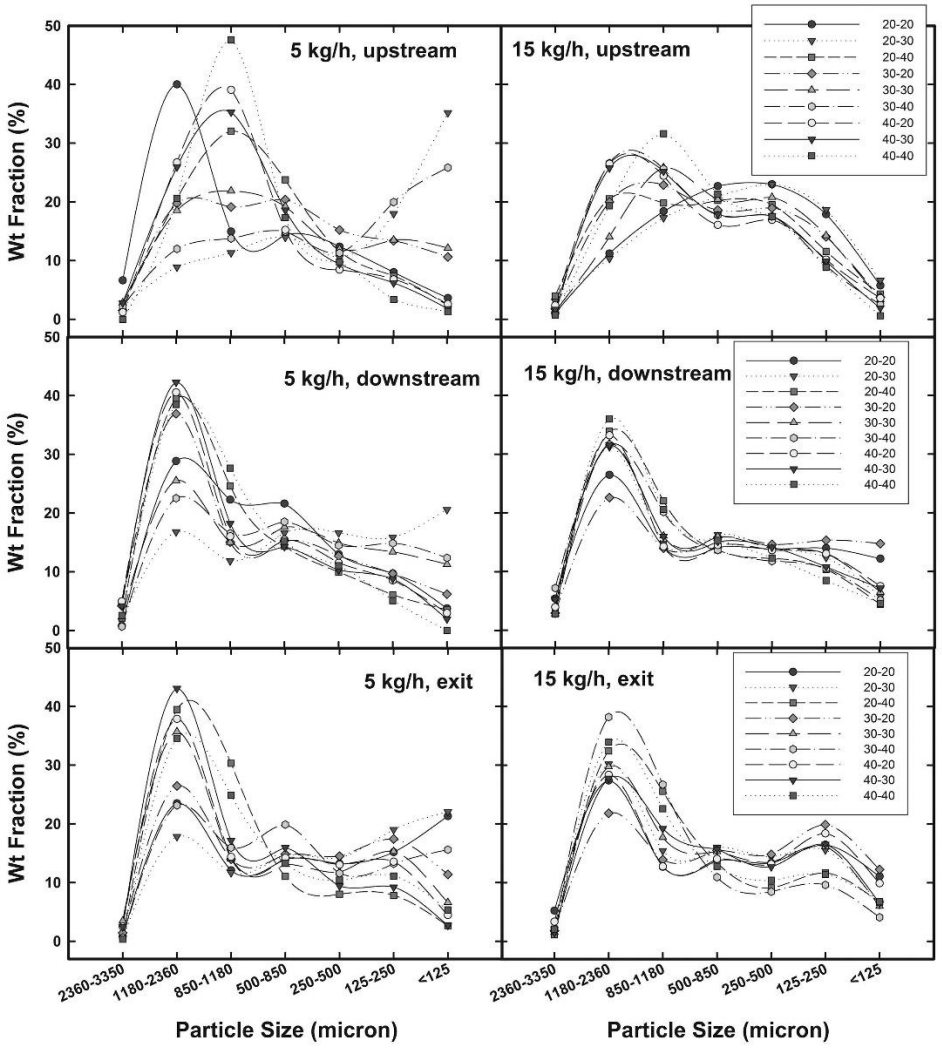

Figure 3-2: Particle size distributions for collected samples from the upstream, downstream and exit zones at both flow rates. Legends show the upstream pitch-downstream pitch for the corresponding screw design.

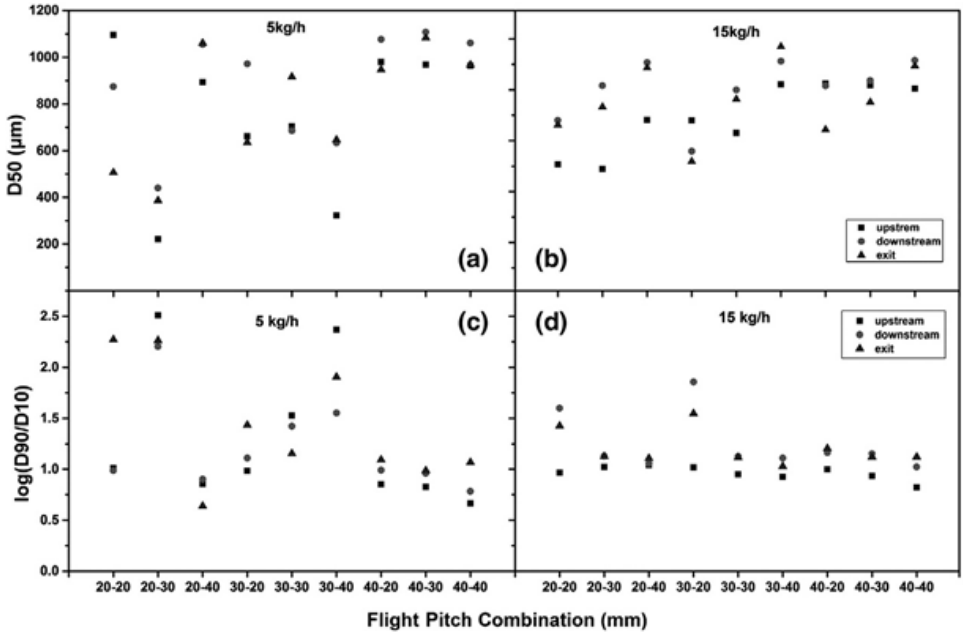

Figure 3-3: Nominal particle size (D_{50}) and corresponding distribution breadth (D_{90}/D_{10}) for the different screw designs (designated by upstream pitch-downstream pitch in mm) based on flow rate and the zone of sample collection.

Analysis of the particle size distributions with respect to the experimental factors for both conveying zones was done by classifying the size fractions into groups containing coarse ($F_{> 1180\ \mu m}$), medium ($F_{500–1180\ \mu m}$) or fine ($F_{< 500\ \mu m}$) particles, with the grouped fractions summarized in Table 1, where F_x is the cumulative weight fraction of particle sizes 'x'. The uncertainty for the measurement was estimated by three repeats (n = 3) corresponding to the 20-20 configuration and found to be 14%, 9% and 8% RSD for the upstream, downstream and exit, respectively. Flow rate was not found to be a significant factor influencing the group fractions in either of the two conveying zones. This was an interesting result as it meant the higher extent of consolidation within and upstream of the kneading block as flow rate increased did not significantly influence the granules present;

the increased state of consolidation mentioned around a kneading block has been visually shown in a previous paper [3]. The downstream flight pitch was not influential on the upstream zone nor was the upstream flight pitch found to influence granule size in the downstream section. The compacted powders inside the kneading block isolated the state of granulation between the two conveying zones. The flight of the upstream conveying element was found to be influential ($P = 0.1$) on the medium size granules found within, which increased in weight fraction as its pitch increased. That flight also exhibited a significant influence on the fines ($P = 0.05$) found upstream, yielding a decreased weight fraction as its pitch increased. In the downstream zone, the flight pitch of the conveying element did not significantly affect the coarse particles or fines of granules found within yet was capable to alter the medium size fraction increased with pitch ($P = 0.1$).

Table 3-1: Particle size classified based on grouped size fractions.

Flow rate	Pitch (mm)	Lumps (%)	Yield (%)	Fines (%)	Lumps (%)	Yield (%)	Fines (%)	Lumps (%)	Yield (%)	Fines (%)
5 kg/h	20-20	47	29	24	30	44	26	24	26	50
	20-30	11	25	64	18	28	53	18	26	55
	20-40	23	56	21	42	39	19	40	41	18
	30-20	21	40	39	41	30	29	28	29	43
	30-30	21	41	38	28	33	40	39	27	34
	30-40	14	29	57	23	35	42	24	36	40
	40-20	28	54	18	46	31	23	40	29	31
	40-30	29	54	17	46	32	21	46	33	21
	40-40	21	65	14	41	43	16	35	38	27
15 kg/h	20-20	12	41	47	32	28	40	33	27	41
	20-30	13	38	48	37	31	32	32	31	36
	20-40	24	40	35	37	36	27	34	39	27

30-20	22	41	37	26	30	45	24	29	47
30-30	15	46	38	35	32	33	31	33	36
30-40	27	43	29	39	34	27	40	38	22
40-20	29	41	31	37	29	34	32	27	41
40-30	27	43	29	37	31	32	29	35	36
40-40	20	53	27	39	36	25	36	35	29

Analysis of samples exiting the machine showed the cumulative effect of the full screw design on granulation and presented samples from a location in the process commonly reported in the literature (i.e. few studies have collected granules directly from within the screws). The pitch of the downstream conveying element was the only significant factor found to correlate with the particle size of the exiting granules and only for the medium fraction ($P = 0.002$) and fines ($P = 0.01$). A higher pitch increased the medium fraction and decreased the fines content. Despite the high content of coarse particles in the exit samples, no significance was found for its variation that could be attributed to the factors under study. This could be a formulation specific finding as previous studies with MCC/lactose systems (different weight ratios) have shown these two materials together to exhibit a self-regulating nature where growth and attrition occurred simultaneously in conveying elements and the compressive forces of a kneading block have only minor influence on size compared to those granules entering that screw element [13]; the blend ratio selected is not unusual for industrial granulation and was to be consistent with granulation studies by other groups in the literature [1,2]. Analyzing the responses of d_{50} and d_{90}/d_{10} for exiting granules found that nominal size was significantly affected by the downstream flight pitch ($P = 0.07$) while the distribution breadth, as represented by

d_{90}/d_{10}, was only affected by the upstream flight pitch (P = 0.1). A larger d_{90}/d_{10}corresponded to using a smaller pitched upstream conveying flight.

3.4.2 Aspect ratio

Due to an observable variance in the particle shape among the collected samples, particle size analysis alone was insufficient to characterize the influence of flight pitch on granulation. Fig. 4 plots the aspect ratio of selected particles showing its variation among the different screw configurations for granules found on a 14 Mesh screen (i.e. 1180 μm openings). The plotted error bars in the figure represent the deviation in aspect ratio found among particles on the screen for an indicated sample. Analyzing the extent that this deviation in aspect ratio varied among all size fractions for a sample showed that it was negatively influenced by flow rate ($P < 0.05$), deviating to a smaller degree at higher flow rate, which appears consistent with the observation that particle size was also less variable at the higher flow rate condition. In the upstream zone, the deviation increased with upstream flight pitch ($P = 0.0006$) whereas in the downstream zone and exit, it increased with downstream flight pitch ($P < 0.08$). The variance in granule shape was always largest for conveying elements with a 40 mm pitch ($p/D = 1.33$). The concerns being brought forth with this analysis of aspect ratio deviation and the previously noted variance in particle size were that the factors of pitch and flow rate affected not only granule properties but should also be recognized as influencing process stability.

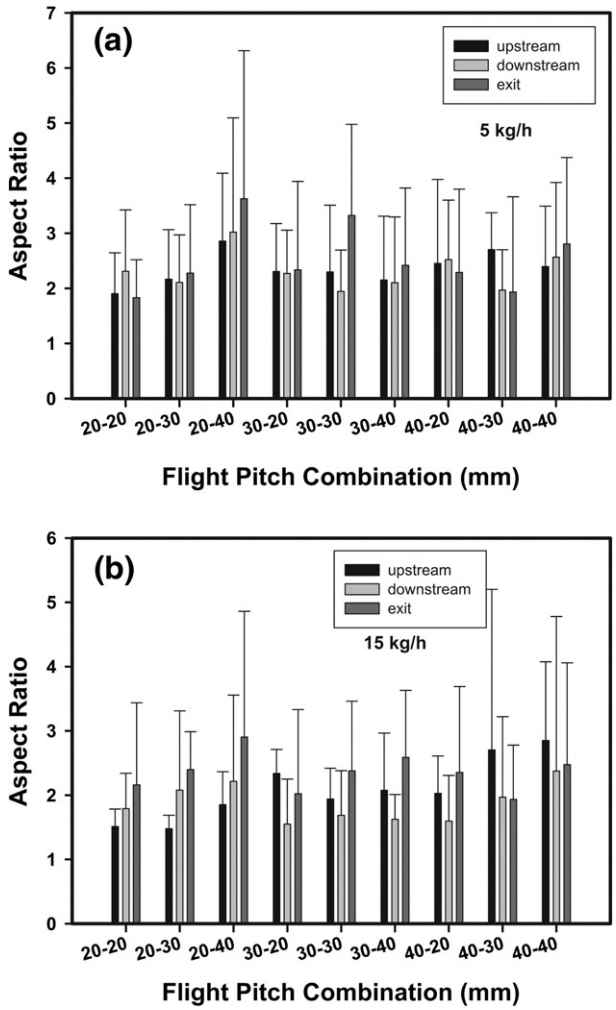

Figure 3-4: Variation in aspect ratio (major axis/minor axis) for the different screw designs (designated by upstream pitch-downstream pitch in mm) based on flow rate and the zone of sample collection.

Statistical analysis found that the nominal aspect ratio corresponded in a positive linear manner with particle size. The shape of fines in both conveying zones as well as the machine exit were unaffected by the studied factors, largely due to the fact that these

granules consisted of too few primary particles to deviate significantly from a near spherical shape (1.67 ± 0.14). In the upstream zone, the larger size particles (both coarse and medium fractions) showed an increase in aspect ratio with increasing upstream flight pitch and decreasing flow rate ($P < 0.01$ for both factors); the maximum aspect ratio reached was 3.04 at 5 kg/h and 2.85 at 15 kg/h. The downstream flight pitch had no influence upstream, as noted with particle size. For the downstream zone, the influential factors on aspect ratio differed based on the size fraction. The shape of coarse particles was only influenced by flow rate ($P = 0.05$), decreasing in ratio as flow rate increased. Conversely, increasing the downstream flight pitch created granules with higher aspect ratio ($P = 0.05$) for the medium size group yet flow rate had no significant effect on this group. The upstream flight pitch had no influence on the shape of particles in the downstream zone. Interestingly, the maximum aspect ratio reached in the downstream zone was 3.01 at 5 kg/h and 2.82 at 15 kg/h, quite similar in value to the upstream zone though these specific measurements corresponded now to samples found for different screw designs.

At the exit of the machine, increasing the downstream flight pitch produced a significant increase in the aspect ratio of all granules ($P < 0.03$) whereas flow rate was only noted to have a significant negative impact ($P = 0.008$) on the medium size fraction. The maximum aspect ratio found across all conditions for exiting particles was 3.32 at 5 kg/h and 2.90 at 15 kg/h showing that attrition following the kneading block did little to improve the sphericity of the granular product. The upstream flight pitch had no discernable influence on the aspect ratio of exiting granules though a significant two-way

interaction was found between the upstream and downstream pitch (P = 0.09). Images of the granule shape at the machine exit are shown in Fig. 5 for the two flow rates as evidence of the observed sphericity. Although the aspect ratio between the two flow rates were not radically different, the granules produced at a higher flow rate always appeared more spherical.

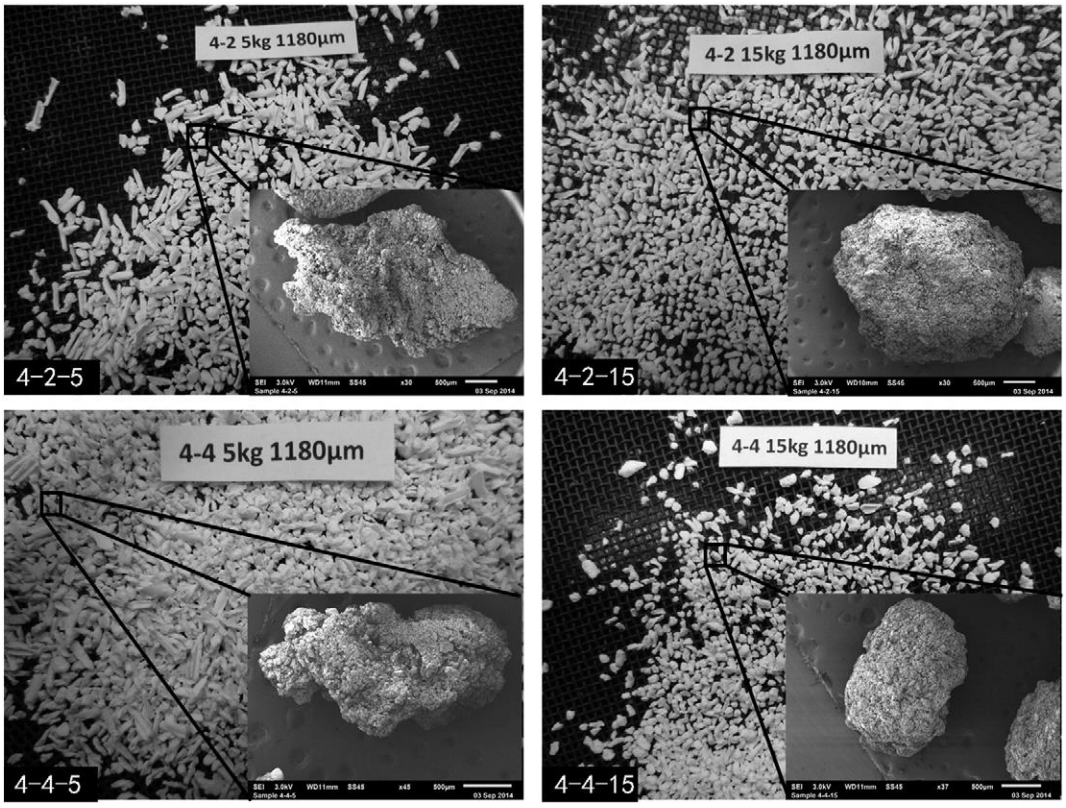

Figure 3-5: SEM micrographs superimposed on images of the sieve with 1180 µm opening, showing the characteristic particle morphology of samples collected at the exit for flow rates of 5 kg/h and 15 kg/h. Results corresponded to screw designs with 40-20 and 40-40 conveying element configurations.

3.4.3 Porosity and granule fracture strength

The size and shape of granules were found to be similar between the upstream and downstream zones, and the factors influencing these variables responded similarly. However, other studies in the literature that focused on the kneading block have reported the internal structure of granules (and their corresponding strength) to be strongly dependent on whether or not the wetted solids has passed through a compression-type screw element [1-4]. Consequently, the apparent porosity and granule fracture strength was determined for the sieved size fraction of 1180–2360 μm of collected granules sampled from the upstream, downstream and exit zones, as plotted in Fig. 6 ; Fig. 7, respectively. The uncertainty reported for upstream and downstream fracture strength was estimated by repeated measurements for the exiting granules (n = 3) as there was insufficient material collected within the screws to conduct their own repeated tests.

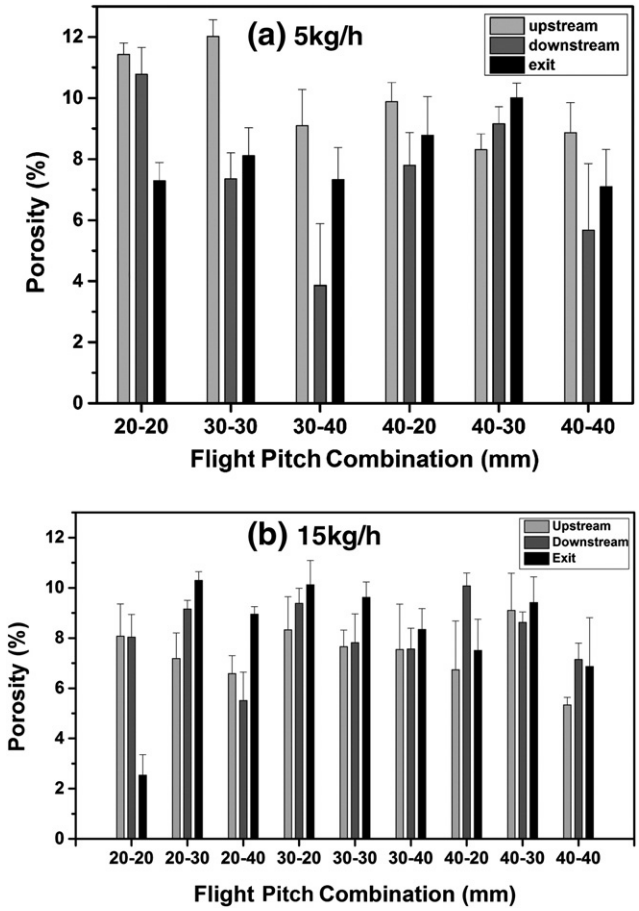

Figure 3-6: Apparent porosity for samples from the different screw designs (designated by upstream pitch-downstream pitch in mm) based on flow rate and the zone of sample collection.

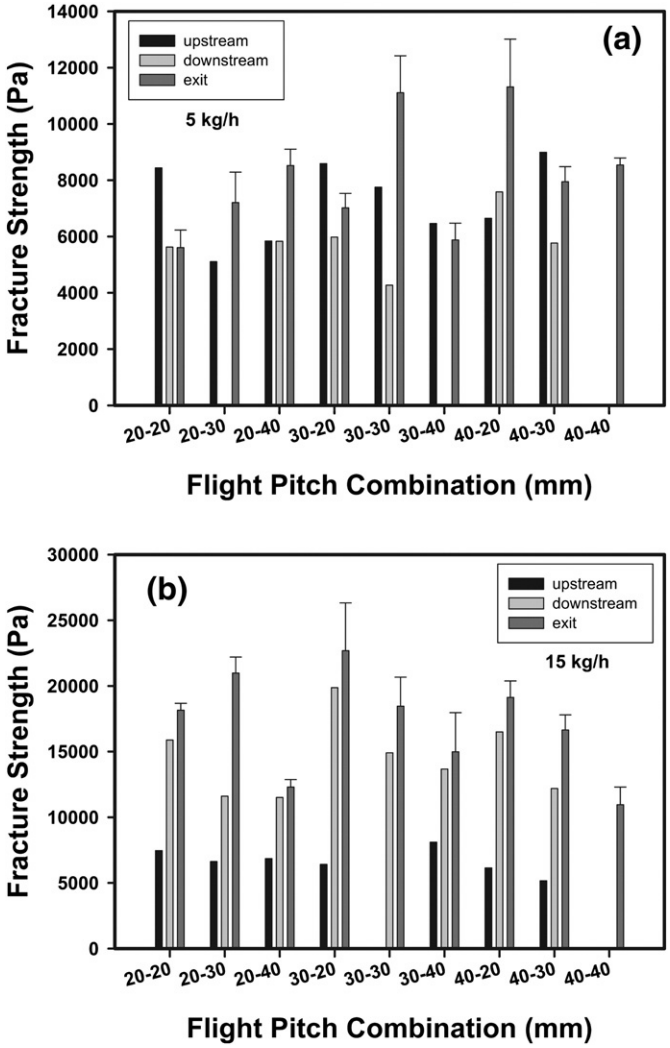

Figure 3-7: Characteristic fracture strength for samples from the different screw designs (designated by upstream pitch-downstream pitch in mm) based on flow rate and the zone of sample collection.

The apparent porosity measurements in Fig. 6 did not include values for the configurations of 20-30, 20-40, or 30-20 at 5 kg/h as those samples lacked sufficient granule content in the tested size range (i.e. < 0.1 g in each case) to be considered reliable

for testing. The apparent porosity of the granules collected from upstream, downstream and exit zones ranged from 6% ~ 11%; a low value presumably based on the high wettability by kerosene, indicating that this method of measurement was limited to resolving differences only among the fine pore structures of these particles. The intra-granular porosity appeared notably higher in the upstream zone at 5 kg/h compared to 15 kg/h, though this trend was difficult to observe among the plotted data. Statistical analysis of the results for apparent porosity in the downstream zone found that the pitch of the downstream conveying flight was significant ($P = 0.006$) but not flow rate; porosity decreased with a higher p/D in the downstream zone. For the upstream zone, the apparent porosity decreased with increased flow rate ($P = 0.005$) with no notable dependency on pitch. No factor influence was noted for porosity of the exiting particles.

The results for granule fracture strength, shown in Fig. 7, gave different indications of the significant factors compared to the apparent porosity measurement. Significant differences were seen between 5 kg/h and 15 kg/h in the displayed results of granule strength in spite of some missing data. The strength of the granules from the exit and downstream zone of the extruder showed a strong correlation with flow rate ($P < 0.002$) and the downstream flight pitch ($P < 0.09$), with no effect by upstream pitch in either case. Fracture strength increased with flow rate (as low as 5.2 MPa at 5 kg/h to as high as 22.7 MPa at 15 kg/h) and smaller p/D. The strength of granules in the upstream zone showed no dependency on flow rate or flight pitch, with a narrow range of values from 5 MPa to 9 MPa.

3.4.4 Influence of formulation

To examine the applicability of the results above to a non-placebo system, a formulation with 15 wt% ibuprofen was tested at 15 kg/h and only considered two pitches, 20 mm and 40 mm, for the upstream and downstream conveying elements. All other operational variables were kept the same. The particle size distributions from the exit gave consistent results to those with the placebo formulation. A higher downstream pitch yielded fewer fines and more medium sized particles, except now the coarse size fraction showed the same significant increase as the medium size fraction. The fines content varied from 36% (20-20) to 14% (20-40), and from 32% (40-20) to 12% (40-40). Correspondingly, the coarse content varied from 25% (20-20) to 53% (20-40) and from 30% (40-20) to 55% (40-40); the bracketed values refer to the pitch before and after the kneading block in each case. There was no significant influence found by the upstream pitch on the particle size of these granules. The intra-granular porosities ranged from 6% to 11% for all three zones. Similar to the placebo case, porosity decreased for exiting samples with higher downstream pitch. However, apparent porosity decreased with smaller upstream pitch and, unlike with the placebo, this case was a stronger effect. In both cases, the influence of pitch on porosity was minor. Fracture strength varied between 7.5 MPa (40-20) to 11 MPa (20-20, 20-40 and 40-40) for the exit collection, with no evident trend.

3.5 General Discussion

Conceptually, the upstream and downstream conveying zones identified in this study exhibit different mechanisms regarding granulation, as discussed below. The kneading block between them has been shown from the results above to effectively isolate the influences of these two zones from each other. This alone was a positive finding as it meant a formulator could approach the design of these zones independently in regards to their desired effect on granulation.

The loosely consolidated, wet solids found in the upstream zone of the screws has been well described by discrete particle simulations [8] to be a result of collision-dominated agglomeration due to the complex velocity profile present in conveying elements. Until a kneading block is encountered in the flow path, this will be the expected mechanism of granulation. The binder distribution varies considerably among different particle sizes in such conveying zones but never becomes homogenous [14], which was likely a key contributor to the lower fracture strengths measured upstream. For formulations containing MCC, granule growth is notably rapid in the extruder [13], accounting for the substantial coarse fraction already present in the upstream zone. The nominal particle size was generally smaller in this zone than after the kneading block. The 3 L/D conveying element appeared sufficiently long to produce differences in granulation such that increasing the flight pitch increased the content of medium sized granules though doing so had no effect on the interstitial structure which constituted the strength and porosity of the granules. The higher content of large particles found in this

zone of the screws with a greater pitch indicated that aggregate growth increased in correspondence with higher particle velocity. Increasing the flight pitch of a conveying element increases the velocity (U) of solids being conveyed forward, i.e. U = pN where N is the rotational speed of the screw in rev/s [15]. The images in Fig. 8 of the filled screw sections at 15 kg/h reflect the state of granulation around the kneading section. Compared to the upstream conveying element with 20 mm pitch, the solids in the 40 mm pitch element in the images appeared to have a dramatically longer zone of consolidated mass prior to the kneading block (approximately 40 mm long for a 40 mm pitch vs 20 mm long for a 20 mm pitch). This was also seen at 5 kg/h but to a less obvious degree, as shown in Fig. 9 (approximately 20 mm long for a 40 mm pitch vs no perceivable consolidation for a 20 mm pitch). The limited capacity to grow coarse particles was attributed to the relatively low L/S ratio used for the selected fillers. The absent influence of such acceleration on porosity was not without reason when considering the extent of granule growth that occurs for formulations with MCC early along the screws [13]; only relatively large granules were agglomerating by this zone of the screw. The porosity of these granules would therefore have been defined further upstream of the zone of interest. Increasing flow will increase the degree of fill by powders in the conveying zone yet in the present case, not to a sufficient degree to change the agglomeration mechanics (for either conveying zone). More solids in the conveying element only served to reduce the size and shape variation seen in the granules sampled from the zone. That variability increased when flow rate was low and flight pitch was increased due to the relatively

reduced frequency of collisions (despite the higher velocity) in a wider channel (i.e. $W = p \bullet \cos\theta$, where W is the channel width and θ is the helix angle of the flight).

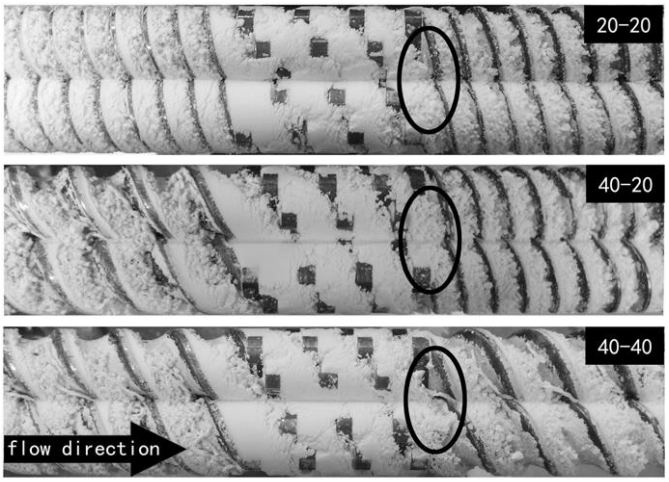

Figure 3-8: Screw pull-outs for three screw configurations showing the granulation progress along the screws in the region of the kneading block at 15 kg/h. Circle highlights exiting particles from the kneading block. Screw configurations shown were 20-20 (top), 40-20 (middle), and 40-40 (bottom) referring to the upstream pitch-downstream pitch arrangement.

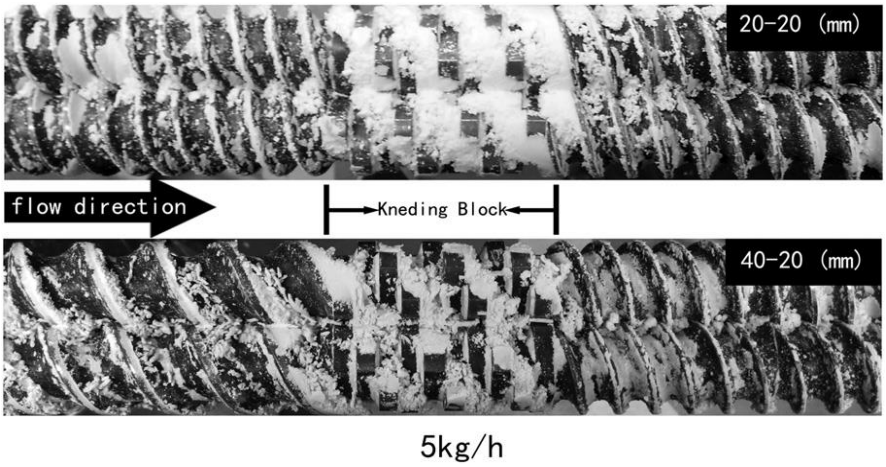

Figure 3-9: Screw pull-outs for two screw configurations showing the granulation progress along the screws in the region of the kneading block at 5 kg/h. Screw configurations shown were 20-20 (top) and 40-20 (bottom) referring to the upstream pitch-downstream pitch arrangement.

The downstream conveying element after a kneading block has been noted to influence the size of particles exiting the process without altering their porosity [4]. The literature has recognized the downstream zone as contributing to the fragmentation of compacted solids exiting the last set of discs of a kneading block [1-3,16] though the relevance of pitch until now had not been considered. It is evident from the present results that a larger pitched conveying element downstream allowed for a greater number of large particles (medium group in the case of this formulation) and more elongated particles to be present. Considering the compacted solids exiting the kneading block were being extruded towards the flight of this downstream conveying element, increasing the angle of that obstructing planar wall must reduce the chances (and energy) of impact. These larger, irregular shaped particles may therefore be a closer representation of the

attrition produced by the kneading block alone. Considerably larger granules are seen in both Fig. 8 ; Fig. 9 downstream of the kneading block. Porosity and fracture strength decreased in the zone with a higher p/D element (for both formulations), which is seemingly a contradiction but perhaps this is not the case. Uneven intragranular porosity of each individual granule makes the unmeasurable pores in the granules fluctuate the granule strength.

The results at the end of the extruder represent the combined influence of the two conveying zones (along with all other screw elements). Only the conveying element downstream of the kneading block seemed to significantly influence the particle size, aspect ratio and fracture strength for product exiting the machine. The test with the more hydrophobic formulation containing ibuprofen did not significantly alter this conclusion. The resulting material exhibited larger granules with a higher aspect ratio for the larger pitched conveying elements downstream. Correspondingly, the larger granules may exhibit lower fracture strength; formulation appeared to influence whether porosity and fracture strength will respond to the flight pitch. These findings point out that formulators may wish to select a flight pitch closer to p/D = 1 to balance size and strength in their produced granules.

As flow rate has reported significant influence on granule size and porosity in the literature [3, 6,9,17,18], its negligible effect on the results of this study may be attributed to the formulation but may also be related to the fact that the selected factor levels were insufficiently different to note change. It is not believed that flow rate can, in general, be

disregarded as a factor affecting granulation. However, this work has demonstrated that process consistency is related to flow rate (i.e. the degree of channel fill) and that higher flow rates should be selected to reduce granule property variance.

3.6 Conclusions

This study has examined the influence of conveying elements around the kneading section of a twin-screw granulation process for a formulation consisting of lactose and microcrystalline cellulose, in some cases with the inclusion of ibuprofen. The results have led to recommendations concerning the selection of screw elements that hopefully represent general rules of design, though future work is necessary to understand the scope of these results. Conveying elements downstream of a kneading block should be selected appropriately, recognizing their significance in altering the powder state in the screw channels as well as the final product in twin screw wet granulation. Higher downstream pitch increased the content of medium sized particles and their aspect ratio in the final samples, while decreasing granule porosity fracture strength in the downstream zone. Higher flow rate was found helpful to strengthen the granular structure and decrease the irregularity of the granules. The upstream conveying elements had no interaction with the kneading block or influence on the finished sample.

Acknowledgements

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Chapter 4

Effect of Temperature on the Wetting Behavior of Hydroxypropyl Methylcellulose in a Twin-Screw Granulator

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4.1 Abstract

Temperature has rarely been examined in twin-screw wet granulation despite the obvious capabilities of the extruder for operating at elevated temperatures. The present

work investigates the wetting behavior of a mixture of powders with different sorption characteristics at various temperatures to explain the unique granulation behavior witnessed with high molecular weight hydroxypropyl methylcellulose in a twin-screw extruder. The work studies the twin-screw granulation of a controlled release formulation at three different temperatures, namely 30 °C, 55 °C and 80 °C and attempts to interpret the granular properties of collected samples relative to characterized moisture sorption isotherms measured for the individual ingredients as well as the mixtures. A result of higher temperature processing was reduced coarse particles and a final product with more spherical granules. Increasing temperature was found to reduce water absorption capacity among the ingredients, especially hydroxypropyl methyl cellulose and microcrystalline cellulose, leaving more of the added water for particle bridging. The gel layer of hydroxypropyl methyl cellulose particles was diminished by the higher temperatures which did not appear to impact the strength of the particle bridges formed. Inclusion of a more hydrophobic ingredient like acetaminophen complicates the distribution of water in a granule.

4.2 Introduction

Parameters that affect twin-screw wet granulation (TSWG) have been widely investigated, including the process configuration [1-3], properties of feed materials [4], and wetting methods [5]. Both machinery configuration and formulation selection have the capacity to alter particle size, particle shape and other granular characteristics in this continuous process. As summarized in a recent review, these studies have more favorably

focused on immediate-release formulations to guarantee that the granulation process would be more controllable [6]. Those formulations, primarily based on lactose monohydrate and microcrystalline cellulose, were helpful in simplifying the wetting conditions of the experiment so as to concentrate on non-formulation specific factors related to granule growth and stabilization mechanisms within the extruder. Consequently, TSWG has received very little attention in the literature with controlled released formulations intended for solid oral dosage forms [7]. These complex powder systems respond very differently to wetting and hence need deeper study to ensure the TSWG process is properly understood.

Preliminary work by the authors leading up the present study had revealed some unique behavior with a formulation including hydroxypropyl methylcellulose (HPMC) as an extended release agent, which demanded more detailed investigation. Working without an active pharmaceutical ingredient, a suitable liquid-to-solids (L/S) ratio was found with the formulation to produce desired granules in the 0.5–2 mm range. However, the introduction of as little as 10 wt% acetaminophen resulted in a loss of control and large chunks even though the drug load did not seem challenging for a sustained release formulation. This conflicted with the results of recent research where metoprolol tartrate was used as a model drug and the researchers successfully obtained granular samples of normal size with different controlled release formulations [8]. Although the difficulties in granulation caused by adding acetaminophen were partly relieved at lower L/S ratios, noodle-like granules with high aspect ratio were found in all samples collected, which radically decreased the quality of the granular product; these noodle-like granules were

highlighted recently as undesirable agglomerates resulting from a rolling mechanism at the screw flight-barrel interface with the use of adhesive polymeric binders like high molecular weight HPMC or copovidone [7]. The difficulties of controlling granule size with HPMC have also been noted in batch studies, where higher molecular weight leads to larger final granules on account of a higher viscosity bridge being formed between particles [9, 10]. The influence of the confined shear environments in a twin-screw granulator on granulation with HPMC has not received adequate attention, though some studies looking at HPMCs under TSWG are emerging [7, 8, 11]. The problems of granule growth with the HPMC formulation were solved by a re-designed screw previously [7] whereas this paper looked at a different approach. The issue proved to be more effectively resolved by increasing the temperature of the extruder instead of seeking a new screw design or a narrow range of useful L/S ratios.

To date, insufficient work has been done to understand the influence of temperature on TSWG, partly because heat is generally believed to be harmful to active pharmaceutical ingredients. Temperature has only been studied as a processing factor for the TSWG by Fonteyne et al. [12], who attributed the observed increase in granule size at elevated temperature conditions to stronger liquid bridge formation due to the enhanced solubility of lactose. This present work attempts to further understand the effects of temperature as an operational variable on the wetting mechanism of TSWG.

This paper examines the temperature dependent wetting characteristics of a heterogeneous mixture of ingredients, demonstrating differing water sorption

characteristics, which has received little attention in the literature. The work performs dynamic moisture sorption testing and a simple compression test of the starting powders at temperatures from 30 to 80 °C, and relates these modeled wetting behaviors to the characterization of final granular samples produced by twin-screw granulation. Inclusion of acetaminophen was done to perturb the stability of the process.

4.3 Materials and Methods

4.3.1. Materials

The model active pharmaceutical ingredient (API) used in the study was acetaminophen (APAP) (Spectrum Chemical; Gardena, CA) to provide a hydrophobic ingredient; the API was considered stable for the temperature range used in this study due to its high melting point of 169 °C and its shown stability in hot melt granulation studies [8] at much higher temperatures than 80 °C. The excipients were Flowlac® 100 spray-dried α-lactose monohydrate (Meggle Pharma, Germany), Avicel® PH101 microcrystalline cellulose (FMC Biopolymer; Newark, NJ), METHOCEL™[1] K4M PREMIUM CR hydroxypropyl methylcellulose (The Dow Chemical Company; Midland, MI) and magnesium stearate (Sigma Aldrich; Mississauga, ON). METHOCEL™ K4M has a USP 2208 classification for its degree of substitution, noted high molecular weight, and a cloud point of 61.7 °C [9]. The binding liquid in this work consisted of a 4% hydroxypropyl methylcellulose (METHOCEL™ E3PLV, The Dow Chemical Company; Midland, MI) dissolved in distilled water.

4.3.2 Twin-screw granulator

Wet granulation was performed in a ZSE-HP 27 mm 40 L/D co-rotating intermeshing twin-screw extruder (American Leistritz Extrusion Corp.; Somerville, NJ). Fig. 1 shows the screw configuration and general setup of the extruder. The screws mainly consisted of conveying elements with a non-conveying compression section made up of a 5-disc 60° offset kneading block (bilobal discs with a thickness of 5.6 mm) followed by a comb mixing element in zone Z(8) (which is one zone away from the exit). The non-conveying zone was followed by a 20 mm pitch conveying element to improve granule breakup [13]. Granulation proceeded at a screw speed of 200 rpm.

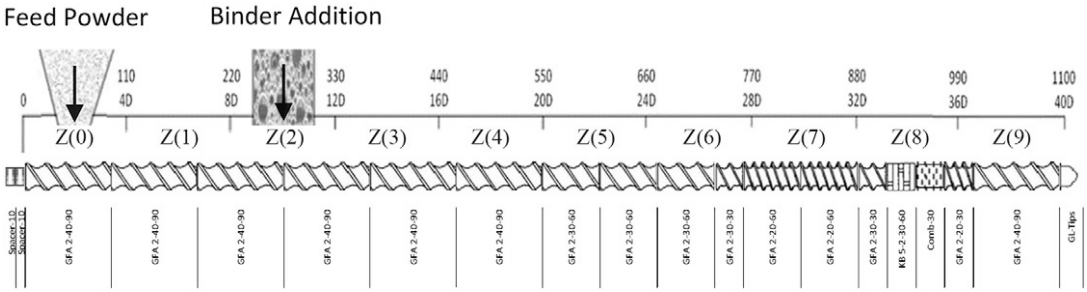

Figure 4-1: Configuration of the twin-screw granulator along with its screw design.

The premixed formulation was added into the feed zone, zone Z(0), of the extruder by a T-20 gravimetric feeder (Brabender Technologie Ltd., Mississauga, ON) at a flow rate of 5 kg/h. Red colored binder liquid was delivered as a semi-rigid foam (85% foam quality) into the twin-screw extruder by a side stuffer. The foam was prepared by a continuous foam generator, as described in a previous study [5].

4.3.3 Granulation Trials

Details of the formulations are given in Table 1. An extended release (CR) formulation with and without API was compared against an immediate release (IR) formulation with API for twin-screw granulation. Since the IR formulation was included to aid in identifying the effect of HPMC on wetting, a formulation without API was not considered necessary; information on the TSWG of an 80%/20% mixture of lactose monohydrate and MCC is readily available in the literature from the authors as well as other research groups for reference [4]. A Mettler-Toledo HG63 moisture analyzer using an isothermal heating profile at 105 °C determined initial moisture contents of the feed powders.

Table 4-1: Ingredients and details of tested formulations.

Ingredient	**Particle size (μm)**	**Moisture content (%)**	**CR Formulation with API/wt%**	**CR Formulation without API/wt%**	**IR Formulation with API/wt%**
α-lactose monohydrate	125	2.32	47.6	52.9	77.6
Microcrystalline cellulose (MCC)	50	6.89	11.9	13.2	11.9
Acetaminophen (APAP)	75	0.69	10		10
Hydroxypropyl methylcellulose (K4M)	100	7.60	30	33.3	
Magnesium stearate (MgSt)	15		0.5	0.6	0.5

Three barrel temperatures (30 °C, 55 °C, 80 °C) and five L/S ratio (6%, 9.6%, 12%, 18%, 24% (w/w)) made up an 2 × 3 × 5 experimental design with two CR formulations. Every barrel zone was set to the same temperature except the feed zone that was chilled to 10 °C. Different L/S ratios were necessary for the IR formulation but they also had to differ based on the selected temperature in order to produce collectable samples for analysis (30%, 36%, and 42% L/S ratios for 30 °C and 55 °C separately; 18%, 24%, and 30% L/S ratios for 80 °C). Each sample was referenced according to level of each factor varied. For instance, '30–12%-CD' refers to a sample produced at 30 °C barrel temperature, 12% L/S ratio, with the CR formulation including drug (D). The suffix 'ID' in 55–36%-ID refers to IR formulation with drug. Conversely, the CR formulation without drug is denoted by only the suffix '-C′, for example 30–6%-C. Uncertainty in the experiments was estimated by three repeats of the trial conditions for 80–24%-CD.

4.3.4 Residence time distribution

The exit-age residence time distribution (RTD) was measured in a similar manner to previous work [2, 14] by adding 0.6 g cocoa powder as a pseudo Dirac pulse. Three repeats (n = 3) of cocoa addition enabled an uncertainty estimate for this measurement. Images were extracted from the video and analyzed for their color intensity using Photoshop CS4 (Ver 11.04, Adobe System Inc.; San Jose, CA). The results were fitted to a common curve function for the twin-screw extruder which is referred as a Zusatz distribution [15], shown as:

$$E(t) = at^{-c-1}b^{c+1}exp[(b^c t^{-c} - 1)(\frac{-c-1}{c})] \quad (1)$$

Where *t* is time, 'a' relates to the peak height, 'b' is the residence time at peak height and 'c' is a fitted parameter related to the peak breadth but lacks any direct physical interpretation. The model fitting was completed in Originlab (Version 9.0; OriginLab Corporation, MA)

4.3.5 Moisture absorption isotherms

Moisture absorption rates of different formulation ingredients were measured in the presence of humidified air to characterize their capability for water uptake. The initial water content values of the ingredients were consistent with the condition of the fed formulations into the twin-screw granulator. In the test, neat powder was held in a customized round dish with 10 cm diameter and 2 mm depth, to offer adequate surface area to the humid air. A rod was carefully drawn along the top of the dish to produce a flat surface, attempting to minimize consolidation. Then the dish was exposed to a controlled environment where the relative humidity (RH) and temperature had been pre-equilibrated. The conditions inside the customized chamber were controlled by an external humidifier and built-in digital temperature controller; a thermocouple sensor located inside the chamber was used to measure air temperature. Dishes were removed periodically followed by weighing with a precision balance. The moisture absorption test was done at 95% ± 0.7% RH and three temperatures (30 °C, 55 °C and 80 °C). Pure APAP, α-lactose monohydrate, MCC and HPMC, as well as the two CR formulations (with and without API) were tested under each experimental condition. To ensure the

accuracy of the experiment, all six samples were placed into the chamber at the same time at each condition. Reported data are averaged values based on three repeats (n = 3).

The progression of moisture absorption was modeled by fitting the results to an empirical model known as the Parallel Exponential Kinetics (PEK) model [16, 17] which has been successfully applied to various cellulosic textile materials [18]. The model describes two stages (fast and slow) of dynamic moisture absorption or desorption with the following equation:

$$M_t = M_{1\infty}(1\text{-}e^{-t/\tau 1}) + M_{2\infty}(1\text{-}e^{-t/\tau 2}) \quad (2)$$

where M_t is the water content at time t and the terms $M_{1\infty}$ and $M_{2\infty}$ are the water contents associated with the fast and slow processes once the equilibrium state is reached; τ^1 and τ^2 are characteristic times for the fast and slow stages, respectively. The fast and slow stages of water sorption are considered to reflect the state of contacting water, either being initially chemically associated with the dry particles (sometimes referred to as bound water) or subsequently freely associated (i.e. free water), respectively [19]. The sorption kinetics consists of two exponential terms that refer to the fast $M_{1\infty}(1 - e^{-} t/\tau^1)$ and slow $M_{2\infty}(1 - e^{-} t/\tau^2)$ water uptake processes for the characteristic times of τ^1 and τ^2, respectively. The experimental data of dynamic moisture content at each time was curve-fitted and the parameters of $M_{1\infty}$, $M_{2\infty}$, τ^1 and τ^2 were obtained from the fitting results. The rates of the two processes are expressed as $R_1 = M_t/\tau^1$ where $t = \tau 1$ and $R_2 = M_t/\tau^2$ where $t = \tau^2$ for the fast and slow stages, respectively.

4.3.6 Thermal analysis of the water state

Around 10 mg samples from the moisture absorption test (Sec. 2.5) were subsequently analyzed in an open DSC aluminum pan for their thermal properties in order to estimate the ratio of bound water to free water in the wet powders. By assuming that only free water in the wet mass could freeze at 0 °C, the water state was determined by a differential scanning calorimeter (DSC) at a heating rate of 10 °C min^{-1} from − 30 °C to 120 °C. The approach is based on the predictably lower freezing point of bound water which should show no transition in this analysis [20, 21]. By assuming that the specific enthalpy of fusion for water is a known constant (333.55 J/g) [22] during in the DSC, the amount of free water can be calculated from integration of heat flow from − 15 °C to 10 °C.

A similar method was also used to determine the bound water and free water content of the wet mass at different L/S ratios comparable to the extrusion trials. Wet mass was manually prepared at room temperature by mixing the blended powder and distilled water homogeneously according to each L/S ratio. These mixtures were sealed in a container and vigorously shaken for several minutes before being given 3 days to equilibrate at room temperature. The DSC measurement was done after the sample had been allowed to equilibrate.

4.3.7 Compression test

The amount of free water that could be extracted by mechanical force was investigated. Wet masses of differing L/S ratio were manually prepared three days in advance, similar to the DSC test, before being compressed at different temperatures. This is meaningful for the redistribution of the water during the granulation, especially in a kneading block section which is recognized to be a significant element for the re-distribution of liquid during processing [2, 11, 23]. Wet powder samples were prepared similarly to the wet sample with added L/S ratio in DSC analysis and then were prepared as small round films of 20 mm diameter and 1 mm thickness. After weighing, the specimen was sandwiched by two sheets of 100 mesh stainless steel wire screening. Whatman cellulose filter paper was affixed to the exteriors of both wire screens forming a five-layer sandwich structure intended to quantify the amount of sorbed water that could be mechanically extracted by compression. The sandwiched sample was compressed in a Carver benchtop hot press with 23 cm × 23 cm platens (Carver Inc.; Wabash, IN) at 2 MPa, which is similar to the recorded pressure in the kneading block during granulation [2]. The duration of compression was 3 s, which is close to the estimated mean residence time in kneading blocks.

4.3.8 Particle size analysis

The particle size distribution (PSD) of a sample taken from the twin-screw granulator was determined by a Ro-Tap RX-29 sieve shaker (W.S. Tyler Inc., Mentor, OH, USA) with a series of sieves openings of 3350 μm, 2360 μm 1180 μm, 850 μm,

500 μm, 250 μm and 125 μm, as well as a bottom pan. A 100 g granular sample was sieved by mechanical agitation for 5 min. Uncertainty was estimated by repeats (n = 3) of sample collected for the condition of 80–24%-CD.

4.3.9 Fracture strength characterization

The granule fracture strength of samples taken from the twin-screw granulator was determined following the Adams method, as described in a previous study [13]. Before fracture testing, all samples were pre-dried for 3 days at 85 °C and 20% RH to eliminate the capillary forces between particles and hence the true strength of internal solid bridges of granules are measured. A 0.6 g granular sample corresponding to the 1180–2360 μm size fraction was uniaxially compressed to a maximum load of 4200 N at a crosshead speed of 3.5 mm/min and its bulk fracture strength determined from the stress-strain curve; the size fraction selected corresponded to the most frequent fraction of produced granules within the desired size range, which was considered as a representative measure of granule strength from the granulation trials. The presented fracture strength corresponded to the average value of three repeats (n = 3).

4.3.10 Porosity measurement

A technique known as kerosene displacement [24, 25] was employed to define the apparent density of granules within the size range of 1180–2360 μm. A customized flask with narrow neck (4 mm) was utilized to increase the resolution of the measurement. To minimize the interference of penetration into relative large pores in these granules during the displacement measurement, a sample needed to be pre-saturated in kerosene for 1 h.

After draining the kerosene from the granules over an additional hour, the granules were re-saturated into the kerosene and then the displacement volume was determined; the method is an improvement upon our previous work [13]. The true density of the dry granular sample was determined with a MVP-6 DC Multipycnometer (Quantachrome, Boynton Beach, FL) using ultrahigh purity nitrogen gas. The amount of sample used for a measurement was approximately 0.2 g. The uncertainty in the determined porosity was determined by five repeats (n = 5).

4.3.11 Aspect ratio

Based on photographs of particles in the size range of 1180–2360 μm while still in the sieve, the aspect ratios of granules were evaluated using image analysis software, ImageJ (Version 1.48, U. S. National Institutes of Health, USA). The average ratio was calculated based on the ratio of the measured major axis over minor axis for 25 particles randomly picked within an image; this number of particles corresponded to an image magnification where the particle edge was readily visible in the software for manual measurement. The uncertainty is based on three repeats (n = 3) of an image.

4.3.12 Statistical analysis

The significance of experimental factors to the responses of particle size, aspect ratio and fracture strength was evaluated using software Minitab v17 (Minitab, Inc., State College, PA). A factor was considered significant having a P-value < 0.05.

4.3.13 Dissolution test

In vitro drug release profiles of prepared tablets were obtained following the United States Pharmacopeia 〈711〉 dissolution test (Apparatus II) at 100 rpm and 37 °C in 900 mL phosphate-buffered saline (PBS, pH 7.3 ± 0.05). Tablets were prepared with a thickness of 5 mm ± 0.5 mm and 11 mm diameter. Aliquots (3 mL) were withdrawn periodically from the vessel at 1, 2, 3, 4, 5, 6 and 24 h after immersing the tablet. An additional sample was also collected from final release solution when the tablet totally collapsed by dramatically increasing the agitation speed from 100 rpm to 300 rpm. Drug concentration from each sample was determined using ultraviolet-visible spectrophotometer (DU® 800 Spectrophotometer, Beckman Coulter, Mississauga, ON) based on calibration data at 241 nm. The percentage of drug release was determined related to the final sample. Dissolution test were repeated three times (n = 3) to assess the uncertainty in the measurement.

4.4 Results and Discussion

According to reported results in the literature, the interactions between water and controlled release agents are significantly different from immediate release agents [26]. Unlike immediate release agents that either exhibit high solubility or no barrier to diffusion in aqueous solutions, diffusion-controlling polymers that provide an extended duration for active ingredient release, will swell or erode to form a semi-permeable barrier. Researchers have identified the mobility of constrained water in HPMC to be subject to pH and temperature [28, 29]. Temperature, being a readily adjustable parameter

in an extruder and far more controllable than pH in a low hydrated solid, appeared as the more suitable variable of control in TSWG for overcoming wetting problems with this ingredient. To understand the initial dispersion of water upon wetting of dry powders in a twin-screw granulation process and attempt to understand the effect of temperature therein, the first characterization was to understand the water sorption characteristics of the individual ingredients in comparison to mixed formulations.

4.4.1 Moisture sorption characteristics

These tests characterized the water sorption capacity of different powders, including the API, and estimated whether the water had been absorbed or adsorbed based on the PEK model; liquid bridging in granulation is more often reliant upon surface water and so the state of water was important to understand in this study. Since HPMC will gel in the presence of water forming a viscous layer that prevents deeper penetration [29], use of water vapor rather than liquid was preferred for the characterization. Admittedly, humidified air will have a higher molecular mobility than liquid in the solids making our determined rates higher than likely seen in the extruder, but comparatively among the tested ingredients the trends will be reflective of how water distributes during granulation and thus provide better assurances using vapor that the findings are related to a homogenous response.

Moisture sorption behavior of the individual ingredients and the two CR formulations at 95% ± 0.7% RH is shown in Fig. 2 presenting their moisture contents over time relative to their initial moisture contents. At 30 °C, the K4M powder had the

highest absorption capacity based on moisture content at any moment in time; the maximum reached content of 41% corresponds closely to the onset point after which free water formation should occur for K4M (i.e. 45%, [30]). The sorption capacities of APAP and α-lactose monohydrate were the lowest among the tested powders. The equilibrium moisture content of MCC was comparable to the 16% (w/w) reported elsewhere at 95% RH [31] whereas for the other ingredients, no comparisons could be found in the literature. According to DSC analysis (data not shown), the amount of free water in APAP humidified at 30 °C was high (based on a strong endotherm found at 0 °C), even though the data in Fig. 2 show that its total water uptake was small; no thermal transitions for free water were observed at 0 °C in the thermograms of the other ingredients. This suggests that water sorption for APAP resulted in almost exclusively free water. The mixed powder formulations with and without API showed similar sorption capacities to each other as well as to MCC. The moisture sorption capacities appeared to decrease in Fig. 2 for all ingredients as temperature increased; the negative values presented at elevated temperatures are a result of using the initial water content as the datum but it was felt this manner of reporting provided clearer trends. At 55 °C, APAP started to show a preferential loss of its initial water content whereas the other ingredients still showed evidence of water uptake. α-Lactose monohydrate showed the least change in relative water content compared to data at 30 °C among the ingredients. By 80 °C, all materials were predominantly displaying desorption where the initial water content of each ingredient (in reference to Table 1) decreased to near zero over 65 h. Such desorption at 80 °C is seen in the extruder as well, where the controlled release formulation without

API and no additional liquids had a reported loss of 10 wt% corresponding to the residual moisture evaporating.

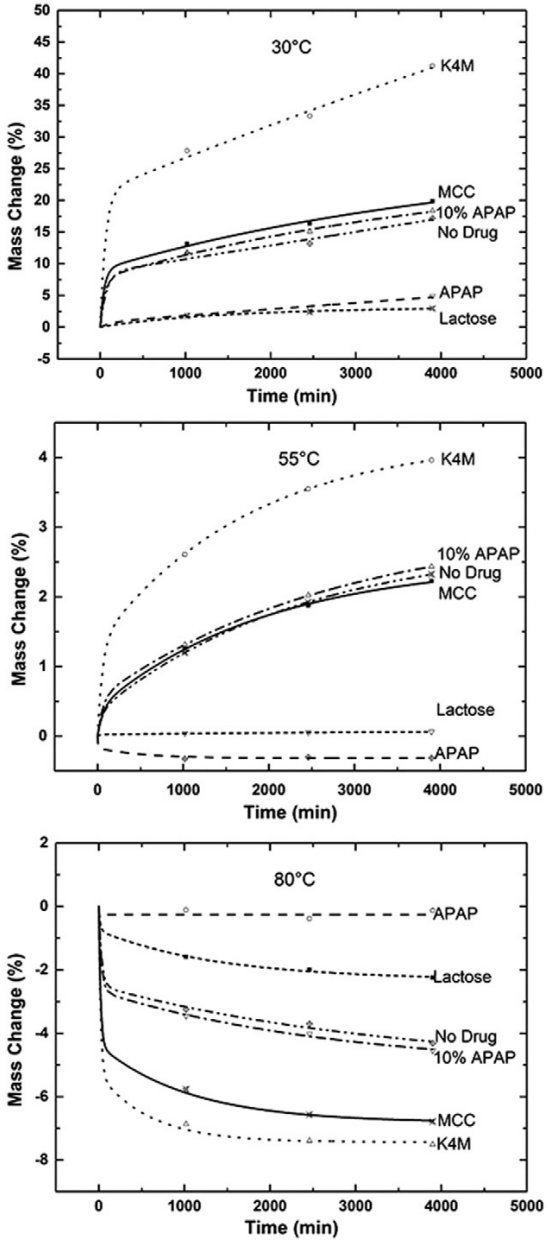

Figure 4-2: Fitting results of PEK model for the moisture sorption process at three different temperatures (30 °C, 55 °C, 80 °C). Plots show the fitting qualities between the experiment data and PEK model.

The analysis of sorption kinetics focused on the fast stage of the PEK model since it more closely reflects phenomena on the timescale of the twin-screw granulator (approximately 40 s according to the RTD analysis in Section 3.4) and has been noted as referring to the bound water in solids [31]; the timescale of the fast stage was typically in the order of minutes while the timescale of the slow stage was in the order of days. The fitted results for 30 °C (given in Table 2) show the fast stage sorption rate constants for APAP and α-lactose monohydrate were 2.93×10^{-3} and 0.88×10^{-3} min^{-1}, respectively which were significantly lower than the other ingredients. APAP and lactose also exhibited the longest characteristic times, and lowest M_1 values. K4M gained moisture at the highest average sorption rate during the fast stage with a constant of 0.131 min^{-1} and had the highest equilibrium absorbent amount, M_1. The rate for MCC was less than HPMC (0.075 min^{-1}) but its characteristic time τ^1 was shorter at 46.08 min which can be attributed to its large known specific surface area (1.2 m^2/g; [32]). The two CR formulations exhibited rates and M_1 values closer to MCC yet their characteristic times were close to both K4M and MCC; K4M and MCC showed dominant behavior within the mixtures even though lactose was the main component. The inclusion of APAP in the CR formulation increased its sorption rate and slightly reduced its characteristic time; both behaviors were predicted based on a weighted summation of the sorption characteristics of all ingredients. By increasing the system temperature to 55 °C, all equilibrium absorbent amounts of M_1 decreased for the fast stage but APAP was the only ingredient to show no sorption behavior. In fact, APAP showed only desorption of its initial moisture at this temperature. Lactose showed a significant drop in its characteristic time (down to

25.6 min from 1242 min) which is possibly due to its increased solubility at this temperature, but its sorption rate and equilibrium absorption amount were still substantially less than K4M and MCC. Water sorption capacity of K4M decreased dramatically as a result of the elevated temperature, going from *M1* = 21.35% at 30 °C to 1.32% at 55 °C but remained the highest among the ingredients. K4M and MCC shared equivalent characteristic times and not surprisingly, based on their dominance, the two CR formulations equally shared this characteristic time. Inclusion of APAP in the formulation produced a larger M_1 than without the drug present, opposite to the behavior seen at 30 °C though its sorption rate was now more comparable (4.79×10^{-3} min^{-1} with 10% APAP vs. 3.21×10^{-3} min^{-1} with no drug). Upon reaching 80 °C, evaporation of water became the primary mechanism in the fast stage, as noted by the negative equilibrium absorbent values in the table. The water sorption kinetics of K4M more closely resembled MCC at this temperature than at lower temperatures. The two CR formulations also displayed identical sorption kinetics at 80 °C.

Table 4-2: Fitting results of moisture sorption at 95% RH.

Mat.	T [°C]	Fast stage			Slow stage			Adj. R^2
		M^*_1/%	τ1 [min]	R_1 [x1000·min^{-1}]	M^*_2 [%]	τ2 –[min]	R_2 [x1000·min^{-1}]	
Lactose	30	2.58	$1.24x10^3$	0.88	5.77	$1.34x10^5$	0.00	0.977
	55	$2.00x10^{-2}$	25.6	0.39	0.07	$5.11x10^3$	0.01	0.993
	80	-0.77	17.5	-17.55	-1.54	$1.41x10^3$	-0.01	0.996
MCC	30	9.08	46.1	75.43	18.29	$4.51x10^3$	1.71	0.950
	55	0.40	60.1	3.54	2.10	$1.98x10^3$	0.39	0.999
	80	-4.37	21.1	-70.84	-2.45	$1.06x10^3$	-0.85	0.991
APAP	30	0.82	$1.57x10^2$	2.93	1.74	$9.29x10^3$	0.00	0.971
	55	-0.17	4.7	-18.05	-0.15	$5.50x10^2$	-0.09	0.955
	80	-0.13	$8.00x10^{-3}$	-33.06	-0.13	0.1	0.00	0.986
K4M	30	21.35	62.8	131.31	45.47	$2.09x10^3$	4.58	0.977

	55	1.32	56.9	10.52	2.97	$1.77x10^3$	0.62	0.982
	80	-5.28	22.3	-90.73	-2.15	$6.02x10^2$	-0.005	0.995
10% APAP	30	7.71	52.5	59.98	17.69	$4.32x10^3$	1.66	0.994
	55	0.54	59.7	4.79	2.51	$2.79x10^3$	0.33	0.997
	80	-2.67	31.4	-32.38	-2.46	$2.86x10^3$	-0.32	0.995
No Drug	30	8.58	72.3	47.06	21.75	$5.60x10^3$	2.15	0.998
	55	0.34	51.9	3.21	2.45	$2.37x10^3$	0.38	0.985
	80	-2.50	32.1	-30.21	-2.59	$3.41x10^3$	-0.28	0.976

*: relative to the initial water content

The slow stage of the PEK model is thought to refer to sorption characteristics that take longer to increase water content in solids and is sometimes related to the presence of free water [1]. As mentioned above, the DSC thermograms indicate no free water was present under these humid conditions, with the exception of APAP at 30 ^oC, so the results pertain to extrapolated behaviors. The trends discussed for fast stage seemed to equally apply to the slow stage though lactose now performed much closer in water sorption behavior to MCC and K4M.

4.4.2 Thermal analysis of water content

DSC thermograms of the wetted granular samples produced at 30 °C for different L/S ratios in the twin-screw granulator, are shown in Fig. 3; thermograms for samples produced at 55 °C and 80 °C are not shown as they included no transitions near 0 °C under any L/S condition. The endothermic peak near 0 °C seen in the figure corresponds to the free water content in the ingredients capable of solidification, whereas the second broad peak seen in the thermograms at higher temperatures corresponded to the vaporization of water. The included tables in the figure show the calculated free water content by this method for the two CR formulations. Free water was apparent in both

formulations for L/S > 12%; a moisture content of 12–14% was the maximum reached in the moisture sorption kinetics confirming our assertions that no free water was present in those tests. The formulation with APAP showed a higher free water content than that in the CR formulation without APAP for an equivalent L/S ratio; this is understandable based on the moisture sorption data which shows the formulation with APAP absorbs less of the available water leaving more at the surface of particles. The difference was most obvious at the highest L/S ratio of 24%, where the free water content was 12.32% for the CR formulation with APAP in comparison to 5.45% for the CR formulation without APAP.

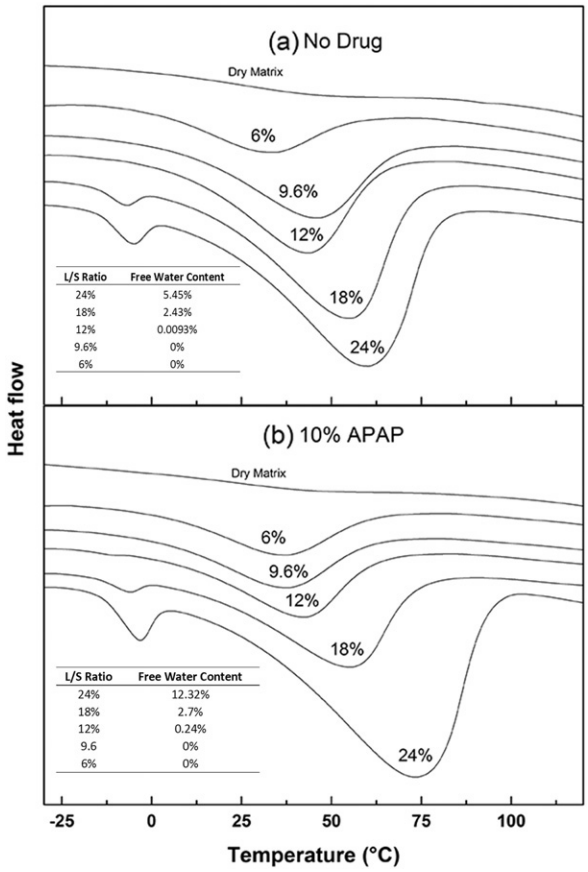

Figure 4-3: DSC thermograms for the free water ratio within the CR formulation (a) without drug and (b) with drug at different L/S ratios.

4.4.3 Compression test

It is recognized that the granules produced by a twin-screw granulator are not exclusively created by the layering and coalescence of wet particles but rather, include significant mechanical contributions from forces in the process that compact and fragment the solids; these mechanical contributions were absent from consideration in the

discussions in the previous sections. The non-conveying sections of a screw design have recognized importance to the characteristic granulation behavior of a twin-screw granulator, by compacting and fragmenting the wetted mass [2, 23, 33, 34], and so a largely qualitative test was devised to note differences in the water distribution based on compression between the two CR formulations. To see the influence of HPMC on the formulation, the IR formulation was included in this test.

In the compression test (results shown in Fig. 4), water was more readily lost from the powders under applied pressure (2 MPa) at higher temperatures. At 30 °C, a higher quantity of water could be lost from the IR formulation relative to both CR formulations. The HPMC reduced the mobility of water, making it more difficult to be withdrawn or in the case of twin-screw granulation, less likely to distribute water among the dense granular bed while compressed. Comparing the two CR formulations, a higher water loss was reported with the inclusion of APAP due to its higher content of free water which offered more mobility for the liquid present. As the temperature rose to 55 °C, differences in water loss by compression between the formulations decreased (consistent with Sections 3.1 and 3.2) but some minor differences were still noted. Taking the formulations prepared with 24% L/S ratio as an example, the difference between the two CR formulations is 2.91% at 30 °C, which decreased to only 0.34% at 55 °C even though more water could be extracted from all three formulations at this temperature than at 30 °C. The greatest amount of water could be compressed out at 80 °C, but differences between formulations become more difficult to identify. In this case, water in the CR

formulation without drug can be compressed out more easily than from the CR formulation with drug.

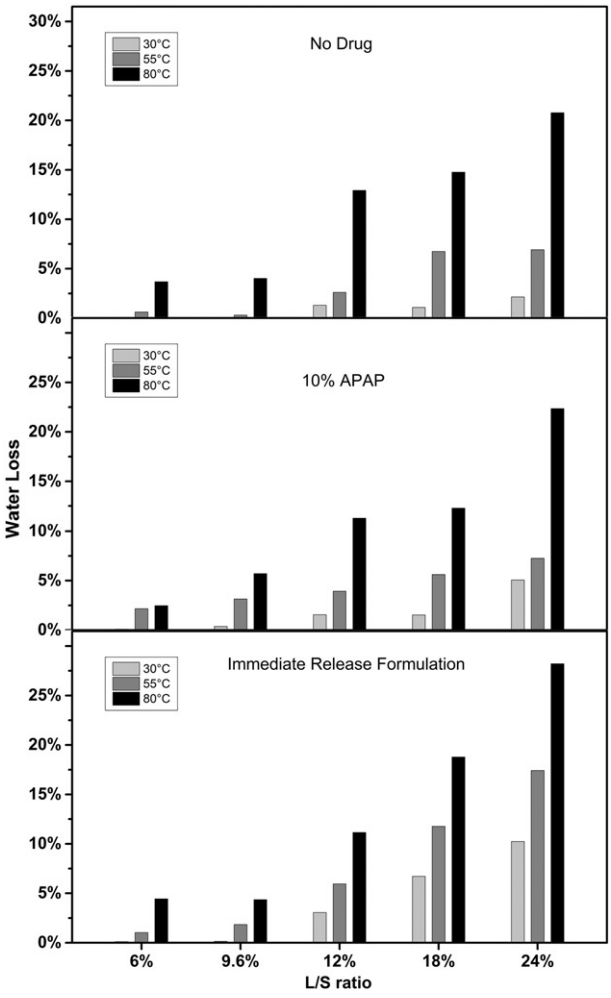

Figure 4-4: Results of the compression test for three formulations (CR formulation without drug at the top, CR formulation with drug at the middle and IR formulation at the bottom). The relative error for this test was 13%, averaged for the 30 °C, 55 °C, and 80 °C condition.

4.4.4 Residence time distribution

The measured residence time data along with the fitted distributions (RTD) are shown in Fig. 5 for the two CR formulations at three temperatures and their calculated moments are summarized in Table 3. The CR formulation with APAP had a higher mean residence time (MRT) which was persistently at 44 s in comparison to when the API was not present, whose MRT varied between 35 and 40 s for the three temperatures. Increased temperature had no definitive effect on the MRT of either formulation but appeared to shorten the delay time and increase the state of mixedness (based on the increase of the mixing indices, σ^2/τ^2) for the formulation without API.

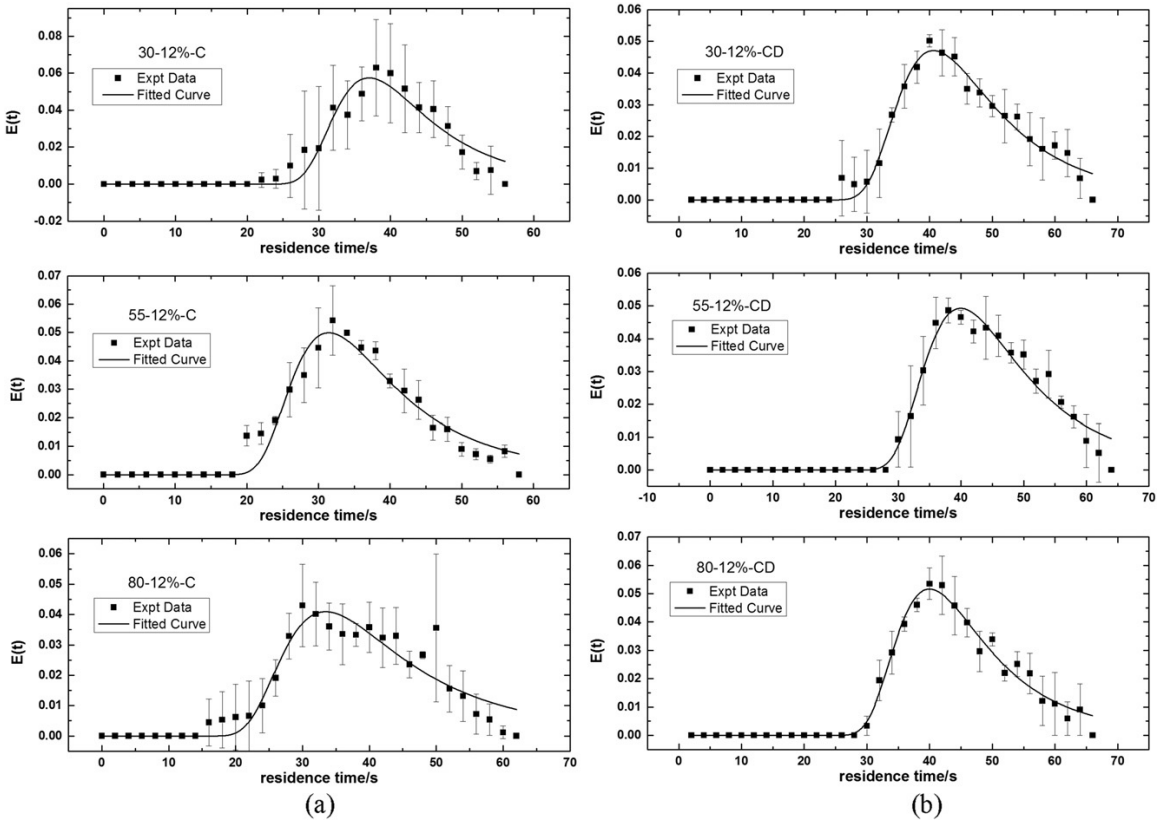

Figure 4-5: Residence time distribution measurement for CR formulations for 12% L/S ratio. Plot shows the quality of fit between the color data and the Zusatz model for (a) CR formulations without drug, and (b) CR formulations with drug.

Increasing viscous drag has been stated as a cause for longer MRT in a TSWG process when the main difference between trial conditions were liquid content, according to Dheng et al. [35]. However, that explanation seems implausible in our case as there was too little free water present for the L/S = 12% condition, even at 30 °C. Besides, a higher state of lubrication would foreseeably make the increased mixedness of the system noted at 30 °C seem unlikely. It is more likely the RTD analysis is revealing differences in friction within the beds of the two formulations. The results suggest that the inclusion

of APAP yielded hindered flow possibly by higher friction or cohesion stresses [36] but those retarding stress contributions were also temperature insensitive. The difference in MRT seen between the two formulations was unlikely the cause for significant differences in water distribution among the ingredients but this finding indicates that the APAP had effects on the process beyond wetting.

Table 4-3: Moments of the RTD model for the twin screw wet granulation process based on a fixed L/S ratio of 12% for the two CR formulations at different temperatures.

	Delay time [s]	**MRT, τ [s]**	**σ^2/τ^2**	**Adjusted R^2**
30-12%	24	39.44	43.62	0.91084
55-12%	18	35.92	68.41	0.93734
80-12%	18	38.47	90.3	0.88638
30-12%-D	26	44.25	69.7	0.97283
55-12%-D	27	44.7	66.37	0.96905
80-12%-D	26	44.86	66.97	0.97841

4.4.5 Particle size distribution

Particle sizes of granular samples from the exit of the extruder were described by their weight fraction distributions, as shown in Fig. 6. A relative error in the size measurement of 12.7% was estimated by three repeated trials for the 80–24%-CD

condition. At any fixed temperature, the fraction of small particles (< 1180 μm) decreased relative to larger particles (1180 μm–2360 μm) as the L/S ratio increased ($P = 0.05$). For the CR formulation without APAP, temperature had minimal influence ($P = 0.81$) on the PSD, although the fraction of large particles did increase slightly with higher temperatures. For instance, the fraction $F_{1180–2360\ \mu m}$ increased from 29% to 30% and then to 35% as temperature changed from 30 °C to 55 °C and then to 80 °C, respectively. Increasing system temperature for the processing of the CR formulation with APAP had a more profound effect ($P = 0.02$) on particle size. Instead of simply varying the weight fraction between the two main size groups, $F_{< 1180\ \mu m}$ and $F_{1180–2360\ \mu m}$ as seen with the other formulations, a significant weight fraction of chunks ($F_{> 2360\ \mu m}$) was present at lower temperatures which decreased in content as temperature increased. This phenomenon was more pronounced at higher L/S ratios such as 12%, 18% and 24% (where free water was present, as noted by DSC). The PSD for this formulation was narrower and more consistent in size at 80 °C showing little variance among all L/S ratios. In this case, the impact of L/S ratio on particle size was too small to be clearly identified. For the IR formulation which includes APAP as well, its PSD was bimodal and comparable to its placebo formulation (i.e. no drug) reported in an earlier study [13]; granulation of the 20%/80% MCC/lactose mixture never presented any difficulties at 30 °C in obtaining good granules even with the inclusion of APAP in the formulation. As temperature increased for this formulation, the weight fraction of chunks ($F_{> 2360\ \mu m}$) increased significantly ($P < 0.01$) going from 30 °C to 55 °C and then remained unchanged with the further increase to 80 °C. The growth was likely attributed to the

increased lactose present and its higher solubility in water at these elevated temperatures with no HPMC to sequester a portion of that water (referring to the compression data in Fig. 4); the solubilization of lactose in water at higher temperatures has been considered to increase the liquid viscosity of the binder resulting in stronger particle bridges among agglomerated solids [12].

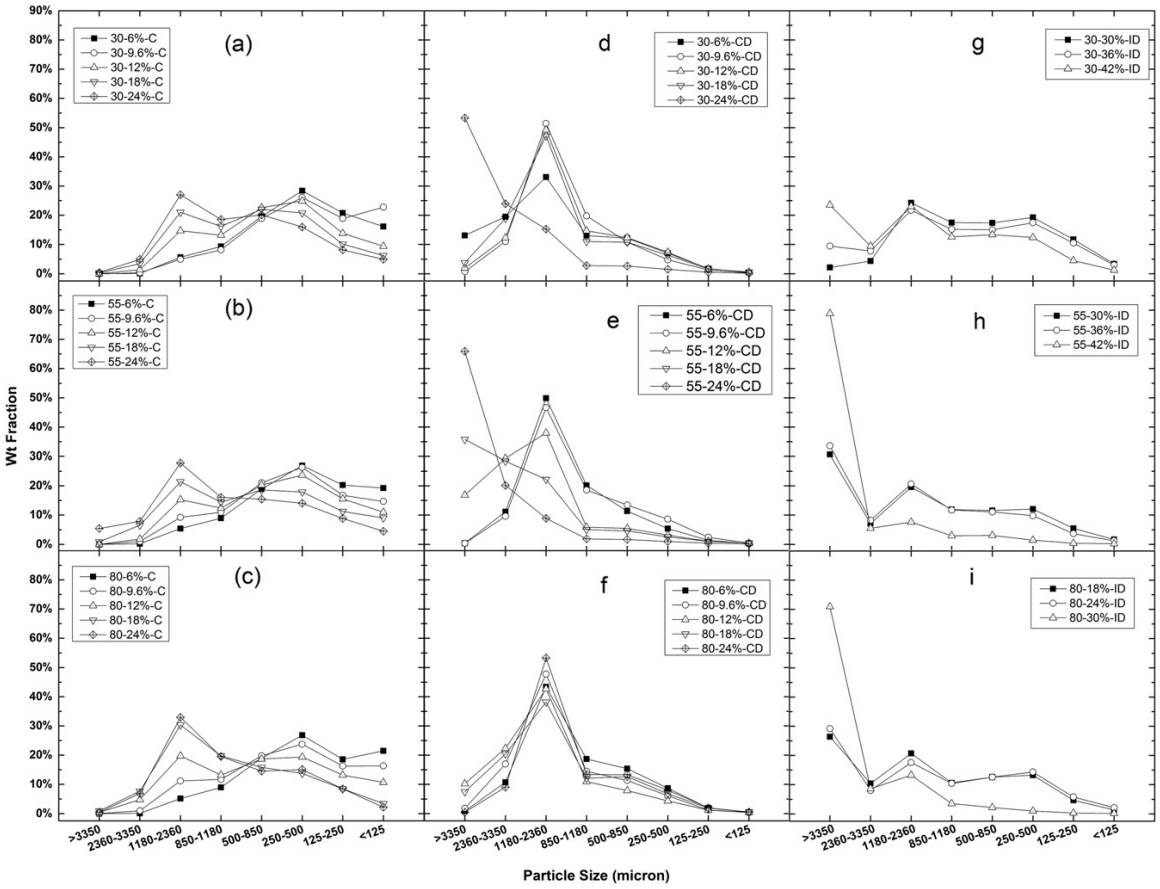

Figure 4-6: Particle size distributions of granular product from the twin-screw granulator for the CR formulation without drug (a, b, c) and with drug (d, e, f) versus the IR formulation (g, h, i). Variation depending on temperature for 30 °C (a, d, g), 55 °C (b, e, h) and 80 °C (c, f, i).

4.4.6 Aspect ratio

An aspect ratio of 1.5 is characteristic of acceptable granules by TSWG [7]. The granules for the CR formulation without APAP were slightly larger in this study, being nominally 2.0 but were generally more spherical than those prepared with the inclusion of APAP (nominally 3.0) as shown in Fig. 7. At low temperature (30 °C), higher L/S ratios increased the aspect ratio of granules ($P < 0.01$) for the CR formulation with APAP. The granules reported in Fig. 6 for this formulation at 55 °C manifested high aspect ratios well above 3, even at the lowest L/S. However, by elevating the system temperature to 80 °C, the formulation showed diminished sensitivity to L/S ratio ($P = 0.47$), comparable to the granulation behavior of the formulation without APAP. The aspect ratio for CR formulation without APAP showed very little sensitivity to L/S ($P = 0.16$) except at very high values of L/S = 18% and 24%.

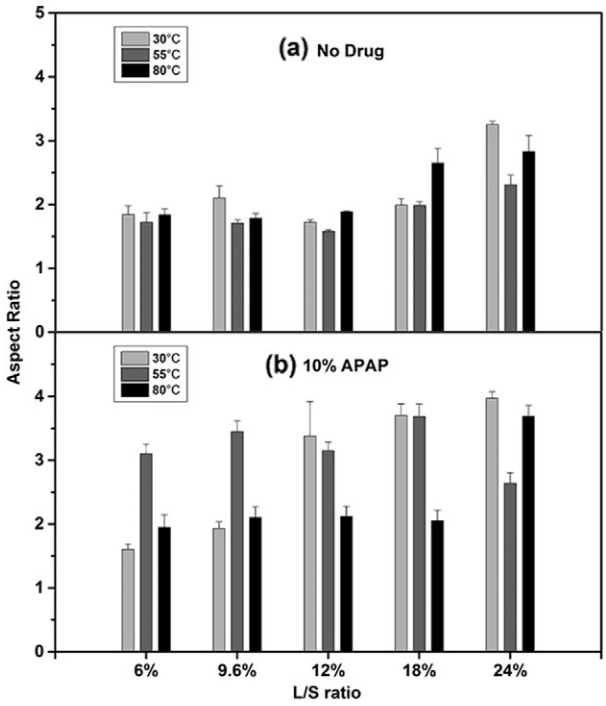

Figure 4-7: Aspect ratio of granules with respect to L/S ratio and extruder barrel temperature for (a) CR formulation without drug, and (b) CR formulation with drug.

The high aspect ratio particles originate from the 'rolling mechanism' inherent to twin screw granulation where wet particles caught against the flight tip will roll together and bind into large, elongated noodle-like particles [7]. The integrity of these large particles is dependent upon the bridge strength, which can be sufficiently strong in the presence of a high molecular weight HPMC when wet [9]. Without a high L/S ratio, the particle bridges among the CR formulation without APAP lacked sufficient strength to maintain the noodle-like particle without fracturing. However, the higher free water content in the assembly when APAP was present meant a strong wet bridge formed (attributed to both K4M chains and dissolved lactose in the bridging liquid) and hence a high resistance to fracture was witnessed until the water content was substantially reduced

at 80 °C. It would be interesting in future studies to consider how the different components of the formulation, especially MCC, affect the rolling mechanism.

4.4.7 Fracture strength and porosity

The granule fracture strength and porosity of samples produced on the extruder are shown in Fig. 8. For the CR formulation without drug, increasing the temperature had a minor influence to decrease the fracture strength ($P = 0.11$) and similarly, the impact of changing L/S ratio was minimal ($P = 0.21$). At 80 °C, almost no difference could be identified in the fracture strength of granules based on different L/S. The trends were the same for porosity with this formulation. With the inclusion of APAP, the impact of temperature was more considerable ($P = 0.02$) and changed with L/S ratio ($P = 0.04$). For L/S ratios < 10% increasing temperature generally resulted in decreased granular strength. In contrast, at higher L/S ratios the granule strength increased with increasing temperature. The results of porosity at low L/S mirrored the trend with granule strength; however, porosity showed little dependency with temperature for L/S > 10%.

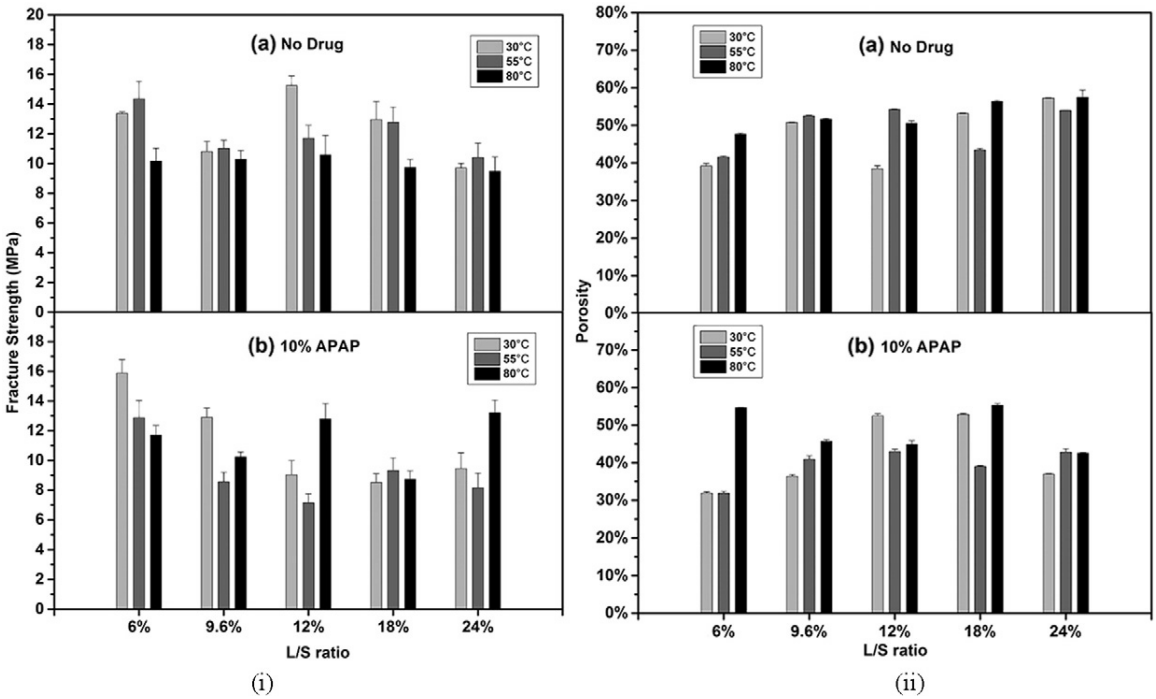

Figure 4-8: Fracture strength (i) and porosity of granules (ii) for CR formulations (a) without drug and (b) with drug. Temperatures in the plot refer to the barrel temperatures during granulation.

When comparing the two CR formulations, including APAP generally increased the strength at lower temperature and lower L/S but there was no obvious trend for the formulation without drug. This is consistent with the porosity results, especially for the porosities when no drug was used.

4.4.8 Dissolution test

AAs seen in the dissolution profiles of tablets shown in Fig. 9, drug release rate changed based on the granulation processing temperature as well as the L/S ratio. Similar to granule fracture strength, the dissolution behavior differed depending upon whether the L/S ratio was above or below 10%. Higher dissolution rate was detected for the tablets

made from granules produced at higher barrel temperature. For example, between L/S ratios of 9.6–24%, the percentage of drug release for granules produced at a barrel temperature of 30 °C was consistently lowest for the entire duration of testing and this trend is more obvious at higher L/S ratios such as a L/S ratio of 24%. However, for the lower L/S ratio of 6%, the drug dissolution rates of granules produced at higher barrel temperatures were similar to that found at 30 °C. During the initial release stage, it appeared that higher L/S ratios increased the drug release rate for the granules from higher barrel temperatures. Taking the 55 °C as an example, percentage of drug release at 1 h increased from 21 ± 3% (L/S ratio = 6%) to 24 ± 3% (L/S ratio = 12%) and then to 30 ± 2% (L/S ratio = 24%). This can be caused by more exposure area of HPMC to the water due to the thicker gel bridge at higher L/S ratio. The increased exposure area is beneficial to the hydration of HPMC in the beginning of the drug dissolution and hence increases the initial drug release rate.

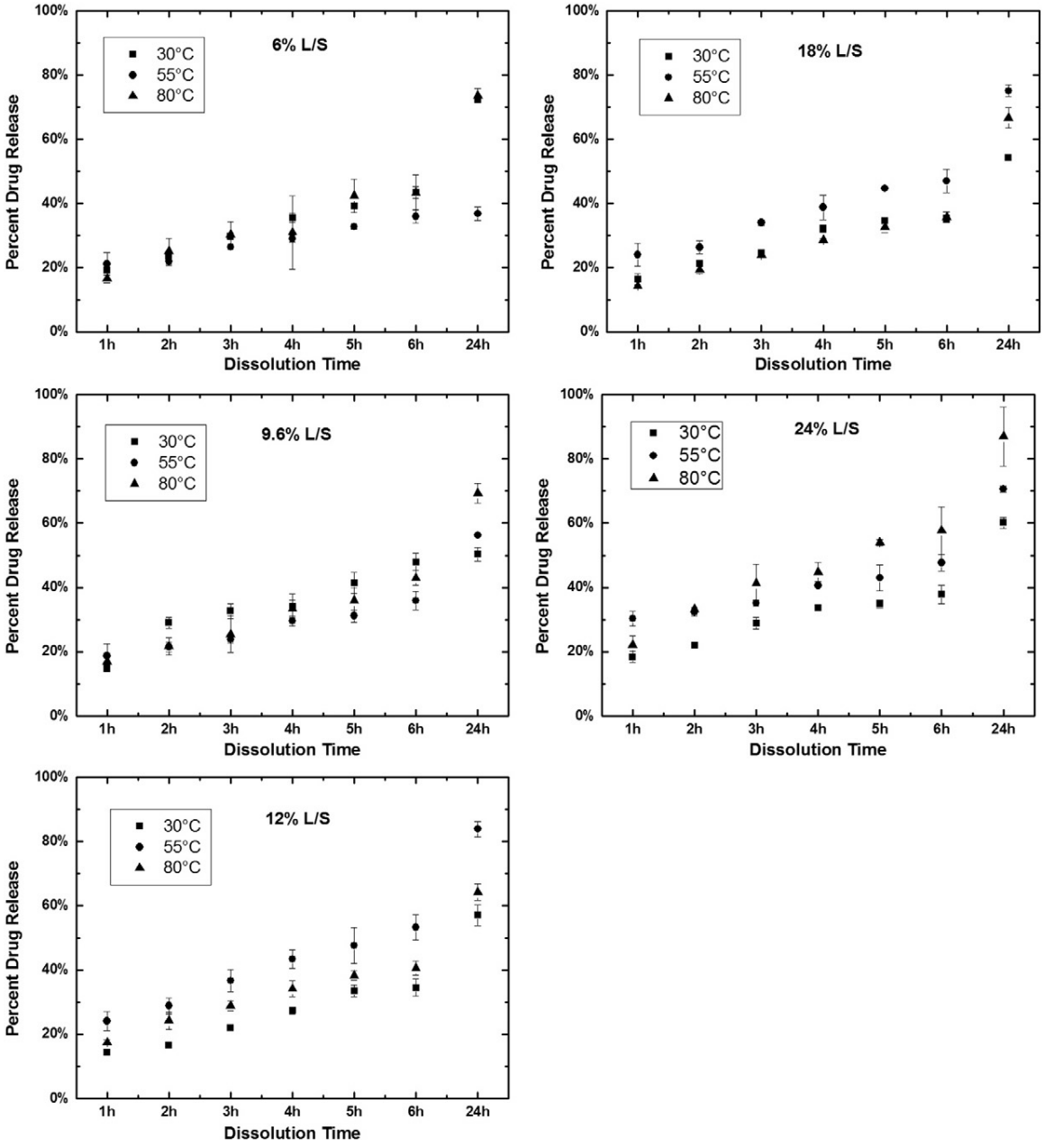

Figure 4-9: Drug dissolution profiles of tablets made with the CR formulation containing acetaminophen. Temperatures in the plot refer to the barrel temperatures of the extruder during granulation.

4.5 General Discussion

4.5.1 Proposed mechanism of chunks produced with the CR/APAP formulation

The results above have shown that APAP and K4M are sensitive to wetting, together producing the undesirable frequency of chunks in the exiting granulate from the extruder. Without one or the other, smaller granules of lower aspect ratio were possible under room temperature conditions. Particle sizes and aspect ratios of granular products are generally related to the strength of liquid bridges formed among primary particles during granulation. MCC is also sensitive to wetting but as an immediate release bulking agent, like α-lactose monohydrate, this bridging formed with free water at the surfaces of particles [36, 37]. However, bridging with HPMC, particularly with molecular weight variants like K4M, is significantly different.

When HPMC particles are exposed to water during the granulation process, the hydrated long chains are known to trap liquid [38, 39]. In the presence of water, the chains of HPMC relax to form a viscous gel layer, which prevents further water penetration [40]. These gelled particles can be seen to act as ‘binders’ in a consolidated assembly of solids, agglomerating local particles with bridges formed by these relaxed chains in the viscous layer. Thus, the capacity of fine particles to cluster together is determined by the thickness of the viscous gel layer which is related to the molecular weight, degree of hydroxypropyl substitution [30], primary particle size and particle shape [41]. In this regards, HPMC is not reliant upon free water in order to initiate bridging with other particles (wet or dry), as is necessary with lactose or MCC, but the

presence of water is still important to mobilizing its chains. According to the absorption results in Section 3.1, water is preferentially absorbed by both MCC and HPMC particles (based on their higher water uptake rates) among the different ingredients in the CR formulation. In their equilibrium sorption state at 30 °C, these two ingredients will trap 90% of the present water (> 79% of that trapped water is allocated to HPMC), at least initially until fully saturated, and will draw away present water faster than either APAP or lactose. With so little surface water to participate in liquid bridging between particles, even as the wet mass passes through a kneading block (as highlighted by the compression test), agglomerating can be considered to be dominated by the bridge forming capacity of the viscous gel layer of HPMC. The question then becomes, what contribution by APAP made agglomerating by this viscous bridge so difficult to control?

APAP appeared as a more hydrophobic ingredient in the present formulations, showing little affinity for water, as shown by the moisture absorption results. The low water affinity of APAP increased the available free water content (as evident by DSC and in the compression test). The higher available water can contribute to further liquid bridging (as evident by the tendency of the IR formulation to produce a growing fraction of chunks above L/S = 30% despite smaller particles being reported in [13] for comparable L/S in the absence of APAP) or thicken the viscous gel layer of HPMC to provide more chains within the bridges across particles (which similarly leads to increased granule sizes). The PSD results in Fig. 6 showed a reduction in the smaller particles (< 1180 μm) in the product when 10% APAP was included in the CR

formulation, whereas the higher fracture strength and lower porosity found at 30 °C shows that this particle growth was attributed to more bonding among particles.

4.5.2 Impact of temperature on the granulation process

Temperature was shown to resolve the wetting issue with the CR formulation containing 10% APAP, now with acceptable particle sizes being produced. According to the experimental results, different formulations (and different individual ingredients) have differing sensitivities to water with respect to temperature. The amount of water uptake (defined here by the fast stage equilibrium coefficient) and the rate of moisture absorption for the two dominant components, MCC and HPMC, dramatically decreased with increasing temperature. Conversely, the moisture sensitivity of lactose with respect to temperature was minor and the moisture absorption property of APAP was non-sensitive to temperature. As a result, wetting heterogeneity among ingredients was reduced.

According to the compression test, the content of distributable water (expectedly found in a kneading section of a twin-screw granulator) can increase with temperature due to the collapse of the HPMC hydrogel [42], and subsequent dehydration of the wet cellulose [43]. The noted thermoreversible gelation behavior of HPMC reported in solutions whereby it precipitates at cloud point around 60 °C may be contributing to the noted increase in free water content [44]. In general, the lower capacity for moisture absorption by all ingredients at higher temperatures translates to increased free water content in a wet matrix, though rapidly being lost by desorption once at 80 °C. The greater potential for liquid bridges with increased free water was evident in the IR

formulation by the increased content of chunks at elevated temperatures despite the fact that no ingredient melted to contribute to these bridges. In the samples with K4M, the increased potential for liquid bridging at higher temperatures (noted by similar amounts of free water now being present by the compression test as with the IR formulation) did not seem to translate into particle size enlargement, at least based on the PSD results of the CR formulation without APAP. This suggests a robustness to the gel bridging mechanism; that only small amounts of water are necessary despite evident dehydration of the gel, at least by 80 °C. It is possible that the K4M was agglomerating partially by bridging with the added binder at this high temperature (in the same manner as lactose and MCC rather than by its viscous layer). The liquid bridge will be strengthened due to the increased free water content with higher temperature but the strength of the granules was still offset by the decreased viscosity of the gel bridge at higher temperature [44], so the results do not show any radical change in granulation behavior.

The hydrophobic APAP species was insensitive to temperature with regards to wetting behavior and based on the compression results, it simply made more free water available to the other ingredients for bridging. Invariably this API weakens the strength of granules by retarding the development of bridges within the consolidated bed (i.e. defects in the agglomerated structure) but it can improve the bridges of other components when their water sorption characteristics are favorable (e.g. at lower temperatures). At lower temperature, the additional free water present when APAP is included in the CR formulation thickened the gel layer to make bridges strong enough to overcome these defects and form chunks as a result. By 80 °C, the thinner gel layer due to dehydration

could not compensate for these defects and generally led to smaller, more fragile particles; the fracture strength was observed to be higher in some cases at higher temperature but the trend (for fracture strength, porosity and particle size) suggests the particles are ultimately weaker. The individual granular strength is still determined by the gel bridge and the dominance of the gel bridge was reflected by the results of fracture strength and porosity where at higher temperature, the difference of fracture strength and porosity between two CR formulations is inconsiderable.

4.6 Conclusion

Higher temperatures were shown in this study to decrease the water absorption capability of all ingredients in the controlled release formulation, especially for the more hydrophilic species, and hence increased the free water content in the wet mass. This was helpful for particle agglomeration by increasing the liquid bridges, particularly for IR formulations. For high molecular weight HPMCs such as K4M, which form a viscous gel layer when exposed to water, the gel bridge appears to be a dominant mechanism for particle growth, likely because when it is present in a formulation it sequesters much of the added water. Increased temperature will retract the gel layer of wet HPMC particles due to dehydration but the bridges formed appear to remain sufficiently strong to produce similar particle sizes from the extruder compared to the 30 °C condition. Inclusion of the hydrophobic APAP produced very coarse particles at 30 °C despite its interference with the developed network of liquid bridges within a granule, on account of its low water sorption behavior which increased the free water content and thickened the gel layer of

the HPMC. At higher temperatures when the gel layer of HPMC was not so accepting of water, the APAP only served to weaken the strength of the granules.

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Chapter 5

Heat Assisted Twin Screw Dry Granulation

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5.1 Abstract

A new ‘assisted’ dry granulation method has been devised for the twin-screw granulator. The method may be beneficial to drug preparation as it limits heat exposure to only one barrel zone, much shorter than melt granulation. Its mechanism was investigated using four placebo formulations, each containing a polymer binder with a glass transition temperature lower than 130 °C. Variables of study included screw configuration, screw speed, barrel zone temperature and moisture content. Granulated samples were characterized for size and porosity while feed powders were examined for their thermal transitions, inter-particle friction, cohesion, and sintering rate. Results indicated that granule coalescence relied upon melting of polymer binder in the kneading blocks by a combination of heat conducted from barrel and generated from screw speed friction. Successful granulation was possible with minimal addition of water, though varying the moisture content showed the relevance of the polymer’s glass transition temperature and sintering progress.

5.2 Introduction

Three main granulation strategies exist in the pharmaceutical industry: wet, melt, and dry granulation. For the process of twin-screw granulation, the majority of research is limited to wet granulation where water or organic liquids are necessary as a solvent for the binder, and to provide modest granule strength until the product dries [1–4]. The disadvantages of wet granulation are obvious when the powder formulation contains a water sensitive drug. However, other well-known disadvantages include a sensitivity to downstream unit operations leading to undesirable hardening [5], and the costs related to a time-consuming drying process. For twin-screw granulation, studies have revealed difficulties in achieving a homogeneous liquid distribution in conveyed powders for both immediate release formulations [4,6] and controlled release formulations [7,8]. Conversely, melt granulation has been studied to a far lesser degree [9,10] but recent activities in the pharmaceutical community suggest some are favoring the approach for commercial adoption of twin-screw granulation. Melt granulation takes advantage of the excellent heat control of the twin-screw extruder, which occurs because of the closely confining flow path for powders in the machine. Granules by this method cool within seconds of leaving the process and therefore do not require any time-consuming downstream steps to make them suitable for tableting. The main disadvantages of melt granulation are related to the perceived (or real) concerns for thermal damage since the length of the extruder operates at high temperatures (often well above the glass transition temperature of the polymer binder). Few studies have looked at thermal degradation in

the twin-screw granulator, though it has been pointed out in at least one case that the absence of drug damage can be attributed to the extremely short residence time of the process relative to traditional batch methods of granulation [10].

Different from the liquid bridging methods of wet or melt granulation, dry granulation relies upon high mechanical forces to compact powders which are commonly achieved through roller compaction[11,12]. The mechanism is unclear [13] though particles are proposed to combine together by mechanical interactions and cohesion[1]. The decision to choose this method for granulation is often based on limitations by the formulation [14] and other difficulties [15,16]. There are no known approaches to the use of dry granulation with a twin-screw extruder due its low internal compressive forces, as proven by early attempts at direct compression [17]. However, a recent modification referred to as moisture-activated dry granulation (MADG), expanded its processability to a broader class of powders and opens the possibility for granule growth without high mechanical forces and has been proved in high shear batch mixers [5,18]. The basis of the modification could be suitable for twin-screw granulation as well.

Seeking a new dry processing method for continuous granulation, an ‘assisted’ dry granulation is contemplated in this paper as part of a current research effort to minimize downstream requirements (i.e. milling, drying) as well as to reduce concerns regarding drug efficacy as a result of degradation caused by the influences of moisture and heat during manufacture. Solely following a MADG method would likely succeed, but since the twin-screw extruder was designed for excellent heat control there exists an

opportunity to combine 'heat-assisted' and 'moisture-assisted' methods for optimization without the disadvantages of wet granulation or melt granulation. The premise of the method is to rely upon a single heated zone containing a non-conveying kneading block to cause powders to compact and sinter such that granulation occurs with minimal exposure to barrel temperature. While the approach has been found possible with heat alone (data not provided), it seems to lack stable operation without the presence of a small quantity of water. The purpose of this paper is to disclose the method developed in detail and through the aid of studied experimental factors including screw speed, temperature, kneading block configuration, and formulation, explain the mechanism of granule development. The binding polymer used is shown to have critical importance in the success of the technique.

5.3 Materials and Methods

5.3.1 Materials

Four placebo formulations were tested, each consisting of 59.5 wt% Flowlac® 100 spray-dried α-lactose monohydrate (Meggle Pharma; Germany), 40 wt% polymer binder and 0.5 wt% magnesium stearate (Sigma Aldrich; Mississauga, ON). The binder content was fixed and comparable with formulations used in dry granulation[15]. A small amount of magnesium stearate was premixed into formulations similar to previous studies[17,19] as a lubricant for tableting.

Each formulation contains one polymer excipient, such as Kollidon® VA64 (BASF; Florham Park, NJ), Kollidon® SR (BASF; Florham Park, NJ), Soluplus® (BASF;

Florham Park, NJ) and one grade of AFFINISOL™ HPMC HME (The Dow Chemical Company; Midland, MI) and a stated viscosity of 15 cP (as a 2% aqueous solution); all quoted initial moisture values were based on testing after having been used and stored in the lab for at least one month. The initial moisture content and glass transition temperature (T_g) of these materials are listed in table 1. All selected polymers are well recognized for use in pharmaceutical drug applications, though only Kollidon® VA64 is commonly used for dry granulation in batch manufacturing. Attributes of the polymer binder were not directly studied in the current work, which focused on mechanism of granulation whereas future studies will examine the effects of viscosity and binder concentration.

Table 5-1: Initial moisture content and T_g of materials.

	Kollidon® SR	**Kollidon® VA64**	**Soluplus®**	**AF15**	**α-lactose monohydrate**
T_g (°C)	46.6	103.9	62.1	118.2	
Moisture Content	3%	4%	3.40%	2%	2.3%

These four polymers of Kollidon® VA64, Kollidon® SR, Soluplus®, and AFFINISOL™ HPMC HME 15LV were symbolized by Kollidon® VA64, Kollidon® SR, Soluplus® and AF15 in the study, which also stands for the formulation containing the corresponded polymer.

5.3.2 Feedstock preparation

Formulations with total moisture contents of 5% and 10% were prepared by starting with the original powders (at initial moisture content) being passed through a 50 Mesh sieve and then tumble blended for 5 minutes. A mixed formulation, or in the case of some tests just a neat polymer, was spread out in a large open container (zeroed prior to addition), and sprayed with distilled water by shaking the container simultaneously until the mass of formulation reached the intended weight of the corresponding moisture content. Neat materials at their initial moisture content or wet powders adjusted to a total moisture content of 5% or 10% (by spraying water over tumbling powder) were then stored in sealed containers for 3 days at 20 °C to equilibrate. The small amount of water added did not produce any agglomerates in the desired size range of 0.5-2 mm at this stage due to the negligible bridging effect of dissolved lactose[20].

For the case of understanding this new processing method, formulations with different moisture content were prepared to investigate the impact of initial moisture content. Though 10% moisture condition was considered very high, it was included to extend the trend up to a wetted state more closely resembling condition for wet granulation. The intent of future studies will be to remain close to 3-4%, which is considered an acceptable moisture level for direct tableting [21].

5.3.3 Granulation trials

Granulation trials were performed in a ZSE-HP 27 mm 40 L/D co-rotating intermeshing twin-screw extruder (American Leistritz Extrusion Corp.; Somerville, NJ). Screw configurations used in the study are shown in Figure 1, consisting of typical granulation designs based on combinations of conveying element, and 60° or 30° offset kneading blocks for a comparison of screw configurations. Only one mixing zone was used since it was found effective and with longer zones there was concerns of heat build up in the granules that may damage the drug. Details of specification of the screw elements can be found in an early study [22,23]. The temperature for zone 2 was a variable set in the trials at either 60 °C, 80 °C, 100 °C or 120 °C, while the other zones were constantly held at 30 °C. This barrel temperature profile is in contrast to a regular melt granulation setup where all zones are set to elevated values (often above 100 °C) to give the binder time to melt conductively before bridging particles. The current process is reliant upon friction/viscous dissipative heating, as will be disclosed by the study, and as a result the heated zone of the extruder can be very narrow.

A prepared formulation was fed into zone 0 of the extruder by a T-20 gravimetric feeder (Brabender Technologie Ltd.; Mississauga, ON) at a fixed mass flow rate of 5 kg/h. The experimental trial matrix of granulation conditions is shown in Table 2. Not all conditions could be tested for every polymer due to their broad range of glass transition temperatures and molecular weights chosen for the study. After each run reached steady state, motor load was recorded along with pressure readings. Pressure data was collected

at 100 Hz sampling rate by a Dynisco PT460XL-10M-9 transducer in the barrel to monitor stresses in the kneading block area, as shown in Figure 1. Granular sample temperature from the exit of the granulator was measured using a hand-held infrared pyrometer (Omega Engineering; Laval, QB). Analysis of particles in the screws were done by the "screw pullout" technique disclosed in previous studies [24] which stops the screws abruptly during stable granulation processing and withdraws the screws from the barrel so that they can be photographed. This methodology is able to reasonably 'freeze' the state of powder bed internally and the large size of the extruder ensures a large population of granules will be present for analysis.

Table 5-2: Granulation trial conditions based on parameter combinations.

Formulation	**Zone 3 temperature**	**Moisture content of formulation**	**Screw speed**	**Kneading block offset**
Kollidon® SR	80 °C	neat / 10%	100 rpm / 200 rpm	60°
		neat	150 rpm	30°
		5%	200 rpm	60°
	60 °C/100 °C/ 120 °C			
Kollidon® VA64 / Soluplus® / AF15	80 °C	neat / 10%	100 rpm / 200 rpm	60°

				30°
		5%	150 rpm	60°
	60 °C/100 °C/ 120 °C			

Each granulation condition was referenced according to the formulation, screw speed, barrel temperature, moisture content and kneading block offset, respectively. For instance, SR-200-80-°C-5%-60° refers to the granulation condition with Kollidon® SR formulation at 5% moisture being processed at 200 rpm with 80 °C in zone 2, and using a screw design with a kneading block of 60° offset. Furthermore, a shortened granulation condition symbol was also used. Taking SR-80 °C-5%-60° as an example, absent parameter of screw speed means this experiment was conducted at screw speed of 100, 150 and 200 rpm. Uncertainty for granulation was represented by three repeated trials for the condition of AF15-150-80 °C-5%-60°.

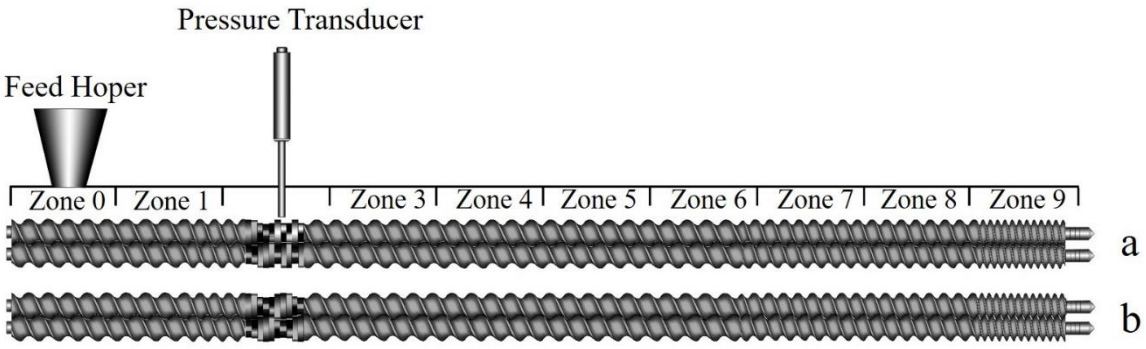

Figure 5-1: Granulator setup and screw configurations. Configuration a includes 30 mm 30° offset kneading blocks followed by 30 mm 60° offset kneading blocks; configuration b includes 60 mm 30° offset kneading blocks.

5.3.4 Mean residence time measurement

To determine the exit-age mean residence time (MRT), 0.6 g food-grade cocoa powder (Fry's premium cocoa powder; Cadbury) was added as a tracer into the feed port of the extruder to simulate a pseudo-Dirac pulse after 5 min granulation run to allow a stable process. The exit of the extruder was visually recorded at a frequency of one image per second with a high-resolution camera. Three repeats (n=3) of tracer addition allow an uncertainty estimate for the measurement. Images were analyzed afterward by Photoshop CS4 (Ver 11.04, Adobe System Inc.; San Jose, CA) according to their color intensity. To calculate the MRT, color analysis results was fitted to a Zusatz distribution [25] as: $E(t) = at^{-c-1}b^{c+1}\exp[(b^{c}t^{-c}-1)(\frac{-c-1}{c})]$

$$E(t) = at^{-d-1}b^{d+1}\exp\left[\left(b^{d}t^{-d}-1\right)\left(\frac{-d-1}{d}\right)\right] \quad (1)$$

where *t* is time, 'a' relates to the peak height, 'b' is the residence time at peak height and 'd' is a fitted parameter related to the peak breadth but lacks any direct physical interpretation. The model fitting was completed in Originlab (Version 9.0; OriginLab Corporation, MA)

5.3.5 Heating sintering profile

Different modes exist in the process to cause the polymer binders to wet and bridge particles into granules, and while shear forces play a foreseeable strong role, there will be contributions related to sintering that do not rely upon mechanical action. Melt coalescence behaviours were monitored for the different binders in a zero-shear, offline testing apparatus [26]. The sintering apparatus consisted of a custom-built, deep-well hot stage optical microscopy setup being heated at a rate of 1 °C/s. Temperature in the apparatus is ramped from room temperature to 200 °C, measured by a thermocouple located next to the particles. At room temperature, a single layer of a polymer was placed in a glass crucible and then mounted in the heated well; the mixed powder formulations were also tested. Time lapsed photos of the particle clusters were captured with a frequency of one picture per second by a digital camera connected to the optical microscope. Profile curves of the relative liquid bridge radius (commonly referred to as a neck radius in sintering literature) adjoining two particles, *y/a*, versus temperature were analyzed from the obtained photos using image analysis software, ImageJ (Version 1.48, U. S. National Institutes of Health, USA), where *y* is the neck radius and *a* is nominal radius averaged for the two adjacent particles, as demonstrated in Figure 2. The

measurement was repeated three times (n = 3) for each excipient at three levels of moisture content (initial, 5% and 10%).

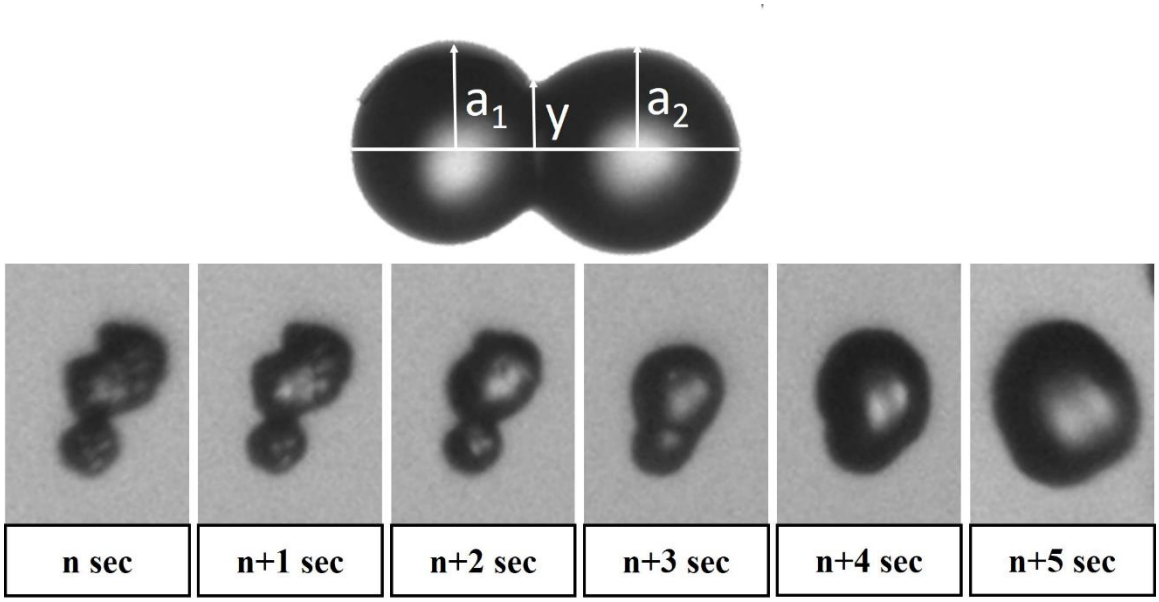

Figure 5-2: Demonstration sintering neck radius y and average particle radius a = $(a_1 + a_2)/2$ of two particles.

5.3.6 Cohesion and coefficient of friction measurement

The cohesion and coefficient of friction (internal, COF) of each formulation at different moisture contents and temperatures were estimated from direct shear testing, DST [27–29]. Classic Mohr-Coulomb Failure Criterion were used in the current test, which suggests a linear relationship between shear strength τ and normal stress σ_n as given by,

$$\tau = c + \sigma_n \tan\phi \quad (2)$$

where c is cohesion (which is treated as a constant) and ϕ is the angle of internal friction; $\tan\phi$ is assumed to equal the COF in the test. During the test, a pair of conventional rectangular shear boxes with inner dimension of 60 mm × 60 mm × 45 mm were used. The powder bed in the shear boxes was sheared at a displacement rate of 1 mm/min. COF and cohesion were calculated from applied normal pressure *vs* yield shear stress. Testing was done at room temperature, and at approximately 40 °C and 60 °C but not higher to prevent melting. Since the DST does not include temperature control, sealed sample-filled boxes were pre-heated up to the setpoint temperature for around 30 minutes in a neighboring oven and then rapidly moved into position in the DST. To monitor cooling, sample temperatures right after testing were measured. All sample temperatures were collected by an exposed junction thermocouple. The uncertainty of the method was estimated by three repeats of the AF15 formulation.

5.3.7 Differential scanning calorimetry and moisture analysis

The glass transition temperatures (T_g) of the neat powder ingredients at different moisture contents were determined by a differential scanning calorimeter (DSC) at a heating rate of 5 °C min^{-1} from -20 °C to 200 °C. Around 10 mg of sample was placed in a hermetically sealed T-zero aluminum pan (TA Instruments; Switzerland). To increase the resolution of the transition, a modulated DSC (MDSC) method was used with a temperature oscillation of 0.5 °C at a frequency of 40 seconds.

Moisture content measurements in this study were conducted with a Mettler-Toledo HG63 moisture analyzer (Mettler Toledo Canada; Mississauga, ON) at 120 °C for three minutes to minimize the degradation of materials.

5.3.8 Particle size distribution

Particle size distributions (PSD) of the granular products from the granulator exit were determined by a Ro-Tap RX-29 sieve shaker (W.S. Tyler Inc., Mentor, OH, USA) with a series of sieves with openings of 3350 μm, 2360 μm 1180 μm, 850 μm, 500 μm, 250 μm and 125 μm, as well as a bottom pan. Around 100 g sample was placed in the unit and sieved by mechanical agitation for 5 min. The uncertainty of the method was estimated by 3 repeats (n = 3) for the conditions of AF15-150-80 °C-5%-60°.

5.3.9 Fracture strength of granular samples

Fracture strength was measured for the granular samples to detect voids or weaker assemblies of particles produced by the process. The fracture strength was determined on an Instron 3366 benchtop universal mechanical testing system (Instron Corporation; Canton, MA) following the Adams method[30]; consistent with the stated method procedure only a narrow particle size range was used, 1180 ~ 2360 μm, which were selected as a desirable size for tableting. Before fracture testing, all granular samples were pre-dried for 3 days at 50 °C and 20% RH to reduce capillary force contributions between particles so the true solid bridge strength was measured. At a crosshead speed of 3.5 mm/min, a 0.6 g sample was compressed in an 11.05 mm diameter bore until a maximum

load of 4200 N was reached. Bulk fracture strength was determined from the stress-strain curve. Uncertainty of the test is determined by three repeats (n = 3) of each sample.

5.3.10 Porosity measurement of granular samples

Consistent with the fracture strength measurement, granular samples for the porosity measurement used the same particle size range of 1180 ~ 2360 μm. An improved method was used based on the kerosene displacement method [31,32]. A 0.2 g sample was pre-saturated in kerosene for 1 hour to penetrate into the large pores of the granules, followed by draining the kerosene for an additional 1 hour. The drained samples were re-immersed in kerosene within a customized flask with narrow neck (4 mm) and the displaced volume was determined. The true density of the dry granules was measured by MVP-6DC Multipycnometer (Quantachrome, Boynton Beach, FL) using ultrahigh purity nitrogen gas. Presented porosity values corresponded to the mean value of five repeats (n = 5).

5.3.11 SEM and optical microscope

Optical and scanning electron microscopy (SEM) were conducted at the Canadian Centre of Electron Microscopy (CCEM). Particles of 1180 ~ 2360 μm were examined using a stereo microscope (Stemi 2000 C, Carl Zeiss, Jena, Germany) and initial pure excipient particles are examined by an optical microscope (Axioplan 2, Carl Zeiss AG, Göttingen, Germany). Particle samples examined in the stereo microscope were subsequently analyzed by SEM (Jeol, JSM-6610LV, Japan) by mounting on carbon tape

and sputter coating with 15 nm gold. The SEM was operated with an accelerating voltage of 3.0 kV.

5.3.12 Statistical analysis

Relevance of the different experimental parameters studied were tested for their significance by the Student's t-test (P-value) using the software package, JMP v10.0 (SAS Institute Inc.; Cary, NC). Relationships were sought between the different measurements and the operation parameters of screw speed, zone temperature and moisture content. Statistical analysis results were summarized in Table 3, differentiated based on the binder used. When the P-value was less than 0.05, impact of parameters were considered as strongly significant. Considering the limited sample size for the statistical analysis and noting trends in the data that appeared relevant for discussion, factors with P-value from 0.05 to 0.1 were not neglected.

Table 5-3: P values for impact of screw speed, moisture content and zone temperature.

	Pressure	Load	Sample temperature	D50	Porosity	Fracture strength
Screw speed	0.022*	0.596	0.058	0.015	0.106	0.097
Moisture content	0.418	0.001	0.0001	0.004	0.001	0.015
Zone temperature	0.857	0.746	0.015	0.128	0.212	0.155

■ $p < 0.05$, ■ $0.05 < p < 0.1$

*Underlined values correspond to minus coefficient

5.4 Results and Discussions

5.4.1 Influence of moisture content on the glass transition temperature

The determined T_g of the neat binding polymers were ranked in order as AF15 > Kollidon® VA 64 > Soluplus® > Kollidon® SR. Water was an expected lubricant on particle flow inside the extruder but could also be a plasticizer [33] reducing the T_g of these binding polymers. Results displayed in Figure 3(A) show a consistent trend where higher moisture content lowered the T_g. The relationship between moisture content and T_g has been reported by others [34]. All four polymers showed similar relative changes in their estimated T_g with moisture content. Amongst the polymers, this trend was much more obvious for the AF15 polymer than with Soluplus®. It was noted that the change from neat to 5% moisture content was more dramatic for Kollidon® VA64 than other polymers due to strong polymer-water interactions and had the least effect on SR due to weaker polymer-water interactions.

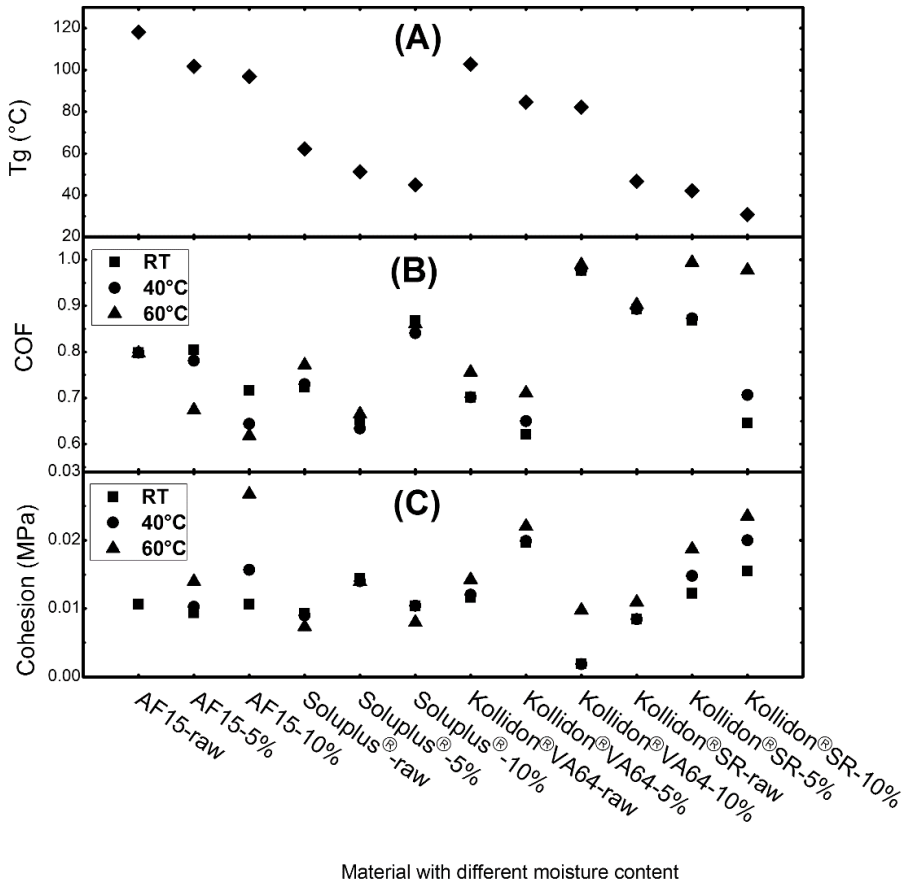

Figure 5-3: Results combination of DST and DSC. From top to bottom, Y axis respectively represent Tg of polymers with different moisture content, COF of formulations with different moisture content and cohesion of formulations with different moisture content. The relative error for Tg test was assessed by 3 repeats of AF15 which is 0.5 %. The uncertainty for the DST experiment was estimated by neat AF15, where relative uncertainty of COF is 10.7% and relative uncertainty of cohesion is 5.4%.

5.4.2 Cohesion and coefficient of friction

Testing for particulate flow characteristics, specifically their cohesion and the coefficient of friction, for temperature dependency was challenging since the apparatus had no thermal control. The results presented are given based on the pre-heated sample temperature, though the final measured temperatures at the end of the tests were still reasonably close, being 37 °C±3 °C for the 40 °C condition and 53 °C± 5 °C for the 60 °C condition. The flow parameters, cohesion and coefficient of friction, as determined for the three setpoint temperatures of all four formulations are shown in Figures 3(B) and 3(C). The coefficient of friction showed the most variability in the tests. As shown in Figures, the COF of AF15, decreased and cohesion increased with increasing moisture contents of 5% or greater. The COF of Soluplus® and Kollidon® VA64 formulations increased with temperature but showed a minima with respect to moisture content. The T_g of these two polymers at 10% moisture content were too close to the operating temperatures in the test and hence some melting likely occurred causing the COF to rise. The Kollidon® SR formulation showed no sensitivity in its neat state but its COF showed increasing temperature dependency for moisture contents of 5% or greater. At 60 °C, its COF rose from 0.9 to close to unity for moisture contents of 5% or greater. The T_g of Kollidon® SR was the lowest in the study which meant that 60 °C was sufficient to soften the polymer particles regardless of the plasticizing effect of moisture (Figure 3(A)). At room temperature and 40 °C, the COF for Kollidon® SR was high (~0.9) in its neat state yet decreased with increasing moisture content (Figure 3(B)).

The parameter of cohesion increased slightly with temperature in almost all cases except the formulation with Soluplus®, which showed no dependency (Figure 3(C)). Cohesion was highest in the study at 0.027 MPa for the AF15 formulation at the conditions of 60 °C and 10% moisture content. In fact, this formulation was the only one tested to show a strong temperature effect on cohesion. Though less affected by temperature than AF15, the Kollidon® SR formulation still showed the influence of temperature better than other formulations. Moisture had a much greater impact on cohesion than COF but did not always cause the cohesion to increase. Increased cohesion corresponded with increasing moisture content for AF15 and Kollidon® SR formulations. The gel layer of a hydrated HPMC like AF15 would be expected to be cohesive; this more lubricious form of HPMC similarly explains the decrease in COF witnessed for AF 15. The increase in cohesion and decrease in COF with moisture level for Kollidon® SR suggests the moisture was more likely to be present as surface water for sliding and bridging than absorbed, at least below 60 °C. Moisture content had little effect on cohesion for the Solplus® formulation, showing a slight maxima for 5%. With Kollidon® VA64, the same maxima appeared at 5% though it was much more obvious for this formulation with larger variance in the cohesion value. The decline at 10% moisture content in both cases corresponded to a rise in COF.

5.4.3 Transient sintering analysis

Sintering profiles for transient heating are combined for the different polymers in Figure 4. The plots show that sintering rates for particle coalescence had no apparent

relationship with T_g amongst these polymers, though it was generally found that the onset temperature for coalescence (i.e. temperature where the neck radius began to increase) decreased with decreasing T_g. This can be explained by the fact that polymer sintering is affected by viscosity, to which T_g shows an influence, and surface tension [35,36].

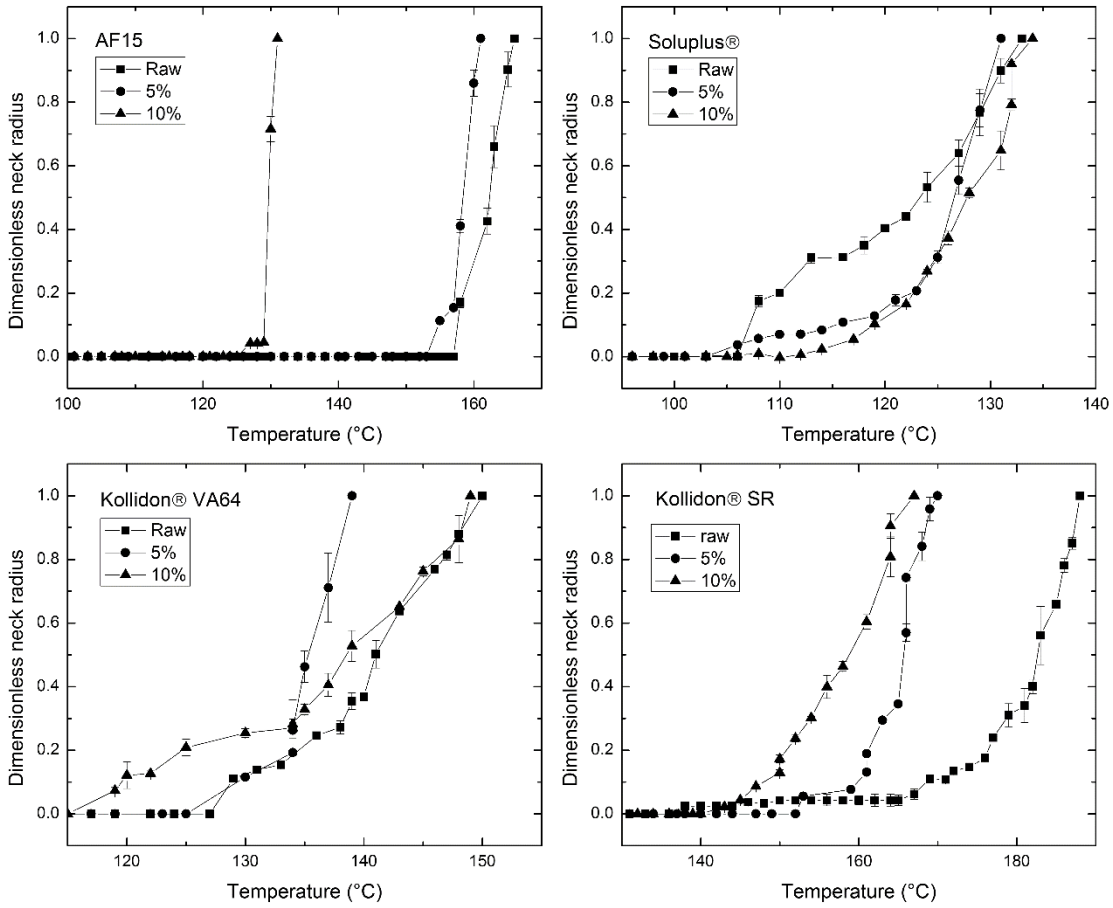

Figure 5-4: Sintering profiles of pure excipients with different moisture contents, heated at 1 °C/min.

Sinter progress in this test was defined by the span of temperatures from the onset temperature to the temperature at which all particles had totally sintered (y/a =1) and then

the midpoint temperature of sintering process was examined. Midpoint temperature for Kollidon® SR appeared to be higher than the other polymers, particularly for its particles at neat (initial) moisture content, whereas Soluplus® and Kollidon® VA64 showed the lowest onset temperatures for melt coalescence though not the fastest sintering rate. The midpoints of sintering process for binders decreased in order: Soluplus® (~120 °C) < Kollidon® VA64 (~130 °C) < AF15 (~145 °C) < Kollidon® SR (~160 °C)..

The impact of moisture had the anticipated effect of reducing the midpoint temperature with increased content, based on its influence on T_g, for all polymers. Comparing the sintering results with other characterizations, a correlation was notably observed for polymers showing lower sintering midpoint exhibiting higher motor load and seemingly higher MRT when their corresponding formulations were processed.

5.4.4 Operational state of assisted dry granulation

Nominal pressure, motor load and sample temperature measurements collected for the new processing method are summarized in Figure 5, where an indicated zero pressure value meant that the value was too low (< 0.005 MPa) to be detected by the transducer. As seen in the Figure 5, the majority of reported experimental runs were done at 80 °C since it was the most successful temperature for granulation with all of the binding polymers. Formulations containing Kollidon® VA64, Soluplus® and AF15 could be suitably granulated at all tested temperatures.

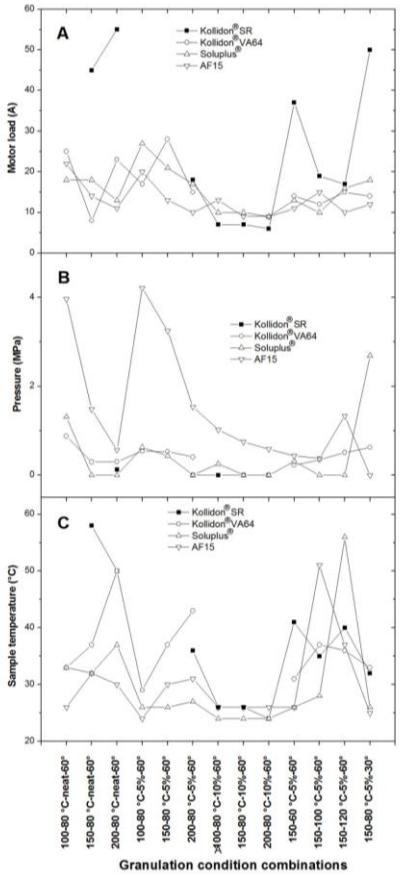

Figure 5-5: A: Motor load (Load) during granulation. Relative uncertainty is 7.7 % estimated by three repeated trials for the condition of AF15-150-80 °C-5%-60°. B: Pressure in kneading block during granulation. Relative uncertainty is 4.3 % estimated by three repeated trials for the condition of AF15-150-80 °C-5%-60°C and reported zero pressure indicates that the pressure is too low to be detected by the pressure sensor. C: Sample temperature from exit during granulation. Relative uncertainty is 2.0 % estimated by three repeated trials for the condition of AF15-150-80 °C-5%-60°. Absence of data indicates that motor of the granulator seized at this condition. For Kollidon® SR, screw speed is 200 rpm for label of 150-60 °C-5%-60°, 150-100 °C-5%-60° and 150-120 °C-5%-60° and moisture content is initial for label of 150-80 °C-5%-30°.

Increasing screw speed decreased the zone pressure for all formulations as seen in Figure 5(B) and Table 3 (P = 0.022), regardless of the kneading block configuration. This trend was most obvious with the Soluplus® and AF15 formulations. The drop in pressure was a result of the decreasing degree to which the kneading block volume was filled by powder as particle velocity through the zone increased. No trend was detected for the impact of moisture content (P = 0.418) and zone temperature (P = 0.857) on pressure.

The trends seen on motor load did not match the pressure data, as shown in Figure 5(A). In terms of motor load, increasing screw speed appeared to decrease mechanical energy demand (P = 0.022), which was especially noted with the formulations containing AF15. Comparatively, the load was more likely to vary with moisture content (P = 0.001). For all formulations the load was lowest at 10% moisture. Zone temperature was not seen to affect the motor load (P = 0.746). With Kollidon® SR, the highest load (37 amps) was produced at 60 °C, while 120 °C had the lowest load (17 amps). Runs with Kollidon® VA64 and Soluplus® exhibited their highest load (28 amps and 21 amps, respectively) by varying zone temperature at 80 °C while for AF15, load peaked (15 amps) at 100 °C. Load varied the most for the Kollidon® SR formulation among all experiments, reaching 55 amps (out of a maximum of 61 amps) for 200-80 °C-neat-60° while dropping to its lowest value of 6 A for 200-80 °C-10%-60°. With the exception of Kollidon® SR, loads for 30° offset kneading block are lower than 60° offset kneading for 3 formulations and this might be due to the lower shearing effect.

Lower sample temperatures were always found with lower screw speeds (P = 0.058), as shown in Figure 5(C). This effect was minor for Soluplus® because its final sample temperatures were already close to the system setpoint (around 30 °C) but it was particularly significant with Kollidon® VA64. For the runs with Kollidon® VA64, temperature decreased as low as 33 °C and 29 °C (100-80 °C-neat-60° and 100-80 °C-5%-60°) while being as high as 50 °C and 43 °C (200-80 °C-neat-60° and 200-80 °C-5%-60°). Higher zone 2 temperatures result in higher sample temperatures as P value was 0.015. Higher moisture content appeared to decrease the sample temperature (P = 0.0001). Finally, the lower kneading block offset angle decreased the sample temperature.

Relationships amongst the studied responses of pressure, load and temperature appeared complex, with no consistent trend with the tested experimental factors. This finding was felt to indicate that interactions were dominant among the factors, as will be outlined in the subsequent discussion.

5.4.5 Residence time

The calculated mean residence time is plotted versus different operating conditions in Figure 6. Peclet numbers (Pe) for all granulation conditions were almost identical, Pe~0.57, which indicates the mixing behavior during granulation was not strong. Higher screw speeds decreased the residence time, which is understandable since particle velocity is directly proportional to the rate of revolution in a screw extruder or auger. Similarly, a lower MRT was found with the kneading block of 30° offset since the kneading discs in this configuration formed the appearance of a more continuous flight

versus 60°. For these operational factors, a lower MRT corresponded to a lower sample temperature, as previously noted. As zone 2 temperature increased from 80 °C to 120 °C, MRT increased for the formulations Soluplus®, Kollidon® VA64 and Kollidon® SR but decreased for AF15. Additionally, higher moisture content decreased MRT for AF15, but increased MRT for the other formulations. Interestingly, the MRT varied between 25 s and 55 s for all four formulations regardless of low or high moisture content.

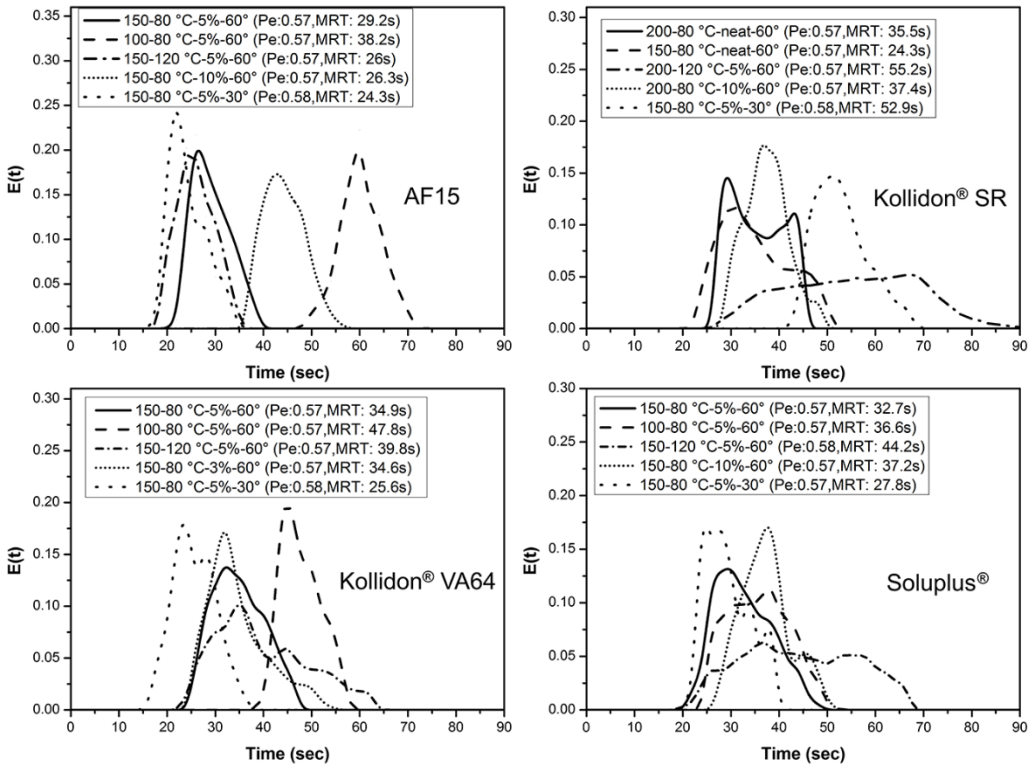

Figure 5-6: Mean residence time for different granulation conditions.

When comparing however results among the different formulations, MRT was lower with AF15 and Soluplus®, compared to Kollidon® VA64 and Kollidon® SR. In fact,

runs with Kollidon® SR had the longest residence time, with the MRT exceeding 55s for 150-80°C-neat-60°. Comparatively, the process residence time was often shortest with AF15, being below 25s.

5.4.6 Particle size distribution

Average particle size was used to understand the influences of experimental factors on this technique for granulation. Overall, the size distributions looked very similar to one another in shape, being bimodal which is consistent with reported distribution for wet granulation in the twin screw extruder [8].

The average granule sizes of the different conditions, given as D50, are plotted in Figure 7(C). The relative uncertainty for the value was determined to be 8.2%. According to the results, higher screw speed tended to slightly ($P = 0.015$) increase D50 for most of the granulation conditions. Higher zone 2 temperatures could cause chunks (>3350 μm) even though the impact was minor during granulation. Surprisingly, increasing moisture content resulted in decreasing D50 ($P = 0.0001$), though the effect was minor for Kollidon® VA64; the influence of moisture on granulation is significantly different from observations with twin-screw wet granulation [37–39]. Excluding the samples with Kollidon® VA64, use of the 30° kneading block slightly decreased D50. In general, D50 was approximately 1000 μm with the Soluplus® and AF15 formulations and very consistent across a range of conditions, while granules were relatively smaller compared to formulations containing Kollidon® VA64 or Kollidon® SR. D50 varied to a much larger

degree for the formulations with Kollidon® VA64 and Kollidon® SR, nominally 1160 μm for Kollidon® VA64 and 1080 μm for Kollidon® SR.

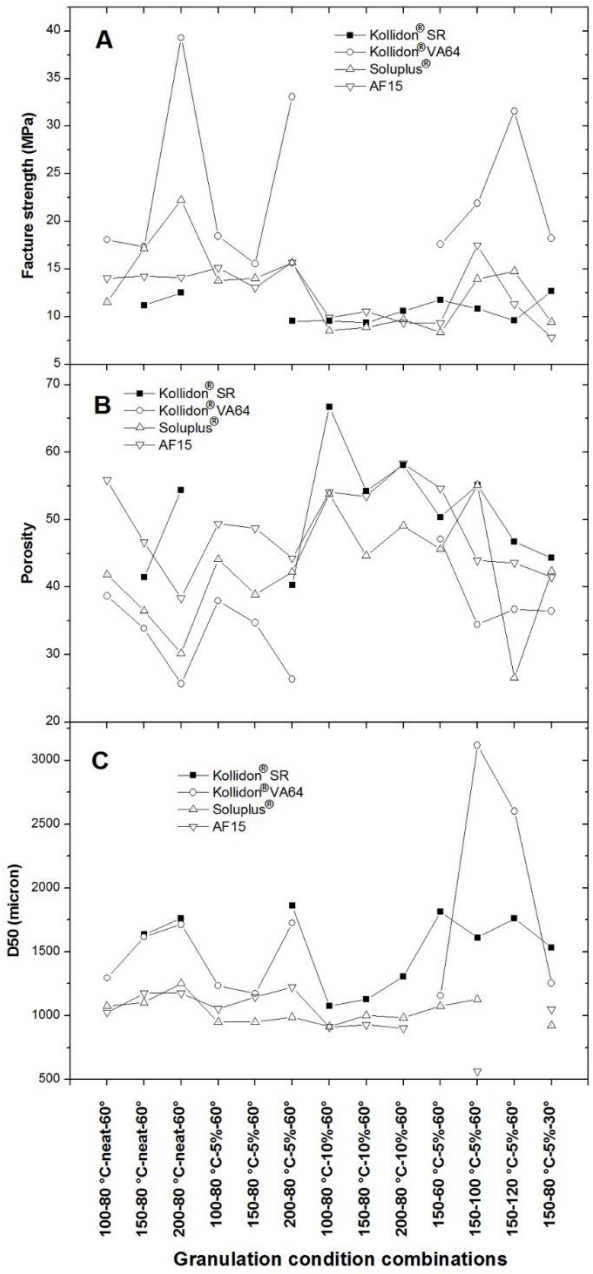

Figure 5-7: Granule fracture strength produced in the assisted granulation experiments, differentiated based on the polymer binder used in each formulations. Relative uncertainty is mainly ranges from 10% ~ 15%. B: Granule porosity produced in the assisted granulation

experiments, differentiated based on the polymer binder used in each formulation. Relative uncertainty is mainly ranges from 1% ~ 15%; C: Calculated D50 for particle samples from different granulation conditions. Relative uncertainty of D50 was 8.2% as estimated by repeats (n=3) of AF15-150-80 °C-5%-60°.

5.4.7 Fracture strength and porosity

Fracture strength and porosity results from the assisted granulation trials are shown in Figure 7(A) and 7(B). Modeled compression curves for all samples were showing similar trends that when natural strain is greater than 0.2, liner region implies the plasticity of granules when samples start to crush. Increased screw speed tended to weakly strengthen the granules (P = 0.097) and correspondingly decrease porosity. Higher barrel temperature for zone 2 slightly contributed to stronger granules (P = 0.055). Higher moisture content decreases granule strength (P =0.015) and this is also supported by increased porosities (P = 0.001). Most fracture strength values for Kollidon® VA64 were higher than 15 MPa and even reached 40 MPa for granulation condition of Kollidon® VA64-200-80 °C-neat-60°. The porosity tends to be the lowest for Kollidon® VA64 and to be highest for Kollidon® SR. The porosity and granule strength of AF15 and Soluplus® binders however were very similar.

5.5 Mechanism of Assisted Twin Screw Dry Granulation

5.5.1 Observations of the dry granulation process and granular samples

Screw pull-out photos strongly pointed to the kneading block as the decisive element in this new granulation process, triggering granulation by melting/softening and compacting particles. Two images of screws removed from the extruder still containing solids are shown in Figure 8 following the 'screw pullouts' method [23], for granulation conditions corresponding to AF15-150-80 °C-neat-60° and AF15-150-80 °C-5%-60°. The images show that powder packed in the kneading block in a manner consistent with earlier reported screw pullouts for twin-screw wet granulation [40] and subsequently broke up in the conveying elements immediately afterwards [7]. Packed powders in the kneading block were present in a semi-molten state, which will be highlighted in given SEM micrographs in the following discussion. The screws could not be extracted for examination in regards to runs with Kollidon® SR, Kollidon® VA64 or Soluplus® formulations because of the highly consolidated state of powder in the kneading block; however, granulation behaviour could still be observed for Kollidon® SR through the barrel opening above this section, as shown in Figure 8. Softening of Kollidon® SR in the kneading block was found to be more thorough than with the other tested formulations. Observations for Kollidon® VA64 and Soluplus® could not be made in the same manner because the melted material stuck on the cover placed over the opening during operation of the extruder and its removal disturbed the state of material in the kneading section.

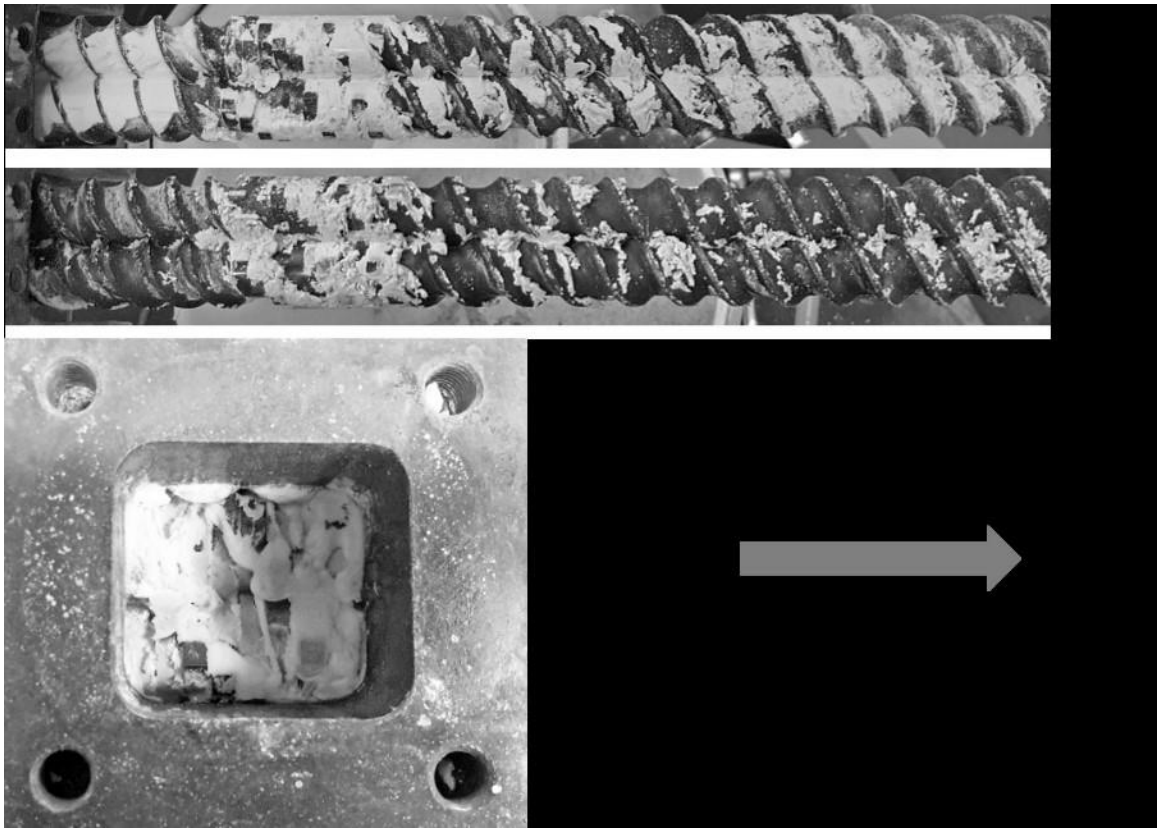

Figure 5-8: Screw pictures taken by ‘screw pullouts’ technology and kneading block pictures removing cover. The picture of screws a is from granulation condition of AF15-150-80 °C-neat-60°; the picture of screws b is from granulation condition of AF15-150-80 °C-5%-60°. Some granulation conditions were not ‘screw pullouts’ permitted as screws will be stuck in barrel once screws were stopped abruptly. Picture c is from granulation condition of Kollidon® SR-150-80 °C-neat-60°.

SEM micrographs presented in Figure 9 show evidence of molten polymer under shear flow in the granules, noted by smooth planar regions and drawn fibrillar masses (most clearly shown in the image of granules based on the Kollidon® VA64 formulation but seen to differing degrees for all formulations). The rough irregular areas seen in the

images corresponded in size (~125 μm) to the lactose excipient which had too high of a melt point (219 °C) to be expected to soften in the studies; the lactose particles appear crystalline with sharp edges and corners unlike other excipients with rounded surfaces. The micrographs show the lactose being bound by the polymer.

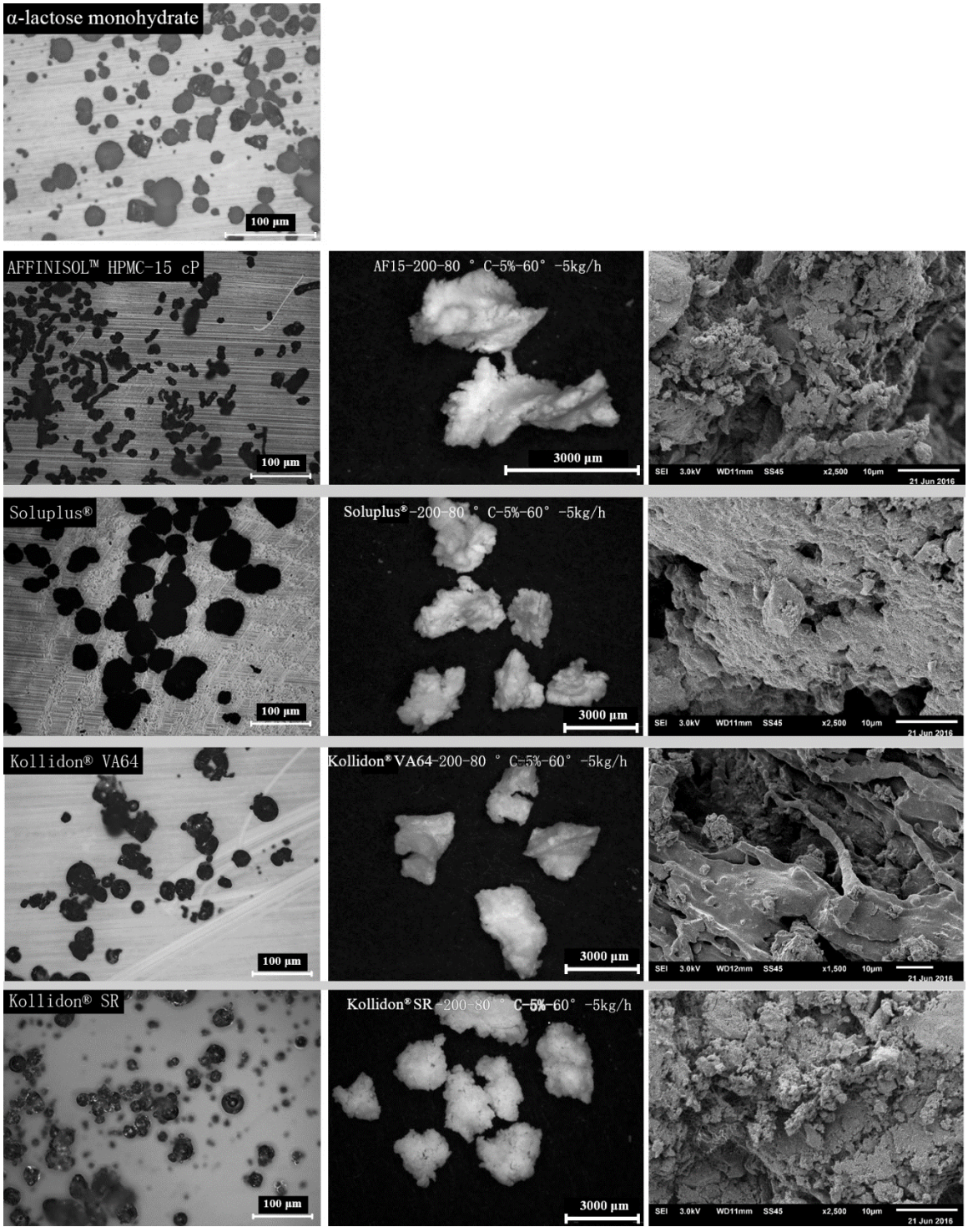

Figure 5-9: Combination of results of optical microscope of initial pure ingredient particles (left column), stereo microscope of granules with size of 1180-2360 µm (medium column) and SEM of

granules from stereo microscope (right column). Initial pure α-lactose monohydrate particles were also detected by optical microscope. Lactose particle are crystal-like with edges and corners and particle size ranges from 10 to 30 μm.

5.5.2 Influence of parameters on the assisted dry granulation

Sensitivity of the process to conveying forces in the kneading block was highlighted by a comparison in performance between a 30° and 60° offset block design. Powders through the kneading block with 60° offset experienced more flow resistance than with the 30° offset, as evident by higher reported motor loads. The MRT for 60° kneading block was higher than the MRT for 30° kneading block as a result of this reduced conveying capacity, which was helpful in heating the powders. Overall, the 60° kneading block tended to produce larger sized granules with higher sample temperature in the process.

Barrel temperature around the kneading section largely determined the success of the assisted dry granulation process. Operated at 30 °C, similar to the other barrel zones, no granulation occurred for any tested formulation implying the necessity of an elevated zone temperature, though such testing was only done for formulations with their initial moisture content. Raising the zone temperature appeared to have no discernable influence on COF for the tested polymers, based on direct shear testing, with the exception of Kollidon® SR. The COF for Kollidon® SR showed a significant increase with temperature, which was attributed to it being the only binder with a T_g close to the direct shear test conditions; testing for COF near the T_g of the other polymers was not possible due to the

design of the instrument. This leaves the possibility that the COF was influential to the process but implies then that softening of the binders was necessary.

The observed importance of the T_g on granulation points to the relevance of chain mobility in granule growth. In a softened state, any of these polymers should exhibit an increased apparent COF, adhering to the extruder wall and any local particles, as well as contributing to bridging. Continual increase in temperature, once the polymer flows though, would decrease its melt viscosity and hence lower bridge strength such that granules may break readily in the presence of high process stresses into smaller particle sizes. The weak particle size dependency on temperature for Kollidon® SR despite having the lowest T_g, further suggests the importance of viscosity in what is being observed.

Higher screw speeds reduced the MRT, which reduced the amount of heat possibly transferred by conduction and yet a greater number of bridges and stronger bridges occurred based on the evidence that particle size increased along with fracture strength of the corresponding samples. Processing at increased screw speed was noticed to coincide with higher sample temperatures at the exit, which cannot occur by shortening the residence time unless heat modes other than conduction were present. There appears to be a relationship between heat generation and sliding velocity/shear that is leading to the conclusion that polymer melting, and hence the binding mechanism of this assisted dry granulation method, was being brought about by frictional energy dissipation. Since higher screw speeds will decrease the fill volume of the screws, noticed by the decrease in pressure and motor load, the asserted importance on sliding velocity to generate heat is

felt to be reinforced. The repeated observations that pressure was not always detectable in zone 2 when granules were produced diminishes the belief that plastic energy dissipation significantly contributed to binder melting but since the pressure transducer may not detect squeezing forces on powders in the intermeshing region between the two rotating kneading block elements, this mode of heating was not fully discounted either. The dependency on friction energy dissipation (and possibly plastic energy dissipation) means that the mechanism for granule development by assisted dry granulation is different from twin-screw melt granulation [41], which are primarily reliant on conductive heating.

The addition of moisture was tested as a means to explore its influence on the mechanism, though it was recognized that the least amount should be added if no drying was to occur downstream. The residual moisture content of granular samples collected at the exit was measured immediately after the trial run completed. The reported values showed that moisture was not completely removed but experienced a decline by approximately 0.3%, 0.6% and 1.7% corresponding to original conditions of neat, 5% and 10% moisture content, respectively for the operating conditions of 150 rpm and 80 °C (zone 2 temperature). The partial moisture loss was caused by the heat generated during granulation. While higher moisture contents of 5% or 10% were included for testing, all neat formulations could be granulated. Preliminary tests with oven-dried powders showed that granulates could be produced but only as the system was on the verge of blockage by varying the flow rate and screw speed and was deemed to be largely uncontrollable, though a more powerful granulator might function better. Therefore, some minor amount of moisture appears beneficial in controlling the system. Higher moisture content

increased the cohesion of binders, though in some cases only slightly, and hence contributed to retarding material flow through the kneading block (which is necessary to bulk compaction). However, it appeared at times that the water was acting as a lubricant to reduce the heat generated by decreasing the COF which will weaken the bridge strength and thereby decrease the particle size and fracture strength. Increasing moisture content decreased the T_g of polymer and the midpoint temperature of sintering between polymer particles leading to higher motor load. Binders with a lower T_g should certainly be considered for the technique as they would allow granulation at lower barrel zone temperatures, which reduces thermal degradation concerns.

5.5.3 Conceptual outline of the mechanism

The mechanism of particle agglomeration in the kneading block for this assisted dry granulation technique is conceptualized in Figure 10. Particle agglomeration initially begins with frictional forces acting on the particles as they rub against each other under compression (stage a). Due to the reduction in T_g caused by the presence of any moisture, the generated heat is sufficient to result in partial sintering of the polymeric binder (stage b). The agglomerates containing melted or softened binder are deformed by shear and compression (stage c) which can produce additional heat to enable the particles to more fully coalesce (stage d).

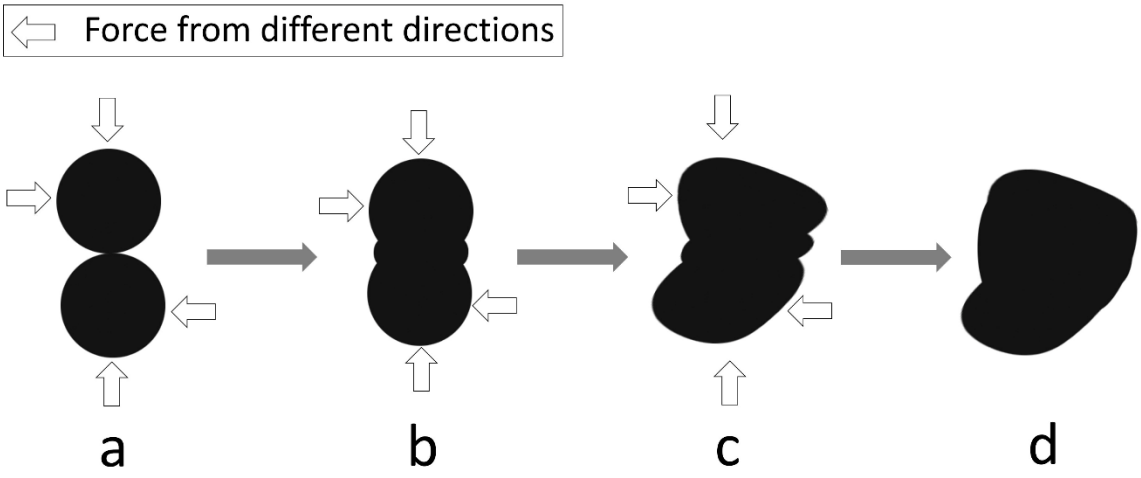

Figure 5-10: Regime of twin screw dry granulation.

When polymers start to melt, at least at the particle surface, the combination of particles is related to the polymer's sintering rate; high midpoint temperature correlates with increased motor load and can even result in seizing of the screws, as seen with Kollidon® SR at lower moisture content (5% or less). As a result, the binder selected should exhibit a low T_g but also show a low midpoint temperature in order to be suitable for this assisted dry granulation technique.

5.6 Conclusion

Assisted dry granulation was accomplished in a twin screw granulator with simple screw configurations. The mechanism of twin screw dry granulation is different from other granulation strategies, such as wet granulation, hot melt granulation or roller compaction. When powders containing a polymer binder are pushed through the kneading section, heat is produced rapidly by friction. The deformable binder particles melt to

varying degrees such that particles are able to fuse to one another. During granulations, the initial moisture content of fed material and barrel temperature before and in kneading blocks zone are major factors. Some moisture was beneficial, particularly for high T_g polymers but overall, the neat moisture of incoming ingredients was sufficient to produce well granulated products. Selected polymer particles are more prone to soften and flow under frictional forces if their T_g was closer to the barrel zone temperature in the kneading section. A higher zone temperature highly increase the opportunities for successful granulations. Screw speed was a major cause for friction heating while the kneading block offset was only minor in its influence on the granulation process. Sintering measurement is an eligible benchtop technology to investigate the heated twin-screw twin screw granulation process for different materials.

5.7 References

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Chapter 6

Impact of non-binder ingredients and molecular weight of polymer binders on heat assisted twin screw dry granulation

This chapter is a manuscript in preparation.

6.1 ABSTRACT

Two grades of commercial AFFINISOL™ HPMC HME were used as polymer binders to explore the influence of viscosity and their concentration on a dry granulation process with a twin screw extruder. Contributions of other non-binder ingredients in the formulations were also studied for lactose, microcrystalline cellulose and an active pharmaceutical ingredient of caffeine. As sensitive indicators of processing conditions

that expose the drug to high internally generated heat, dehydration of α-lactose monohydrate and polymorphic transformation of caffeine were monitored by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD). Additionally, any decomposition of caffeine was determined by high-performance liquid chromatography (HPLC). Granular samples were characterized by particle size, circularity, fracture strength and their temperature on the exit of extruder. High screw speed and low feed rate were found to help particles to agglomerate by allowing feed particles to increase in temperature. Lower binder molecular weight and higher binder concentration enable granules to build stronger strength and hereby lead to higher particle size. The twin screw dry granulation was found to be advantaged over conventional hot melt granulation by protecting the ingredients from degradation.

6.2 Introduction

Twin screw dry granulation (TSDG) was introduced in a previous work, with a novel mechanism for granule agglomeration being proposed based on the processing of four different placebo formulations. Heat for binder softening in this new method came, not only from the barrel like in hot melt granulation (HMG), but was primarily generated from the frictional and plastic dissipation internal to the particle matrix. In a previous paper, this granulation process was found to be significantly impacted by the polymer binder but because the study used different yet commercially relevant polymers, the relevance of viscosity and concentration still need to be studied.

The influence of binder viscosity has been shown by numerous twin screw wet granulation [1–3] and high shear wet granulation [4–6] studies to strongly affect particle size. Most of those researchers concluded that larger particle size were caused by use of higher viscosity of binder [2,7] and likewise observed lower granulation rate [1] and poor liquid distribution [8]. For hot melt granulation, fluidized bed studies [9–12] on the influence of binder viscosity have found the opposite effect with smaller particle sizes were always obtained with binders of higher viscosity. However, this trend seems reversible with more intensive mixing, as Mu [13] found particle size was increased for higher viscosity binders in twin screw melt granulation. In fact, compared to wet granulation, the viscosity of a binder is often considered more crucial for hot melt granulation (HMG) in batch processes since a minimum viscosity is required [4,6] even though lower viscosities might be preferable for spreading [14]. For HMG, the influence

of binder viscosity is more significantly related to initial particle size than in wet granulation [11,13,14].

Binder viscosity, as a variable of study, have never been discussed in dry granulation processes. This could be attributed to the fact that dry granulation, for batch processes like roller compaction, use a non-melt binding mechanism[15,16]. Since twin screw dry granulation takes aspects of particle agglomeration from hot melt granulation but is much more strongly reliant on frictional heat, it is expected that viscosity will influence the granulation process in a somewhat more significant way.

The current work will, therefore, focus on a polymer binder with two different molecular weights and used at different concentrations to examine how its impacts system viscosity of the granulation process. Non-binder fillers will also be investigated to explore the relationship between their properties and the heat of the system on final granular product. The polymorphic nature of an active pharmaceutical ingredient (API) was meanwhile used as a tool to estimate the heat generated by friction and plastic dissipation within TSDG, and the process was compared to HMG for such ingredient transitions to demonstrate the merit of the new technique.

6.3 Materials and Methods

6.3.1 Materials

Anhydrous caffeine (Sigma-Aldrich; Canada) was used as the model API. It was annealed at 90 °C for 24 hours prior to its use to ensure the caffeine was completed

converted to its Form II crystal structure [17]. Two grade of hydroxypropyl methylcellulose (HPMC) were used as binders: AFFINISOL™ HPMC HME , 100LV and 4M, kindly donated by The Dow Chemical Company (Midland, MI). These two binders were subsequently referenced in this study as 100LV and 4M, having stated viscosities of 100 cp and 4000 cp in 2% aqueous solution, respectively. Two commercial non-binder fillers were used in the study; Flowlac 100 spray-dried α-lactose monohydrate (Meggle Pharma; Germany) is referred to as LAC, and Avicel PH101 microcrystalline cellulose (FMC Biopolymer; Newark, NJ) is referred to as MCC. Generation of the dehydrated lactose form in this study will be referred to as DeLac. The dehydrated lactose that was intentionally made for characterization purposes (i.e. not arising from the extrusion trials) was prepared by heating α-lactose monohydrate for 3 hours at 140 °C in oven and monitored by a Mettler-Toledo HG63 moisture analyzer until all hydrate groups were lost.

Initial moisture contents of individual materials were obtained by an Mettler-Toledo HG63 moisture analyzer for 100LV (2.1±0.1 %), 4M (2.1±0.1 %) LAC (2.3 ±0.2 %) and MCC (5.4%±0.3 %). These ingredients were used without subsequent drying.

6.3.2 Dry granulation and hot melt extrusion

Hot melt and dry granulation were both performed with the same formulations and screw configurations to compare differences in the phase transition of lactose and caffeine. A ZSE-HP 27 mm 40 L/D co-rotating intermeshing twin-screw extruder (American Leistritz Extrusion Corp.; Somerville, NJ) was used as a twin screw granulator in this

study. Formulations were fed into the extruder through a T-20 gravimetric feeder (Brabender Technologie Ltd.; Mississauga, ON). Screw configurations from a previous work were further simplified to reduce the motor load and thereby prevent the screws from locking up. As shown in Figure 1, a shorter kneading block (60° offset) with 5 discs was used instead of 10 discs in the previous study. The exit of the extruder was kept open without a die. Granular products were immediately measured from the exit of the extruder for their temperature using an infrared pyrometer.

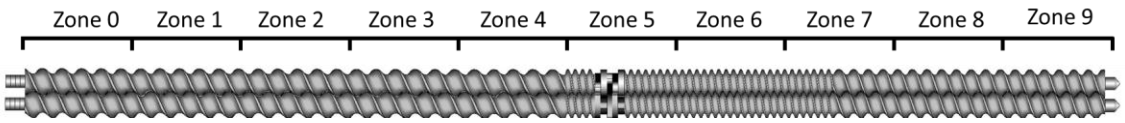

Figure 6-1: Screw configurations with conveying elements and 30 mm 60° offset kneading blocks.

Operating as hot melt granulation, all zones were maintained at 160 °C, which was recommended as suitable for the polymer to flow [18]. A flat barrel profile is common for hot melt granulation to give time for the polymer to melt coalesce via conductive heating (with some zones providing intensive shear as well). For dry granulation, only the temperature of Zone 2 in the barrel was constantly held at 160 °C while the other zones were held at 30 °C.

In some instances, wet granulation with a low liquid/solid (L/S) ratio was also performed to make comparisons with the dry granulation. Distilled water was injected into Zone 1 by a pair of interlinked ISCO 260D high pressure syringe pumps (Teledyne-ISCO Inc.; Lincoln, NE).

Current research is mainly looking at the variables of formulation, screw speed and feed rate while barrel temperature is constant as illustrated above. Two series of formulations were used by including two binders of 100LV and 4M, individually. Screw speed were increased if no granules could be obtained until powder formulations start to granulate or screw speed reached the limit of the granulator. Granulation samples were referenced to according to their conditions of study by combining the formulation composition and process parameters in the name, taking sample 40%100LV-60%LAC-N-200rpm-3kg/h for example which stands for granulation using a formulation with 40% HPMC 100LV (40%100LV) and 60% α-lactose monohydrate (60%LAC) without drug (N) at a screw speed of 200 rpm and feed rate of 3kg/h. The symbol "D" stands for the API when it was added in the formulation, such as 40%4M-50%LAC-10%D-200rpm-1kg/h where "10%D" meant that 10% caffeine was included. The quoted uncertainty in granulation was estimated by repeating conditions (n = 3) for 40%4M-60%LAC-N-200rpm-3kg/h, 40%4M-50%LAC-10%D-200rpm-3kg/h, 40%100LV-60%LAC-N-200rpm-3kg/h and 40%100LV-50%LAC-10%D-200rpm-3kg/h and by calculating the relative mean standard error for their particle size distributions.

6.3.3 Heating sintering profile

Sintering measurement were found as the most efficient offline method to evaluate properties of binders for the twin screw dry granulation in a previous study. Without shearing, bridging ability can be estimated by the sintering rate (defined by the midpoint temperature when binder particles coalesce with each other). Higher sintering

rate implies that bridges can more easily be formed during processing, making that material more applicable for dry granulation. With higher sintering rates, lower motor load and lower sample temperature can be expected.

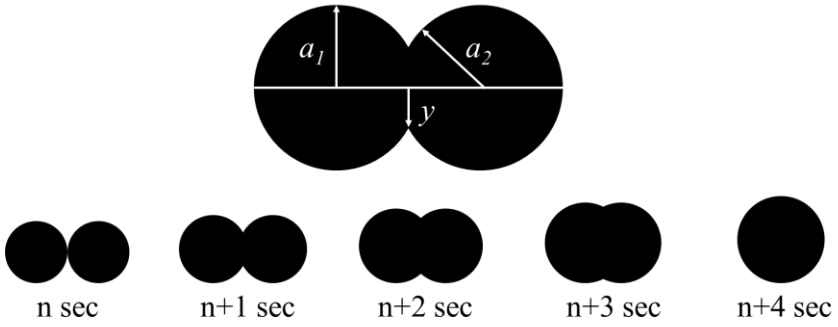

Figure 6-2: Demonstration *time-elapse* sintering neck radius *y* and particle radius *a as*

The sintering test apparatus consists of a deep-well hot stage apparatus for sample heating and an optical microscope connected to a digital camera to collect photographs of the wielding among a single layer of particles observed on the stage as time elapsed [19]. The theory of midpoint temperature of sintering can referenced in a previous work and the measurement is demonstrated in Figure 2 that shows the relative melt bridge radius adjoining two particles calculated as y/a, where y is the melt bridge radius (neck radius) and a is the average of a1 and a2 for the radius of two neighboring particles. The values of y, a1 and a2 were determined by ImageJ (Version 1.48, U. S. National Institutes of Health, USA). During a test, the hot stage was heated at a rate of 1 °C/s from room temperature to 200 °C and images were captured at a rate of one per second. Uncertainty was determined from three repeats (n = 3) of the measurement.

6.3.4 Cohesion and coefficient of friction measurement

The cohesion and coefficient of friction (internal, COF) of each pure ingredient were measured by direct shear testing (DST) [20–22]. COF and cohesion were calculated from the classic Mohr-Coulomb Failure Criterion which suggests a linear relationship between yield stress τ and normal pressure σ_n as given by,

$$t = c + s_n \tan f \quad (1)$$

where c is cohesion (treated as a constant) and ϕ is the angle of internal friction; tan ϕ is assumed to equal the COF in the test. A schematic of the DST is shown in Figure 3 where powder specimens were sheared in a pair of conventional rectangular shear boxes with inner dimension of 60 mm × 60 mm × 45 mm, at a displacement rate of 1 mm/min. The uncertainty of the method was estimated by three repeats (n = 3).

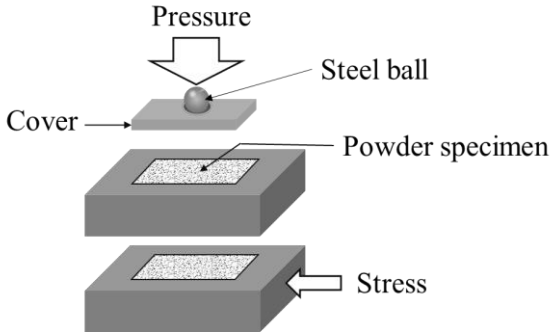

Figure 6-3: Schematic of apparatus for Direct Shear Test. Instrument mainly consist of cover and shear box. Shear box is divided into two parts, upper and lower one, buckled together and holding powder sample within it. During the test, weight was applied onto the steel ball and the lower part will move horizontally on a pair of rail.

6.3.5 Differential scanning calorimetry

The glass transition temperature (Tg) of the two binders was determined by a TA Instruments (New Castle, Delaware) Model Q200 differential scanning calorimeter (DSC) at a high heating rate of 40 °C min-1 from -20 °C to 250 °C using 10 mg of sample in a T-zero aluminum pan (TA Instruments; Switzerland); the high heating rate was necessary to properly resolve the transition from the heat flow baseline. The DSC was purged under nitrogen flow (50 ml/min).

DSC is also known as a method to quantitatively determine the polymorphic transformation of caffeine [17,23,24]. It was used to measure the percent of ingredient transition after granulation for the polymorphism transformation of caffeine and dehydration of LAC. A 1 g extruded sample was gently ground and mixed in a mortar and 20 mg was measured into a T-zero aluminum DSC pan. A heating rate of 10 °C min-1 was used. The uncertainty of the measurement was from three repeats (n = 3).

6.3.6 X-ray powder diffraction

Crystal structure of initial caffeine and polymorphic transformation of caffeine in granular sample was also estimated by a scanning X-ray diffractometer (Bruker D8 DISCOVER) using a cobalt sealed tube source (λ_{avg} = 1.79026 Å) with voltage of 35 kV and current of 45 mA. Specimen was scanned in the range from 5° to 70° 2θ at 0.2° increments. Obtained X-ray powder diffraction patterns were compared to the crystal

structure reported in the Cambridge Structural Database [25] to calculate the changes in crystallinity.

6.3.7 High-performance liquid chromatography

To determine if drug degradation occurred, high-performance liquid chromatography (HPLC) was used to confirm the content of caffeine in the formulation. Based on a method from Weatherley [26], approximate 100 mg of granular sample was exactly weighted and dissolved by a mobile phase (H_2O : Methanol = 70 : 30) into a 100 ml flask. These solutions were equilibrated in a refrigerator overnight and brought to 100 ml after being brought back to room temperature. After filtration through a 0.2 μm syringe filter, samples were prepared into two independent HPLC vials. Separation was achieved using a Waters Symmetry300C18 column (250×4.6 mm2, 5 μm particle size) with an injection volume of 20 μL. Each granular sample was analyzed for three times (n = 3) and a pure standard drug solution was prepared and measured as reference for drug concentration calculation.

6.3.8 Particle size distribution

Granular samples were collected from the exit of the twin screw granulator and then air dried at 35% relative humidity for two days and subsequently sealed in bags prior to testing. Size of particles for a specific sample was quoted by its D50 calculated from the particle size distribution (PSD) measured with a Ro-Tap RX-29 sieve shaker (W.S. Tyler Inc., Mentor, OH, USA). A sample of 100 g was placed in the shaker housing a series of sieves with openings of 3350 μm, 2360 μm 1180 μm, 850 μm, 500

μm, 250 μm and 125 μm, as well as a bottom pan, and mechanically agitated for 5 min. The uncertainty of the method was estimated by three repeats (n = 3).

6.3.9 Fracture strength of granular samples

An Instron 3366 benchtop universal mechanical testing system (Instron Corporation; Canton, MA) was used to determine the fracture strength of granules from stress-strain curve by following the Adams method [27]. Refer to earlier studies for the calculation [28]. After equilibrating for 3 days at 23 °C and 20% RH, 0.6 g of a granular sample was placed in die press with an 11.05 mm diameter bore and compressed at speed of 3.5 mm/min until a maximum load of 4200 N was reached. The uncertainty is based on three repeats (n=3) for each sample.

6.3.10 Shape factor measurement

To present a better description of the granule appearance, a shape factor of circularity, also known as the isoperimetric quotient, was measured where the circularity is a function of the perimeter *P* and the 2-D transposed area A as given by equation (1):

$$\text{Circularity} = \frac{4\pi A}{P^2} \tag{3}$$

Granular samples in the size range of 1180 ~ 2360 μm were measured for consistency with previous fracture strength characterizations. To obtain the circularity, 1 g granular sample was spread out over a black background stage and then top-view photographs of the granules were collected. Circularity was directly calculated using image analysis

software, ImageJ (Version 1.48, U. S. National Institutes of Health, USA). The uncertainty is based on three repeats (n=3) for each sample.

6.4 Results and Discussions

6.4.1 Process-related properties of the ingredients

The main mechanism of granule growth during TSDG was proposed in an earlier work whereby initially particles slow down upon approach to a kneading zone causing the solids assembly to build pressure, as shown in Figure 4, such that under shear the powders generate enough frictional heat to soften/melt the included polymer binder and melt coalesce with neighboring ingredients. Adhesive forces are felt to be crucial to enabling powders to slow down and pressurize, which will be dependent upon the softening point of the ingredients (using Tg as a reference for the polymer binders), amount of softening mass, and the restrictive geometry of the kneading zone; COF will be treated as the relative indicator of the amount of frictional heat possibly generated. To understand the contributions of each ingredient to the COF and cohesion parameters, pure materials were characterized individually.

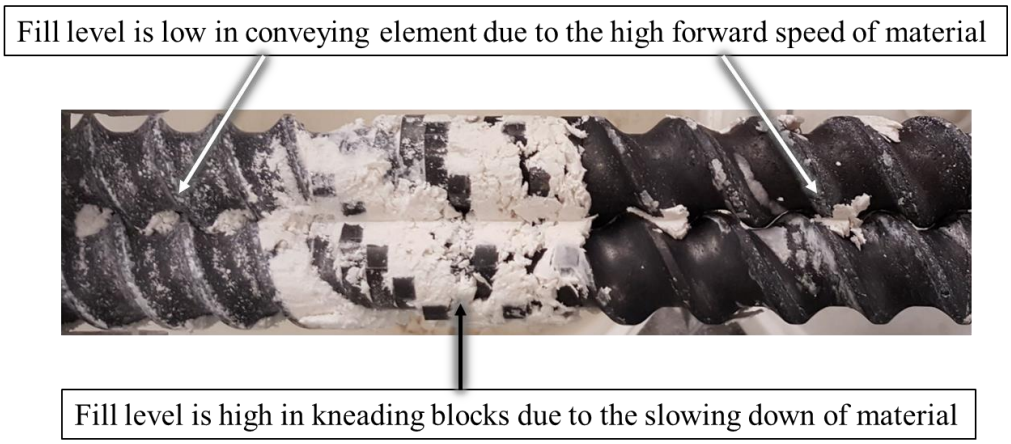

Figure 6-4: Demonstration of pressure build-up in kneading block

As shown in Figure 5, the cohesion value of 4M (17 KPa) was higher than 100LV (13.5 KPa) which can be a result of their differences in chain length [29–31]. Cohesion can be amplified by dehydration for LAC due to the increased specific surface area caused by the decreased particle size [23]. The increased cohesion could lead to formulations with DeLAC slowing down more readily in the kneading block. In terms of COF, caffeine had the lowest value (0.22) of all tested ingredients while MCC had the highest (0.90). When comparing the two binders, 100LV seemed to exhibit a slightly higher COF than 4M but it is considered insignificant. Similar to the cohesion, smaller particles of DeLAC compared with LAC exhibits higher COF. Another factor also needs to be considered that dehydration of lactose will increase the porosity of lactose particles [23] which helped to increase the COF.

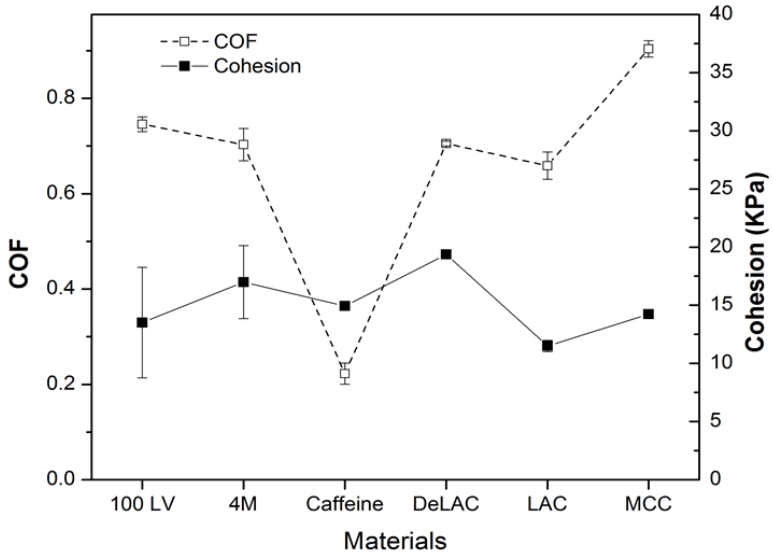

Figure 6-5: Results combination of DST and DSC.

When inspecting the sintering results of the binders, seen in Figure 6, the onset temperatures for 100LV (157 °C) is lower than 4M (169 °C), while midpoint of temperature for 100LV (166 °C) was lower than 4M (175 °C) due to the higher viscosity of 4M. This finding indicated that 100LV softened at a lower temperature and was more capable of binding particles together quickly, which for a short residence time process like twin screw granulation, will impact the state of agglomeration. The onset temperature of sintering indicates the lowest possible internal temperature of the powder bed during granulation for melt bridging to occur. Below this temperature, only adhesive forces are likely to hold granules together. One have to keep in mind that onset temperature of sintering for particles might decreased when stress applied in the twin

screw extruder so that formulation could be processed at 160 °C which is lower than the onset temperature of 4M, 169 °C.

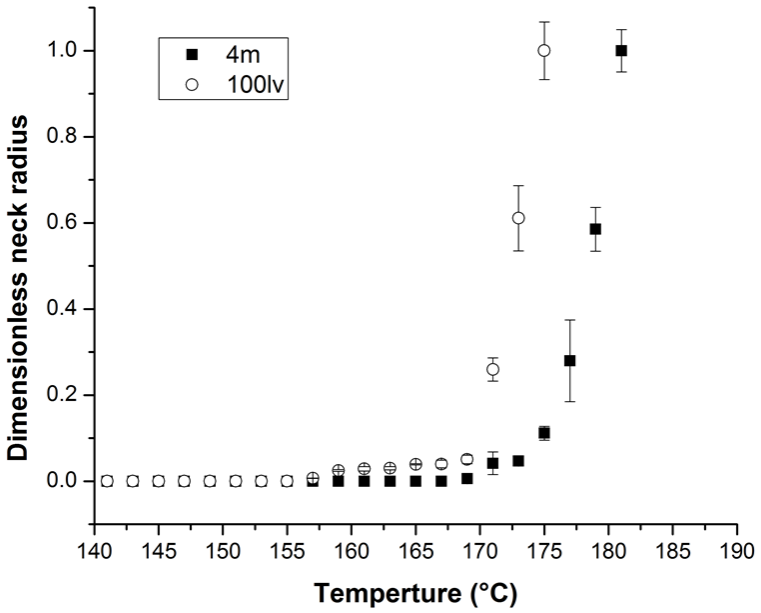

Figure 6-6: Sintering profiles of 100LV and 4M based on 3 repeats.

6.4.2 Impact of granulation parameters

Higher screw speeds in the previous study proved helpful for particle agglomeration which is also supported in the current results, as shown in Figure 7 and Figure 8; Figure 7 presents the nominal particle size and circularity results while Figure 8 presents the exiting temperature and fracture strength results of samples prepared by TSDG. In cases, speeds as high as 400 rpm or 500 rpm were used for granulation conditions in order to successfully obtain granules. Current results showed that particle

size generally increased with lower feed rate for a fixed screw speed, which is opposite in effect to wet granulation which relies upon compaction in the kneading zone for agglomeration. In fact, the granulation process at lower feed rates was more likely to be successful for TSDG. Lower feed rate increases the mean residence time [33] for particles inside the barrel and hence enables more heat transferred to individual particles such that cohesion of the bed increases and particles are slowed around the kneading zone. However, higher feed rates will help to build up pressure in the kneading zone, and this may be why some exceptions existed, like 40%100LV-60%LAC-N-200rpm-3kg/h and 40%100LV-50%LAC-10%D-200rpm-3kg/h.

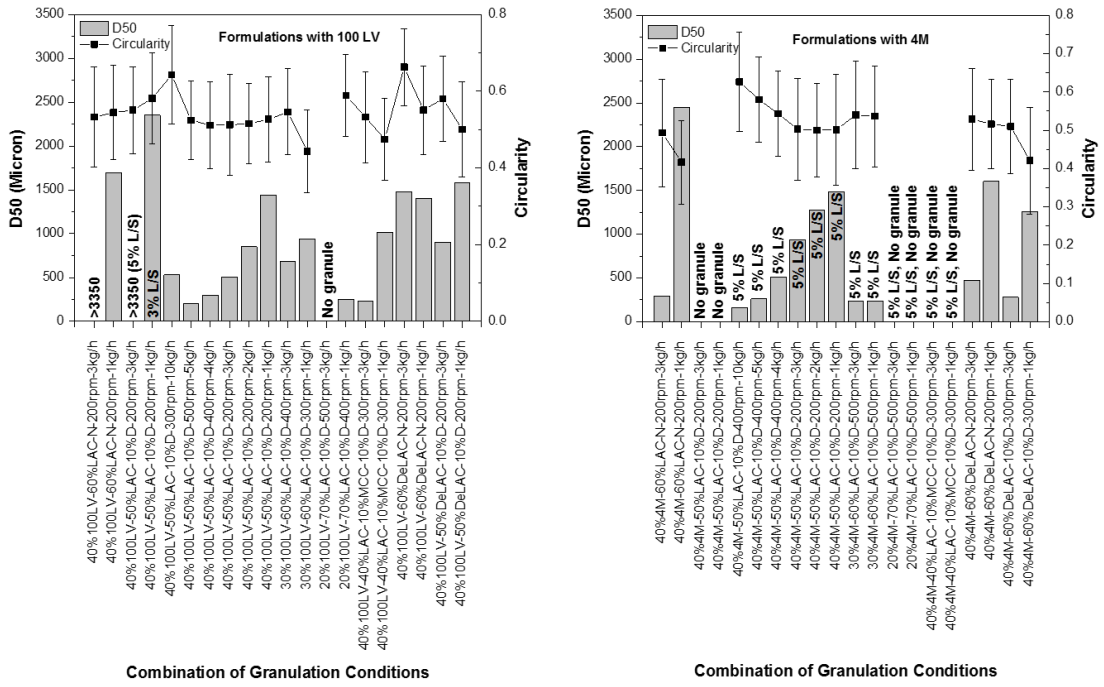

Figure 6-7: D50 and Circularity of granular samples. Water addition is noted by form of L/S in the plot. The uncertainty of D50 was estimated by 3 repeats for 7% average relative error.

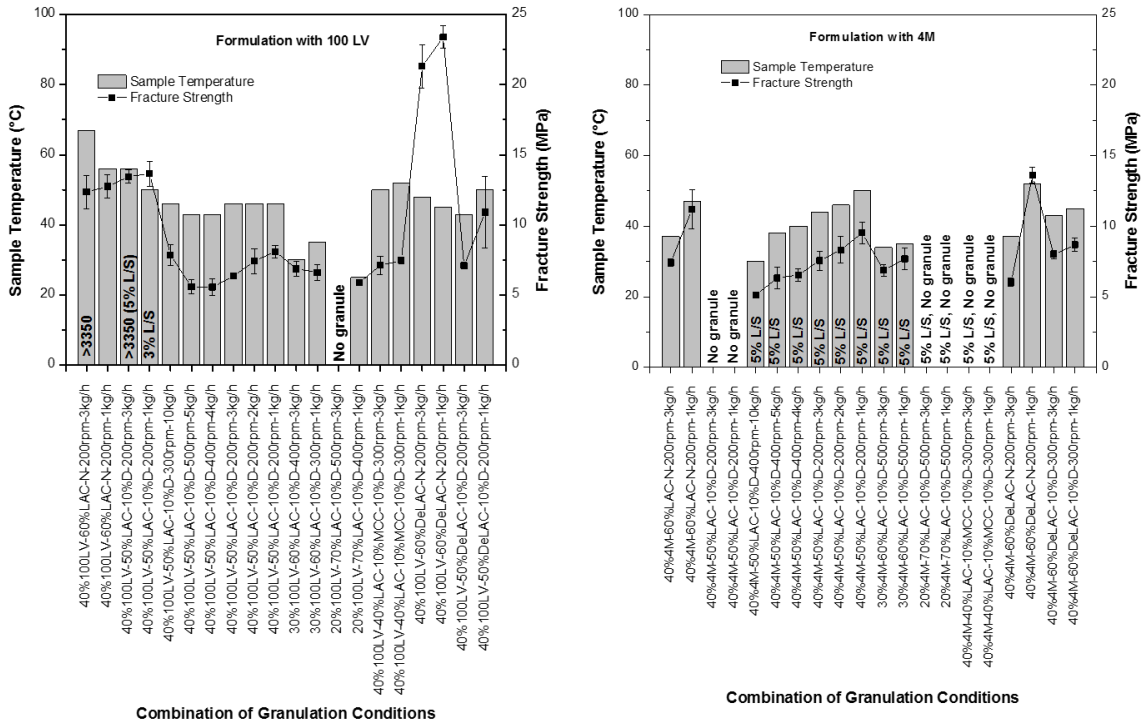

Figure 6-8: Sample temperature and fracture strength of granular samples. Uncertainty of sample temperature were estimated by 3 repeats for the average relative error of 1.7%.

6.4.3 Impact of non-binder ingredients

Not only being functional during drug delivery, non-binder fillers in a formulation will influence the TSDG process by their inherent properties of COF and cohesion. The presence of MCC significantly decreased the particle size by more than 50% (Figure 7), taking 40%100LV-40%LAC-10%MCC-10%D-300rpm-3kg/h as an example where its D50 was only 227 μm compared to the condition of 40%100LV-50%LAC -10%D-200rpm-3kg/h. For binder 4M, the effects of MCC were more pronounced, preventing particles from agglomerating in cases of 40%4M-40%LAC-

10%MCC-10%D-300rpm-3kg/h and 40%4M-40%LAC-10%MCC-10%D-300rpm-1kg/h.

The significantly lower COF of caffeine compared to other ingredients potentially decreased heat generation from friction, which meant that its addition often lead to smaller particles or even no granulation, as in the cases of 40%4M-50%LAC-10%D-200rpm-3kg/h and 40%4M-50%LAC-10%D-200rpm-1kg/h.

Dehydrated lactose seemed to decrease the particle size due to the moisture content lost. No granules could be obtained for conditions of 40%4M-50%LAC-10%D-200rpm-3kg/h and 40%4M-50%LAC-10%D-200rpm-3kg/h. Though granules were produced for the same conditions with LAC instead of DeLAC.

6.4.4 Impact of molecular weight and concentration of binder on properties of granules

Since 100LV and 4M are chemically identical except for their molecular weight, their comparison was considered to be solely examining differences in viscosity. In fact, even thermally, the two species shared nearly identical glass transitions temperatures of 111 °C. The lower viscosity of 100LV which resulted in a notably higher sintering rate, proved to be more suitable for granulation at lower screw speed than that with 4M when inspecting the particle size in Figure 7 especially when higher feed rate or lower binder content was used. However, larger particle sizes could be found with 4M formulations compared to 100LV but only under appropriate conditions. Higher polymer viscosity led

to increased particle size though the stronger bridge present but only when binder softening or melting was not impeded by the selected extrusion conditions for granulation. Circularity of granules formed from 4M formulations were lower than those based on 100LV formulations, as shown in Figure 7.

For most of the trial conditions, granule strengths measured with 100LV formulations were higher than from 4M, as shown in Figure 8, because of the limiting conditions inside the extruder to cause the latter binder to soften and bridge. Strength of the particle-particle bridge will be decided by the viscosity of binder and the thickness of the bridge in this study. The latter is related to the extent of sintering. The lower onset temperature and lower midpoint temperature of sintering of 100 LV improved bridging compared to 4M. For some conditions, as found with particle size above, the strengths of granules from 4M formulations were higher for extrusion conditions that matched its sintering rate. Operating at lower feed rate helped the 4M binder particles to soften more extensively, as seen in the cases of 40%4M-50%LAC-10%D-400rpm-2kg/h and 40%4M-50%LAC-10%D-400rpm-1kg/h. Consistent with the trend for granule strength, sample temperatures were higher for 100LV formulations than 4M at most conditions, indicating a greater capacity to slow in the kneading zone and generate heat by friction and plastic dissipative forces.

Since the polymer binder is more prone to softened or melt than other non-binder ingredients, formulations with higher binder content could be more readily granulated at lower screw speed or higher feed rate. By inspecting the granular samples in Figure 7, a

lower concentration of binder was found to decrease the particle size for either binder. Granules were even absent in granulation with the formulation with 20% 100LV at feed rate of 3kg/h and formulation with 20% 4M at both feed rate of 3kg/h and 1kg/h. Lower binder concentration was also noted to slightly decrease the strength of granules, foreseeably due to a thinner bridge while binder concentration had a minimal effect on the shape and temperature of granules.

The trend on how binder impacts the granulation process for TSDG is similar to the HMG where particle size were increased by lower binder molecular weight and higher binder concentration [9–12,14]. This is likely due to the binder bridge being reliant on melting/softening phenomenon in both cases, although the drivers for melting appear different.

6.4.5 Polymorphic transformation of API and Dehydration of LAC

Questions arise due to the reliance of TSDG on heat as to whether it lessens the potential for thermal damage to the drug formulation compared to hot melt granulation. To test this, the study relies upon the fact that caffeine will undergo crystal structure transformation [34,35][36] and α-lactose monohydrate will lose its hydrate group [23] close to the temperature of the granulation process. Their transition temperatures were individually confirmed by DSC measurement, as shown in Figure 9 (a). At a heating rate of 5 °C/min, the onset and peak temperatures for the transformation of caffeine were 146 °C and 153 °C, respectively and increased with higher heating rates. Taking a heating rate of 50 °C/min for instance, the onset and peak temperatures for the

transformation of caffeine increased to 162 °C and 178 °C, respectively. The shift in transformation temperature of caffeine with the heating rate is consistent with other studies [36]. Since the heating rate in the extruder will vary based on operating conditions and location along the extruder, in a manner that could not be detected in this study, one must consider that the transition temperature range for caffeine will overlap with the dehydration temperature range of α-lactose monohydrate which is from 147 °C to 163°C, and that both reactions can occur for the selected conditions of this study. This was another reason for purposely considering DeLAC in the current research.

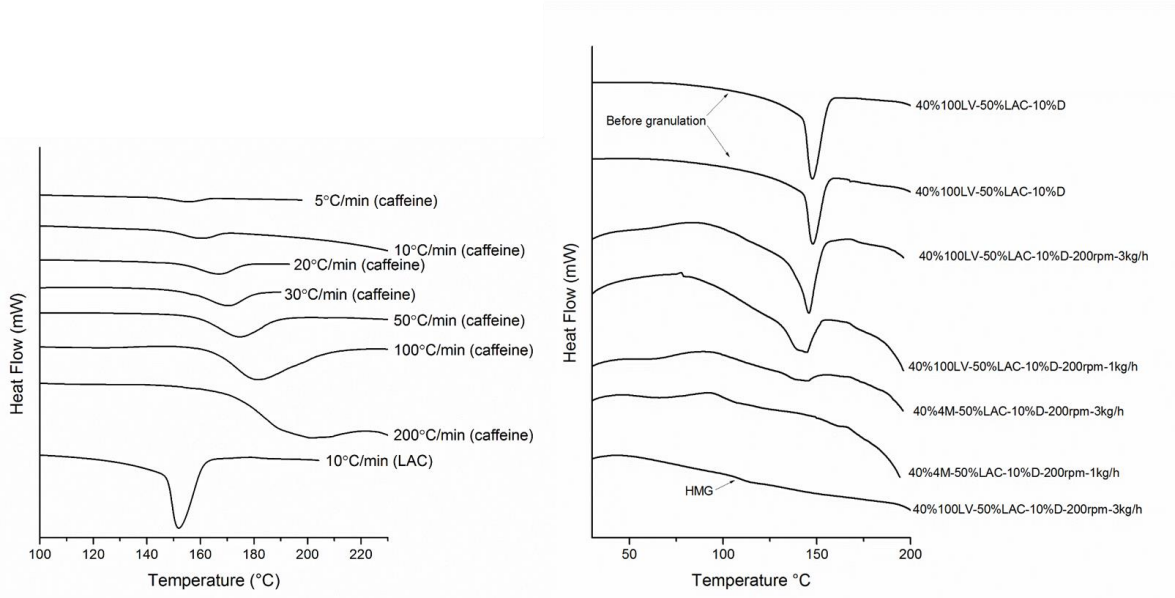

Figure 6-9: DSC analysis of pure caffeine and LAC (a) and formulation and granular sample (b). Heating rate of 10 °C/min was used for granular sample analysis. Four conditions from TSDG and one condition from HMG were exhibited for instance.

Due to the overlapping nature of the transitions for α-lactose monohydrate and caffeine during granulation process, the extent of their changes was analyzed by powder XRD of selected samples for comparison to DSC. X-ray diffraction patterns for the pure ingredients and four representative granulated samples are shown in Figure 10 for conditions of 40%100LV-50%LAC-10%D-200rpm-3kg/h, 40%100LV-50%LAC-10%D-200rpm-1kg/h, 40%4M-50%LAC-10%D-200rpm-3kg/h and 40%4M-50%LAC-10%D-200rpm-1kg/h. No strong peaks were detected for the two binders because of their non-crystal structure. The peak at $2\theta = 30.7°$ is a characteristic peak of Form II caffeine, showing a considerable amount was still present in the granulated products. The peak at $2\theta = 15.7°$ is characteristic of dehydrated lactose, according to Raut *et al*. [23]. The small intensity of this peak at $2\theta = 15.7°$ indicates that only a small percentage of α-lactose monohydrate had lost its hydrate group during TSDG. Conversely, the peak at $2\theta = 19°$ is a characteristic peak for LAC, and among the shown diffractograms, it indicates that less lactose monohydrate was dehydrated for the higher feed rate (3kg/h). Additionally, less caffeine was transformed to Form I at higher feed rate based on the lower intensity of its characteristic peak at $2\theta = 31.5°$ [35]. These results confirm earlier findings that more heat occurred at the lower feed rate. Accurate crystalline content of each ingredient in the granules was not possible to model due to highly overlapping peaks.

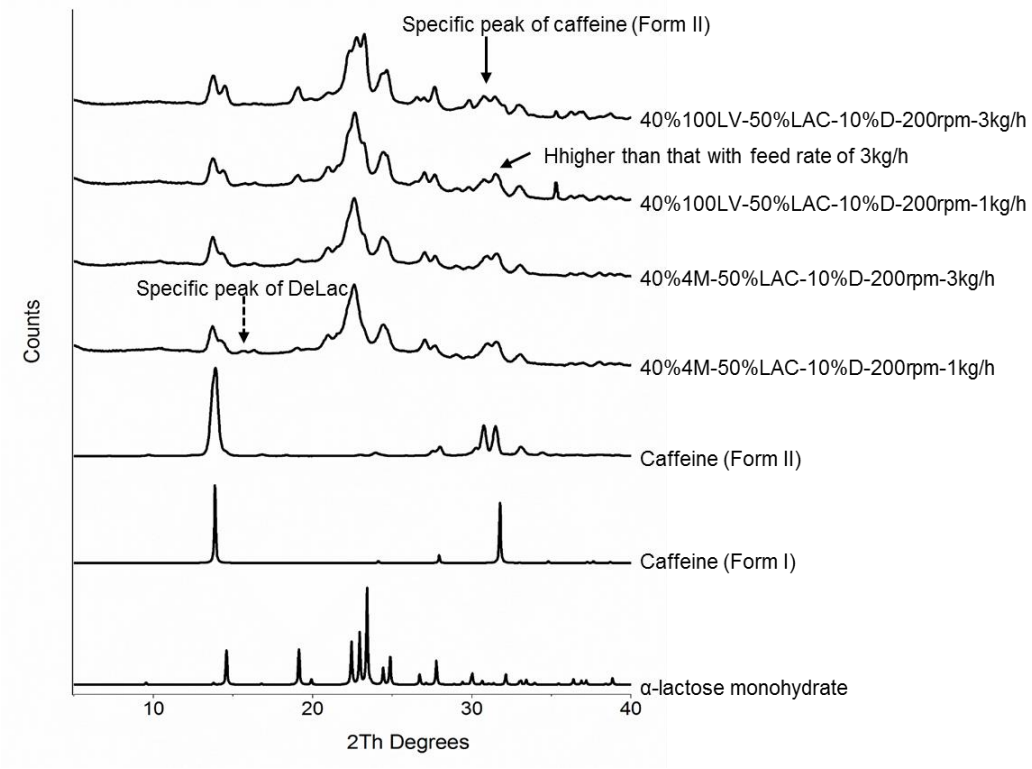

Figure 6-10: Powder XRD measurement for selected four granulation conditions. Characteristic reflection of DeLAC is at 2θ = 15.7°; characteristic reflection of Caffeine in Form II and Form I is separately at 2θ = 30.7° and 2θ = 31.5°. 2θ = 19° is a characteristic reflection for LAC.

To more quantitatively estimate the degree to which structural transitions occurred for lactose and caffeine by TSDG, all granulated products were tested by DSC with selected results shown in Figure 9(b). Due to the interference between the transition of LAC and caffeine, peaks could be wide like those found for 40%4M-50%LAC-10%D-200rpm-3kg/h and 40%4M-50%LAC-10%D-200rpm-1kg/h. To better estimate the individual ingredient transition, the peaks were analyzed using deconvolution methods within Originlab software (Version 9.0; OriginLab Corporation, MA). An

example for condition of 40% 100LV-50%LAC-10%D-200rpm-1kg/h is shown in Figure 11. The percent of ingredient transition was calculated by equation (2) as

$$P_t = \frac{\Delta H_g}{\text{ingredient concentration } (\frac{wt}{wt}\%) \times \Delta H_{pure}} \quad (2)$$

where P_t is the percent of ingredient transition, ΔH_g is the specific enthalpy of the transition of individual ingredient in a granular sample, and ΔH_{pure} is the specific enthalpy of the transition for a pure material. Combined results of P_t for LAC (dehydration) and caffeine (polymorphic transformation) during granulation is given in Figure 12. The data reveals that ingredient degradation increased with granular sample temperature (Figure 8), confirmed that the exiting sample temperature reflected the total heat generated by friction and plastic dissipation; due to the early location of the kneading block in the screw, there were initial concerns that the exit temperature did not reflect the mechanism of granulation that these findings dispel. On the same point, the result in Figure 12 are also confirming that the heat can negatively affect ingredients during granulation, which is generally believed by earlier researchers but not proven [37,38]. A higher content of 4M, which has a higher viscosity, seems to increase the ingredients transition due to the higher temperature of granules. Although water could play as a coolant, its high flowability and heat capacity (4.183 J/(kg °C)) might result in heat distribution and decrease heat dissipation causing granular sample temperatures with water addition to be higher as shown in Figure 8 and this consequently was reflected by higher ingredients transitions as shown in Figure 12.

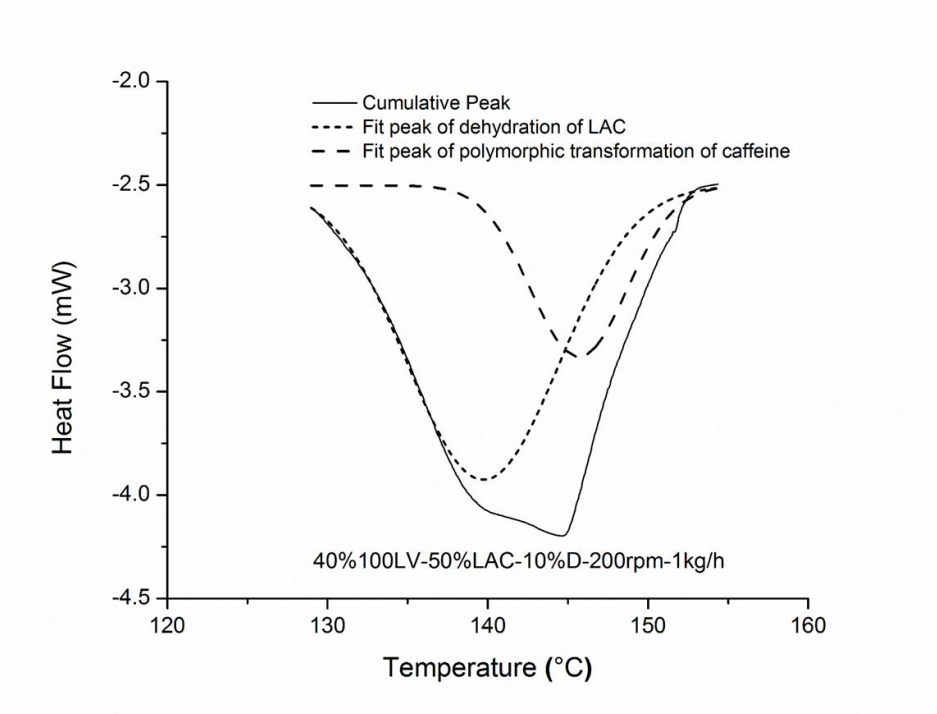

Figure 6-11: Example of multiple peaks analysis for ingredient transition by deconvolution from condition of 40%100LV-50%LAC-10%D-200rpm-1kg/h.

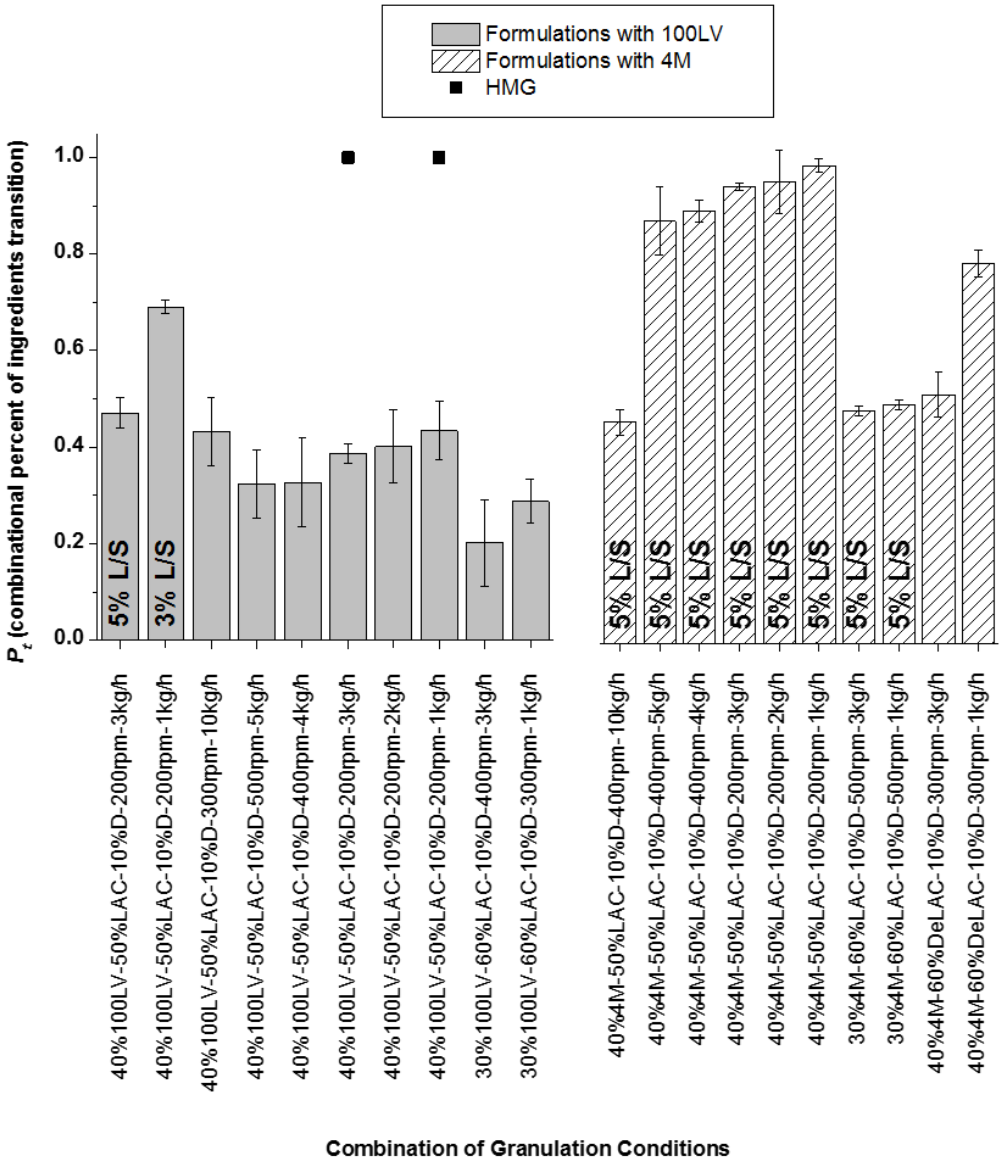

Figure 6-12: Summary of ingredients degradation combining Caffeine of Form II and LAC.

Drug degradation during the granulation process was assumed as zero for the calculation of polymorphism transformation of caffeine. This assumption was then checked by HPLC analysis for four selected samples which had been simultaneously

analyzed by powder XRD, 40%100LV-50%LAC-10%D-200rpm-3kg/h, 40%100LV-50%LAC-10%D-200rpm-1kg/h, 40%4M-50%LAC-10%D-200rpm-3kg/h and 40%4M-50%LAC-10%D-200rpm-1kg/h. The results demonstrated that no chemical degradation occurred for API during granulation which confirmed that the previous assumption is true.

6.4.6 TSDG *vs.* HMG

As discussed above, transitions of the ingredients were highly related to the sample temperature which reflected the amount of heat generated during TSDG. However, twin screw dry granulation was believed to generate comparatively little heat relative to hot melt granulation because they have similar machinery setup but different heating method; hence TSDG was compared to hot melt granulation for ingredient transitions s. A thermogram included in Figure 9(b) for HMG (40%100LV-50%LAC-10%D-200rpm-3kg/h condition) showed no transition, indicating that all caffeine had transformed from Form II to Form I, and all lactose monohydrate was dehydrated. The similar observations were shown in Figure 12, which demonstrates that 100% transition occurred in HMG compared to only 38% and 43% in TSDG for same conditions looking at 40%100LV-50%LAC-10%D-200rpm-3kg/h and 40%100LV-50%LAC-10%D-200rpm-1kg/h, individually. This indicates that the total heat input by HMG was much higher than TSDG. It is felt that these findings indicate the frictional heating approach by TSDG is safer for drug processing than conductively heating with HMG.

6.5 Conclusion

Consist to our previous study for TSDG, screw speed was confirmed as the crucial factor for the heat generation and a small amount of water addition also proved again to help particle agglomeration. Even though water seems it would act as a coolant, it was found in the current paper to functionally increase the sample temperature by assisting heat transfer and decreasing heat dissipation, which lead to more API transformation. Feed rate is another essential factor to alter the granulation process where lower feed rate enable powder formulation to gain more heat and hence increase the chance of successful granulation. But a lower feed rate will increase granule temperature and potentially harm the ingredients. Non-binder fillers could vary the granulation process as well because of their melting point, COF or cohesion. A low melting point, high COF or cohesion could be expected to optimize the granulation process. Lower binder concentration in the formulation will weaken the bridge and moderate the sample temperature and thereby decrease the ingredients transition. When comparing two polymer binders with different molecular weight, the binder with a lower melt viscosity will permit formulations to more ready granulate due to the higher sintering rate. Less ingredient transitions were correspondingly found with a binder of lower melt viscosity. More transformation of ingredients for HMG revealed that binder softening/melting strategy is significantly more efficient and hence is able to protect API by avoiding overheat.

6.6 References

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Chapter 7

Conclusions and Recommendations

7.1 Conclusions

The mechanismmechanism of twin screw wet granulation was further explored by investigating the function of conveying elements adjacent to the kneading blocks and wetting behavior of formulation powders. By using complicated formulations, a greater understanding of the function of the kneading block was explored and heat assisted twin screw dry granulation was thereafter developed based on the previous wetting granulation studies. Comprehensive studies revealed that this new technique is significantly affected

by the molecular weight, or melt viscosity, of the binder and properties of non-binder excipients. Merits of this novel granulation strategy over conventional hot melt granulation were exhibited through comparison. The major accomplishments of this thesis are:

Individual elements along the screws could perform unique functions but also co-influence the granulation process by their association with neighbouring elements. Instead of solely functioning to transport material, conveying element have a significant effect on the properties of granules by employing different pitches after a kneading block. Higher pitched downstream conveying elements increase the ratio of medium sized particles (500–1180 μm) and their aspect ratio for the final samples, but decrease granule porosity and fracture strength. These effects are insensitive to the fill level. This new knowledge proved incapable of preventing difficulties with processing formulations with controlled release ingredients, and hence variables besides screw design were subsequently focused upon.

When the interactions between powder formulation and water are stronger than the formation of capillary and viscous forces, the mechanism of particle agglomeration in the twin screw wet granulation appears different forming noodles in some cases or large chunks. Dominant liquid bridge for simple immediate formulations is replaced by a hydrogel layer for more complicated formulations when using higher molecular weight binder of HPMC. Elevating the barrel temperature was discovered to significantly decrease the adhesive nature of wetted HPMC powder by damaging the gel structure and

thereby diminishing the uncontrolled agglomeration. In the course of that study, the ingredients at times fully dried out within the extruder yet still exhibited some granule growth. That observation led to the next course of studies on how to controllably operate a dry granulation process.

Twin screw dry granulation has not existed until now because of insufficient compressive forces in the extruder compared to a roller compactor/fluidized bed. Different from conventional hot melt granulation within a twin screw extruder, a new granulation technique has been studied relying upon considerable amounts of heat to be generated internally from friction and by plastic deformation dissipation of polymer binders as they are compressed and sheared in a kneading block zone. If the screw speed is high enough, the generated heat will be sufficient to soften the polymer binder, combining particles and then achieving granulation. Polymer binders with different chemical compositions have been shown to vary the granulation process by their initial particle sintering rate, which can be affected by their T_g. Water can be used as a plasticizer for some difficult-to-use binders so as to decrease their T_g and thereby make binders more readily to be softened.

Twin-screw dry granulation is seen to offer advantages over twin-screw melt granulation by reducing thermal effects on key ingredients. Polymer binders with a low molecular weight show advantages in this new twin-screw dry granulation process for producing strong, well-shaped granules with less chance to become excessively heated that might otherwise produce a polymorph of key ingredients. Low coefficients of friction

for non-binder ingredients could negatively impact the process due to the decreased heat generation.

7.2 Recommendations for Future Work

This thesis has developed promising techniques for twin screw wet and dry granulation and the following work is recommended for future research:

- Investigating the interaction between initial particles and different liquids aside from water.
- Systematically characterizing formulations with diverse properties and then correlating to the properties of granular produced by twin screw wet/dry granulation.
- Further exploring the mechanism of twin screw dry granulation by measuring the local details of internal pressure and temperature within a powder bed going through a kneading block.
- Assessing the ability of steam to control twin screw dry granulation, more closely resembling MADG.
- Optimizing the extruder design by increasing the motor power and screw speed limit; modifying the surface of the inner barrel and kneading block to increase the heat generated from friction which in turn would increase the capability of powders to build up pressure in this zone.