UNDERSTANDING PHARMACEUTICAL WET GRANULATION IN A TWIN SCREW EXTRUDER

UNDERSTANDING PHARMACEUTICAL WET GRANULATION IN A TWIN SCREW EXTRUDER

By

HUIYING LI

A Thesis

Submitted to the School of Graduate Studies

In Partial Fulfillment of the Requirements

For the Degree

Master of Applied Science

McMaster University

© Copyright by Huiying Li, September 2014

(Chemical Engineering) Hamilton, Ontario Understanding Pharmaceutical Wet Granulation in A Twin TITLE: Screw Extruder Huiying Li AUTHOR: B. Eng. (Beijing University of Chemical Technology) SUPERVISOR: Dr. Michael R. Thompson NUMBER OF PAGES: ix, 135

University

McMaster

MASTER OF APPLIED SCIENCE (2014)

ABSTRACT

Granulation is an important process for industries ranging from plastics to food and pharmaceutics. In the last decades, the twin-screw extruder has been more and more studied as a continuous method for granulation. But there are many questions remaining to be answered such as the functions of kneading block and the granulation behavior in this zone, the influence of the wetting method, and also the influence of the active pharmaceutical ingredient (API) properties on the granulation process. Therefore, in this project, a series of experiments were performed based on a new technique to the granulation field named 'screw pullout' for understanding the granulation process within the twin-screw extruder.

In order to understand the specific function of an important screw element known as a kneading block, the physical particle motion reflecting progress of granulation was monitored along the screw. Different feed rate and formulations were studied; the residence time and pressure in kneading block were measured; and the granules along the screw were characterized for their porosity and size distribution. It was found that granule consolidation and breakup within the kneading block allowed the production of granules with consistent properties and excellent mechanical strength. However, the changes produced by a kneading block are dependent upon the formulation. For example, the kneading block demonstrates no observable function with formulations containing a significant content of microcrystalline cellulose. The most notable benefit of the kneading

block to all tested materials appeared to be distribution of the interstitial binding liquid rather than to compact the powders.

A new wetting method using a foam binder has been studied intensively in this work to assess its influence on the granulation process. A series of studies have been performed to compare the granule development along the screws as powder formulation and screw design were varied to test for the differences induced by the two wetting methods (foam delivery or liquid injection). The evolution of the granules along the screw was characterized by analyzing the particles size distribution, porosity, and fracture strength. It was found that the wetting method had minor impact on the particle size distribution due to the strong mechanical dispersion inherent to the extruder. The major finding for the pharmaceutical industry was that the foam method reduces the required amount of liquid to granulate, thereby dropping drying time after the process. The foamed binder was also found to be preferred when the formulation contains powder components with poor spreading properties.

Finally, the influence of an API's physical properties on granulation was studied by comparing formulations with varying API hydrophobicity. It was found that the API and binder distribution was not affected by the hydrophilicity of API, while the particle size distribution, porosity and fracture strength were strongly dependent on the properties of the API.

ACKNOWLEDGEMENTS

First of all, I would like to express my deepest gratitude and appreciation to my supervisor Dr. Michael R. Thompson for his excellent guidance, patience and valuable advice on this project.

I would like to express my gratitude to the Natural Science and Engineering Research Council (NSERC) of Canada for the funding, and the Dow Chemical Company for their technical advices.

I would like to thank Ms. Elizabeth Takacs for her training on instruments; Mr. Paul Gatt for his technical support for making mold and other technical needs; Dr. Steve Kornic in Chemistry and Chemical Biology Department for his training on press device for FI-IR analysis and valuable advices; Zhuyuan Zhang and Jingyun Wang for training on centrifuge and UV-Vis. And I also would like to thank Ali Goger and Yang Liu for help with running extrusion experiments.

In the end, specially thank to my husband Jianfeng Zhang for his love, encouragement and support.

Without the help and support of all of the kind people around me, I would not have been able to write this master thesis, I am very glad to thank the people who helped and support me through out my life at McMaster University.

TABLE OF CONTENT

ABSTRACT	i
ACKNOWLEDGEMENTS	iii
TABLE OF CONTENT	iv
LIST OF FIGURES	vi
LIST OF TABLES	ix
Chapter 1: Introduction	1
1.1 GRANULATION	1
1.2 CONTINUOUS WET GRANULATION WITH EXTRUDER	2
1.3 FACTORS AFFECTING GRANULATION IN TWIN SCREW EXTRUD	ER5
1.4 FOAM GRANULATION – A NOVEL WET GRANULATION USING T	WIN
SCREW EXTRUDER	12
1.5 OBJECTIVES OF THE THESIS	13
REFERENCES	14
Chapter 2: Understanding Wet Granulation in the Kneading Block of Twin	ı Screw
Extruders	
ABSTRACT	19
2.1 INTRODUCTION	20
2.2 MATERIALS AND METHODS	24
2.2.1 Materials	24
2.2.2 Twin screw granulator	25
2.2.3 Process Characterization	27
2.2.4 Particle Characterization	29
2.3 RESULTS AND DISCUSSION	
2.3.1 Pressure development during granulation	
2.3.2 Residence time distribution	
2.3.3.1 Particle size development versus feed rate	
2.3.3.2 Particle size development based on formulation	
2.3.4 Particle porosity across the kneading block	
2.4 FUNCTION OF A KNEADING BLOCK	54
2.5 CONCLUSIONS	
2.6 ACKNOWLEDGEMENIS	
KEFEKENCES	
Chapter 3: Progression of Wet Granulation in a Twin Screw Extruder Con	iparing
Two Binder Delivery Methods	
ABSTRACT	63
3.1 INTRODUCTION	63
3.2.1 Materials	66
3.2.2 Twin screw granulator	68
3.2.3 Methods of liquid binder delivery to the extruder	69
3.2.4 Process analysis by screw pullouts	71
3.2.5 Particle size analysis	72

3.2.6 Porosity, pore size and fracture strength characterization	72
3.2.7 Binder penetration time	73
3.3 RESULTS	74
3.3.1 Characteristic saturation behavior of the different formulations	74
3.3.2 Granulation profiles for α -lactose monohydrate	77
3.3.3 Granulation profiles for the 20% HPMC formulation	
3.3.4 Granulation profiles for the 50% MCC formulation	
3.4 DISCUSSION	93
3.5 CONCLUSIONS	
3.6 ACKNOWLEDGEMENTS	
REFERENCES	
Chantar 4: The Effect of Drugs on Wet Cremulation in a Twin Screw I	Extrudor 107
ADSTDACT	2X11 UUCI 102 102
ADSTRACT	103
4.1 INTRODUCTION	105
4.2 EATERINE TAL	106
4.2.1 Materials	100
4 3 RESULTS AND DISCUSSION	
4 3 1 Calibration curves for APIs	112
4 3 2 API distribution	115
4 3 3 Binder distribution	116
4 3 4 Particles size distribution	120
4.3.5 Apparent porosity and characteristic fracture strength	
4.3.6 Granulation of APIs with different hydrophilicity	
4.4 CONCLUSIONS	
REFERENCES	
Chanton 5. Conclusion	100
Unapter 5: Conclusion	

LIST OF FIGURES

- Figure 1. 1 (A) The influence of input rate on the properties of granules (lactose monohydrate, with 7.5% of PVP aqueous solution as binder, screw speed = 450 rpm. () Granule yield, (Δ) F_{1000-1400 µm}, (¢) granule friability, (n) F_{<250 µm}.(Keleb et al., 2004b) (B) 100% degree of filling in channel observed from a transparent viewing port above.(Thompson et al., 2012b)
- Figure 1. 2 Images of elements with different function (A) conveying elements (B) kneading blocks, and (C) combing mixer.(Djuric and Kleinebudde, 2008) 6
- Figure 1. 3 (A) the size distributions with different powder feed rates. (B) porosity of granules produced from different compartments at varying powder feed rates.(Dhenge et al., 2011) 8
- Figure 1. 4 The change in size distribution of formulations containing pharmatose 200 M (A) impalpable, (B) and supertab 30GR (C) as the lactose grade at different L/S ratios using water as the granulating liquid. Photographic images of granules produced from different liquid content (D) 0.15, (E) 0.3, and (F) 0.45. The scale = 1000 μm.(El Hagrasy et al., 2013a)
- Figure 1. 5 (A) Illustration of the machine configuration for granulation.(Thompson et al., 2012a) (B) Photo image for the extruder setup in Dr. M. R. Thompson's lab: (1) extruder, (2) side-stuffer, (3) foam generator, (4) liquid injector, (5) powder feeder, and (6) viewing port.(Thompson et al., 2012b)
 13
- Figure 2. 1 Screw layout and magnified view of a kneading block with a 60° offset between kneading discs. Cross-sectional view of the kneading block highlights the three powder-carrying zones as the screws rotate.
- Figure 2. 2 Time variation plots of pressure measured at three locations over the kneading block as the screws rotated. Pressure traces for lactose monohydrate at feed rates from 10 to 30 kg/h. 32
- Figure 2. 3 Residence time distribution measurement for twin screw granulation of lactose. Plot (a) shows the quality of fit between the color data and the Zusatz model whereas (b) shows the fitted Zusatz distributions for feed rates of 10 to 30 kg/h.
- Figure 2. 4 Particle size fraction plots determined along the length of the screws from screw pullout trials with lactose monohydrate for feed rates of (a) 10 kg/h. (b) 20 kg/h, and (c) 30 kg/h. 40
- Figure 2. 5 Particle size distributions of lactose monohydrate, (a) sampled at shown locations before and after the kneading block and (b) sampled from zone Z8 and at the machine exit. Comparison based on feed rate conditions from 10 kg/h to 30 kg/h.
- Figure 2. 6 Images from the screw pullouts for lactose monohydrate over the kneading section for (a) 10 kg/h, (b) 20 kg/h, and (c) 30 kg/h. Flow direction left to right in shown images.
 43
- Figure 2. 7 Particle size fraction plots determined along the length of the screws from screw pullout trials for a feed rate of 10 kg/h with formulations (a) 50% MCC. (b) lactose monohydrate, and (c) 20% HPMC.

- Figure 2. 8 Magnified view of the granules found in the upstream conveying elements prior to the kneading section at 10 kg/h, for formulations (a) 50% MCC. (b) 20% HPMC, and (c) lactose monohydrate.
- Figure 2. 9 Images from the screw pullouts at 10 kg/h over the kneading section for formulations a) 50% MCC. (b) 20% HPMC, and (c) lactose monohydrate. Flow direction indicated.
 50
- Figure 2. 10 Particle size distributions, (a) sampled at shown locations before and after the kneading block and (b) sampled from zone Z8 and at the machine exit, at 10 kg/h. Comparison based on formulation.
- Figure 3. 1 Comparison of the two screw designs examined in the study with the non-conveying kneading block located at barrel zone Z8 or zone Z4 (#2). Top screw design include the nine barrel zones and their spatial locations relative to the start of the feed zone (Z0) with values quoted in mm (upper) and L/D (lower).
- Figure 3. 2 Photograph of a screw pull-out for the 50% MCC formulation at 10 kg/h and 220 RPM with the kneading block located at zone Z8. The screw is oriented such that zone Z2 is to the far left and zone Z9 is to the far right.
 72
- Figure 3. 3 Specific penetration time relative to the binder atop a static bed of lactose monohydrate and the 50% MCC formulation compared based on wetting method. 76
- Figure 3. 4 Granulation profile for α-lactose monohydrate comparing results on Screw design #2 (a,c) vs. #1 (b,d). Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).
- Figure 3. 5 Particle size distributions for the three formulations upon exiting the extruder, showing results for the two screw designs and two method of wetting. 83
- Figure 3. 6 Micrographs for granules of lactose (a.b), 20% HPMC (c,d) and 50% MCC (e,f) produced at 10 kg/h and 220 RPM on screw design #1. Particles on the left produced by liquid injection (a,c,e) versus on the right by foam delivery (b,d,f).
- Figure 3. 7 Granulation profile for the 20% HPMC formulation comparing results on Screw design #2 (a,c) vs. #1 (b,d). Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).
- Figure 3. 8 Granulation profile for the 50% MCC formulation comparing results on Screw design #2 (a,c) vs. #1 (b,d). Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).
- Figure 4. 1 Screw configuration with the kneading block located at zone 8 (880-990 mm). 109
- Figure 4.2 The FT-IR spectrum for (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine. 114
- Figure 4. 3 Calibration curves for (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine in regions of FT-IR spectrum around 1721 cm⁻¹, 1704 cm⁻¹, 1708 cm⁻¹, and 1655 cm⁻¹, respectively. The R² for (A), (B), (C), and (D) are 0.99528, 0.98886, 0.9895, and 0.98266, respectively. 114
- Figure 4. 4 The distribution of the APIs along the length of the screws. (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine. 116

- Figure 4. 5 The distribution of nigrosin (binder) in the granules for four formulations. (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine. The uncertainty in the analysis for binder distribution based on the size fraction on the screen 1180 um is at 1.03%RSD based on the measurements from duplicate trails for formulation containing caffeine.
- Figure 4. 6 Particles size fraction plots against the axial barrel distance for formulation with (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine, or (E) without API. The uncertainty in the analysis for particle size distribution is at 1.03%RSD based on the measurements from duplicate trails for formulation containing caffeine. The kneading block locates at zone 8 (880 990 mm).
- Figure 4. 7 (A) The characteristic fracture strength of the granules (1180 2100 μm) with different APIs against the axial barrel distance. (B) The porosity of the granules (1180 2100 μm) with different APIs against the axial barrel distance. The kneading block locates at zone 8 (880 990 mm).
- Figure 4. 8 The proposed granulation mechanism for APIs with different hydrophilicity. (A) No API, (B) hydrophilic APIs, (C) hydrophobic APIs. The hypothesis was made that the lactose and MCC gain the strongest bonding interaction (denote as blue); the bonding interaction between hydrophilic API and lactose/MCC is less intense (denoted as orange); the interfacial interaction between hydrophobic API and lactose/MCC is the weakest (denoted as orange as well).

LIST OF TABLES

Table 2. 1 Trial conditions	26
Table 2. 2 Dimensions and relevant parameters ^a of the kneading blocks used in the present study	27
Table 2. 3 Variation in pressure relative to flow rate and location in the kneading block	34
Table 2. 4 Granule porosity and average pore diameter of samples before (Z7) and after (Z8) the kneading block. Testing of sieve fraction 850-1180 μm.	1e 53
Table 3. 1 Properties of the formulation powders	67
Table 3. 2 Nucleation ratio (K _m)	77
Table 3. 3 Granule porosity for samples of lactose monohydrate across the kneading block	81
Table 3. 4 Granule porosity for the 20% HPMC formulation*	88
Table 3. 5 Granule porosity for the 50% MCC formulation*	93
Table 3. 6 Influence of flow rate on the operating conditions for lactose monohydrate	96

Chapter 1: Introduction

1.1 GRANULATION

Granulation generally refers as a size enlargement process; during the process powders are bound together forming a collection of agglomerates, however, the constructing unit (particulates) can still be identified.(Parikh, 1997) The granulation process has been widely introduced into many fields, including polymeric and pharmaceutical industries. In the form as granules, materials are expected as having improved flow and compression characteristics. Other benefits are also accrued, such as improved hardness, bulk density, appearance, and dust control.(Kristensen and Schaefer, 1987) In the pharmaceutical industry, this process is beneficial because of the convenience of adding drugs as a uniform distribution even at low drug contents.(Faure et al., 2001)

Generally, the granulation process, depending the form of binder, could be cataloged into dry and wet granulation.(Agrawal and Naveen, 2011) Dry granulation, obviously, is a process producing granules by mechanical compression, while without using any liquid. This process is suitable for moisture and heat sensitive products.(Agrawal and Naveen, 2011) Wet granulation, on the other hand, is more attractive due to its performance in producing granules with high dosages or in fine powder form,(Solanki et al., 2010) and adaptability to wide range of equipment.(Lee, 2013) Wet granulation, which involve a

2014

liquid solution, is a complex process containing the following three basic stages: wetting and nucleation, consolidation and growth, and breakage and attrition.(Agrawal and Naveen, 2011) The mechanisms of these three stages had been comprehensively reviewed by Iveson and Hapgood.(Hapgood et al., 2007, Iveson et al., 2002) Depending on the different procedures used, granulation can be cataloged as either a batch or continuous process.(Betz et al., 2003, Leuenberger, 2001) Currently, granulation processes commonly found in the pharmaceutical industry are based on the batch concept, mainly because it is believed to facilitate quality control.(Betz et al., 2003) Continuous processes are not practical for most pharmaceutical manufacture not only due to its excess capacity, but also because of difficulty on controlling the equilibrium during the process.(Leuenberger, 2001) However, continuous granulation processes are attracting more and more attention for their merits in avoiding scale-up problems and concerns regarding product consistency.(Betz et al., 2003)

1.2 CONTINUOUS WET GRANULATION WITH EXTRUDER

Extrusion, mostly known as a processing technology for the plastics industry, has been developed and spread into many diverse industrial fields, including food and pharmaceutical processing. The popularity of extrusion is due to the capability to integrate different functions into one operation, such as mixing, melting, and compounding.(Ghebre-Selassie and Martin, 2003) The single-screw was first introduced for pharmaceutical granulation, and factors like granulating fluid, endplate design,

number of mixing anvils, and screw speed as they influence the granulation process have been comprehensively studied by Goodheart.(Goodhart et al., 1973) The features of this continuous process promise large scale production. When a die plate is used to produce granules, this process is known as extrusion spheronization. More recently, Gamlen and Eardley have employed a twin-screw extruder for producing extrudates in the same manner with high drug loading, although defects (rough and shark skinning surface) were inevitable.(Gamlen and Eardley, 1986) However for granulation, Linderg is the first to use a twin-screw extruder.(Lindberg et al., 1988) The anhydrous citric acid and sodium bicarbonate were granulated with ethanol via twin-screw extruder. The mean residence time was obtained by adding a colored tracer and found to be significantly influenced by the process variables screw speed and powder flow rate. This pioneering work led to a growing interest and research on using the twin-screw extruder for continuous granulation.

Among the advantages of extruder granulation, the barrier of production capacity between laboratory and industry is very minor. Using the same equipment, the input rate could be varied from 5.5 to 18.5 kg/h without significantly changing the properties of granules and tablets (an example shown in Figure 1.1A).(Keleb et al., 2004b) Experiments that are close to pilot-scale or actual production, were performed by Thompson et al. with the input rate ranging from 20 to 40 kg/h.(Thompson et al., 2012b) In this case, without the obstacle of the shallow screws used in Keleb's experiment,(Keleb et al., 2004b) such a

2014

high input rate was achieved by nearing 100% degree of filling in the channels (Figure 1.1B).(Thompson et al., 2012b)



Figure 1. 1 (A) The influence of input rate on the properties of granules (lactose monohydrate, with 7.5% of PVP aqueous solution as binder, screw speed = 450 rpm. (•) Granule yield, (\blacktriangle) F_{1000-1400 µm}, (**o**) granule friability, (**n**) F_{<250 µm}.(Keleb et al., 2004b) (B) 100% degree of filling in channel observed from a transparent viewing port above.(Thompson et al., 2012b)

Moreover, different from the granules produced by batch processing, the extruder can produce granules with stable properties. The attempts made by Keleb et al. demonstrated that granules produced over a period of 8 h had no significant difference in friability, tensile strength, disintegration time.(Keleb et al., 2004b) More recently, a real-time quality assessment was developed to monitor the critical parameters during extrusion by incorporating with Raman, Near Infrared (NIR) spectroscopy, and a particle size distribution analyzer.(Fonteyne et al., 2013) Compared to the conventional quality control systems, this real-time system requires less off-line laboratory work, and also gives instant notification of defective products.

1.3 FACTORS AFFECTING GRANULATION IN TWIN SCREW EXTRUDER

The interests in twin-screw granulation has shifted from simply characterizing the final products to investigating its many factors which impact and control the properties of granules. Generally, the process of granulation and the final properties of produced granules are strongly influenced by the following factors: design of the screws, extrusion screw speed, feed rate (including powder and liquid feed rate), ingredients of the powder formulation, liquid-to-solid ratio, binder concentration in solution, binder viscosity, and the method of binder addition.

The screws of the extruder are assembled with discrete elements of different functions; about 10 to 50 elements are placed in certain order along the shaft to control granulation behavior during the process.(Thompson and Sun, 2010b) However, the elements could be classified by their functions into three main configurations: conveying elements (GFA), combing mixer (GFM or GLC) and kneading blocks (KB), as shown in Figure 1.2. Several studies have been carried out to understand the relationship between these elements and the granulation process, as well as the properties of produced granules.



Figure 1. 2 Images of elements with different function (A) conveying elements (B) kneading blocks, and (C) combing mixer.

Because of the differences in shear forces, properties of granules from different elements are certainly different. It was found that porous, friable granules were formed in conveying elements; by contrast, the granules that were compacted in kneading blocks formed dense, strong granules; and the properties of granules from combing mixer elements were somewhere in between.(Djuric and Kleinebudde, 2008) In conveying elements the major granulation mechanisms are coalescence and breakage, with consolidation being very limited; but consolidation and breakage are quite dominant mechanisms in kneading block.(Dhenge et al., 2012a) Therefore, agglomerating powders moving along the screw length will become more denser, smoother, and spherical with time.(Dhenge et al., 2012a, Dhenge et al., 2011) In the kneading blocks, the granules properties can be tuned by adjusting the offset angle. For example, Djuric et al. found the porosity of granules in kneading block with offset angles of 30 - 60° are higher than that of 30–90°, owing to the differences in shear forces and bypass possibilities for the material around its element lobes.(Djuric and Kleinebudde, 2010) This however is also

dependent upon the degree of channel fill.(Thompson and Sun, 2010b) The liquid distribution efficiency in kneading blocks is also influenced by the offset angle with 30 $^{\circ}R > 60 ^{\circ}R > 90 ^{\circ} > 30 ^{\circ}F > 60 ^{\circ}F$ (efficiency from best to worst, R = reversing angle and F = forwarding angle).(El Hagrasy and Litster, 2013) They also found that the size distribution of granules in a 60 °F kneading block was similar to that of a conveying zone, and that the distribution was not influenced by the block length.(El Hagrasy and Litster, 2013) But, increasing the length of kneading blocks caused higher torque, and consequently, resulted in less fine powders and mostly oversized granules.(Vercruysse et al., 2012)

Except the screw design, among the processing parameters, powder flow rate is the only that determines the granulation process maior factor and properties of granules.(Kleinebudde and Lindner, 1993, Keleb et al., 2002) Screw speed has a very limited, if negligible, role. During the extrusion process, screw speed and feed rate must be optimized to avoid either overloading the motor or flow surges.(Keleb et al., 2001) At a certain feed rate, the residence time decreases with increased screw speed; the consequent intense shear forces cause irregularity of granule development without changing the average dimension significantly. (Dhenge et al., 2010) Similarly, in the same system the feed rate shows limited effects on granule properties but instead affects the granulation yields and strength; Keleb et al. explained these results by the degree of filling of granulator barrel.(Keleb et al., 2004a) With a varying degree of filling of granulation barrel, the residence time and torque vary with the feed rate. As shown in

Figure 1.3A, the size distribution of granule shifts left with increasing feed rate, because the torque increased while residence time decrease.(Dhenge et al., 2011) No matter the feed rate, the porosity always decreased along the screw (Figure 1.3B).(Dhenge et al., 2011) Although the effects of powder feed rate and screw speed on granules have been studied, their influence in the mechanism of twin screw granulation is still not clear. The experiments designed by Dhenge systematically studied the relationship between granule properties and feed rate, furthermore developing a science behind granule formation for guiding the design of products.(Dhenge et al., 2011)



Figure 1. 3 (A) the size distributions with different powder feed rates. (B) porosity of granules produced from different compartments at varying powder feed rates.(Dhenge et al., 2011)

The liquid content (liquid-to-solid ratio) is one of the most important factors in the granulation process, not only because it determines the drying method and time, but italso influences the interaction between the powders.(Keleb et al., 2004b, Dhenge et al., 2010) The liquid content should be in an appropriate range; too low or too high will result in insufficient granulation or over aggregation.(Keleb et al., 2004b) The residence time of the powder increases with the liquid content. With higher liquid content, longer time and

8

higher torque are required when powder is forming a paste; moreover, the liquid bridges increased in granules as well. Therefore, the resultant granules have smoother surface and higher strength.(Dhenge et al., 2010) The size distribution of granules is also influenced by liquid content. Although the size of the granules increases with the liquid content, the size distribution becomes narrower; by contrast, a broad granule size distribution with both fine granules and lumps is more commonly observed at lower liquid content, as shown in Figure 1.4.(El Hagrasy et al., 2013a) At high liquid content, the liquid is sufficient and uniformly distributed in powder bed, thus forming a narrow size distribution; while at lower liquid content, the liquid is insufficient and distributed poorly in powder bed.(El Hagrasy et al., 2013a) More recently, a regime map describing five different regions (under-wetted, dry, nuclei, crumb, granules, and over wetted or paste) was proposed for increasing liquid content. (Dhenge et al., 2012b) The porosity of granule was also impacted by the liquid content. Because the increase in liquid content causes stronger interactions between powder (until a paste is formed) and better deformability of granules, the porosity of granule decreases. (Dhenge et al., 2010, El Hagrasy et al., 2013a)



Figure 1. 4 The change in size distribution of formulations containing pharmatose 200 M (A) impalpable, (B) and supertab 30GR (C) as the lactose grade at different L/S ratios using water as the granulating liquid. Photographic images of granules produced from different liquid content (D) 0.15, (E) 0.3, and (F) 0.45. The scale = 1000 μ m.(El Hagrasy et al., 2013a)

Binder, including the polymer type, addition method, and concentration, has a significant influence on the properties of granulation and finished tablets. The added binder significantly improves the strength of granules and its resultant tablet; however, the higher the binder content also causes a decrease in drug release rate.(Varshosaz et al., 1997, Tan et al., 2011) The binder demonstrates a strong influence over the process of granulation, with its addition significantly improving granule flowability.(Keleb et al., 2004b) However, depending on its content, the dominated granulation behavior may vary. For example, a balance between attrition and growth may be achieved with a low (proper) amount of binder in solution; such an equilibrium results in more spherical granules.(Bouwman et al., 2005) Conversely, an excess of binder will alter the deformability of granules, resulting in irregularly shaped granules;(Bouwman et al., 2005)

at the same time, due to the high binder content, the resulting viscous solution is slow to penetrate a bed of powder, and thus causes a non-uniform distribution of binder throughout the granules.(Dhenge et al., 2013) Any influence on the granulation process will certainly be reflected in the properties of granules, most significantly on the size distribution of granules. Compared with the use of excess binder, a higher yield and a lower F $_{>1400 \text{ um}}$ could be achieved with proper amounts of binder without loss of granule strength.(Keleb et al., 2004b) It seem the distribution of the binder could be the reason for the bimodal size distribution of granules.(Crean et al., 2010) However, the mechanism for such a size distribution is still unknown, and the uniformity of the binder distribution in granules is also a subject of debate. (Fonteyne et al., 2014) Moreover, the binder type and the addition method of the binder also influence on granulation process. For example, smaller average sizes and narrower size distribution are observed when using PVP rather than Gelatin/starch as binders.(Varshosaz et al., 1997) Compared with adding binder in its dry state, using a liquid binder solution reduces the level of fines in a granular sample; however, advanced wettability and excellent dispersibility of the binder could be achieved by adding it as foam.(El Hagrasy et al., 2013b)

Other processing parameters, such as extrusion temperature and the addition of surfactant can also influence the granulation process and the properties of the granules; however, their effects are minor compared to the factors discussed above.

1.4 FOAM GRANULATION – A NOVEL WET GRANULATION USING TWIN SCREW EXTRUDER

As mentioned above, other than having advantages in wetting and dispersion, foamed delivery of a binder has many other benefits, such as reducing the processing time, improving the reproducibility of a product, and more importantly requiring less water content (and hence less drying times downstream). Foam granulation was original devised for the high-shear batch mixing of pharmaceutical ingredients.(Keary and Sheskey, 2004) Hapgood et al. have performed comprehensive research on the influence and mechanism of batch foam granulation. They found that wetting with the foamed binder was less sensitive to the properties of powder (i.e. their surface tension), resulted in a more uniform sized and structured nuclei.(Tan et al., 2013) However, the properties of final granules (size and size distribution), are not simply determined by the quality of foam (i.e. the volume fraction of gas entrained), but also by other processing parameters.(Tan and Hapgood, 2011)

More recently, this foam binder technology was introduced to the twin-screw granulation and systematically studied.(Thompson and Sun, 2010a, Thompson et al., 2012b, Thompson et al., 2012a, Weatherley et al., 2013) Due to its solid nature the input of foamed binder to the process requires a sider stuffer. A typical setup for foam granulation in an extruder is shown in Figure 1.5. Compared to conventional wet granulation with a liquid, the foamed binder has many merits like achieving stable operations for production immediately and preventing the formation of unstable powder flow for poor wetting.(Thompson et al., 2012a, Thompson et al., 2012b) However, similar to foam granulation in batch, the processing parameters dominate the properties of the resultant granules; the property of the foam (i.e. gas volume fraction) exerts very limited influence on the average size and distribution of granules.(Thompson et al., 2012a)



Figure 1. 5 (A) Illustration of the machine configuration for granulation.(Thompson et al., 2012a) (B) Photo image for the extruder setup in Dr. M. R. Thompson's lab: (1) extruder, (2) side-stuffer, (3) foam generator, (4) liquid injector, (5) powder feeder, and (6) viewing port.(Thompson et al., 2012b)

1.5 OBJECTIVES OF THE THESIS

The main objectives of the thesis were:

- 1) To understand how the kneading block impacts on the wet granulation process.
- To study how the binder delivery method impacts on the wet granulation process, as well as the properties of the granules.

 To examine how the properties of drug impact on the granulation, and also to study binder distribution in granules by a color tracer.

The layout of this thesis is a sandwich type based on three manuscripts. The first paper (now published) examines the physical phenomena that are dictating the granulation process along the screw, specifically around a kneading block, by a screw pullout technique (Chapter 2). This same technique employed in the second paper (manuscript submitted) to understand the novel granulation process using foamed binder by comparing how granule growth differs when using foamed binder or conventional liquid binder (Chapter 3). Finally, the third paper (manuscript in draft) examines the influence of a drug's physical properties on granulation by looking at ingredients with varying hydrophobicity; the screw pullout technique once again allowed understanding the granulation process inside the extruder (Chapter 4).

REFERENCES

- AGRAWAL, R. & NAVEEN, Y. 2011. Pharmaceutical processing–A review on wet granulation technology. *International J Pharmaceutical Frontier Research*, 1, 65-83.
- BETZ, G., JUNKER-BÜRGIN, P. & LEUENBERGER, H. 2003. Batch And Continuous Processing In The Production Of Pharmaceutical Granules#. *Pharmaceutical Development and Technology*, 8, 289-297.
- BOUWMAN, A. M., HENSTRA, M. J., WESTERMAN, D., CHUNG, J. T., ZHANG, Z., INGRAM, A., SEVILLE, J. P. K. & FRIJLINK, H. W. 2005. The effect of the amount of binder liquid on the granulation mechanisms and structure of microcrystalline cellulose granules prepared by high shear granulation. *International Journal of Pharmaceutics*, 290, 129-136.

- CREAN, B., PARKER, A., ROUX, D. L., PERKINS, M., LUK, S. Y., BANKS, S. R., MELIA, C. D. & ROBERTS, C. J. 2010. Elucidation of the internal physical and chemical microstructure of pharmaceutical granules using X-ray micro-computed tomography, Raman microscopy and infrared spectroscopy. *European Journal of Pharmaceutics and Biopharmaceutics*, 76, 498-506.
- DHENGE, R. M., CARTWRIGHT, J. J., DOUGHTY, D. G., HOUNSLOW, M. J. & SALMAN, A. D. 2011. Twin screw wet granulation: Effect of powder feed rate. *Advanced Powder Technology*, 22, 162-166.
- DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2012a. Twin screw granulation: Steps in granule growth. *International Journal of Pharmaceutics*.
- DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2012b. Twin screw wet granulation: Effects of properties of granulation liquid. *Powder Technology*, 229, 126-136.
- DHENGE, R. M., FYLES, R. S., CARTWRIGHT, J. J., DOUGHTY, D. G., HOUNSLOW, M. J. & SALMAN, A. D. 2010. Twin screw wet granulation: Granule properties. *Chemical Engineering Journal*, 164, 322-329.
- DHENGE, R. M., WASHINO, K., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2013. Twin screw granulation using conveying screws: Effects of viscosity of granulation liquids and flow of powders. *Powder Technology*, 238, 77-90.
- DJURIC, D. & KLEINEBUDDE, P. 2008. Impact of screw elements on continuous granulation with a twin screw extruder. *Journal of pharmaceutical sciences*, 97, 4934-4942.
- DJURIC, D. & KLEINEBUDDE, P. 2010. Continuous granulation with a twin-screw extruder: Impact of material throughput. *Pharmaceutical Development and Technology*, 15, 518-525.
- EL HAGRASY, A., HENNENKAMP, J., BURKE, M., CARTWRIGHT, J. & LITSTER, J. 2013a. Twin screw wet granulation: influence of formulation parameters on granule properties and growth behavior. *Powder Technology*, 238, 108-115.
- EL HAGRASY, A. & LITSTER, J. 2013. Granulation rate processes in the kneading elements of a twin screw granulator. *AIChE Journal*, 59, 4100-4115.
- EL HAGRASY, A. S., HENNENKAMP, J. R., BURKE, M. D., CARTWRIGHT, J. J. & LITSTER, J. D. 2013b. Twin screw wet granulation: Influence of formulation parameters on granule properties and growth behavior. *Powder Technology*, 238, 108-115.
- FAURE, A., YORK, P. & ROWE, R. C. 2001. Process control and scale-up of pharmaceutical wet granulation processes: a review. *European Journal of Pharmaceutics and Biopharmaceutics*, 52, 269-277.
- FONTEYNE, M., FUSSELL, A. L., VERCRUYSSE, J., VERVAET, C., REMON, J. P., STRACHAN, C., RADES, T. & DE BEER, T. 2014. Distribution of binder in granules produced by means of twin screw granulation. *International Journal of Pharmaceutics*, 462, 8-10.

- FONTEYNE, M., VERCRUYSSE, J., DÍAZ, D. C., GILDEMYN, D., VERVAET, C., REMON, J. P. & BEER, T. D. 2013. Real-time assessment of critical quality attributes of a continuous granulation process. *Pharmaceutical Development and Technology*, 18, 85-97.
- GAMLEN, M. J. & EARDLEY, C. 1986. Continuous Extrusion Using a Raker Perkins MP50 (Multipurpose) Extruder. *Drug Development and Industrial Pharmacy*, 12, 1701-1713.
- GHEBRE-SELASSIE, I. & MARTIN, C. 2003. *Pharmaceutical Extrusion Technology*, Taylor & Francis.
- GOODHART, F. W., DRAPER, J. R. & NINGER, F. C. 1973. Design and use of a laboratory extruder for pharmaceutical granulations. *Journal of Pharmaceutical Sciences*, 62, 133-136.
- HAPGOOD, K. P., LVESON, S. M., LITSTER, J. D. & LIU, L. X. 2007. *Chapter 20 Granulation rate processes.*
- IVESON, S. M., BEATHE, J. A. & PAGE, N. W. 2002. The dynamic strength of partially saturated powder compacts: the effect of liquid properties. *Powder Technology*, 127, 149-161.
- KEARY, C. M. & SHESKEY, P. J. 2004. Preliminary Report of the Discovery of a New Pharmaceutical Granulation Process Using Foamed Aqueous Binders. Drug Development and Industrial Pharmacy, 30, 831-845.
- KELEB, E., VERMEIRE, A., VERVAET, C. & REMON, J. P. 2002. Continuous twin screw extrusion for the wet granulation of lactose. *International journal of pharmaceutics*, 239, 69-80.
- KELEB, E., VERMEIRE, A., VERVAET, C. & REMON, J. P. 2004a. Twin screw granulation as a simple and efficient tool for continuous wet granulation. *International journal of pharmaceutics*, 273, 183-194.
- KELEB, E. I., VERMEIRE, A., VERVAET, C. & REMON, J. P. 2001. Cold extrusion as a continuous single-step granulation and tabletting process. *European Journal of Pharmaceutics and Biopharmaceutics*, 52, 359-368.
- KELEB, E. I., VERMEIRE, A., VERVAET, C. & REMON, J. P. 2004b. Twin screw granulation as a simple and efficient tool for continuous wet granulation. *International Journal of Pharmaceutics*, 273, 183-194.
- KLEINEBUDDE, P. & LINDNER, H. 1993. Experiments with an instrumented twinscrew extruder using a single-step granulation/extrusion process. *International Journal of Pharmaceutics*, 94, 49-58.
- KRISTENSEN, H. G. & SCHAEFER, T. 1987. Granulation: A Review on Pharmaceutical Wet-Granulation. *Drug Development and Industrial Pharmacy*, 13, 803-872.
- LEE, K. T. 2013. Continuous granulation of pharmaceutical powder using a twin screw granulator. University of Birmingham.
- LEUENBERGER, H. 2001. New trends in the production of pharmaceutical granules: batch versus continuous processing. *European Journal of Pharmaceutics and Biopharmaceutics*, 52, 289-296.

- LINDBERG, N.-O., MYRENAS, M., TUFVESSON, C. & OLBJER, L. 1988. Extrusion of An Effervescent Granulation with a Twin Screw Extruder, Baker Perkins MPF 50D. Determination of Mean Residence Time. *Drug Development and Industrial Pharmacy*, 14, 649-655.
- PARIKH, D. M. 1997. Handbook of Pharmaceutical Granulation Technology, Taylor & Francis.
- SOLANKI, H. K., BASURI, T., THAKKAR, J. H. & PATEL, C. A. 2010. Recent advances in granulation technology. *Int J of Pharm Sci Rev Res*, 5, 48-54.
- TAN, L., CARELLA, A. J., REN, Y. & LO, J. B. 2011. Process optimization for continuous extrusion wet granulation. *Pharmaceutical Development and Technology*, 16, 302-315.
- TAN, M. X. L. & HAPGOOD, K. P. 2011. Foam granulation: Liquid penetration or mechanical dispersion? *Chemical Engineering Science*, 66, 5204-5211.
- TAN, M. X. L., NGUYEN, T. H. & HAPGOOD, K. P. 2013. Drug distribution in wet granulation: foam versus spray. *Drug Development and Industrial Pharmacy*, 39, 1389-1400.
- THOMPSON, M. & SUN, J. 2010a. Wet granulation in a twin screw extruder: Implications of screw design. *Journal of pharmaceutical sciences*, 99, 2090-2103.
- THOMPSON, M. R., MU, B. & SHESKEY, P. J. 2012a. Aspects of foam stability influencing foam granulation in a twin screw extruder. *Powder Technology*, 228, 339-348.
- THOMPSON, M. R. & SUN, J. 2010b. Wet granulation in a twin-screw extruder: Implications of screw design. *Journal of Pharmaceutical Sciences*, 99, 2090-2103.
- THOMPSON, M. R., WEATHERLEY, S., PUKADYIL, R. N. & SHESKEY, P. J. 2012b. Foam granulation: new developments in pharmaceutical solid oral dosage forms using twin screw extrusion machinery. *Drug Development and Industrial Pharmacy*, 38, 771-784.
- VARSHOSAZ, J., KENNEDY, R. A. & GIPPS, E. M. 1997. Effect of Binder Level and Granulating Liquid on Phenylbutazone Pellets Prepared by Extrusion-Spheronization. *Drug Development and Industrial Pharmacy*, 23, 611-618.
- VERCRUYSSE, J., CÓRDOBA DÍAZ, D., PEETERS, E., FONTEYNE, M., DELAET, U., VAN ASSCHE, I., DE BEER, T., REMON, J. P. & VERVAET, C. 2012. Continuous twin screw granulation: influence of process variables on granule and tablet quality. *European Journal of Pharmaceutics and Biopharmaceutics*, 82, 205-211.
- WEATHERLEY, S., THOMPSON, M. R. & SHESKEY, P. J. 2013. A study of foam granulation and wet granulation in a twin screw extruder. *The Canadian Journal* of Chemical Engineering, 91, 725-730.

Chapter 2: Understanding Wet Granulation in the Kneading Block of Twin Screw Extruders

This chapter is a paper accepted as:

H. Li, M.R. Thompson, K.P. O'Donnell. Understanding Wet Granulation in the Kneading Block of Twin Screw Extruders, *Chemical Engineering Science*, published, **2014**, 113: 11-21. Huiying Li is the major contributor to this work, M.R. Thompson is supervisor, and K.P. O'Donnell from Dow Chemical Company is technique adviser.

ABSTRACT

The adoption of twin screw granulation to pharmaceutical manufacturing requires detailed understanding of the process, with one notable area of influence being screw design. A kneading block is a common screw element that is used to compress the wet granular mass, seemingly controlling the particle size and fracture strength of an end product. The present study provides a detailed examination of how this screw element functions for the wet granulation process, looking at the influences of feed rate (10-30 kg/h) and formulation on its operation. Trials were done in a 27 mm twin screw extruder with different powder formulations consisting of lactose monohydrate, microcrystalline cellulose and hydroxypropyl methyl cellulose which were wetted with a foamed binder. The process was characterized by its pressure profile and residence time distribution. A visualization technique known as 'screw pullouts' was used to directly observe the state of granulation along the screw length and samples were collected from each screw segment for particle size and porosity analysis. The kneading block was found to provide a unique compaction-fragmentation step that increases the consistency and strength of a granular product. However, its effectiveness in doing so is strongly influenced by the granular state of powders entering this non-conveying element, which is formulation dependent. The compressive stress developed in the kneading block appeared generally low and allowed for deagglomeration or fragmentation of the agglomerated mass in downstream conveying zones depending upon the fracture strength of the powder. For the formulation containing microcrystalline cellulose, the kneading block served no function whereas for other tested powders, it was highly influential to granule size and porosity. The most notable benefit of the kneading block to all tested materials appeared to be distributing the interstitial binding liquid rather than to compact the powders.

2.1 INTRODUCTION

With growing interest in continuous granulation technologies like twin screw granulation, the majority of studies have focused on characterizing their final products against more familiar batch process operations. In regards to familiar processing variables, namely binder concentration, binder viscosity, binder drop size relative to the primary particle, all these influence granulation in the same manner whether done in an extruder or in a high shear batch mixer (Keleb et al., 2004). This similarity has led some to propose nucleation regime maps following methodologies developed for high shear batch mixers (Tu et al., 2013). However, this classical approach was found to have limited usefulness in describing twin screw granulation. Unlike the batch mixer which shows only a few design variants based on the equipment manufacturers, the screw design of a twin screw extruder is readily manipulated by the user into a multitude of configurations based on a large selection of conveying elements and non-conveying elements (most notably but not exclusively being kneading blocks and combing elements). This means that a nucleation map is not manufacturer-specific but rather will change each time a process incorporates a new screw design. The sensitivity of granule properties to the size of the extruder (Djuric et al., 2009, Shah, 2005) will further restrict how broadly a nucleation map may be used from lab scale to production scale operations. Success in predicting the operations of an extruder should start with understanding the elementary functions of its screw

2014

elements upon granule development, as well as recognizing the additive influence of screw elements immediately upstream and downstream. The purpose of this paper is to examine granule size development in one of the most popular non-conveying screw elements of a twin screw extruder, the *kneading block*, and recognize upstream and downstream influences on its performance.

Non-conveying elements like kneading blocks have a distinctive role in the process since unlike conveying zones where the extruder operates starved, these zones of the screw are fully filled with powder and are pressurized, except under states of extreme starvation which have no practical economic value. The kneading block is the most commonly used type of non-conveying element in screw designs, whether for wetting, granulation, or hot melt extrusion in the pharmaceutical field. The term 'block' refers to the fact that it is comprised of a stack of kneading discs offset from each neighbor by angles of 30° , 45° , 60° or 90° . Each disc is normally bilobal, meaning it has two tips, and is shaped such that side-by-side discs wipe one another as they rotate. Refer to the kneading block shown in Figure 2.1 for an example of its configuration. Increasing the *offset angle* of kneading discs notably increases the fraction of coarse particles (> 1 mm) in the product and those larger particles exhibit a correspondingly lower friability as well as irregular shape (Djuric and Kleinebudde, 2008, Van Melkebeke et al., 2008, Thompson and Sun, 2010). Compaction of the wet powder due to increased compressive stresses on the material

2014

through the kneading block has been assumed as the principle cause for such large granule growth. The offset angle ceases to have any influence on particle size only when the process is highly starved and the channel experiences a low degree of channel fill (Thompson and Sun, 2010, Vercruysse et al., 2012) – likely a situation to rarely occur in industrial processes. The frequency of oversized particles can be notably diminished if the kneading block is not located at the very end of the screw but rather moved further back, which appears to affect the size but not the density of granules (Van Melkebeke et al., 2008). The friability or density of a granule is strongly influenced by the length of the kneading block, with a higher number of discs or thicker discs leading to a more highly compacted state for the powders (Van Melkebeke et al., 2008, Djuric and Kleinebudde, 2008, Thompson and Sun, 2010, Vercruysse et al., 2012).



Figure 2. 1 Screw layout and magnified view of a kneading block with a 60° offset between kneading discs. Cross-sectional view of the kneading block highlights the three powder-carrying zones as the screws rotate.

2014

While the design variables of a kneading block named above have a significant effect on the state of granule development in a twin screw granulation process, operating conditions are similarly important though in a less definitive manner. Feed rate is reportedly the strongest process variable influencing particle size and granule density/strength for screw designs including kneading blocks (Dhenge et al., 2012, Thompson and Sun, 2010, Thompson et al., 2012b) yet not in all cases (Vercruysse et al., 2012). Screw speed has a smaller influence on granule properties with larger extruders (27mm dia.) (Thompson and Sun, 2010, Thompson et al., 2012b), though for small extruders (16-19mm dia.) some have reported minimal influence (Dhenge et al., 2010, Vercruysse et al., 2012) while others have indicated a much stronger influence (Keleb et al., 2001, Keleb et al., 2002). There appears to be no clear rule in the use of these process variables for the moment.

The mentioned studies above have all hypothesized upon the function of a kneading block but mostly without direct measurement or observation. The only rigorous study to date to look at the progressive development of granules along the screw and relate physical changes of those granules to the kneading block was done by Dhenge et al. (Dhenge et al., 2012). They adjusted the configuration of a screw so that different zones of the original screw design were moved closer to the machine exit in order to build up a size profile for granule development along the screw length; samples were collected upon exit. In the present paper, a classic technique to the polymer industry was used, known as *screw pullouts*, to make direct observations and measurements of granules as they
developed along the length of the screw. The purpose of this paper is to definitively identify the physical phenomena that are dictating granule development along the screws, particularly around a kneading block. The study is specifically focused on two critical variables affecting the state of compaction in the kneading block, namely feed rate and powder formulation. Other variables like offset angle, screw speed and kneading block length were kept constant for the present paper.

2.2 MATERIALS AND METHODS

2.2.1 Materials

Three formulations were examined in this study due to their prevalence in granulation processes for the pharmaceutical industry. The simplest formulation consisted solely of Flowlac® 100 spray-dried α -lactose monohydrate (Meggle Pharma; Germany). The second formulation consisted of 42 wt% microcrystalline cellulose (Avicel® PH101, FMC Biopolymer; Newark, NJ), 15 wt% ibuprofen USP (Spectrum Chemical; Gardena, CA) and 0.5 wt% fumed amorphous silica (Sigma-Aldrich; Toronto, ON) blended with α -lactose monohydrate; this formulation is denoted in this paper as MCC-containing due to it being a dominant component. The third formulation consisted of 20 wt% METHOCELTM E3PLV hydroxypropyl methylcellulose (The Dow Chemical Company; Midland, MI) blended with α -lactose monohydrate; this formulation is denoted in the

paper as HPMC-containing as it is the distinguishing component. The binding solution used for all three formulations consisted of 4 wt% METHOCELTM E3PLV (The Dow Chemical Company; Midland, MI) dissolved in distilled water.

2.2.2 Twin screw granulator

Wet granulation trials were performed in a Leistritz ZSE-HP 27mm 40L/D co-rotating intermeshing twin screw extruder (American Leistritz Extrusion Corp.; Sommerville, NJ). Its barrel consisted of a water-chilled (10°C) feed zone (Z0) and nine barrel zones (Z1-Z9) heated to 35°C. Powders were fed into the feed zone (Z0) of the extruder by a T-20 gravimetric feeder from Brabender Technologie Ltd (Mississauga, ON). The binding solution was metered as a foam (85% foam quality, (Thompson et al., 2012b)) into the second barrel zone (Z2) of the extruder at different rates specific to the needs of each formulation. The liquid-to-solids (L/S) ratio was optimized for each formulation to achieve exiting particles in the size range of 0.5-2 mm, desirable for tableting. The L/S ratios along with the varied operating conditions tested for the different formulations are summarized in Table 2.1. The extruder exit was open without a die but included a custom-built restraining plate that prevented the screws from moving axially while not obstructing the flow of powder.

Trial	Formulation	L/S ratio	Flow rate (kg/h)	Screw	Exit	Moisture
No				speed	Temperature	content at
1.0.				(RPM)	(°C)	exit (%)
1	Lactose	8	10	220	30	8
2	Lactose	8	20	220	30	8
3	Lactose	8	30	220	36	7
4	20% HPMC	16	10	220	36	14
5	50% MCC	60	10	220	33	35

 Table 2. 1 Trial conditions

The screw design consisted primarily of conveying elements and included a 10-disc 60° offset kneading block. The kneading discs were bilobal and each was 5.6mm thick. Important dimensions for the kneading block are given in Table 2.2, with some values calculated using the mathematical expressions of Potente et al. (Potente et al., 1994). The general screw design used is shown in Figure 2.1 and remained constant for all screw pullouts. The kneading block was only moved for a specific set of trials to evaluate its pressure profile since the position of a pressure sensor is very limited as to where it can be located in the barrel; however, the kneading block always remained within \pm 30mm of its stated position in the figure. Pressure data was collected in those trials with a 0-34 MPa pressure transducer (Dynisco Corporation; Franklin, MA) centrally located over the

intermeshing region between the two screws, at the start (L=0mm), mid-point (L =30mm) and end (L=60mm) of the 10-discs kneading block.

Physical Dimensions	Calculated Parameters		
Outer diameter, D _s (mm)	27.08	Intermeshing angle, Ω (deg.)	63.7
Center-to-center distance, a (mm)	23	Pitch angle, ϕ_s (deg.)	13.2
Flight count of element, <i>i</i> (lobality)	2	Flight angle, ϕ (deg.)	26.3
Offset angle, α (deg.)	60	Mean channel depth, \overline{h} (mm)	3.01
NT C1 1' 1' '	10	Cross-sectional area per	2047
No. of kneading discs, J _{Kn}		element, $A_{Ke} (mm^2)$	384./
Avial length of the block I (mm)	59.90	Cross-sectional area of the	1112 /
Axial length of the block, L_{Kn} (mm)		barrel, A_{Bar} (mm ²)	1112.4
Dital (mm)	20	Free cross-sectional area, A_{fr}	343.0
		(mm ²)	

Table 2. 2 Dimensions and relevant parameters^a of the kneading blocks used in the present study

^a calculated from the mathematical expressions of Potente (Potente et al., 1994).

2.2.3 Process Characterization

Measurement of the residence time distribution (RTD) followed a method previously published (Mu and Thompson, 2012). A visual technique is appropriate in this case since

27

the mean residence time for this size of extruder and typical screw design is 5-40 s, making a sampling cup method (Dhenge et al., 2010) undesirable. The granulation process was allowed to proceed for five minutes to ensure steady state (as determined by the pressure sensor above the kneading block) when the tracer, 1 g food-grade cocoa powder (Fry's premium cocoa powder; Cadbury), was added into the feed port as a pseudo dirac pulse. The exiting mass from the end of the extruder was video recorded against a white background with a 16 Mpixel digital camera and then extracted images were analyzed for their color intensity using Photoshop CS4 (Ver 11.04, Adobe System Inc.; San Jose, CA, USA). To analyze the results, data were fitted to a commonly used curve function for extrusion studies, given as:

$$E(t) = a \cdot t^{-c-1} \cdot b^{c+1} \exp\left[\left(b^{c}t^{-c} - 1\right) \cdot \left(\frac{-c-1}{c}\right)\right]$$
(1)

where 'a' corresponds 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; this function is often referred to as a Zusatz distribution (Poulesquen et al., 2003). The model fitting was done using open-source software, Fityk (Version 0.9.3) with the parameters of the function (Eqn 1) adjusted using a Levenberg-Marquardt non-linear optimization solver.

To directly observe granulation within the extruder, a technique known as '*screw pullouts*' was used in this work. The extruder was stopped after running at steady state for

a minimum of five minutes so that screw rotation was abruptly halted without allowing the drive controller to gradually slow the motor. This best preserves the granules of the steady state process (though it can be somewhat damaging to the motor). The screws were then pulled from the barrel with an extraction device, withdrawn one zone (11 cm) at a time, to allow visual inspection of the granules present and collect all material in the exposed section for particle characterization; all material in the zone was combined together to ensure a large enough sample for size analysis by sieving. The highly compacted mass around the kneading block was measured for its length but no particle analysis was possible; the compacted mass in the kneading section often remained intact needing to be broken for removal from the screws and hence any particle attributes would have been unrelated to the process. Screw extraction was done progressively until reaching the zone where the binder was being added (i.e. Z2). The technique is similar to the screw pushout method of Maddock (Maddock, 1959) used for studying the melting mechanism of polymers, though providing in this case a time evolution of granules down the length of the extruder.

2.2.4 Particle Characterization

The particle size distribution (PSD) was determined using a Ro-Tap RX-29 sieve shaker (W.S. Tyler Inc.; Mentor, OH) using different screens with nominal opening widths of 2100 μ m, 1180 μ m, 850 μ m, 500 μ m, 250 μ m, 125 μ m, and 75 μ m, as well as a bottom pan. The amount of sample used for PSD characterization was approximately 5 g per

zone of the screw and 100 g for the collected material at the extruder exit, which was sieved by mechanical agitation for 5 min. The uncertainty in the analysis was determined to be 12.7%RSD based on measured samples from duplicate trials for the MCC-containing formulation. Porosity was estimated by mercury intrusion porosimetry (AutoPore Series; Micromeritics Instrument Corp., Norcross, GA). Pressure was varied

from 0.1-60,000 Psia for low- and high-pressure measurements. The sample size was

approximately 200 mg. The determined uncertainty was 3%RSD.

2.3 RESULTS AND DISCUSSION

2.3.1 Pressure development during granulation

The pressure along the kneading block was measured for powder flow comprised of lactose monohydrate from 10 kg/h to 30 kg/h; for context the extruder was approximately 60-65% filled at 30 kg/h though the kneading block was fully filled for all feed rate conditions. The pressure values reported refer to normal stresses by the powder exerted on the transducer; there is no inference being made that these are isotropic stresses across the bed of particles. Data was collected to characterize the pressure gradient along the section as well as to provide a sense of magnitude for the compaction taking place within the kneading block as feed rate varied. Figure 2.2 shows the time variance in pressure as the screws rotated underneath the sensor at the entrance (0mm, immediately before disc 1), mid-point (30mm, disc 5) and exit (60mm, disc 10) of the kneading block, presenting

only a one second duration (i.e. 3.7 revolutions at 220 RPM) for ease of viewing the profile. The sawtooth-like profile is typical of the cross-channel pressure variance in rotating screws with the lowest value per revolution corresponding to the retreating side of the left kneading disc tip (Bravo et al., 2000); consider left and right discs to be referring to the cross-sectional view seen in Figure 2.1 and realize that the pressure sensor is located at the top of the intermeshing region between the two adjacent discs. The pressure value increased as the powder closer to the advancing (pushing) side of the left disc tip approached and then the pressure dropped as that tip passed by the sensor until the retreating side was reached once again. This cross-sectional pressure variation highlights a point too often overlooked in that there are dynamic lateral compressive forces acting on the powder as it rotates between the two adjacent screws as well as being subjected to axial compressive forces which are more often discussed as compacting granules. Due to stress fluctuations indicative of granular flow, the baseline was noisy in this analysis and pressures below 0.5 MPa were considered indistinguishable from zero, meaning that the data at 60 mm (Fig. 2.2c) was indicating a non-pressurized region in the kneading block. The noisy baseline also made it desirable to use peak pressures to characterize the pressure profile in the kneading block (which are summarized in Table 2.3).



Figure 2. 2 Time variation plots of pressure measured at three locations over the kneading block as the screws rotated. Pressure traces for lactose monohydrate at feed rates from 10 to 30 kg/h.

Pressure increased for the powder from the entrance through the axial mid-point of the kneading block and then dropped at the end. Increasing feed rate increased both peak and valley pressure values seen in Figure 2.2 except at the end of the block which remained

non-pressurized for all cases; in other words, both nominally and spatially the pressure in the powder increased with flow rate. The increase in pressure is a result of the available volume for the powder being 12% smaller in the kneading block but also due to the reduced drag flow contribution from the absence of a continuous pushing flight compared to a conveying element; considering these two facts, kneading blocks are often referred to as a *restrictive elements* with respect to flow. Considering the data in Table 2.3, pressure increased linearly with feed rate for the tested conditions. Correlated with visual analysis of the screws to be shown later in the paper, the increased pressure corresponded to a more highly consolidated state for the powder bed in the kneading section; the term 'kneading section' in this paper refers to the kneading block and upstream conveying zone involved in compacting the powder. Correspondingly, the length of the compacted powder bed extended upstream of the kneading block as feed rate increased. From the screw pull-outs the densified bed was observed to span back 30 mm into the upstream conveying zone at 10 kg/h (though was apparently non-pressurized as noted at L=0 mm in Table 2.3), growing to 120mm back at 20 kg/h (now pressurized at L=0 mm) and reaching 240 mm back at 30 kg/h. By 30 kg/h, the pressure of the packed solids at positions L=0 mm and L=30 mm of the kneading block (seen in Table 2.3) were similar. Considering the visual observations (shown in Section 2.3.3) where the packed bed appeared uniform over the entire kneading section, the similar recorded pressures at L=0mm and L=30 mm at 30 kg/h were felt to be indicating that the powder bed was approaching its maximum state of consolidation for the limited compressive forces that could be derived by the pushing capacity of the upstream conveying elements.

Max Pressure per rotation (MPa)				
L = 0 mm	30 mm	60 mm		
0.43	1.27	0.54		
1.36	1.89	0.52		
2.53	2.56	0.51		
	Max Pre L = 0 mm 0.43 1.36 2.53	Max Pressure per rota L = 0 mm 30 mm 0.43 1.27 1.36 1.89 2.53 2.56		

Table 2. 3 Variation in pressure relative to flow rate and location in the kneading block

The pressure rise across the fully filled zone of the kneading block can be approximated by the viscous shearing solids-conveying model of Chung (Chung, 1975). The model is applicable to solids moving based on drag forces created by the rotating screw and yet partially retarded by viscous stresses at the screw and barrel walls (as opposed to frictional forces). The model seems very applicable to the lubricated powder in this study but it is difficult to directly use since it was intended for single screw extruders not twin screw and especially not for a discontinuous flight like in a kneading block. The pressure gradient for this model is calculated as:

$$\frac{\Delta P}{\Delta z} = \frac{C_1 \beta_b}{H} \left[\frac{\sin \phi}{\sin(\theta + \phi)} V_s \right]^{\alpha_b} (C_1 \cos \theta \cos \phi - \sin \theta \sin \phi) - \beta_s \left[\frac{\sin \theta}{\sin(\theta + \phi)} V_s \right]^{\alpha_s} \cdot \left[\frac{C_2}{H} \left(\frac{C_2}{C_1} \right)^{\alpha_s} \left(\sin^2 \phi + C_2 \cos^2 \phi \right) + \frac{2}{\pi D \sin \phi} \left(\frac{1}{C_1} \right)^{\alpha_s} \right]$$
(2)

where z is the channel length, C_1 and C_2 are geometric parameters related to the channel depth, H and screw diameter, D, ϕ is the flight angle; θ is the powder bed conveying

2014

angle, V_{sp} is the solid bed velocity, and (α_b, β_b) and (α_s, β_s) are rheological constants of the power-law relationship, $\tau = \beta V_{sp}^{\alpha}$, for the barrel and screw surfaces respectively. The equation shows that the solid bed velocity will decrease as the pressure gradient decreases in a manner corresponding to the exponent of $1/\alpha_b$. Since rheology is difficult to assess for powders, the model is only used here to highlight changing conditions inside the extruder. Examining the pressure gradient between L = 0 and L = 30 mm for the three feed rates, the model indicates that the velocity of the solid bed would have decreased significantly from 10 kg/h to 30 kg/h across these two locations in order to produce the pressure gradient measured. In other words, the compressive forces that created the kneading section. The main limitation to using the model is the lack of consideration for porosity which is hypothesized herein to be decreasing progressively along the length of the kneading section (based on the visual observations below) though it is conceivable to consider the bed conveying angle as functions of porosity.

The pressure rise across the kneading block was a result of the compressible nature of the powder flow as its velocity decreased. The response of the powder flow is similar to the phenomenon of densification seen at the end of a downwards pneumatic conveying pipe (Sheer, 1995).

2.3.2 Residence time distribution

The residence time distributions measured for the process as flow rate increased from 10 kg/h to 30 kg/h at 220 RPM are shown in Figure 2.3. Plot (a) demonstrates the quality of fit ($R^2 = 0.86$) by the Zusatz function (Eq. 1) to the color intensity tracer data (compiled from three repeats) collected at the exit of the extruder. The fit to the Zusatz function was considered sufficient for the purposes of analyzing the mean residence time and breadth of the distribution. The lower plot in the figure showed the fitted RTD curves, featuring an increase in peak residence time and narrower distribution breadth as feed rate increased. The increase in peak residence time corresponded with increasing pressure in the kneading block, indicating slower passage of powders through the restrictive element with increasing feed rate. The narrowing distribution indicated that the state of mixedness within the powder bed originally aided by shear dilatancy (Tardos et al., 2003) under starved flow conditions, was decreased as compressive forces more densely consolidated the bed. In fact, the authors have strongly resisted making any reference in this paper to the kneading block as a mixer since that does not appear to be a good descriptor for its function in wet granulation.



Figure 2. 3 Residence time distribution measurement for twin screw granulation of lactose. Plot (a) shows the quality of fit between the color data and the Zusatz model whereas (b) shows the fitted Zusatz distributions for feed rates of 10 to 30 kg/h.

The mean residence time for 10 kg/h and 20 kg/h was found to be similar at 19.5 s and 19.2 s, respectively yet increased to 24.6 s at 30 kg/h. The condition at 20 kg/h marked a transition for the process, i.e. a local minima in residence time, where the peak residence time was starting to significantly increase but the distribution also significantly narrowed so that its mean residence time was comparable to the lower feed rate condition. By 30

kg/h the increase in peak residence time dominated the calculation of mean residence time as little further densification was possible (as noted by the pressure gradient between 0-30mm of the kneading block) to affect the distribution breadth. The findings of Dhenge et al. (Dhenge et al., 2010) who measured residence time for a 16mm twin screw extruder found only that the mean residence time decreased for their tested conditions.

The highly consolidated state of the powder exiting the kneading section has reported beneficial influences on friability and particles size (Djuric and Kleinebudde, 2008, Van Melkebeke et al., 2008) but the longer mean residence times that correspondingly arise are not necessarily advantageous to the process. Longer residence times in the machine correspond to increased material temperature for exiting product and the motor demand expectedly increases. The measured exit temperature (by an infrared pyrometer) was 30°C for both 10 kg/h and 20 kg/h and 36°C at 30 kg/h; up to 20 kg/h the powder residence time was too short to equilibrate with the barrel but by 30 kg/h the powder matched the barrel temperature. Motor demand in the present study similarly increased by 33% at 30 kg/h compared to the constant power value (i.e. 2.1 KW) for the two lower feed rates. Exit temperature, motor demand and residence time are process-wide parameters which do not specifically represent a single zone inside the extruder; however, all other regions of the screw are generally starve-filled and so a fully filled zone like a kneading block will have a dominant influence.

2.3.3.1 Particle size development versus feed rate

Screw pullouts were performed after runs with lactose monohydrate at 10-30 kg/h for a fixed screw speed of 220 RPM. Seeking to produce granule sizes in the order of 0.5-2 mm for solid oral dosage form products, granulation with a L/S ratio of 8% has been reported as optimal for this excipient (Thompson and Sun, 2010, Keleb et al., 2002). The axial variation in particle size along the screws based on the mass fraction found on each sieve is plotted in Figure 2.4. The feed particles ($d_{50} = 140 \ \mu m$, $d_{99} = 250 \ \mu m$) saturated by the introduced binder at 110-220 mm (Z2) showed only minor granule development initially with the lumps being related to the distribution of the liquid at the immediate point of contact. The saturated bed of lactose monohydrate changed little in its particle size distribution right up to the kneading block (i.e. zones Z2-Z7), predominately reflecting the characteristics of the original feedstock. However, the state of consolidation in the kneading section had some backwards influence on the starved upstream conveying zone (Z2-Z7) with a larger fraction of lumps (>2100 μ m) being created closer to the wetting zone as feed rate increased, likely a result of the longer powder residence time which meant the lactose dwelled longer at the liquid addition site. The function of the kneading block appeared quite aggressive, with the feed particles (<250 µm) being almost completely incorporated into larger granules upon exiting the section into zone Z8 (880-990 mm). Increasing feed rate (and increased compaction) produced a higher fraction of lumps after the kneading block in zone Z8. Figure 2.5 in plot (a) highlights the differences in particle size distribution for samples collected before and after the kneading

section with respect to feed rate. At all three feed rates a very similar transition from fine powder to large granule was seen over this section with only minor variance related to the state of compaction (presumably since the measured pressures are relatively low).



Figure 2. 4 Particle size fraction plots determined along the length of the screws from screw pullout trials with lactose monohydrate for feed rates of (a) 10 kg/h. (b) 20 kg/h, and (c) 30 kg/h.



Figure 2. 5 Particle size distributions of lactose monohydrate, (a) sampled at shown locations before and after the kneading block and (b) sampled from zone Z8 and at the machine exit. Comparison based on feed rate conditions from 10 kg/h to 30 kg/h.

Particle size determination was not done for the kneading section as the mass was densely packed but the resulting compression was visually apparent in the screw pullouts. Figure 2.6 shows images of the powder that did not fall off the screws as they were pulled from the extruder, for the conditions of 10 kg/h to 30 kg/h at 220 RPM with lactose monohydrate; the consolidated mass that clung to the screws was used to define the length of the zone being compressed. As a general observation first, it is noted from the images that the powder was less consolidated in the top of the right screw (looking from

the machine exit) along the whole length of the kneading block but also in the immediate upstream conveying elements. The powder there was being pushed towards the intermeshing region where it experienced abrupt changes in velocity while passing from one screw to the other, creating a crushing or grinding action on the compact bed. This comminution was only visible where pressure was nearly negligible, primarily at the retreating edge of the flight or disc. The same crushing action occurred on the underside of the left screw (not shown) where material was once again being brought into the intermeshing region. The loose powder created by this crushing action disappeared (compacted again) once past the intermeshing region on its transverse path around the circumference of the screws, provided the zone was pressurized.

Two distinctive differences were observed concerning the state of consolidation between the three flow conditions shown in Figure 2.6: one related to the kneading block and one related to the upstream conveying elements. To the latter point first which was briefly discussed in Section 2.3.1, the densely compacted powder (denoted by the smooth, less porous bed surface) extended back towards the feed zone of the extruder with increasing axial distance as the feed rate increased, spanning one screw turn into the conveying zone at 10 kg/h (Fig 2.6a), four screw turns at 20 kg/h (Fig 2.6b) and increasing to eight turns by 30 kg/h (beyond the view to the left in Fig 2.6c). Thus a longer zone of compaction was being developed as more material was required to pass through the relatively restrictive path within the kneading block. To the former point regarding the observations within the kneading block, the state of consolidation varied more distinctly in both axial and transverse directions at 10 kg/h with some distinctiveness of individual granules making up the bed being evident. Conversely, by 30 kg/h the powder was found to be densely packed (shown by its glassy-like surface) across the entire section with no distinctive granules apparent except for minor crushing seen at the retreating sides of the flight and discs.



Figure 2. 6 Images from the screw pullouts for lactose monohydrate over the kneading section for (a) 10 kg/h, (b) 20 kg/h, and (c) 30 kg/h. Flow direction left to right in shown images.

Across zones Z8-Z9 (barrel locations from 880 mm to 1100 mm in Figure 2.4) the largest particles (above 2mm) diminished in number while the fraction of smaller particles, most notably 500-1180 μ m, increased. Minor agglomeration occurred as noted by further decreases in the mass fraction of fine particles. The collected product exiting from the extruder (shown in Figure 2.5b) showed the cumulative effects of compression and fragmentation on the lactose along the screws. While feed rate had only a small influence on the exiting particle size from the kneading section (i.e. $d_{50} = 950 \ \mu$ m at 10 kg/h versus $d_{50}=1000 \ \mu$ m at 20 kg/h and 30 kg/h), it distinctly affected the size of particles in the collected product; fewer large particles were found in the collected product as feed rate decreased.

2.3.3.2 Particle size development based on formulation

The composition of a powder formulation will expectedly influence the state of granulation, due to characteristics including its wetting nature. The excipients chosen for this work were common examples of diluents used in pharmaceutical formulations, each with different wetting properties with respect to water. Lactose monohydrate requires very little water to produce surface wetting (minimum 3% w/w) due to its solubility, HPMC immediately wets to demonstrate an adhesive behavior, and MCC has weak swelling tendencies requiring much higher water addition (minimum 27% w/w) before surface water is apparent (Miwa et al., 2000). This is the most obvious difference in granulation between the formulations containing these ingredients in this study; however,

it is not being implied that wetting characteristics are solely influential on granule growth and neither should the ibuprofen in the formulation with MCC be considered as having no significance. The discussion that follows is simply identifying the dominant ingredient in each formulation thought to be the chief cause for the differences in granulation that were

observed.

Figure 2.7 shows the axial variation in particle size along the screws based on the mass fraction found on each sieve, for the three tested formulations comprised of ingredients mentioned in Table 2.1 and at 10 kg/h and 220 RPM. Since MCC and HPMC create distinctively different wetting characteristics compared to pure lactose, higher L/S ratios were required when blended with lactose to achieve similar sized granules; the basis for comparing results between the three formulations in this section comes from the fact that the chosen L/S for each led to comparable granule size by the end of the machine since a common state of saturation was not possible. The formulation with HPMC required a L/S ratio of 16% for a granulate product in the 0.5-2mm range whereas the formulation with MCC required a L/S ratio of 60%; the same L/S ratio of 60% was required even in the preliminary studies when no ibuprofen was included in the formulation (data not shown). These two excipients possessed smaller feed particles compared to the lactose (i.e. $d_{50} =$ 50 μ m, d₉₉ = 150 μ m for MCC and d₅₀ = 35 μ m, d₉₉ = 200 μ m for HPMC) and so the feed particle size of lactose was still considered to define the upper limit for 'fines' (i.e. <250 um) in the analyzed samples. As seen in the figure, the higher amount of liquid added at Z2 for the two blended formulations created a correspondingly higher frequency of particles greater than 2mm in the early zones of the screws. However, progressively through the conveying zones Z2-Z7 the saturating liquid was absorbed by the MCC and HPMC formulations and these lumps decreased in frequency. The lumps were replaced by smaller but still significantly sized particles (850-1180µm) that were predominantly spherical for the MCC-containing formulation and oblong-shaped for the HPMC-containing formulation. In both cases, the powder upstream of the kneading block possessed a discrete granular organization which was different from the largely uniform wetted mass seen with only lactose (as seen by the images from conveying zone Z6 in Figure 2.8). The pure lactose particles in Figure 2.8 were large, often spanning half of a screw turn but also extremely fragile and readily broken into smaller particles when handled, whereas the granules of the other two formulations were small, distinct and strong enough to be handled.



Figure 2. 7 Particle size fraction plots determined along the length of the screws from screw pullout trials for a feed rate of 10 kg/h with formulations (a) 50% MCC. (b) lactose monohydrate, and (c) 20% HPMC.



Figure 2. 8 Magnified view of the granules found in the upstream conveying elements prior to the kneading section at 10 kg/h, for formulations (a) 50% MCC. (b) 20% HPMC, and (c) lactose monohydrate.

The kneading block functioned in the same manner for all three formulations, to compact the wetted solids and reduce the number of fine particles through agglomeration. However, the mass in the kneading block for the two blended formulations appeared more porous compared to pure lactose, most notably with the MCC-containing formation, as shown by the images from the kneading section presented in Figure 2.9. The retained granular nature of the compacted bed seemed important since the particle size of highest weight fraction in downstream zone Z8 was smaller (1180-2100 µm) for the MCCcontaining formulation versus the other two formulations, which were predominately $>2100 \mu m$. In fact, the MCC-containing formulation showed the least change in its granule size at zones Z7 and Z8, on either end of the kneading block, compared to the other two formulations. The MCC-containing formulation was also the only case where an increase in the mass fraction of fines occurred across the kneading block. Similar deagglomeration with pure MCC powder has been reported in the tableting literature when the compressive pressure was low (i.e. <15 MPa) and the aggregates of MCC charged into the tablet press exhibited low to intermediate porosity (Johansson and Alderborn, 2001). Figure 2.10(a) presents the particle size distributions from upstream (Z7) and downstream (Z8) of the kneading block for all formulations, showing excellent granulation across the section with less than 15% fines exiting. In the last two downstream zones of the screws (Z8-Z9, barrel locations spanning 880 mm-1100 mm in Figure 2.9), the occurrences of particle fracturing appeared size specific to lumps which most commonly occurred for both lactose and the HPMC-containing formulations, reducing the weight fraction of this particle size from 40% to 20%. No agglomeration was witnessed for the HPMC-containing formulation in zone Z8-Z9 unlike the minor amount noted with pure lactose. These observation correspond to those made by van Melkebeke who noted in her work that without including a downstream conveying zone more lumps were present in the exiting product (Van Melkebeke et al., 2008). For the MCCcontaining formulation which only included 20% lumps in zone Z8, no evidence of lump fragmentation was noted between zones Z8 and Z9. Only agglomeration of the smaller particles was seen in Figure 2.7 across these two downstream zones for the MCCcontaining formulation. The renewed granule growth after the kneading section highlights the fact that the compressive forces are squeezing interstitial liquid to the granule surfaces (Salman et al., 2007).



Figure 2. 9 Images from the screw pullouts at 10 kg/h over the kneading section for formulations a) 50% MCC. (b) 20% HPMC, and (c) lactose monohydrate. Flow direction indicated.

The particle size distributions of the collected products from the exit of the extruder for the three formulations are shown in Figure 2.10(b). For the MCC-formulation, further fragmentation of the larger particles (lumps and 1180-2100 μ m range) occurred upon exiting to produce a final increase in the 500-850 μ m size fraction. The resistance of this formulation to compact in the kneading block corresponded with the seemingly low fracture strength of granules in the downstream zone. For the other two formulations, they exited the process very much in the same state as found in zone Z9.



Figure 2. 10 Particle size distributions, (a) sampled at shown locations before and after the kneading block and (b) sampled from zone Z8 and at the machine exit, at 10 kg/h. Comparison based on formulation.

2.3.4 Particle porosity across the kneading block

The fracture strength of granules produced by the kneading block will be a function of the inter-particle bridging forces, dictated by binder-particle chemical interactions, and their pore structure (Rumpf, 1962). The resulting porosities of samples taken before and after the kneading block are summarized in Table 2.4, confirming the observations noted in Sections 2.3.2 and 2.3.3. The particle size fraction from 850-1180 µm was chosen for the analysis as it was representative of significant agglomeration and falls within the region of 0.5-2 mm normally considered for tableting. For the two samples consisting of purely lactose monohydrate, their porosity and the average pore size determined by high pressure mercury porosimetry decreased across the kneading block. Differences between these two samples prior to the kneading element were negligible, though their particle size distributions in Sec 2.3.2 suggest minor compressive influences on agglomeration even before the kneading section for the higher feed rate condition. However, it was evident after the kneading block that as zone pressure increased there was a significant increase in the compact state of the granules, with the average pore size decreasing by 68% as feed rate increased from 10 kg/h to 30 kg/h.

Sampla	Granule porosity (%)		Avg pore size (μm)	
Sample	Z 7	Z8	Z 7	Z8
Lactose, 10 kg/h	49.89	41.21	5.25	1.72
Lactose, 30 kg/h	48.92	36.94	4.72	0.54
Ibuprofen/MCC/Lactose, 10	42.87	43.20	0.35	0.38
kg/h				
HPMC/Lactose, 10 kg/h	54.08	41.59	0.39	0.30

Table 2. 4 Granule porosity and average pore diameter of samples before (Z7) and after (Z8) the kneading block. Testing of sieve fraction 850-1180 um.

The HPMC-containing granules showed similar porosity to the lactose granule for the same feed rate (10 kg/h), though their average pore size was significantly smaller. The porosity of these granules dropped considerably from 54% to 42% across the kneading block, much higher than anticipated from the particle size analysis and observations above, though their pore size did not differ much.

Finally, the results for the MCC-containing granules showed good agreement with the analyses in Sec 2.3.3. There was no evidence of their porosity or average pore size being changed across the kneading block for this formulation. The pore size, similar in size to the HPMC-containing granules for the same feed rate condition, was significantly smaller than found with pure lactose monohydrate.

2014

2.4 FUNCTION OF A KNEADING BLOCK

The functions of a kneading block in twin screw granulation include compaction and comminution upon a wetted powder mass. Both actions occur repeatedly (cyclically) along the entire length of the kneading section as the screws rotate, but it is the last comminution cycle occurring at the last kneading discs of the block (where compressive forces were no longer significant) that influences the final particle size of the process. According to El Hagrasy and Litster (El Hagrasy and Litster, 2013) granule break-up following a kneading block is proposed to occur by either fragmentation or extensional deformation depending on its offset angle. In the present study, observation of the particles in the conveying element immediately after the kneading section suggested both occurred though fragmentation was the dominant mechanism. The state of compaction has a vital role in the particle size produced by comminution as it knowingly influences the fracture strength (σ_t) of wetted powders (Rumpf, 1962, Bałdyga et al., 2008). This was well demonstrated by the results with lactose where differences in particle size based on feed rate became apparent only after the kneading block where impact damage caused weaker granules (produced at lower feed rates and containing larger pores) to fragment/erode more frequently. However, this study also recognized the importance of a formulation to that fracture strength. This was highlighted particularly by the MCC blend where chemical interactions created granules sufficiently strong to resist being altered in the kneading section despite an absence of compressive forces (visually confirmed by a lack of channel fill) in the upstream conveying section to mechanically form such strong particles. And so, the effectiveness of a kneading block should be directly related to its capability to increase the fracture strength of passing powder formulation. Mixing did not appear to be an important function for this screw element in granulation, as least not at the fine particle level. However, macro-scale distributive mixing has been observed by others (Dhenge et al., 2012) among aggregate-sized particles, which was likely attributed to the crushing action and re-agglomeration noted in our screw pullouts.

The compressive forces speculated in the literature to cause compaction (Djuric and Kleinebudde, 2008, Thompson et al., 2012a, Thompson and Sun, 2010, Van Melkebeke et al., 2008, Vercruysse et al., 2012, Dhenge et al., 2012, Tu et al., 2013) were recorded in this study by pressure measurements, RTD analysis and visualization. The pressure rise, increased residence time and narrower RTD pointed to ever compacting powder as powder velocity decreased (i.e. lower V_{sp} in Eq (2)). Though, the pressure developed across the kneading block related to this powder compaction was notably low (0-2.5 MPa), much lower than the 50-200 MPa normally applied for tableting. Hence, it was not surprising that the developed compressive forces produced no observable plastic deformation of the local structures within the compacting beds (particularly evident with the MCC-containing formulation). The compressive forces seemed predominantly important to squeezing the interstitial liquid to the periphery of the wet-dry powder interface, which for lactose created strong enough agglomerated structure in the kneading section to resist disintegration while the other two formulations, which resisted change to their particle size across the kneading block, went on to further agglomerate in the downstream conveying zone. The relevance of 'squeezing' liquid-saturated particles in aiding granule growth has been reviewed elsewhere (Salman et al., 2007). Besides granule growth, this squeezing effect will bear importance to process stability since poorly lubricated powders have been noted in the past to create adverse conditions in twin screw granulation (Thompson et al., 2012b).

The end of the kneading block represents its comminution zone where the final crushing cycle creates a fragmented granular mass. This granulated material experiences further breakage, attrition and possibly agglomeration in the downstream conveying zone. Thompson and Sun (Thompson and Sun, 2010) described the function of a kneading block as providing a chopping action, which is a bit ambiguous regarding the actual modes of comminution. The stress modes of comminution in a granulation process can be impact, compression or tensile; however, among these three modes the confined space of the kneading block limits the feasibility of impact damage being the dominant stress mode for producing the particle size distribution found in Zone Z7 (880-990mm). It is most likely that tangential compressive stresses causing buckling within the compacted powder, noted as a crushing action above, were the dominant mechanism of comminution in the kneading block. This occurs at every kneading disc along a block of discs else the 'mixing' of colored granule fragments noted by Dhenge et al. (Dhenge et al., 2012) could not have occurred. Re-agglomeration occurs unless the solids are located at the end of the kneading block where pressure was no longer found. However, while this may be the apparent cause for granule generation exiting the kneading section, it does not preclude some tensile induced fragmentation of the compacted mass; solids are weaker in tensile strength than compressive strength (Rumpf, 1962) and the change in velocity as the compacted mass enters the downstream conveying zone could be sufficient to extensionally deform.

What seems much clearer now is why a nucleation map was unsuccessfully applied to a twin screw granulator (Tu et al., 2013). Granulation ceases to be readily described as a rate process around a kneading block where granule growth is discontinuous. Rather its operations are strongly affected by the granular state entering a kneading section as well as operating parameters. Nucleation maps rely upon only a few key variables affecting granule development and a linear relationship between nucleation and the final stable granule, neither of which seem true for twin screw granulation while applicable to high shear batch mixers. There are still many adjustable variables to be considered regarding the function of a kneading block in the wet granulation process; however, it is believed that the fundamentals highlighted in this study are sufficient at this point to aid formulators in approximating how this specific screw element will influence granule development in screw designs they create.

2.5 CONCLUSIONS

The kneading block is a critical screw element in wet granulation processes of powders within twin screw extruders. It provides a unique compaction-fragmentation step that

increases the consistency and strength of the granular product, though its effectiveness in doing so is strongly influenced by the granular state of powders entering this nonconveying element. Use of this screw element complicates a rate-process description for granulation in the machine as there is a discontinuity in particle size development over its compression region. The compressive stress developed in a kneading block appeared generally low and allowed for deagglomeration or fragmentation of the agglomerated mass in downstream conveying zones depending upon the fracture strength of the powder. The consistent benefit to the compressive forces developed in the section appeared largely related to distributing the interstitial binding liquid rather than to densify the powder. The pressure profile across the kneading section indicated increasing axial compressive forces right up to the last disc where it abruptly dropped. Though, the pressure gradient within the kneading block decreased as feed rate increased, indicating a limit to the capability of an extruder to compact these powders that likely resulted from the need to continue conveying the mass forward despite it's ever decreasing bed velocity. The formulation to be granulated has a significant influence in the state of the compacted mass in the kneading block, with some materials that readily granulate prior to the section resisting dense consolidation in the actual element which in turn produced smaller particles in the final product. It appears important for formulators to first gauge the fracture strength that arises from simply conveying a wetted formulation in order to determine whether kneading blocks are necessary in a screw design.

2.6 ACKNOWLEDGEMENTS

The authors would like to extend their thanks to the Natural Sciences and Engineering Research Council of Canada for their funding of this project and to the Dow Chemical Company for their technical advice and donation of materials. In addition, we would like to specifically thank Charles Broomall from Dow Chemical for running the mercury intrusion porosimetry measurements.

REFERENCES

- BAŁDYGA, J., MAKOWSKI, Ł., ORCIUCH, W., SAUTER, C. & SCHUCHMANN, H. P. 2008. Deagglomeration processes in high-shear devices. *Chemical Engineering Research and Design*, 86, 1369-1381.
- BRAVO, V. L., HRYMAK, A. N. & WRIGHT, J. D. 2000. Numerical simulation of pressure and velocity profiles in kneading elements of a co-rotating twin screw extruder. *Polymer Engineering & Science*, 40, 525-541.
- CHUNG, C. I. 1975. Maximum pressure developed by solid conveying force in screw extruders. *Polymer Engineering & Science*, 15, 29-34.
- DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2012. Twin screw granulation: Steps in granule growth. *International Journal of Pharmaceutics*, 438, 20-32.
- DHENGE, R. M., FYLES, R. S., CARTWRIGHT, J. J., DOUGHTY, D. G., HOUNSLOW, M. J. & SALMAN, A. D. 2010. Twin screw wet granulation: Granule properties. *Chemical Engineering Journal*, 164, 322-329.
- DJURIC, D. & KLEINEBUDDE, P. 2008. Impact of Screw Elements on Continuous Granulation With a Twin-Screw Extruder. *Journal of Pharmaceutical Sciences*, 97, 4934-4942.
- DJURIC, D., VAN MELKEBEKE, B., KLEINEBUDDE, P., REMON, J. P. & VERVAET, C. 2009. Comparison of two twin-screw extruders for continuous granulation. *European Journal of Pharmaceutics and Biopharmaceutics*, 71, 155-160.
- EL HAGRASY, A. S. & LITSTER, J. D. 2013. Granulation rate processes in the kneading elements of a twin screw granulator. *AIChE Journal*, 59, 4100-4115.
- JOHANSSON, B. & ALDERBORN, G. 2001. The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose. *European Journal of Pharmaceutics and Biopharmaceutics*, 52, 347-357.
- KELEB, E. I., VERMEIRE, A., VERVAET, C. & REMON, J. P. 2001. Cold extrusion as a continuous single-step granulation and tabletting process. *European Journal of Pharmaceutics and Biopharmaceutics*, 52, 359-368.
- KELEB, E. I., VERMEIRE, A., VERVAET, C. & REMON, J. P. 2002. Continuous twin screw extrusion for the wet granulation of lactose. *International Journal of Pharmaceutics*, 239, 69-80.
- KELEB, E. I., VERMEIRE, A., VERVAET, C. & REMON, J. P. 2004. Extrusion granulation and high shear granulation of different grades of lactose and highly dosed drugs: A comparative study. *Drug Development and Industrial Pharmacy*, 30, 679-691.
- MADDOCK, B. 1959. A visual analysis of flow and mixing in extruder screws.
- MIWA, A., YAJIMA, T. & ITAI, S. 2000. Prediction of suitable amount of water addition for wet granulation. *International Journal of Pharmaceutics*, 195, 81-92.
- MU, B. & THOMPSON, M. R. 2012. Examining the mechanics of granulation with a hot melt binder in a twin-screw extruder. *Chemical Engineering Science*, 81, 46-56.
- POTENTE, H., ANSAHL, J. & KLARHOLZ, B. 1994. Design of Tightly Intermeshing Co-Rotating Twin-Screw Extruders. *International Polymer Processing*, 9, 11-25.
- POULESQUEN, A., VERGNES, B., CASSAGNAU, P., MICHEL, A., CARNEIRO, O. S. & COVAS, J. A. 2003. A study of residence time distribution in co-rotating twin-screw extruders. Part II: Experimental validation. *Polymer Engineering and Science*, 43, 1849-1862.
- RUMPF, H. 1962. Agglomeration, New York,, Interscience Publishers.
- SALMAN, A. D., HOUNSLOW, M. J. & SEVILLE, J. P. K. 2007. *Granulation,* Amsterdam; Boston, Elsevier.
- SHAH, U. 2005. Use of a modified twin-screw extruder to develop a high-strength tablet dosage form. *Pharmaceutical Technology*, 29, 52-66.
- SHEER, T. J. 1995. Pneumatic conveying of ice particles through mine-shaft pipelines. *Powder Technology*, 85, 203-219.
- TARDOS, G. I., MCNAMARA, S. & TALU, I. 2003. Slow and intermediate flow of a frictional bulk powder in the Couette geometry. *Powder Technology*, 131, 23-39.
- THOMPSON, M. R., MU, B. & SHESKEY, P. J. 2012a. Aspects of foam stability influencing foam granulation in a twin screw extruder. *Powder Technology*, 228, 339-348.
- THOMPSON, M. R. & SUN, J. 2010. Wet Granulation in a Twin-Screw Extruder: Implications of Screw Design. *Journal of Pharmaceutical Sciences*, 99, 2090-2103.
- THOMPSON, M. R., WEATHERLEY, S., PUKADYIL, R. N. & SHESKEY, P. J. 2012b. Foam granulation: New developments in pharmaceutical solid oral dosage forms using twin screw extrusion machinery. *Drug Development and Industrial Pharmacy*, 38, 771-784.

- TU, W.-D., INGRAM, A. & SEVILLE, J. 2013. Regime map development for continuous twin screw granulation. *Chemical Engineering Science*, 87, 315-326.
- VAN MELKEBEKE, B., VERVAET, C. & REMON, J. P. 2008. Validation of a continuous granulation process using a twin-screw extruder. *International Journal of Pharmaceutics*, 356, 224-230.
- VERCRUYSSE, J., CÓRDOBA DÍAZ, D., PEETERS, E., FONTEYNE, M., DELAET, U., VAN ASSCHE, I., DE BEER, T., REMON, J. P. & VERVAET, C. 2012. Continuous twin screw granulation: Influence of process variables on granule and tablet quality. *European Journal of Pharmaceutics and Biopharmaceutics*, 82, 205-211.

Chapter 3: Progression of Wet Granulation in a Twin Screw Extruder Comparing Two Binder Delivery Methods

This chapter is submitted as:

H. Li, M.R. Thompson, K.P. O'Donnell. Progression of Wet Granulation in a Twin Screw Extruder Comparing Two Binder Delivery Methods, *American Institute of Chemical Engineers*, submitted. Huiying Li is the major contributor to this work, M.R. Thompson is supervisor, and K.P. O'Donnell from Dow Chemical Company is technique adviser.

ABSTRACT

The two available wetting methods for twin screw granulation, namely foam delivery and liquid injection, were studied in detail by examining granule development along the screws as powder formulation and screw design were varied. Granulation profiles were determined by particle size analysis of samples along the screws collected using the "screw pullout" technique. Analysis of the particle size and porosity of produced granules revealed only minor differences between the two methods of wetting despite the larger dropsize of liquid injection compared to foam delivery. Excipients like microcrystalline cellulose or hydroxypropyl methyl cellulose with poor spreading properties, quantified by their specific penetration time and nucleation ratio, made the differences more apparent. The general similarities in granulation independent of wetting method implied that binder dispersion in an extruder was dominated by mechanical dispersion. Screw design (i.e. location of kneading block) had the dominant effect on the granulation process in this study.

3.1 INTRODUCTION

The rapid and uniform wetting of powder excipients and active pharmaceutical ingredients is considered to be one of the more pressing challenges to developing a stable, consistent continuous wet granulation processes with twin screw machinery (Shah, 2005, Thompson et al., 2012b, El Hagrasy et al., 2013). In twin screw granulation all steps of

wetting, granule growth (i.e. layering and coalescence), compression and comminution must occur within a very short period of time (i.e. seconds) and must do so sequentially for the most part (El Hagrasy and Litster, 2013, Li et al., 2014, Dhenge et al., 2012). There is a demand that the liquid distribution within all powders be as uniform as possible prior to compression or else the final product will likely consist of a high fines content. In addition, inadequate lubrication of conveyed powders against interior metal surfaces while being compressed will often result in material overheating, motor surging, and considerable variation in final particle size (Thompson et al., 2012b, Rocca et al., 2014). The main complication to uniformly wetting any powder within the extruder is the enclosed flow path which is generally beneficial as it provides a uniform shear history but also dictates where and how the binding liquid may be added. The *relative wetting area* is defined by the fluid cross-sectional area exiting an injection port versus the surface contact area of powders within the screw channels underneath said port. Therefore the issue of poor wetting is expected to occur more often in larger machines where the relative wetting area is normally well below unity and diminishes as the screw diameter of the machine (i.e. scale of the process) increases.

The necessary quantity of liquid for granulation that satisfies pendular saturation is normally added at a single port in the extruder (close to the powder feed port) to minimize equipment and operational costs but the high volumetric flow rate unfortunately creates local regions in the feed powder that can be severely over-saturated initially. Adding the same quantity of liquid over two or three ports spaced down the length of the process minimizes the state of initial over-saturation (Shah, 2005), but complicates the steps of granule growth and demands more equipment (which includes higher maintenance and control requirements).

In high shear batch mixers or fluidized beds, increasing initial binder dispersion within powders is achieved by spraying whereby the reduced droplet size relative to feed particles leads to consistency in size and porosity among the developing granules (Nguyen et al., 2009, Hapgood et al., 2003, Iveson et al., 2001). However, insufficient clearance in an extruder negates this as a feasible solution for liquid addition. The staggering of injection sites down the length of the extruder proposed by Shah (Shah, 2005), as mentioned above, seems the best solution currently disclosed in the literature to directly injecting the binding liquid when a process encounters surging and poor granulation. Alternatively, a new method was introduced recently where the binding liquid is delivered to the process as a semi-rigid, unstable foam with the consistency of shaving cream. The technique is known as *foam granulation*, named by its inventors (Keary and Sheskey, 2004). Foam granulation has been demonstrated to be a robust technique for wetting of either batch (Tan and Hapgood, 2011, Tan et al., 2013) or continuous processes (Thompson et al., 2012a, Thompson et al., 2012b). Similar to its benefits in the textile industry, introducing a foamed binder into granulation processes allow the liquid to be spread over a larger relative wetting area than possible by liquid injection without over-saturation of the initially contacted powder. A review of foam delivery versus liquid injection in a twin screw granulator was recently given (Thompson

and Sheskey, 2013) with pros and cons stated for each. The present paper probes in greater detail the differences between the two methods of binder addition to granule development when using a twin screw granulator.

It is the purpose of this paper to present results on granule size and porosity based on different operating parameters and different powder formulations which are characteristic of the pharmaceutical industry. The study uses a screw pull-out technique disclosed in a recent paper (Li et al., 2014) to directly access particles along the process length of the extruder, providing understanding of how granule growth differs based on the chosen method of wetting: foam delivery versus liquid injection.

3.2 EXPERIMENTAL

3.2.1 Materials

Three formulations were examined in this study using powders commonly employed in the pharmaceutical industry for solid oral dosage forms. The simplest formulation consisted solely of Flowlac® 100 spray-dried α -lactose monohydrate (Meggle Pharma; Germany). The second formulation consisted of 42.5% microcrystalline cellulose (Avicel® PH101, FMC Biopolymer; Newark, NJ), 15% ibuprofen USP (Spectrum Chemical; Gardena, CA), 43% α -lactose monohydrate and 0.5% fumed amorphous silica (Sigma-Aldrich; Toronto, ON); this formulation is denoted as 50% MCC due to its ratio to lactose. MCC is a fine powder with strong water absorption capacity and improves the fracture strength of produced granules. The third formulation consisted of 20% METHOCELTM E3PLV hydroxypropyl methylcellulose (The Dow Chemical Company; Midland, MI) blended with α -lactose monohydrate; this formulation is denoted as 20% HPMC. This grade of hydroxypropyl methylcellulose has minimal controlled release properties but gels on contact with water and improves the fracture strength of granules produced. Powder properties of the formulation used in the study are summarized in Table 3.1.

The preparation of the binding liquid consisted of 4wt% METHOCEL[™] E3PLV (The Dow Chemical Company; Midland, MI) dissolved into distilled water. Hydroxypropyl methylcellulose is an effective binder but also exhibits excellent foaming properties necessary to this study.

Formulation	Bulk	Tap Density	d_{10}	d ₅₀	d ₉₀
	Density	$(kg/m^3)*$	(µm)	(µm)	(µm)
	(kg/m ³)*				
Lactose	$646 \pm 1.1\%$	$737 \pm 1.1\%$	125	150	180
20% HPMC	$570\pm0.3\%$	$660\pm0.4\%$	50	125	180
50% MCC	$491\pm0.3\%$	$589\pm0.8\%$	125	150	250

Table 3.1 Properties of the formulation powders

* Included stated uncertainty, RSD (%)

The twin screw granulator was a ZSE-HP 27mm 40L/D co-rotating intermeshing twin screw extruder (American Leistritz Extrusion Corp.; Somerville, NJ). Its barrel consisted of an unheated feed zone (Z0) and nine barrel zones (Z1-Z9) heated to 35°C. Each formulation was individually tested, fed into the feed zone (Z0) of the extruder by a T-20 weight-in-loss feeder from Brabender Technologie Ltd (Mississauga, ON). The end of the extruder was left open without a die but included a custom-built restraining plate that prevented the screws from moving axially while not obstructing the flow of exiting powder.

Two screw designs were examined in the study, both primarily composed of conveying elements but including a 10-disc 60° kneading block that spanned 2 L/D in length. In one design, the kneading block was located at barrel zone Z8 to be closer to the die (denoted as Screw design #1) while the other design had the kneading block at zone Z4 to be closer to the site of binder addition (denoted as Screw design #2). Screw design #1 allowed a comparatively longer duration for binder dispersion throughout the powder by shear-induced particle collisions prior to compression in the non-conveying zone with the kneading block. The kneading block provided both compaction and comminution to the wet granulation process which has been reported to reduce granule friability and improve binder dispersion (Dhenge et al., 2012, Djuric and Kleinebudde, 2008, El Hagrasy and Litster, 2013, Li et al., 2014, Van Melkebeke et al., 2008). By moving the kneading block

to zone Z4 in Screw design #2 the heterogeneity in binder dispersion produced by a selected method of wetting should be better revealed. Both screw designs and the barrel configuration denoting the zone numbering are shown in Figure 3.1. In this study, flow rate and screw speed were kept constant at 10 kg/h and 220 RPM, respectively.

The characteristic residence time (RT) for the process was estimated for these two screw design using the 50% MCC formulation and procedure outline in a previous study (Li et al., 2014). The procedure described in the briefest sense used a tracer of cocoa introduced as a pseudo dirac pulse which was monitored for its exit age distribution with a video recorder.



Figure 3. 1 Comparison of the two screw designs examined in the study with the nonconveying kneading block located at barrel zone Z8 or zone Z4 (#2). Top screw design include the nine barrel zones and their spatial locations relative to the start of the feed zone (Z0) with values quoted in mm (upper) and L/D (lower).

3.2.3 Methods of liquid binder delivery to the extruder

For liquid injection (LI), the binding solution was directly metered into the extruder at barrel zone Z2 from a pair of interlinked ISCO 260D high pressure syringe pumps (Teledyne-ISCO Inc.; Lincoln, NE) configured for continuous flow; accuracy of the pumps was ± 0.01 ml/min. The injector stem had an exit diameter of 1.5 mm. For foam delivery (FD), a mechanical foam generator supplied by The Dow Chemical Company (Midland, MI) was used to entrain air into the binding liquid to yield an 85% foam quality; foam quality (FQ) refers to the volume fraction of air in the produced foam. The foam was continuously metered into the extruder using a side stuffer (American Leistritz Extruder Corporation; Somerville, NJ) mounted at barrel zone Z2. (Thompson et al. 2012b) The equivalent diameter of the opening into the extruder for the side stuffer was 32 mm calculated for its dual annular flow areas.

The liquid-to-solids (L/S) ratio was optimized from preliminary studies with Screw design #1 at 220 RPM and 10 kg/h for each formulation to achieve exiting particles in the size range of 0.5-2 mm, which is desirable for tableting. The L/S ratios required for successfully granulation were 8% for pure lactose, 16% for the 20% HPMC formulation and 60% for the 50% MCC formulation. It is not the intention of this paper to make direct comparisons between the different formulations and hence the use of different L/S did not influence the discussion. The use of common pharmaceutical ingredients with different wetting behaviors relative to water, and needing different amounts of water to develop cohesive properties was simply meant to perturb the granule development profile in the extruder and offer the most insights into how the method of wetting impacted granulation.

3.2.4 Process analysis by screw pullouts

To directly observe granulation within the extruder, a technique known as 'screw *pullouts*' was used in this work. The extruder after running at steady state for a minimum of five minutes was stopped in such a manner that screw rotation was abruptly halted, preventing the drive controller from gradually slowing the motor. This best preserved the granules as being representative of the steady state process. The screws were then pulled from the barrel with an extraction device, withdrawn one zone (11 cm) at a time, to visually inspect the granules present and collect all material in the exposed section for subsequent particle characterization; all materials collected from said zone were combine together to create a large enough sample for size analysis by sieving. The highly compacted mass in the kneading block was not analyzed since in many cases it had to be pried off the screws with a tool. Screw extraction in this stepwise manner was continuously done until reaching the zone where the binder was added (i.e. Z2). An intact example of a screw pull-out where the particles were not removed but left in place is shown in Figure 3.2. Samples collected from along the screws and at the exit of the machine were air-dried for 48 hours in a lab held at 23°C and 35% relative humidity, and then stored in sealed plastic bags for later characterization.

Figure 3. 2 Photograph of a screw pull-out for the 50% MCC formulation at 10 kg/h and 220 RPM with the kneading block located at zone Z8. The screw is oriented such that zone Z2 is to the far left and zone Z9 is to the far right.

3.2.5 Particle size analysis

The particle size distribution (PSD) was determined using a Ro-Tap RX-29 sieve shaker (W.S. Tyler Inc.; Mentor, OH) using different screens with nominal opening widths of 2100 μ m, 1180 μ m, 850 μ m, 500 μ m, 250 μ m, 125 μ m, and 75 μ m, as well as a bottom pan. The amount of sample used for PSD characterization was approximately 5 g per zone of the screw and 100 g for the collected material at the extruder exit, which was sieved by mechanical agitation for 5 min. The uncertainty in the analysis varied based on the size fraction being largest on the 2100 μ m screen at 12.7%RSD based on measured samples from duplicate trials for the MCC-containing formulation.

3.2.6 Porosity, pore size and fracture strength characterization

Porosity was measured by mercury intrusion porosimetry (AutoPore Series; Micromeritics Instrument Corp., Norcross, GA). Pressure was varied from 0.1-60,000 Psia for low- and high-pressure measurements. The sample size was approximately 200 mg. The determined uncertainty was 3%RSD.

Characteristic fracture strength of a granule was determined by confined uniaxial compression of a sample initially screened to consist of 500-850 µm particles. The value for fracture strength was calculated according to the equation and method described by Adams (Adams et al., 1994). A mass of 0.60 g was introduced into a die press described in (Thompson et al. 2012b) and compressed to maximum load of 4200 N at a crosshead speed of 3.5 mm/min, consistent with Adams. Between samples the die press was lubricated with magnesium stearate.

3.2.7 Binder penetration time

Each formulation was first sieved through a 300 μ m screen. A sample of the powder (~100 g) was then poured through a funnel suspended 5 cm above a glass petri dish (10 cm in diameter and 1.5 cm deep). A ruler was used to carefully spread the powder evenly around the perimeter of the dish and then drawn across the top of the dish to create a flat surface for the bed; preparation of the powder bed was done in this manner to minimize differences in porosity between repeats. Variation in the porosity by this method of filling was 1.89% RSD. Differing masses of foam or liquid were added atop of the powder bed. The dispensed liquid was monitored visually till it had fully penetrated into the bed. The binder-saturated powder bed was left for 48 hours to air dry before the resulting granule

nuclei was removed by inverting the dish above a 300 μ m screen and weighing. The specific penetration time (t_p) was defined as the elapsed time till the binder had fully penetrated normalized with respect to the binder mass whereas the nucleation ratio (K_m) referred to the mass of the resulting granule nuclei relative to the binder mass. This method of penetration study corresponds to the method devised by Hapgood and coworkers (Hapgood et al., 2002, Tan et al., 2009).

3.3 RESULTS

3.3.1 Characteristic saturation behavior of the different formulations

To understand how liquid penetrate into the different formulations tested, based on wetting method, and under more controlled circumstances than within the extruder, a binder penetration test was used according to the method set out by Hapgood and coworkers (Hapgood et al., 2002, Tan et al., 2009). The specific penetration times for lactose and the 50% MCC formulation are shown in Figure 3.3, though no data could be provided for the 20% HPMC formulation; the uncertainty in the time measurement was 6.6% RSD by foam and 17.1% RSD by drop addition. In the case of the latter formulation, the binding solution never fully saturated the powder by either droplet or foam since the HPMC immediately gelled upon wetting, forming a barrier which prevented the remaining liquid from penetrating into the bed. The other two formulations provided reasonable results, allowing the binder to fully penetrate into the powder. The

passage of liquid through the bed consistently took longer for pure lactose compared to the 50% MCC formulation, due to its lower affinity for water; this difference was only statistically significant by foam delivery. The difference between lactose and MCC is consistent with results reported in an earlier study (Rocca et al., 2014). As previously found by Hapgood (Hapgood et al., 2002, Tan et al., 2009), the smaller the dispensed binder mass atop of the powder the longer the time to fully penetrate, by either method of wetting, which relates to the state of powder saturation as it affects liquid mobility. The difference in the specific penetration time between foam versus droplet was significant, taking almost two orders of magnitude longer to fully penetrate the powder by the former approach. This is attributed to the fact that liquids drain from a semi-rigid foam slowly, following a tortuous path along the boundaries (i.e. plateau borders and film walls) of its numerous gas bubbles rather than allowing all of its retained liquid to be immediately available like a droplet (Keary and Sheskey, 2004).



Figure 3. 3 Specific penetration time relative to the binder atop a static bed of lactose monohydrate and the 50% MCC formulation compared based on wetting method.

The nucleation ratio which represents the spreading of binder in a powder system was measured from each penetration test, with average values being quoted in Table 3.2. The wetted mass was largest for pure lactose as it has less tendency to absorb and hold the water locally unlike HPMC or MCC, allowing it to spread further within the interstitial regions of the powder (Rocca et al., 2014). The results for the 20% HPMC formulation did not properly convey the wetting nature of this powder as the liquid remained trapped atop of the bed due to rapid gelation of the cellulose ether ingredient as mentioned above. The 50% MCC formulation generated much smaller K_m values compared to lactose due to its high water absorbing capacity retarding interstitial distribution of the binder. Comparing the state of saturation based on the selected wetting method found that granule nuclei were consistently larger by foam versus droplet; a result consistent with

2014

other studies comparing the two wetting methods looking at lactose (Tan et al., 2009) and a glass ballotini/salicylic acid blend.(Tan et al., 2013) The higher spread-to-soak characteristic of foam versus a droplet that produced these larger nuclei in the tests was predominantly related to the larger contact area made with the powder bed; This is due to the occupied volume of a foam being much larger than the liquid it contains due to the inclusion of a high volume fraction of entrained air (85% v/v in the present case).

Formulation	State of the binding liquid			
	Foam, 85% foam quality	Droplet		
	K _m	K _m		
Lactose monohydrate	4.63±0.21	3.79±0.20		
20% HPMC	1.57+0.07	0.80±0.23		
50% MCC	1.14±0.03	0.95±0.01		

Table 3. 2 Nucleation ratio (K_m)

3.3.2 Granulation profiles for α -lactose monohydrate

Figure 3.4 presents granulation profiles corresponding to the wetted length of the screws (i.e. from zone Z2 to Z9) for pure lactose monohydrate using the two screw designs and operating conditions of 10 kg/h and 220 RPM. The plots for both wetting methods are shown. By either screw design or wetting method the profiles showed little granulation in the upstream conveying zones prior to the kneading block, with fines (<250 μ m) being

predominant in the screws. The only difference by wetting method seen was a higher content of large particles (> 1mm) being immediately formed upon binder addition by liquid injection, retained up to the kneading block. For Screw design #1, the kneading block brought about an abrupt increase in the weight fraction of large particles (>850 μ m) by either method of wetting. The largest of particles produced by the kneading block appeared to fragment (referring to the lumps, i.e. > 2mm) in the downstream conveying zone.



Figure 3. 4 Granulation profile for α -lactose monohydrate comparing results on Screw design #2 (a,c) vs. #1 (b,d). Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).

Moving the kneading block from zone Z8 to zone Z4 had no significant effect on the nuclei size distribution in the wetting zone (zone Z2). This demonstrates that the kneading block had no backwards influence on particle movement or bed density at the site of binder addition despite now its closer proximity. However, the downstream granule profiles now showed greater sensitivity based upon the method of wetting. By foam

delivery, the content of lumps significantly increased ($F_{>2100\mu m} = 3\% \rightarrow 21\%$) across the kneading block, though to a lesser degree than previously found with Screw design #1 $(F_{>2100um} \sim 40\%)$. In the downstream conveying section of Screw design #2, higher stability in granule size was noted using foam delivery with only minor attrition of the created lumps the kneading block producing more particles between 0.5-1 mm in size. In comparison, with liquid injection more lumps were present before the kneading block $(F_{>2100um} \sim 15\%)$ but that weight fraction did not change through the kneading block. In general, the amount of lumps were fewer than with foam. Despite the fewer lumps by liquid injection, the nominal particle size was larger than by foam (though smaller than with Screw design #1) due to a high fraction of particles, 1-2mm in size. In addition, the weight fraction of 850-1180µm particles by liquid injection significantly increased along the longer downstream conveying region while the remaining fines decreased. Between the two methods, the lactose showed more change in granule size along the longer downstream conveying zone by liquid injection compared to foam delivery – possibly reflecting the greater need to distribute the liquid after being initially being highly segregated. The early kneading block made the system more sensitive to binder distribution though eventual growth/attrition balanced out most of the differences between the two wetting methods.

The exiting particle size distributions from the extruder are shown in Figure 3.5 with the top plot corresponding to the lactose samples. Granulation of lactose produced only mono-modal size distributions in this study. The nominal particle size was larger with the

kneading block in zone Z8 yet identical based on the method of wetting. Conversely, the nominal particle size was smaller by having the kneading block in zone Z4, though slightly greater by liquid injection in comparison to foam delivery.

Screw Design	Location	Liquid Injection		Foam Delivery	
		Avg. Pore	Porosity (%)	Avg. Pore	Porosity (%)
		Size (µm)		Size (µm)	
#1	Z7	2.74	44	5.25	50
	Z8	0.73	36	1.72	41
#2	Z3	-	-	-	-
	Z5	0.72	36	0.71	38

Table 3. 3 Granule porosity for samples of lactose monohydrate across the kneading block

To examine changes in the granule structure based on the wetting method and screw design selected samples were analyzed for their porosity and fracture strength. Table 3.3 presents the results for granules of lactose monohydrate before and after the kneading block. Measurements from zone Z3 for Screw design #2 were not possible as the granules lacked integrity and readily fell apart. In general, porosity and pore size of granules decreased from compression in the kneading block. Based on the method of wetting, bulk porosity was slightly lower by liquid injection. Pore size was smaller by liquid injection but only in the case of Screw design #1. The fracture strength of exiting particles from the extruder were 13.5 ± 1.6 MPa and 12.3 ± 0.3 MPa for foam delivery and liquid injection,

respectively, with Screw design #1 and, 12.4 ± 0.5 MPa and 10.5 ± 0.3 MPa for foam delivery and liquid injection, respectively, with Screw design #2. In general, the results indicate comparable compaction between the two screw designs and wetting methods.

Selected particles (found on the 850 µm sieve) from granulation with Screw design #1 were analyzed by SEM. Figure 3.6 included images of lactose particles based on the method of wetting; there was no notable difference in average particle shape (for any of the formulations actually) and so the particles shown should not be construed to be indicating a shape dependency based on wetting. The lactose particles showed no discernable difference in their structure based on wetting. They appeared well agglomerated and dense in structure.



Figure 3. 5 Particle size distributions for the three formulations upon exiting the extruder, showing results for the two screw designs and two method of wetting.



Figure 3. 6 Micrographs for granules of lactose (a.b), 20% HPMC (c,d) and 50% MCC (e,f) produced at 10 kg/h and 220 RPM on screw design #1. Particles on the left produced by liquid injection (a,c,e) versus on the right by foam delivery (b,d,f).

3.3.3 Granulation profiles for the 20% HPMC formulation

The granulation profiles presented in Figure 3.7 show more distinct differences between the methods of wetting for both screws for the formulation containing 20% HPMC than previously seen with purely lactose. Using liquid injection with Screw design #1, only ~35% of the original feed particles (i.e. <250 μ m) were present after wetting with considerable generation of particles of 0.25-2 mm in size, followed by a more gradual increase in their content along the upstream conveying zones while fines content was reduced. Few lumps were found upstream of the kneading block (F_{>2100µm} ~5%). However, after the kneading section the lumps increased significantly in content and continued to grow in number over the short conveying zone (reaching F_{>2100µm} ~30%) while particles between 1-2mm in size decreased through coalescence.

By foam delivery, the profile and nominal particle size across the screw length resembled the findings with pure lactose, however a substantial quantity of lumps ($F_{>2100\mu m} \sim 25\%$) was formed in the wetting zone by its higher relative wetting area. Those lumps decreased to a stable content of ~18% while still upstream of the kneading block. As the lump content decreased, the number of fines increased producing the only case in the entire study where the fraction of particles less than 75 µm increased after initially being consumed upon wetting. All fines appeared to be subsequently consumed through compaction in the kneading block in aid of growth for the larger particles. The lumps in the downstream conveying zones exhibited significantly more fragmentation than seen by liquid injection. The exiting particle size distributions for this screw design, included in Figure 3.5, showed no observable difference based on wetting method, having a narrow Gaussian shape and broad tail comprised of smaller particles. The particles prepared with 20% HPMC, as visually shown in Figure 3.6, looked slightly looser in composition with more and larger pores when prepared with liquid injection in comparison to foam wetting (though porosity measurements below do not corroborate this observation).



Figure 3. 7 Granulation profile for the 20% HPMC formulation comparing results on Screw design #2 (a,c) vs. #1 (b,d). Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).

Moving the kneading block close to the site of liquid addition (i.e. Screw design #2) for this formulation had the most dramatic effect on granulation seen in this study compared to the other two formulations. Prior to the kneading block, granule growth was similar to Screw design #1 in zones Z2-Z3 with only lumps significantly increasing in content. The only difference in the upstream conveying section was noted with liquid injection where the lump content increased much more significantly on Screw design #2 and in this case, was similar in amount as produced by foam delivery (i.e. $F_{>2100\mu m} \sim 30\%$). Exiting the kneading block there was an excessive amount of lumps ($F_{>2100\mu m} \sim 60\%$) generated – more than double what was found with Screw design #1 and this occurred by either wetting method. Few other particle sizes were found immediately after the kneading block. The lumps appeared to readily fracture passing through the closest conveying zones after the kneading block (zones Z4-Z6) resulting in an increase of particles 1-2mm in size. The only difference downstream between the two wetting methods was that the lumps began to increase in content again, after zone Z6 for foam delivery but not until zone Z8 by liquid injection, consuming the particles of 1-2mm in size to grow. The final particle distribution exiting the process with Screw design #2 was dominated by lumps, as seen in Figure 3.5, but more so by foam ($F_{>2100 \text{ um}} \sim 70\%$) than by liquid injection ($F_{>2100 \text{ um}}$ \sim 40%). Neither product was considered desirable based on the excessive fraction of lumps present however as the L/S ratio had been optimized for Screw design #1.

The porosity and pore size results across the kneading block for the 20% HPMC formulation are listed in Table 3.4. As found with lactose samples, particles from zone Z3

could not be tested due to their highly friable nature. Prior to compression, the pore sizes were arguably similar based on wetting method though bulk porosity was slightly higher by foam delivery (based on data for Screw design #1). Across the kneading block both pore size and porosity decreased, as seen previously with pure lactose. Differences based on the method of wetting were negligible with similar pore size and bulk porosity observed after the kneading block. However, having the kneading block closer to the wetting zone produced significantly denser granules. The fracture strength of granules exiting the process were 15.5 ± 0.3 MPa and 17.8 ± 1.9 MPa for foam and liquid injection, respectively on Screw design #1, and were 5.0 ± 1.4 MPa and 7.5 ± 1.0 MPa for foam and liquid injection, respectively on Screw design #2. The fracture strength values for Screw design #2 are not considered accurate as larger granules than 850 µm had to be tested since there was insufficient product collected in the 500-850 µm range for testing and these lumps made for difficulties filling the die press cavity.

Screw Design	Location	Liquid Injection		Foam Delivery	
		Avg. Pore	Porosity (%)	Avg. Pore	Porosity (%)
		Size (µm)		Size (µm)	
#1	Z7	0.45	46	0.39	54
	Z8	0.32	41	0.30	42
#2	Z3	-	-	-	-
	Z5	0.18	33	0.14	30

Table 3. 4 Granule porosity for the 20% HPMC formulation*

* operating condition, 10 kg/h and 220 RPM, particle size 850-1180 µm

3.3.4 Granulation profiles for the 50% MCC formulation

Granulation profiles for the 50% MCC formulation are presented in Figure 3.8 for each of the two screw designs and by both methods of wetting. With Screw design #1, a modest amount of lumps were found in the screws at zone Z2 upon initial wetting by liquid injection ($F_{>2100um} \sim 28\%$) while their content was less (~19%) for foam delivery. By either method the frequency of those lumps decreased steadily along the conveying zones upstream of the kneading block, suggesting a weak and friable nature. Using foam delivery, the fragmentation of lumps was progressive, with particles of 1-2mm size being generated in the earlier zones (Z2-Z4) and subsequently decreasing to 0.8-1 mm sized particles along zones Z4-Z7. The conveying elements in zone Z3 had a smaller flight pitch than in zone Z2 and hence the reduced channel volume may have initiated the observed fragmentation of large granules. Such a conveying element was needed in that position to aid compaction when the kneading block was moved to zone Z4 for Screw design #2 as the general screw design for this study had to function for two kneading block locations. Few fines existed after foam wetting though those present appeared to be steadily consumed along zones Z2-Z7. By liquid injection, more fines remained upon initial wetting suggesting a highly segregated liquid distribution but steadily fines decreased in content along the upstream conveying zones. The lumps and fines decreased in content to steadily produce more and more granules of 0.8-1 mm in size, with none of the staggered attrition between size fractions seen with foam. By both wetting methods, minor granule growth resulted from compression in the kneading block. However,

significantly less change in particle size was observed than seen with the other formulations for this screw design. It was the particles of 1-2 mm size, rather than lumps, that experienced the most significant increase in content upon exiting the kneading block. The exiting particle size distributions from the extruder are shown in Figure 3.5, revealing a bimodal shape by either wetting method. The nominal particle size based on these distributions was significantly smaller by liquid injection in comparison to foam delivery. Selected particles analyzed by SEM from these samples visually seen in Figure 3.6, showed the granules were distinctly more porous when prepared by foam delivery.



Figure 3. 8 Granulation profile for the 50% MCC formulation comparing results on Screw design #2 (a,c) vs. #1 (b,d). Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).

Examining results when the kneading block was moved to zone Z4 revealed this was the only case in the study where lumps were reduced by going through the kneading block. Before the kneading block, lumps predominated the solids composition yet a considerable amount of fines remained. The particle size distribution appeared similar with either method of wetting though more lumps were present by foam delivery ($F_{>2100um} \sim 38\%$ by

foam and ~30% by liquid injection). After the kneading block, the granules were predominantly 1-2mm in size ($F_{1180-2100\mu m}$ ~30%) by either method of wetting though all other size fractions, 125 µm and above, remained significantly present (around 10% each). Most granule sizes remained constant in their weight fraction along the downstream conveying zones. The small difference in particle size seen in zones Z8-Z9 between the two wetting methods was not observed in the exiting samples from the process. The particle size distributions of collected samples from the machine exit, are given in Figure 3.5, and appeared identical based on wetting method. The exit particle size distributions remained bimodal as found with Screw design #1 but the nominal

particle size was now much larger with Screw design #2.

The porosity and pore size results for the 50% MCC formulation across the kneading block are listed in Table 3.5. With Screw design #1, there was no porosity or pore size change by passage through the kneading block for foam wetted granules yet evidence of a minor decrease in both measures for liquid injection. The powder upstream of the kneading block had a higher bulk porosity by liquid injection compared to foam delivery but much lower porosity after compression. The fracture strength of granules exiting the machine with this screw design were 27.8 ± 0.4 MPa and 40.2 ± 1.5 MPa for foam and liquid injection, respectively. The fracture strength reflected the difference in porosity of the granules after the kneading section in Screw design #1. For Screw design #2, the expectation of similar granule structure due to similar granule development was substantiated by pore size measurement and also reflected in similar fracture strength

results. The fracture strength values of exiting granules were 30.8 ± 1.6 MPa and 30.0 ± 0.7 MPa for foam and liquid injection, respectively with Screw design #2. However, the bulk porosities after the kneading block were not the same, though the liquid injection approach produced only a slightly higher porosity compared to foam delivery.

Screw Design	Location	Liquid Injection		Foam Delivery	
		Avg. Pore	Porosity (%)	Avg. Pore	Porosity (%)
		Size (µm)		Size (µm)	
#1	Z7	0.32	48	0.35	43
	Z8	0.22	41	0.38	43
#2	Z3	-	-	-	-
	Z5	0.25	44	0.24	39

Table 3. 5 Granule porosity for the 50% MCC formulation*

* operating condition, 10 kg/h and 220 RPM, particle size 850-1180 µm

3.4 DISCUSSION

The binder droplet size contacting these dry formulations differed from 1mm by liquid injection to 120 μ m by foam delivery; the estimated droplet size for foam was calculated based on the diameter of plateau borders along bubble boundaries, using an equation for foam drainage corresponding to channel-dominated flow (Kruglyakov et al., 2010) and foam drainage results presented in an earlier study (Thompson et al., 2012a). The overall

similarity in granule development seen in this study between the two methods of wetting, despite their seemingly different state of nuclei saturation based on powder-to-droplet size, implied that the means by which the binder was distributed is dominated by mechanical dispersion (Hapgood et al., 2003). This conclusion was hypothesized in an earlier work by the authors (Thompson et al., 2012a) though now reaffirmed based on a more detailed analysis. The alternative mechanism for binder dispersion, drop controlled (Hapgood et al., 2003), where spreading dictates growth rather than agitation, seems unlikely as the penetration times presented in Figure 3.3 suggested the short characteristic time scale of the process (~22 s) was too short; residence time (RT) data from the extruder for 220 RPM and 10 kg/h found no observable difference between foam delivery versus liquid injection with identical peak RT and mean R. The dominance of mechanical dispersion in an extruder for granule development implied a certain degree of robustness towards either choice of wetting method as shear should dictate the ultimate distribution of liquid in a powder bed rather than how it was initially added; later discussion will review the influence of formulation on binder distribution. However, for twin screw granulation it is not just granule growth which should concern an operator in regards to the wetting method but also the state of powder lubrication upon reaching a nonconveying zone. The state of lubrication must occur quickly before a kneading block (or other non-conveying screw element) else negatively influence process stability and material temperature (Rocca et al., 2014, Thompson et al., 2012b). As the exiting temperature of granules were within 30-36°C for all experiments and motor load was constant, there were no concerns of poor lubrication in the study despite the early position of the kneading block in Screw design #2. To highlight how quickly the liquid dispersed within the powder by either method of wetting, higher flow rates were tested with lactose monohydrate and the results form 30 kg/h versus 10 kg/h are shown in Table 3.6. Temperature and motor load increased with flow rate yet not based on the method of wetting. The data in the table also shows a point that was observed in the granulation profiles though not well distinguished, that particle size is generally larger by foam delivery for all formulations, a result previously reported (Thompson et al., 2012b, Sheskey et al., 2007). The method generally requires less liquid for granulation and creates granules of near identical porosity. Certainly from the perspective of drying time downstream of the granulation unit operation, less liquid present can mean lower overall energy requirements and potential less of a bottleneck in operating rates.

Each formulation tested represents a different wetting situation for granulation to differentiate the influence of the method of wetting. Lactose monohydrate is representative of powders with a low capacity to absorb water, leaving most at the periphery of the granules (Miwa et al., 2000) and hence required a low L/S to produce reasonably sized granules. The penetration trials indicated that liquid spreading with that excipient required mechanical action, else under static conditions there was too little time for binder dispersion in the extruder (which may be why only feed particles were predominately seen before the kneading block). Only the compressive force of the kneading block appeared sufficient to significantly improve binder dispersion within lactose such that granules developed to an appropriate size and strength. This reliance
upon mechanical force for binder dispersion meant that the wetting method had no impact on granulation.

Screw	Liquid Injection			Foam Delivery		
design/flow	Motor	Exiting	Nominal	Motor	Exiting	Nominal
rate	Load	temperature	particle	Load	temperature	particle
	(Amp)	(°C)	size, d ₅₀	(Amp)	(°C)	size , d_{50}
			(µm)			(µm)
#1/10 kg/h	4	30-31	1040	6	29-30	1030
#1/30 kg/h	7	35	1190	8	35-36	1460
#2/10 kg/h	4	29	870	4	29	860
#2/30 kg/h	12	37	1370	12	37	1610

 Table 3. 6 Influence of flow rate on the operating conditions for lactose monohydrate

The 50% MCC formulation included ibuprofen which as an ingredient has a lower affinity to water compared to the other powders in the mixture but since the penetration times decreased for this blend compared to pure lactose, the water absorption characteristics of MCC will be considered more relevant in this discussion of wetting. The relatively high water absorption capacity of MCC meant a higher L/S ratio was required for granulation before adequate surface water was present for bridging particles (Miwa et al., 2000). This formulation exemplifies conditions opposite to lactose as the liquid is 'locked away' during granulation (as noted by the low nucleation ratio values

seen in the penetration test) and hence resulted in smaller granules. Granule nucleation displayed no sensitive to the wetting method as the amount of liquid required (i.e. L/S=60%) was very high for addition at a single site, as evident by the large amount of lumps created initially by foam or liquid injection. However, the greater initial dispersion of liquid by foam delivery must be seen beneficial as granule growth occurred more quickly and much fewer fines were present in the exiting product. Moving the

compression zone closer to the wetting zone similarly reduces the fines content, in fact

the process could be made quite short in length if this approach is chosen.

Finally, the nature of HPMC as a powder excipient dramatically hinders binder dispersion, as indicated by the poor results in the penetration test. Like MCC this excipient locked away the liquid but in this case formed a viscous gel (Larsson et al., 2008) with adhesive properties to bind with local particles (i.e. layering). Assuming that adhesion rather than liquid bridging was the dominant form of agglomeration, this would explain the largely different results between liquid injection and foam delivery seen for the 20% HPMC formulation. The large contact area of the foam, despite its smaller droplet size, immediately created a large content of lumps whereas the larger droplet size yet relatively smaller contact area by liquid injection produced very few lumps but far more particles in the 0.5-1mm range. Other particles unable to contact the adhesive gel remained in their original powder state. The granules entering the kneading block largely resembled their nuclei size distribution. The compressive forces of the kneading block only seemed to compact more of the sticky particles together leaving the dry smaller

97

particles unaffected. Larsson et al (Larsson et al., 2008) have reported that HPMC creates a segregated binder distribution inside a bed of powder which often results in a bimodal size distribution. With HPMC, it seems the initial nature of wetting bears paramount consideration in granule development and in such a case, the smaller contact area made by liquid injection was a better choice over foam in order to reduce lumps.

Obviously, practical formulations may possess a blend of all these components and hence granule development will change in accordance. The results suggest that excipients which limit binder dispersion even in the presence of mechanical shear may benefit more from the use of foam versus liquid injection, particular if controlling the presence of fines and lumps is important. Future studies need to look at long term stability and product consistency.

3.5 CONCLUSIONS

Detailed studies of granule development along the screws of a twin screw extruder for three different powder mixtures have largely found that the method of wetting, either by foam delivery or liquid injection to have only a small influence on the process. Mechanical dispersion in the operation of an extruder significantly aids binder distribution throughout a bed of powder; however, for excipients like MCC and HPMC where the contacting liquid may remain more localized a wetting method like foam delivery with its higher wetting area has more relevance. More often the state of binder dispersion in a powder had a more pronounced effect on granule development when the compression zone (i.e. kneading block in the case of this study) was close to the site of liquid addition but even here the effects of the method of wetting were minor. There was evidence that the granule size by foam for a fixed L/S was slightly larger than by liquid injection while the porosity was similar. It seems overall that selection of one of these wetting methods should be made based on knowledge of the excipients within a formulation influence the distribution of liquid. However, more often it seems that consideration of screw design is more important to granulation than the wetting method.

3.6 ACKNOWLEDGEMENTS

The authors would like to extend their thanks to the Natural Sciences and Engineering Research Council of Canada for their funding of this project and to The Dow Chemical Company for their technical advice and donation of materials. The SEM micrographs were conducted at the Canadian Centre of Electron Microscopy (CCEM). This contribution was identified by William Ketterhagen (Pfizer Inc) as the Best Presentation in the session *Applications of Continuous Processing in Manufacture of Pharmaceuticals: Drug Product* of the 2012 AIChE Annual Meeting in Pittsburgh, PA.

REFERENCES

- ADAMS, M. J., MULLIER, M. A. & SEVILLE, J. P. K. 1994. Agglomerate strength measurement using a uniaxial confined compression test. *Powder Technology*, 78, 5-13.
- DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2012. Twin screw granulation: Steps in granule growth. *International Journal of Pharmaceutics*, 438, 20-32.
- DJURIC, D. & KLEINEBUDDE, P. 2008. Impact of Screw Elements on Continuous Granulation With a Twin-Screw Extruder. *Journal of Pharmaceutical Sciences*, 97, 4934-4942.
- EL HAGRASY, A. S., HENNENKAMP, J. R., BURKE, M. D., CARTWRIGHT, J. J. & LITSTER, J. D. 2013. Twin screw wet granulation: Influence of formulation parameters on granule properties and growth behavior. *Powder Technology*, 238, 108-115.
- EL HAGRASY, A. S. & LITSTER, J. D. 2013. Granulation rate processes in the kneading elements of a twin screw granulator. *AIChE Journal*, 59, 4100-4115.
- HAPGOOD, K. P., LITSTER, J. D., BIGGS, S. R. & HOWES, T. 2002. Drop penetration into porous powder beds. *Journal of Colloid and Interface Science*, 253, 353-366.
- HAPGOOD, K. P., LITSTER, J. D. & SMITH, R. 2003. Nucleation regime map for liquid bound granules. *Aiche Journal*, 49, 350-361.
- IVESON, S. M., LITSTER, J. D., HAPGOOD, K. & ENNIS, B. J. 2001. Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review. *Powder Technology*, 117, 3-39.
- KEARY, C. M. & SHESKEY, P. J. 2004. Preliminary report of the discovery of a new pharmaceutical granulation process using foamed aqueous binders. *Drug Development and Industrial Pharmacy*, 30, 831-845.
- KRUGLYAKOV, P. M., ELANEVA, S. I., VILKOVA, N. G. & KARAKASHEV, S. I. 2010. Investigation of foam drainage using foam pressure drop technique. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 354, 291-297.
- LARSSON, A., VOGT, M. H., HERDER, J. & LUUKKONEN, P. 2008. Novel mechanistic description of the water granulation process for hydrophilic polymers. *Powder Technology*, 188, 139-146.
- LI, H., THOMPSON, M. R. & O'DONNELL, K. P. 2014. Understanding Wet Granulation in the Kneading Block of Twin Screw Extruders. *Chemical Engineering Science*.
- MIWA, A., YAJIMA, T. & ITAI, S. 2000. Prediction of suitable amount of water addition for wet granulation. *International Journal of Pharmaceutics*, 195, 81-92.
- NGUYEN, T., SHEN, W. & HAPGOOD, K. 2009. Drop penetration time in heterogeneous powder beds. *Chemical Engineering Science*, 64, 5210-5221.
- ROCCA, K. E., WEATHERLEY, S., SHESKEY, P. J. & THOMPSON, M. R. 2014. Influence of filler selection on twin screw foam granulation. *Drug Development and Industrial Pharmacy*, 0, 1-8.
- SHAH, U. 2005. Use of a modified twin-screw extruder to develop a high-strength tablet dosage form. *Pharmaceutical Technology*, 29, 52-66.

- SHESKEY, P., KEARY, C., CLARK, D. & BALWINSKI, K. 2007. Scale-up trials of foam-granulation technology - High shear. *Pharmaceutical Technology*, 31, 94-108.
- TAN, M. X., NGUYEN, T. H. & HAPGOOD, K. P. 2013. Drug distribution in wet granulation: foam versus spray. *Drug development and industrial pharmacy*, 39, 1389-1400.
- TAN, M. X. L. & HAPGOOD, K. P. 2011. Foam granulation: Binder dispersion and nucleation in mixer-granulators. *Chemical Engineering Research and Design*, 89, 526-536.
- TAN, M. X. L., WONG, L. S., LUM, K. H. & HAPGOOD, K. P. 2009. Foam and drop penetration kinetics into loosely packed powder beds. *Chemical Engineering Science*, 64, 2826-2836.
- THOMPSON, M. R., MU, B. & SHESKEY, P. J. 2012a. Aspects of foam stability influencing foam granulation in a twin screw extruder. *Powder Technology*, 228, 339-348.
- THOMPSON, M. R. & SHESKEY, P. J. 2013. Foam Granulation. *Pharmaceutical Technology*, 37, 68-72.
- THOMPSON, M. R., WEATHERLEY, S., PUKADYIL, R. N. & SHESKEY, P. J. 2012b. Foam granulation: New developments in pharmaceutical solid oral dosage forms using twin screw extrusion machinery. *Drug Development and Industrial Pharmacy*, 38, 771-784.
- VAN MELKEBEKE, B., VERVAET, C. & REMON, J. P. 2008. Validation of a continuous granulation process using a twin-screw extruder. *International Journal* of *Pharmaceutics*, 356, 224-230.

Chapter 4: The Effect of Drugs on Wet Granulation in a Twin Screw Extruder

This chapter is formatted as:

H. Li, M.R. Thompson, The Effect of Drugs on Wet Granulation in a twin screw extruder Huiying Li is the major contributor to this chapter. M.R. Thompson is the supervisor.

ABSTRACT

The influence of the APIs' physical properties on granulation is also studied by comparing the granulation with varying APIs hydrophobicity. Four different APIs, including two considered more hydrophilic (caffeine and acetaminophen) and two more hydrophobic (ibuprofen and griseofulvin) were used. In order to understand the properties of API on the granulation process, the API and binder distribution, the particle size distribution, porosity, and fracture strength were performed by screw pullout technique. It was found that the API and binder distribution was irrelevant to the hydrophilicity of API, while the particle size distribution, porosity and fracture strength were strongly depending on the properties of API. A mechanism was proposed to explain the process based on considering the interfacial interaction between lactose/MCC and APIs. With increasingly reduced affinity for the API to wet granule growth was notably delayed further down the length of the screw. The results shown in this paper and the proposed mechanism advance the understanding of the granulation process in twin-screw extrusion, specifically using a foamed binder.

4.1 INTRODUCTION

Twin-screw extrusion has been widely used in many fields ranging from the plastic industry to food processing. Due to the advantages of continuous processing, such as low cost, ease of scale-up, and consistency of product properties, the extrusion has attracted

increasing attention from the pharmaceutical industry (Betz et al., 2003). As a result, twin screw granulation has emerged as a highly attractive method for the wet granulation of pharmaceutical ingredients. Great efforts and progress have been made to not only characterize the final products by this process but also to investigate the influence of processing variables. With regards to common processing variables, the screw design, extrusion screw speed, feed rate, liquid-to-solid ratio, binder concentration, and binder viscosity have been most studied. However, very limited work has been done on binder and API (active pharmaceutical ingredients) distribution within the extruder and granules at different stages along the process (El Hagrasy and Litster, 2013b). There is concern that the modes of transport inside the extruder could foster de-mixing of the API depending upon its properties. It is the intent of this paper to begin examining this concern.

The configurations of the screws have a significant impact on the properties of granules due to the differences in shear forces; friable or dense granules are characteristically developed within conveying elements and kneading blocks, respectively (Djuric and Kleinebudde, 2008). Such differences in consolidation also reportedly cause the distribution of binder to vary from zone to zone in the granules, and also among granules of different sizes. The distribution of binder can be very heterogeneous and shows a strong dependence on granule size in conveying elements; however, the distribution is improved after passage through a kneading block (El Hagrasy and Litster, 2013b). Similar to the porosity of granules in kneading blocks, the binder distribution also demonstrates a

strong dependency on the kneading disc offset angle (Djuric and Kleinebudde, 2010, El Hagrasy and Litster, 2013b). The focus of binder distribution has been based on screw configuration; however, it may be influenced by other factors like feed rate, method of binder addition or the liquid-to-solid ratio.

The uneven distribution of the binder with the powder bed originates within the conveying elements is due to the binder addition method. Recently, a novel method for adding binding liquid was introduced for wet twin-screw extrusion granulation (Thompson and Sun, 2010, Thompson et al., 2012b, Thompson et al., 2012a, Weatherley et al., 2013). Foamed delivery of binder was original used for pharmaceutical ingredients mixing in batch (Keary and Sheskey, 2004). The foamed delivery of binder can improve the wetting by its high spread-to-soak ratio, resulting in more uniform sized and structured nuclei, and consequently excellent dispersion of binder. In twin-screw extrusion granulation, use of the foamed binder can have further benefits by minimizing unstable powder flow (Thompson et al., 2012a, Thompson et al., 2012b). Although this approach for binder addition could improve the wetting behavior during granulation, the property of the binder and the interaction between binder solutions with other components in the formulation are likely to have a strong influence on the process. An obvious interaction of concern affecting binder distribution is its interfacial interaction with the API.

The granulation process varied with difference in hydrophilicity of the packed powder bed.(Tan et al., 2013) It is obvious that the affinity of the granulation reagent would influence the granulation process. The hydrophobic materials are separated from hydrophilic reagents.(Zhang et al., 2002) When the foamed binder was used, the wetting of the powder bed shows little dependence on its hydrophilicity; however, the granulation process, especially for the nucleation process, changed with the difference of affinity between the powder bed and additive.(Tan et al., 2013) Although granulation involving liquid or foamed binder has been comprehensive study, to the best of our knowledge, how the hydrophilicity of API would influence the granulation has not been considered in understanding twin-screw granulation. In this paper, we report a systematic study of binder and API distribution along the extrusion screw. We also use nigrosin as the tracer to indicate binder distribution; and four different API were introduced to understand how drugs influence the granulation process. The porosity and strength of the granules were also characterized.

4.2 EXPERIMENTAL

4.2.1 Materials

The four active pharmaceutical ingredients (API) used in this study were ibuprofen (Spectrum Chemical; Gardena, CA), caffeine (Sigma-Aldrich; China), griseofulvin (Spectrum Chemical; Gardena, CA), and acetaminophen (Spectrum Chemical; Gardena, CA). Excipients were Flowlac® 100 spray-dried α -lactose monohydrate (Meggle Pharma; Germany) and microcrystalline cellulose (MCC) (Avicel® PH101, FMC Biopolymer; Newark, NJ). Each formulation consisted of 15% API, 42.5% α -lactose and 42.5% MCC. And one formulation containing of 50% α -lactose and 50% MCC without API was used as blank formulation for comparison. METHOCELTM E3PLV (The Dow Chemical Company; Midland, MI) was dissolved in distilled water and used as the binder liquid for all of the formulations. Binder solutions with two different concentrations were prepared at 4 wt% and 4.78 wt% respectively. Nigrosin (Sigma-Aldrich; USA), a water-soluble dye, was used as the tracer in the binder with a concentration of 0.2 wt%.

4.2.2 Methods

4.2.2.1 Twin screw granulator

A ZSE-HP 27mm 40L/D co-rotating intermeshing twin screw extruder (American Leistritz Extrusion Corp.; Somerville, NJ) was used in this study. The barrel consisted of one unheated feed zone (Z0) and nine barrel zones (Z1-Z9) heated to 35 °C; and the length of each barrel zone was 11 cm. The pre-mixed raw powder was fed into the extruder by a T20 gravimetric feeder from Brabender Technologie Ltd (Mississauga, ON). The binder solution was metered into the second barrel zone (Z2) of the extruder as foam produced by a mechanical foam generator supplied by The Dow Chemical Company (Midland, MI); the foam quality (FQ) was 85% which corresponds to the

volume fraction of air. A side stuffer (American Leistritz Extruder Corporation; Somerville, NJ) was used to convey the foam continuously into the extruder at barrel zone Z2. No die was applied at the end of the extruder; but a custom-built restraining plate was used to prevent the screws from moving axially while not obstructing the flow of exiting powder. The liquid-to-solids (L/S) ratio was optimized at 50% (binder concentration was 4.78 wt%) for formulations with acetaminophen and caffeine and 60% (binder concentration was 4 wt%) for ibuprofen and griseofulvin, to get desirable sized granules between 0.5-2 mm.

Extrusion experiments were done at the same condition with the powder flow rate of 10 kg/h and screw speed at 220 RPM. The screw design primarily contained conveying elements with a 10-disc 60° kneading block located at Z8, as shown in Figure 4.1. This screw configuration and design also had been discussed in our previous work.(Li et al., 2014) A *"screw pullout"* technique was used in order to directly observe granulation within the extruder and collect samples from each zone. The extrusion process was frozen after five minutes running at steady state by using the emergency stop. This operation causes the screw rotation to be abruptly halted without concern for the influence of gradually slowing the screws and motor on granulation. Then the screws were pulled from the barrel with an extraction device. The screws were withdrawn one zone (11 cm) each time. The materials exposed were collected for further particle characterization, except for the kneading block due to the high compaction of materials. The screws were withdrawn until reaching the position corresponding to Z2 where the binder was added.



Figure 4.1 Screw configuration with the kneading block located at zone 8 (880-990 mm).

All the samples collected within the extruder (around 5 g for each zone) and at the exit of the machine (around 100 g) were air-dried at least for 48 hours at 23°C and 35% relative humidity. All of the samples were sized by a Ro-Tap RX-29 sieve shaker (W.S. Tyler Inc.; Mentor, OH) for particle size distribution (PSD) study, using different screens with widths of 2100 μ m, 1180 μ m, 850 μ m, 500 μ m, 250 μ m, 125 μ m, 75 μ m and a bottom pan for 5 min.

4.2.2.2 API quantitative analysis by FI-IR

The FI-IR analyses were performed with a Thermo Scientific Nicolet 6700 FT-IR spectrometer. The samples were characterized within the mid-range infrared region (400-4000 cm⁻¹, with a resolution of 4 cm⁻¹ and 64 scans per spectrum). In order to study the particle samples, potassium bromide (Sigma-Aldrich; Germany) was induced to prepare pellets. A pellet, containing KBr and the target sample was molded in a 13-mm die with 690 bars pressure for 3 minutes.

Because the fingerprint region of every API studied was not affected by the excipients in the formulation, a calibration curve could be built to characterize the content of API in a granule sample. Firstly, a stock mixture containing known amount of API and KBr was prepared. In order to ensure the homogeneous dispersion of API in KBr, the mixture was initially ground in a mortar to obtain a fine powder, and then further shaken in a mechanical mixer for 30 seconds within a polystyrene vial. Secondly, the mixed samples, with different API concentrations, for the calibration curve were made from stocked solution and KBr by varying the ratio of these two components. The typical procedure for preparing such sample is described as follows: the stock mixture and KBr in different ratiowere weighed keeping the total weight for 130 mg; then this mixture (containing stock mixture and KBr) was ground and mixed following the same procedure as a stock mixture preparation. The pellet for calibration was then prepared by weighing 100 mg from the 130 mg mixture. The characteristic peak for different API is not identical. The characteristic peak for ibuprofen, caffeine, griseofulvin, and acetaminophen was found at 1721 cm⁻¹, 1704 cm⁻¹, 1708 cm⁻¹, and 1655 cm⁻¹, respectively. Finally, the calibration curve was obtained by plotting the intensity of characteristic peak against API concentration in KBr, as shown in Figure 4.3.

The pellets for API in granules were prepared following the same procedure described above. The granules collected from Z2, Z4, Z6 and Z8 with classified particle sizes of 1180-2100 µm, 850-1180 µm and 500-850 µm were analyzed by infrared.

4.2.2.3 Porosity and Fracture strength study

Porosity is the volume fraction of pores in granule and was calculated from granule apparent density and true density in this study. The apparent density of the granules was measured by a technique named "kerosene displacement".(Hinkley et al., 1994) The kerosene (0.7769 g/ml) was used due to its low viscosity, low vapour pressure and immiscibility with water. Due to the limit amount of samples collected within screws, a 1 ml syringe instead of volumetric flask was used in this study to ensure the accuracy. The sample was accurately weighed and immersed in kerosene (Fisher Scientific; USA) within a 1 ml syringe. The syringe was weighed. The displaced kerosene was then removed and the syringe was weighed again. The volume of the sample was obtained by calculating the weight and density of kerosene. The volume was recorded to calculate the apparent density of granules. The true density of granule was measured by Multipycnometer True Density Analyzer(Quantachrome instruments, MVP-D160-E). The true density of granules was determined by the components in each formulation, with each formulation repeated three times.

Characteristic fracture strength was measured by confined uniaxial compression of a sample initially screened to 1180 µm particles. The value for fracture strength was calculated according to the equation and method described by Adams(Adams et al., 1994). A mass of 0.60 g of sample was introduced into a die with an 11.05 mm diameter bore and compressed to maximum load of 4200 N with a crosshead speed of 3.5 mm/min

using an Instron 3366 bentchtop universal mechanical testing system (Instron Corporation; Canton, MA). The die press was lubricated with magnesium stearate between samples.

4.2.2.4 Binder distribution

Nigrosin (Sigma-Aldrich, USA) was used as a tracer for binder distribution study, following the approach of other studies(Smirani-Khayati et al., 2009, El Hagrasy and Litster, 2013a). The granule sample (0.28±0.05 g) was extracted in 5 ml distilled water for 12 h, followed by applying sonication (BRANSON 2510) for 30 min. Then the suspension was centrifuged (Allegra X-12R centrifuge, Beckman Coulter) at 3750 RPM for 30 min in order to collect the supernatant containing the tracer. The supernatant was characterized with a UV-Vis spectrometer (DU-800, Beckman Coulter) at 574 nm and an absorption spectrum was collected in the range of 400-800 nm. The absorbance measured at 574 nm was converted to the nigrosin concentration by a calibration curve. Only visible light was used to record the spectrum in order that the API had no effect on the absorbance of nigrosin; other excipients also had no effect on the absorbance of nigrosin.

4.3 RESULTS AND DISCUSSION

4.3.1 Calibration curves for APIs

112

The analysis of API content in granules could be done by spectrophotometry, highperformance liquid chromatography (HPLC) or liquid chromatography/mass spectrometry (LC/MS). However, all of these measurements generally are time consuming and expensive. Recently, FT-IR spectroscopy had been introduced for the quantitative analysis of API in pharmaceutical formulation which overcomes these issues.(Muhammad Ali et al., 2012) FT-IR is a robust technique for characterizing chemicals, providing information on the functional groups present. Generally, the characteristic vibrational peaks of an API must be identified and their intensity compared against calibration standards first before they can be quantitated within experimental formulations. For the APIs used in this experiment, the characteristic peaks for griseofulvin, ibuprofen, acetaminophen, and caffeine are carbonyl groups, which could be found in regions around 1721 cm⁻¹, 1704 cm⁻¹, 1708 cm⁻¹, and 1655 cm⁻¹ in the FT-IR spectrum, respectively, as shown in Figure 4.2. A calibration curve for each API based on the peak intensities of these frequencies is based on the principles of the Beer-Lambert Law where absorbance is directly proportional species concentration. Figure 4.3 shows the calibration curves for the four APIs. A remarkably high correlation coefficient (R^2) was obtained ranging from 0.98266 to 0.99528 between the different APIs. Moreover, other components in the tested formulations including lactose and MCC, were not found to interfere with the FT-IR spectra at this characteristic range. (Muhammad Ali et al., 2012) Therefore, an accurate API concentration could be expected when the experimental FT-IR absorbance falling within the calibration range.



Figure 4. 2 The FT-IR spectrum for (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine.



Figure 4. 3 Calibration curves for (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine in regions of FT-IR spectrum around 1721 cm^{-1} , 1704 cm^{-1} , 1708 cm^{-1} , and 1655 cm^{-1} , respectively. The R² for (A), (B), (C), and (D) are 0.99528, 0.98886, 0.9895, and 0.98266, respectively.

4.3.2 API distribution

Figure 4.4 illustrated the APIs distribution along the length of the screws from zone 2 to zone 8. The distribution of each API within granules showed only minor differences among the different particles sizes and also along screws, except for the ibuprofen containing formulation. Specific to the ibuprofen containing formulation, the variances of API content was different based on the size of particles, as shown in Figure 4.4B, being 16% in the 1180-2100 μ m granules while only 14% in 850-1180 μ m granules. However, this variance seems minor for ibuprofen and in general all results indicate a uniform distribution of the different APIs within the granules immediately from the site of wetting.

In the kneading block the consolidation and breakage are very intense, however, in contrast to the results obtained by using liquid binder, (Dhenge et al., 2012) the distribution of APIs had no significant difference before and after traveling through the kneading block. The reason for such uniformity could be attributed to the method of binder addition. With the gradual draining of liquid from foam into the powder bed, the high tendency to spread the binder uniformly produces a much larger wetted surface than traditional dropwise addition can accomplish. (Thompson et al., 2012b) The inference here is that the wetting nature of an API, provided it is a minor component in a formulation, need not influence granule growth or its dispersion within the granules, as it will be 'caged' by adjacent hydrophilic excipients. This is consistent with other findings

that the hydrophilicity of a powder has limited impact on the wetting process when a foamed binder is used.(Tan et al., 2013) Therefore, although the hydrophilicity of the APIs was different (griseofulvin and ibuprofen being more hydrophobic; while acetaminophen and caffeine are more hydrophilic), the distributions of the APIs along the screw and in different size of granules were seemingly identical.



Figure 4. 4 The distribution of the APIs along the length of the screws. (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine.

4.3.3 Binder distribution

To confirm the hypothesis above related to the capacity of foam to uniformly wet the powders, the physical distribution of the drained liquid needed to be tracked through the

2014

process. Tracers have been ideal for determining attributes of the process such as mean residence time since twin-screw extrusion was introduced.(Lindberg et al., 1988) A colored tracer has also been used for understanding the mass transport of a binder within powders during granulation. (Ramaker et al., 1998) Nigrosin dye has been preferentially selected as the tracer in a number of cases to study the distribution of binder within granules. (El Hagrasy and Litster, 2013b, Smirani-Khayati et al., 2009) The hypothesis being made in these cases was that the dissolved polymeric binder and nigrosin dye were distributed in the granules in an identical manner, traveling with the water without absorption into the solids. The distributed nigrosin in a dried granular product could then

be extracted into water and measured for its content by reading the UV-Vis absorbance. In order to compare the nigrosin (binder) distribution within the granules, the nigrosin content was presented as the ratio of mass of nigrosin per gram of granule over mass of nigrosin per gram of powder:

Normalized nigrosine ratio =
$$\frac{[N]_i}{[Granule\ mass]_i} / \frac{[N]_{tot}}{[Powder\ mass]_{tot}}$$

where the [N] is the concentration of nigrosine, *i* is the specific zone that characterized, *tot* refers to the total mass of nigrosin of powder bed).

Figure 4.5A to D shows the dye distribution in different sized granules containing different APIs with respect to their sampling position along the screw whereas Figure 4.5E showed the binder distribution for the case without any API (i.e. wet granulated placebo). It appeared that the nigrosin (binder) was evenly distributed regardless of the

2014

different sized granules and the total content of nigrosin (binder) was gradually decreasing along the screws. Moreover, the time/distance of reaching consistent binder distribution for formulation without API was shorter than that with APIs. Except for the formulation containing griseofulvin, it generally required 5-7 zones of traveling distance for the nigrosin (binder) to be evenly distributed in all granules. By contrast, the formulation without API reached the same distribution in less than 5 zones. The interfacial property of the APIs seemed to have no impact on the distribution of nigrosin (binder).

As discussed above, the distances necessary to reach a consistent binder distribution within the extruder for any formulation was the same. Also, the size of granules had no significant influence on the distribution of nigrosin (binder). This is different from when the liquid binder is injected directly rather than foamed. In that case, the distribution of binder was significant different in different sized granules and along the screw.(Smirani-Khayati et al., 2009, El Hagrasy and Litster, 2013b, Sayin et al.) Because the liquid binder has a smaller spread-to-soak ratio, it requires more time and shear force to achieve an even distribution. However, the foamed binder with its high spread-to-soak ratio allowed the process to achieve homogeneous mixing of binder and powder quickly, also producing very uniformly sized and structured nuclei. Therefore, the binder could distribute more evenly in the granules by applying foamed binder. This reiterates the feasibility that the API was 'captured' into a granule, being surrounded by uniformly wetted powder, regardless of the interfacial property of the specific compound, as stated in the previous section.

The gradually observed decrease in nigrosin seen for all samples in Figure 4.5 has not been reported in the literature, but then that prior work did not look at time effects down the length of the process nor report sample concentration relative to the initial tracer content. The issues appears related to the excipients as the placebo showed the same occurrence; however, tests of these two ingredients (i.e. lactose and microcrystalline cellulose) in a beaker with a solution of nigrosin and monitored continuously did not show any change. If this is not an artifact of absorption then the cause is somewhat elusive.



Figure 4. 5 The distribution of nigrosin (binder) in the granules for four formulations. (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine. The uncertainty in the analysis for binder distribution based on the size fraction on the screen 1180 um is at 1.03%RSD based on the measurements from duplicate trails for formulation containing caffeine.

4.3.4 Particles size distribution

At the outset of this work there were expectations that the wettability of the powder bed, including the API, would impact the process of granulation. Because of the differences in hydrophilicity, more hydrophilic APIs might have stronger interfacial interaction with the binder, being comparable to that of lactose monohydrate and MCC. By contrast, the hydrophobic APIs, poorly wetted by the aqueous binder solution, should have weaker interactions with the powder bed. Figure 4.6 showed the axial variation in particles size along the screw based the weight fraction of classified granules. The desired granule size from the process was 0.5-2mm, suitable for tableting. It is significant that the formulations containing hydrophilic APIs tended to form larger granules, despite the fact that a lower L/S ratio was used (i.e. 50%) during granulation. For the formulation containing acetaminophen or caffeine, the granules with size ranging 1180 - 2100 µm, and 850 - 1180 μ m reached a maximum weight fraction at zone 4 (440 - 550 mm)(F₁₁₈₀- $_{2100} = 38\%$ for acetaminophen, and 47% for caffine), and zone 5 to zone 6 (550 - 770 mm)($F_{850-1180} = 33\%$ acetaminophen, and 30% for caffine), respectively. However, for the formulations with griseofulvin or ibuprofen, the same particles size ranges reached their maximum approximately one or two zones later (550 - 660 mm and 770 - 880 mm) (F_{850} - $_{1180} = 33$ to 35% and $F_{1180-2100} = 41$ to 51%).

For the formulation without any API, larger particles were formed preferentially for the same L/S compared to the griseofulvin- and ibuprofen-containing formulations. As shown in Figure 4.6E, the fraction for particle size larger than 2100 µm is over 40% within zone

3 (330 - 440 mm) whereas with the two hydrophilic API formulations the weight fraction of such coarse particles remained below 30%.

2014

A similar trend of major granule growth was found for each formulation passing through the kneading block (zone 8, 880mm - 990 mm), although the weight fraction of suitable granules (sizes 1180 - 2100 μ m) with hydrophilic APIs increased faster than those with hydrophobic APIs (the F₁₁₈₀₋₂₁₀₀ increased ~25% and ~15% for hydrophilic and hydrophobic APIs, respectively). The wettability of the APIs by binder solution also impacted on smaller granules. The initial F_{<75} for formulation containing no APIs is the highest (5%); with the values decreased to ~3% for hydrophilic APIs, and further to close to 0 for hydrophobic APIs. The F₅₀₀₋₈₅₀ and F₂₅₀₋₅₀₀ for hydrophobic APIs were consistent over the granulation process. Because of poor wettability, the particles of hydrophobic APIs within a granule either reduced the strength of binder bridges between particles or simple reduce the total number of polymer bridges within a granule of specific size, thereby impacting consolidation and breakage. Therefore, for the formulation containing hydrophobic APIs, the weight fractions of smaller particles (F₇₅₋₈₅₀) were consistent over the granulation process.



Figure 4. 6 Particles size fraction plots against the axial barrel distance for formulation with (A) griseofulvin (B) ibuprofen (C) acetaminophen (D) caffeine, or (E) without API. The uncertainty in the analysis for particle size distribution is at 1.03%RSD based on the measurements from duplicate trails for formulation containing caffeine. The kneading block locates at zone 8 (880 - 990 mm).

4.3.5 Apparent porosity and characteristic fracture strength

The apparent porosity and fracture strength of granulated matter influences its flowability as well as the properties of a finished tablet. Figure 4.7 reports on the variation in the fracture strength of granules with different APIs along with porosity for the different zones along the screws. It should be bore in mind that porosity could be used as an absolute value for comparison between samples of different formulation in this work as it is a physical variable related to the granular internal structure and hence directly represents the effect of hydrophilicity of the API on granulation (assuming the minor differences in particle size between the APIs had no significant influence). Conversely, fracture strength is a function of granular internal structure but also the inherent stiffness of the individual constituent particles which means that this parameter had much less significance for use in comparing granule development between different formulations. As shown in Figure 4.7B, the porosity of all four formulations was different, however, the individual value were relatively consistent before the kneading block. After compaction in the kneading block the porosity was noted to significantly decrease for two formulations but not those containing ibuprofen and acetaminophen. The porosity of caffeine was the highest in the study at 10% before kneading block and decreased to 6% after kneading block; griseofulvin had similar trend with 6.7% and 2.6% before and after kneading block, decreasing by about 4% from compaction. The porosity of ibuprofen and acetaminophen had no obviously change after kneading block with stable porosity of 7% and 4%, respectively. A similar phenomenon with an ibuprofen-containing formulation was found in the study discussed in Chapter 3; the porosity, characterized in Chapter 3 by mercury intrusion porosimetry showed no differences before and after kneading block. The griseofulvin had highest fracture strength while lowest porosity. With the mixing of binder and powder, the powder was getting wetted more uniformly and forming stronger bonding interaction between particles. Therefore, although the porosity was stable before the kneading block, the fracture strength was increasing steady.



Figure 4. 7 (A) The characteristic fracture strength of the granules (1180 - 2100 μ m) with different APIs against the axial barrel distance. (B) The porosity of the granules (1180 - 2100 μ m) with different APIs against the axial barrel distance. The kneading block locates at zone 8 (880 - 990 mm).

4.3.6 Granulation of APIs with different hydrophilicity

The mechanisms involved in granulation within a twin-screw extruder are still unclear. Currently, there has been no proper model put forth to describe the granulation process using a liquid binder, which is the most commonly used approach by pharmaceutical manufacturers. This need to understand is further complicated in the present case as use of a foamed binder is believed to involve different mechanisms for wetting and nucleation but may further impact granule growth and attrition.(Thompson et al., 2012b) This difference is never more obvious than by the fact that hydrophilicity of a powder has little impact on granulation with foamed binder yet strong dependency with liquid injection – at least that was the finding from batch studies.(Tan et al., 2013) Observations from the present study within the continuous extrusion process showed that API distribution and binder distribution was not significantly influenced by the hydrophilicity of API was changing, partly confirming those earlier conclusions by others. However, particle size distribution, porosity and fracture strength differed in this study based on API, which were related to differences in granule development axially along the screws. Figure 4.8 showed the proposed mechanism for the granulation process without API or with different API. The granulation process was divided into three stages. Stage 1 referred to the phenomena starting at zone 2 (wetting zone) to the zone for larger particles reaching their maximum weight fraction. Through this stage the shearing forces were relative weak due to the low degree of filling in the channels. Stage 2 referred to the zone from the ending of "Stage 1" up to the kneading block. Over this stage, the degree of filling was increasing gradually due to the presence of the kneading block downstream. Stage 3 referred to the zone defined by the kneading block. Figure 4.8A showed the evolution of granules without API. At "Stage 1" the foamed binder readily wetted the lactose/MCC, and the shear forces aided granule growth rather than precipitated breakage. Unimpeded by breakage, a high weight fraction of larger granules could be generated within only one zone of traveling distance. However, that growth can not continue indefinitely since the bond strength weakens between particles as the interstitial liquid is spread further throughout the mass. By "Stage 2", the larger particles became susceptible to the increased shearing force (based on the particle size and fill volume of the screw channel) leading to higher frequencies of breakage and the formation of smaller granules. But the shear forces were still not so intense for attrition to dominate; the granule sizes 1180 -2100 µm were still noted to be increasing. The consolidation and breakage was very intense at "Stage 3". This dynamic equilibrium improved the uniformity in the distribution of granule sizes. In comparison to the placebo, Figure 4.8B demonstrated the evolution of granules with hydrophilic APIs. Compared to the lactose/MCC placebo, which was readily wetted by the aqueous binder, these hydrophilic APIs were less wettable yet at 15wt% constituted a significant portion of the solids. Therefore, these formulations required longer distances along the screw to reach the maximum weight fraction value for larger granules. At "Stage 2", the process was similar to that without API. The larger granules started to be broken with the increasing shear force. It was found that the higher the solubility of API in water, the faster the rate for larger granules to be broken up (at room temperature the solubility of caffeine and acetaminophen in water are around 16 mg/ml and 13 mg/ml, respectively).(Lustig-Gustafsson et al., 1999, Granberg and Rasmuson, 1999) It might be that small amounts of the dissolved API weakened the bridge integrity with neighboring particles. Those reduced bridging forces (or the more pliable wall integrity of the API particles now partly dissolved) were however beneficial at "Stage 3" where consolidation and breakage dominated the process, resulting in a more

even distribution in particle size. The result was that the porosity of the granules decreased, while the fracture strength increased. Finally, Figure 4.8C illustrates the evolution of granules with the more hydrophobic APIs. The uniformity of the API implies that these particles were wrapped by excipient particles rather than being bridged with, due to their hydrophobic nature. At "Stage 1" the binder might only wet the lactose/MCC powder but with the high spreading related to foam delivery a rapid shell was conceivable formed around the API provided the API was initially uniformly mixed into the incoming powder. There was still an evident influence of the hydrophobic API on granulation as agglomeration of small granules was slower. The weight fraction maximum for larger granules was delayed for one more zone of distance further than with the hydrophilic APIs. Meanwhile, because the API could not be wetted, the ratio of binder to lactose/MCC is much higher than the formula containing hydrophilic API or no API. The higher liquid/solid ratio might cause stronger interaction between the lactose/MCC powders. This could explain why the granulation with griseofulvin had very low porosity and very high fracture strength, especially from zone 3 and 4. Granulation behaviours at "Stage 2" for all of these three cases are identical. But due to the lubricating of hydrophobic API, the weight fraction of larger granules was decreasing smoothly. At "Stage 3", due to the high compaction function of the kneading block, the granules were consolidated to form particles of lower porosity and higher fracture strength compared with granules before entering kneading block. However, due to high rate of consolidation and breakage and the tendency for lower surface tension, the hydrophobic API powders

might prefer to locate on the surface of granules, as shown in the "Stage 3" of Figure 4.8C; however, further characterizations were required to support this hypothesis.



Figure 4. 8 The proposed granulation mechanism for APIs with different hydrophilicity. (A) No API, (B) hydrophilic APIs, (C) hydrophobic APIs. The hypothesis was made that

the lactose and MCC gain the strongest bonding interaction (denote as blue); the bonding interaction between hydrophilic API and lactose/MCC is less intense (denoted as orange); the interfacial interaction between hydrophobic API and lactose/MCC is the weakest (denoted as orange as well).

4.4 CONCLUSIONS

In this study, four different APIs, including two considered more hydrophilic (caffeine and acetaminophen) and two more hydrophobic (ibuprofen and griseofulvin) APIs, were induced to understand how hydrophilicity would influence the wet granulation mechanism and process. It was found that the hydrophilicity of the API had a very limited impact on the distribution of the chemical species as the binder. However, the particle size distribution, porosity and fracture strength did show being significantly influenced by the properties of the APIs. In order to understand this process, a mechanism based on considering the interfacial interaction between lactose/MCC and APIs was proposed. The granulation process was divided into three stages: the first stage involves the process mainly for forming larger granules; the second stage has higher filling degree, resulting further mixing and decreasing of granule size; the third stage is particular refers to the kneading block, involving intense consolidation and breakage. With increasingly reduced affinity for the API to wet granule growth was notably delayed further down the length of the screw. The results shown in this paper and the proposed mechanism advance the understanding of the granulation process in twin-screw extrusion, specifically using a foamed binder.

REFERENCES

- ADAMS, M., MULLIER, M. & SEVILLE, J. 1994. Agglomerate strength measurement using a uniaxial confined compression test. *Powder Technology*, 78, 5-13.
- BETZ, G., JUNKER-BÜRGIN, P. & LEUENBERGER, H. 2003. Batch And Continuous Processing In The Production Of Pharmaceutical Granules#. *Pharmaceutical Development and Technology*, 8, 289-297.
- DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2012. Twin screw granulation: Steps in granule growth. *International Journal of Pharmaceutics*.
- DJURIC, D. & KLEINEBUDDE, P. 2008. Impact of screw elements on continuous granulation with a twin screw extruder. *Journal of pharmaceutical sciences*, 97, 4934-4942.
- DJURIC, D. & KLEINEBUDDE, P. 2010. Continuous granulation with a twin-screw extruder: Impact of material throughput. *Pharmaceutical Development and Technology*, 15, 518-525.
- EL HAGRASY, A. & LITSTER, J. 2013a. Granulation rate processes in the kneading elements of a twin screw granulator. *AIChE Journal*, 59, 4100-4115.
- EL HAGRASY, A. S. & LITSTER, J. D. 2013b. Granulation rate processes in the kneading elements of a twin screw granulator. *AIChE Journal*, 59, 4100-4115.
- GRANBERG, R. A. & RASMUSON, Å. C. 1999. Solubility of Paracetamol in Pure Solvents. *Journal of Chemical & Engineering Data*, 44, 1391-1395.
- HINKLEY, J., WATERS, A., O'DEA, D. & LITSTER, J. 1994. Voidage of ferrous sinter beds: new measurement technique and dependence on feed characteristics. *International journal of mineral processing*, 41, 53-69.
- KEARY, C. M. & SHESKEY, P. J. 2004. Preliminary Report of the Discovery of a New Pharmaceutical Granulation Process Using Foamed Aqueous Binders. Drug Development and Industrial Pharmacy, 30, 831-845.
- LI, H., THOMPSON, M. & O'DONNELL, K. 2014. Understanding wet granulation in the kneading block of twin screw extruders. *Chemical Engineering Science*, 113, 11-21.
- LINDBERG, N.-O., MYRENAS, M., TUFVESSON, C. & OLBJER, L. 1988. Extrusion of An Effervescent Granulation with a Twin Screw Extruder, Baker Perkins MPF 50D. Determination of Mean Residence Time. *Drug Development and Industrial Pharmacy*, 14, 649-655.
- LUSTIG-GUSTAFSSON, C., KAUR JOHAL, H., PODCZECK, F. & NEWTON, J. M. 1999. The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronisation. *European Journal of Pharmaceutical Sciences*, 8, 147-152.
- MUHAMMAD ALI, M., SYED TUFAIL HUSSAIN, S., SARFARAZ AHMED, M. & ABDUL RAUF, K. 2012. Simultaneous Quantification of Ibuprofen and Paracetamol in Tablet Formulations Using Transmission Fourier Transform Infrared Spectroscopy. *American Journal of Analytical Chemistry*, 2012.
- RAMAKER, J. S., JELGERSMA, M. A., VONK, P. & KOSSEN, N. W. F. 1998. Scaledown of a high-shear pelletisation process: Flow profile and growth kinetics. *International Journal of Pharmaceutics*, 166, 89-97.
- SAYIN, R., EL HAGRASY, A. S. & LITSTER, J. D. Distributive mixing elements: Towards improved granule attributes from a twin screw granulation process. *Chemical Engineering Science*.
- SMIRANI-KHAYATI, N., FALK, V., BARDIN-MONNIER, N. & MARCHAL-HEUSSLER, L. 2009. Binder liquid distribution during granulation process and its relationship to granule size distribution. *Powder Technology*, 195, 105-112.
- TAN, M. X. L., NGUYEN, T. H. & HAPGOOD, K. P. 2013. Drug distribution in wet granulation: foam versus spray. *Drug Development and Industrial Pharmacy*, 39, 1389-1400.
- THOMPSON, M. & SUN, J. 2010. Wet granulation in a twin screw extruder: Implications of screw design. *Journal of pharmaceutical sciences*, 99, 2090-2103.
- THOMPSON, M. R., MU, B. & SHESKEY, P. J. 2012a. Aspects of foam stability influencing foam granulation in a twin screw extruder. *Powder Technology*, 228, 339-348.
- THOMPSON, M. R., WEATHERLEY, S., PUKADYIL, R. N. & SHESKEY, P. J. 2012b. Foam granulation: new developments in pharmaceutical solid oral dosage forms using twin screw extrusion machinery. *Drug Development and Industrial Pharmacy*, 38, 771-784.
- WEATHERLEY, S., THOMPSON, M. R. & SHESKEY, P. J. 2013. A study of foam granulation and wet granulation in a twin screw extruder. *The Canadian Journal of Chemical Engineering*, 91, 725-730.
- ZHANG, D., FLORY, J. H., PANMAI, S., BATRA, U. & KAUFMAN, M. J. 2002. Wettability of pharmaceutical solids: its measurement and influence on wet granulation. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 206, 547-554.

2014

Chapter 5: Conclusion

Among all of the granulation methods, twin-screw extrusion is becoming more and more attractive for is continuous features. However, the mechanism of granulation using a twin-screw extruder still has many remaining challenges. Recently, a novel idea was introduced from batch granulation, using foamed binder that now has been developed for twin-screw extrusion. Therefore, a comprehensive set of research has been performed into properly understanding the new approach to wetting in a twin screw granulation process, including changes to granule development relative to the classic liquid injection method and whether its novel robustness to wetting hydrophobic powders previously noted in the batch granulator by other researchers held true to the extruder.

All of the research results discussed in this thesis featured a new technique to the granulation field namely the 'screw pullout' method, which allowed direct study of the granulation process along the screw and understanding of the evolution of the granules.

It is known that the kneading block is a critical screw element for wet granulation, significantly affecting granule development, although previous work never directly looked at how it functioned. To understand how granulation was affected by foam it was necessary to first understand the function of this element better. Through this element, intensive consolidation and breakup was found to produce consistent granule properties

with respect to size and density. The gradual increase in compressive force through the zone appeared to effectively distribute the binder between particles, noted by new growth downstream. An important note was that it was found that the process and its related parameters such as pressure through the kneading block, were most strongly dependent upon the formulation used for granulation as well as the feed rate. Moreover, attempts should be made to compare the granulation process with or without using kneading block since the kneading block may cause the granules smaller than required size. The most important outcome of the chapter is the function of kneading block was found to distributing the binder rather than compacting powders.

It is generally stated in the published literature that the screw design is the most important parameter to the granulation process; however, the wetting method also shows some minor impact. Three different formulations and two screw designs have been studied for granulation with either liquid or foamed binder, which were found to have very limited influence on the process due to the intense mechanical mixing in the extruder. But the larger wetting area of foamed binder results in more uniform nuclei. Also, compared with liquid binder, the foamed binder produces larger granules while keeping the porosity similar at a fixed liquid/solid ratio. It was interesting and somewhat surprising that the proximity of the screw element to the wetting area, regardless of the method, also did not affect granule development strongly. It had been previously thought that a considerable length was needed in the extruder for the binder to become well spread throughout the powder bed. Therefore, comprehensive consideration for screw design and wetting method is required based on specific formulation before granulation.

The influence of the API hydrophilicity on the granulation process has not been studied in twin-screw extrusion with a foam binder. A series of experiments were performed with four APIs of differing hydrophilicity. The results found that adding an API influences the granulation process; however, not specifically the API and binder distribution. The hydrophilicity of API affected granule development, the particle size distribution, porosity and fracture strength to a significant degree.