TWIN SCREW GRANULATION: GRANULE PROPERTY OPTIMISATION

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ABSTRACT

This thesis aims to design granule properties with narrower size distributions and controlled bulk strength through the optimisation of formulation parameters and processing parameters in twin screw granulation with a consideration of binder in solid and liquid forms, respectively. In this thesis, lactose (soluble) and microcrystalline cellulose (insoluble) were chosen as the objective powders. Hydroxypropyl cellulose was used as the main binding excipient.

From a perspective of formulation development, a novel approach to predict the optimal L/S ratio for twin screw granulation was developed through the study of single drop behaviour, which reduces the waste from trial and error in formulation development process, in order to producing the granule with narrower size distribution.

In addition, the solid binder particle size in formulation was studied. Through evaluating the binding capability of different sized HPC and sieved lactose, it was found that the solid binder with smaller particle size could achieve better binding capabilities which is important on granule size distribution and strength. Moreover, a new solid binder-micronized lactose was evaluated and examined for twin screw granulation. Due to its instant dissolution rate, it was proved to be excellent in binding capability and also leads to a produce of more uniformed granule for both materials.

On the other hand, investigations from processing parameter to design the granule properties was also carried out. At first, granulation temperature, especially the liquid temperature was studied. It was found to be effective to enhance the binding capability of HPC in both forms. In addition, more uniformed granule for both material could be obtained when a high temperature applied, especially when HPC solution was used.

In addition, process parameters including screw speed and configurations was studied with a constant materials mass in the barrel (Barrel loading, g). This study clarified the effect of process parameter especially screw speed on granule properties which is quite contradictory in the literature. It was found that similar to the use of kneading elements, the screw speed is quite important in narrowing granule size distribution and enhance granule strength especially when kneading elements were used.

Publication

Paper and oral presentation

- Ai, Q., Dhenge, R.M., Hounslow, M.J. and Salman, A.D., 2016. Developing a miniaturized approach for formulation development using twin screw granulation. Powder Technology, 300, pp.83-91.
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Dedication

To my parents and girlfriend

Acknowledgement

Firstly, I would like to express my sincere gratitude to my advisor Prof. Salman for the continuous support of my Ph.D. study and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my Ph.D study.

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Contents

Figure list

Table list

Nomenclature

Roman Symbols

A	contact area between indenter and powder bed-nucleus	mm^2
BL	Barrel loading	g
d_{die}	diameter of the die	mm
$d_{indenter}$	diameter of Brinell sphere indenter	mm
d_{pore}	powder bed pore diameter	m
d_{10}	granule size at which 10% of sample's size is smaller than this value	mm
d_{50}	granule size at which 50% of sample's size is smaller than this value	mm
d_{90}	granule size at which 90% of sample's size is smaller than this value	mm
$d_{4,3}$	volume based mean size	%
F	force from granule bulk strength	N

h	indentation depth	mm
$h_{compactpowderbed}$	powder bed height	mm
h_o	initial bed height	m
L	penetration distance	mm
$m_{compactpowderbed}$	powder bed mass	kg
m_{powder}	powder gravimetrical feed rate	kg/h
m_{liquid}	liquid gravimetrical feed rate	kg/h
m_{total}	the total feed rate (powder and liquid)	kg/h
P	compression stress	kPa
t_r	average residence time	s
T	torque in twin screw granulator	N·m
V	volume of material in twin screw granulator	m^3
$V_{compactpowderbed}$	powder bed volume	m^3
V_0	droplet volume	m^3
W_A	adhesion energy for an interface per unit area	J/m^2
W_{CL}	the cohesion energy for a liquid per unit area	J/m^2

W_{CS}	cohesion energy for a solid per unit area	J/m^2

Greek symbols

α	a constant related to the friction	-
β	deformation value	-
γ_{lf}	liquid surface tension	N/m
γ_{lv}	liquid-vapour interfacial tensions	N/m
γ_{sl}	solid-liquid interfacial tensions	N/m
γ_{sv}	solid-vapour interfacial tensions	N/m
δ	punch displacement	m
ε	bed porosity	%
ε_n	the natural strain	-
θ	thermos dynamic contact angle	degree
θ_Y	Young's contact angle	degree

λ	spreading coefficient	-
λ_{LS}	spreading coefficient for the condition that liquid tends to spread over solid and create a surface film	-
λ_{SL}	spreading coefficient for the condition that solid may spread or adhere to liquid but no liquid film will be established	-
μ	viscosity	Pa·s
ρ_{bulk}	bulk density	m^3/kg
ρ_{true}	true density	m^3/kg
σ	stress (σ) exerted during granulation	Pa
τ	strength of dry granules	Pa

Chapter 1. Introduction

1.1. Twin screw granulation

1.1.1. Introduction

Granulation is a particle agglomeration process. Compared with powder, granular materials have improved flowability, dissolution and disintegration rate, compressibility etc. (Barrasso et al., 2013). Currently, it has been applied widely in industries including detergent, food, and fertilizer. However, one of the biggest applications is to produce intermediate products in pharmaceutical industry.

Twin screw granulator (Figure 1-1) is one of the most commonly used wet continuous granulators in industry (Dhenge et al., 2010). It was initially used and firstly reported by Gamlen and Eardley in 1986 for paracetamol extrudates production (Gamlen and Eardley, 1986). It has two screws rotating to convey and mix powder and liquid. Due to the variable configurations of screw elements available, twin screw granulator can produce granules with different properties from a wide range of materials. Apart from this, short residence time, good mixing ability and good consistency in granule quality are also some of its outstanding advantages (Thompson and Sun, 2010).

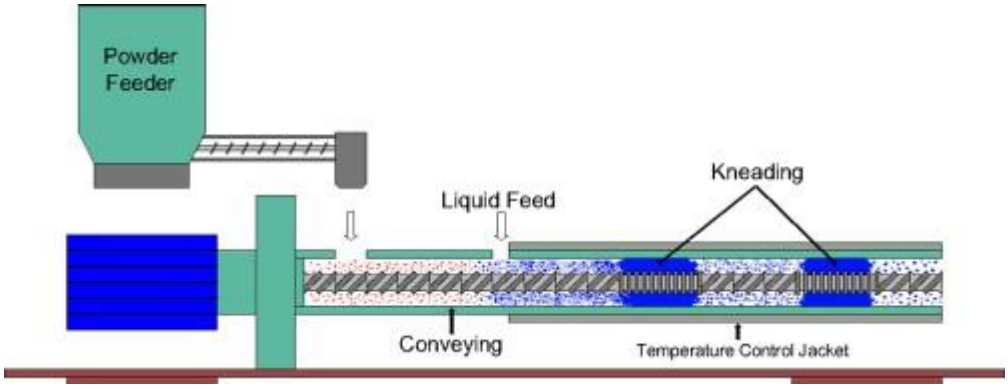


Figure 1-1. Twin screw granulator (Seem et al., 2015).

1.1.2. Screw configurations

1.1.2.1. Conveying element

As is shown in Figure 1-2, two sets of conveying elements are applied in twin screw granulator. Each conveying element has a continuous helical flight, which is designed to allow more materials to be conveyed. When the screws are rotating, the flights can generate forces, pushing powder and liquid to the next zone (Djuric and Kleinebudde, 2008). The distance between flights influences its conveying and mixing capability. The long pitch conveying elements (LPCE, Figure 1-2) allow more material to be contained and transported and thus they are usually found near to the inlet of a twin screw granulator. Whereas, short pitch conveying elements (SPCE, Figure 1-2) have narrower gaps which allow less material to be conveyed for each rotation but could make the materials more compacted.

Due to the fact that both sets of conveying elements cannot mix powder and liquid as aggressively as kneading elements, at the first zone, immersion and wetting are dominant and large, wet and loose lumps are usually formed (Lee et al., 2013). It is stated that

conveying elements can also have a shearing capability apart from material transportation (Van Melkebeke et al., 2008). Therefore, other than the use in the nucleation zone, the SPCE could also be used between kneading zones. It is pointed out that the SPCE could help granule fragments resulted from kneading elements re-agglomerate and promote liquid binder dispersion (Dhenge et al., 2012c).

Figure 1-2. Conveying element (left: long pitch conveying element, LPCE; right: short pitch conveying element, SPCE)

1.1.2.2. Kneading element

Kneading elements (shown in Figure 1-3) is one of the most commonly used elements for granulation and the critical element in liquid-powder mixing (Kohlgrüber, 2012). Space in kneading elements zone is much narrower than that in conveying elements zone, which provides less free space and could exert more intensive stress. The shearing stress could break wet granules into small fragments and the compression could squeeze the liquid from the core, which encourages granule growth. During this process, the liquid could be distributed more evenly among the granules and the strength can be enhanced (Thompson and Sun, 2010).

The kneading zone could be consisting of different assembled kneading elements with different angles. The effects of mixing and dispersing ability depend on the angle between kneading elements and the number of kneading elements in one screw. The angle between discs affects the mixing capability significantly. The increase in the angle can improve the degree of binder dispersion and lead to a higher mixing and shearing ability when the filling level of mixture in barrel is high enough (Thompson and Sun, 2010). However, the kneading element is weak in conveying material and its mixing capability is very much related to the fill level which is an indicator of the quantity of materials in the twin screw barrel.

Figure 1-3. Kneading elements with an angle of 60º

1.1.3. Liquid distribution

Water, as a low viscosity and high surface tension liquid, has been widely used to form liquid bridges between particles in twin screw wet granulation processes. It could spread and distribute easily bettwen the particles. In some cases, the bonds may not be strong enough, resulting in the production of large amount of fines or weak granules. Therefore, extra binding excipient would be needed to enhance the binding capability of water.

Binding excipient (binder) addition can be divided into two methods. Firstly, the binding excipient could be dissolved in water and used as a liquid binder to enhance the strength of liquid bridge between particles increasing the strength of granule effectively. Consequently, liquid with increased viscosity would be harder to penetrate and distribute in the powder (Ai et al., 2016). In this case, the binder solution and powder may not be mixed evenly, leading to a wider granule size distribution and increase in the proportions of oversized granule and fines (Saleh et al., 2015). To tackle this problem, the surface tension of liquid was varied by adding surfactant, in order to improve the liquid dispersion even if it contans a high concentration of binding exipient (Dhenge et al., 2012c). However, the reduction of surface tension was proved to be less effective on improving the dispersion of liquid binder solution.

In addition, the binding excipient could be premixed with powder in advance (solid form), in order to make sure the binding excipient particles distribute before water comes in contact with the powder material (Saleh et al., 2015, El Hagrasy et al., 2013b). In this case, the liquid (water) would be easier to distribute in the powder during granulation. However, the limited amount of water may be insufficient to dissolve the binder particles, especially big-sized particles, and thus reduce the efficiency of the binding excipient. Therefore, more binding excipient would be needed to compensate its relatively low efficiency. Recently, the effect of the presence of hydroxypropyl cellulose (HPC) particles in compacted powder bed was studied (Ai et al., 2016). They found that the undissolved HPC delayed the liquid penetration in the powder bed and caused a reduction in nuclei hardness in the powder bed. To tackle the problem that solid binder particles could not dissolve properly in order to enhance the bonding during granulation effectively, assessment for the effect of smaller binder particles was carried out in both high shear

mixer and fluidised bed (Alvarez-Lorenzo et al., 2000, Van der Watt, 1987, Nyström and Glazer, 1985, Nyström et al., 1982, Schæfer and Mathiesen, 1996, Kato et al., 2006, Li et al., 2011). It was found that the use of smaller sized binder particle could promote the growth of granules and have positive effects on the strength of granules due to its outstanding specific surface area. In terms of twin screw granulation, limited work has been founded.

1.2. Importance of granule property in pharmaceutical industry

The criteria of granule property assessment are normally built based on the specific application (Kato et al., 2006, Meier et al., 2017, Picker-Freyer and Dürig, 2007). In pharmaceutical industry, granules are normally used as an intermediate products before tabletting or capsulation (Djuric and Kleinebudde, 2008). Therefore, the following properties are quite important (Salman et al., 2007):

- Uniform size distribution

In pharmaceutical industry, the granule size distribution is quite important, as only granules within a certain size range would be selected for tabletting or encapsulation (Hansson and Lindner-Olsson, 2004, John and Charles, 2002, Šantl et al., 2012, Ai et al., 2016). On one hand, a wider size distribution is normally positive in tabletting and could enhance the tablet strength; on the other hand, a batch of granules with a wide size distribution would contain large proportions of fines or lumps, which is less suitable in dosage control. In general, pharmaceutical industry would prefer to produce the granules with narrower size distribution, as the loss in tablet strength could be compromised

through a higher compression load during tabletting process. A narrower granule size distribution could guarantee a higher proportion of granules being used for tabletting, which is related to process efficiency. Therefore, the size distribution of the granules produced is an important variable which needs to be considered in the pharmaceutical industry.

Span of distribution is a typical method to evaluate the granule size distribution curves. A smaller span value indicates a narrower size distribution, which is always a target for pharmaceutical industry. Tu et al. (2013) developed a regime map based on twin screw granulation and they stated that normally the allowed span of distribution is in between 1.5 to 4.5. However, this is just an empirical range is mainly to limit the upper limit (4.5) and 1.5 is the value that the most of the experiments could achieved (in the best situation). In addition, in their regime map, the minimum variation of span of distribution was about 10%, indicating that 10% difference in span value could be deem as “effective” to affect granular product properties. To quantify the variation of span of distribution, the span value would be firstly compare to this range, in order to check whether the obtained span of distribution is in the allowed range. Then, the span of distribution obtained would be compared to that in a standard condition (powder feed rate: 1 kg/h, screw speed: 200 rpm), in order to evaluate the improvements of the corresponding approaches.

- Strength

Granule strength is a feedback of the bond strength between particles. In pharmaceutical industry, properties of tablets including strength and dissolution rate are directly influenced by the strength of granules (Mangwandi, 2009, Kato et al., 2006, Meier et al., 2017, Vercruysse et al., 2012b).

Normally, weaker granules tend to produce strong tablets with slower dissolution rate. As granule strength is related to the tablet disintegration speed, different tablets with various API(s) may be required different disintegration speed (immediate release and controlled release) and consequently the strength of granules required are varied (even if the same formulation and equipment are used) (Liu et al., 2016). As a result, it is impossible to generalize a "range of value" to represent the optimal granule bulk strength universally. However, it does not mean that there is no requirement on granule bulk strength.

Granules from twin screw are relatively weaker than those from a roller compactor in drying granulation process. In this case, the over-strong granules are less possible to be produced from a twin screw granulation process and the concern is mainly about how to produce granules which are strong enough for transportation and operation, in order to reduce the amount of fines from granule breakage and maintain their size. For example, before tabletting, granules may be transported into a silo for storage. Granules at the bottom of the silo need to be strong enough to bear the gravity from the granules above. Therefore, the granules produced should be sufficiently strong to avoid being damaged and produce dusts. Therefore, in literature the granule bulk strength required from twin screw granulation is larger than 0.1 MPa (Dhenge et al., 2012d, Dhenge et al., 2013, Saleh et al., 2015). As long as the granule strength is larger than 0.1 MPa, its variation would be mainly rely on the requirement of the specific medicine. In this thesis, one of the objectives is mainly to develop approaches to enhance the granule strength, which in another word is to develop approaches to control the granule strength bidirectionally (increase or decrease).

To quantify granule bulk strength, whether obtained strength value was larger than 0.1 MPa would be compared at first. Then the granule strength would be compared to that in a standard condition and the improvements (%) would be obtained. As was reported by Horisawa et al. (1995) that ~5% difference in granule strength could make distinctive difference in granular product properties (e.g. tablet tensile strength, disintegration rate, etc.), the obtained improvement (%) was then checked to justify whether more than 10% difference it could be achieved, in order to draw the conclusion whether the approach is effective or not.

The twin screw granulator utilized for this research is a standard twin screw granulator used in industry for research in the lab. Therefore, the approach developed could be applied for further research in industry directly (Dhenge et al., 2011d). For the real production process, the scale-up and skill transfer are really depend on the specific compony, medicine, etc., which are normally commercially confidential. Therefore, the approach could be used for industry research directly, but the detail about how to transfer it to the real production line is out of the scope.

1.3. Influencing factor

Due to the importance of granule properties, numerous research has been carried out on the design of granule properties, which could be classified into two main aspects: formulation parameter development and processing parameter development. Formulation development is mainly focussed on the composition and properties of material and how variation of it would affect the granule properties including dissolution, compressibility, etc., which is mainly about the material itself. Processing development mainly refers to

improvement of operation parameters t which is about the relationship and interaction between material and equipment such as screw speed, configurations, etc.

Currently, although a twin screw regime map has been developed by (Dhenge et al., 2012c) to reveal the effect of some typical parameters on granule size distribution, it is still experiment based. In other words, it is not capable to predict the relationship between influencing parameters and granule properties in advance. In addition, in terms of the effect of processing parameter including screw speed, etc. insufficient information was given. Therefore, the investigation of how to improve granule properties including a narrow size distribution and a controlled granule strength is still needed and an approach that could predict the granule property before granulation would be more appreciated.

1.4. Objective

Granule properties such as size and strength are of vital importance in pharmaceutical industry, it always demands new understandings, new approaches to improve the granule properties, to enhance the manufacturing efficiency and to reduce the waste in expensive materials, especially when dealing with new formulations or materials. The objective is mainly about:

- From a perspective of formulation development, developing new approaches to improve the granule properties by increasing granule bulk strength and narrowing the granule size distribution.

- From a perspective of process parameter, developing new approaches to improve the granule properties by increasing granule bulk strength and narrowing the granule size distribution.

To achieve the objectives mentioned, a series of single drop study will be carried out at first to establish and accomplish the theory about how the liquid-powder interaction occurs at different compression stresses and binder delivery methods.

1.5. Thesis structure

- **Chapter 1** was a general introduction on the importance of the research.
- **Chapter 2** was the literature review chapter. Basically, this chapter introduces the current research related to twin screw granulation and highlight the importance of the work.
- **Chapter 3** introduced the equipment and methods applied in this thesis.
- **Chapter 4** carried out the single drop study to understand the effect of the form of binder on liquid distribution based on the compact powder bed.
- **Chapter 5** developed an approach to reduce the trial and error in formulation development to optimise the L/S ratio (in twin screw granulation process) by using compact powder bed.
- **Chapter 6** evaluated the effect of particle size on granule properties and micronized lactose as a new binding excipient was introduced and examined.
- **Chapter 7** studied the effect of temperature (which is the only process parameter which could affect the properties of formulation) on the granulation liquid and granule properties.

- **Chapter 8** investigated the effect of processing parameters including screw speed, screw configurations on granule properties with a controlled barrel loading (BL).

- **Chapter 9** is the conclusion and the future work. Reference list was listed after.

The experiment chapters distinctively involve three main aspects: single drop study (**Chapter 4**), formulation parameter improvements (**Chapter 5** and **Chapter 6**) and processing parameter improvements (**Chapter 7** and **Chapter 8**).

Chapter 2. Literature review

2.1. Twin screw granulation mechanism

2.1.1. Classical wet granulation mechanism

Based on high shear granulation process, steps of granulation could be classified into wetting and nucleation, consolidation and growth, breakage and attrition (Litster and Ennis, 2013). Figure 2-1 illustrates the details of each step clearly and was initially adapted to explain the mechanisms in twin screw granulation processes (Vonk et al., 1997, Dhenge et al., 2012a).

When liquid binder is initially added, the minimal mixing between powder and liquid is not even at the primary stage, leading to the production of large and loose lumps and a high proportion of fines (Iveson et al., 2001). Due to the uneven distribution of liquid binder, these lumps usually have weak shells which are quite easy to be broken and the broken fragments are reassembled to produce granules due to compaction forces in the granulator. The result of the aforementioned process is that the liquid binder will be distributed more evenly, followed by consolidation process which will further densify the granules. The granules obtained from consolidation are usually smaller than the lumps from the first step but stronger in mechanical strength. As is showed in Figure 2-1, the breakage and coalescence occur simultaneously; therefore, the size distribution of the final granules is determined by both coalescence and breakage.

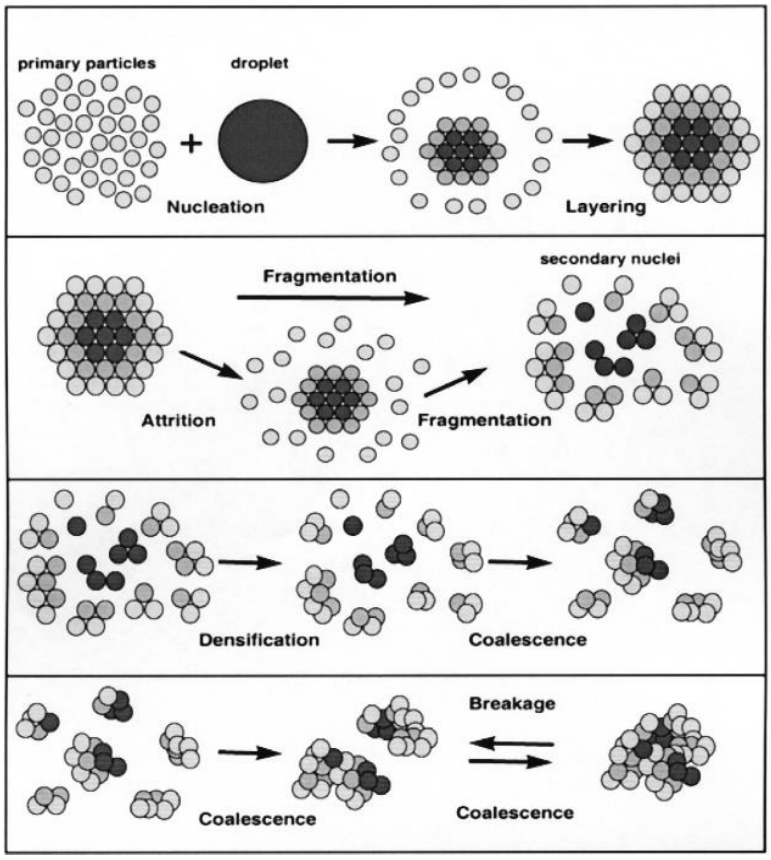


Figure 2-1. Granulation process and mechanism (Vonk et al., 1997).

Although twin screw granulation which is similar to high shear granulator is also a type of wet granulation technology, differences in granule growth were gradually realized (Lee et al., 2013, Dhenge et al., 2012b).

2.1.2. Twin screw granulation mechanism

However, it is improper to simply adapt the granule growth mechanisms from a high shear mixer and use it for twin screw granulation. It is because the high shear mixer consists of one or two types of impellers, while twin screw granulator normally has three types of elements. Because of this, the movement of material in the twin screw barrel is supposed to be more complex. In addition, Dhenge et al. (2012b) stated that in twin screw granulator, the granulation is a continuous process and processes including nucleation,

growth and breakage could occur in succession along the length of the screws, whilst in high shear mixer, different process could occur simultaneously. Thirdly, in a high shear mixer or fluidized bed, due to the large free space, the kinetic energy is hardly to fully act on granule deformation. Whereas in twin screw granulator, the limited free space in the barrel causes higher proportion of kinetic energy to exert on granules directly and thus the granules in the barrel are more deformed and cut (Dhenge et al., 2012b). Because of this, in twin screw granulation, the layering growth is rarely to see.

Combined with the work done by Dhenge et al. (2012b), it could be summarized in Figure 2-2. After the powder and liquid are added, due to the relatively milder barrel environment, penetration mainly occurrs in this zone. When the material arrives to the first kneading zone, the pushing force from the conveying elements would squeeze the mixture through much narrower space in the kneading zone and the nuclei formed from the previous section would be shaped (cutting, breaking) by the elements. In addition, the high stress from kneading elements would squeeze the liquid from the nuclei core to their surface, which is easier for further coalescence growth of the nuclei fragments. After the first kneading zone, the material was transported into the second SPCE (short pith conveying elements) zone. In this zone, reassembling of nuclei fragments would occur. Simultaneously, breakage would also happen as the SPCE could also provide certain shearing forces. When the material arrives to the second kneading zone, similar process could occur where the material would be chopped and the liquid would be distributed further. Finally, material would reagglomerate to be the product and flows out from the outlet.

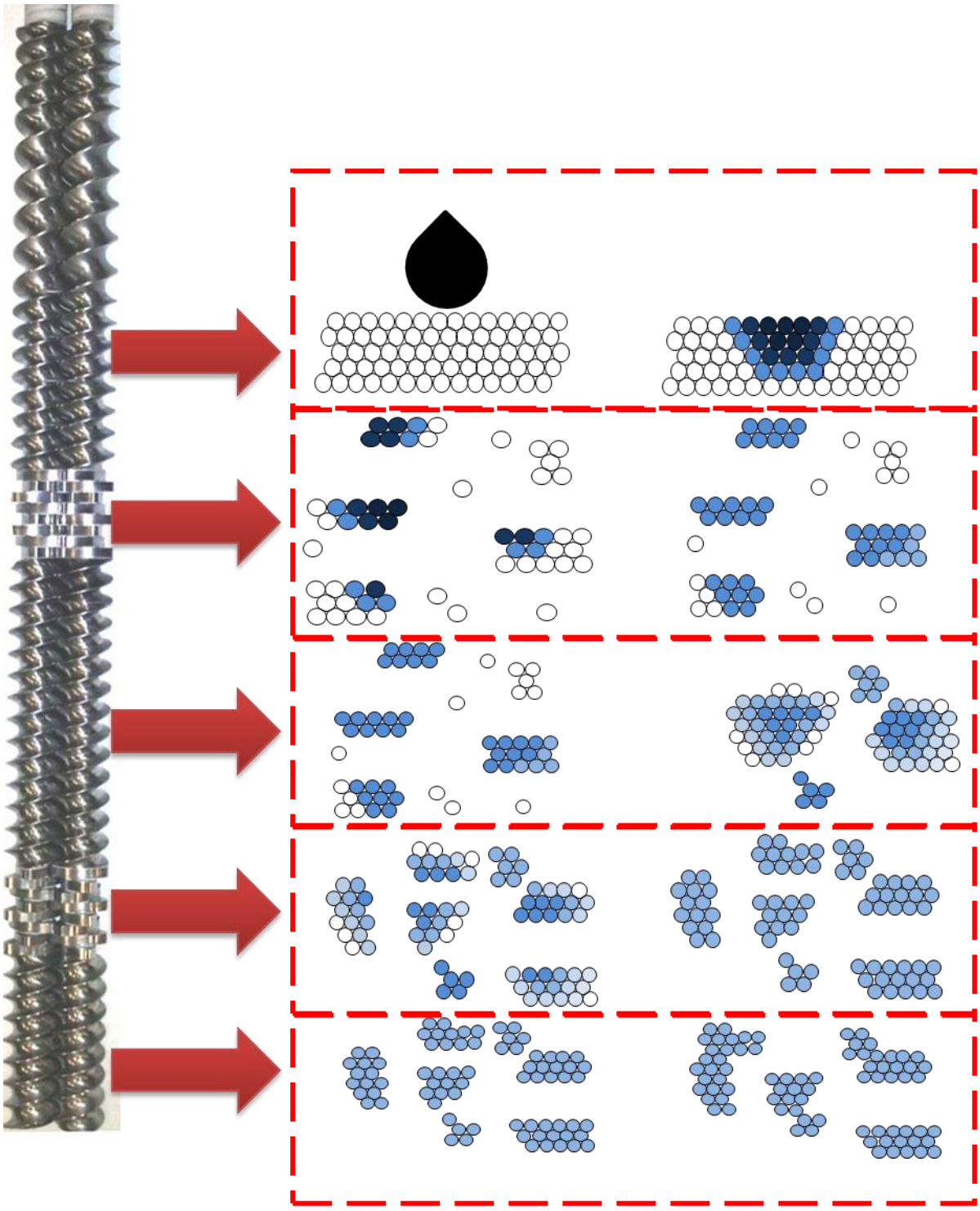


Figure 2-2. Twin screw wet granulation mechanism.

2.2. Regime map

2.2.1. Regime map for batch granulation

Regime map functions as a guide to granulation process. Ideally, if the granulation condition is known, by checking the map, some of the granule properties can be obtained. Most granulation regime maps are designed for traditional wet granulator including high shear mixer and fluidized bed. Figure 2-3 shows the first regime map designed with the deformation number and maximum pore saturation as its axes (Iveson and Litster, 1998). This regime map illustrates the different regimes of granule growth behaviour.

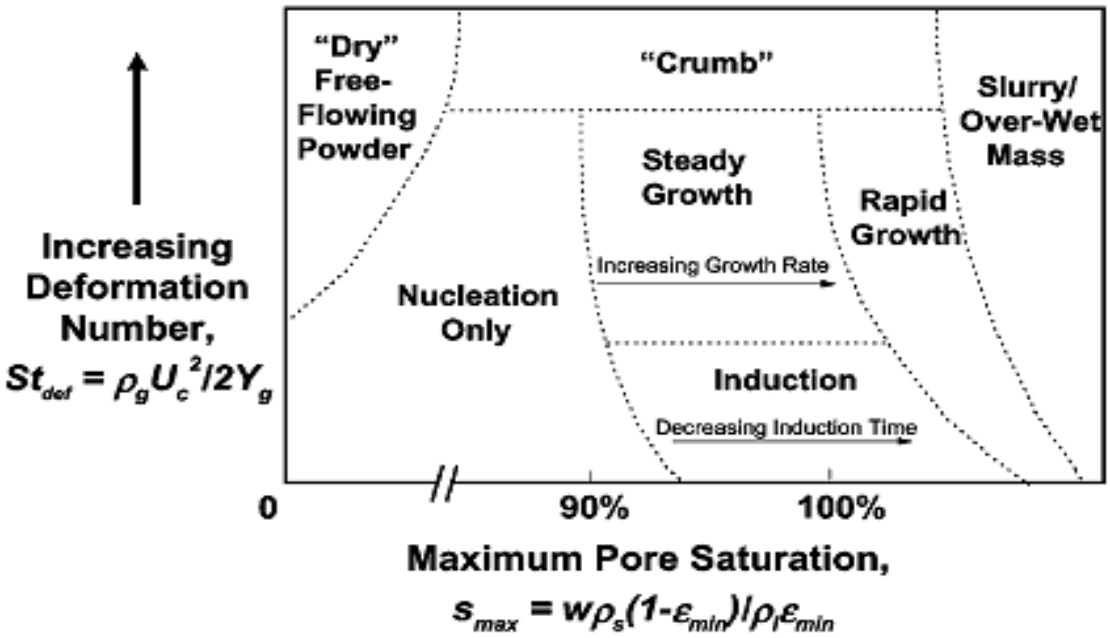


Figure 2-3 Growth regime map proposed to use Stdef instead of De (Iveson and Litster, 1998).

It is shown on the map that steady growth and induction growth are the two main types of growth behaviour in batch granulation process (Iveson and Litster, 1998). As is shown in Figure 2-3 above, steady growth is the process when granule size increases steadily. In this process granules are deformable and weak, leading to an increase in contact area upon

collision between granules, and hence promoting the coalescence process. Induction growth describes a process in which granules grow slowly for a long time. The next process is the rapid growth step. Granules in this step are usually strong and hard to deform; therefore, it is difficult to for coalesce to happen.

Iveson and Litster (1998) stated that the growth behaviour in a system is only based on the pore liquid saturation and the degree of granule deformation during granulation process. Since the pore liquid saturation is variable during operation due to binder evaporation, granule consolidation and dissolution of soluble components into liquid phase, therefore the maximum granule pore saturation is used instead.

$$\boldsymbol{s_{max} = \frac{w\rho_s(1-\varepsilon_{min})}{\rho_l \varepsilon_{min}}} \qquad (2\text{-}1)$$

where ω is the mass ratio of liquid to solid, ρ_s is the density of powder particles (solid), ρ_l is the density of liquid binder and ε_{min} is the minimum porosity that the formulation can reach for particular sets of operating conditions.

Furthermore, the degree of deformation during progress is quantified by a dimensionless number as follow:

$$\boldsymbol{De = \frac{\rho_g U_c^{\,2}}{2Y_g}} \qquad (2\text{-}2)$$

where U_c is the representative collision velocity in granulator and ρ_g and Y_g are granule density and dynamic yield stress, respectively. Iveson et al. (2001) stated that the

deformation number is the ratio of "impact kinetic energy to the plastic energy absorbed per unit strain".

Tardos et al. (1998) found that granule deformation and breakage are controlled by the Stokes deformation number:

$$St_{def} = \frac{\rho_p \alpha^2 \dot{\gamma}^2}{2\tau_y} = \frac{\rho_p U^2}{2\tau_y} \qquad (2\text{-}3)$$

where ρ_p is the density of powder particle, α is the granule radius, $\dot{\gamma}$ is the shear rate, τ_y is the characteristic flow stress of the particle binder "slurry" and U ($\approx \alpha\dot{\gamma}$) is the granule velocity.

The growth of nuclei mainly depends on the amount of initial kinetic energy before a collision and the amount of energy dissipated during this collision (Ennis et al., 1991). Energy may be consumed by viscous dissipation from the surface or the inside of granules or plastic deformation of the materials that make these granules (Kayrak-Talay and Litster, 2011). In Figure 2-3, two dimensionless parameters which are St_{def} and maximum pore saturation are taken into consideration. Stokes deformation number (ST_{def}) measures the amount of energy consumed during a collision process to plastically deform the granules involved. When ST_{def} is low, the amount of energy dissipated is high and there is no granule growth happening and the nuclei do not deform sufficiently to allow the liquid inside to connect with other nuclei for coalescence (Kayrak-Talay and Litster, 2011). If the Stokes deformation number falls within the following range $0.001<ST_{def}<0.2$, a steady growth condition occurs. A larger surface is available on granules at this stage, which promotes coalescence even if the amount of liquid binder is not sufficient. If ST_{def} keeps

increasing, “crumb” will occur. The occurrence of this regime is caused by the breakage of large granules due to a low strength in the inner structure of these granules. The maximum granule pore saturation (S_{max}) is “the ratio of granule liquid volume to granule void volume”. When S_{max}<0.7, the insufficient liquid could only afford the growth of nuclei. When S_{max} >100%, a rapid growth step would occur, possibly leading to the formation of a slurry or paste.

The regime map improves our understanding on what growth behaviour could happen in a granulation process from given formulation and process conditions. Several sets of experimental data were attempted to be plotted on this regime map and the results were found to be acceptable (Iveson et al., 2001).

2.2.2. Regime map for continuous granulation process

Compared with batch granulators such as high shear mixer and fluidized bed, the study of twin screw granulator is relative newer. Research conducted on regime map of twin screw granulator is relatively scarce.

Figure 2-4 is a regime map for twin screw granulator using conveying elements and kneading elements. Compared with the growth mechanism in batch granulation process, twin screw granulation process is different in a number of parts (Dhenge et al., 2012c). In batch granulation process, granulation happens in a closed environment and the growth steps occur simultaneously. Dhenge et al. (2012) stated that in twin screw granulator, due to the continuous flow of materials, it is easier to distinguish and physically separate each growing step. Secondly, the materials being granulated are subject to higher stress compared to batch granulator, as the free volume in twin screw is much smaller than that in high shear mixer and fluidized bed. In order to quantitatively represent the stress (σ)

exerted during granulation, torque (T) and volume of material in twin screw granulator (V) were used.

$$\sigma \approx \frac{T}{V} \qquad (2\text{-}4)$$

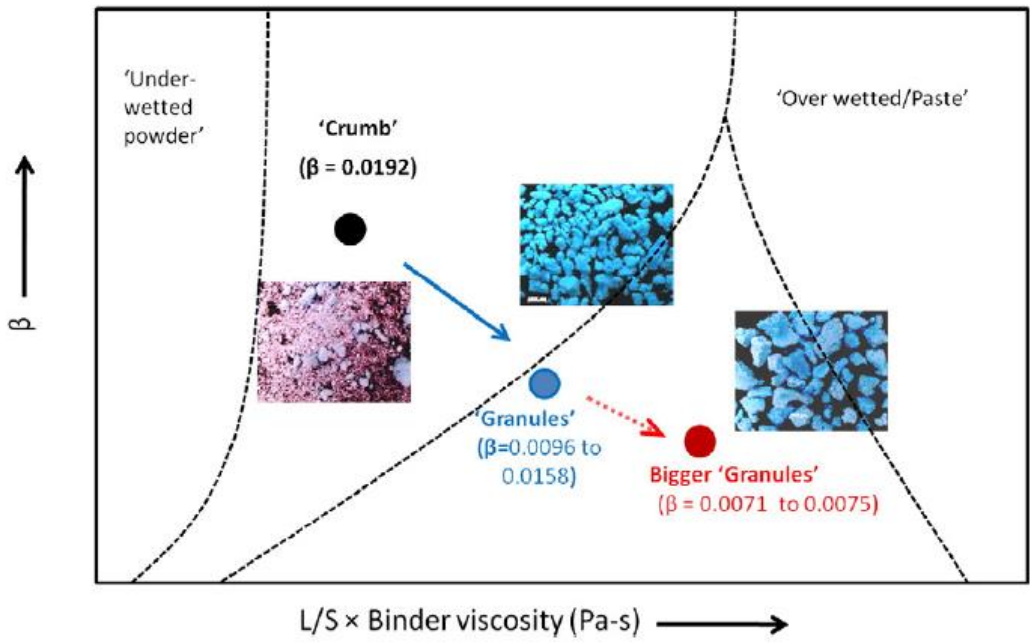


Figure 2-4 Regime map for granule growth behaviour in twin screw granulation (Dhenge et al., 2012c)

The deformation value (β) here was used instead of ST_{def} in Figure 2-4, which is the division of stress acting onto the material being granulated by the strength (τ) of dry granules produced.

$$\boldsymbol{Deformation\ value}\ (\boldsymbol{\beta}) = \frac{\boldsymbol{\sigma}}{\boldsymbol{\tau}} \qquad (2\text{-}5)$$

As is known, the regime map developed by Iveson and Litster (1998) used the maximum pore saturation as an axis to represent the influence from formulation. In wet granulation, the L/S ratio is one of the most important parameters to influence pore saturation in granulation process. Furthermore, the viscosity of granulation liquid can also affect pore saturation. Therefore, viscosity × L/S ratio was chosen to be the x-axis, which can be regarded as the binding capability.

However, the regime map in Figure 2-4 also has its limitations. Current regime map could only be valuable after the product has been obtained, which could not avoid the process of trial and error especially in formulation development process. As a guidance for granulation, if the properties of product could not be predicted before granulation, its application would be limited.

Tu et al. (2013) developed a regime map to find out the optimal condition to achieve a good granulation process using MCC. Basically, they ran the experiment in different liquid to solid ratio (L/S) and screw speed and granule size distributions were obtained. By plotting the corresponding granule mean size and distribution span into Figure 2-5, the regime map could be seen. Theoretically, based on Figure 2-5, to achieve a narrower size distribution and large granules, high screw speed and L/S ratio would be required. However, only limited screw speed and L/S ratio were sampled and it is only suitable for MCC. In addition, similar to the previous regime map from Dhenge et al. (2012c) that the establishment of the regime map was experimentally based, which could not avoid numbers of trial and experiments of granulation.

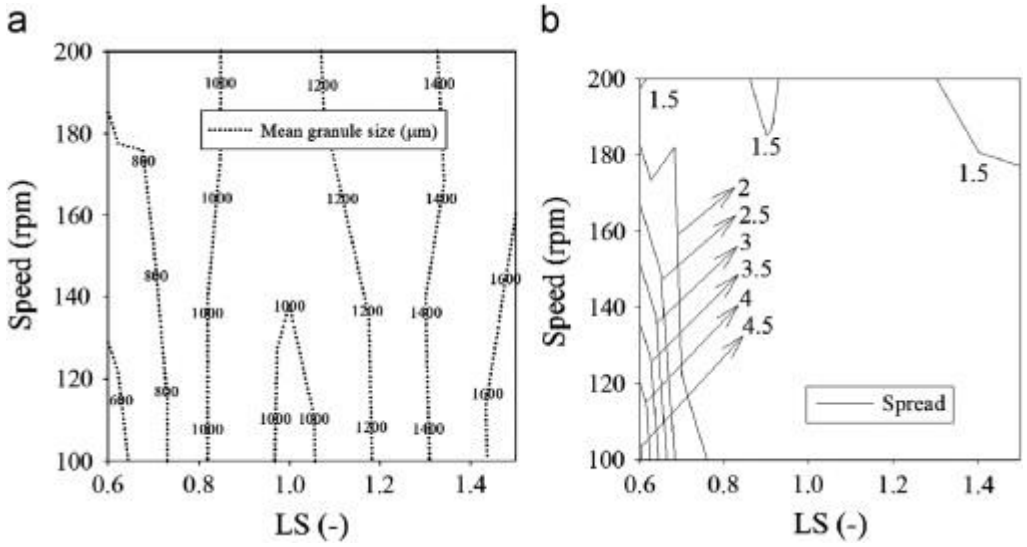


Figure 2-5. GSD for the experiment. (a) Mean granule size (b) spread (Tu et al., 2013).

2.2.3. Regime map for nucleation using single drop study

Apart from the regime map for the whole process of granulation, nucleation regime map was proposed (Hapgood et al., 2003). In their work, the nucleation process was postulated to be a combination of both single drop behaviour and the interaction of multiple drops. In Figure *2-6*, τ_p and Ψ_a are the single drop penetration time and dimensionless spray zone for multiple drops, respectively. A smaller Ψ_a represents less droplets are overlapping.

In the drop controlled regime, the nucleus size is mainly controlled by the size of droplet, as less overlapping and fast penetration process happens in this regime. While a high $\Psi_{a \text{ and }} \tau_p$ would lead the nucleation into mechanical dispersion regime, where nucleation and binder dispersion can only achieved by mechanical mixing and agitation.

However, this regime map is only based on the droplet behaviour, which is mainly occurred on the surface of the powder, which consider few about the liquid behaviour in

the powder bed. In reality, it is highly possible that before Ψ_a arrives at 1.0, the nucleation regime has already be in the mechanical dispersion regime.

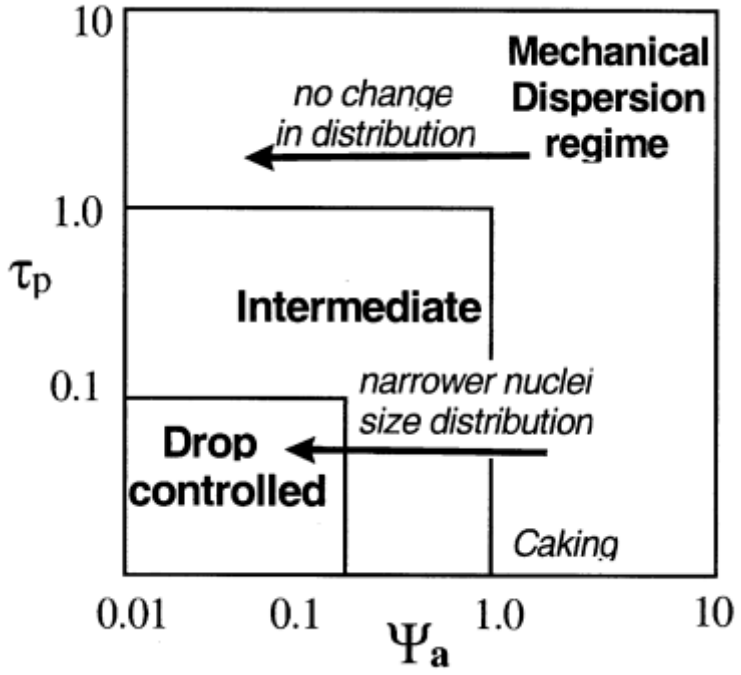


Figure 2-6. Nucleation regime map (Hapgood et al., 2003).

2.3. Single drop study

Single drop study aims to reveal the liquid powder interaction which is difficult to be directly observed from enclosed granulator (Charles-Williams et al., 2011, Emady et al., 2011, Hapgood et al., 2002, Ai et al., 2016). It is mainly carried out by studying droplet behaviour on a powder bed and the nucleus (which is the wetted powder area) formation. The single drop study is regarded as a useful method to understand the liquid powder interaction and granule growth mechanism. Based on the single drop study, Hapgood et al. (2003) developed a drop controlled nucleation regime map which is significant for

high shear wet granulation. Their study based on the assumption that one droplet forms one granule. To achieve the drop controlled nucleation regime, a fast penetration and little liquid overlapping are required (Hapgood et al., 2003).

In general, a certain amount of research studied the droplet penetration and contact angle on loose powder bed and tried to make a link with batch granulation including high shear mixer and fluidized bed (Emady et al., 2011, Reis et al., 2004, Hapgood et al., 2002). However, as was introduced, the twin screw granulation process is different from high shear granulation and the use of loose powder bed may be less applicable for the study of liquid-powder interaction in twin screw granulation process.

Contact angle

In the droplet study, penetration time and contact angle have become the most important elements in single drop study, as it could reflect how easy for the droplet to penetrate and dispersed in the powder bed and is an indicator of the wettability (Aulton and Banks, 1979, Charles-Williams et al., 2011, Hapgood et al., 2002). Contact angle is defined as the angle between the liquid-solid interface and the liquid-vapour interface, which reflects the wettability when a solid interacts with a liquid. In a wet granulation process, wettability may affect liquid spreading and distribution in the powder and thus influence the product properties. For example, a mixture of hydrophobic and hydrophilic powder was used in a fluidised bed granulator (Aulton and Banks, 1979) and it was found that an increase in the content of hydrophobic powder can increase this contact angle, leading to a decrease in the size of final granules produced. Therefore, contact angle is quite important when studying the single drop behaviour on the powder bed.

Ideally, the contact angle is defined by the mechanical equilibrium of the drop affected by three interfacial tensions (Young, 1805):

$$\gamma_{lv} \cos \theta_Y = \gamma_{sv} - \gamma_{sl} \quad (2\text{-}6)$$

where γ_{lv}, γ_{sv} and γ_{sl} represent the liquid-vapour, solid-vapour, and solid-liquid interfacial tensions, respectively, and θ_Y is the Young's contact angle.

Although the contact angle on powder bed is based on the same mechanism, due to the liquid penetration, it is hard for the liquid to reach a static status for contact angle measurement. It was reported that the contact angle on a porous powder surface is larger than on a smooth surface. In addition, the contact angle is also affected by surface roughness, particle swelling and tablet porosity (Langmuir and Schaefer, 1937, Buckton and Newton, 1986, Hansford et al., 1980, Buckton and Newton, 1985, Fowkes, 1964). Therefore, the maximum apparent contact angle as one of the ways to evaluate the wettability of powder bed will be used, which refers to the maximum dynamic contact angle when the droplet become stable from bouncing (Meiron et al., 2004).

Penetration time

Penetration mechanism

Penetration time is the time that a liquid drop distributes into a powder bed. For a porous powder bed, the penetration is mainly driven by the capillary force which is presented as Laplace Capillary Suction pressure P_c (Charles-Williams et al., 2011, Yuan and Lee, 2013).

$$p_c = \frac{2\gamma_{lf}\cos\theta}{d_{pore}} \qquad (2\text{-}7)$$

where γ_{lf}, d_{pore} and θ represents liquid surface tension, powder bed pore diameter and thermos dynamic contact angle, respectively.

Binder penetration models

The penetration process of a liquid binder into a powder bed is quantitatively governed by a model developed by Washburn through Equation **(2-8**) (Yuan and Lee, 2013).

$$L^2 = \frac{\gamma_{lf} d_{pore} \tau \cos\theta}{4\mu} \qquad (2\text{-}8)$$

where L, $\gamma_{lf,}$, d_{pore}, τ, θ and μ refers to penetration distance, liquid surface tension, pore diameter, penetration time, thermodynamic contact angle and liquid viscosity, respectively. It is firstly assumed that a powder bed consists of bundles of "concentric non-interconnected tubes". The penetration process is described as driven by capillary force and resistance from the dispersion of viscous binder.

As is shown in Figure 2-7, there are two limitations of liquid penetration behaviour exist, which are constant drawing area (CDA) and decreasing drawing area (DDC) (Hapgood et al., 2002). In CDA case, it is assumed that the contact area is kept constant but the apparent contact angle decreases as the penetration process proceeds. In DDA, the contact area decreases but the apparent contact angle remains constant.

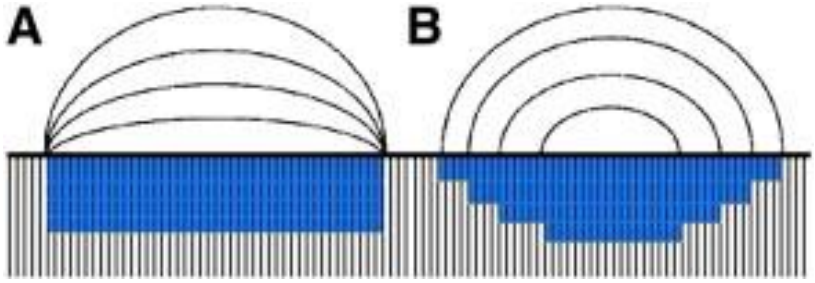


Figure 2-7 Liquid penetration models: A) constant drawing area, B) decreasing drawing area (Charles-Williams et al., 2011).

Nucleus properties

In a powder bed, the wetted powder material resulted from the liquid penetration is named as “nucleus”. The study of nucleus properties and its formation mechanism could reveal the granulation mechanism. Currently, most of the researches focussed on the droplet behaviour such as spreading and penetration on a loose powder bed and tried to make a link to the batch granulation mechanism including high shear mixer and fluidized bed (Hapgood et al., 2002, Hapgood et al., 2003, Iveson et al., 2001). In addition, the nucleus dimension was also studied to reveal the liquid movement inside the powder bed. Specifically, nucleus dimensions were measured using a microscope and a shape factor was defined as the ratio of diameter of the nucleus projected area to the maximum vertical height (Emady et al., 2011).

However, the study of single droplet on loose powder bed was initiated to target the granulation process in a high shear mixer or fluidised bed. In twin screw granulator, due to the narrower space in the barrel and the use of kneading elements, the effect of stress plays a more important role in granulation process and would be less dissipated. Therefore, the current liquid droplet study on loose powder bed should not be simply adapted to the study of twin screw granulation process.

2.4. Granule property improvement

2.4.1. Introduction

The study of granule properties is mainly carried out in two directions: formulation parameters and process parameters. Formulation development is mainly focussed on the composition and properties of the materials and formulations and how the variation of it would affect the granule properties including dissolution, compressibility, etc., which is mainly about the material itself. Processing development mainly refers to the improvement of operation parameters which is about the relationship and interaction between material and equipment such as screw speed, configurations, etc.

2.4.2. Formulation parameter

Liquid/Solid ratio

Liquid binder flow rate required for granulation process has been studied by number of authors. Liquid to solid ratio (L/S ratio) refers to the mass ratio of the liquid binder to the powder materials. As a wet granulation process, powders granulated in different conditions using twin screw granulator require different amount of liquid to build up liquid bridges between particles. It is significantly related to the properties of materials, including wettability, the primary particle size, formulation, etc.

In wet granulation, particle agglomerations are mainly resulted from the formations of liquid bridges. Therefore, the amount of liquid used in twin screw granulation could directly affect the granule strength. It could be supported by Figure 2-8 that an increase in L/S ratio leads to an increase in granule bulk strength.

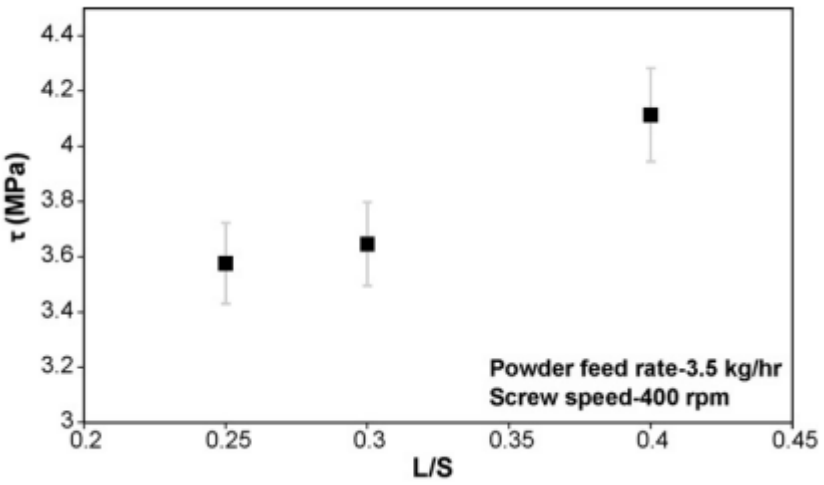


Figure 2-8. . Granules strength for three L/S.

Dhenge et al. (2010) also explored the effect of L/S ratio on granule size distribution. In Figure 2-9, the curve representing the granule size produced at a low L/S ratio is more like multi-modal. As the L/S ratio increases, the curve becomes mono-modal. When the L/S ratio is low, the fines fraction becomes high and the large granules fraction becomes low. Such a tendency concludes that a higher L/S ratio leads to the production of large sized granules and reduction of small sized granules. In general, with an increase of L/S ratio, the large granules fraction decreases. With the increase of liquid content, the granules become fully wetted and form liquid bridges and the inner strength is enhanced, which causes the granules to have a higher strength to resist the shearing forces and friction in the barrel and thus increases the large granule fraction (Dhenge et al., 2010). Similar effect was also found by Lee et al. (2013) that more liquid in the barrel would enhance the granulation efficiency and decrease the unwanted fines fraction using MCC (Figure 2-10).

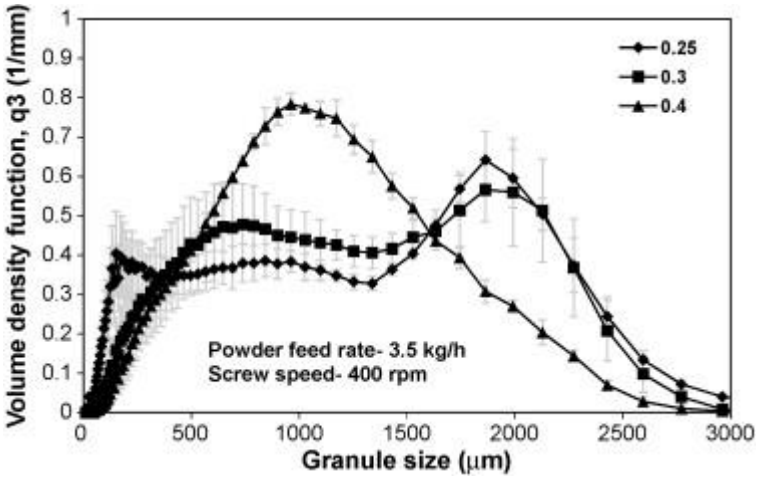


Figure 2-9. Size distributions for three L/S (Dhenge et al., 2010).

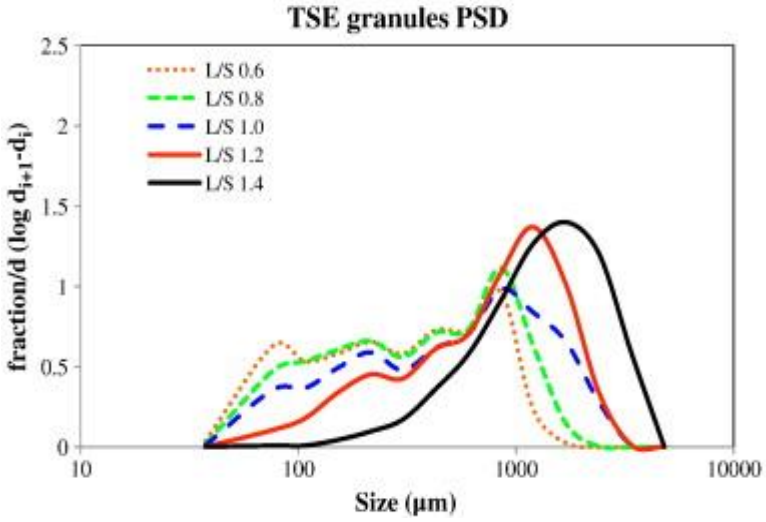


Figure 2-10. PSD of granules produced by TSE at 300 rpm with different L/S ratios (Lee et al., 2013).

Insufficient amount of water may not be capable to form enough liquid bridges. Consequently, a high proportion of fines would be obtained. Oppositely, if too much liquid was used, particles would be over-wetted. In this case, over-sized pastes and lumps would be produced. At the same time, too much liquid around particles would behave like a lubricant rather than a sticker and cause a reduction in granule strength (Tu et al., 2013).

For this reason, choosing the optimal liquid flow rate or L/S is always regarded one of the most important issues for a granulation process, in order to improve the yield and the granule strength. The determination of an optimal L/S ratio is complicated. On one hand, the optimal L/S ratio is not a fixed value for different granulation systems and has to be determined specifically for different granulators, materials and requirements. In this case, trial and error method has to be used, which may lead to a waste of material and labour. On the other hand, for a certain material, the optimal L/S ratio does not change dramatically. As is shown in Table 2-1, although different methods used different screw speed, feed rate, etc., all L/S ratios for α-lactose are close to each other.

Table 2-1. Optimal L/S ratio for granulation.

Journal	Material	L/S ratio
(Keleb et al., 2002)	α-Lactose monohydrate	0.086
(Li et al., 2014b)	α-Lactose monohydrate	0.08
(Kumar et al., 2014)	α-Lactose monohydrate, PVP (premixed)	0.0672
(Vercruysse et al., 2012a)	α-Lactose monohydrate, PVP	0.099
(Keleb et al., 2004)	α-Lactose monohydrate, hydrochlorothiazide (premixed)	0.093
(Lee et al., 2013)	MCC	0.8-1.2
(Tu et al., 2013)	MCC	0.9-1.2

In the pharmaceutical industry, a certain granule size range is required to achieve applicable, stable and constant tabletting properties. To fulfil this requirement, various granulation parameters need to be optimized and L/S ratio is one of the most straightforward ways to control granule size distribution and strength. Therefore, there is a need to develop a method which could predict the optimal L/S ratio to avoid the waste of material and labour due to an improper L/S ratio, especially in formulation development process.

Liquid addition

Liquid is normally acting as binding materials in wet granulation process. Its distribution can significantly influence the yield of final products which are often expressed by the granule size distribution. In respect of this, the method by which a liquid is added is important. If the droplet size of a liquid binder has a wide range, a wide granule size distribution is generally obtained (Iveson and Litster, 1998). To realise a better liquid distribution, droplet atomisation or a good mixing between liquid and powder by mechanical forces are required. Experiments have been conducted by using different liquid addition methods at different agitating speeds. Results showed that both atomised liquid binder and high impeller speed produced the most uniform granule size distribution (Holm et al., 1983).

There are typically three ways to add liquid including pouring, spraying and melting. In twin screw granulator, liquid is mainly added by pouring. This addition method tends to cause a local high liquid content, giving rise to a wide nuclei size distribution, compared with atomised liquid addition or the addition followed by dispersion by intensive agitation. To compensate for the poor liquid addition way in terms of liquid dispersion, a much narrower granulation space in the barrel and consequently a more intensive agitation is required to break the nuclei and can increase the flux of powder through the binder addition zone (Kokubo and Sunada, 1996). Similar statement on high shear mixer was also made by some other authors (Holm et al., 1983).

Binder delivery method

Water, as a low viscosity and high surface tension liquid, has been widely used to form liquid bridges between particles in twin screw wet granulation process. It could spread and distribute easily between particles. In some cases, the bonds may not be strong enough, resulting in the production of large amount of fines or weak granules. Therefore, extra binding excipient would be needed to enhance the binding capability of water.

Binding excipient (binder) addition can be divided into two methods. Firstly, the binding excipient could be dissolved in water and used as a liquid binder to enhance the strength of liquid bridge between particles increasing the strength of granules effectively. In addition, the binding excipient could be premixed with powder in advance (solid form), in order to make sure the binding excipient particles distribute before water comes in contact with powder material (Saleh et al., 2015, El Hagrasy et al., 2013b). El Hagrasy et al. (2013a) utilized three materials to investigate the effect of binder delivery method. It was found in Figure 2-7 that the overall granule size distribution are quite simlilar for three materials. However, it could still be seen that the use of liquid binder leads to a lower production of fines and the granule size distribution is narrower. They finally stated that the use of binder in the granulation liquid is a better option to enhance the binding efficiency and the granule size distribution is narrower. This statement was supported by Vercruysse et al. (2012a) who concluded that the binder was more effective when added in the liquid phase. Although they hypothesize that it might be due to the insufficient residence time in the barrel, no comprehensive study was given.

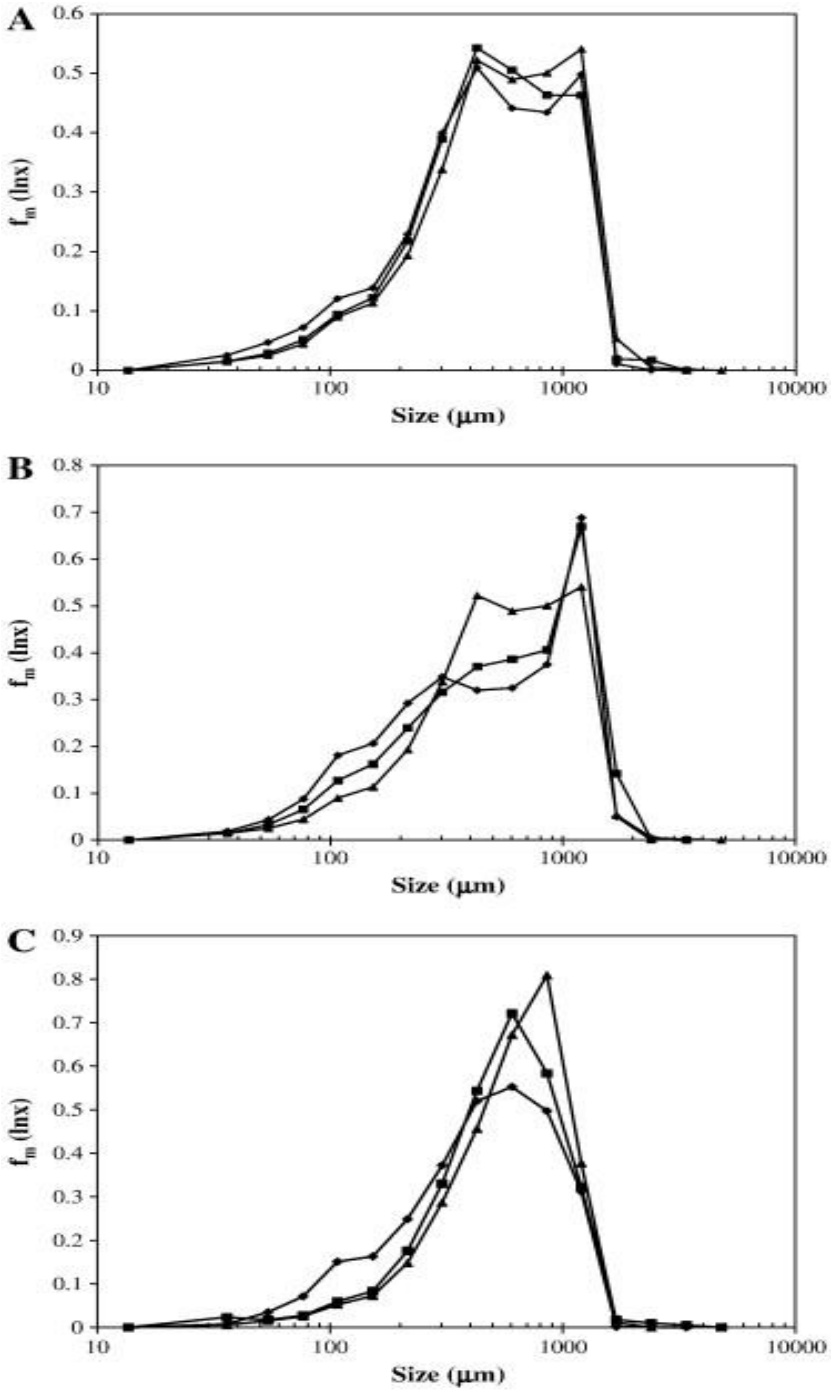


Figure 2-11.The change in granule size distribution for formulations containing pharmatose 200 M (A), impalpable (B), and supertab 30GR (C) as the lactose grade using dry binder (♦), 1:1 liquid:dry binder (■) and liquid binder (▲) at L/S = 0.3 (El Hagrasy et al. 2013a).

Saleh et al. (2015) also studied the different effect of binder delivery methods on granulation. Figure 2-12 shows the granule size distribution in different binder delivery methods. It could be seen that the use of solid binder leads to a more uniform granule size distribution than the use of liquid binder. Through a seris of single drop study, Saleh et al. (2015) stated that it is becuase liquid was easier to distribute in the powder when solid binder was used, as it has the least infleucne on the liquid viscosity.

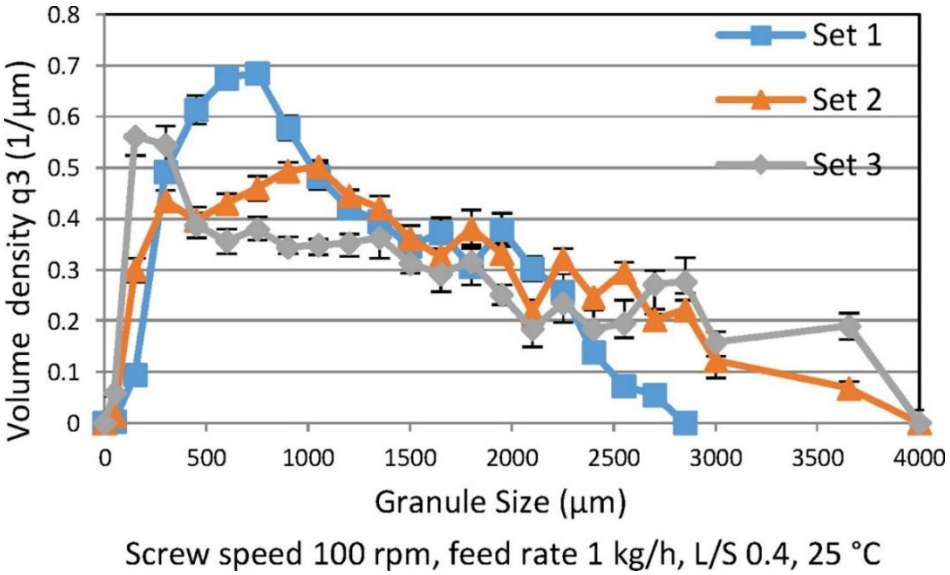


Figure 2-12. Size distribution of granules as the binder delivery varied (Sets 1–3) using conveying elements only (Set 1: solid binder; Set 2: mixed; Set 3: liquid binder) (Saleh et al. (2015)

Liquid binder addition

Binder in liquid form normally has a higher viscosity than water. Its high vicosity is helpful to enhance liquid bonds and make the granules stronger. It could be seen in Figure

2-13 that a higher HPC concentration and L/S ratio could all cause an increase in granule strength.

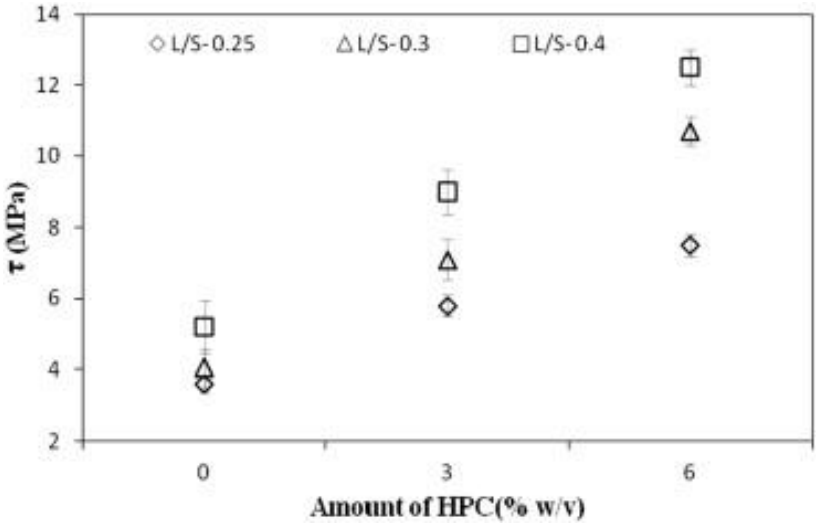


Figure 2-13. Strength of granules produced at different amounts of HPC (Dhenge et al., 2012c).

However, high viscosity could cause a reduction in liquid distribution, making an uneven liquid-powder mixing. Figure 2-14 shows the relationship between binder concentration (viscosity) and granule size distribution (Dhenge et al., 2012c). A higher HPC concentration leads to a higher proportions of fines, which indicates that a poorer liquid distribution and mixing.

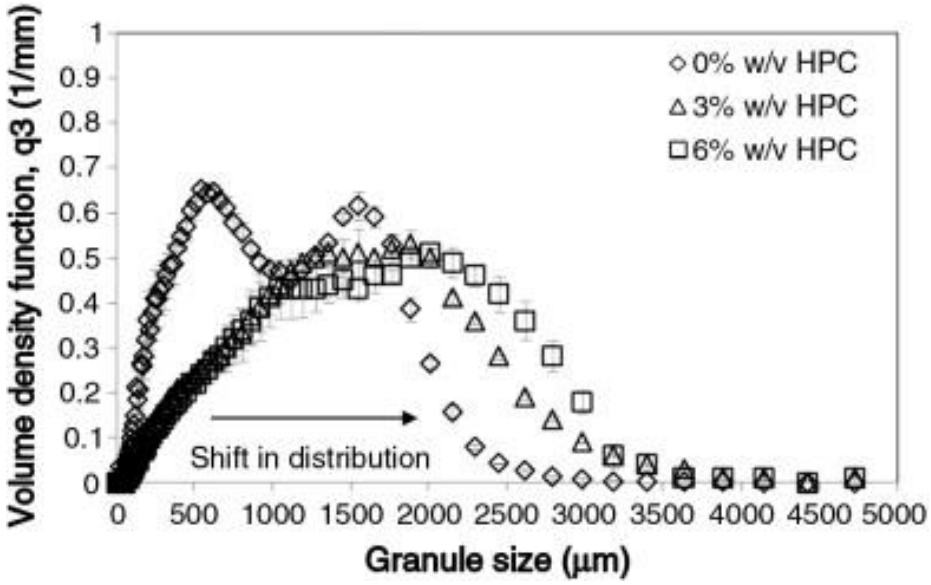


Figure 2-14.Size distributions for different amounts of HPC at liquid to solid ratio of 0.3 (Dhenge et al., 2012).

Similar statement was also stated by Keleb et al. (2004) that a higher concentration of PVP binder in a solution could reduce the granulation yield by producing more over-sized granules and fines as seen in Figure 2-15.

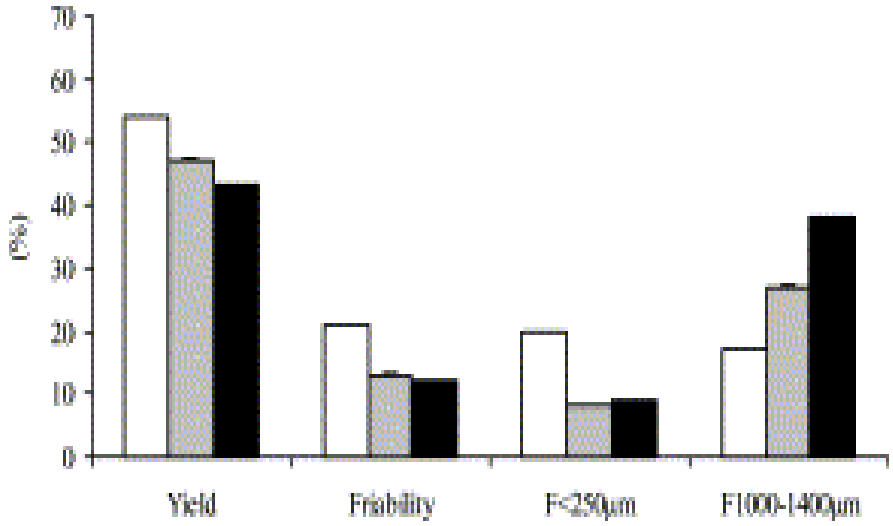


Figure 2-15. Influence of PVP concentration on the properties of α-lactose monohydrate granules containing 0 (white), 1.25 (grey and 2.5% PVP (black) (Keleb et al., 2004).

To tackle this problem, the surface tension of liquid was varied by adding surfactant, in order to improve the liquid dispersion even if it contains high concentration of binding exipient (Dhenge et al., 2012c). It could be seen in

Figure 2-16 that in general, the addition of surfactant is not effective on varying the granule size distribution. Therefore, the reduction of surface tension was proved to be less effective on improving the dispersion of liquid binder solution.

It might be because the addition of surfactant could increase the contact angle making the liquid easier to be squeezed out. Simultaneously, it would reduce the surface tension, making the liquid more difficult to disperse due to the capillary forces. Therefore, the effect of surfactant may be offset by increased contact angle and reduced surface tension

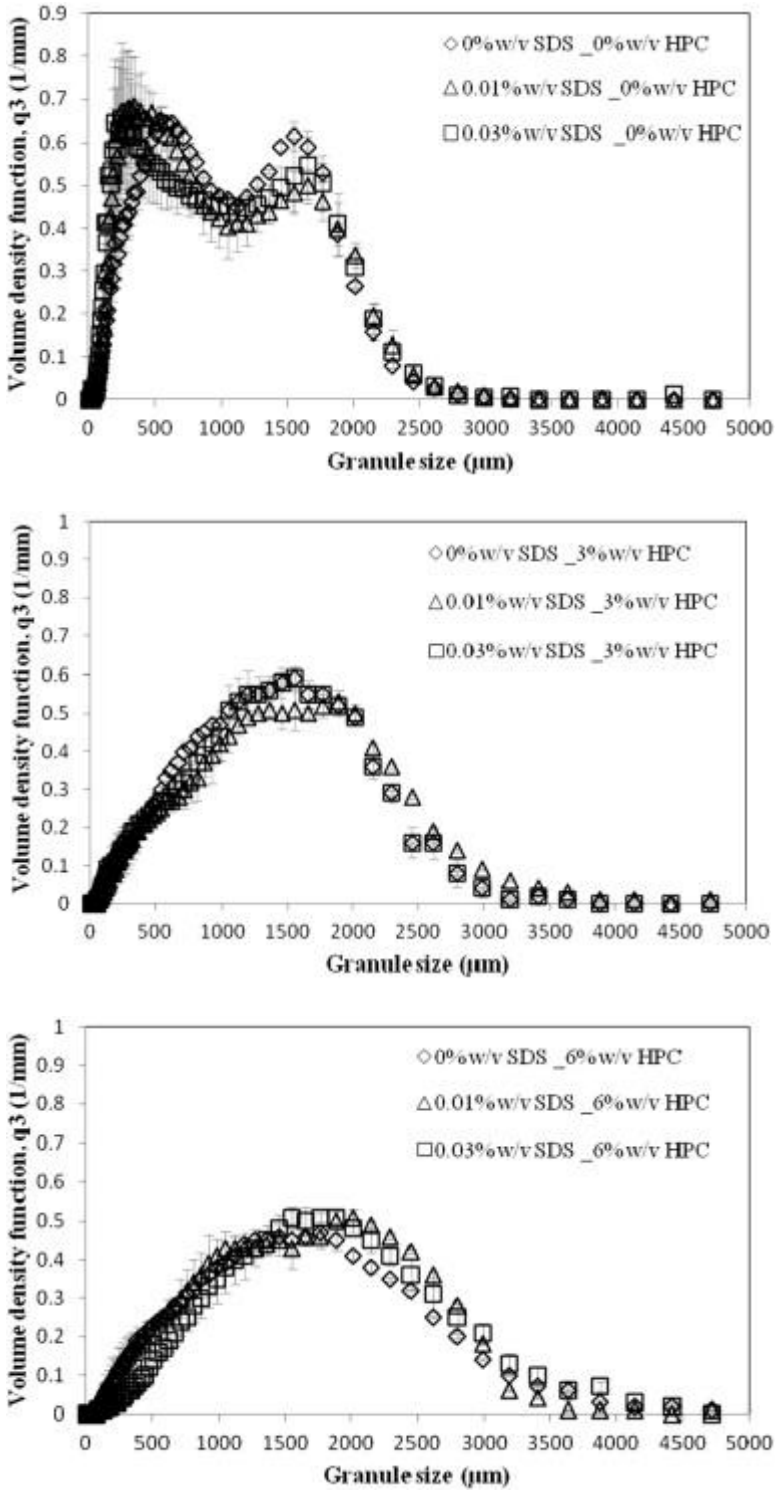


Figure 2-16. Size distributions for varying amounts of SDS in a granulation liquid with 3, 6, 9% w/w HPC (Dhenge et al., 2012c).

based on the Laplace capillary equation. In addition, Nowak et al. (2016) studied the effect of surfactant on the geometry of liquid bridge, none obvious improvement was observed, which indicates that the surfactant is not quite effective in promote granule properties.

Solid binder addition

In addition, the binding excipient could be premixed with powder in advance (solid form), in order to make sure the binding excipient particles distribute before water comes in contact with powder material (Saleh et al., 2015, El Hagrasy et al., 2013b). In this case, the liquid (water) would be easier to distribute in the powder during granulation. However, the limited amount of water may be insufficient to dissolve the binder particles, especially big-sized particles, and thus reduce the efficiency of the binding excipient. Therefore, more binding excipient would be needed to compensate for its relatively low efficiency.

To tackle the problem that solid binder particles could not dissolve properly in order to enhance the bonding during granulation effectively, assessment for the effect of smaller binder particles was carried out in both high shear mixer and fluidised bed (Alvarez-Lorenzo et al., 2000, Van der Watt, 1987, Nyström and Glazer, 1985, Nyström et al., 1982, Schæfer and Mathiesen, 1996, Kato et al., 2006, Li et al., 2011). It was found that the use of smaller sized binder particles could promote the growth of granules and has positive effects on the strength of granules due to their outstanding specific surface area. In terms of twin screw granulation, none of the previous work has been found.

2.4.3. Processing parameter

Processing parameter interaction

Feed rate

Feed rate normally refers to the mass based powder flow rate and could directly affect the granule productivity.

Due to the “back mixing”, the variation of feed rate affects the residence time which refers to the time granules consume in the barrel (Dhenge et al., 2011). It could be seen in Figure 2-17 that an increase in powder feed rate delays the residence time. Similar results were also obtained by Dhenge et al. (2011), Lee et al. (2013) and Unlu and Faller (2002).

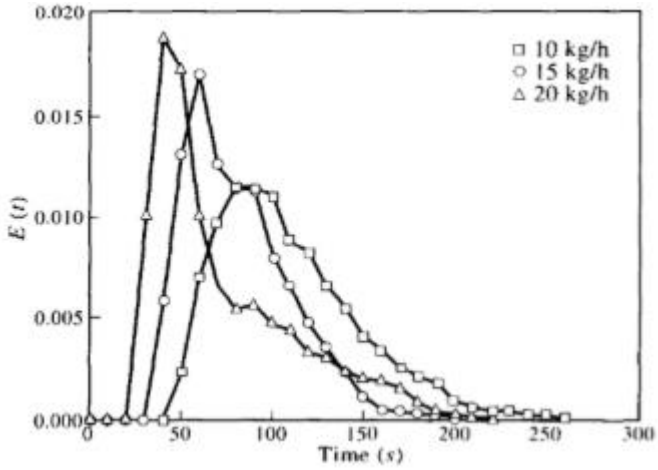


Figure 2-17. E(t) curves for feed rates of 10, 1.5 and 20 kg/h. Screw speed 200 rpm, moisture content 43%, product temperature 60-65°C (Ainsworth et al., 1997).

Apart from the effect on residence time, Dhenge et al. (2011) found that as the powder feed rate is increased, the volume of powder in the barrel increases which enhances the liquid powder interaction (Figure 2-18). As a result, narrower size distribution could be obtained.

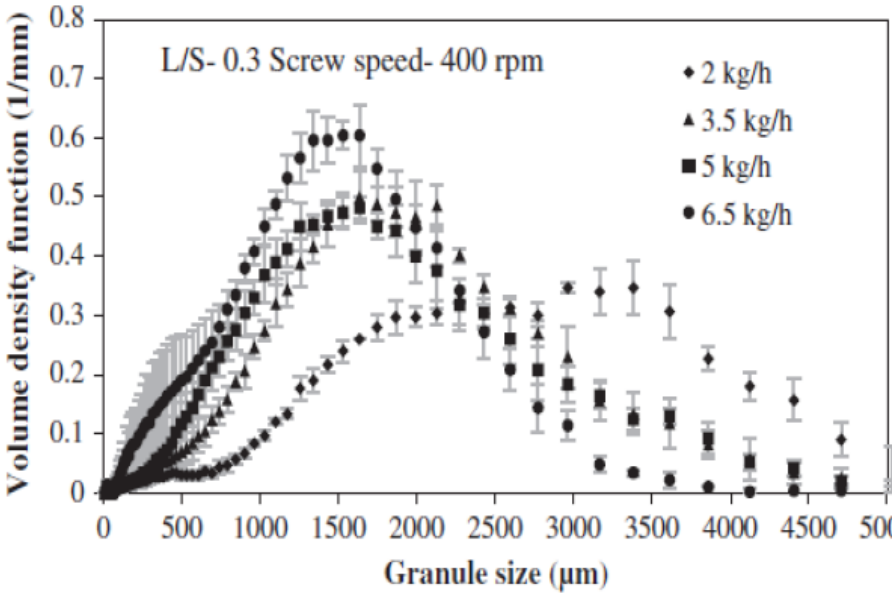


Figure 2-18.Size distributions for changing powder feed rates (Dhenge et al., 2011).

Furthermore, as the feed rate increases, the higher rotation of screws consumes more energy and generates a higher torque which is an indicator of compaction in the system (Tu et al., 2013). As a result, a high feed rate leads to production of stronger granules (Dhenge et al., 2011).

Variation of feed rate could affect the level of material in the barrel (fill level) and influence the granulation process (Dhenge et al., 2011). Due to the importance of fill level in varying processing parameters such as screw configurations and screw speed, series of

researches about the effect of fill level was carried out. Due to the complexity in volume based fill level controlling, a parameter called “specific feed load” was defined as the ratio of feed rate and screw speed (Kolter et al., 2012). However, the study of fill level is mainly focussed on its effect on granule properties. The effect of screw speed and screw configuration with a controlled fill level has not been covered. Actually, the current definition of fill level is not applicable to the study of the effect of screw configurations, as it assumes the powder properties including flowability and screw conveying capability for different configurations as constants (Meier et al., 2017).

Screw configuration

As was introduced in the previous section, two screw elements are normally applied in twin screw wet granulation process, which are conveying element and kneading element. Numbers of literature pointed out that using kneading elements could promote the binder dispersion by breaking nuclei and help with collision and coalescence (El Hagrasy and Litster, 2013, Li et al., 2014a, Dhenge et al., 2012a, Thompson and Sun, 2010). In most cases, this statement was corroborated by the span of granule size distribution. Specifically, a bimodal size distribution is normally regarded as a symbol of poor liquid binder mixing. However, an intensive agitation could enhance the breakage of granules and may lead to production of a high proportion of small granule fragments, which is also possible to produce a bimodal granule size distribution. Therefore, a more scientific method should be utilized to further examine the binder dispersion capability of kneading elements.

It is known that the kneading elements are deficient in conveying materials (Thompson and Sun, 2010). In this case, two sets of screw configurations may have different

conveying capability, leading to a difference in fill level (Gorringe et al., 2017). In this case, a comparison of screw configurations (such as yields) by maintaining feed rate, screw speed and L/S ratio could still be bothered by the variation of fill level. Therefore, a method to achieve a more systematic evaluation between different configurations should be developed.

Screw speed

Screw speed is related to the rotation speed of the screws. It is easy to see that an increase in screw speed could intensify the agitation and improve the mixing (Dhenge et al., 2010). Theoretically, an increase in screw speed would contribute to binder dispersion and granule consolidation. However, in terms of its effects on granule properties, there is no universal agreement in the literature as other parameters such as feed rate, L/S ratio (Lee et al., 2013, Karunanithy and Muthukumarappan, 2011, Dhenge et al., 2010, Reitz et al., 2013).

For example, a comparison of the twin screw extruder and the high shear mixer is shown in Figure 2-19 where when other parameters are fixed, for a higher speed, the twin screw extruder can produce granules with a narrower distribution. However, it is difficult to show one tendency regardless of the fines fraction or the large size granule fraction (Lee et al. 2013). On the other hand, Dhenge et al. (2010) held opposite statement and as shown in Figure 2-20 that a high screw speed would widen the size distribution, as the intensive stress would enhance the granule breakage.

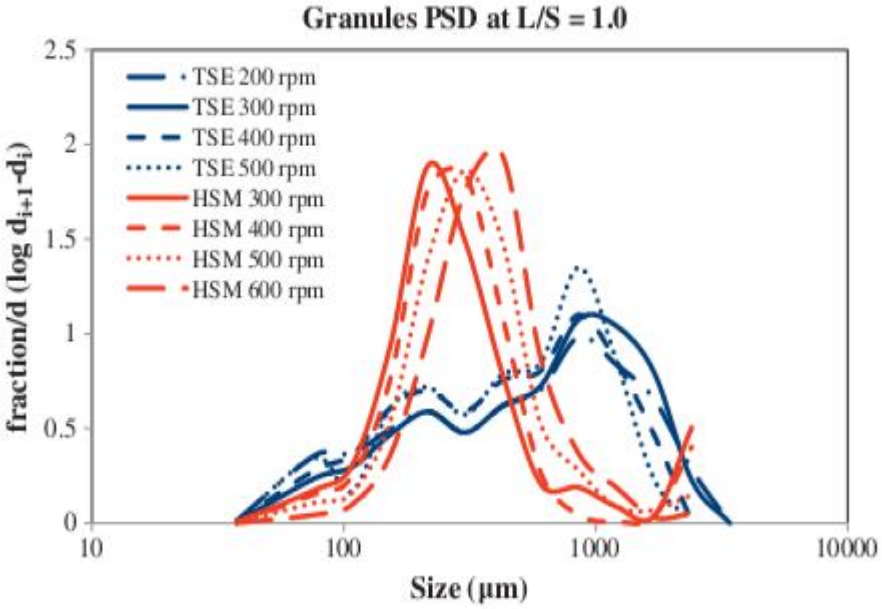


Figure 2-19. Granule size distribution for changing screw speeds using MCC (Lee et al., 2013).

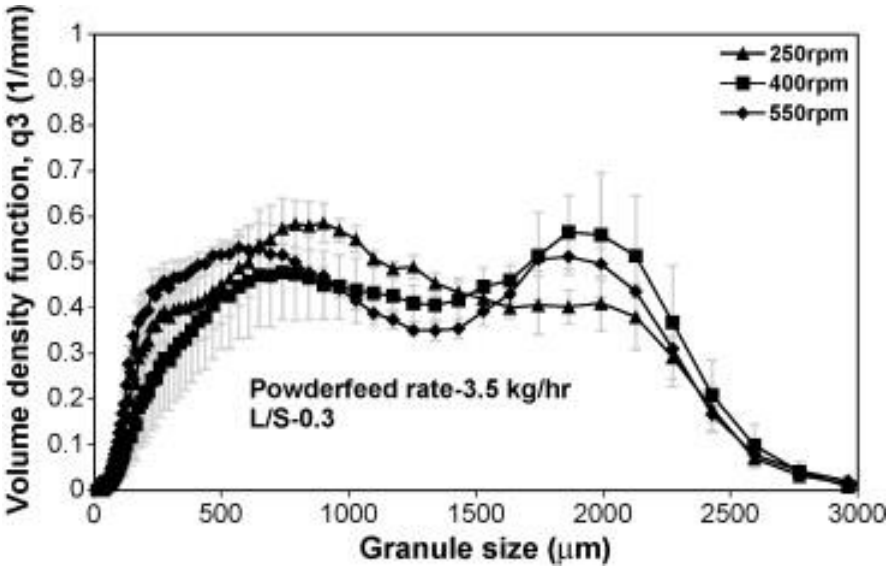


Figure 2-20. Granule particle size distribution (Dhenge et al., 2010).

A higher screw speed leads to a lower fill level in the barrel (Dhenge et al., 2011). As a result, the friction of mixture between the screw and wall also decreases and thus

increases the size (Dhenge et al., 2011). On the other hand, an increase in screw speed intensifies the agitation, which increases the energy transferred to the material. Therefore, the effect of screw speed is fairly difficult to conclude and reproducible for different equipment and condition. Apart from this, the effect of screw speed on granule strength is rarely to see.

Fill level

The fill level is defined as the amount of material in the barrel of the twin screw granulator and directly affects the compaction of materials which determines the granule attributes e.g. size and strength (Kolter et al., 2012, Dhenge et al., 2011). Seem et al. (2015) stated that the material fill level mainly depends on three aspects: the screw and barrel geometry, the screw speed and the material feed rate and the variation of screw speed and feed rate could all affect the fill level and distort the result. This statement could be supported by Figure 2-21. Unlu and Faller (2002) studied the parameters which could affect the barrel fill and found that an increase in screw speed or a decrease in feed rate could reduce the amount of materials in the barrel. It indicates that when varying feed rate or screw speed, the fill level would be varied simultaneously and consequently the result obtained would be masked.

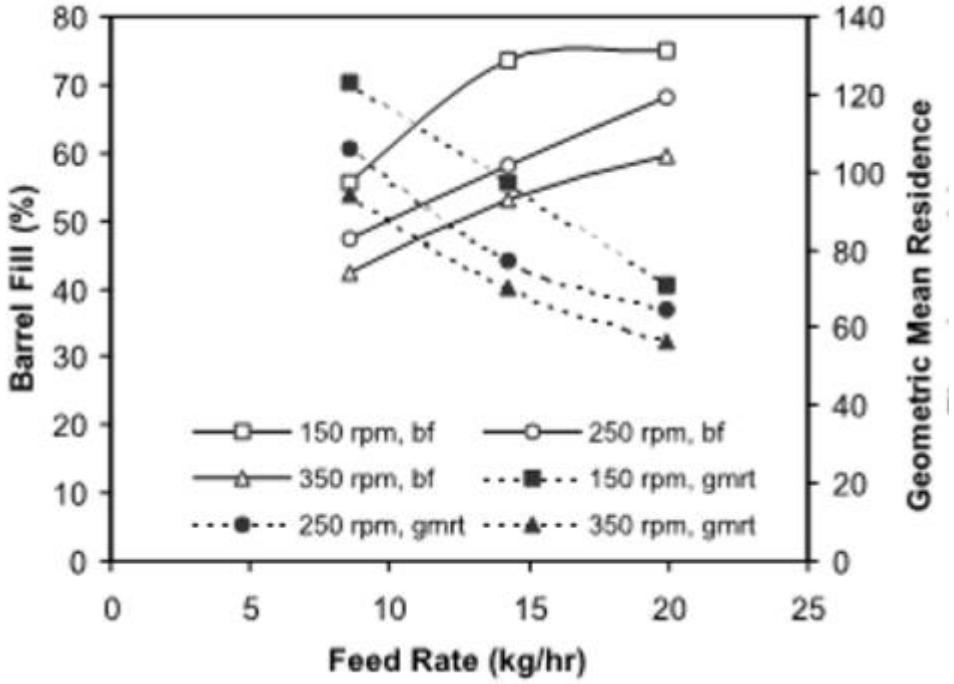


Figure 2-21. Barrel fill vs. feed rate at different screw speeds (bf: barrel fill, gmrt: geometric mean residence time, rpm: revolutions per minute)(Unlu and Faller, 2002).

To overcome this problem, a parameter of "specific feed load" was raised and defined as the ratio of feed rate and screw speed (Kolter et al., 2012). It was applied to provide a constant fill level environment. However, the research about the specific feed load was limited in "one applied system" and is invalid for different screw configuration, formulation, etc. (Meier et al., 2017). Particularly, based on the definition of "volumetric fill level", as long as the feed rate and screw speed are constants, the variation of screw configurations, material properties and granulator dimensions does not affect the fill level.

Although the fill level is quite important to determine for granule properties, quantifiable determination of fill level is noticeably absent within paper which is mainly

due to the complicated calculation to determine the volume and residence time determination (Seem et al., 2015). In addition, due to the difference in conveying capability, the variation of screw configuration could also affect the fill level. However, it is quite rare to be mentioned in the current research on fill level.

Temperature

Temperature is also an important parameter that could affect the granule properties. Vercruysse et al. (2012a) stated that the rise of barrel temperature had effect on granules, as it could enhance the production of large lactose granules., as a high temperature could acclerate the dissolution of lactose, leading to production of stronger lactose granules. However, their research focused on the effect of temperature on the granulation powder, but did not investigate the effect of temperature on binder solution and liquid distribution. Thoretically, a higher temperature could reduce the liquid viscosity and enhance its flowability. As a result, the granule size distribution should be quite uniform rather than a production of high proportion of large granules. It might be due to the neglection of liquid binder temperature condition. Specifically, the liquid binder should also be conditioned before granulation, otherwise the relatively short residence time in twin screw granulation may be insufficient to heat the liquid binder properly.

Liu et al. (2016) studied the wetting behaviour of hydroxypropyl methylcellulose (HPMC) on twin screw granulation process with a temperature range from 30 to 80 ºC. However, from their study the effect of temperature on immediate release (IR) and controlled release (CR) formulations was studied, which is mainly focused on the tablet dissolution.

Currently, no literature has comprehensively study the effect of liquid temperature for twin wet screw granulation process in both binder delivery methods. It is necessary to explore the effect of temperature, especially the liquid temperature on granule properties.

2.5. Objective review

Twin screw granulation is based on the dynamic liquid-powder interaction. There are many parameters could control or affect the granulation process and granule properties. They could either affect the formulation property, or affect the inner environment in the barrel. Although numbers of work have done to study the twin screw granulation, producing granules with excellent properties is still quite challenging.

Binding excipient is commonly used to enhance the granule strength and help the granule growth. The presence of binder would influence (delay) liquid distribution and cause different effects on granule properties. Water is one of the most commonly used liquid for wet granulation, as it could be easily distributed and mixed with powder material. An even liquid distribution could lead to granules with uniform size distribution. Due to the requirement of granule strength, the binding excipient are added in different forms (liquid and solid). With the presence of binder, liquid distribution would be influenced. It is quite necessary to investigate the approaches to optimize the liquid distribution with the existence of binder in different forms, in order to produce granules with required size distribution and strength.

In addition, trial and error is still a mainstream in formulation development, even though the twin screw regime map has been preliminary developed. For example, L/S ratio is one of the easiest handling parameters to control the granule properties. However, when facing on a new formulation or new material, the optimal L/S ratio has to be

obtained by numbers of trials. It is quite necessary to develop a new approach to predict the granule properties before granulation.

The thesis structure is shown in Figure 2-22.

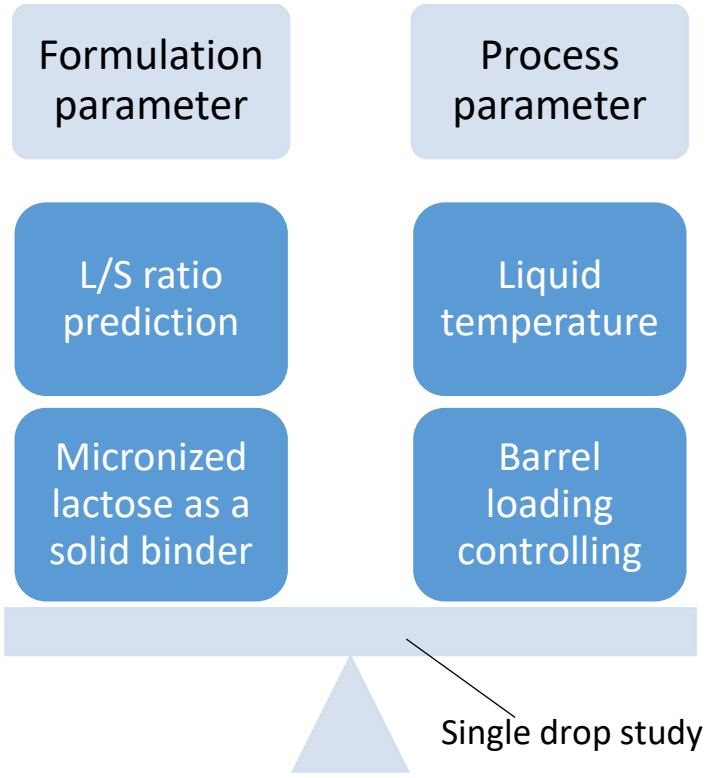


Figure 2-22. Schematic of research objective.

Chapter 3. Materials and methods

3.1. Introduction

This chapter presents the materials, equipment and methods for the experiments.

3.2. Materials

α-lactose monohydrate (Pharmatose 200M, DMV-Fonterra Excipient GmbH and Co., Goch, Germany) and microcrystalline cellulose (Avicel PH 101, FMC Biopolymer, Cork, Ireland) were used as the experimental powder. Hydroxypropyl cellulose (HPC, Klucel-EF Pharm, Aqualon,Wilmington, DE, USA) are used as the binder. Some of the information and size distribution are shown in Table 3-1 and Figure 3-1 obtained from a size tester (Camsizer XT, Retsch Technology, Germany).

Table 3-1. Material in experiment.

Powder	Supplier	Particle size (μm, d_{50})	True density (kg/m^3)
α-lactose monohydrate	GmbH and Co.	44.1	1540
microcrystalline cellulose	Sigma-Aldrich	52.8	1561
hydroxypropyl cellulose	Klucel-EF Pharm	308.3	1214

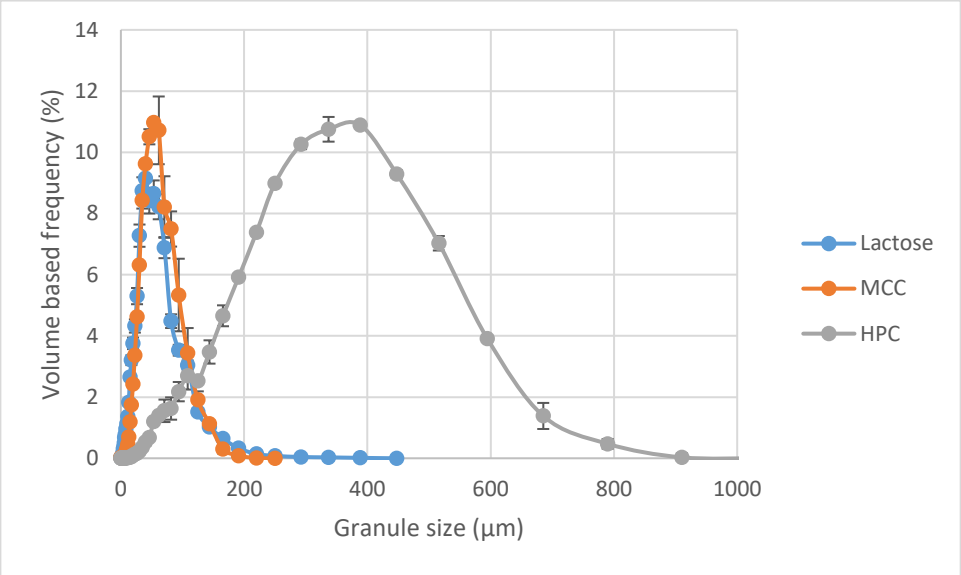


Figure 3-1. Primary particle size.

α-lactose monohydrate is a white or off-white crystalline material which produced by crystallisation from a supersaturated solution. Figure 3-2 shows its particle morphology. It is commonly exist in the milk of mammals and therefore is quite cost effectiveness. α-lactose monohydrate is free soluble in water. In pharmaceutical industry, it is used as an ideal tabletting filler or filler-binder which has excellent physical and chemical stability and is compatibility with active ingredients or other materials.

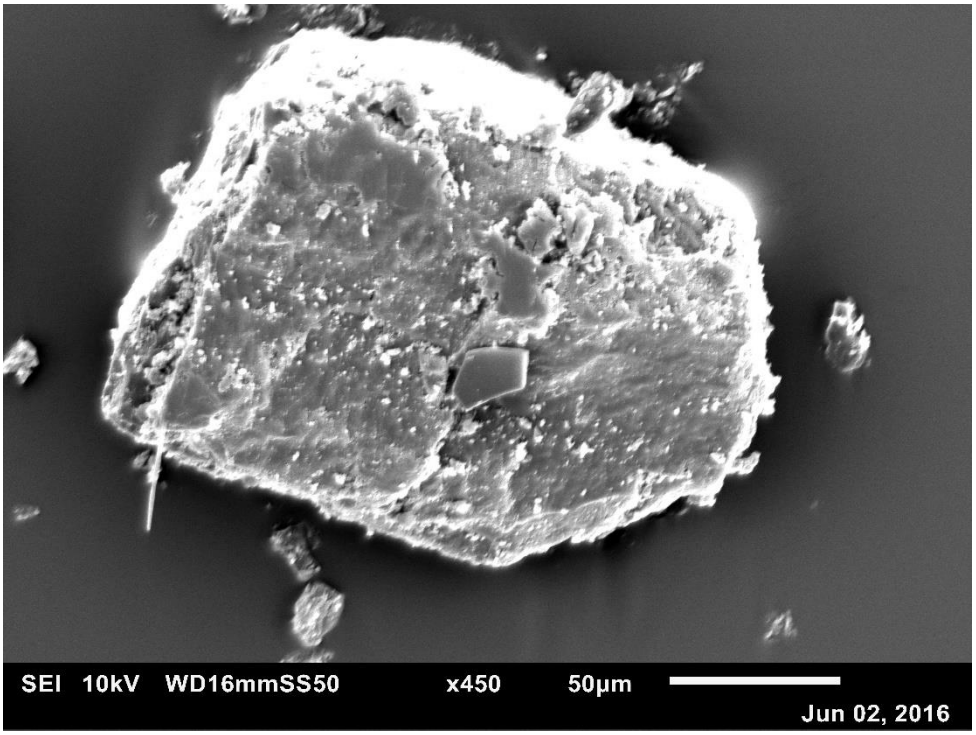


Figure 3-2. Lactose particles.

Microcrystalline cellulose is a white, purified, partially depolymerized cellulose which could be obtained from wood. Similar to lactose, MCC is also a common used filler and disintegrant for tabletting, due to its excellent compressibility and compatibility. Due to its chemical inactivity, absence of toxicity and hygroscopicity, MCC has been widely used in the pharmaceutical industry. Due to its special structure, water exsting in the MCC particles are in various form such as hydrogen bonds linked with molecules and free water held in sub microscopic pores, cracks and crevices between fibrils (Luukkonen et al., 2001). In wet granulation process, MCC is considered to be a porous sponge due to its high water absorption capacity. Specifically, when pressure applied, the free water could be squeezed out; when the pressured is removed, MCC particles would absorb water and exapand back to its original shape and size (Fielden et al., 1988).

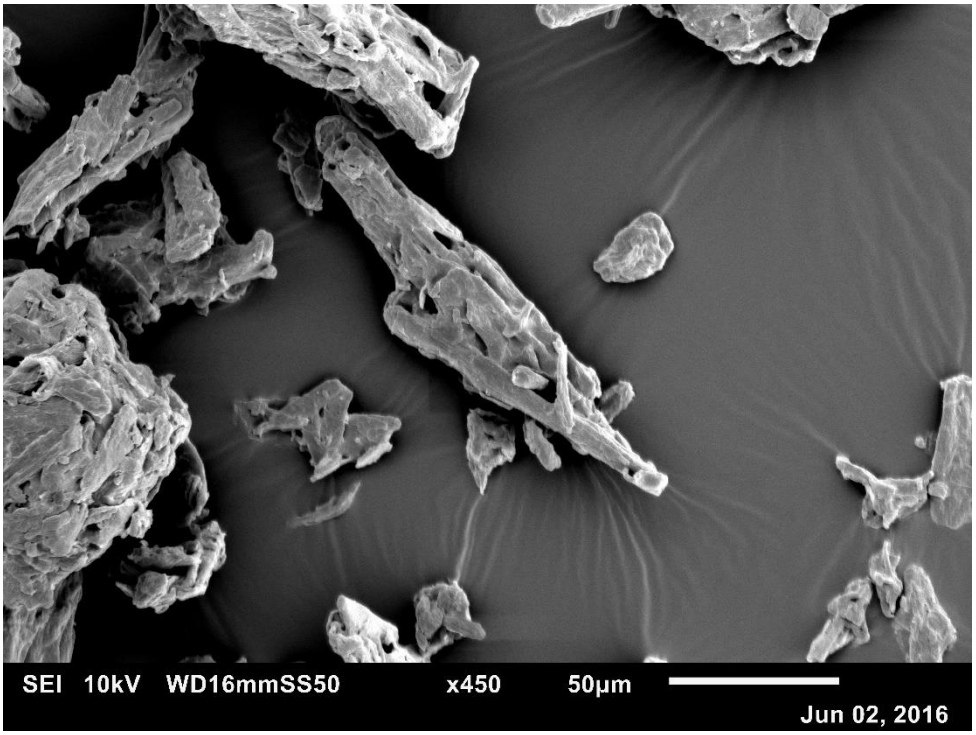


Figure 3-3. MCC particles.

Hydroxypropyl cellulose is non-ionic, water-soluble cellulose ether with a remarkable binding capability, which is widely used in pharmaceutical industry as a binding excipient to enhance the strength of products including granules, tablets, etc. In twin screw granulation, it could be utilized either as a solution or premixing with the granulation powder.

3.3. Prepare of binder

In twin screw granulation process, the use of binding excipient could be classified into two methods: solid binder delivery and liquid binder delivery. In terms of solid binder delivery experiment, HPC was premixed with lactose and with MCC by using a high shear granulator (Romaco Roto Junior) for 5 min with a impeller speed of 300 rpm,

respectively (Saleh et al., 2015). Powder was then conditioned in an environment chamber (Camlab, Memmert, UK) with a temperature of 25 °C and relative humidity of 40% for 48 h before the experiment. The liquid binder was prepared by dissolve HPC particles into distilled water. The dissolution process was accelerated by using a moter-driven stirrer with a speed of 800 rpm and the temperature was kept at 60 ºC. Then, due to the containing of bubble during HPC dissolution, the solution was then stand for 24 hours in the environment chamber with a relative humidity of 40% and temperature of 25 ºC. Parafilms were used to reduce the loss of water from evaporation.

Table 3-2. Prepare of binder

	Powder feed rate (kg/h)	HPC in powder (w/w, %)	HPC in water (w/w, %)	Liquid feed rate (kg/h)
MCC	1 kg/h	0	0	0.8
MCC	1 kg/h	2	0	0.8
MCC	1 kg/h	0	2.5	0.8
MCC	1 kg/h	4	0	0.8
MCC	1 kg/h	0	5	0.8
Lactose	1 kg/h	0	0	0.08
Lactose	1 kg/h	2	0	0.08
Lactose	1 kg/h	0	2.5*	0.08
Lactose	1 kg/h	4	0	0.08
Lactose	1 kg/h	0	5	0.08

* *Due to the small L/S ratio of lactose (0.08), the equivalent concentrations of HPC solution are supposed to be 25% and 50% (w/w) respectively, which are beyond the dissolution rate of HPC and may damage the twin screw granulator due to its stickiness. Therefore, 2.5% and 5% (w/w) HPC solution will be used to provide a qualitative comparison with the use of HPC in solid form (2 & 4%).*

In this thesis, coloured HPC was also prepared. The solid binder (HPC) was dissolved in distilled water and then mixed with red dye, erythrosine B which was used as a tracer (Osborne et al., 2011). The solution was then left in an oven at 120 °C to evaporate all the water content for 24 hours. The coloured dried binder was milled using a ball mill and sieved with a mesh diameter of 300 μm (<d_{50} of HPC particle size).

3.4. Liquid viscosity

A rheometer (Kinexus, Malvern Instruments, UK) was used to determine the liquid dynamic viscosity. To proceed the measurement, the cone and plate geometry (1º/50 mm) was used at a shear rate of 1 - 1000 s^{-1}. To obtain the effect of temperature on liquid viscosity, three different temperatures (25, 40, 60 ºC) were used for all HPC liquid binders. It was found that all liquids were displayed Newtonian behaviours at the given shear rate.

3.5. Single drop study on the compact powder bed

3.5.1. Prepare of the compact powder bed

A static compact powder bed was produced by using a Zwick Roell strength tester (Zwick GmbH and Co., Ulm, Germany). 2.5 g of powder was weighted and poured in a die with an inner diameter of 30 mm and height of 25 mm. Different compression forces (100, 200, 300, 450 N) were applied using a punch to produce the powder bed. To simulate the different stresses in a twin screw granulator, corresponding compression stresses (142 kPa, 283 kPa, 425 kPa, 637 kPa) from the punch were obtained using:

$$\boldsymbol{P = \frac{4F}{\pi d^2}} \qquad (3\text{-}1)$$

where P is the compression stress (kPa), F is the force used, d_{die} is the diameter of the die.

The compression stresses used in the study were in the range of stresses exerted in twin screw granulator (Li et al., 2014b). The compression speed was set as slow as 1 mm/min, aiming to give particles in the powder bed sufficient time to arrange themselves so that reproducibility of the powder beds produced can be ensured.

3.5.2. Powder bed porosity

The powder bed porosity (ε) is calculated using the powder bed bulk density (ρ_{bulk}) and material true density (ρ_{true}). The equation is shown as follow:

$$\boldsymbol{\varepsilon = 1 - \frac{\rho_{bulk}}{\rho_{true}}} \qquad (3\text{-}2)$$

The bulk density was obtained by using the ratio of powder bed mass ($m_{compact\ powder\ bed}$) and volume ($V_{compact\ powder\ bed}$).

$$\boldsymbol{\rho_{bulk} = \frac{m_{compact\ powder\ bed}}{V_{compact\ powder\ bed}} = \frac{m_{compact\ powder\ bed}}{\frac{d^2}{4} \times \pi \times h_{compact\ powder\ bed}}} \qquad (3\text{-}3)$$

where d_{die} represent the diameter of the die, which is 30 mm; hcompact powder bed represent the height of the compact powder bed and could be obtained from the software. The mass of the powder bed was weighted using a high accurate scale (0.0001g). The average heights of the compact powder bed are shown in Table 3-3 and the corresponding porosity is shown in Table 3-4.

Table 3-3. Powder bed heights (mm)

Compression (kPa)	Lactose	Lactose + 2% HPC	Lactose + 4% HPC	MCC	MCC+ 2% HPC	MCC+ 4% HPC
142	4.70±0.14	4.64±0.08	4.68±0.08	8.63±0.02	8.36±0.04	8.11±0.07
283	4.39±0.07	4.34±0.15	4.45±0.04	8.22±0.01	7. 85±0.03	7.72±0.03
425	4.24±0.01	4.22±0.07	4.30±0.07	7.93±0.02	7.62±0.00	7.42±0.01
637	4.03±0.01	4.02±0.03	4.09±0.01	7.56±0.01	6.95±0.06	7.09±0.03

Table 3-4. Compact powder bed porosity (%)

Compression (kPa)	Lactose	Lactose + 2% HPC	Lactose + 4% HPC	MCC	MCC+ 2% HPC	MCC+ 4% HPC
142	50.5±1.1	50.3±1.3	49.8±1.7	71.9±0.1	72.8±2.1	69.9±0.4
283	47.0±0.8	46.8±0.7	47.3±0.2	70.5±0.1	71.0±0.6	68.4±0.2
425	45.0±0.3	45.3±0.1	45.4±0.6	69.4±0.3	70.1±0.7	67.1±1.0
637	42.3±0.3	42.6±0.3	42.7±0.1	68.0±0.5	67.2±0.1	65.6±1.3

3.5.3. Measurement of penetration time and maximum apparent contact angle

The powder bed was placed on a substrate with an electronic pipette (Eppendorf, multipette stream, Germany) 10 mm away from the surface of the powder bed, in order to reduce the effect of kinetic energy on liquid penetration and spreading (shown in Figure 3-4). The electronic pipette could control the speed of piston to generate the droplet. The volume of the droplet was set at 15 µL. The speed of droplet formation was set as 1

ml/min to reduce the influence of pressure on droplet size. The penetration process was captured using a high speed camera (Photron, Fastcam, 100 K, USA) using a frame rate of 1000 fps. Due to the high frame rate, an extra light source was utilized. The end point of penetration was marked by the disappearance of the light reflection. By requiring a high speed camera, the dynamic motion of droplet penetration and spreading was closely observed and the penetration time was obtained. After the observation of the penetration process, powder bed nuclei, which is the wetting area, formed on a bed of powder were taken to the Zwick Roell strength tester for the indentation experiment. For each powder bed, maximum three penetration processes were captured.

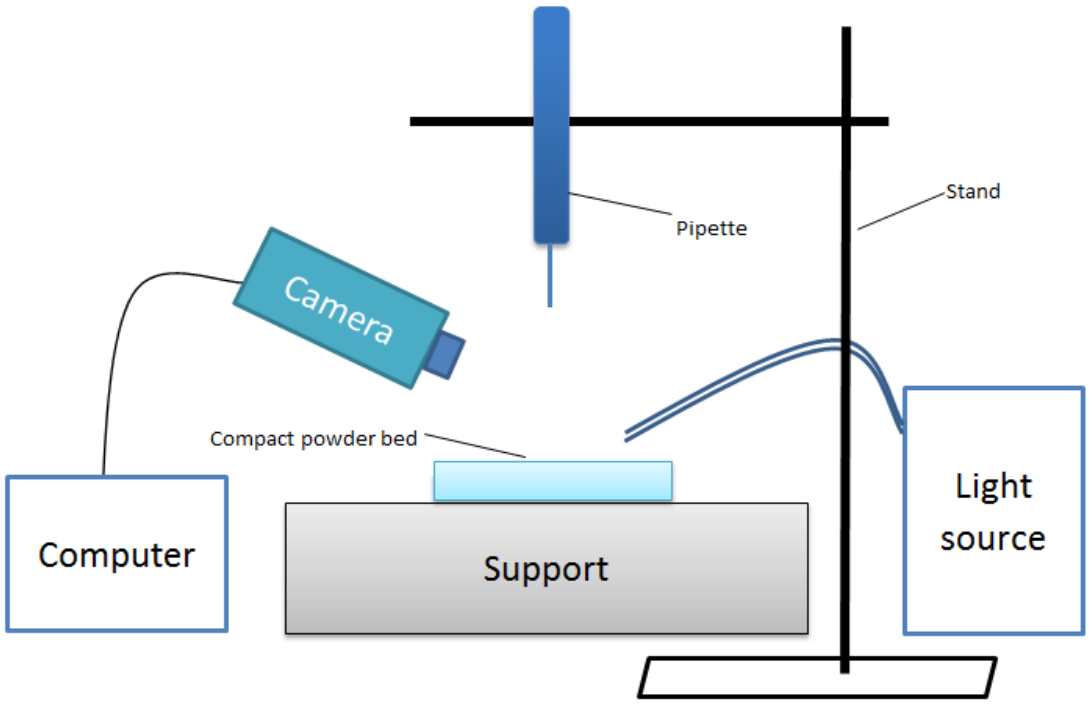


Figure 3-4. Experiment set up during contact angle measurement.

The maximum apparent contact angle is defined as the maximum dynamic contact angle after the droplet has stabilized. It was analysed using FTA32 contact angle software (First Ten Angstroms, Inc., USA). By selecting points at the boundary between liquid, air and solid surface, the software could figure out the outline of the droplet and provide the corresponding contact angle.

3.5.4. Nucleus hardness measurement

Powder bed nuclei hardness was measured using a series of indentation experiments. An indenter with a tip diameter of 2.5 mm connected to the Zwick Roell strength tester was used to indent the powder bed-nucleus with a speed of 1 mm/min till a certain depth (0.5mm). A minimum force of 0.01 N was required before the recording of the force could be triggered (Ai et al., 2016). The contact area (*A*) between the indenter and the powder bed-nucleus being tested can be calculated on the basis of Equation (3-2). By using the force detected using Zwick Roell, the hardness of material would be obtained.

$$\boldsymbol{A = \pi d_{indenter} h = 2.5 \pi h} \qquad (3\text{-}4)$$

where *A* is the contact area between indenter and powder bed-nucleus which is basically the surface area of a spherical cap, *h* is the indentation depth, $d_{indenter}$ is the diameter of Brinell sphere.

Nucleus hardness test results are mainly shown in the Appendix A and B.

Figure 3-5 Indentation experimental set up

After the hardness test of wet powder bed nuclei, the compact powder bed was placed in an environment chamber (Camlab, Memmert, UK) for controlled drying at a temperature of 25 ºC and relative humidity of 40 % for 48 h. Dry powder bed nuclei were then retrieved for the dry powder bed nuclei hardness test which employed the same indentation procedure as described above.

3.5.5. Scanning Electron Microscope on nucleus surface

The sample was firstly stabilized onto a metal stub with carbon tape and coated with a thin gold layer by using a sputter coater (Agar Scientific Ltd, UK). The sample was then placed in the microscope chamber with a vacuum environment. A Scanning Electron Microscope (SEM, Jeol, USA) is based on the interaction between the scanning electron and atoms in the sample. The position of the electron beam would be combined with the signal to generate an image. To examine the surface morphology varied by the formulation, the powder bed compressed by 450 N was used.

3.5.6. Microscopic observation

An optical microscope (Keyence, Digital Microscope VHX-6000 Series, UK) was used to observe the HPC dissolution in the compact powder bed. A lens with a maximum magnification of 500X was used in this thesis.

3.5.7. Nucleus weight and diameter measurement

The nuclei from the compact powder bed was picked out and placed on a 4-digit high accurate balance (UMT 2, Mettler-Toledo, UK) for weight measurement and minimum 10 nuclei was measured for each condition and the average value will be used. The diameter of the nucleus was measured using a calibre. Its maximum diameter was recorded (which may not be the surface diameter).

3.6. Granulation experiment

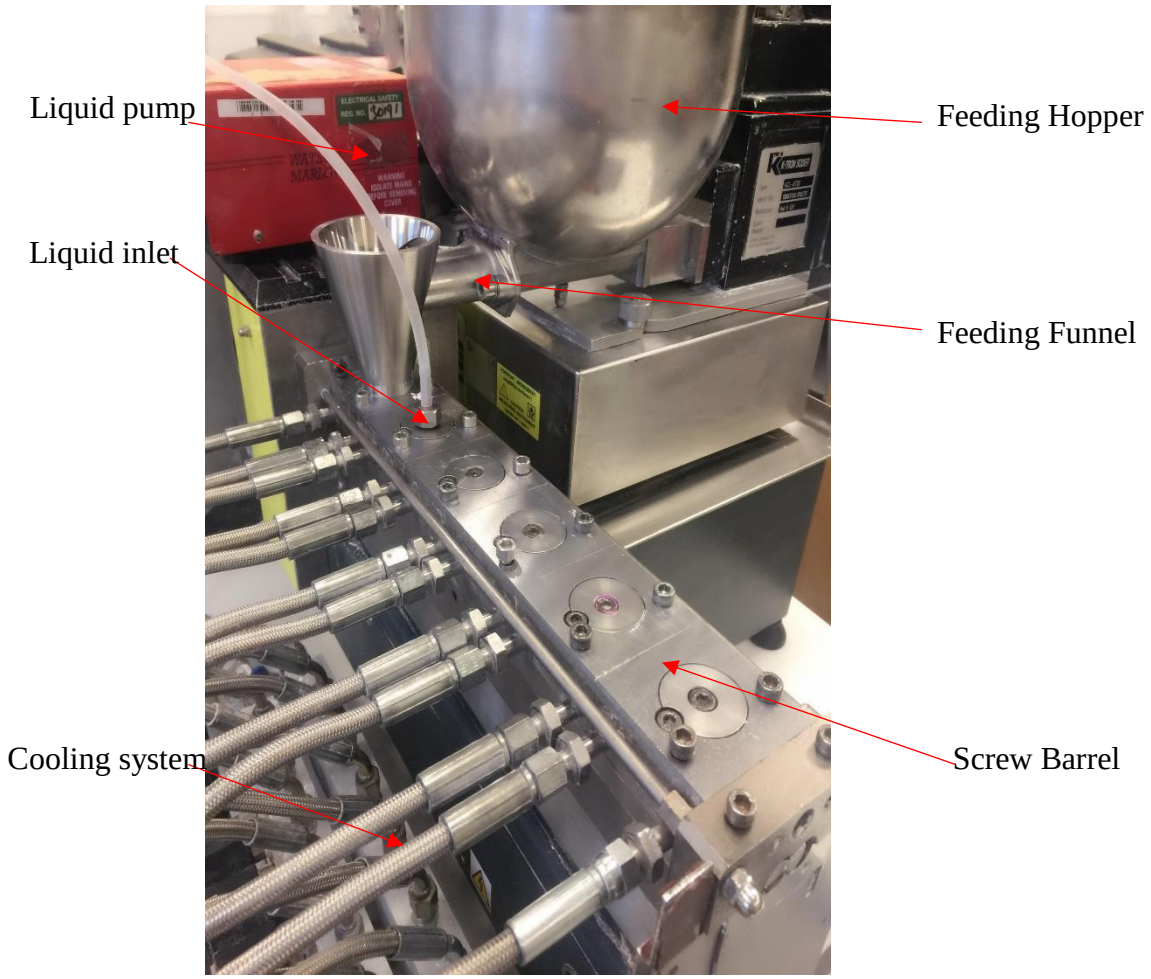
3.6.1. Preparation of granule

The granulation experiments were carried out using a co-rotating twin screw granulator (16 mm Prism Euro Lab TSG, Thermo Fisher Scientific, Karlsruhe, Germany) with a length to diameter ratio of 25:1 (shown in

Figure 3-6). The barrel length is about 40 cm and the diameter is about 16 mm. As a lab-scaled equipment, the twin screw granulator could achieve the maximum screw speed at 1000 rpm and the maximum torque at 12 Nm. Powder is fed by using a gravimetric, loss-in-weight twin screw feeder (K-PH-CL-24-KT20, K-Tron Soder, Niederlenz, Switzerland) and a maximum powder feed rate is 25 kg/h. Liquid binder was pumped into the granulator using a peristaltic pump (101U, Watson Marlow, Cornwall, UK). In most

cases, the granule was produced with a controlled temperature of 25 ºC. To study the effect of temperature, three temperatures of 25, 40, 60 ºC were varied.

Figure 3-6. Twin screw granulator used in experiment.



The screw configurations used in the experiment is shown in Figure 3-7. To produce low shear stress, the screw configurations of Set 1 was applied with conveying elements only. To exert intensive stress and provide sufficient mixing, Set 2 was used with two kneading zones and the angle between kneading elements was 60 º.

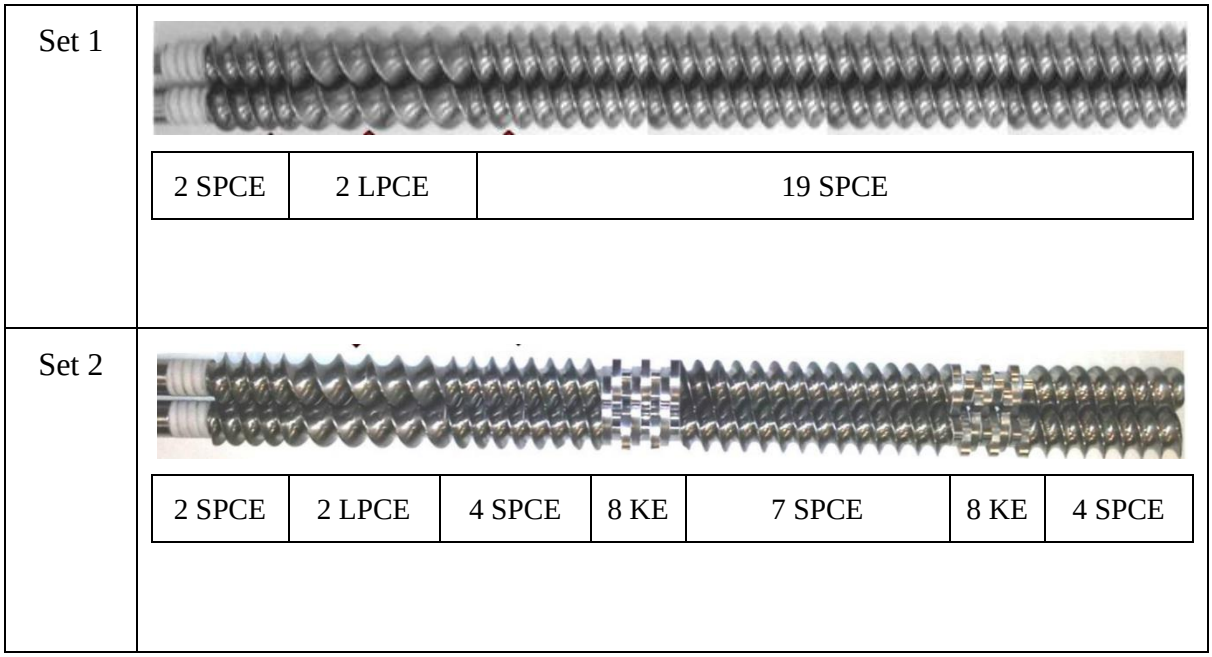


Figure 3-7. Screw configurations for experiment (SPCE: short pitch conveying element; LPCE: long pitch conveying element; KE: kneading element).

3.6.2. Residence time measurement

Residence time indicates the time required for the material to be granulated in the granulator. In this thesis, the high speed camera introduced was placed at the end of the twin screw granulator. A light source was used to provide light. 10 mg of red dye (Ebest Rhodamine B, European OGD Ltd, UK) was added at the powder feeding port. Simultaneously, the camera started to capture the flow of granules coming out from the outlet, until the coloured material appeared. Images were analysed and the time from the dye was added till when colour material was appeared was recorded as the residence time. in this experiment, a framerate of 100 FPS was used.

3.6.3. Granule drying

To minimize the reagglomeration and caking during drying process, the wet granule was spread out into a thin layer in a tray when collecting. Granules were then dried in an

environmental chamber (Camlab, Memmert, UK) with a temperature of 25 ºC and relatively humidity of 40 % for 48 hours.

3.6.4. Granule size measurement

The granules size was measured using Camsizer (Retsch Technology, Germany). The Camsizer utilizes two cameras to capture images of granules in the measurement zone. The basic camera measure the large granule and the zoom camera captures the small granules. Images from these two cameras were combined to provide granule size details. The sample of dried granule was poured into the hopper at the beginning of a vibratory feeder. To evaluate the population of granule in each class range, a mean granule size was used according to:

$$\boldsymbol{d_{4,3}} = \frac{\sum_1^i \boldsymbol{n_i d_i^4}}{\sum_1^i \boldsymbol{n_i d_i^3}} \qquad (3\text{-}5)$$

where n_i is the number/volume percentage of particles of the *i*th size class; d_i is the mean granule size of the *i*th size class

In addition, based on the data of size distribution, software will automatically provide the span of distribution, which will be used to evaluate the granule size distribution in this thesis.

$$\text{Span of distribution} = \frac{d_{90} - d_{10}}{d_{50}} \qquad (3\text{-}6)$$

where d_{10}, d_{50} and d_{90} represents a granule size at which 10%, 50% and 90% of sample's size is smaller than this value, respectively. The average accumulative distribution curves for each chapter are shown in Appendix D and E.

3.6.5. Granule strength measurement

Sieving was used to obtain the granule for strength measurement. Granule with a size in range of 180- 710 μm in granulation experiment was sieved out. The chosen size range has been generally considered as the optimum size range for solid oral dosage forms for pharmaceutical solid oral dosage manufacturing (Hansson and Lindner-Olsson, 2004, John and Charles, 2002, Šantl et al., 2012, Ai et al., 2016). The sieve shaker (Retsch Technology, Germany) was used for 5 min with a magnitude of 1.5.

The granule strength was determined by the confined compression experiments by using Zwick Roell Z0.5 with a 500 N loading cell. A die with diameter and depth of 10 mm and a punch with a diameter of about 9.95 mm was used. Before the test, granules was weighted. After the granule poured into the die, a maximum compression force of 450 N and a compression speed of 10 mm/min were used. The measurement would stop when the sensor on the loading cell detect the maximum force and the displacement was recorded for further analysis. After each test, the die was cleaned to avoid the effect of friction on the reproducibility. The force and displacement data were recorded for strength calculation. For each condition, at least 10 times was repeated.

To obtain the granule strength, the natural strain was calculated using the following equation (Adams et al., 1994):

$$\boldsymbol{\varepsilon_n = ln\left(\frac{h_o}{h_o - \delta}\right)} \qquad (3\text{-}7)$$

where ε_n is the natural strain of material, h_o is the initial bed height, δ is the punch displacement. Then the granule strength could be obtained using:

$$\ln P = \ln\left(\frac{\tau}{\alpha}\right) + \alpha\varepsilon_n + \ln(1 - e^{-\alpha\varepsilon_n}) \qquad (3\text{-}8)$$

where P is the applied pressure, τ is the average agglomerate strength, α is a constant related to the friction. τ and α were determined by non-linear regression fit of the equation **(3-8)** to $ln\ P$ versus ε using Sigmaplot 13.0 (Systat Software Inc.). The granule strength could be obtained by fitting the force and displacement from experiments into the equation above.

3.6.6. Computerized tomography imaging

The scanning was done by X-ray scanner (µCT 35, SCANCO MEDICAL, Switzerland) for 240 slides within 0.84 mm in thickness (the minimum interval distance between each scanning slice is 0.35mm). Granule within a size range of 180- 710 µm was selected and positioned between the x-ray source and detector.

Chapter 4. Single drop study on the compact powder bed

4.1. Introduction

In this chapter, the small-scaled powder and liquid interactions have been studied to develop a miniaturized approach to estimate the optimal amount of liquid required to produce granules with desired particle size distribution.

Single drop study is an simple method to reveal the liquid and powder interaction behaviour and to help the granulation mechanism for wet granulation process, in order to improve the granule properties, including yields, granule strength and so on (Charles-Williams et al., 2011, Emady et al., 2011, Hapgood et al., 2002, Reis et al., 2004). However, most of the traditional single drop studies are based on loose powder bed, which is applicable for high shear mixer and fluidized bed due to their large free space in the granulator. Although Charles-Williams et al. studied the single drop behaviour on the compact powder bed, their study was still based on the high shear mixer and consequently the compression stress applied was incapable to mimic the liquid penetration in the twin screw granulator.

In twin screw process, the limited free space, relatively high load and the use of kneading elements makes higher proportion of stress exerted directly to the material (Dhenge et al., 2012b). Therefore, material in the twin screw granulator would be

exposed on different mechanical stress and would have different effect on granule properties comparing with high shear mixer. In this case, the stress should be considered as a key factor in the single drop study and the compact powder bed would be the preference in the single drop study.

In this chapter, firstly a series of single drop studies were carried out using the compact powder bed. An attempt was made to relate the compression stress to produce the compact powder bed to the stress exerting to the material in the twin screw barrel (Li et al., 2014a, Ai et al., 2016). Therefore, liquid behaviour in the powder bed would be related to the actual situation of the twin screw barrel. In this study, HPC was used as the binder and added in liquid and solid forms, respectively. The effect of binder properties and compression stress on nucleus (the wetted powder) formulation and properties were studied, which provides a better understanding regarding the influencing factors on granule properties in twin screw granulation process under different binder delivery methods.

4.2. Materials and method

4.2.1. Materials

α-lactose monohydrate and microcrystalline cellulose were used as the experimental materials. Hydroxypropyl cellulose was used as the binding excipient. The experiment was carried out by preparing the binding excipient in solid and liquid form (with different liquid viscosities), in order to study the binder dispersion mechanism separately. The preparation of formulations has been mentioned in Section 3.2 and 3.3.

4.2.2. Preparation for single drop study

Single drop study will be carried out in this chapter. The formulation mentioned was used to prepare the compact powder bed. To carry out the single drop study, the droplet behaviour penetration time, maximum contact angle and spreading was studied using a high speed camera (Photron, Fastcam, 100 K, USA) with a frame rate of 1000 fps. The preparation of the compact powder bed and the method about liquid and nucleus characterisation has been introduced in detail in Section 3.5. For each condition, at least 10 repeats were done.

4.3. Result and discussion

4.3.1. Solid binder delivery

Solid binder delivery refers that the HPC was added in solid form by premixing with the granulation powder before granulation and water is used as the granulation liquid (binder).

4.3.1.1. Penetration time

In twin screw granulation, the material will be exposed to a range of stress and consequently affect the granule properties e.g. porosity. To mimic the stress acting on the material, powder bed was compressed using a similar range of stress and the single drop study based on this compact powder bed was carried out. Table 4-1 lists the single drop penetration time on the compact powder bed in different formulations and compression stresses. Penetration time can be regarded as an indicator of liquid-powder interactions.

Firstly, as the compression increases, penetration time becomes shorter when lactose was used. It is because that the surface of the powder bed becomes smoother, resulting in greater spreading of the fluid, allowing the liquid to penetrate into a larger wet surface. Penetration time indicates the wettability of the powder bed, a more intensive stress leads to more powder being wetted. It could be inferred that in twin screw granulation, a higher mechanical stress (e.g. kneading elements) could positively contribute to the wetting of material. In terms of MCC, unclear effect from compression stress could be observed.

Secondly, slower penetration time for lactose based compact powder bed could be observed comparing with that of MCC. It is because although MCC is insoluble, its porous structure allows more water existing in the sub microscopic pores, cracks and crevices between fibrils of MCC particles (Luukkonen et al., 2001). In addition, its porous structure could also provide more routines for liquid to go through. Therefore, a faster penetration could be seen when MCC is used.

Table 4-1. Liquid penetration time for different formulations under a range of compression stress (solid binder delivery)

Powder	Liquid	Penetration time (s)			
		142 kPa	283 kPa	425 kPa	637 kPa
Lactose	Water	0.149±0.010	0.110±0.010	0.067±0.013	0.040±0.027
Lactose+2% HPC	Water	0.160±0.020	0.117±0.015	0.088±0.015	0.057±0.013
Lactose+4% HPC	Water	0.167±0.005	0.122±0.004	0.096±0.016	0.065±0.019
MCC	Water	0.023±0.001	0.022±0.002	0.021±0.001	0.020±0.001
MCC+2% HPC	Water	0.024±0.001	0.024±0.001	0.023±0.000	0.023±0.001
MCC+4% HPC	Water	0.025±0.001	0.025±0.001	0.023±0.002	0.022±0.001

Apart from that, it could be seen that the addition of HPC particles could delay the penetration for both lactose and MCC; lactose is more sensitive to the addition of HPC

particles than that of MCC. One possible reason is the particle size of HPC is much larger than lactose and MCC, which may “prolong” the penetration distance and delay the time.

To figure out the reason behind, the dissolution of HPC particles on a glass layer was carried out. HPC particle dissolution was observed under a microscope camera. Images before and 1 min after the addition of liquid (water) were captured and are presented in Figure 4-1. It is evident from microscopic images that the HPC particles were not dissolved properly. This was most likely caused by the fact that these HPC particles were too large for dissolution in a non-agitated environment. It reveals that the dissolution rate of solid binder can be highly influenced by its size. It can then be expected that the agitation produced by the rotation of the screws in a twin screw granulator has a higher chance of accelerating the dissolution of solid binder mixed with lactose and hence enhances its binding capability.

Further experiment was carried out by using the coloured HPC particles and mixing with lactose and MCC, respectively. From Table 4-2, the HPC particles was much larger than that lactose and MCC, which is, to a certain extent, similar to the size comparison in the real situation. It could be seen that after penetration, the large HPC particles could not dissolve and disperse evenly. This undissolved, large particles would delay the penetration of the liquid. Moreover, water could still be seen on the HPC particle surface.

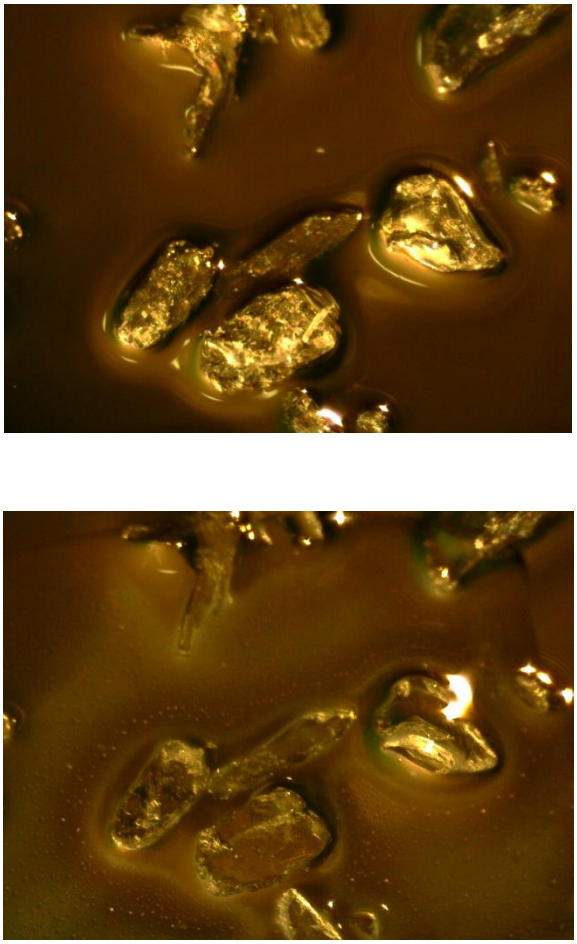
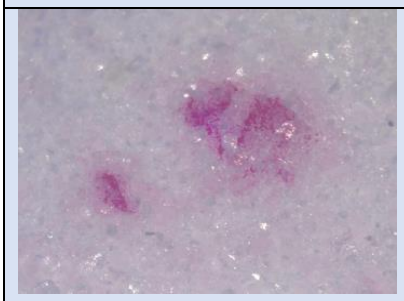
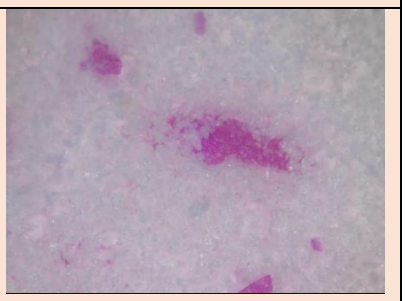
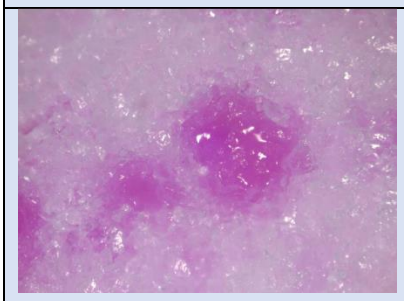
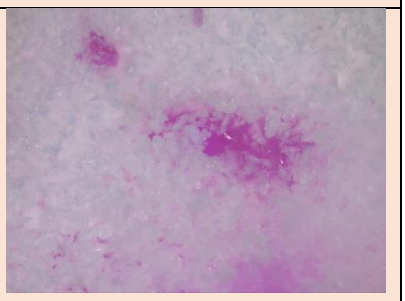


Figure 4-1. Dissolution of HPC particles before (top) and 1 min after (bottom) the addition of distilled water.

It might because the contact between water and HPC particle may dissolve the particle surface and increase the liquid viscosity, making it more difficult to flow.

Table 4-2. HPC during liquid penetration on the compact powder bed.

Lactose	MCC
	
3 min after penetration	3 min after penetration
	

Due to the poor dissolution rate of large HPC particles, the large HPC would not participate in the liquid bridge enhancement properly. As a result, when water penetrates, a longer routine would be required if HPC is added, leading to a delay in penetration (Figure 4-2). Theoretically, water could only reach a relatively shallower level and the nucleus is supposed to be smaller. While MCC was applied, due to its special structure, water could go through the particles, which were less affected by the existence of HPC

particles. Therefore, MCC is less sensitive to the addition of solid HPC particles in terms of penetration time.

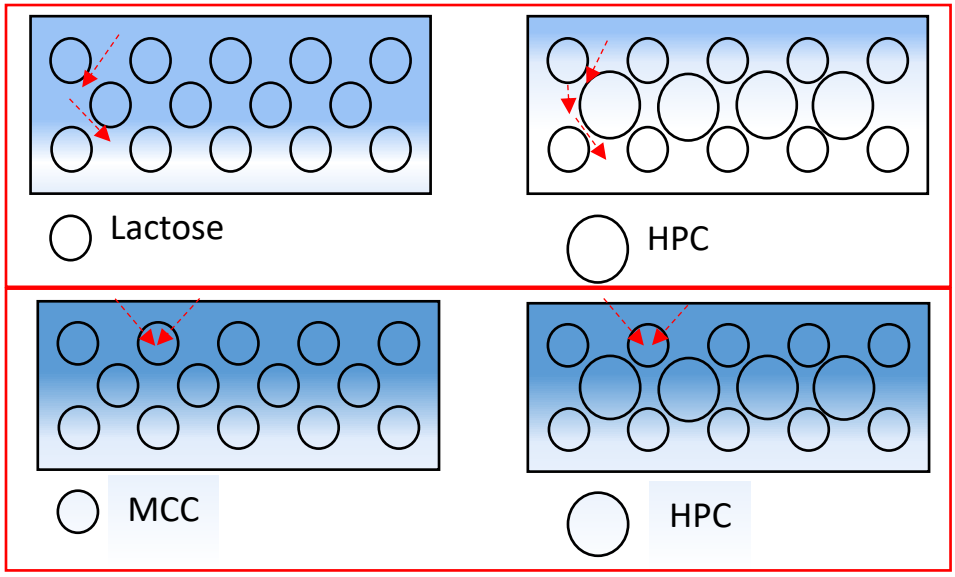


Figure 4-2. Liquid penetration routines

4.3.1.2. Contact angle

Contact angle reflects the relative strength of the liquid, air and solid phase interaction and it a physical property for a constant system. In the study of single drop on the compact powder bed, the maximum apparent contact angle was used, which is the maximum dynamic contact angle after the liquid droplet gets stabilized from dropping. It indicates the wettability of a liquid-powder system on a porous surface. Similarly, a smaller contact angle means a better wettability.

Figure 4-3 and Figure 4-4 show the effect of HPC proportions on the maximum apparent contact angle for lactose and MCC, respectively. In Figure 4-3 the addition of HPC could increase the contact angle, causing a reduction in the wettability of materials and an increase in compression stress leads to a reduction in the contact angle and thus an increase in wettability could be caused. These observation is agree with the result of

penetration that an addition of HPC and an increase of compression stress could all leads to a decrease in penetration time.

However, in Figure 4-4 addition of HPC and the variation of compression stress makes little differences when MCC was used. As was discussed in the last section, it may be because MCC is “water-consuming” material and could hold water into its structure, making HPC particles have fewer chances to interact with water. Although a slight decrease in the mean contact angle could be checked, the error bar produced was too large to provide a clear correlation.

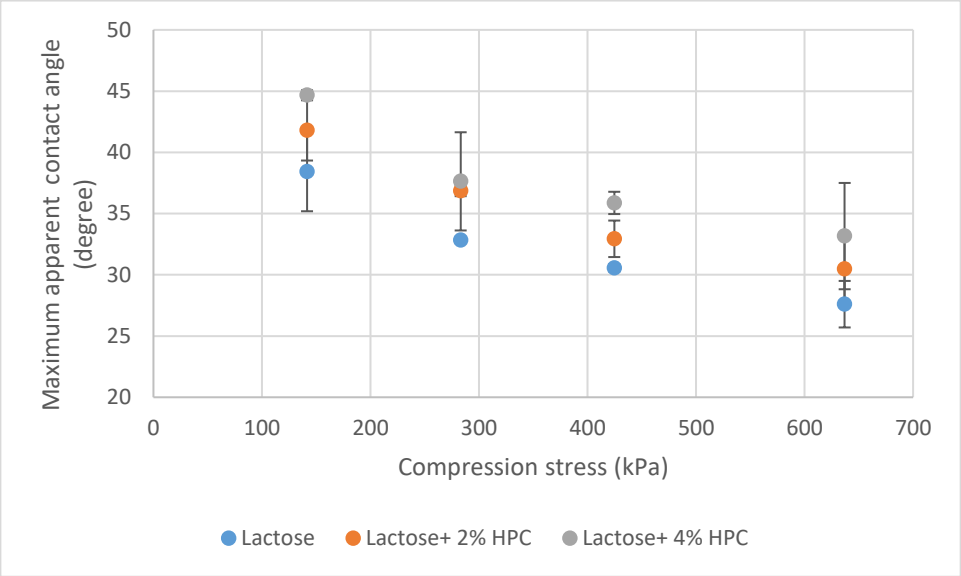


Figure 4-3. Maximum apparent contact angle on lactose based compact powder bed with different proportions of solid HPC binder.

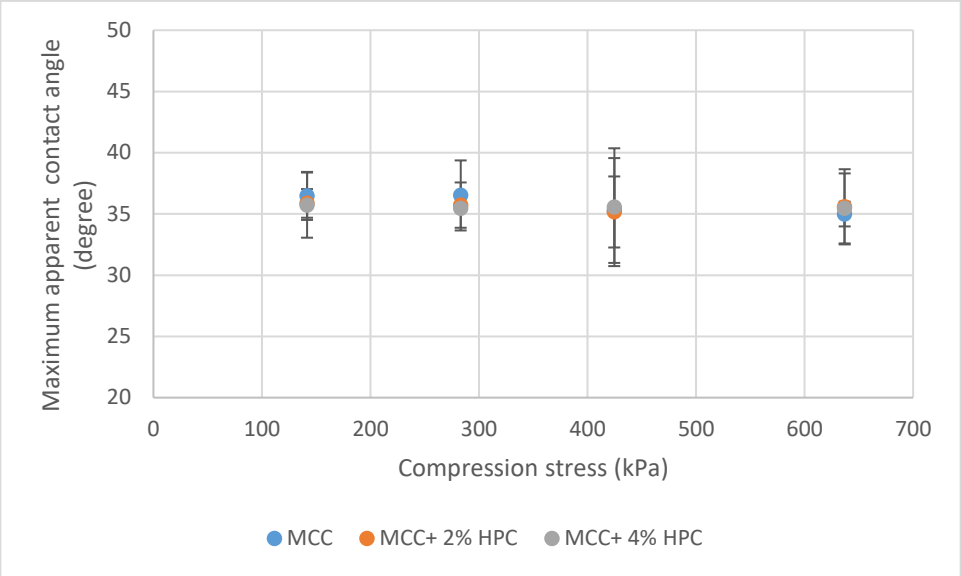


Figure 4-4. Maximum apparent contact angle on MCC based compact powder bed with different proportions of solid HPC binder.

4.3.1.3. Maximum spreading diameter

Maximum spreading diameter refers to the maximum diameter that a single drop could achieve during the penetration process on a compact powder bed. It represents the maximum wetting area on the powder bed surface.

Figure 4-6 shows the maximum spreading on the compact powder bed made of lactose and HPC (0, 2 & 4%). The addition of HPC increases the liquid spreading. A longer time that liquid remained on the surface of the powder bed, a larger spreading it could be achieved (Charles-Williams et al., 2011). Therefore, due to the undissolved HPC delay the penetration (Table 4-1), a larger liquid spreading could be seen. It is in agreement with the result of penetration time shown in that a higher amount of HPC could delay the liquid penetration. Similar effect was also occurred on the MCC based compact powder bed shown in Figure 4-7.

In addition, from both Figure 4-6 and Figure 4-5 as the compression stress increases, liquid spreads in large extents. It is probably because a higher compression would reduce the powder bed porosity (Table 3-4) and consequently smoothen the surface (Sakai and Nakamura, 2005). A large spreading means more wetting area and consequently liquid would have more routines for penetration, which supports the result that a higher compression stress leads to a faster penetration in Table 4-1.

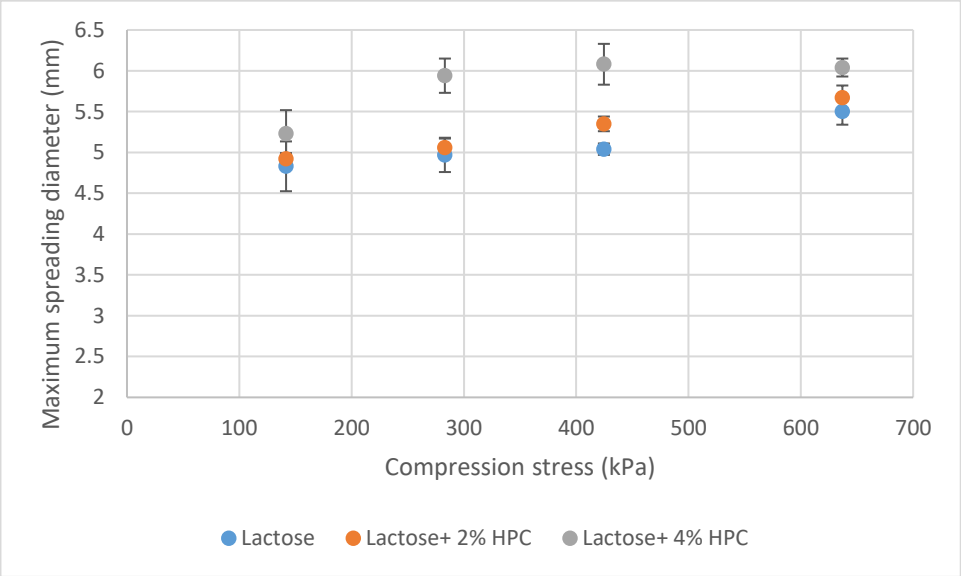


Figure 4-6. Maximum spreading diameter of lactose powder beds (0%, 2%, 4% HPC in solid form) at varying compression stresses.

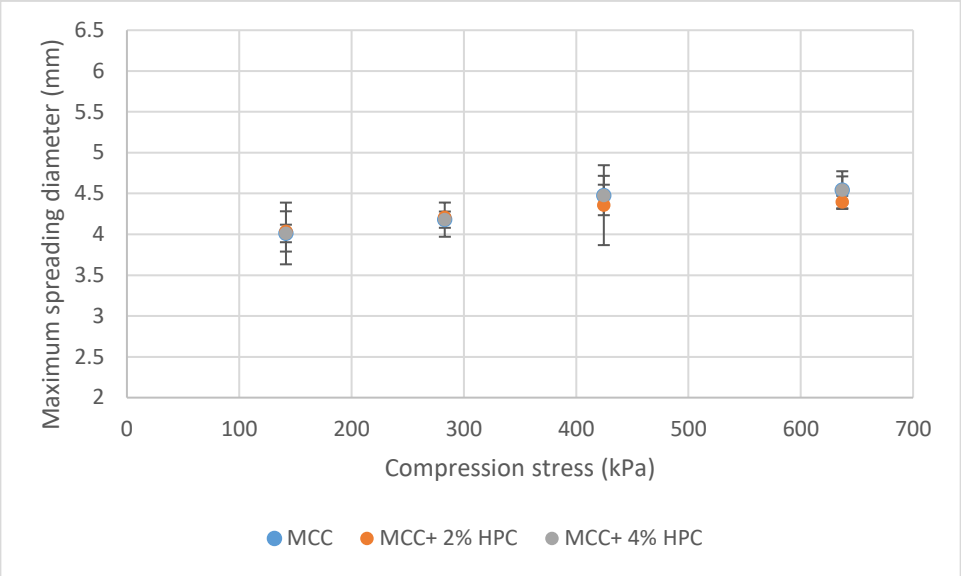


Figure 4-7. Maximum spreading diameter of MCC powder beds (0%, 2%, 4% HPC in solid form) at varying compression stresses.

4.3.1.4. Nucleus diameter

The dry nucleus was taken for the diameter measurement using a calliper. Its diameter represent the maximum liquid migration in the powder bed. Figure 4-8 shows the photo of the typical nuclei using MCC and lactose, respectively. It could be seen using a constant amount of liquid, the nucleus of lactose is much larger than that of MCC.

Figure 4-9 shows the maximum diameter of the nucleus; the use of HPC reduced the diameter of the nuclei, which indicates that the HPC delays the liquid distribution in the powder bed. It agrees with the statement mentioned in the liquid penetration section that the use of solid HPC particles could delay the penetration.

Figure 4-8. Typical nuclei from the compact powder bed (left: MCC; right: lactose).

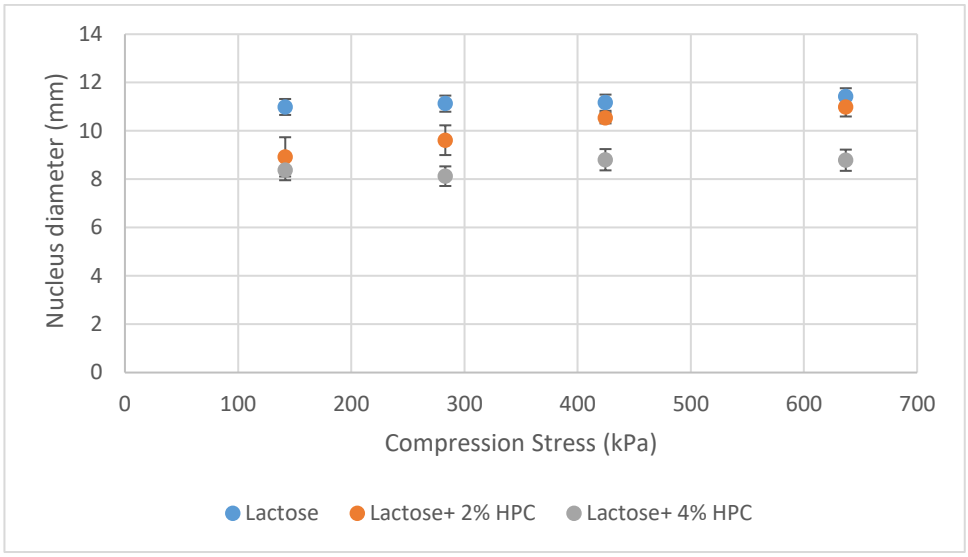


Figure 4-9. Nucleus diameter of lactose powder beds (0%, 2%, 4% HPC in solid form) at varying compression stresses.

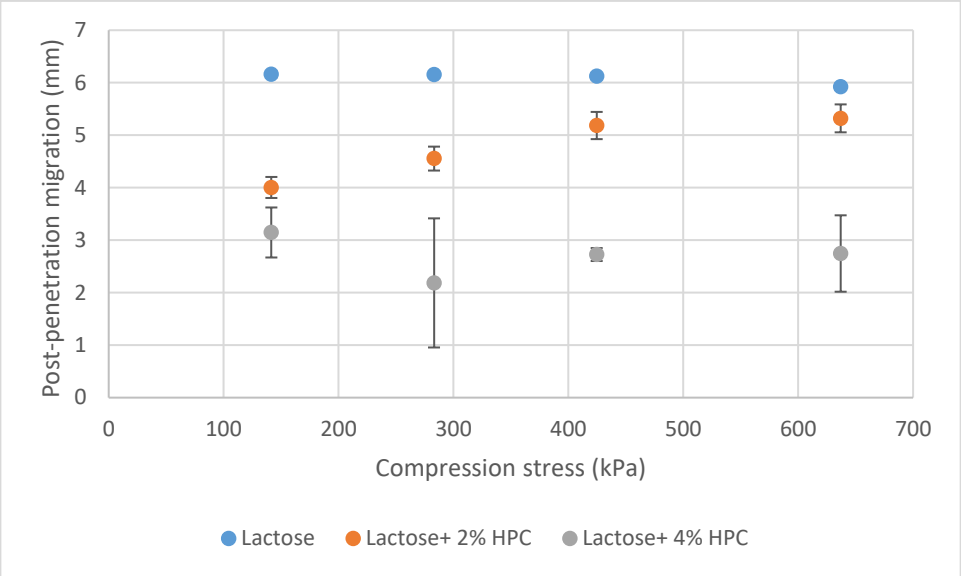


Figure 4-10. Liquid post-penetration migration of lactose powder beds (0%, 2%, 4% HPC in solid form) at varying compression stresses.

When comparing the dry nucleus diameter shown in Figure 4-9 to the liquid maximum spreading shown in Figure 4-6, clear differences could be obtained. To quantify the difference, a parameter named “post-penetration liquid migration” was initiated, which represents the difference from the nucleus diameter to the liquid maximum spreading diameter and shown in Figure 4-10.

It shows that the post-penetration liquid migration occurred mostly on the compact powder bed without HPC. It might due to the similar reason that the undissolved HPC particles could prolong the routine for liquid horizontal distribution and delay the liquid distribution.

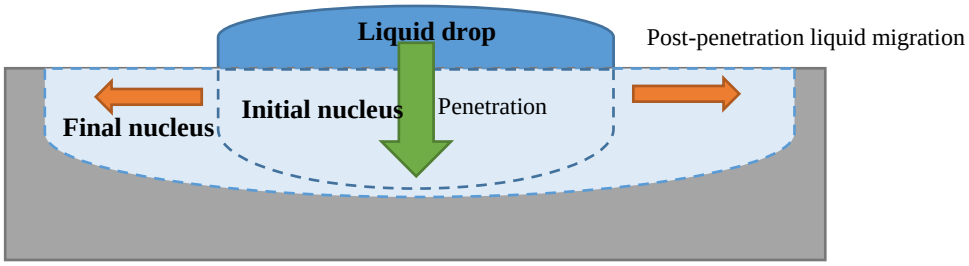


Figure 4-11. Schematic of post-penetration liquid migration.

The post-penetration liquid migration is highly possible to be continued after the liquid penetration (Figure 4-11). When liquid finish penetration, the liquid in the initial nucleus would be continue in distribution due to the capillary pressure, which makes the nucleus produced larger than its original size. It indicates that the nucleus size should not be simply determined by the droplet size and need to be considered for the nucleation regime map from Hapgood et al. (2003).

Concerning about MCC, the effect of formulation on nucleus diameter could be obtained and shown in Figure 4-12. Comparing with that of lactose shown in Figure 4-9, no obvious difference could be obtained, indicating that the variation of HPC proportions represent minor influences on the nucleus diameter, which dues to the special structure that could “swallow” water. Figure 4-13 shows the differences between liquid maximum spreading diameter and nucleus diameter. Minor effect could be seen from the addition of HPC.

It can be seen from the comparison between lactose and MCC that the distribution of liquid in the lactose powder bed is easier. This may be due to the fact that the MCC particle can trap the liquid through its own structure, thus limiting the fluidity of the liquid.

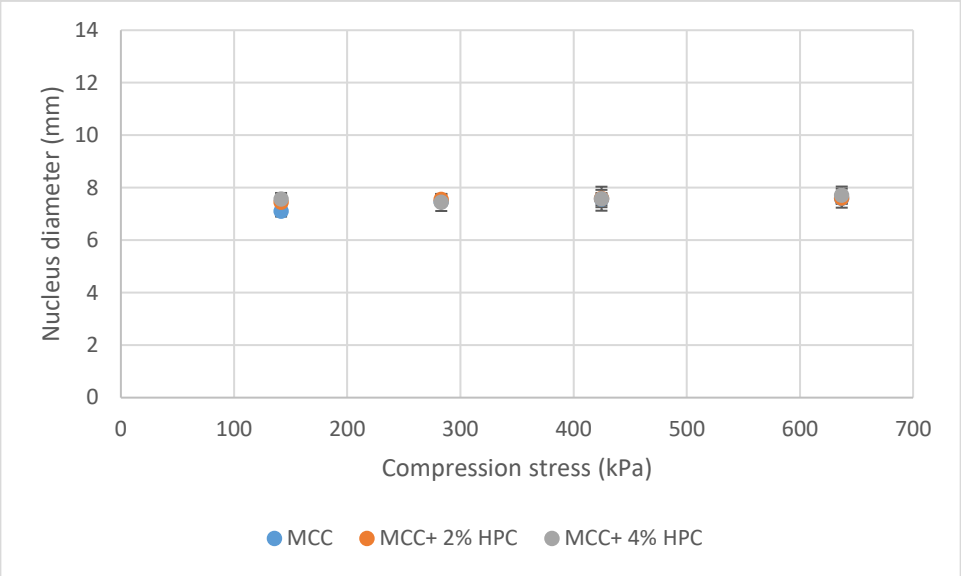


Figure 4-12. Nucleus diameter of MCC powder beds (0%, 2%, 4% HPC in solid form) at varying compression stresses.

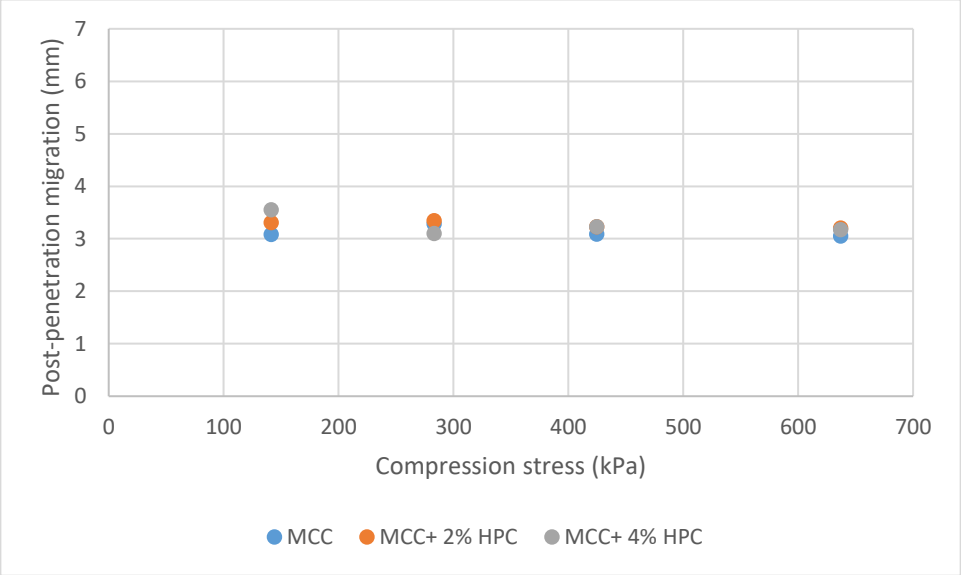


Figure 4-13. Liquid post-penetration migration of MCC powder beds (0%, 2%, 4% HPC in solid form) at varying compression stresses.

4.3.2. Liquid binder delivery

4.3.2.1. Penetration time

Apart from the previous experiments which HPC was premixed in advanced, the HPC was also prepared as binder solution to investigate the effect of HPC concentration in granulation liquid on nucleus formation.

Table 4-3 lists the penetration time of water and the liquid droplet containing different concentrations of HPC (2 & 4%) on the compact powder bed. Comparing with the use of solid HPC shown in Table 4-1, the penetration time was largely delayed if HPC solution was used, indicating a worse liquid distribution and mixing. It is probably because the HPC solution is more viscous and more difficult in flow and distribute in the powder bed. In order to further support the result of Table 4-3, the maximum apparent contact angle was observed and recorded.

In addition, a similar tendency could be observed that as the compression stress increases, the penetration process could be accelerated. From the previous study, it might be caused by an increase in liquid spreading. Therefore, the liquid maximum spreading experiment was also carried out and shown after.

Table 4-3. Liquid penetration time for different formulations under a range of compression stress (liquid binder delivery).

Powder	Liquid	Penetration time (s)			
		142 kPa	283 kPa	425 kPa	637 kPa
Lactose	Water	0.149±0.010	0.110±0.010	0.067±0.013	0.040±0.027
Lactose	2.5 % HPC solution	1.944±0.011	1.866±0.010	1.714±0.008	1.607±0.010
Lactose	5% HPC solution	5.860±0.040	5.768±0.067	5.624±0.009	5.580±0.106
MCC	Water	0.023±0.001	0.022±0.002	0.021±0.001	0.020±0.001
MCC	2.5 % HPC solution	0.248±0.009	0.242±0.001	0.239±0.010	0.239±0.006
MCC	5% HPC solution	1.020±0.002	0.970±0.009	0.968±0.009	0.956±0.005

4.3.2.2. Contact angle

Figure 4-14 and Figure 4-15 shows the maximum apparent contact angle under the influence of binder solution concentrations and compression stresses. An increase in HPC concentration results in an increase in the maximum apparent contact angle, which

indicates a decrease in liquid flowability and distribution capability in the powder bed. Consequently, a slower penetration and wetting would occur if a high viscous liquid is used (Table 4-3).

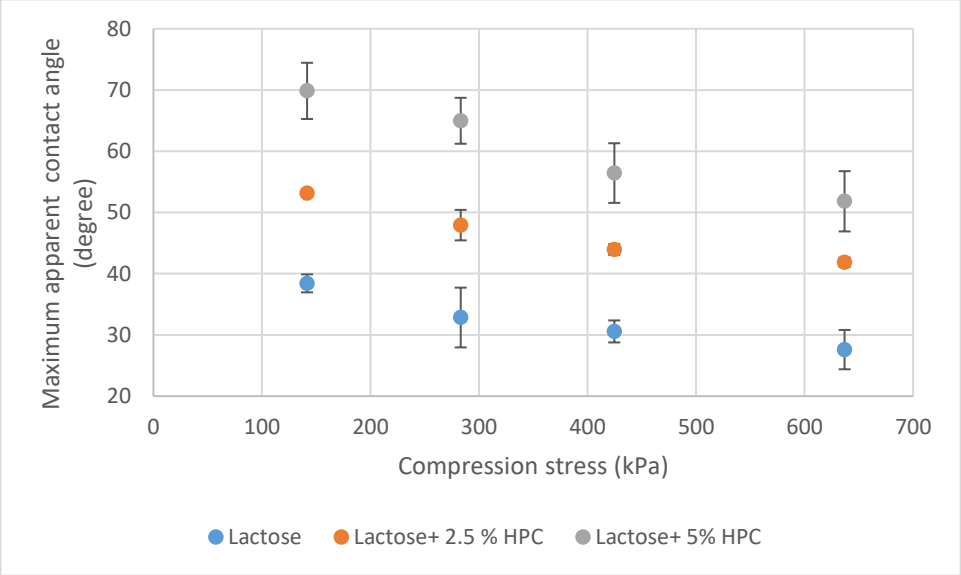


Figure 4-14. Maximum apparent contact angle on lactose based compact powder bed with liquid containing different concentrations of HPC.

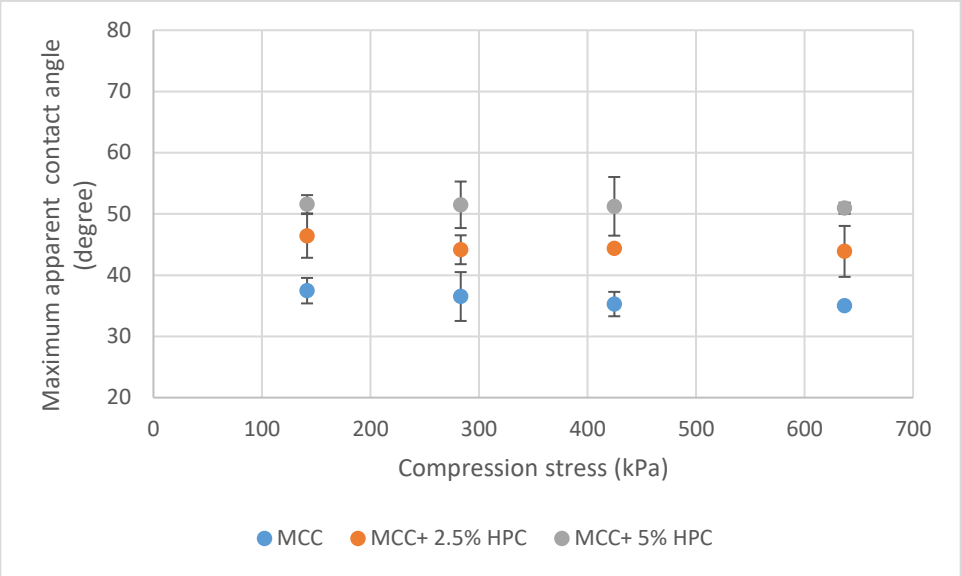


Figure 4-15. Maximum apparent contact angle on MCC based compact powder bed with liquid containing different concentrations of HPC.

Furthermore, an increase in compression stress leads to a decrease in contact angle for both lactose and MCC based powder bed. As was mentioned previously, it may be due to a decrease in the porosity of the powder bed resulted from a higher compression (Le et al., 2011).

Comparing with the use of solid binder delivery method shown in Figure 4-3 and Figure 4-4, a clearer difference could be seen if HPC solution was used. It indicates that the binder concentration in liquid delivery method could significantly affect the liquid distribution in the powder bed; in contrast, the variation of solid binder content in solid binder delivery method has less effects. Therefore, in the premise that the liquid dispersion degree is similar, there is more operational space in varying the amount of binder if solid binder delivery method is used.

4.3.2.3. Maximum spreading diameter

Figure 4-16 and Figure 4-17 shows the variations of maximum spreading diameter affected by the compression stress and the concentration of HPC in the liquid solution. Due to the increase of liquid viscosity, an increase in HPC concentration leads to a decrease in liquid maximum spreading diameter. In addition, as the compression stress increases, the spreading of liquid increases. As was mentioned, it is because a higher compression could reduce the porosity and smoothen the surface, making the liquid spreading more easily.

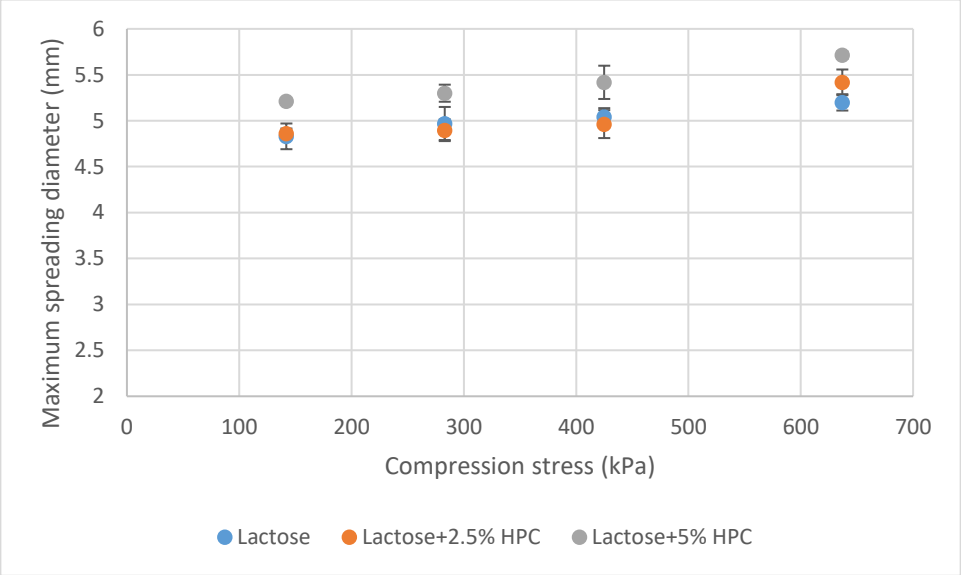


Figure 4-16. Maximum spreading diameter of lactose powder beds (0%, 2.5%, 5% HPC in liquid form) at varying compression stresses.

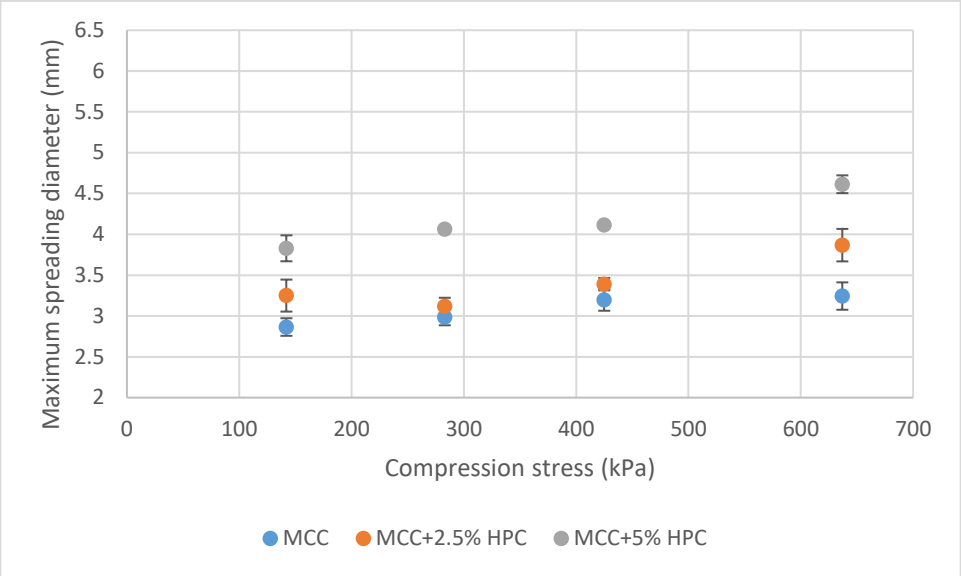


Figure 4-17. Maximum spreading diameter of MCC powder beds (0%, 2.5%, 5% HPC in liquid form) at varying compression stresses.

4.3.2.4. Nucleus diameter

Figure 4-18 shows the variation of nucleus diameter affected by varying the compression stress and HPC concentration in a solution. It could be seen that the use of HPC solution significantly reduces the nucleus diameter, indicating a weaker binder distribution capability comparing with if water is used.

Comparing with the use of solid binder shown in Figure 4-9, the use of HPC solution causes the nucleus diameter to decrease greatly, which indicates that the liquid binder delivery method has a negative effect on liquid distribution due to the increase of liquid viscosity.

When comparing the nucleus diameter with the liquid maximum spreading, similar statement could also be obtained in Figure 4-19. It could be seen the post-penetration

migration is less obvious if HPC solution is used, which shows that the high viscosity in the liquid binder solution could significantly delay the liquid distribution.

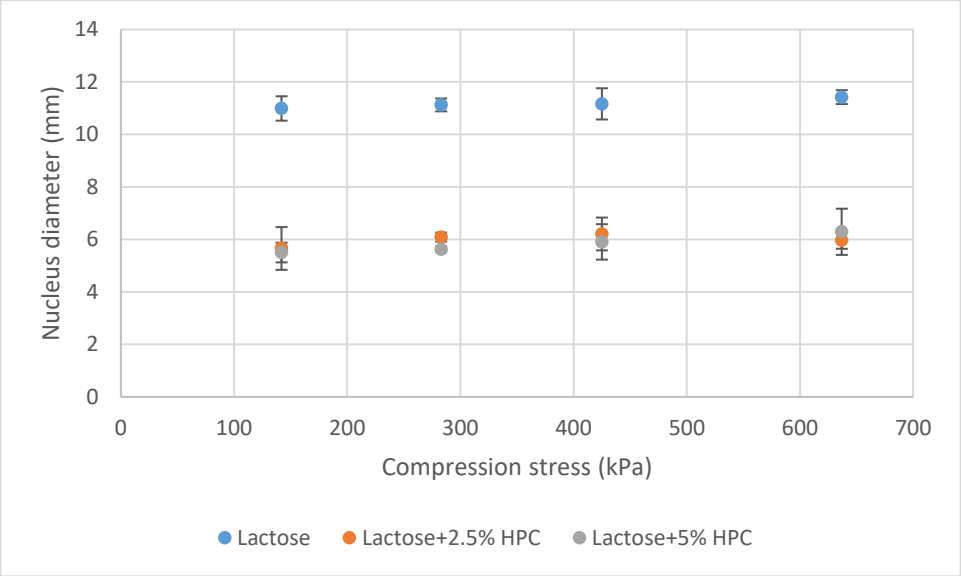


Figure 4-18. Nucleus diameter of lactose powder beds (0%, 2.5%, 5% HPC in liquid form) at varying compression stresses.

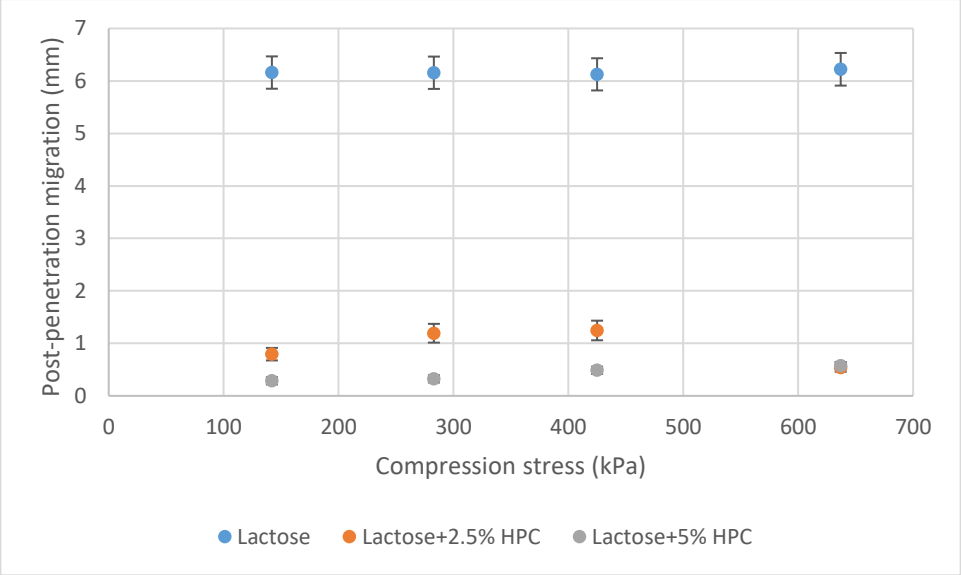


Figure 4-19. Liquid post-penetration migration of lactose powder beds (0%, 2.5%, 5% HPC in liquid form) at varying compression stresses.

The experiment based on MCC compact powder bed was also carried out then. It could be seen in Figure 4-20 that the nuclei produced using water as liquid are the largest in diameter. It indicates that even though MCC is water-consuming and could swallow liquid inside, the use of HPC solution could still slow down the flowability and dispersion capability of liquid.

Figure 4-21 shows the liquid migration capability after penetration on MCC based compact powder bed. Comparing with the use of HPC binder particle shown in Figure 4-13, the use of HPC binder solution significantly delay the liquid migration in the powder bed, indicating that the use of binder solution is not capable in dispersion within a compact powder bed. It might because the MCC would trap the liquid into its structure and the viscous liquid comparing with water is much more difficult to "escape" and achieve a further distribution.

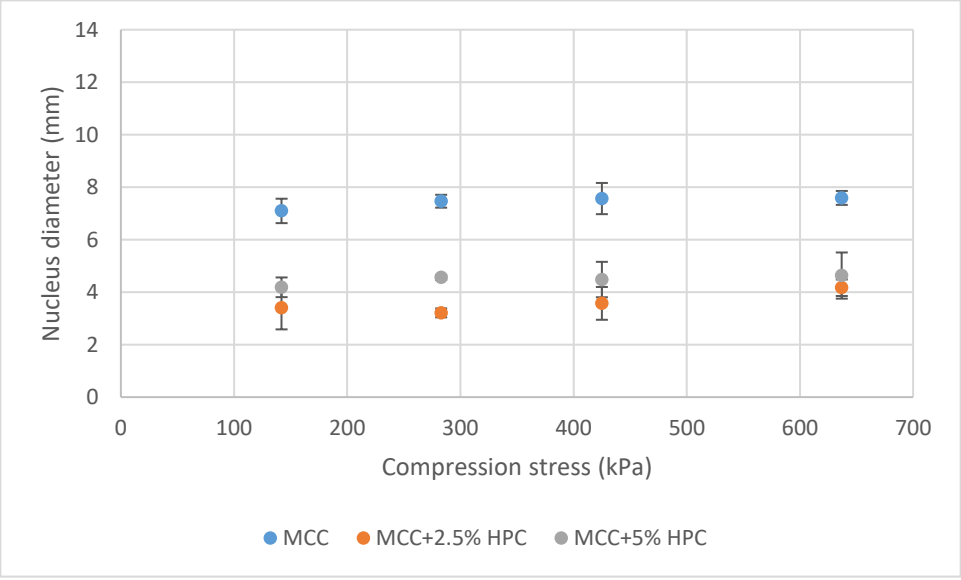


Figure 4-20. Nucleus diameter of MCC powder beds (0%, 2.5%, 5% HPC in liquid form) at varying compression stresses.

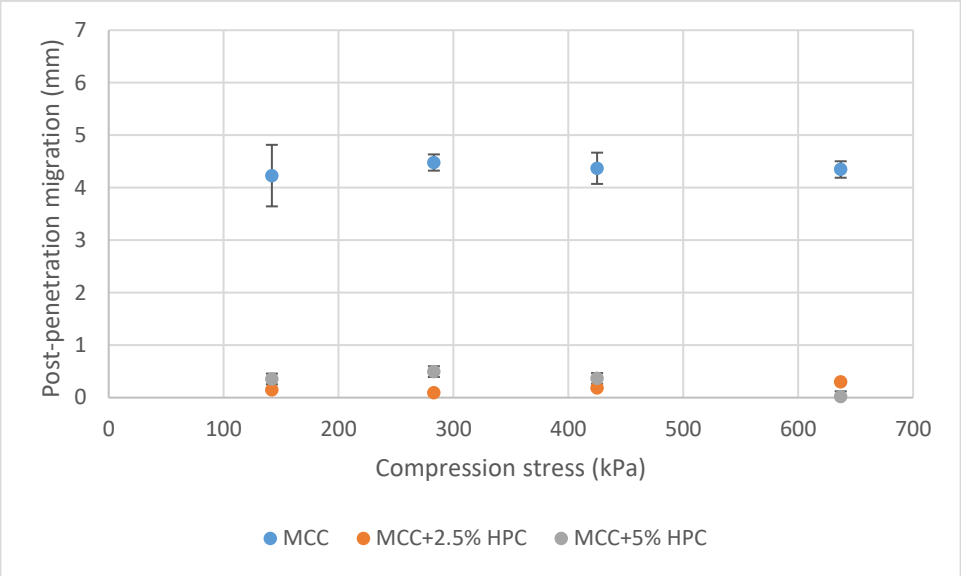


Figure 4-21. Liquid post-penetration migration of MCC powder beds (0%, 2.5%, 5% HPC in liquid form) at varying compression stresses.

Till now, the single drop study on compact powder bed using HPC in different forms were studied systematically. As was mentioned, the use of compact powder bed is to mimic the liquid-powder interaction under stresses in twin screw granulation processes. From the experiments, it could be seen that the reproducibility was quite good and clear tendencies and differences could be obtained between each group of experiment. In terms of the study about penetration time, contact angle, liquid spreading, etc., the experiment was based on a high speed camera which allowed to capture the droplet motion and behaviour clearly and accurately. Owing to the high frame rate the camera could reach, the reproducibility of the study could be guaranteed. In terms of the nucleus dimension study, the maintaining of high reproducibility was mainly resulted from the property of compact powder bed. Specifically, the compressed powder bed has a more homogeneous structure comparing with loose powder bed which is significantly related to how the powder bed prepared. The homogeneous structure made sure that the nucleus produced

are similar in dimensions, which consequently reduce the operating error and guarantee the reproducibility.

4.4. Conclusion

In this chapter, the single drop study was carried out based on the compact powder bed in order to reveal the liquid movement for HPC in both forms (liquid and solid) and materials (lactose and MCC).

A higher compression stress could produce the powder bed with smother surface, which is easier for liquid spreading. Therefore, a higher compression stress leads to a larger spreading and smaller contact angle. As a result, a shorter penetration time could be obtained when high compression stress was applied. In addition, the use of HPC was found to delay the liquid penetration and distribution when lactose was used. For MCC, unclear effect could be obtained.

By comparing with liquid maximum spreading diameter and the actual dry nucleus diameter, clear difference could be seen for all cases, which infers that the liquid would keep migration even after its penetration. It indicates that the size of the nucleus should not be simply determined by the droplet size and its surface spreading. In addition, the use of HPC was found to delay this migration when lactose was used, while the effect of HPC on liquid horizontal migration on MCC based powder bed was unclear.

Chapter 5. A novel approach to predict the optimal liquid/solid ratio for twin screw granulation.

5.1. Introduction

Water amount is of vital importance for wet granulation process. The water amount used in a twin screw granulation process is normally evaluated by the L/S ratio which refers to the mass ratio of liquid and powder (El Hagrasy et al., 2013a, Lee et al., 2013, Dhenge et al., 2012c). A high L/S ratio tends to produce more liquid bridges, which enhances the granule strength and narrows the granule size distribution. However, if the liquid is too much, it may cause the production of lumps. In addition, the liquid would behave like lubricant and reduce the strength of bonds between wet particles.

In pharmaceutical industry, the trial and error is still one of the most commonly used methods to seek out the optimal L/S ratio for twin screw granulation and during this process, high amount of expensive powders and efforts would be wasted (Barrasso et al., 2013). If an approach could be developed to predict the optimal condition rather than try out it through trial and error method, significant wastage of expensive powders from trial and error based product and process optimisation techniques could be saved.

In this chapter, the single drop studied will be used to develop a miniaturized approach to estimate the optimal amount of liquid required to produce granules. The mass ratio

between liquid and the powder it wets, was found to be quite close to the optimal L/S ratio used in the literature. A series granulation experiments were then carried out in order to examine the accuracy of this approach. In the granulation experiment, conveying elements were used only (Set 1 screw configuration, Section 3.6.1.), to provide a relatively milder granulation environment and maintain the properties of nucleus.

5.2. Materials and method

5.2.1. Dry nucleus weight measurement

The dry nucleus from the previous experiment was weighted using a high accurate scale and further details can be obtained in Section 3.5.7. A powder bed based L/S ratio was defined as the mass ratio between the droplet and dry nucleus.

5.2.2. Drop weight measurement

The electronic pipette (details shown in Section 3.5.3) was used to produce the droplet with a constant volume of 0.15 µL. To measure the weight of the droplet, one light (about 0.05g) and plastic container was placed on a high accurate scaled. 10 droplets with constant volume was dropped to this container and the mass shown on the scale was recorded. Then the single drop mass could be obtained by dividing the total mass to the numbers of drops (10). 5 times repeats were done (50 drops in total) and the result is shown in Table 5-1.

Table 5-1. Droplet mass for a constant volume of 15 µL.

Liquid	Water	2.5% HPC solution	5% HPC solution
Density (kg/m^3)	≈1000.0	≈1005.4	≈1010.7
Mass (mg)	16.84±0.03	16.90±0.01	17.01±0.07
Diameter (mm)	1.59	1.59	1.59

5.2.3. L/S ratio on nucleus formation in the compact powder bed

The L/S ratio based on the compact powder bed refers to the mass ratio of single drop and dry nucleus. It has different meaning to the typical L/S ratio in twin screw granulation process.

5.2.4. Preparation of granules

Granules were produced using a twin screw granulator mentioned in Section 3.6.1. To obtain the optimal liquid to solid (L/S) ratio, a series of L/S ratios were used (Table 5-2). Powder feed rate and screw speed were maintained constant at 1 kg/h and 200 rpm, respectively. Temperature was controlled at 25 ºC and Set 1 screw configuration was applied where conveying elements were used only.

Table 5-2. L/S ratio used for granulation experiments.

Formulation	L/S ratio											
Lactose (0, 2, 4% HPC)	0.02	0.04	0.06	0.08	0.10	0.12	0.14	0.16	0.18			
MCC (0, 2, 4% HPC)	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6

5.2.5. Granule size measurement

The granules size was measured using Camsizer (Retsch Technology, Germany). To find out the optimal L/S ratio for granulation, the amount of granule with a size in range of 180- 710 μm in granulation experiment was counted based on the result. The L/S ratio that leads to the production of the most granules (in the chosen range) was regarded as the optimal L/S ratio. The chosen size range has been generally considered as the optimum size range for solid oral dosage forms for pharmaceutical solid oral dosage manufacturing (Hansson and Lindner-Olsson, 2004, John and Charles, 2002, Šantl et al., 2012, Ai et al., 2016, Mangwandi, 2009).

5.3. Result and discussion

5.3.1. Solid binder delivery

Solid binder delivery refers that the HPC particle was premixed with powder materials before granulation and water is used as the granulation liquid.

5.3.1.1. Compact powder bed: nucleus weight

Figure 5-1 illustrates the mass of dry nucleus from various compact beds of lactose containing different proportions of HPC. As can be seen in the Figure 5-1, the change in compressive stress for making compact powder beds had little influence on nuclei weight. In other words, this figure suggested that for the same amount of water, the mass of powder (compressed to different levels) that can be wetted was almost the same.

Concerning about the effect of HPC addition, powder bed made of pure lactose produced the heaviest nuclei. The increase in HPC led to a reduction in the weight of nuclei. This result agrees with the variation of dry nucleus diameter which has been

discussed in the previous chapter that the use of HPC make the liquid less distribute and produces the nucleus with smaller diameter. It might because the HPC particles are relatively larger than lactose and MCC, which may delay the liquid distribution.

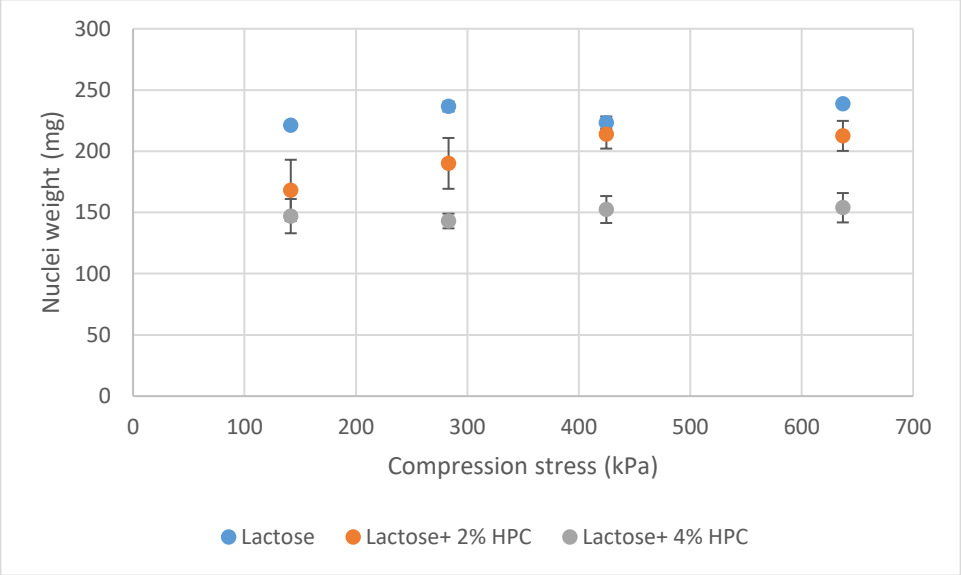


Figure 5-1 Lactose nucleus weight (0%, 2%, 4% HPC solid binder) from compact bed.

Figure 5-2 shows the mass of MCC nuclei obtained from powder beds compressed by different stress and mixed with different concentrations of HPC. It can be seen that the relationship between the weight of nucleus and the proportion of HPC was unclear. This was probably because MCC could keep water into its structure and consequently less affected by the HPC particle in the powder bed. For this reason, the difference among three samples is quite limited.

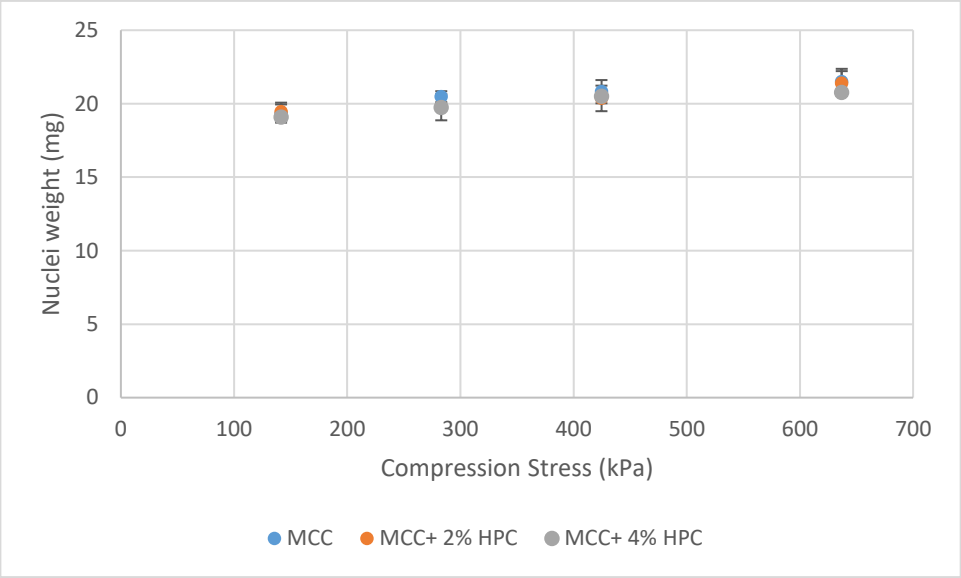


Figure 5-2. MCC nucleus weight (0%, 2%, 4% HPC solid binder) from compact bed.

5.3.1.2. Compact powder bed: L/S ratio in nucleus formation

As the use of powder bed is to mimic the liquid-powder interaction during granulation. Therefore, the mass ratio of droplet and the dry nucleus was obtained and shown in Figure 5-3 and Figure 5-4. It could be found in Table 2-1 (literature review section) that this value is quite close to the value that is used in granulation of lactose presented in literature (Vercruysse et al., 2012a, Kumar et al., 2014, Keleb et al., 2002, Keleb et al., 2004, Vercruysse et al., 2015, Lute et al., 2016). If it is feasible to estimate the optimal L/S ratio by measuring some parameters of powder bed nuclei in the compact powder bed, it could significantly save the cost of establishing granulation conditions for industrial manufacturing by reducing the time of trials and errors. In terms of MCC, limited literatures were obtained.

To examine the feasibility of using the mass ratio of liquid droplet to the mass of dry nucleus, twin screw granulation were carried out.

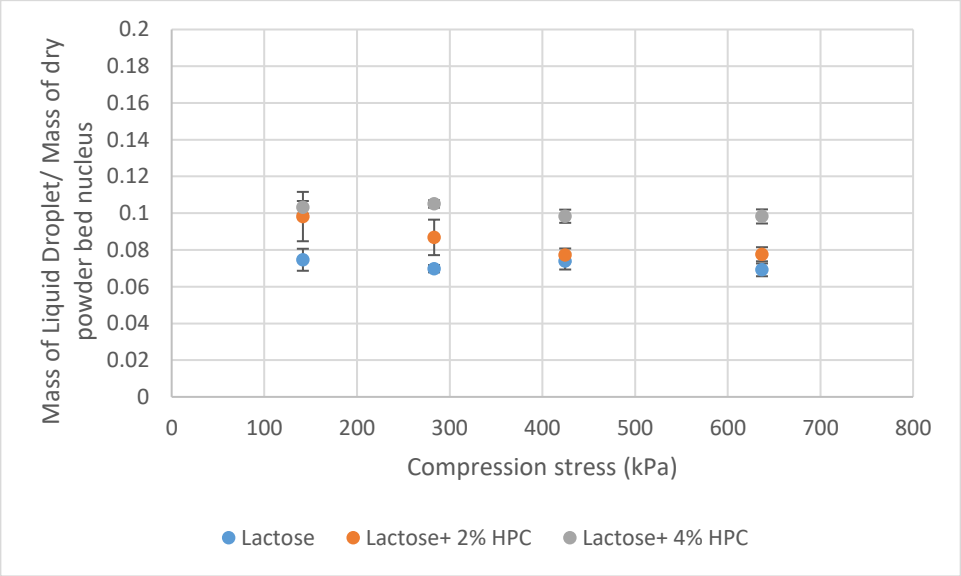


Figure 5-3. Mass ratio of liquid droplet and lactose nucleus from compact bed when solid HPC was used.

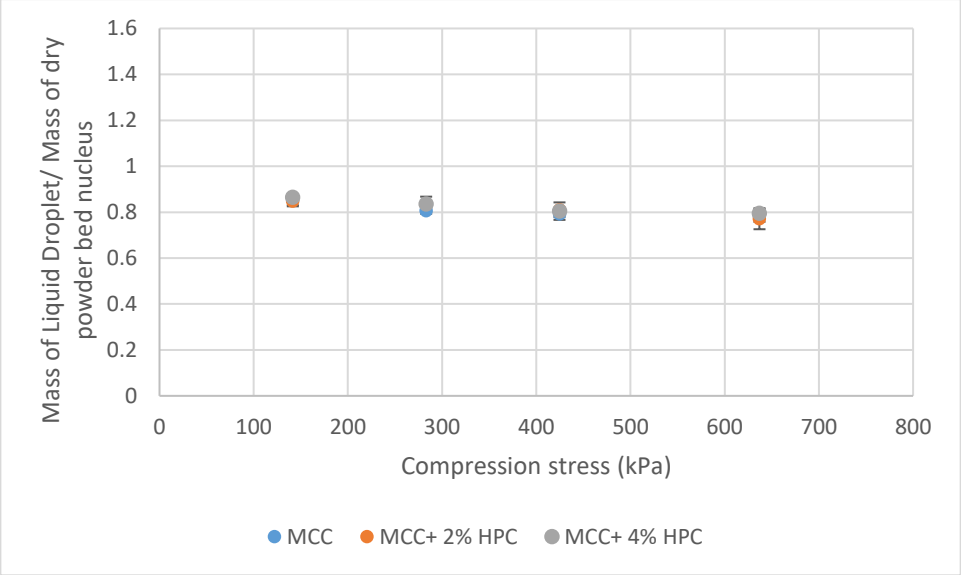


Figure 5-4. Mass ratio of liquid droplet and powder bed nuclei from compact bed when solid HPC was used.

5.3.1.3. Twin screw granulation: optimal L/S ratio using HPC in solid forms

Table 5-3. Optimal L/S ratio for granulation in literature.

Journal	Material	L/S ratio
(Keleb et al., 2002)	α-Lactose monohydrate	0.081
(Li et al., 2014b)	α-Lactose monohydrate	0.08
(Kumar et al., 2014)	α-Lactose monohydrate, PVP (premixed)	0.0962
(Vercruysse et al., 2012a)	α-Lactose monohydrate, PVP	0.099
(Keleb et al., 2004)	α-Lactose monohydrate, hydrochlorothiazide (premixed)	0.093
(Lee et al., 2013)	MCC	~0.9
(Tu et al., 2013)	MCC	~0.95

Choosing the optimal liquid flow rate or L/S is always regarded one of the most important issues for a granulation process, in order to improve the yield and the granule strength. The determination of an optimal L/S ratio is complicated. On one hand, the optimal L/S ratio is not a fixed value for different granulation systems and has to be determined specifically for different granulators, materials and requirements. In this case, trial and error method has to be used, which may lead to a waste of material and labour. On the other hand, for a certain material, the optimal L/S ratio does not change dramatically. As is shown in Table 5-3, although different methods used different screw speed, feed rate, etc., all L/S ratios for α-lactose and MCC are close between different papers.

Generally, the optimal L/S ratio for lactose is about 0.08; when binder was used, the value increased to about 0.1. Although different equipment may applied in different literature, the value was found to be quite close to the optimal L/S ratio obtained from the compact powder bed in Figure 5-3 and Figure 5-4. Whilst, the optimal L/S ratio for MCC is around 1.0 and no result could be obtained when binder was used in the literature.

In the literature, there is no sufficient works covering the optimal L/S ratio in twin screw granulation process. Therefore, a series of granulation experiments were carried out using a twin screw granulator to further examine the feasibility of using small scaled compact powder bed to predict the optimal L/S ratio for twin screw granulation. A size range between 180- 710 μm was set as the target granule size range (Hansson and Lindner-Olsson, 2004, John and Charles, 2002, Šantl et al., 2012, Ai et al., 2016). A series of L/S ratios were applied to find out the L/S ratio which could be used to produce the most of the granules in the target range.

Figure 5-5 shows the yield of granule of lactose with 0- 4% HPC as solid binder in the chosen target range at various L/S ratios. The powder feed rate and screw speed were kept constant at 1 kg/h and 200 rpm, respectively. Since, the yield of granules in the required size range reached the highest value when L/S ratio of 0.07 was used; it was deemed as the optimal L/S ratio for the current granulation process, which was also close to the value in the literature (Keleb et al., 2002, Li et al., 2014b). At this L/S ratio, the twin screw granulator produces the highest proportion of granule within the size range of 180- 710μm. If more liquid was added, the yield will drop, as an increasing amount of lumps would be produced. Furthermore, when 2% and 4% HPC was added, the optimal L/S ratio both changed to 0.09 and 0.10, respectively, which was higher than the case with lactose only.

The value is quite close to the L/S ratio on the powder bed (Figure 5-3) and literature (Kumar et al., 2014, Vercruysse et al., 2012a), which further proves that it was possible to use L/S ratio from powder bed nucleation process to estimate the optimal L/S ratio for granulation.

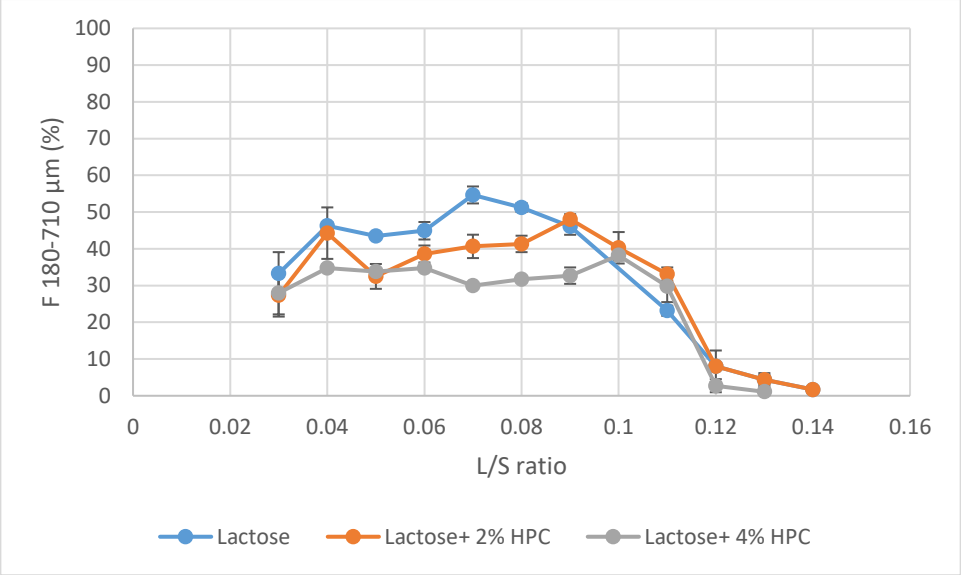


Figure 5-5. The yield of lactose granule at each L/S ratio when solid HPC was used.

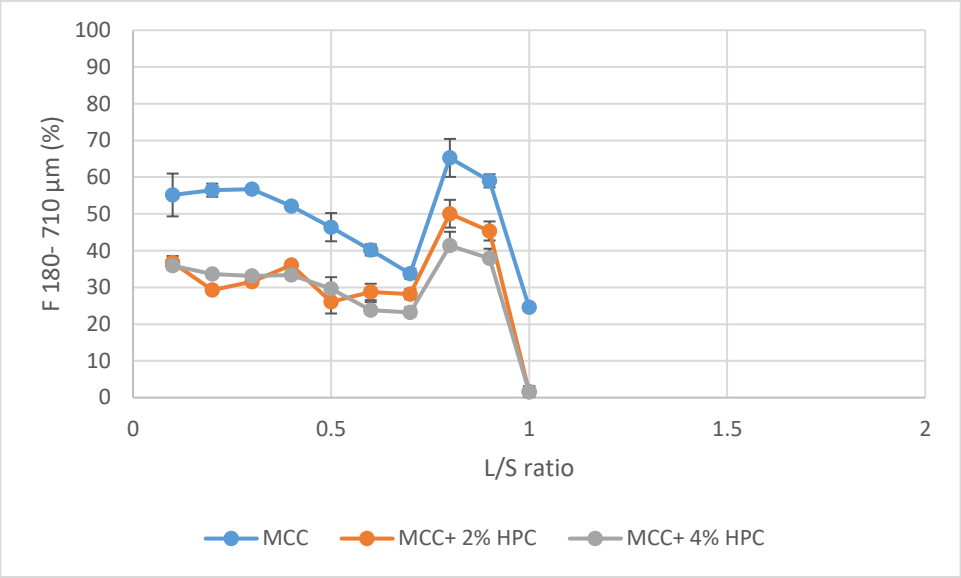


Figure 5-6. The yield of MCC granule at each L/S ratio when solid HPC was used.

Figure 5-6 is the yield of MCC granule within target size range for different L/S ratios. It could be seen that when MCC was used only, an optimal L/S ratio of about 0.8 could be obtained. With the addition of HPC (2% and 4%), the optimal L/S ratio were kept at 0.8. which is also close to the L/S ratio value on the powder bed shown in Figure 5-4. It indicates that the optimal L/S ratio for MCC (0, 2, 4% HPC) granulation is also predictable by using the L/S ratio for compact powder bed nucleation process.

In general, when HPC was added in solid form, using the L/S ratio for nucleus formation from the compact powder bed is capable to predict the optimal L/S ratio in twin screw granulation process.

5.3.2. Liquid binder delivery

In this section, HPC was dissolved in water as solution. HPC solutions with different liquid viscosity were used for the following experiments.

5.3.2.1. Nucleus weight

Figure 5-7 shows the lactose dry nucleus weight when HPC solution was used. With the use of HPC solution, obvious decreases in nucleus weight could be seen. It indicates that comparing with water, HPC solution due to its higher viscosity is more difficult to be distributed in the powder bed and consequently wet less powder. Similar variations are also exist when MCC was applied and shown in Figure 5-8.

Comparing with the use of HPC in solid form in Figure 5-1 and Figure 5-2, the use of HPC solution produces lighter nucleus, indicating that the use of HPC solution is less capable in liquid distribution and mixing with powder.

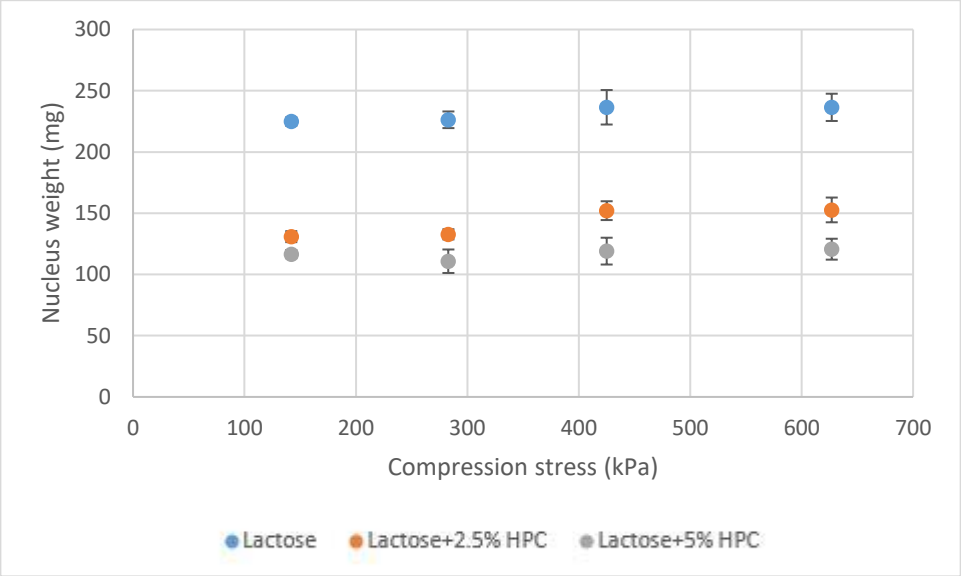


Figure 5-7. Lactose nucleus weight (water, 2.5%, 5% HPC solution) from compact bed.

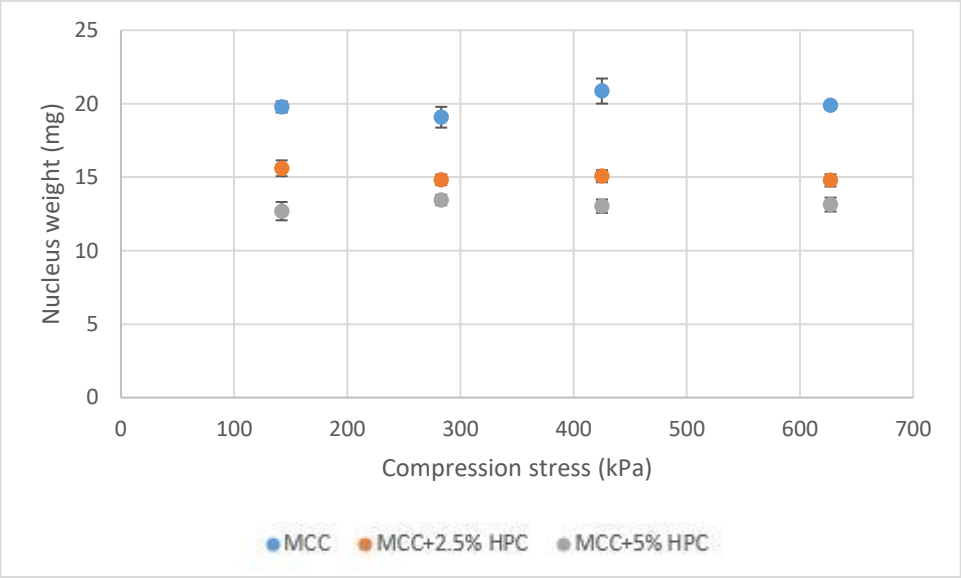


Figure 5-8. MCC nucleus weight (water, 2.5%, 5% HPC solution) from compact bed.

5.3.2.2. Compact powder bed: L/S ratio for nucleus formation

Figure 5-9 and Figure 5-10 are the mass ratio on the compact powder bed when HPC solution was used as the liquid binder. It could be seen that the use of HPC could increase the L/S ratio value clearly. It is because the use of HPC in both forms could delay the liquid from spreading and penetration, leading to a reduction in nucleus weight and consequently have a smaller L/S ratio value. In order to examine if the mass ratio could be sued to predict the optimal L/S ratio for twin screw granulation, a series granulation was carried out with a use of HPC solution for different L/S ratios.

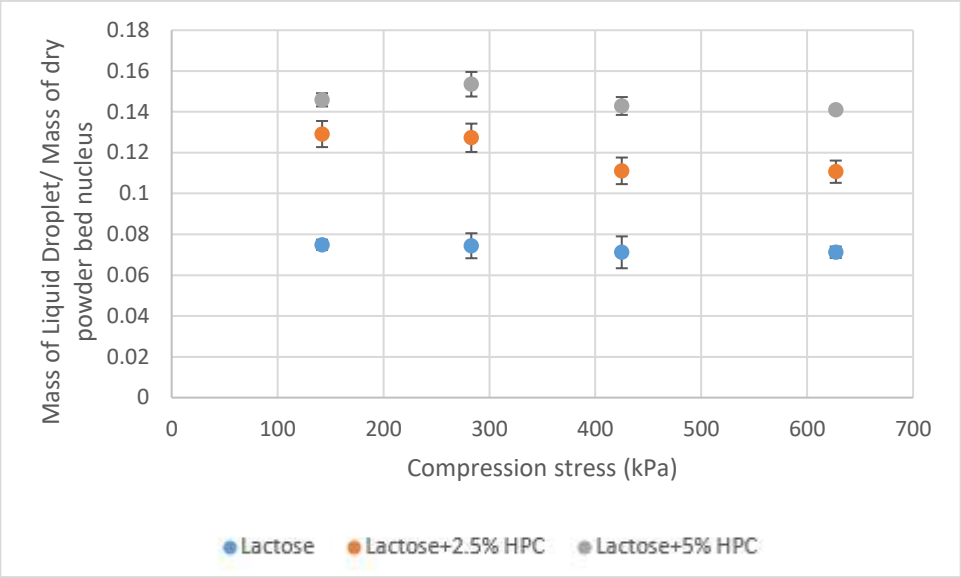


Figure 5-9. Mass ratio of liquid droplet and lactose nucleus from compact bed when water and HPC (2.5%, 5% HPC) solution were used.

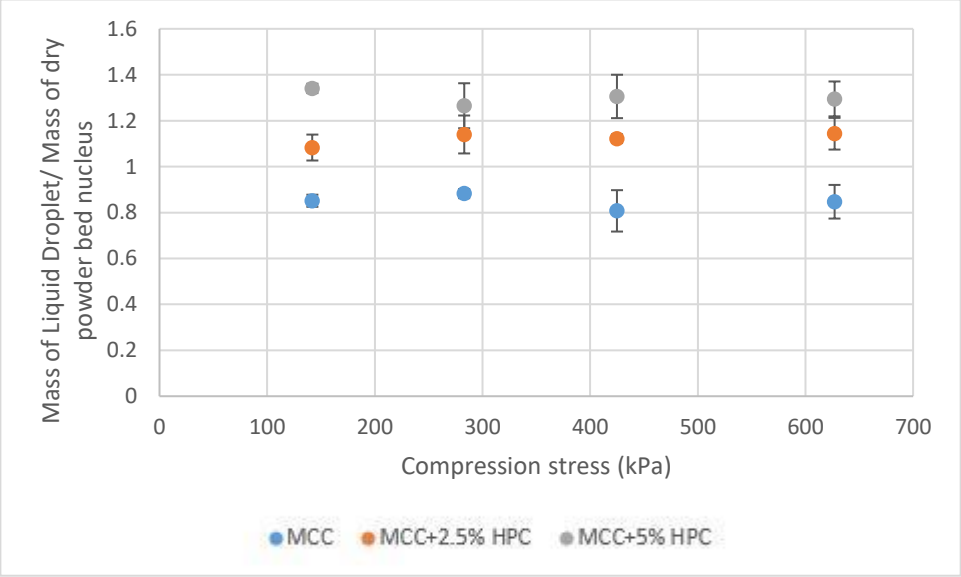


Figure 5-10. Mass ratio of liquid droplet and MCC nucleus from compact bed when water and HPC (2.5%, 5% HPC) solution were used.

5.3.2.3. Twin screw granulation: optimal L/S ratio using HPC in liquid forms

It could be seen in Figure 5-11, when water was used, an optimal L/S ratio of about 0.07 could be obtained. With the use of HPC solution (2.5% and 5%), the optimal L/S ratio becomes about 0.11 and 0.12, respectively. If the L/S ratio smaller than the optimal L/S ratio, more proportions of fines could be produced; it the L/S ratio is larger, more proportions of lumps could be produced. In general, either condition would cause a drop of yield. Comparing with the values shown in Figure 5-9, it could be seen the values are quite close. Similarly, in Figure 5-12, when water was used, the optimal L/S ratio was about 0.8. With the addition of HPC solutions (2.5% and 5%), the optimal L/S ratios (1.1 and 1.3) could be obtained and were also quite close to the (powder bed) mass ratios shown in Figure 5-10.

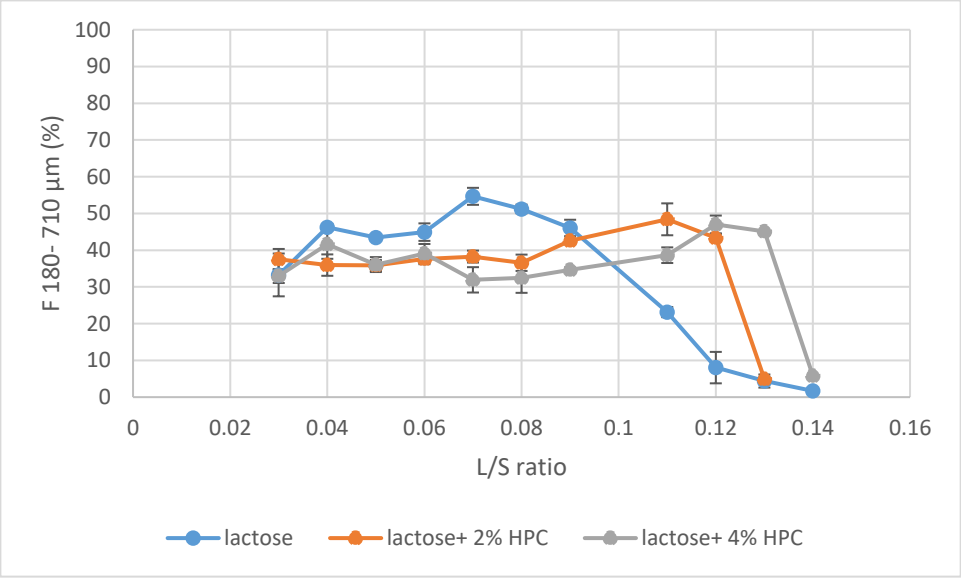


Figure 5-11. The yield of lactose granule at each L/S ratio water and HPC (2.5%, 5% HPC) solution were used

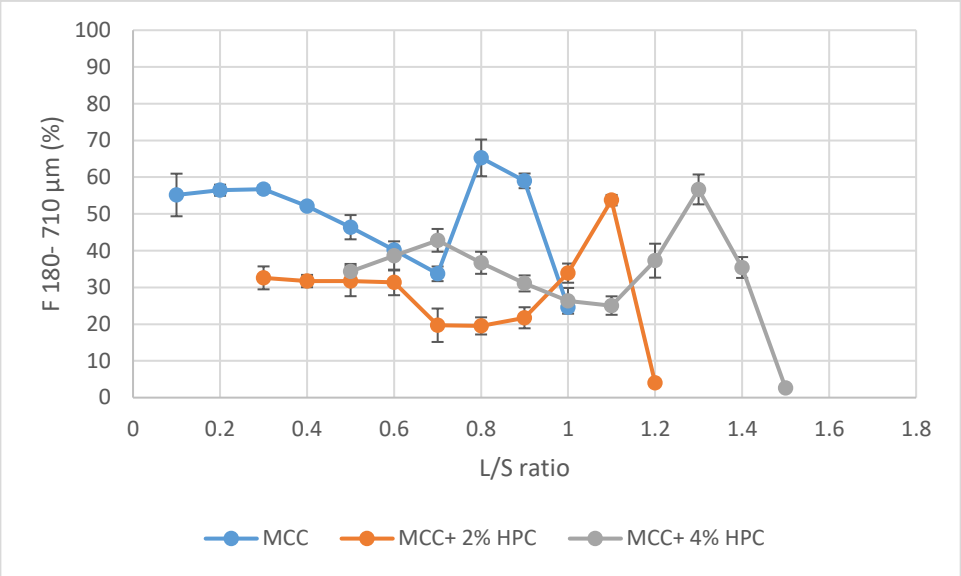


Figure 5-12. The yield of MCC granule at each L/S ratio when water and HPC (2.5%, 5% HPC) solution were used

To examine a new approach, it is impossible to try out every material existed. Therefore, 10 formulation were represented and used in twin screw granulation process to examine the accuracy and feasibility of a new approach by using a small scaled powder bed to predict the optimal L/S ratio. Among these formulations, soluble (lactose) and insoluble (MCC) materials were used and HPC was added in different forms (HPC solid particles and HPC solutions), which covers all possible composition forms in the industry. The approach was found to be adequate for all these formulations and the feasibility of this approach was examined. Theoretically, the approach (by using a small scaled powder bed in predicting the optimal L/S ratio in twin screw granulation process) should be applicable to other materials.

5.4. Conclusion

A novel approach to predict the optimal L/S ratio for twin screw granulation based on the compact powder bed was developed. Currently, trial and error experimentation is still

the main approach for the existing formulation and process development using twin screw granulation, resulting in waste of resources. The present research is focused on developing new approaches or methods which will only use small amount of powders (miniaturise) to estimate the process performance in order to minimize the waste of active materials and time.

Chapter 6. Evaluation of micronized lactose as a solid binder for twin screw granulation process

6.1. Introduction

From the single drop study, it is known that comparing with the liquid binder delivery method, the use of HPC in solid form leads to a much faster penetration time, which infers that a better liquid-powder mixing could be realized if solid binder delivery method is used. However, it has been noticed that the use of solid HPC in the powder bed weakens the liquid distribution capabilities and produced smaller nucleus in the compact powder bed. It might because that the HPC particles are much larger than that of lactose and MCC, which may stop or delay the liquid penetration.

In granulation process, the oversized binder particles could also affect the liquid-powder mixing. Moreover, these oversized binder particles are less possible to be properly dissolved to enhance the strength of liquid bridges. As a result, more solid binder may need to compensate the loss of binding capability. Therefore, assessments for the effect of smaller binder particles was carried out in both high shear mixer or fluidised bed (Alvarez-Lorenzo et al., 2000, Van der Watt, 1987, Nyström and Glazer, 1985, Nyström et al., 1982, Schæfer and Mathiesen, 1996, Li et al., 2011, Kato et al., 2006). It was found that the use of smaller sized binder particle could promote the growth of granule and have

positive effects on the strength of the granules due to its outstanding specific surface area. In terms of twin screw granulation, none of the previous work has been covered.

In this paper, micronized lactose would be introduced as a new type of highly effective binding excipient. In the meantime, HPC in solid form was applied as comparators. Binding capability of micronized lactose was first examined and compared on compact powder bed. Then, twin screw granulator was used to examine its binding capability in the wet granulation process. It was found that micronized lactose has an excellent binding and dispersion capability comparing with HPC in liquid and solid phases.

6.2. Material and method

6.2.1. Material

In the experiment α-lactose monohydrate, microcrystalline cellulose, HPC and micronfine lactose (Lactochem, DMV-Fonterra Excipient GmbH and Co., Goch, Germany, 8 μm) were used and the formulation is shown in Table 6-1. Powder with specific class range was sieved by a sieve shaker (Retsch Technology, Germany) with a magnitude of 1.5 for 5 min and the powder formulation mixing and liquid binder preparation have been mentioned in Section 3.2 and 3.3.

Table 6-1. Experiment materials.

Type	Powder (mixture)	Liquid binder
1	Lactose	Water
2	Lactose + 4% micronized lactose	Water
3	Lactose + 10% micronized lactose	Water
4	Lactose +15% micronized lactose	Water
5	Lactose + 4% HPC	Water
6	MCC	Water
7	MCC + 4% micronized lactose	Water
8	MCC + 10% micronized lactose	Water
9	MCC +15% micronized lactose	Water
10	MCC + 4% HPC	Water

6.2.2. Twin screw granulation: Preparation of granules

The twin screw granulator used has been introduced in Section 3.6.1. Liquid/solid ratios of 0.08 and 0.8 were kept for lactose and MCC, respectively.

Two sets of screw configurations mentioned in Section 3.6.1 were applied. Conveying elements were applied for all materials to provide to reduce the stress acting on the material and to outline the effect of these materials on granule growth. To further examine the feasibility of micronized lactose, Set 2 configurations, which consists of conveying and kneading elements were used.

6.2.3. Twin screw granulation: Granule characterisation

Granule properties measurements has been introduced in Section 3.6.4 and 3.6.5. For granule bulk strength measurement, a specific granule size of 180-710 µm was selected.

6.2.4. Compact powder bed: Penetration time

Penetration time was examined when micronized lactose was studied. Experiments were carried out on the compact powder bed which has been mentioned in Section 3.5.3. To record the liquid penetration process, the framerate of high speed camera was set as 1000 fps.

6.2.5. Compact powder bed: surface morphology

The compacted powder bed compressed using 450 N was used and then placed on a metal stub and coated with a gold layer for 16 seconds. The area where the liquid-powder occurred (nucleus area) was scanned and imaged by a scanning electron microscope (SEM, Jeol, USA) with magnifications of 200 X and 600 X. As a comparison, the SEM image of the powder bed itself was also captured as comparators.

6.3. Result and discussion

Appendix B discussed the nucleus hardness by using HPC in different size on the compact powder bed. It was found that the use of smaller size HPC could achieve a better binding capability than that of normal HPC. It indicates that reducing the particle size could be one of the approaches that enhances the usage efficiency of solid binder.

The micronized lactose has a small particle size where 90% of particles are less than 10 micron. It is mainly used to premix with API in order to prevent segregation (Giry et

al., 2006). In order to comprehensively investigate the effect of the micronized lactose as a solid bind, a series of single drop study was carried out at first.

6.3.1. Analysis of the penetration time of powder bed nuclei

Table 6-2 illustrated the variation of penetration time while changing formulation of powder in different compression stresses. It could be seen in Table 6-2, an increase in the proportions of fine lactose could increase the penetration time for all compression stress. It is probably because the fines would dissolve into liquid instantly and increase its viscosity. More importantly, the micronized lactose could fill the gap between large particles and thus smoothen the surface which makes the liquid spread to a larger extent and accelerate the penetration.

As a comparison, although the addition of micronized lactose or HPC particles in the powder formulation would increase the penetration time, such increase is much lower than when HPC solution was used. As a slower penetration indicated poorer wettability of powder bed, the addition of HPC in water would delay the liquid penetration and binder dispersion in the powder bed, whilst the formulation variation in powder material affects the contact angle quite a little. Consequently, the addition of micronized lactose or HPC particles would not delay the liquid penetration and binder dispersion as much as that when HPC solution was applied. Furthermore, Table 6-2 also illustrates that the increase of the compression stress caused a decrease of penetration time, which is probably due to an increase in liquid spreading on the compact powder bed which has been discussed in Chapter 4.

Table 6-2. Liquid penetration time under different formulations and compression stress on the compact powder bed (blue: repeat results from the previous chapter).

Formulation		Penetration time (s)			
		142 kPa	283 kPa	425 kPa	637 kPa
Lactose	Water	0.149±0.010	0.110±0.010	0.067±0.013	0.040±0.027
Lactose+ 5% ML	Water	0.166±0.005	0.115±0.013	0.079±0.001	0.044±0.014
Lactose+ 10% ML	Water	0.182±0.004	0.136±0.004	0.102±0.006	0.059±0.016
Lactose+ 15% ML	Water	0.226±0.092	0.190±0.007	0.168±0.019	0.096±0.015
Lactose+ 4% HPC	Water	0.167±0.005	0.122±0.004	0.096±0.016	0.065±0.019
MCC	Water	0.023±0.001	0.022±0.002	0.021±0.001	0.020±0.001
MCC+ 5% ML	Water	0.024±0.001	0.022±0.002	0.022±0.002	0.021±0.007
MCC+ 10% ML	Water	0.025±0.002	0.023±0.002	0.023±0.002	0.021±0.001
MCC+ 15% ML	Water	0.026±0.001	0.025±0.003	0.023±0.001	0.022±0.000
MCC+4 % HPC	Water	0.025±0.001	0.025±0.001	0.023±0.002	0.022±0.001

6.3.2. Powder bed surface morphology

As mentioned, the use of binding excipient could enhance the strength of granulation process. Similarly, it could also vary the bonds and structure of the area where had been

wetted (nucleus area). Therefore, SEM images of the compact powder bed and nuclei with different formulations were listed in Figure 6-1. In terms of the compact powder bed itself, as the percentage of micronized lactose increased, the fine particles would fill the gap between large particles and thus reduced the surface porosity. When the water penetrated into the bed, due to the significant specific surface area, the fines around large particles would dissolve instantly into water and the viscous liquid could form strong bridge between particles. Upon addition of more fines, the liquid bridges between particles would be more and more viscous, leading to an increasing enhancement in solid bonds strength.

Meanwhile, the addition of HPC in solid form, compared with pure lactose, made little difference in its surface structure. It was because the HPC particles could not dissolve properly and thus did not contribute as much as micronized lactose did during granulation process. When HPC solution was used, some of the particles were bonded, indicating a relatively effective enhancement in terms of nuclei hardness comparing to the addition of HPC particles. However, the addition of HPC solution could only produce limited bonds between particles when comparing with the addition of micronized lactose.

In general, micronized lactose was found to be more capable in forming strong bonding between particles than the use of HPC in both forms. Theoretically stronger agglomerates could be produced when micronized lactose was used. To examine the behaviour of micronized lactose in twin screw granulation, different proportions of micronized lactose (5, 10 & 15%) was premixed with lactose and MCC, respectively. To quantify the improvement, lactose and MCC were also used individually without the addition of solid binder.

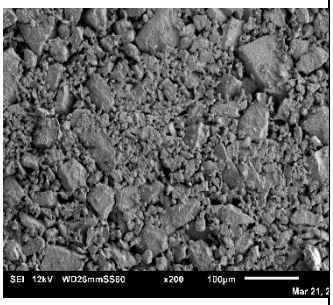
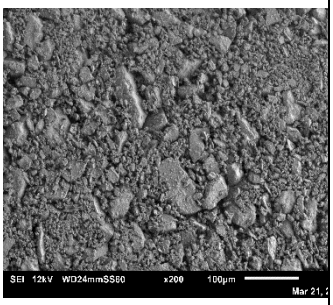
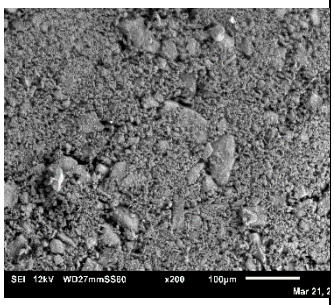
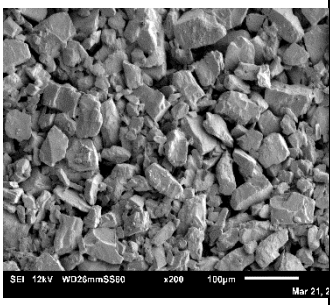
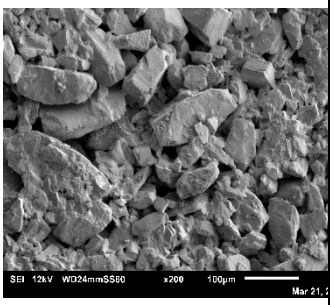
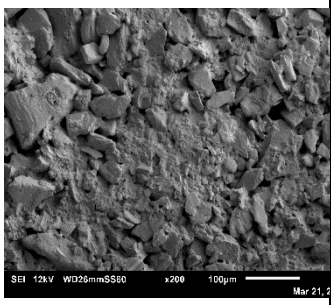
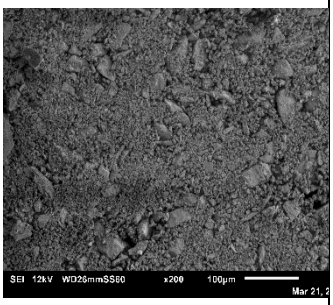
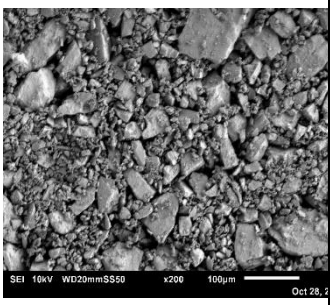
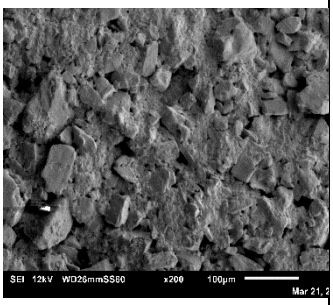
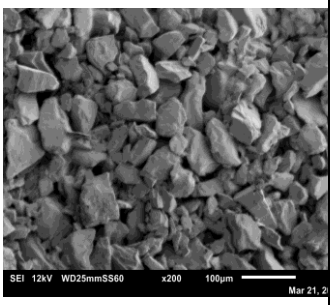
	Lactose	Lactose+ 5% ML	Lactose+ 10% ML
Powder bed			
Nucleus			
	Lactose+ 15%ML	Lactose+ 4% HPC (solid)	
Powder bed			
Nucleus			

Figure 6-1. Lactose compact powder bed surface morphology under different formulations.

Similarly, the SEM images were also captured on the MCC based powder bed and shown in Figure 6-2. The effect of micronized lactose on MCC compact powder bed is less obvious than that of lactose. It is probably because the dissolved micronized lactose were swallowed into the MCC particles due to their special structure. Nevertheless, as the proportion of micronized lactose increased, the gaps between MCC particles were filled by the small lactose particles and a reduction in porosity could be observed. Consequently, the strength of the agglomerates would be increased.

In terms of the powder bed mixed with HPC particles, some oversized particles could be observed. Based on its size and morphology, it was more like to be the HPC particle. After water penetration, the surfaces of dried nuclei were observed. In terms of the use of HPC solution, no clear difference could be seen comparing with the use of micronized lactose.

From the SEM images, the use of micronized lactose could fill the gap between particles, leading to a reduction in voids on the surface. To further examine the binding capability, there is a need to further evaluate the strength of the structure. Therefore, the nucleus hardness was then carried out through the indentation experiment.

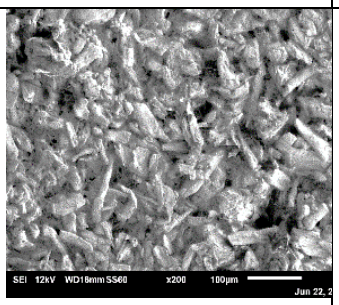
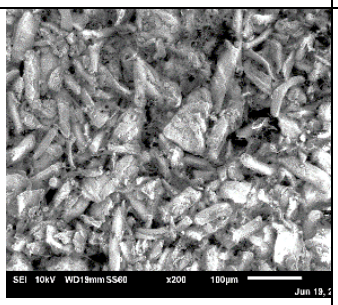
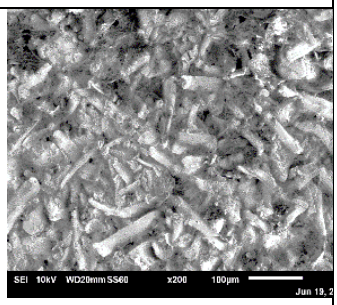
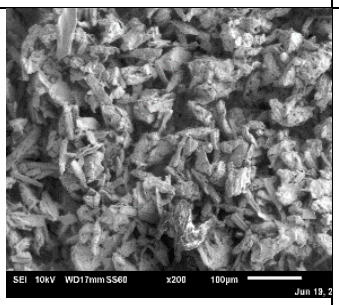
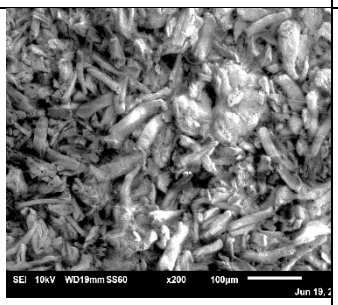
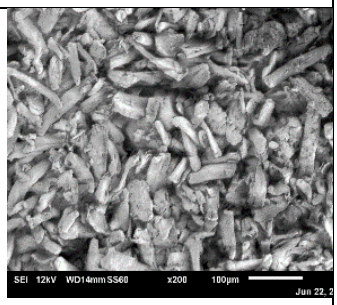
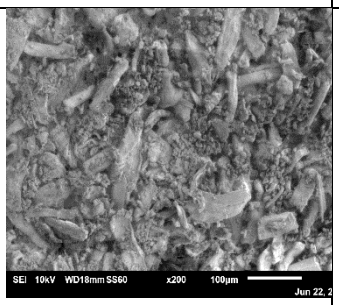
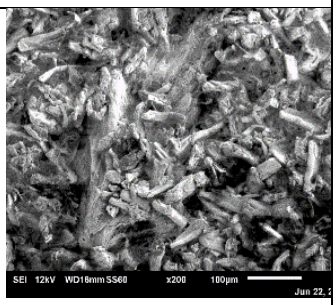
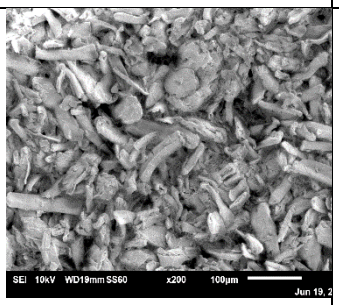
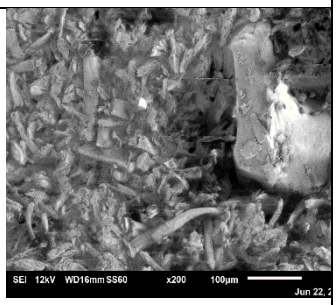
	MCC	MCC+ 5% ML	MCC+ 10% ML
Powder bed			
Nucleus			
	MCC+ 15% ML	Lactose+ 4% HPC (solid)	
Powder bed			
Nucleus			

Figure 6-2. MCC compact powder bed surface morphology under different formulations.

6.3.3. Granule size distribution

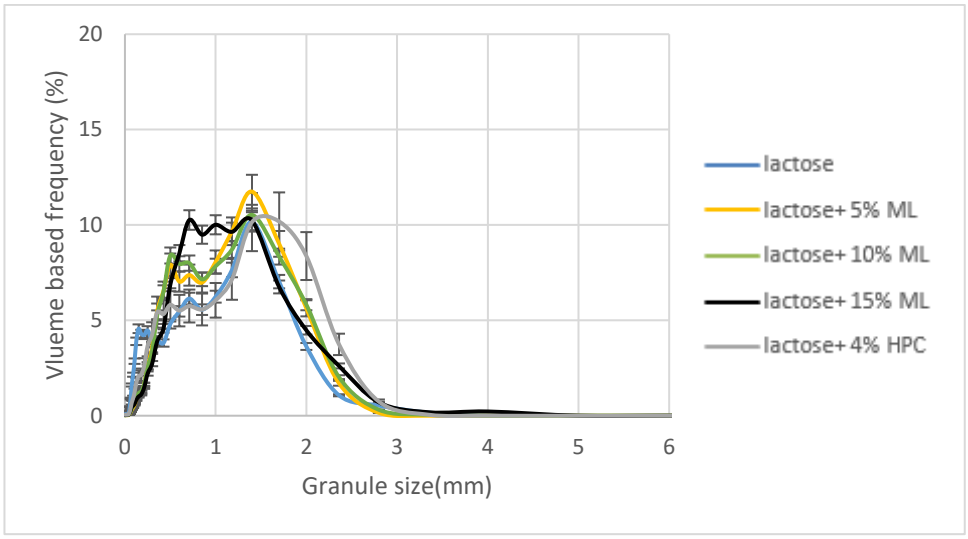
To evaluate the feasibility of a solid binder, HPC was firstly used as an example to examine whether the use of micronized lactose had similar effect or not. Concerning the consistency of the result, HPC here used was with a concentration of 4% and the comparison between micronized lactose and HPC were qualitively. To quantify the effect of micronized lactose on granule size distribution, span of distribution was used and comparisons between the experiments running with and without micronized lactose were made.

At first conveying elements were used only and this screw configuration was mainly used to study the effect of binder on granule growth but not the typical configuration used in the real industry. When conveying elements are used, granules are freely growing and the curves of size distribution could reveal how much the use of binder could promote the growth of granules.

Figure 6-3 displayed the lactose granule size distribution when conveying elements applied. It could be seen that all curves represented are bimodal. It is well-known that conveying elements are more capable in conveying materials but are weak in liquid-powder mixing and agglomerate breakages (Djuric and Kleinebudde, 2008, Lee et al., 2013; Van Melkebeke et al., 2008). Consequently, bimodal curves would be obtained, indicating that large fractions of fines and large granules (lumps) were produced and the produce of bimodal curves were mainly resulted from poor liquid distribution while conveying elements were used (Dhenge et al., 2012a).

In this experiment, HPC was used as a comparison to qualitatively clarify the effect of a solid binder in granulation process. It could be seen that the use of HPC could promote

the growth of granules by producing a higher proportion of large granules with a larger mean size compared with if blue line (no binder). Similarly, the addition of micronized lactose shows similar effect that the addition could promote the granule growth and higher proportions of large granules with larger granule mean size could be produced. This indicates that micronized lactose had a similar effect on lactose powder as HPC (a typical binder) and could effectively promote the growth of granules. Although from Figure 6-3 an increase in micronized lactose was believed to increase the proportion of large granules, the difference on granule size distribution curves was less clear. It might be because lactose (powder material) could also dissolve and enhance the bonding between particles which may potentially mask the effect from the solid binders.



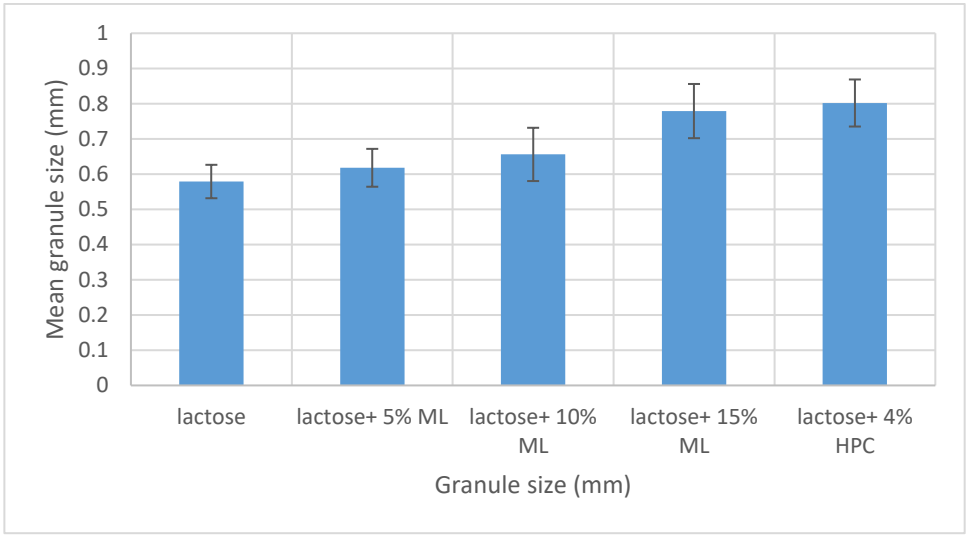


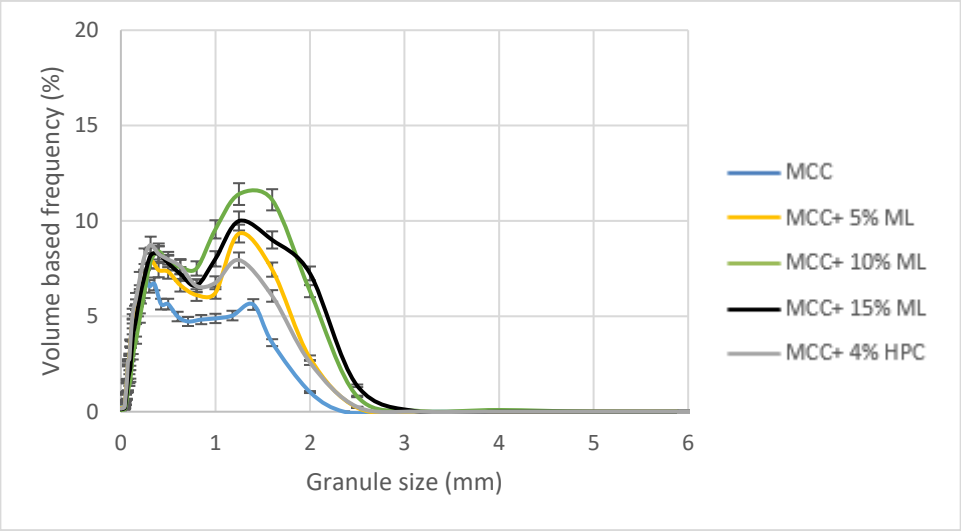
Figure 6-3. Granule size distribution of lactose with different proportions of micronized lactose and lactose with solid HPC (conveying elements).

The effects of micronized lactose on MCC granule size distribution and granule mean size were shown in Figure 6-4. Compared with Figure 6-3, more fractions of fines were produced using all formulations. It is because that MCC is insoluble and consequently the liquid would be less viscous and the bonds between particles are weaker. As a result, the

weak bonds may be insufficient to let the particles agglomerate and high fraction of fines could be produced.

Concerning the binding capability of solid binder particles, similar to that of lactose the addition of solid binder (micronized lactose or HPC) could promote the growth of granule and more large granules were produced. Moreover, an increase in micronized lactose could clearly increase the proportion of large granules. Consequently, an increase in granule mean size could be obtained. It indicates that micronized lactose had a similar effect as HPC and could be used as a solid binder for MCC granulation process. Similar tendency could also be obtained from the variation of granule mean size. It could be seen that the use of HPC could promote the growth of granules and similar effects could also be obtained from the addition of micronized lactose.

Therefore, while conveying elements were used only, although the addition of micronized lactose could promote the growth of granule, but it is still less effective than that of using HPC. However, the evaluation of a solid binder (in terms of granule size destribution) is not based on whether it could produce more over-sized granules but more about whether it could narrow the distribution in order to enhance the production of granule in a certain size range.



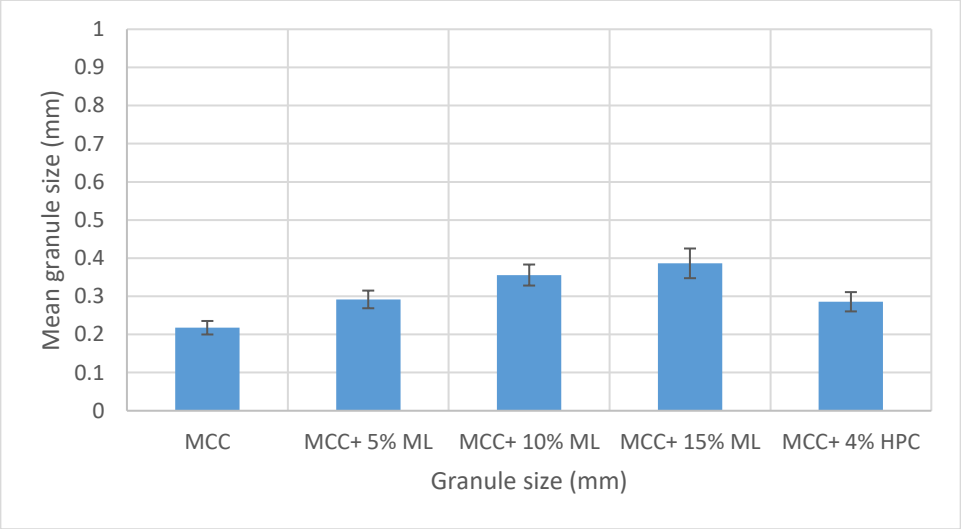


Figure 6-4. Granule size distribution of MCC with different proportions of micronized lactose and MCC with solid HPC (conveying elements).

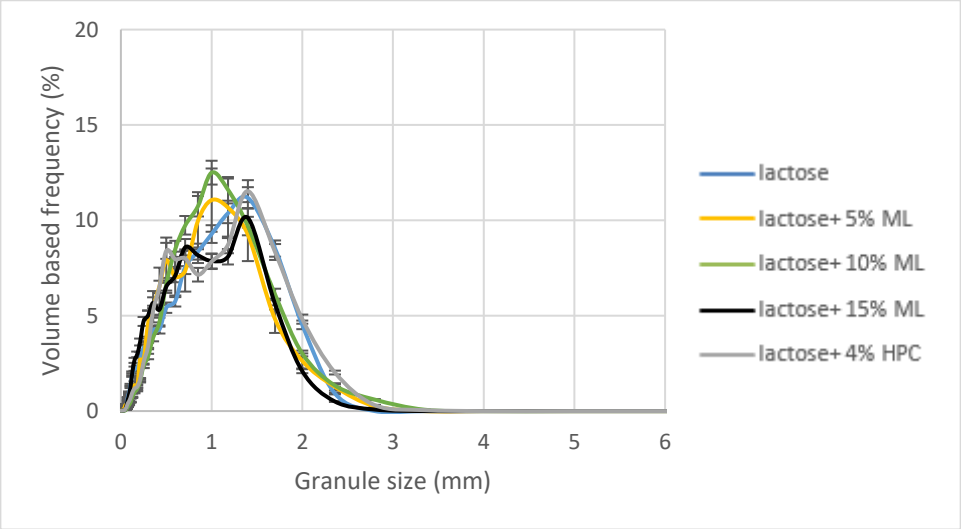
In reality, it is quite rare to use conveying elements only for granulation. The results from conveying elements were mainly used to preliminarily examine whether the use of micronized lactose could promote the granule growth or not. To make the research more applicable to the industry, an industry standard screw configuration (Set 2 configuration,

shown in Chapter 3) with kneading elements was then applied to further examine the feasibility of micronized lactose as a solid binding excipient.

Figure 6-5 presents the granule size distribution and mean size when an industry standard screw configuration was applied by adding kneading elements to the screw elements. In general, compared with the use of conveying elements only (Figure 6-3), the distribution curves are narrower and the mean sizes are smaller. A narrower granule size distribution curves indicates a more even liquid-powder mixing and thus a better liquid distribution. It is because kneading elements could provide higher compaction and shearing (Dhenge et al., 2012b). A higher compaction would break more lumps, promoting the re-agglomeration and liquid dispersion (Dhenge et al., 2012b). Due to the breakage of lumps and a more even liquid-powder mixing, the corresponding mean size reduced.

When lactose was used (Figure 6-3), no clear differences could be observed from the size distribution. As was mentioned, apart from the dissolution of solid binder particles, the dissolution of lactose could further increase the liquid viscosity and thus reduce the liquid flowability and distribution ability, causing the effect of binder on size distribution become unclear (Ai et al., 2016). Nevertheless, a slight decrease in granule mean size could be seen. To quantify the difference, the span of distribution was shown in Figure 6-6. The span of distribution quantifies the width of distribution curves; a higher value of span means a wider distribution and poorer liquid distribution. Tu et al. (2013) stated that in most cases the span of distribution is in a range of 1.5 to 4.5 and about 10% (11.1%) difference in span of distribution was deem as an effective variation which could affect the granular product properties. From Figure 6-6, all distribution curves had spans within

the range above. In addition, adding 5% to 10% of micronized lactose was found to reduce the span of distribution, indicating that the use of micronized lactose could narrower the granule size distribution and promote the liquid-powder mixing. However, 15% of micronized lactose was found to negatively affect the granule size distribution by increasing the span. It is probably because too much of micronized lactose would significantly increase the liquid viscosity and thus delay the liquid distribution, causing uneven mixing and wide size distribution.



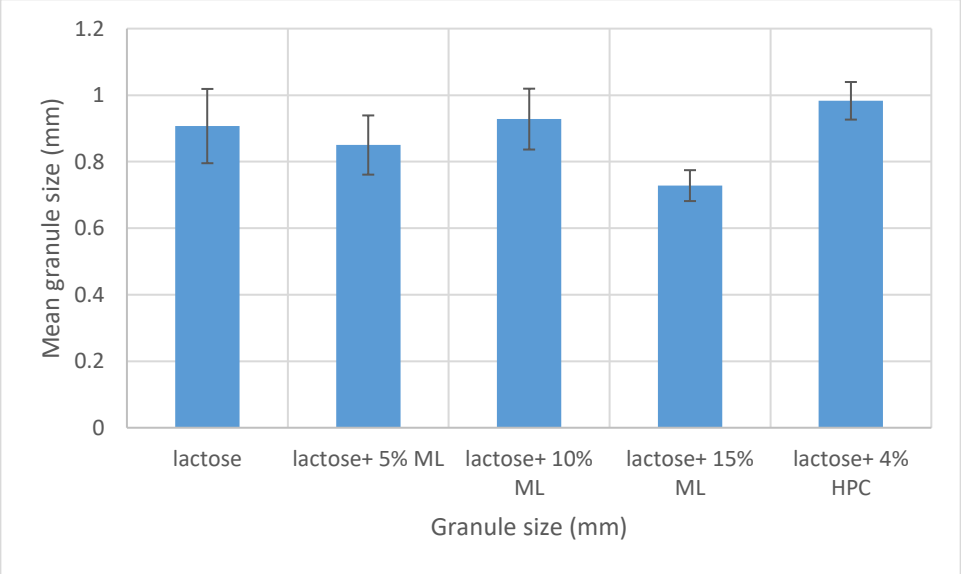


Figure 6-5. Granule size distribution of lactose with different proportions of micronized lactose and lactose with solid HPC (kneading elements).

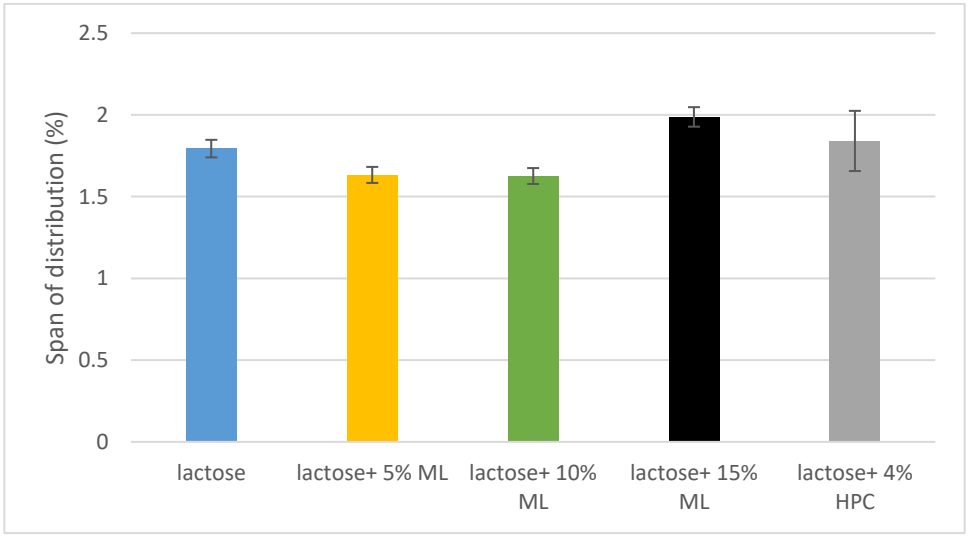


Figure 6-6. Span of distribution for Figure 6-5.

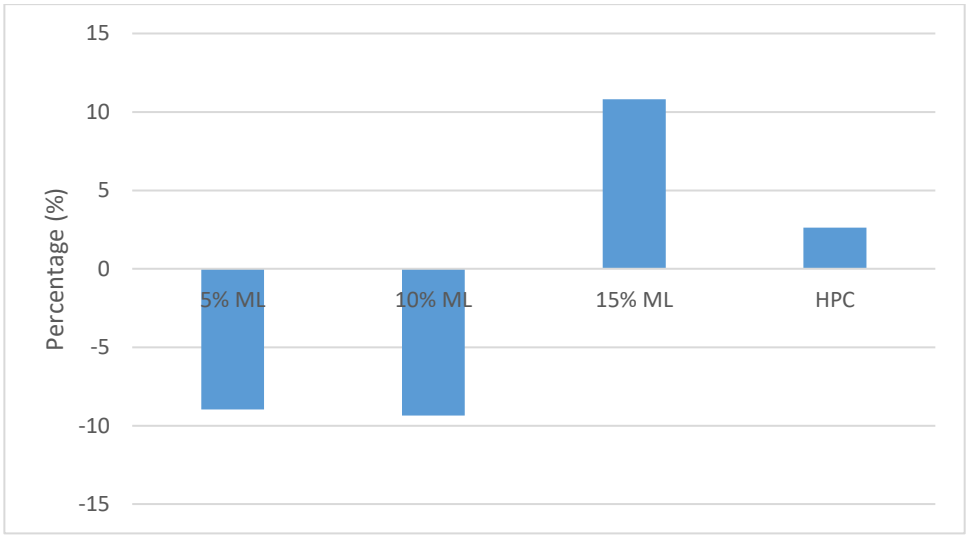


Figure 6-7. Average improvement (%) of span of distribution.

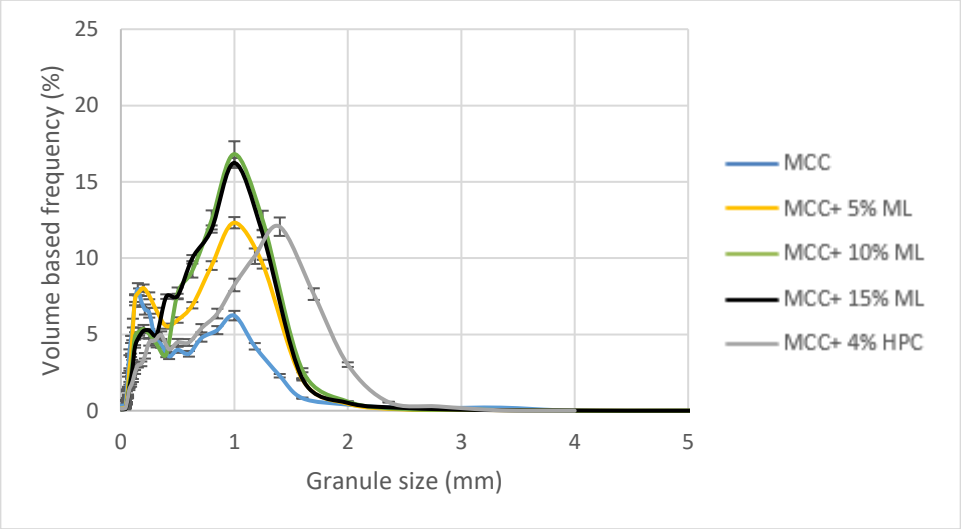
To quantify the variation of span of distribution, the span of distribution using micronized lactose and HPC were compared with that when no solid binder was used. It was found that the addition of micronized lactose (5% and 10%) could reduce the span of

distribution (about 9.0% & 9.4%), while too much of micronized lactose (15%) or the use of HPC would increase the span of distribution to 10.8% and 2.6%, respectively. it might be due to that 15% of micronized lactose or HPC could significantly increase the liquid viscosity and thus delay the liquid penetration based on Washburn equation (Equation 2-7). As only if the variation is about or larger than 10% would effectively affect the granular product properties, it could be concluded that the use of 5% to 10% of micronized lactose could be deem as effective improvement (Tu et al., 2013).

When the micronized lactose was added to MCC, Figure 6-8 shows that MCC produced a high proportion of fines and smaller mean size compared with that of lactose. As was mentioned, it was because MCC is insoluble and the weak bonds between particles were incapable to resist the intensive agitation when kneading elements were applied. The effect of binder on MCC granule size distributions were more obvious than that of lactose, which was because MCC is insoluble and the difference in binders would not be masked by the dissolution of MCC particles. It could be seen that the use of HPC or micronized lactose could all reduce the production of fines and promote the growth of granule.

As was mentioned, the span of distribution is an important indicator to evaluate the size distribution when kneading elements were used (Tompson & Sun, 2010). To quantify the difference, the spans of distribution were extracted. In general, the span of distribution from Figure 6-9 is in a range between 1.5 - 4.5, which indicates that the spans of distribution are in the allowed range (Tu et al., 2013). When HPC was added, a reduction in the span of distribution could be seen indicating that the use of solid binder could narrow the size distribution and enhance the liquid distribution. Similar effects could also

be seen when micronized lactose was used, showing that micronized lactose had similar effect on granule size distribution as the sample binder (HPC) and the micronized lactose could be used as a solid binder for MCC granulation process. To further evaluate the improvement of using micronized lactose, Figure 6-10 quantified of span of distribution. It could be seen that the use of micronized lactose and HPC could all reduce the spans of distribution. In general, an increase in micronized lactose leads to a decrease in span of distribution (from about 26.6% to about 54.5%), indicating that the use of micronized lactose could promote the liquid distribution (Tu et al., 2013).



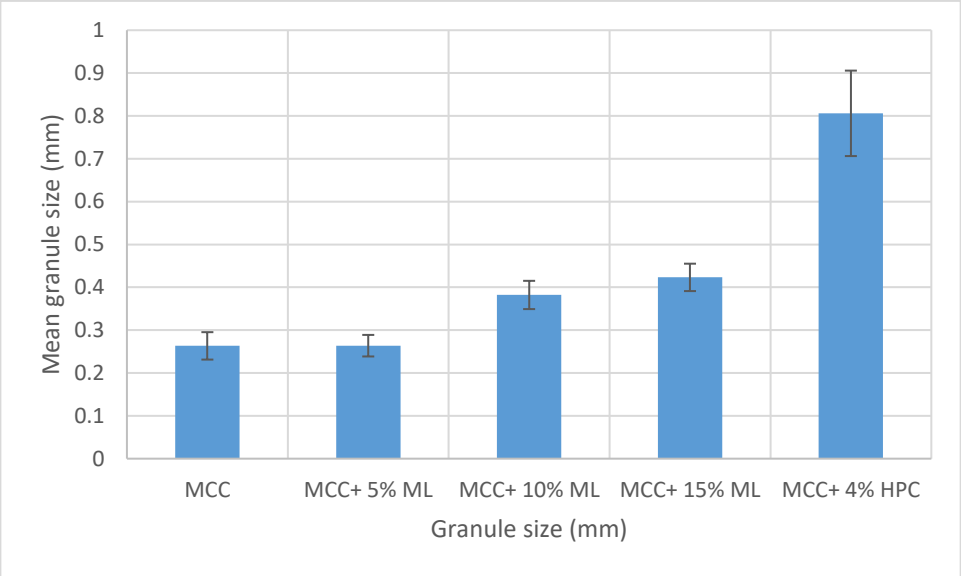


Figure 6-8. Granule size distribution of MCC with different proportions of micronized lactose and MCC with solid HPC (kneading elements).

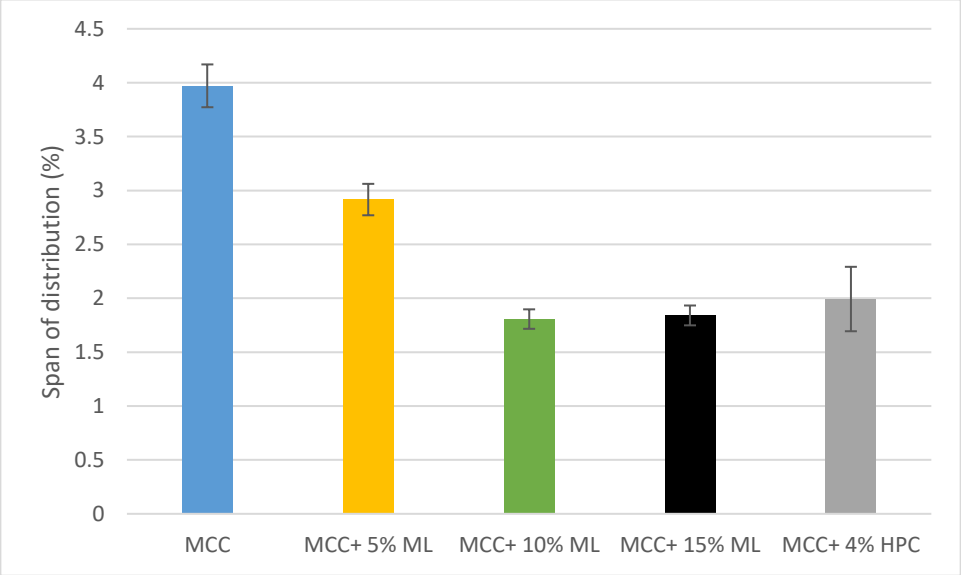


Figure 6-9. Span of distribution for Figure 6-8.

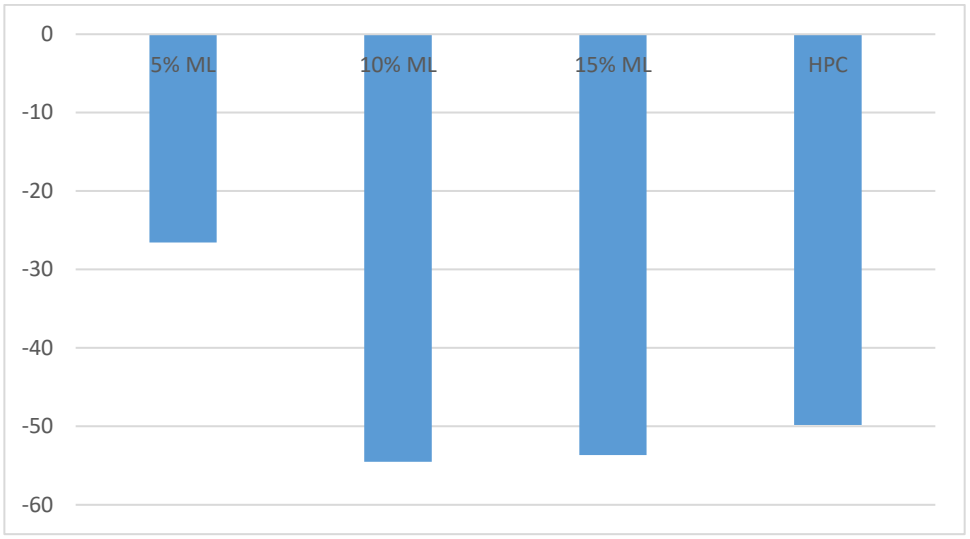


Figure 6-10. Improvement (%) of span of distribution.

In this section, two types of screw configurations were used. At first, conveying elements were used only (Set 1) to qualitatively study the effect of micronized lactose on granule growth. It was found that micronized lactose could promote the growth of granule for both lactose and MCC. MCC shows a clearer difference as it is insoluble, which would not mask the role of binder (micronized lactose and HPC) on granule growth.

Then, an industrial standard screw configuration was used with 32 kneading elements (Set 2). The use of kneading elements could generate much more aggressive agitation in the granulator and would break the large granules, leading to a much more even liquid distribution. Therefore, span of distribution was extracted to quantify the difference of distribution. It was noted that smaller amount of micronized lactose (5% & 10%) could effectively reduce the spans of distribution, leading to narrower size distributions. Similar effect could also be seen when MCC was used as the granulation material.

Therefore, it could be generalized that the use of micronized lactose was able to be used as a solid binder to promote the growth of granules and enhance the liquid

distribution. However, the effect of a binding excipient should also affect the strength of granules. Therefore, granule morphology and bulk strength were investigated in the following chapter.

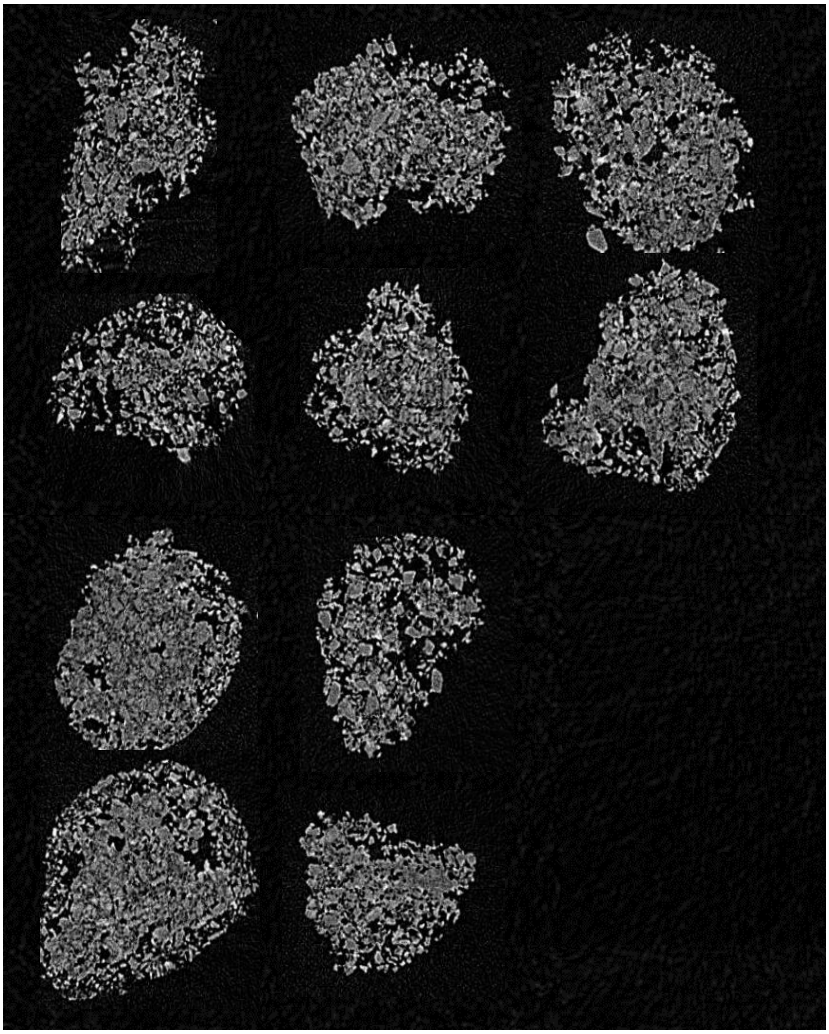


Figure 6-11. CT morphology of lactose with different proportions of micronized lactose and lactose with different phases of HPC (kneading elements)

6.3.4. Granule morphology from CT

To reveal the effect of micronized lactose on the granule structure. The granule inner structure was observed by using an X-ray scanner. Figure 6-11 and Figure 6-14 illustrated the x-ray scanning images of lactose and MCC granules, respectively. It could be seen on both materials that the increase of micronized lactose could reduce the size of voids in

the granules. Compare with the use of HPC, the granules produced using micronized lactose are less porous, indicating a more stable structure. Therefore, it could be

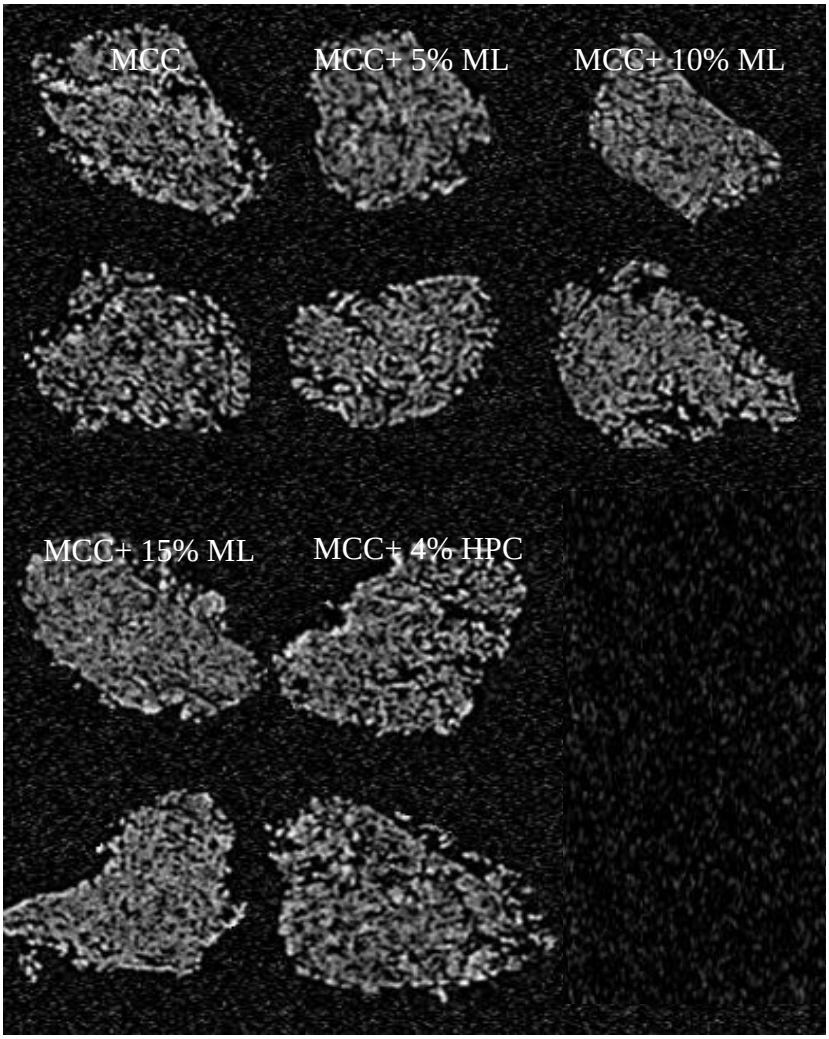


Figure 6-12. CT morphology of MCC with different proportions of micronized lactose and MCC with different phases of HPC (kneading elements)

concluded that the use of micronized lactose could effectively reduce the porosity of granules, making the granular structure more even and stable.

Granule porosity is an important indicator which could indirectly reflect the strength of granule which is an important parameter to evaluate the quality of granules. Normally, a less porous granule tends to be stronger. However, the strength of granules could also

be affected by the amount of bonds between particles. Although the x-ray images illustrates the effect of micronized lactose on granule porosity, there is no strong evidence to prove that the addition of micronized lactose could promote the bonds formation. Therefore, it is still worthy to investigate the effect of micronized lactose on granule strength.

6.3.5. Granule bulk strength

As was mentioned in the introduction, granule strength is related to the tablet properties including strength and dissolution rate (Lee et al., 2013, Litster and Ennis, 2013). Normally, weaker granules tend to produce stronger tablets with a slower dissolution rate. In reality, tablet disintegration speed is relatively more important when varying the granule strength (Liu et al., 2016). It is because normally the compressions for tabletting are no less than 15 kN and the high compression is sufficient to make sure the tablets are strong enough while storing and transporting (Rajkumar et al., 2016); the tablet dissolution rate is related to the releasing speed of the active pharmaceutical ingredients (API) in the tablets which is of vital importance for human health (Salman et al., 2007).

As granule strength is related to the tablet disintegration speed, different tablets with various API(s) may be required different disintegration speed (immediate release and controlled release) and consequently the strength of granules required are varied (even if the same formulation and equipment are used) (Liu et al., 2016). Therefore it is impossible to extract or generalise a standard granule strength or typical “value” or “range of value” which is applicable for all cases. In addition, current methods to obtain the bulk granule strength are based on Adam Equation, which is significantly dependent on the sample properties including granule size, compressibility, packing, etc (Adam et al., 1994); On

the other words, it is difficult to make comparison between literature due to the variation of equipment, granule properties, etc. (Dhenge 2012d, Liu et al., 2016).

However, it does not mean that there is no requirement on granule strength. It is known that the granules from twin screw granulation are quite weak and thus normally granule bulk strength of at least 0.1 MPa should be maintained to avoid the granule breakages during transportation and storage (Dhenge et al., 2012d, Dhenge et al., 2013, Saleh et al., 2015).

Therefore, as long as the granule strength is larger than ~0.1 MPa, qualitive comparisons are the main methodology when investigating the granule strength (Dhenge et al., 2012c, Saleh et al., 2015, El Hagrasy et al., 2013b). To quantify the improvement of micronized lactose, lactose/MCC granulated using water (no binder) with a powder feed rate of 1 kg/h and a screw speed of 200 rpm were used as a standard condition, respectively (Dhenge 2012d). Granule bulk strength from other formulations will be compared with the value obtained from the standard condition to quantify the difference.

Figure 6-13 shows the lactose granule bulk strength affected by the variation of formulations. It could be seen that the granule strength are always larger than 0.1 MPa, which is strong enough during transportation and storage. As a typical solid binder, the use of HPC produced stronger granules than if no binder was used. Similarly, the addition of micronized lactose could also increase the granule bulk strength, which indicates that micronized lactose is capable to be used as a solid binder. In addition, more proportion of micronized lactose used leads to the production of stronger granules.

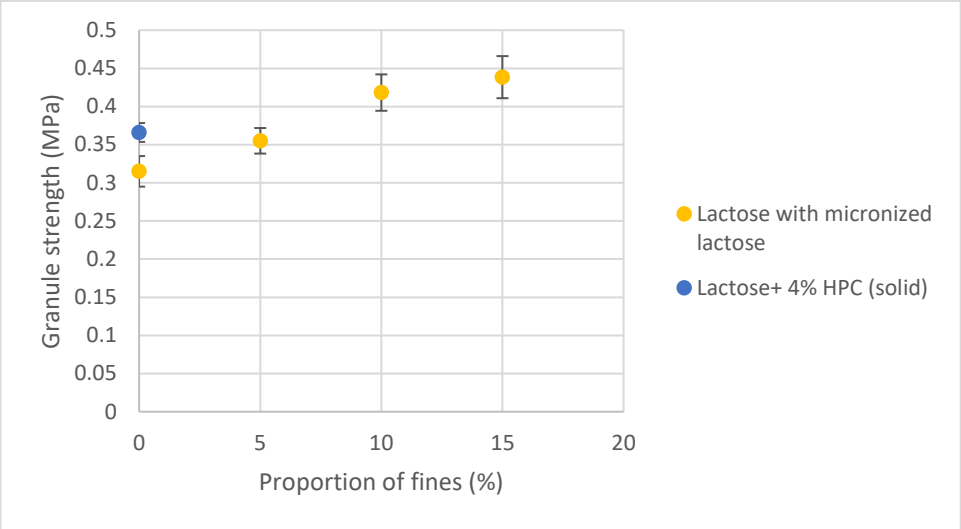


Figure 6-13. Lactose granule bulk strength for different formulations.

To quantify the effect of micronized lactose, the bulk strength of the granules produced with micronized lactose was compared with the standard case (lactose/MCC with water). It could be seen in Figure 6-14 that either HPC or micronized lactose could enhance the granule strength to different extents, indicating that micronized lactose had played a similar role as HPC in granulation. Compared with the use of water, adding micronized lactose could improve the granule strength clearly from about 12.7% to almost 40%. It was reported that the granule strength and tablet tensile strength are quite related that even less than 5% difference could cause obvious difference in tablet tensile strength and disintegration rate (Horisawa et al., 1995). Therefore, an improvement of at least 12.7% was quite able to have clear effect on tablet properties.

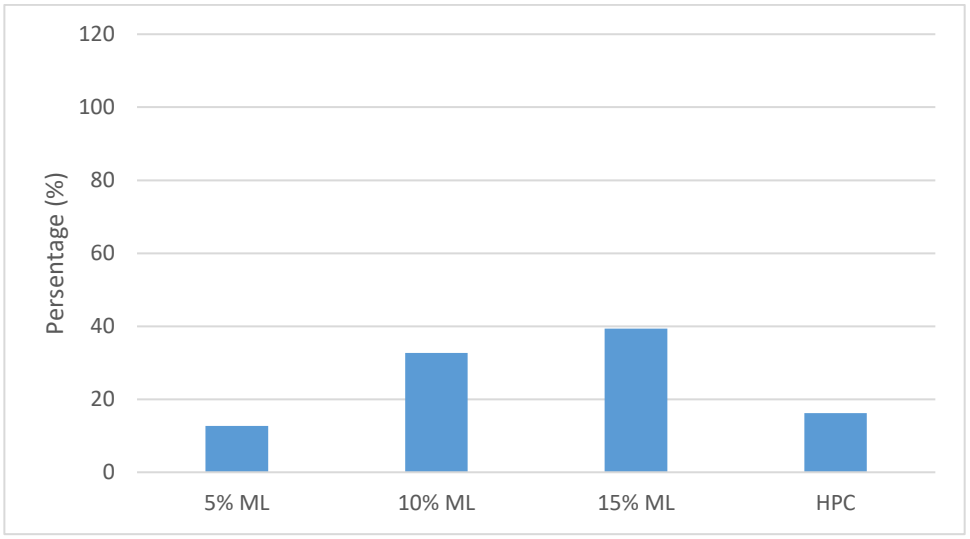


Figure 6-14. Improvement (%) of granule bulk strength using micronized lactose.

Similarly, Figure 6-15 shows the MCC granule strength affected by the addition of different solid binders. When water was used, the granule bulk strength was around 0.14 MPa which is quite close to the value of 0.1 MPa. While the use of either HPC or micronized lactose could effectively enhance the granule and make the granule strong enough to resist breakages. The similar effects on strength enhancements between HPC and micronized lactose indicates that micronized lactose could be used as a binder as HPC for MCC granulation. In addition, the increase in micronized lactose could enhance the strength of granules and the enhancement is believed to be comparable to that when HPC was added. When comparing Figure 6-15 with Figure 6-13, stronger granules could be produced when lactose was used which was due to the fact that lactose is soluble.

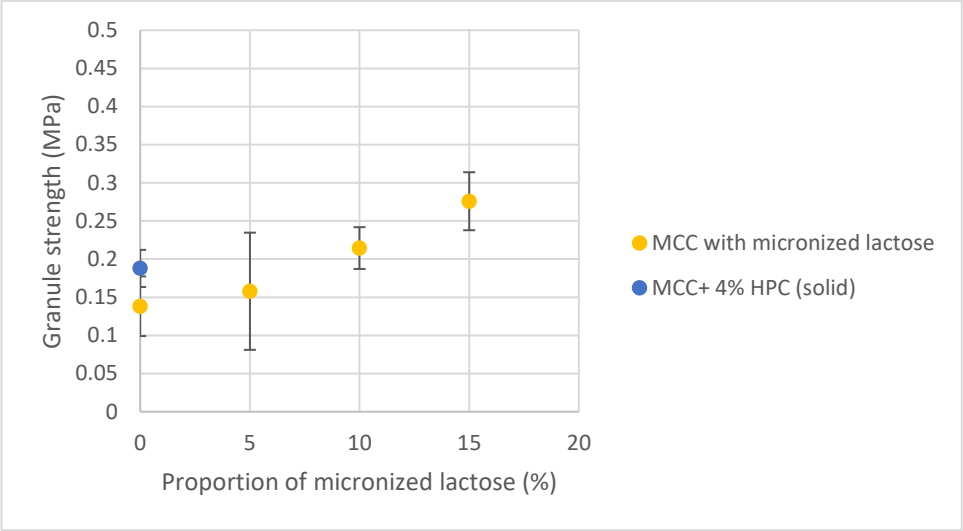


Figure 6-15. MCC granule bulk strength for different formulations.

Figure 6-16 represents the improvements of MCC granule bulk strength by using micronized lactose. When micronized lactose was used, the improvements on granule strength was about 14.5% to 100%, which indicates that the use of micronized lactose is quite effective for insoluble materials. Based on the experiment from Horisawa et al. (1995), such improvements would have obvious effects on the granule product (tablet) properties.

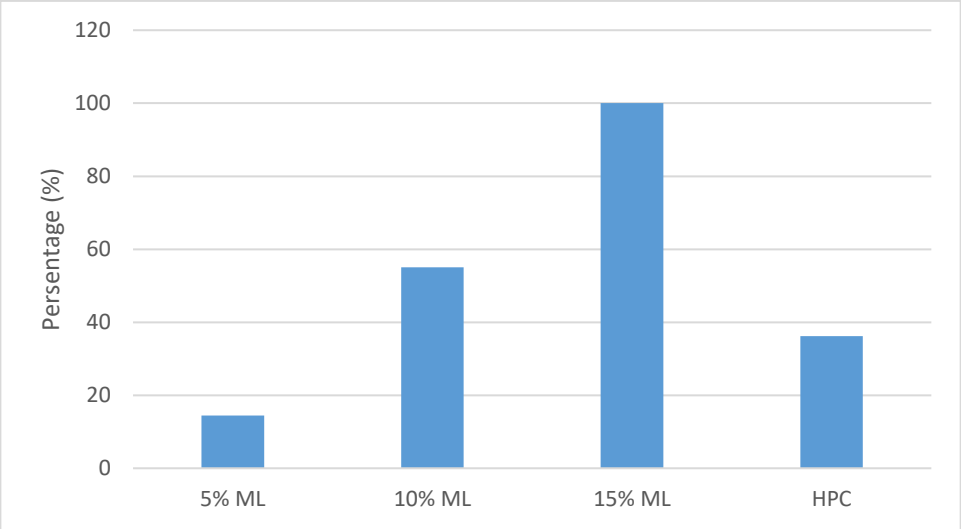


Figure 6-16. Improvement (%) of granule bulk strength using micronized lactose.

6.4. Conclusion

In this chapter, a new type of binding excipient was evaluated from the perspectives of granule size distribution, granule strength.

As a binding excipient, its dissolution would affect the liquid viscosity and consequently delay the liquid distribution and increase the span of distribution. Therefore, the expectation for a "good" binding excipient is always about it could produce stronger granules and promote the liquid distribution (narrower granule size distribution). In general, the spans of distribution (which quantifies the granule size distribution) are all in the allowed range of 1.5-4.5, which indicates that the granule size distribution is allowed for utilisation for the following steps (e.g. tabletting) (Tu et al., 2013). By evaluating the granule size distribution using micronized lactose, it was found that small amounts of micronized lactose (5% & 10%) have positive effects (about 9.0% & 9.4%) on lactose granule size distributions. However, if 15% micronized lactose was added, wider granule size distribution would be obtained and the span of distribution would be increased (for

about 10.4%). For MCC, it was found that the use of micronized lactose could always narrow the size distribution. A increase in micronized lactose from 5% to 15% would cause an reduction in span of distribution from about 26.6% to 54.5%. Overall, a proper use of micronized lactose could guarantee the production of granule with uniform size distribution.

Then the granule bulk strength was studied. It was found that the addition of micronized lactose could effectively enhance the granule strength comparing to the addition of HPC. For lactose, the addition of micronized lactose (from 5% to 10%) could enhance the granule strength from about 12.7% to almost 40%; for MCC the improvements are from 14.5% to 100%. Such improvements in granule strength were supported by the granule morphology obtained from a CT scanner that the use of micronized lactose would effectively reduce the porosity of granules; in addition, such improvements are capable to cause obvious difference in tablet properties (tensile strength, disintegration speed, etc.).

In general, it was found that micronized lactose has an excellent binding capabilities and could also guarantee a narrow size distribution, which provides a new option for the industry when selecting a suitable binding excipient.

Chapter 7. Effect of liquid binder temperature on granule properties

7.1. Introduction

The viscosity of liquid could affect the liquid-powder mixing and consequently affects the granule size distribution and the granule strength. Especially, when HPC solution was used, owing to its high viscosity, it is more difficult to achieve an even liquid-powder mixing than water.

One of the potential approaches to vary the liquid viscosity could be realized by controlling the liquid temperature. Although temperature, as a processing parameter, is controlled by the system, but it is regarded as the only parameter of the system that could affect the formulation properties. The increase in temperature could directly reduce the viscosity of the binder solution, making the liquid easier for distribution. As a result, the liquid solution tends to be more capable in distribution and dispersion and most importantly the effect of temperature on liquid viscosity, to a certain extent, is reversible. On the other hand, when solid binder is used, a higher temperature tends to accelerate binder particle dissolution, which makes more proportion of binder particles dissolve and form liquid bridges. Moreover, if soluble powder is utilized, it could dissolve quickly in a high temperature, which may also enhance the strength of bonds.

Using a higher temperature in twin screw granulation to achieve a better liquid-powder mixing has been discussed and some of the related techniques (hot-melt granulation) have

been applied in the industry. Barbara et al. (2006) used 50 to 60 ^{o}C to melt polyethylene glycol 4000 and used as a liquid binder for twin screw granulation. They concluded that using a high temperature could help PEG 4000 dispersion and the granules produced are stronger and more uniform. Sharleen et al. (2013) also used the hot-melt granulation (100 ^{o}C) to guarantee that the PEG 8000 could stay in the liquid phase while granulating.

Using a high temperature for twin screw granulation has been commonly studied. Although the use of a higher temperature would raise the cost for granulation, it effectively reduces the waste of unwanted granules which significantly increase the usage efficiency of the expensive API materials and reduce the cost of drying operations (Sharleen et al., 2013). Moreover, due to the fact that some of the API are thermolabile, the temperature used for twin screw granulation are normally below 100 ^{o}C, which in a certain extent reduces the concern about safety issue from using a high temperature (Liu et al., 2016).

Although using a high temperature for twin screw granulation has been widely applied, current attention is mainly focused on to melt-granulation process when a binder needs to liquefy. Less attention has been placed onto the improvement of liquid binder distribution using a high temperature.

In this chapter, the effect of granulation temperature, especially the temperature of liquid was studied. 25, 40 and 60 ºC were applied for twin screw granulation to study the effect of temperature on both binder delivery methods. Hydroxypropyl cellulose (HPC) was used as the examining binding excipient and prepared in both forms (liquid and solid).

7.2. Materials and method

7.2.1. Binder solution conditioning

To study the effect of liquid temperature, the binder was sealed using parafilm and heated on a hot plate with a temperature probe to maintain the temperature. In addition, to make sure the temperature could be evenly distributed, a magnetic stirrer was used with a rotation speed of 200 rpm. The temperature used in the experiment was chosen at 25, 40 and 60 ºC, respectively.

6.2.2. Effect of temperature on liquid penetration time

The compact powder bed was conditioned in an environment chamber with temperatures of 25, 40 and 60 ºC, respectively. The relative humidity was set at 40%. The compact powder bed was prepared by using the method in Section 3.5.1. During penetration experiment, the droplet with the same temperature was dropped on to the powder bed. To guarantee a relatively lower loss in heat during experiment, a hot plate was placed underneath the compact powder bed with a corresponding temperature. Equipment and set up utilized has been mentioned in Section 3.5.3.

6.2.3. Granulation temperature control

The barrel temperature was automatically controlled by the heater in the barrel and can be adjusted by using the panel on the twin screw granulator. In this experiment, the temperature and the barrel and liquid binder were controlled at 25, 40, 60 ºC, respectively. To reduce the loss of temperature while the liquid is being pumped through the pipe, a relatively shorter pipe was used and a temporary cover was used to enclose the pipe. During granulating, at least 5 mins are waited for the system temperature being stabilised. In this experiment, kneading elements were used.

7.3. Result and discussion

7.3.1. Viscosity

Among the liquid properties, viscosity is one of the key parameters to evaluate the liquid flowability and distribution capability. Table 7-1 lists the viscosity for HPC solution with different concentrations in different temperature. Firstly, a higher HPC concentration makes the viscosity higher and the liquid would be more difficult to distribute. As the temperature increases, the viscosity decreases for all binder samples, which indicates that a higher temperature could help the liquid distribution, which has a potential to wet more powder. Therefore, the liquid binder solution could achieve a better dispersion capability if a higher temperature is used. The study of binder viscosity enlightens a new direction in optimizing the liquid binder delivery method. Since the variation of temperature could affect the liquid viscosity, it is worthy to investigate if using a higher temperature could enhance the liquid wetting ability through the study of liquid penetration.

Table 7-1. Liquid binder viscosity (Pa·s) with different temperatures.

HPC	Temperature (°C)		
	25	40	60
0	0.0009±0.0008	0.0006±0.0018	0.0004±0.0006
2.5	0.0072±0.0101	0.041±0.0065	0.0015±0.0119
5	0.0245±0.0042	0.0180±0.0037	0.0017±0.0042

7.3.2. Penetration time

Penetration time reflects the distribution speed of liquid in a powder bed and is an indicator of wettability. A faster penetration time indicates a faster liquid distribution. The study of liquid penetration could reveal the effect of temperature on liquid binder distribution, which would further guide the twin screw granulation experiments.

Table 7-2 lists the penetration time affected by the variation of temperature when water or HPC solutions (2.5% and 5%, w/w) were used as a liquid binder. In general, lactose spent longer time for penetration. As was mentioned previously, it is because MCC is quite porous and the micro pores, gaps could enhance the liquid capillary motions, leading to a much shorter penetration time (Luukkonen et al., 2001, Fielden et al., 1988).

As the compression stress increases, penetration time becomes shorter. As was discussed in details in Chapter 4, A higher compression stress would smoothen the surface of the powder bed, making the liquid spread more freely.

In addition, an increase in liquid binder viscosity (higher HPC concentration) led to an increase in penetration time especially when 25 ºC was kept. Upon the increase of temperature, the penetration time reduces. It could be explained by the Washburn Equation **(2-8**) that a reduction in liquid viscosity (shown in Table 7-1) could shorten the time consumed for liquid penetration. Nevertheless, when water is used only, slight increases in penetration time could be seen on lactose powder beds. It is probably because an increase in temperature could increase the dissolution rate of lactose, which consequently increase the liquid viscosity and delay the penetration.

When HPC is used in solid form, penetration time is given in Table 7-3. At first, like the effect of an increase in compression stress, similar decrease in penetration time could be obtained, which is because a higher compresion stess would smoothen the powder bed surface and thus increase the wetting area. In addition, the addition of HPC was found to delay the liquid penetration. As was discussed in Chapter 3, it is because the undissovled HPC particles would delay the liquid from distribution.

Due to the use of water as the granulation liquid, the effect of temperature on liquid viscosity is quite limited. Nevertheless, increases in penetration time could be observed in some cases when lactose was used. It is because warmer liquid could acclerate the dissolution of soluble materials (here are lactose and HPC). A more viscous liquid would cause a delay in penetration. When MCC was used, much shoter penetration time could be observed, which is due to its porous struture. As the temperature increases, a reduction in penetration time could be obatained. The reason why MCC shows different correction to temperature comparing to that of lactose is because MCC is insoluble and would not dissoleve into water and increase the liquid penetration time; although a higher temperature could acclerate the dissolution speed of HPC, the limited penetration time did not provide sufficienct time for dissolution.

In general, when HPC solution was used, using a higher temperature could effectively reduce the liquid penetration, while the variation of temperature showed quite limited effect when HPC solid particles were used. If there was no HPC being added, an increase in temperature would delay the liquid penetration due to the dissolution of lactose. In general, the liquid binder was more sensitive to temperature than that of solid binder, which might be due to the lack of agitation when using a static compact powder bed.

Table 7-2. Penetration time (s) affected by the temperature and HPC solution concentration.

Powder	HPC	142 kPa			283 kPa			425 kPa			637 kPa		
		25 ºC	40 ºC	60 ºC	25 ºC	40 ºC	60 ºC	25 ºC	40 ºC	60 ºC	25 ºC	40 ºC	60 ºC
Lactose	0	0.149±0.010	0.149±0.037	0.149±0.011	0.110±0.010	0.111±0.031	0.112±0.023	0.067±0.013	0.071±0.028	0.071±0.033	0.040±0.027	0.042±0.007	0.047±0.033
	2.5	1.944±0.011	1.618±0.021	0.891±0.041	1.866±0.010	1.633±0.017	0.570±0.024	1.714±0.008	1.527±0.090	0.481±0.008	1.607±0.010	1.498±0.022	0.780±0.084
	5	5.860±0.040	5.135±0.119	1.937±0.021	5.768±0.067	5.135±0.119	1.533±0.021	5.624±0.009	5.135±0.119	0.810±0.021	5.580±0.106	5.135±0.119	0.837±1.021
MCC	0	0.023±0.001	0.023±0.001	0.022±0.003	0.022±0.002	0.022±0.000	0.022±0.005	0.021±0.001	0.020±0.002	0.019±0.001	0.020±0.001	0.021±0.002	0.019±0.005
	2.5	0.248±0.009	0.246±0.002	0.189±0.004	0.242±0.001	0.207±0.008	0.147±0.006	0.239±0.010	0.236±0.001	0.108±0.011	0.239±0.006	0.216±0.001	0.085±0.007
	5	1.020±0.002	0.991±0.027	0.570±0.021	0.970±0.009	0.950±0.011	0.521±0.017	0.968±0.009	0.784±0.015	0.360±0.047	0.956±0.005	0.784±0.001	0.279±0.013

Table 7-3. Penetration time (s) affected by the temperature on powder bed premixed with HPC solid particles.

Powder	HPC (%)	142 kPa			283 kPa			425 kPa			637 kPa		
		25 ºC	40 ºC	60 ºC	25 ºC	40 ºC	60 ºC	25 ºC	40 ºC	60 ºC	25 ºC	40 ºC	60 ºC
Lactose	0	0.149±0.010	0.149±0.037	0.149±0.011	0.110±0.010	0.111±0.031	0.112±0.023	0.067±0.013	0.071±0.028	0.071±0.033	0.040±0.027	0.042±0.007	0.047±0.033
	2	0.160±0.020	0.160±0.003	0.161±0.041	0.117±0.015	0.116±0.018	0.120±0.027	0.088±0.015	0.092±0.003	0.093±0.005	0.057±0.013	0.057±0.027	0.063±0.040
	4	0.167±0.005	0.167±0.039	0.169±0.047	0.122±0.004	0.123±0.009	0.124±0.013	0.096±0.016	0.097±0.005	0.099±0.021	0.065±0.019	0.068±0.011	0.071±0.009
MCC	0	0.023±0.001	0.023±0.001	0.022±0.003	0.022±0.002	0.022±0.000	0.022±0.005	0.021±0.001	0.020±0.002	0.019±0.001	0.020±0.001	0.020±0.013	0.017±0.022
	2	0.024±0.001	0.024±0.002	0.024±0.004	0.024±0.001	0.023±0.008	0.23±0.006	0.023±0.000	0.024±0.008	0.021±0.010	0.023±0.001	0.023±0.009	0.022±0.016
	4	0.025±0.001	0.025±0.020	0.022±0.021	0.025±0.001	0.025±0.011	0.023±0.017	0.023±0.002	0.022±0.007	0.021±0.001	0.022±0.001	0.022±0.007	0.021±0.007

Therefore, it is quite necessary to apply different temperature on the twin screw granulation process to further investigate the effect of temperature and the effect of binder delivery on granule properties.

7.3.3. Granule size distribution

7.3.3.1. Liquid binder delivery

Figure 7-1 shows the granule size distribution in different HPC concentration at 25, 40 & 60 ºC and Figure 7-2 is the span of distribution for the previous figure.

Concerning the effect of temperature, the use of a higher temperature, especially 60 ºC, reduced the production of fines and large granules (lumps), leading to narrower size distribution and smaller span clearly. It indicates that the use of a high temperature could effectively enhance the liquid distribution capability, leading to a more even liquid-powder mixing, as the use of high temperature could reduce the viscosity of liquid. It is reported by Tu et al. (2013) that normally the range of the span of distribution is between 1.5 to 4.5. In Figure 7-2, when 60 ºC was used, the span of distribution could achieve a value about 1.0, which is below this typical range. As is known, a smaller span of distribution indicates a better liquid-powder mixing and a more uniform granule size distribution. Therefore, the use of a high temperature could improve the span of distribution to a new level, which could not be easily achieve by other approaches.

When comparing the effect of HPC binder concentration, it could be seen that a higher HPC concentration leads to a wider granule size distribution and a larger span if the temperature is low. Specifically, a bimodal distribution could be obtained if a more HPC was used. It is because the addition of HPC could increase the liquid viscosity and thus decrease its distribution ability. As a result, the binder solution could not disperse properly

in the powder and cause a liquid uneven distribution. It indicates that if a high temperature is applied, the poor flowability and dispersion capability which widely exist in the liquid binder delivery method could be solved. When 60 ºC was used, the effect of HPC concentration became minor, as a high temperature could reduce the difference in viscosity of HPC solution with different concentrations.

The span of distribution provides a way to quantify the granule size distribution. Figure 7-3 compared the span of distribution obtained at 40 ºC and 60 ºC to that at 25 ºC, respectively. It is believed that, in most cases, the use of a higher temperature could effectively improve the span of distribution and narrow the size distribution. Especially, 37.2%, 39.5% and 42.5% reductions in span of distribution could be obtained when water, 2% HPC and 4% HPC were used at 60 ºC, respectively. Besides, it is noted that such improvement is more obvious when a more viscous liquid (4% HPC) was used.

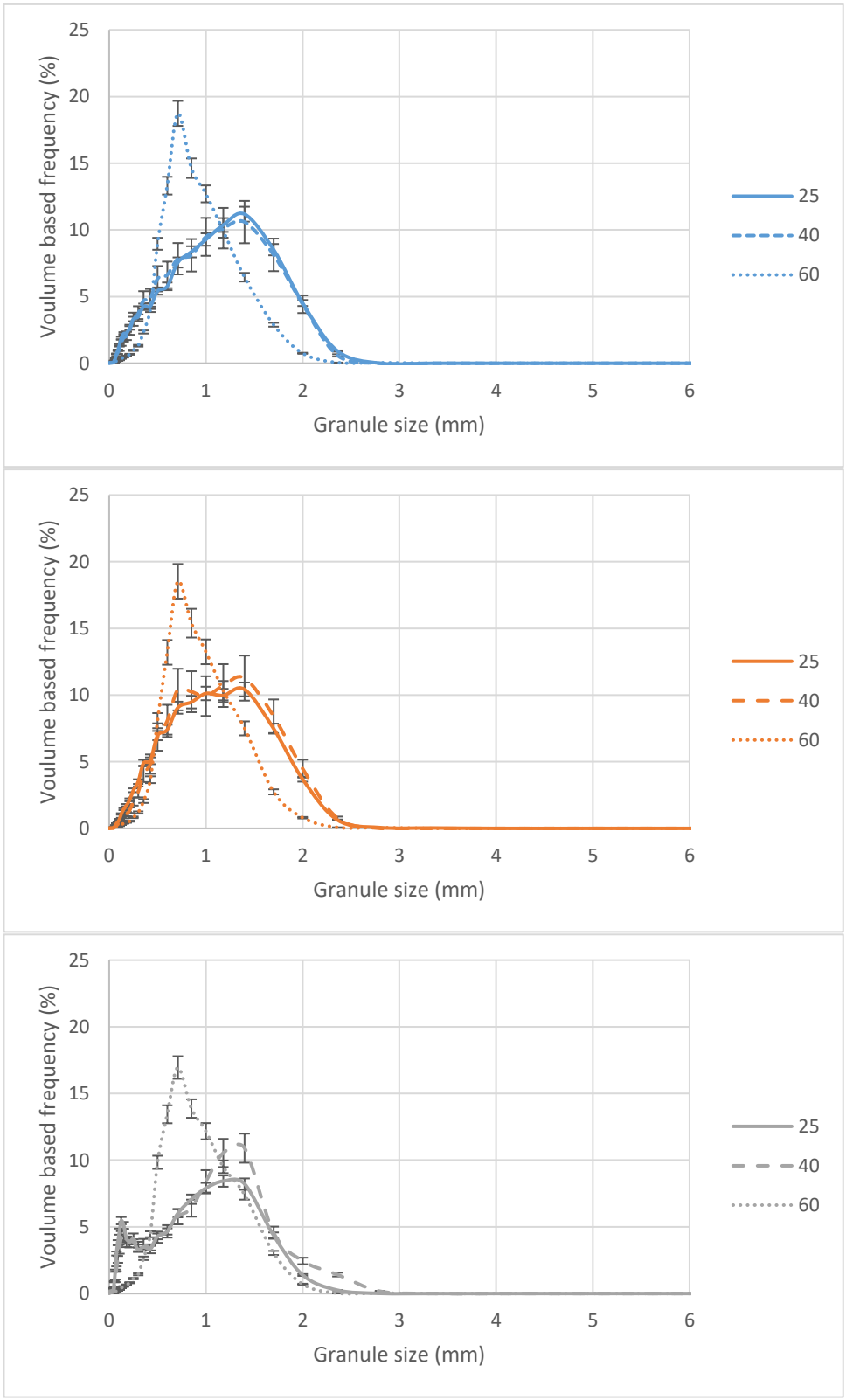


Figure 7-1. Lactose granule size distributions affected by the variation of temperature (25, 40 & 60 ºC) when water and HPC (2.5%, 5% HPC) solution were used.

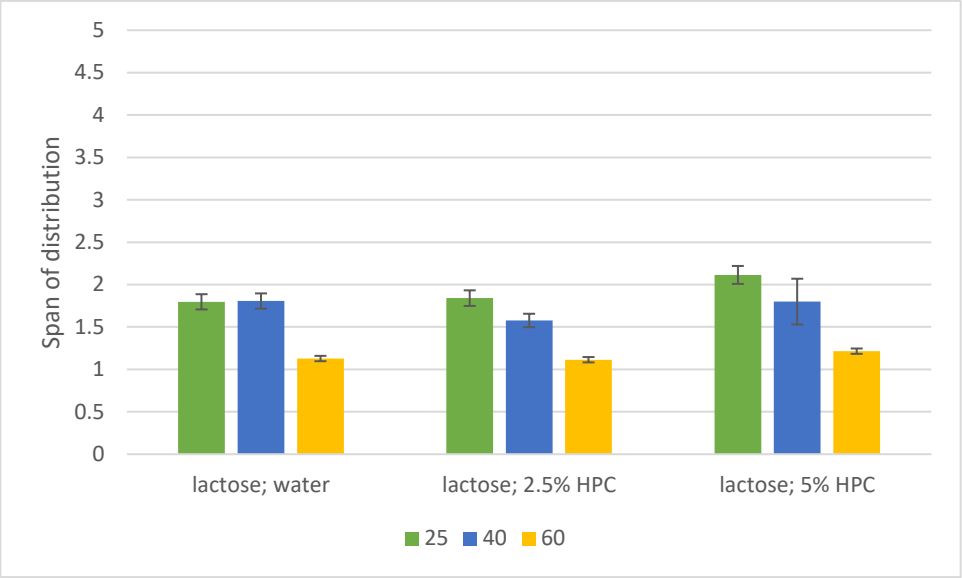


Figure 7-2. Span of distribution for Figure 7-1.

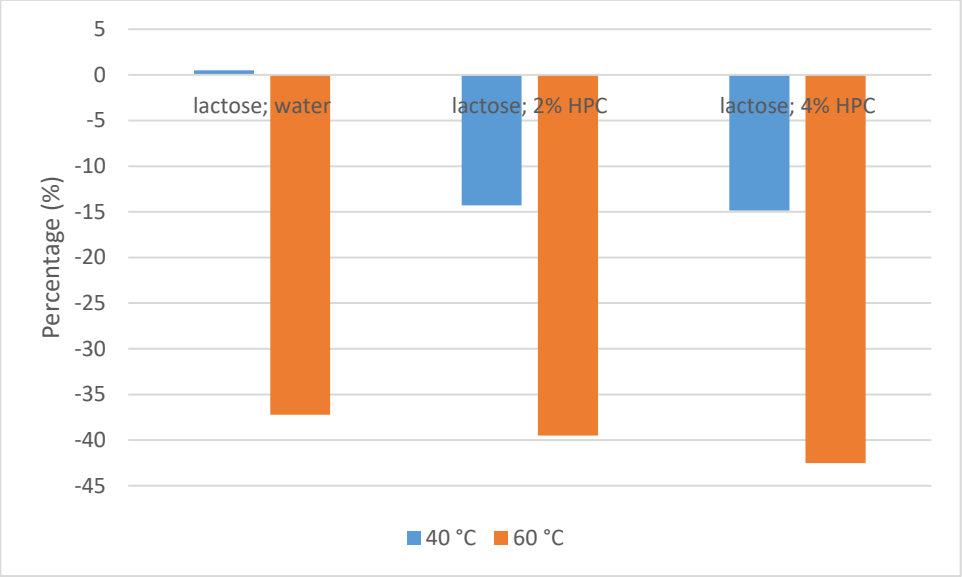


Figure 7-3. Improvement of span of distribution

MCC was also used to study the effect of temperature on granule size distribution and shown in Figure 7-4. When water was used, a higher temperature leads to fewer

proportion of fines being produced. As there is no binder being utilized, the formation of granules is mainly based on the interlocking of particles. The variation in granule size distribution may because a high temperature would make the MCC soften and more deformable, which could enhance the interlocking growth of particle and produces more larger granules. When HPC was applied, the effect of temperature was less obvious compared with that of lactose. It is probably due to the fact that MCC could swallow water and make the liquid become less available for distribution among in the powder.

The span of distribution is shown in Figure 7-5. At first, all spans of distribution are in the allowed range of 1.5 to 4.5. Due to the fact that MCC is insoluble, the span of distribution at 25 °C is larger than that of lactose. In addition, the addition of binder could effectively reduce the span of distribution. It is because the use of binder could help the agglomeration between particles and narrow the size distribution. Besides, it could be seen that the use of a higher temperature produces smaller span, which indicates that a narrower size distribution could be obtained at a higher temperature.

Span of distribution is a way to extract the information of granule size distribution. To quantify the improvement by using a higher temperature on twin screw granulation, the span of distribution obtained at 40 ^{o}C and 60 °C were compared with that at 25 ^{o}C and shown in Figure 7-6. It could be seen that the use of a higher temperature could reduce the span of distribution to different extents. Different from that of lactose, granulating with water at higher temperature achieved a better reduction in span of distribution. It is because water is more free flowing in the MCC particle and the would be easier to soak and soften the MCC particles, making them easier to deform and interlocking (Fielden et

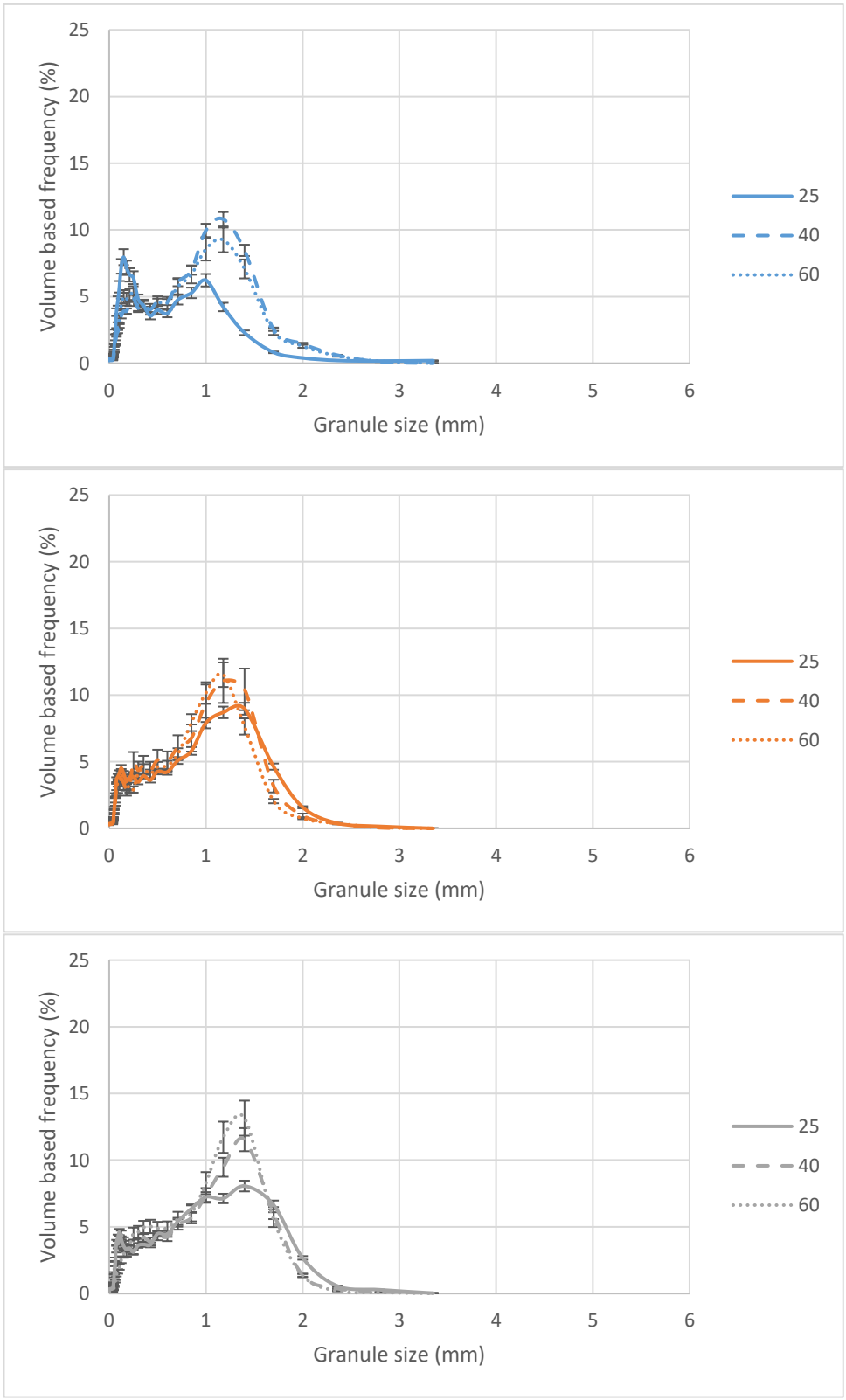


Figure 7-4. MCC granule size distributions affected by the variation of temperature (25, 40 & 60 ºC) when water and HPC (2.5%, 5% HPC) solution were used.

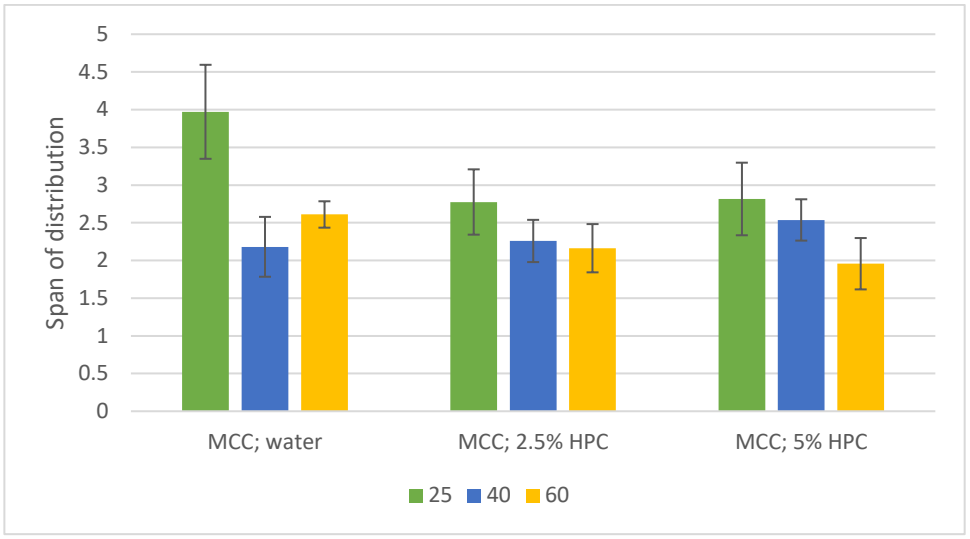


Figure 7-5. Span of distribution for Figure 7-4.

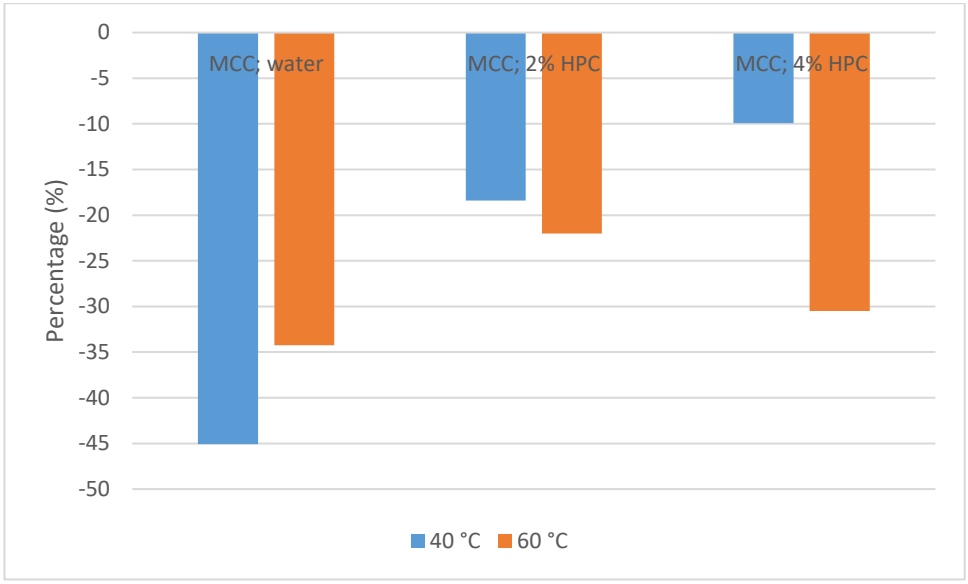


Figure 7-6. Improvement of span of distribution.

al., 1988). When HPC solution was used, a higher temperature of 60 °C could achieve a more significant reduction in span of distribution by 22.0% and 30.5%, respectively.

7.3.3.2. Solid binder delivery

Apart from the addition of HPC in liquid form (solution), HPC was also premixed into lactose and MCC to study the effect of temperature if solid binder delivery was applied. Figure 7-7 and Figure 7-8 shows the lactose granule size distribution and the span of distribution when solid HPC was premixed as a solid binding excipient.

In Figure 7-7, the increase in HPC concentration shifts the curves rightwards. It is because that the use of HPC could promote the growth of granules. Concerning the effect of temperature on granule size distribution, it was found that an increase in temperature could narrow the granule size distribution, indicating that a more even liquid-powder mixing could be realized when a high temperature was used. Therefore, in Figure 7-8 smaller span of distribution could be obtained when a higher temperature was used. It is because the use of a high temperature could intensify the movement of water and enhance its distribution ability. In addition, more HPC solid binder and lactose could be dissolved in a warmer liquid and enhance the strength of liquid bridge, causing more particles could be successfully agglomerated. As a result, when a higher temperature was used, less fines would be left and narrower granule size distribution could be achieved.

To quantify the effect of temperature on granule size distribution, the span of distribution at 40 ^{o}C and 60 ^{o}C were compared to that when 25 ^{o}C was used. It could be seen that, in most cases, the use of higher temperature (40 ^{o}C and 60 ^{o}C) could significantly improve the size distribution by reducing the span of distribution. Specifically, when 60 ^{o}C was used, the span of distribution reduced by 37.2% (for water),

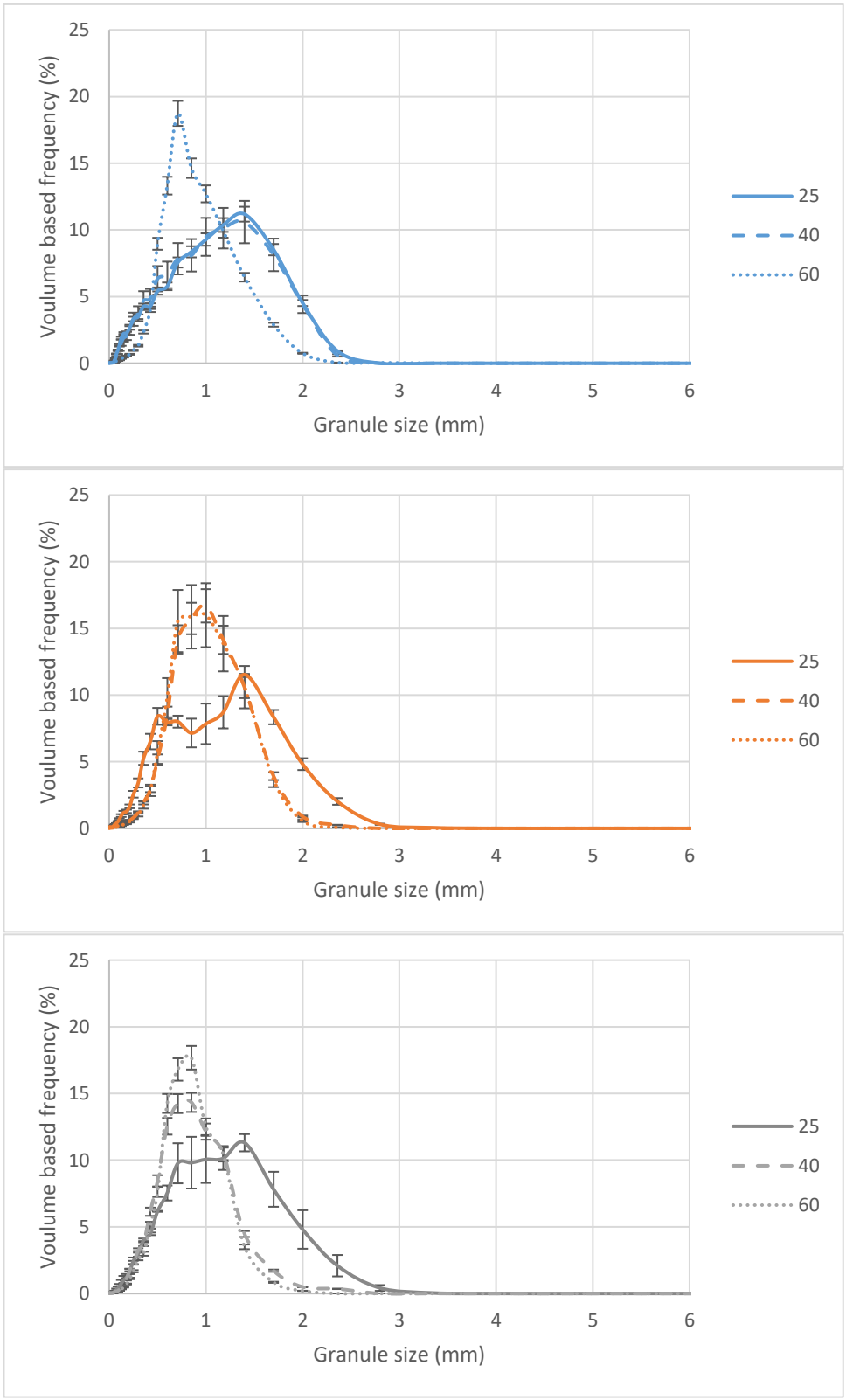


Figure 7-7. Lactose granule size distributions affected by the variation of temperature (25, 40 & 60 ºC) and solid HPC premixing (0, 2 & 4%).

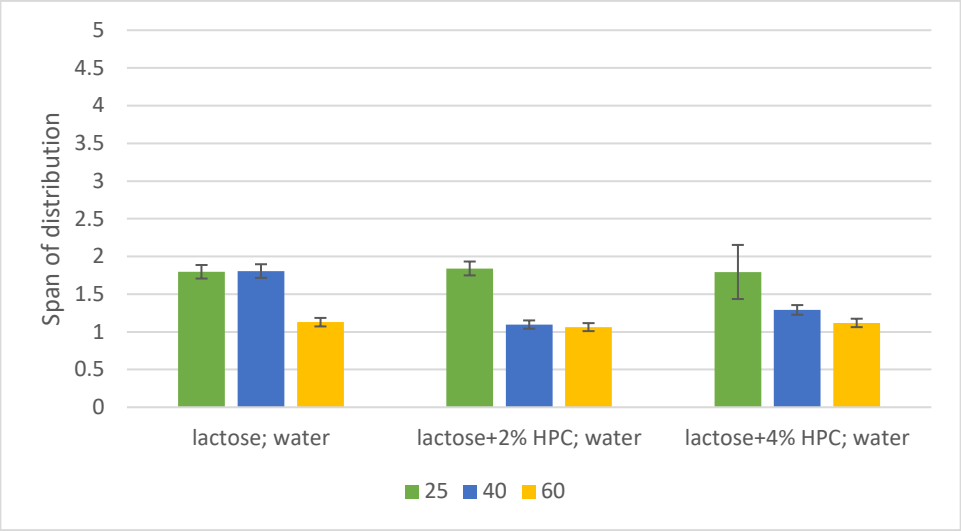


Figure 7-8. Span of distribution for Figure 7-7.

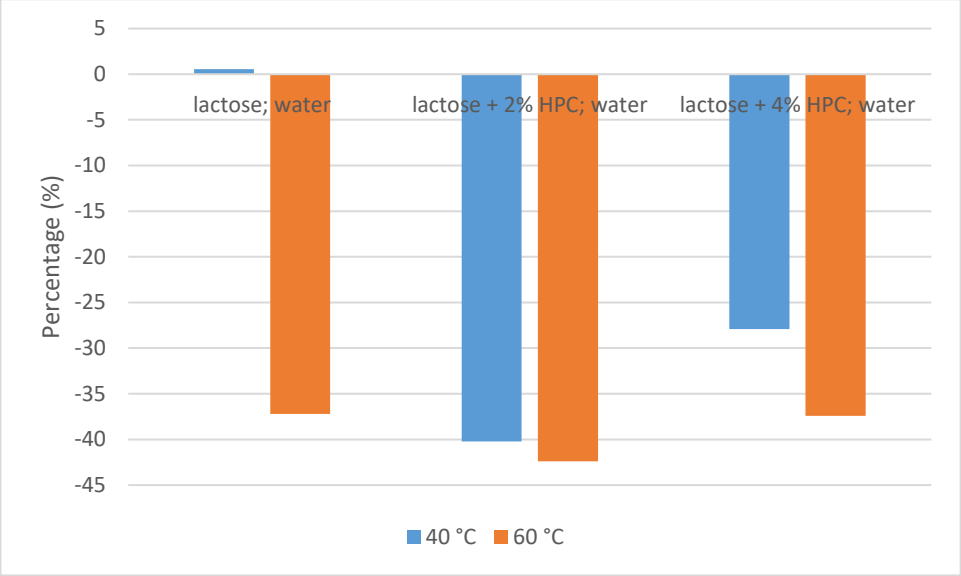


Figure 7-9. Improvement of span of distribution.

42.4% (for 2% HPC) and 37.4% (for 4% HPC), respectively.

Figure 7-10 and Figure 7-11 are the granule size distribution and the span for MCC with the addition of solid HPC. As the increase in HPC concentration, more large granules

(lumps) were produced and less fines were produced. It is because the addition of HPC enhances the binding capability of liquid bridge and thus promote the growth of granules. Overall, the effect of temperature on the granule size distribution is less obvious than lactose. It is because that MCC could hold water in its inner structure, leaving less portion of liquid for HPC dissolution and bonding. When a higher temperature was used, less fines large granules were produced. By checking the span of distribution, spans for 60 ºC are always smaller than 25ºC, indicating a narrower size distribution when high temperature was used. Compared with the Figure 7-5 where HPC solution was used, using HPC particle suggests a relatively smaller span, which indicates that the use of solid binder is more capable to have an even liquid distribution.

Figure 7-12 quantify the effect of temperature on MCC based on the span of distribution. In most cases, the use of a higher temperature reduces the proportion of fines and 60 ºC shows more obvious effect on the reduction of span of distribution (water: 34.3% 2% HPC: 15.7%, 4% HPC: 24.1%). The reason why when 2% HPC at 40 ºC shows a opposite effect may due to the operating error and the large error bar existed (Figure 7-10: middle).

The variation in granule size distribution is mainly resulted from the distribution of liquid and/or binder. In terms of the effect of temperature on binding capability, the granule bulk strength was measured.

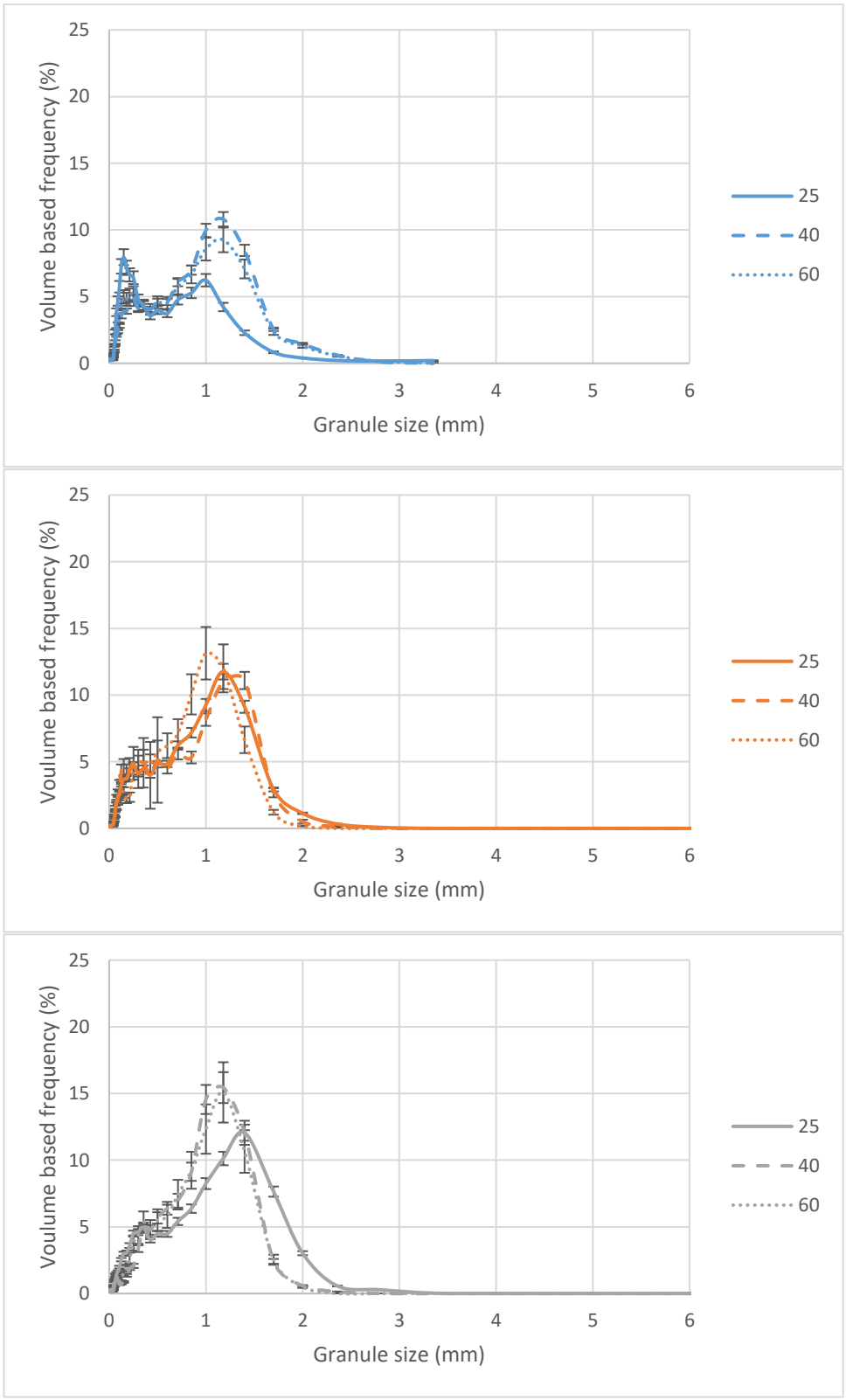


Figure 7-10. MCC granule size distributions affected by the variation of temperature (25, 40 & 60 ºC) and solid HPC premixing (0, 2 & 4%).

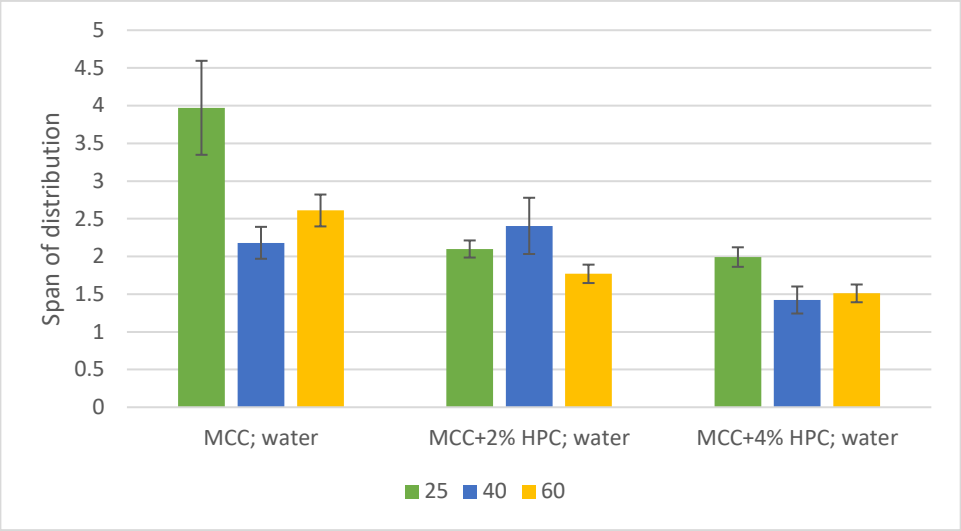


Figure 7-11. Span of distribution for Figure 7-10.

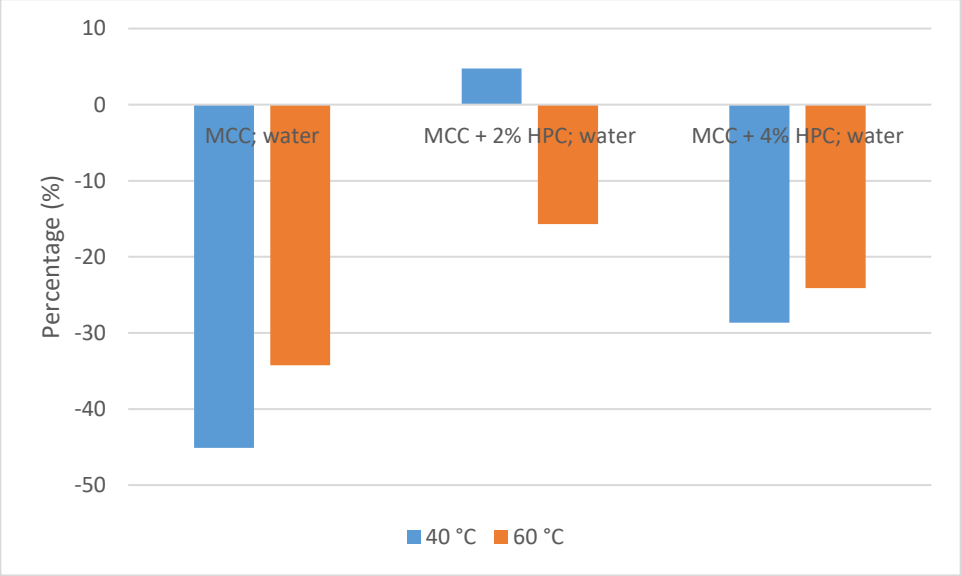


Figure 7-12. Improvement of span of distribution.

7.3.4. Granule bulk strength

Figure 7-13 shows the lactose granule bulk strength affected by the variations of temperature using HPC solutions. At first, it could be seen that all granules are stronger than 0.1 MPa, which indicates that the granule strength are all in the allowed range (Dhenge et al., 2012d, Dhenge et al., 2013, Saleh et al., 2015). The addition of HPC

increased the strength of granule, as it could enhance the strength of liquid bridges between particles. Secondly, as the temperature increased, the strength of granule increased slightly. Although the increase in temperature could promote the distribution of liquid by achieving narrower granule size distributions, its effect on lactose granule strength was less obvious. It might be because the total amount of binder is constant (by keeping the L/S ratio as a constant) during experiments (25, 40 & 60 ºC). Therefore, although the variation of temperature could change the distribution of binder, the total amount of bonds between particles for different temperature are similar. The variation of granule strength are believed to more rely on the variation of lactose dissolution at different temperature.

Figure 7-14 quantifies the effect of temperature on lactose granule bulk strength when HPC was used as liquid binder. It could be seen that liquid binder with higher viscosity shows higher improvement than lower one and the use of higher temperature could all enhance the granule strength to different extents. Especially, the use of 60 ºC could achieve better enhancements on granule bulk strength (water: 12.1%, 2.5% HPC: 28.9%, 5% HPC: 45.9%), which could effectively vary the granular product properties (e.g. tablet tensile strength, dissolution rate, etc.) (Horisawa et al., 1995).

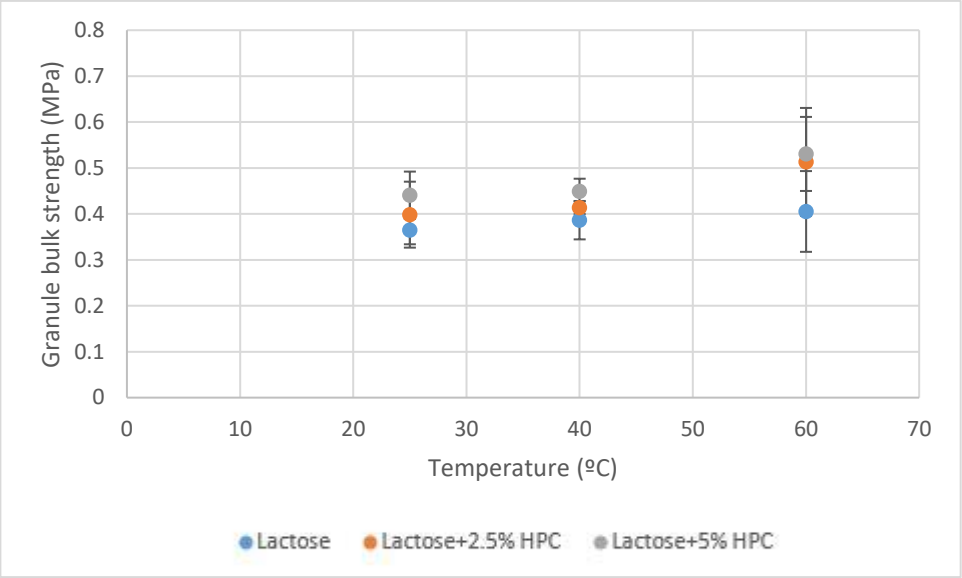


Figure 7-13. Lactose granule bulk strength affected by the variations of temperature (25, 40 & 60 ºC) when water and HPC (2.5%, 5% HPC) solution were used.

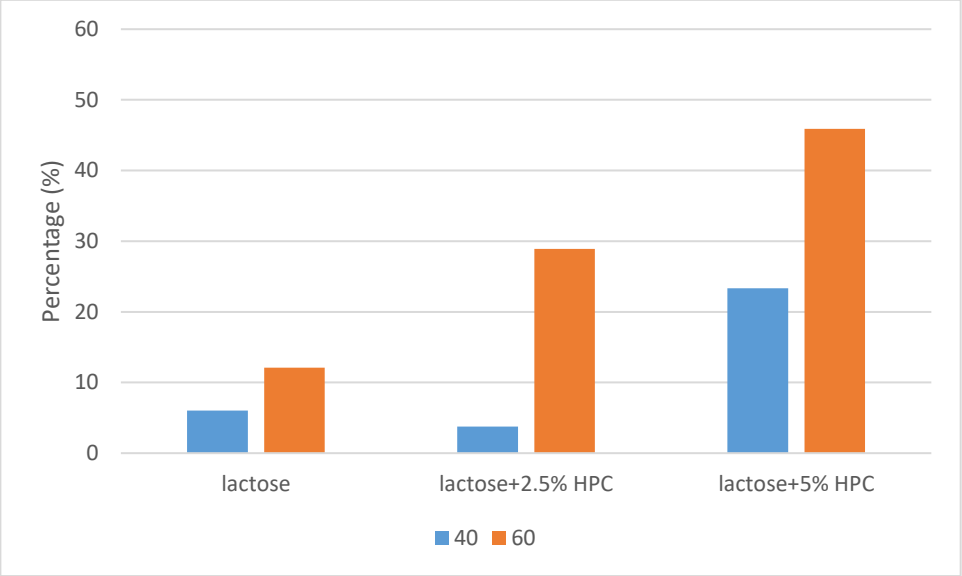


Figure 7-14. Improvement of bulk strength.

Figure 7-15 is the bulk strength when HPC binder particles were premixed and used as solid binder. At first, the addition of HPC could effectively enhance the granule strength for all cases. With the increase of temperature, compared with the use of HPC

solution, the granule strength increases more clearly. It might be because the use of higher temperature could accelerate the dissolution of HPC particles. When solid HPC were used at different temperature, although the total amount of binder was constant, the proportions of HPC which dissolved and participated in bond formations were varied. When a higher temperature was used, more HPC could dissolve and enhance the liquid bridges and bonds between particles, leading to a clearer increase in granule bulk strength. Moreover, an increase in lactose dissolution rate would further enhance the granule bulk strength when higher temperature were used.

To quantify the effect of temperature on granule bulk strength. Figure 7-16 compared the granule bulk strength at 40 ºC and 60 ºC to that at 25 ºC, respectively. In general, the use of high temperature was found to be effective on granule strength enhancement. Comparing with that when HPC solution was used in Figure 7-14, higher improvements could be obtained when HPC solid binder was used. As was mentioned, it is because the use of high temperature could dissolve more solid HPC, making higher fraction of binder participate in granule strength enhancement. A higher temperature was found to be more effective to enhance the granule strength (no binder: 10.7%, 2% HPC: 41.0%, 4% HPC: 57.0%).

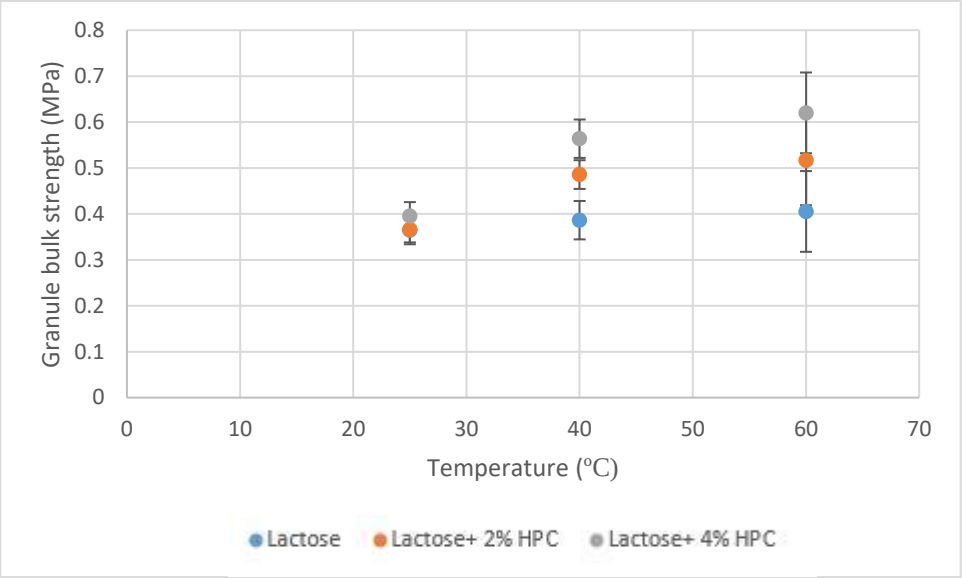


Figure 7-15. Lactose granule bulk strength affected by the variations of temperature (25, 40 & 60 ºC) and using HPC (0, 2 & 4%) in particles.

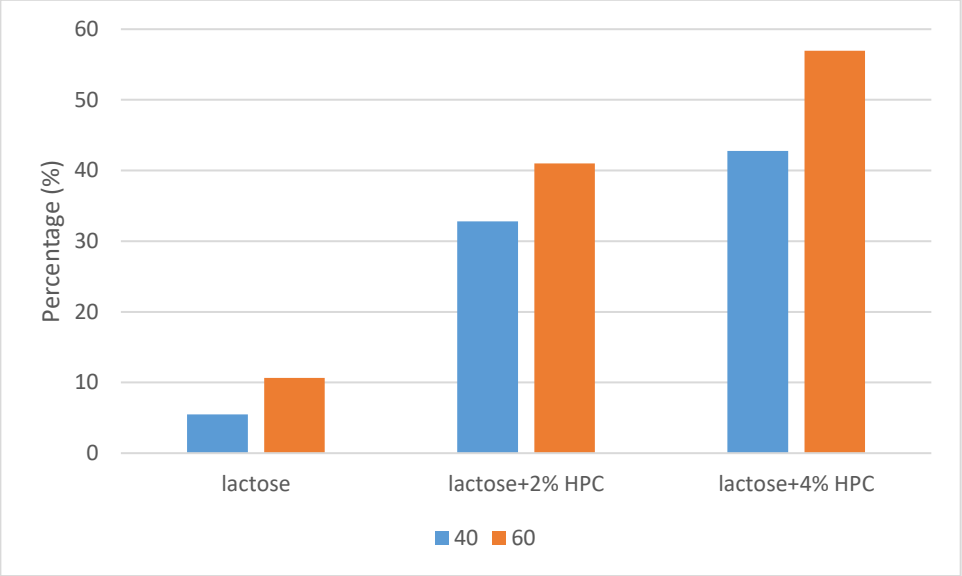


Figure 7-16. Improvement of granule bulk strength.

To reveal the effect of temperature on insoluble material, MCC was used for twin screw granulation and shown in Figure 7-17. Firstly, the addition of binder was found to enhance the granule strength and the granule strength are all in the allowed range (>0.1

MPa) (Dhenge et al., 2012d, Dhenge et al., 2013, Saleh et al., 2015). However, MCC granule strength was found to be much smaller than that of lactose shown in Figure 7-13. It is because MCC is insoluble and could not dissolve to enhance the bonds between particles. As the increase in temperature, the granule strength increases slightly and thus tendency is quite unclear. It is probably because MCC could swallow water and thus the effect of HPC concentration on granule strength would be reduced; In addition, the enhancement in liquid distribution may not directly affect the granule strength as the total amount of HPC for each temperature was constant. Therefore, it could be concluded that the variation of temperature could not vary the MCC bulk strength effectively when HPC solution was used.

Similar statement could also be concluded from Figure 7-18 that effect of temperature contributed limited influences on the granule bulk strength when compared with that of lactose shown in Figure 7-14. It was noted that when MCC was granulated with water, no difference could be obtained at different temperature and the value shown in Figure 7-14 is close to 0. It is because MCC is insoluble and the bonds between particles are resulted from the physical interlocking rather than liquid bridges. Therefore, unclear effect of temperature on granule bulk strength could be obtained. In addition, the difference between 40 ºC and 60 ºC are unclear. It is because that a part of liquid was absorbed and held in the MCC particles, leaving limited insufficient amount of liquid for bonding and the limited bonds between particles may be insufficient to vary the granule strength clearly under different temperature. In general, it could be concluded that the use of HPC solution was incapable to affect the granule bulk strength clearly. Based on literature, such variation in granule strength (larger than 5%) would affect the granular

product properties effectively (Horisawa et al., 1995). Therefore, varying temperature is applicable to enhance the granule properties if HPC solution and MCC were used.

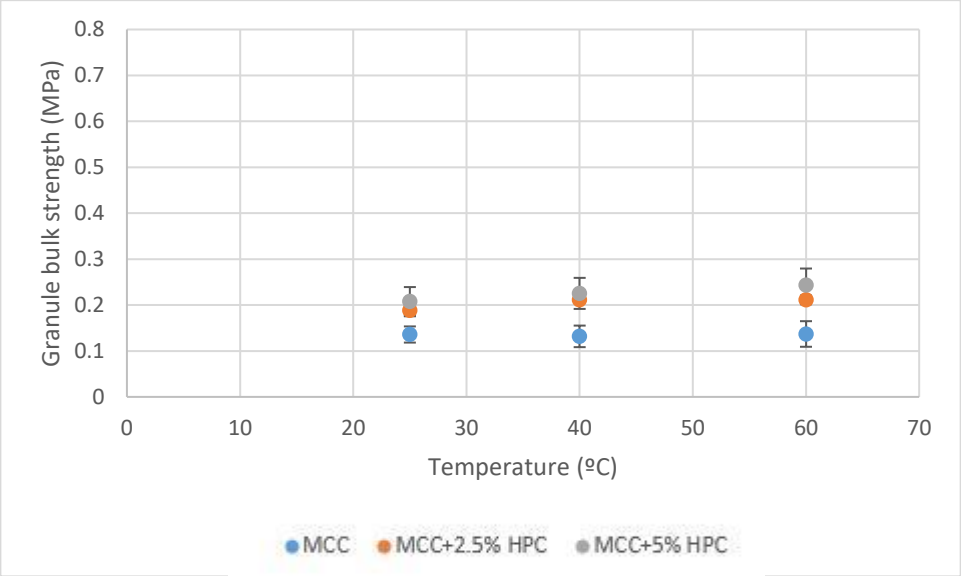


Figure 7-17. MCC granule bulk strength affected by the variations of temperature (25, 40 & 60 ºC) using when water and HPC (2.5%, 5% HPC) solution were used.

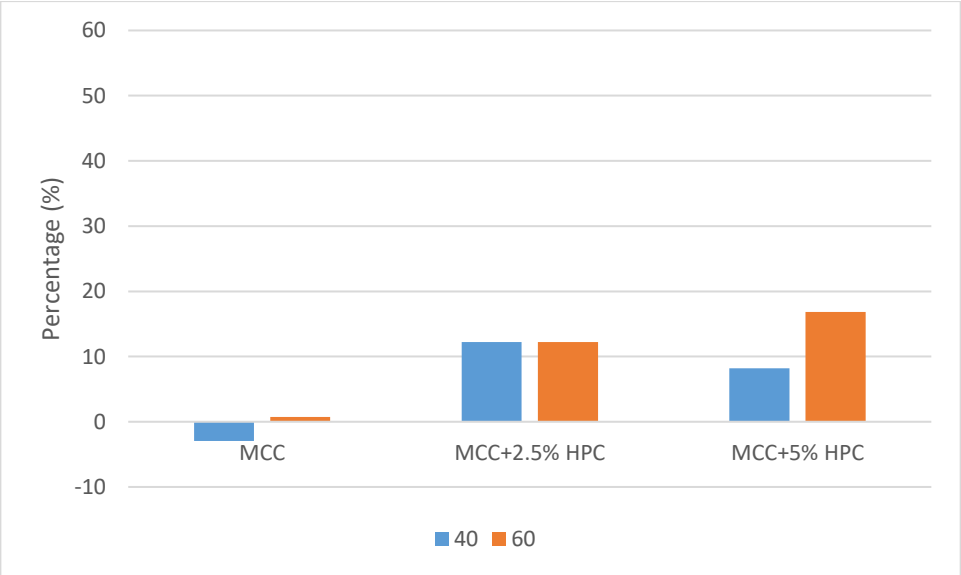


Figure 7-18. Improvement of granule bulk strength.

Compared with the use of HPC, the increase in granule strength was more obvious when HPC particles were used and shown in Figure 7-19. Firstly, the addition of HPC solid binder shows clearly enhancements on granule bulk strength. It is because the addition of HPC could enhance the bond strength between particles. Secondly, it was found that clear increases in granule strength (2% and 4% HPC) could be obtained when higher temperature were used. It is because the use of high temperature could enhance the dissolution of solid HPC particles, making higher proportion of HPC particles dissolve and participate to enhance the liquid bridges, which produced stronger bonds and strengthen the granule. Although liquid would be absorbed into the MCC particles, the wetted and sticky HPC particles would act like bonds between particles and thus enhance the granule bulk strength (Ai et al., 2016).

Figure 7-20 quantifies the effect of temperature on granule strength enhancement. When HPC was added, clearly enhancements in granule strength could be observed. Concerning the effect of temperature, using 60 ^{o}C was found to be more capable to enhance the granule strength by 72.2% and 52.9% when 2.5% HPC solution and 5% HPC solution were used, respectively, which would significantly affect the granular product properties (e.g. tablet tensile strength, dissolution rate, etc.) (Horisawa et al., 1995).

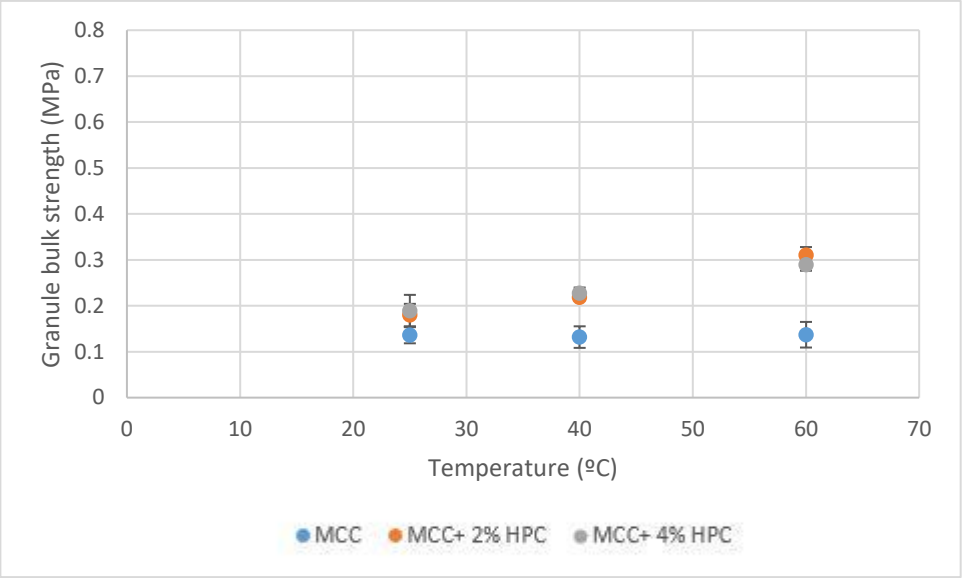


Figure 7-19. MCC granule bulk strength affected by the variations of temperature (25, 40 & 60 ºC) and using HPC (0, 2 & 4%) in particles.

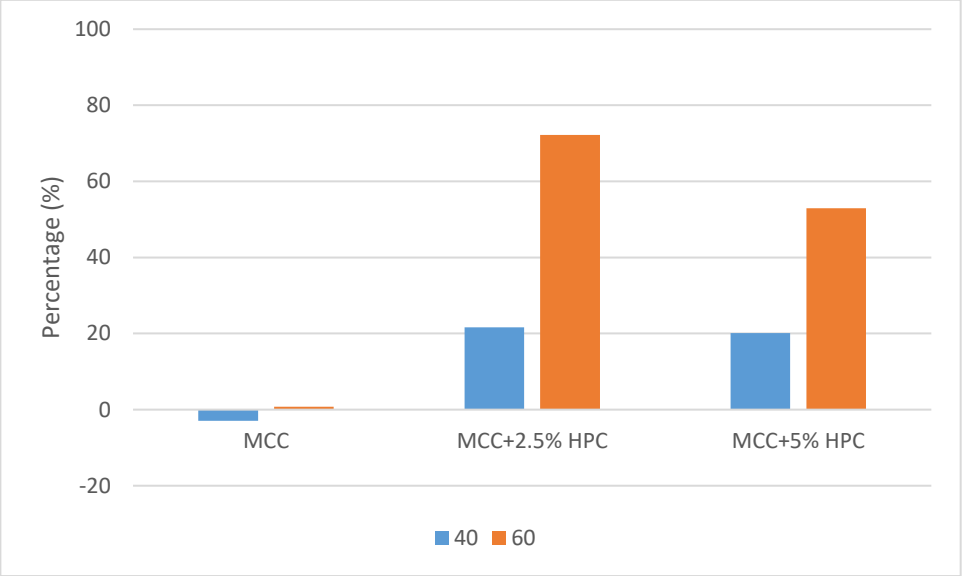


Figure 7-20. Improvement of granule bulk strength.

7.3.5. Granule morphology

Figure 7-21 shows the lactose granule x-ray images using HPC solution at different temperature. At 25 ºC, the increase in HPC concentration made the granule become more

inhomogeneous in structure. Especially, when 5% HPC solution was used, parts of granules were much denser than the rests. As was indicated by Dhenge (2010d), an increase in binder concentration would reduce the granule porosity. Therefore, it is believed that the inhomogeneous in structure was resulted from the uneven distributed liquid binder. As the temperature increases, the granule structure becomes more homogeneous, indicating that the use of high temperature could promote the liquid distribution. Granules with homogeneous structure would be stronger in strength, which agreed with the granule bulk strength experiment that a higher temperature produced stronger granules.

Figure 7-22 lists the MCC granule x-ray images using HPC solution at different temperature. Compared with that of lactose shown in Figure 7-21, MCC granules are denser and more homogeneous. It is because the agglomeration of MCC particles are mainly based on particle deformation. Owing to the compression from kneading elements, MCC granules would deform significantly and the granule would be much less porous. With the increasing of HPC solution, a slightly denser in granule structure could be observed at 25 ºC. As was mentioned, it is because the use of binder could provide more bonds and densify the granules. Such tendency become unclear when higher temperature was used. In Figure 7-22, an increase in temperature was found to produce the granules with higher porosity. Normally, the pores in the granules are regarded as the signature of liquid. The more porous granules at higher temperature may be resulted from more intensive evaporation at higher temperature.

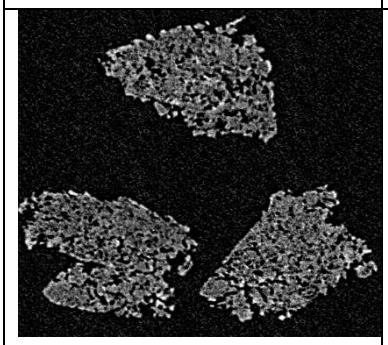
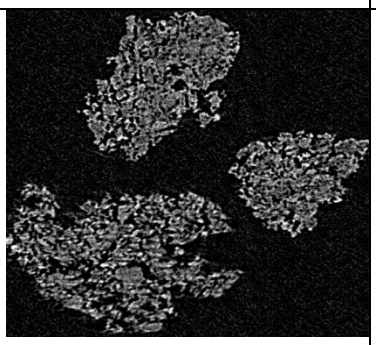
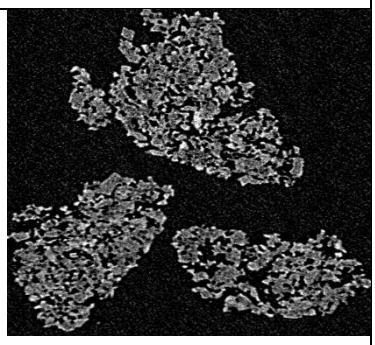
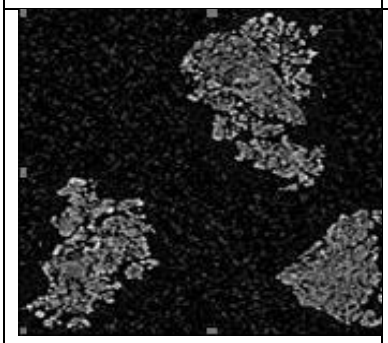
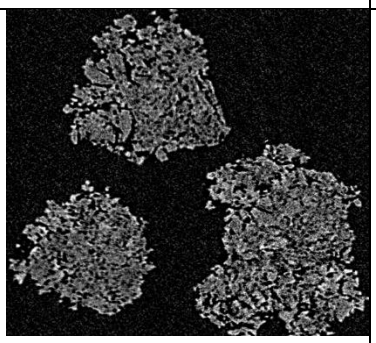
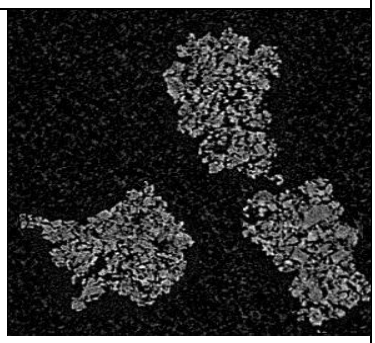
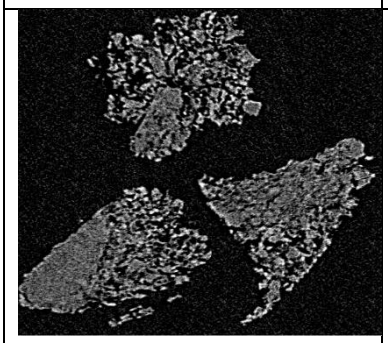
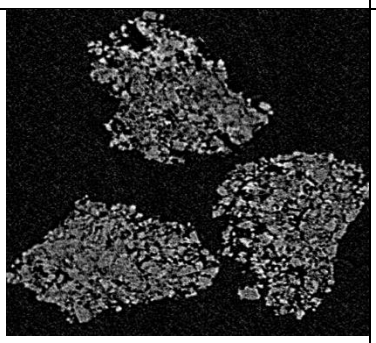
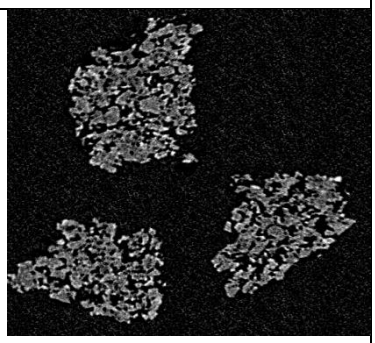
Water 25 ºC	Water 40 ºC	Water 60 ºC
		
2.5% HPC solution 25 ºC	2.5% HPC solution 40 ºC	2.5% HPC solution 60 ºC
		
5% HPC solution 25 ºC	5% HPC solution 40 ºC	5% HPC solution 60 ºC
		

Figure 7-21. X-ray images for lactose granules produced at temperatures of 25, 40 & 60 ºC when water and HPC (2.5%, 5% HPC) solution were used.

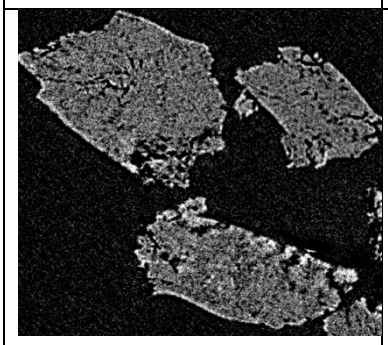
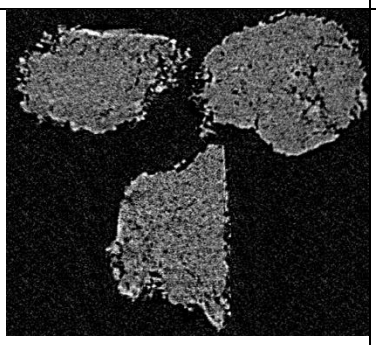
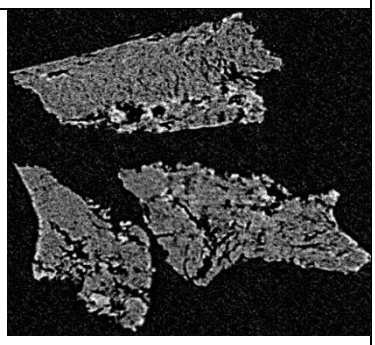
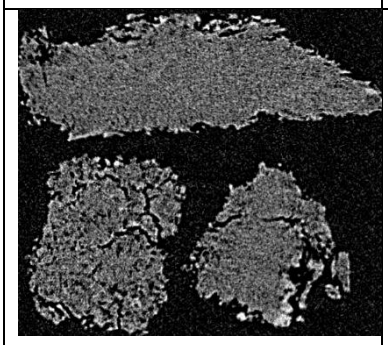
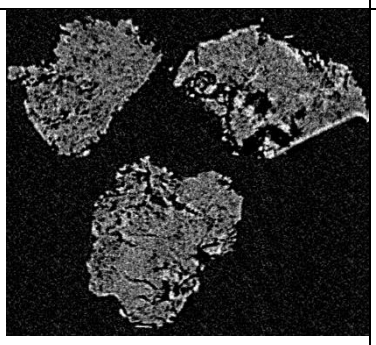
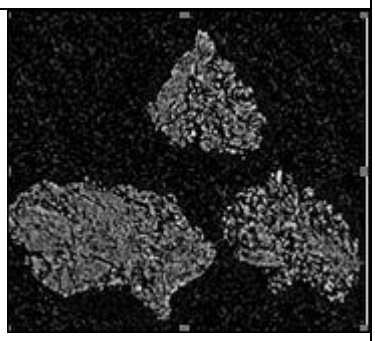
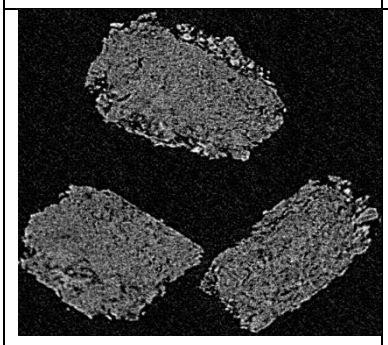
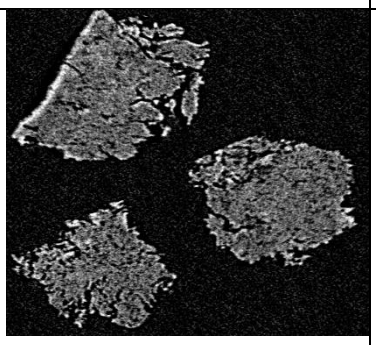
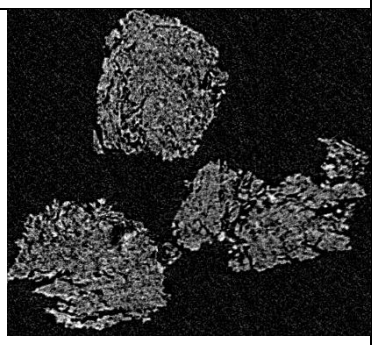
Water 25 ºC	Water 40 ºC	Water 60 ºC
		
2.5 % HPC solution 25 ºC	2.5 % HPC solution 40 ºC	2.5 % HPC solution 60 ºC
		
5% HPC solution 25 ºC	5% HPC solution 40 ºC	5% HPC solution 60 ºC
		

Figure 7-22. X-ray images for MCC granules produced at temperatures of 25, 40 & 60 ºC when water and HPC (2.5%, 5% HPC) solution were used.

Figure 7-23 shows the x-ray images of lactose granules at different temperature using solid HPC binder. Compared with the use of HPC solution, granules produced using HPC solid binder are more homogeneous for all cases. It might be because the liquid used was water. Although part of HPC could be dissolved and affect the liquid viscosity, the effect was less obvious than that if HPC solution was used. Because of this, it could be seen that the effect of temperature on granule porosity was less obvious than if HPC solution was used.

In terms of MCC, Figure 7-24 shows that the MCC granules were much denser than lactose. As was mentioned, it was because the agglomeration of MCC particles are mainly based on particle interlocking. Due to the intensive compression from kneading elements, the particles were deformed and denser granule would be produced. Similar to that of lactose shown in Figure 7-23, there is no clear tendency between granulation temperature and granule porosity. It is because the liquid used was water which was less affected by the temperature. Although HPC particles may participate and dissolve into the liquid, the limited amount of dissolved HPC may not sufficient to vary the liquid property (viscosity) significantly.

In general, it was found that temperature could affect the granule porosity when liquid binder was used that a higher temperature could make the granule structure more homogeneous. When HPC particles were used, no clear effect from temperature could be obtained.

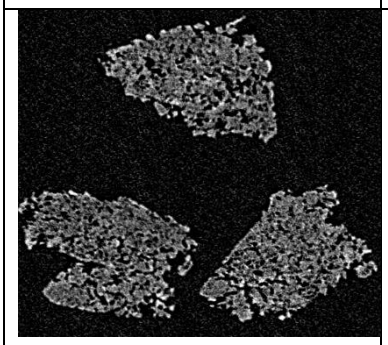
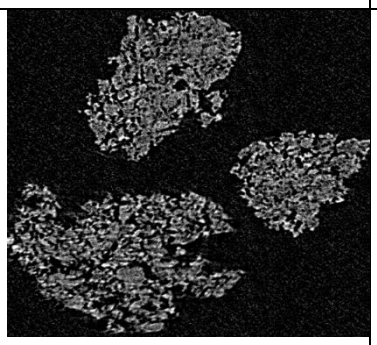
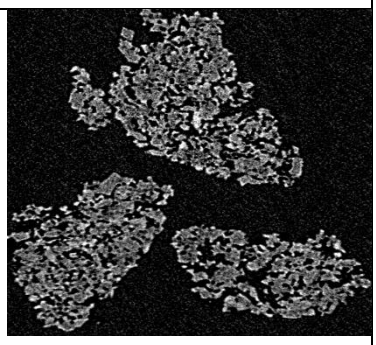
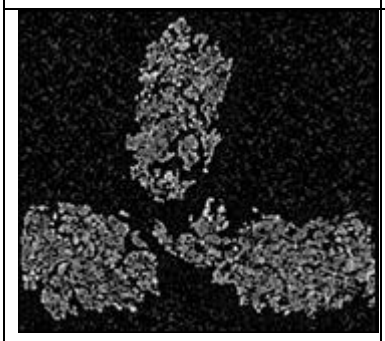
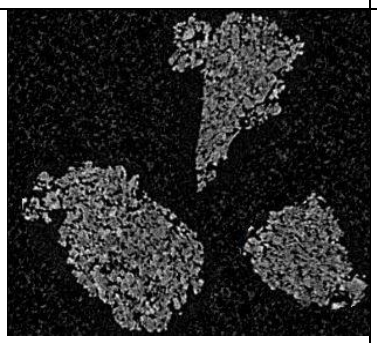
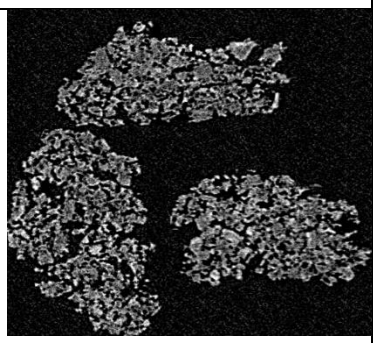
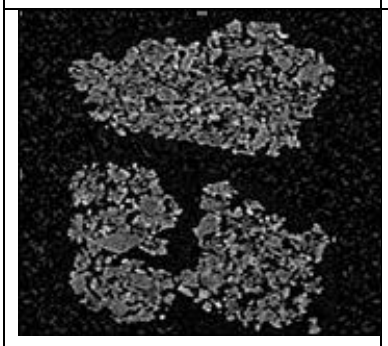
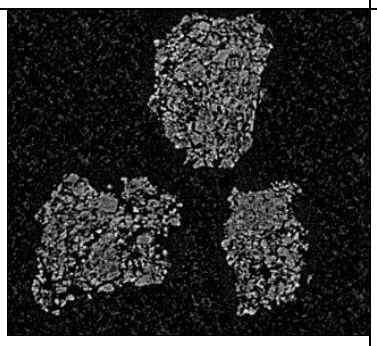
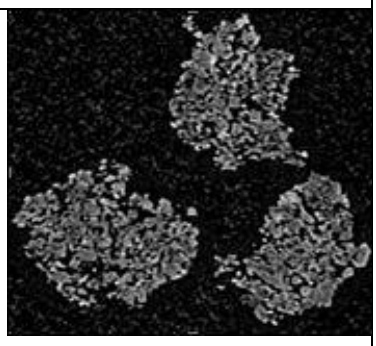
Lactose 25 ºC	Lactose 40 ºC	Lactose 60 ºC
		
2% HPC 25 ºC	2% HPC 40 ºC	2% HPC 60 ºC
		
4% HPC 25 ºC	4% HPC 40 ºC	4% HPC 60 ºC
		

Figure 7-23. X-ray images for lactose granules produced at temperatures of 25, 40 & 60 ºC when HPC (2%, 4% HPC particle) particles were used.

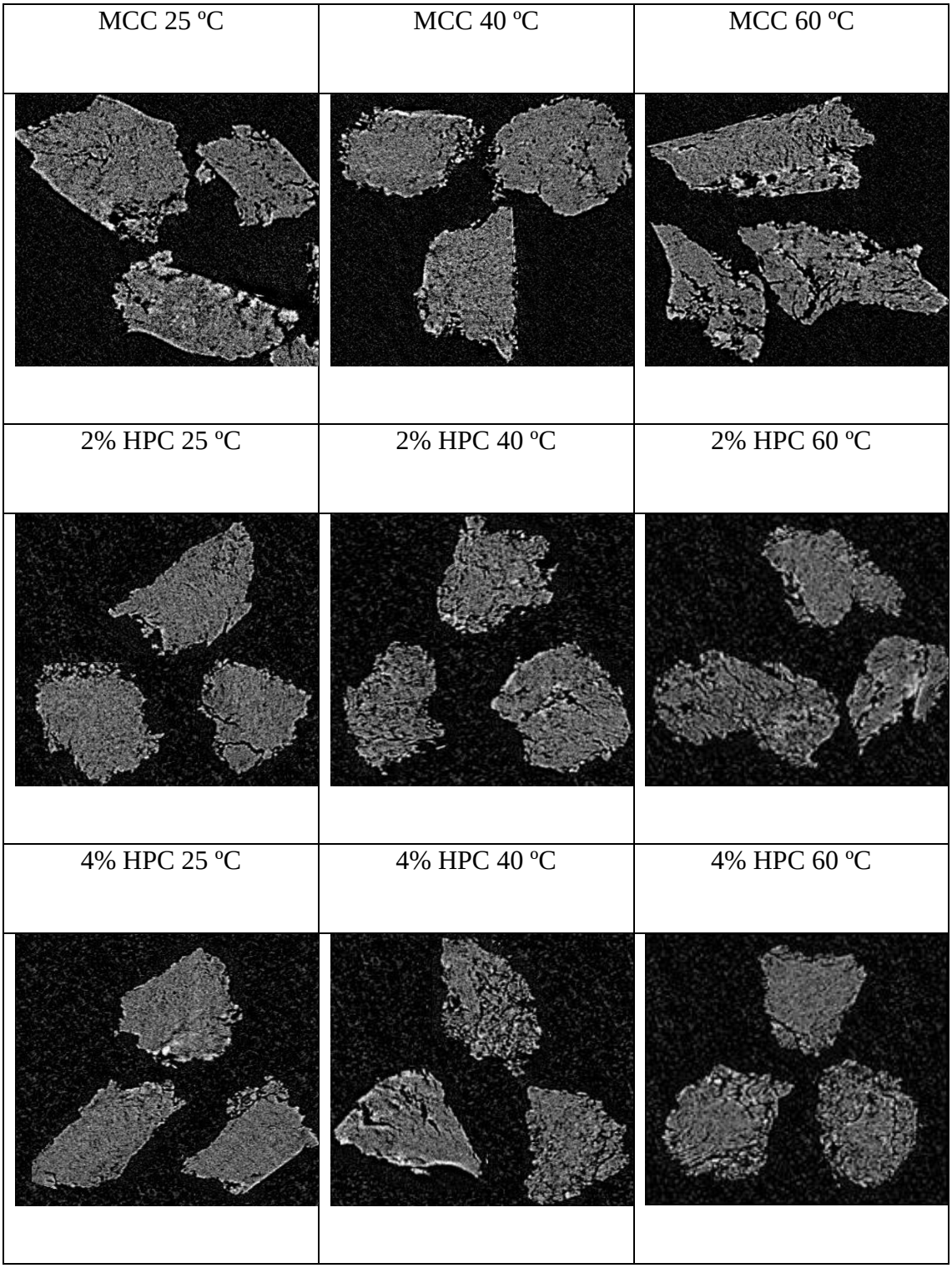


Figure 7-24. X-ray images for MCC granules produced at temperatures of 25, 40 & 60 ºC when HPC (2%, 4% HPC particle) particles were used.

7.4. Conclusion

In this chapter, temperature as an independent variable is investigated. HPC was prepared in two forms: dissolved in water as a solution and premixed with granulation powders.

The use of high temperature was considered to be useful in narrowing granule size distribution and enhancing the granule strength. It is because the use of a high temperature could reduce the liquid viscosity and help the liquid distribution. It was found that Granulating at 60 ºC could significantly enhance the liquid distribution by producing narrower size distribution and smaller spans and such enhancements are more obvious when more viscous HPC solution or HPC particles were added. For liquid binder delivery, using HPC solution at 60 ºC could reduce the span of distribution by about 42.53% for lactose and 30.50% for MCC, respectively. When solid HPC was premixed, using a formulation of HPC particles premixed at 60 ºC could reduce the span of distribution by about 37.43% for lactose and 28.64% for MCC, respectively. In general, it was found that using a high temperature is capable to effectively affect the granular product properties (Tu et al., 2013).

Concerning the effect of temperature on granule bulk strength, higher temperature is more capable to enhance the granule strength when HPC was used in a solid form. It was found that for when solid HPC was used at 60 ºC, the maximum improvement in granule strength could be as much as 45.88% for lactose and 72.22% for MCC, whilst only 45.88% for lactose and 16.83% for MCC could be achieved when HPC solution was used. Therefore, temperature was found to be effectively affect tablet properties and following granular products (Horisawa et al., 1995).

In this chapter, the effect of temperature on twin screw granulation was studied. By compared with the approach from literature, it was found that, in most cases, adjusting the temperature to improve the granule size distribution and granule bulk strength is a useful and effective way, especially for soluble material (e.g. lactose). Although the raise in granulation temperature may potentially increase the costs for granulation, it could significantly save the energy for the following operation steps (e.g. drying) and a batch of granule with more uniform size could save a considerable amount of expensive API in a long term. Therefore, raising temperature to enhance the liquid distribution and binding efficiency should be advised to the industry for further study and application.

Chapter 8. Effects of screw speed and configuration on granule properties for a constant fill level

8.1. Introduction

In batch granulation process, the granulation process parameter is less possible to change the fill level of material. However, as a continuous granulation process, the liquid and powder are "flowing" in the twin screw barrel and consequently the level of material in the barrel can be varied through process parameters easily. The level of the material in the barrel is defined as fill level and it is stated that the change of fill level directly affects the compaction of materials which determines the granule attributes e.g. size and strength (Kolter et al., 2012, Dhenge et al., 2011). In twin screw granulation process, the variation of fill level is often comes with the change of other parameters such as screw speed, which makes conflict and contradictory in literature when parameters such as screw speed was studied.

To overcome this problem, a parameter of "specific feed load" was raised and defined as the ratio of feed rate and screw speed (Kolter et al., 2012). It was applied to provide a constant fill level environment. However, researches about the specific feed load are limited in "one applied system" and are invalid for different screw configuration, formulation, etc. (Meier et al., 2017). Particularly, based on the definition of "volumetric

fill level", as long as the feed rate and screw speed are constants, the variation of screw configurations, material properties and granulator dimensions do not affect the fill level.

In this chapter, a new definition of barrel loading (BL, g) will be raised, which represents the mass of powder and liquid in granulation barrel for the specific condition (screw speed, configuration, etc.). By maintaining the BL, study on the processing parameter e.g. screw configuration, screw speed in dynamic wet granulation can be carried out and their effects on granule properties could be obtained.

8.2. Materials and method

8.2.1. Determine of specific powder feed rate

8.2.1.1. Residence time

The method used for residence time measurement was mentioned in Section 3.6.2. For each formulation, screw speed of 50, 100, 200 rpm has been used. For each screw speed, the feed rate shown in Table 8-1 was used and the residence time is shown in Figure 8-2 and Figure 8-3. In Figure 8-2, the red colour represent the condition which could not be applied, as the amount of material is more than the maximum capacity of the barrel.

Table 8-1. Feed rate applied for residence time recording (Green: used; Red: unused).

Feed rate (kg/h)	50 rpm	100 rpm	200 rpm
0.5			
1			
2			
3			

8.2.1.2. Barrel loading

In order to investigate the effect of processing parameters including screw speed and screw configuration, a controlled barrel loading (BL, g), was required by maintaining the mass of powder and liquid as constant.

To achieve it, the mass of the material (powder and liquid) in different screw speeds and configurations could be obtained using the following equation:

$$\boldsymbol{m_{total} = m_{powder} + m_{liquid} = m_{powder} \times (1 + {}^{L}/_{S}\, ratio)} \quad (8\text{-}1)$$

$$\boldsymbol{BL = t_r \times m_{total}} \quad (8\text{-}2)$$

where m_{powder} refers to the powder gravimetrical feed rate (kg/h); m_{liquid} refers to the liquid gravimetrical feed rate (kg/h); BL refers to the total mass of material in the barrel (powder and liquid, g); t_r (s) refers to the average residence time for the corresponding material, screw speed and configuration.

8.2.1.3. Feed rates

The relationship between BL and total feed rate m_{total} could be plotted and shown in the Appendix C. A typical relationship figure is shown in Figure 8-1. As the powder was overflowed when the BL goes above ~20 g. Therefore, a medium BL 10 grams were chosen as the constant BL value and the corresponding total feed rate for a constant BL of 10 grams could be obtained.

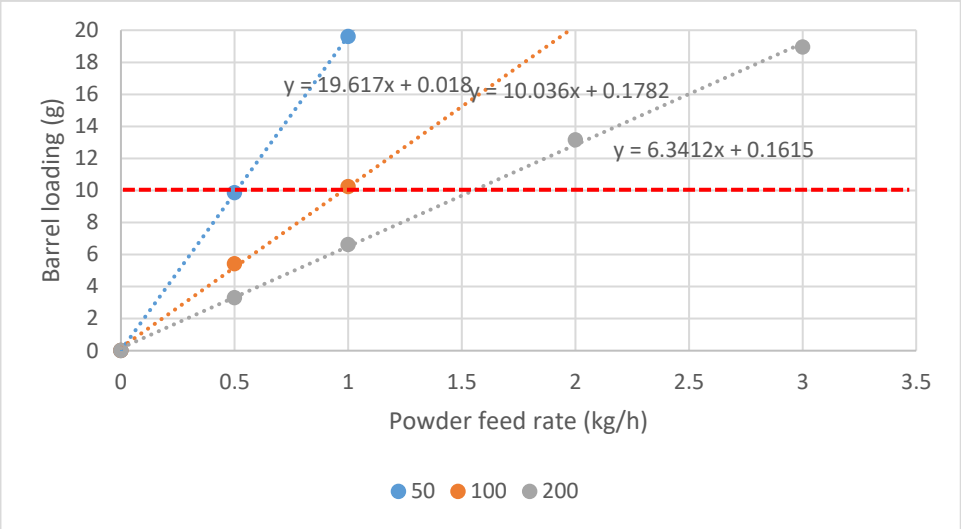


Figure 8-1. Typical barrel loading for feed rate (blue: 50 rpm; orange: 100 rpm; grey: 200 rpm).

8.2.2. Preparation of granules

A constant L/S ratio of 0.08 was utilized for lactose granulation and 0.8 was utilized for MCC granulation. Two sets of screw configurations were applied which has been mentioned in Section 3.6.1. To investigate the effect of screw speed, the screw speed was varied (50, 100 & 200 rpm). Powder feed rate and liquid feed rate was determined by the relationship between the BL and the feed rate and shown in Table 8-2 and Table 8-3.

Table 8-2. Powder feed rate (kg/h).

lactose						
	Kneading			Conveying		
	50 rpm	100 rpm	200 rpm	50 rpm	100 rpm	200 rpm
water	0.509	0.979	1.551	0.760	1.616	3.302
2.5% HPC solution	0.486	0.896	1.457	0.745	1.330	2.818
5% HPC solution	0.456	0.829	1.393	0.733	1.142	2.413
2% HPC particle	0.499	0.929	1.475	0.661	1.601	3.168
4% HPC particle	0.498	0.866	1.458	0.637	1.540	2.999
MCC						
	Kneading			Conveying		
	50 rpm	100 rpm	200 rpm	50 rpm	100 rpm	200 rpm
water	0.313	0.641	1.224	0.376	0.785	1.537
2.5% HPC solution	0.292	0.563	1.169	0.322	0.683	1.420
5% HPC solution	0.279	0.500	1.141	0.300	0.634	1.305
2% HPC particle	0.308	0.631	1.224	0.367	0.749	1.521
4% HPC particle	0.298	0.612	1.207	0.359	0.723	1.502

Table 8-3. Liquid feed rate (kg/h).

lactose						
	Kneading			Conveying		
	50 rpm	100 rpm	200 rpm	50 rpm	100 rpm	200 rpm
water	0.0407	0.0783	0.1241	0.0608	0.1293	0.2642
2.5% HPC solution	0.0389	0.0717	0.1166	0.0596	0.1064	0.2254
5% HPC solution	0.0364	0.0663	0.1114	0.0586	0.0913	0.1930
2% HPC particle	0.0399	0.0743	0.1180	0.0528	0.1280	0.2534
4% HPC particle	0.0398	0.0693	0.1166	0.0509	0.1232	0.2399
	MCC					
	Kneading			Conveying		
	50 rpm	100 rpm	200 rpm	50 rpm	100 rpm	200 rpm
water	0.2506	0.5127	0.9790	0.3004	0.6282	1.2294
2.5% HPC solution	0.2338	0.4504	0.9355	0.2577	0.5465	1.1359
5% HPC solution	0.2233	0.3999	0.9131	0.2402	0.5069	1.0443
2% HPC particle	0.2468	0.5050	0.9790	0.2932	0.5992	1.2168
4% HPC particle	0.2383	0.4899	0.9659	0.2871	0.5785	1.2017

8.3. Results

8.3.1. Residence time

Residence time refers to the time that the material spends in the barrel to produce granules. Figure 8-2 and Figure 8-3 shows the residence time at different screw speed, screw configuration and feed rate for lactose and MCC powders respectively. It was found that material spends longer time if kneading elements were used in all cases, which reflects the weaker conveying capability of kneading elements. It indicates that the use of kneading elements would make the material spend longer time in the barrel and the BL would be higher if kneading elements were used (Equation 8-1 and 8-2).

Furthermore, it is noticed that the increase in HPC amount (in both forms) increases the residence time. It may be because the powder becomes sticky when HPC is added, which then increase the friction with the barrel and therefore increases the residence time. This is in agreement with the finding of Dhenge et al. (2012c) who stated that the use of the binder would cause an increase in the cohesiveness and frictional resistance of the material to flow.

For the effect of the feed rate, due to the size and scale of the figure, no clear difference could be obtained. More detail figures could be seen in Appendix F, it can be seen that there is a slight difference between the residence time at different feed rate. Increasing the feed rate results in a slight decrease in residence time, which is due to the fact that a higher feed rate would reduce the distance/ space between particles and the network between particles would transfer the force more easily. As a result, for a high feed rate, the material would spend less time in the barrel.

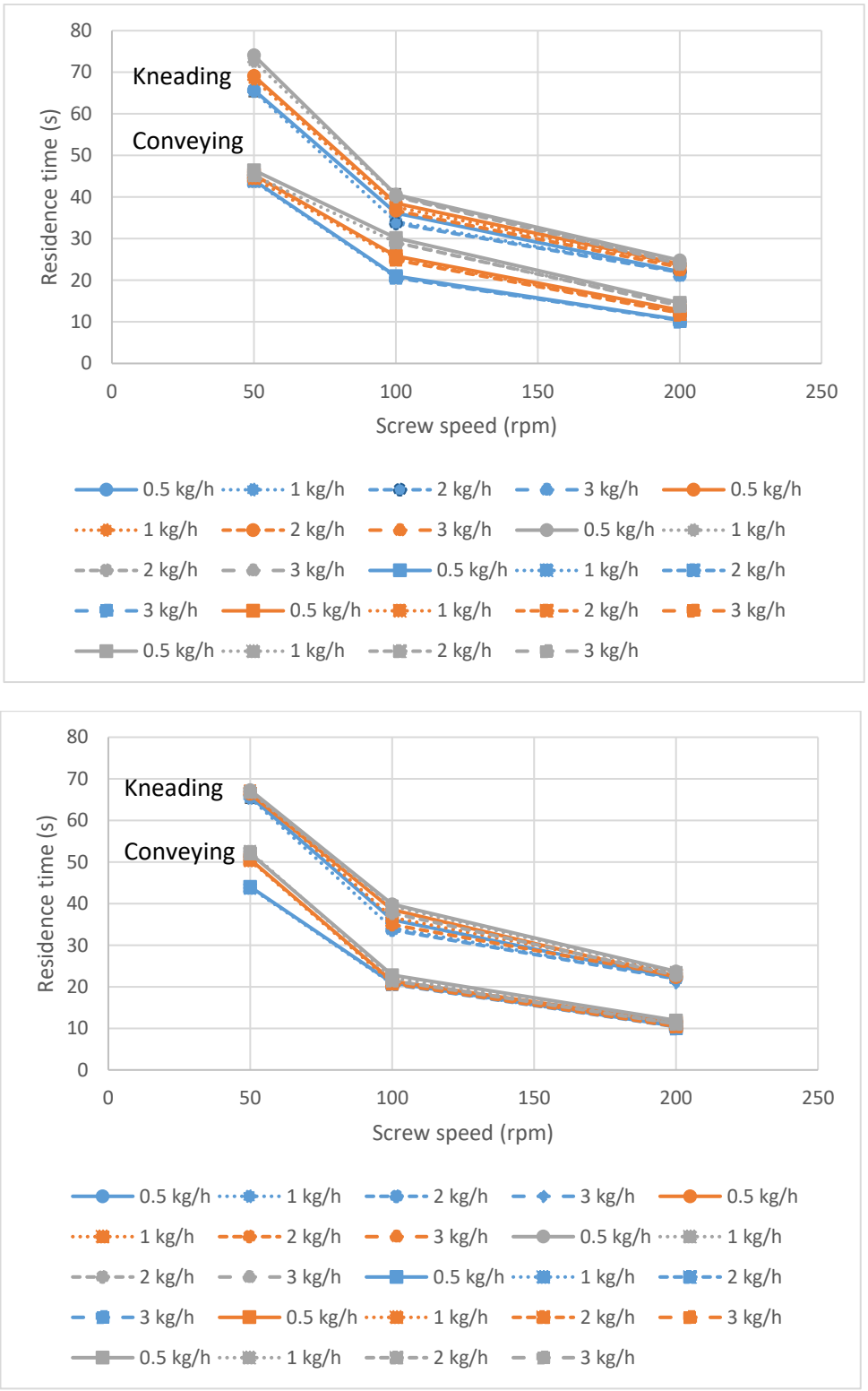


Figure 8-2. Residence time for lactose based material in different powder feed rate, configurations and binder forms (top: HPC solution, orange: 2.5 % HPC; grey: 5 % HPC; bottom: HPC particles; blue: water; orange: 2% HPC; grey: 4% HPC).

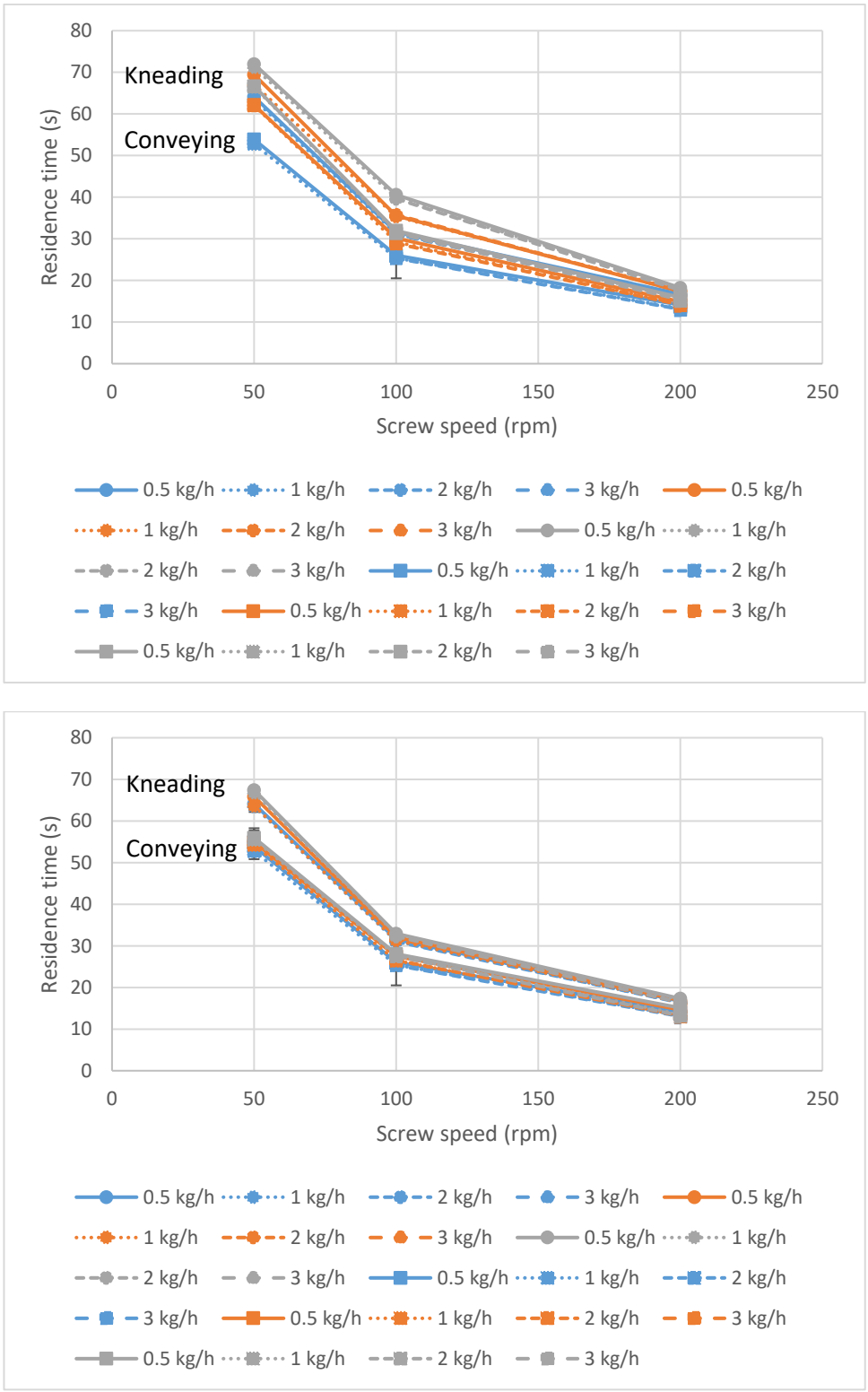


Figure 8-3. Residence time for MCC based material in different powder feed rate, configurations and binder forms (top: HPC solution, orange: 2.5 % HPC; grey: 5 % HPC; bottom: HPC particles; blue: water; orange: 2% HPC; grey: 4% HPC).

8.3.2. Granule size distribution

Figure 8-4 and Figure 8-5 shows the relationship between lactose granule size distribution and screw speed using conveying elements (Set 1 configuration) using water and HPC in different forms (HPC solution and particles), respectively. Generally, the use of HPC leads to growths in large granules and reduces the production of fines.

Furthermore, it is obvious that the use of higher screw speed produces more large granules and the curve for 200 rpm is more bimodal. This result is contradictory to if the BL was not controlled. For example, Lute et al. (2016) presented that the increase of screw speed reduces the production of large granules. Without maintaining the amount of material in the barrel as a constant, the increase of screw speed reduced the amount of material in the barrel, which would reduce the occurrences of coalescence and reduce the granule size (Dhenge et al., 2011).

In terms of the distribution span, Figure 8-6 shows that generally a higher screw speed leads to a wider span, indicating a poor liquid distribution. It may be due to the insufficient residence time when conveying elements were used only. In addition, no clear relationship between HPC amount and span of distribution could be obtained. Nevertheless, at 200 rpm, the use of water shows the largest span, which is not agreed with the observation from the distribution curves. It is because of the high proportion of fines when water was used and consequently reduce the d_{10} for span calculation.

In general, when conveying elements were used, the speed is mainly related to the conveying capability. A higher speed would accelerate the conveying speed and decreases the residence time. Consequently, material would have less time to come an even liquid distribution.

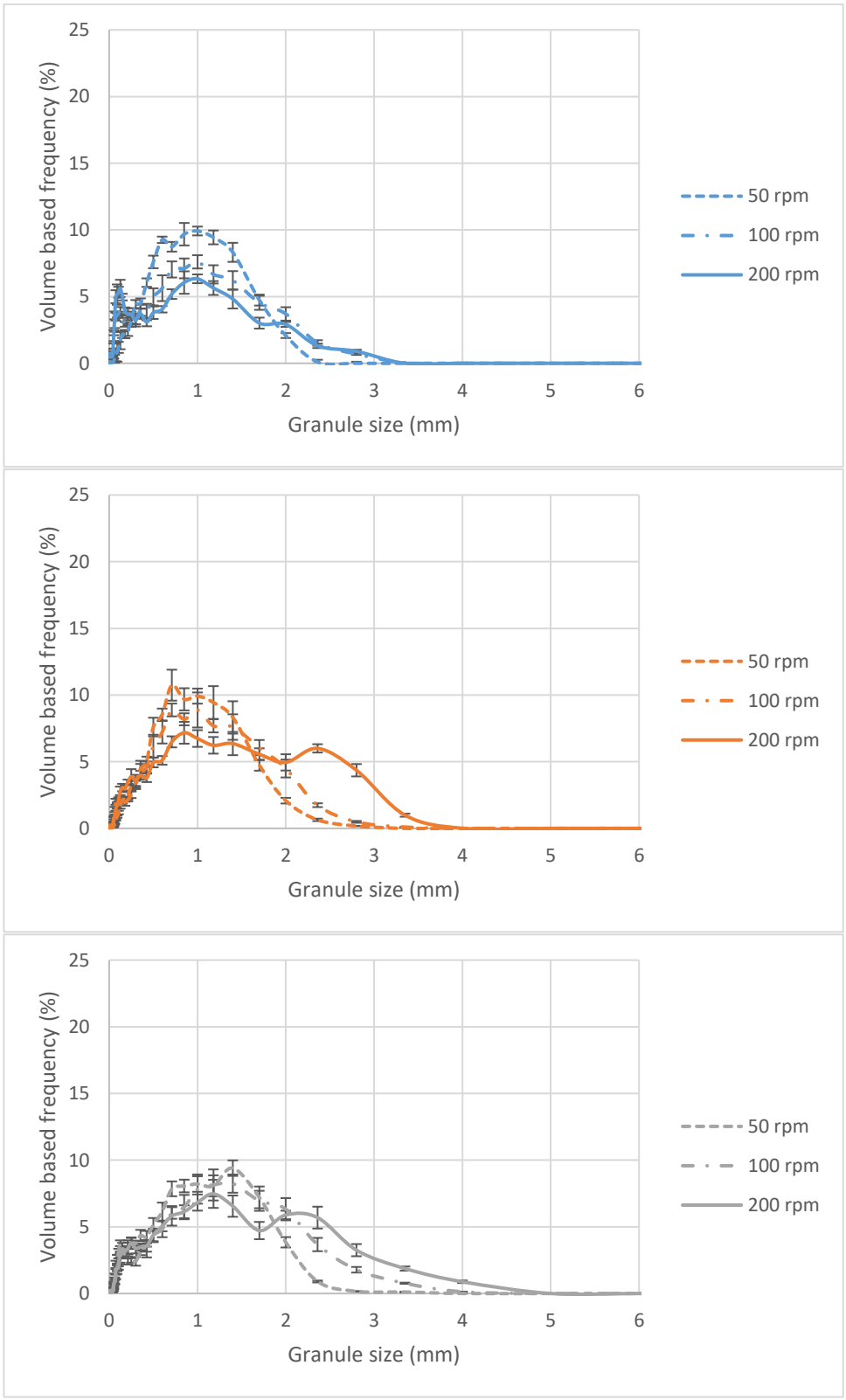


Figure 8-4. Lactose granule size distributions at different screw speeds with a controlled BL (g) and set 1 screw configuration when water and HPC (2.5%, 5% HPC) solution were used.

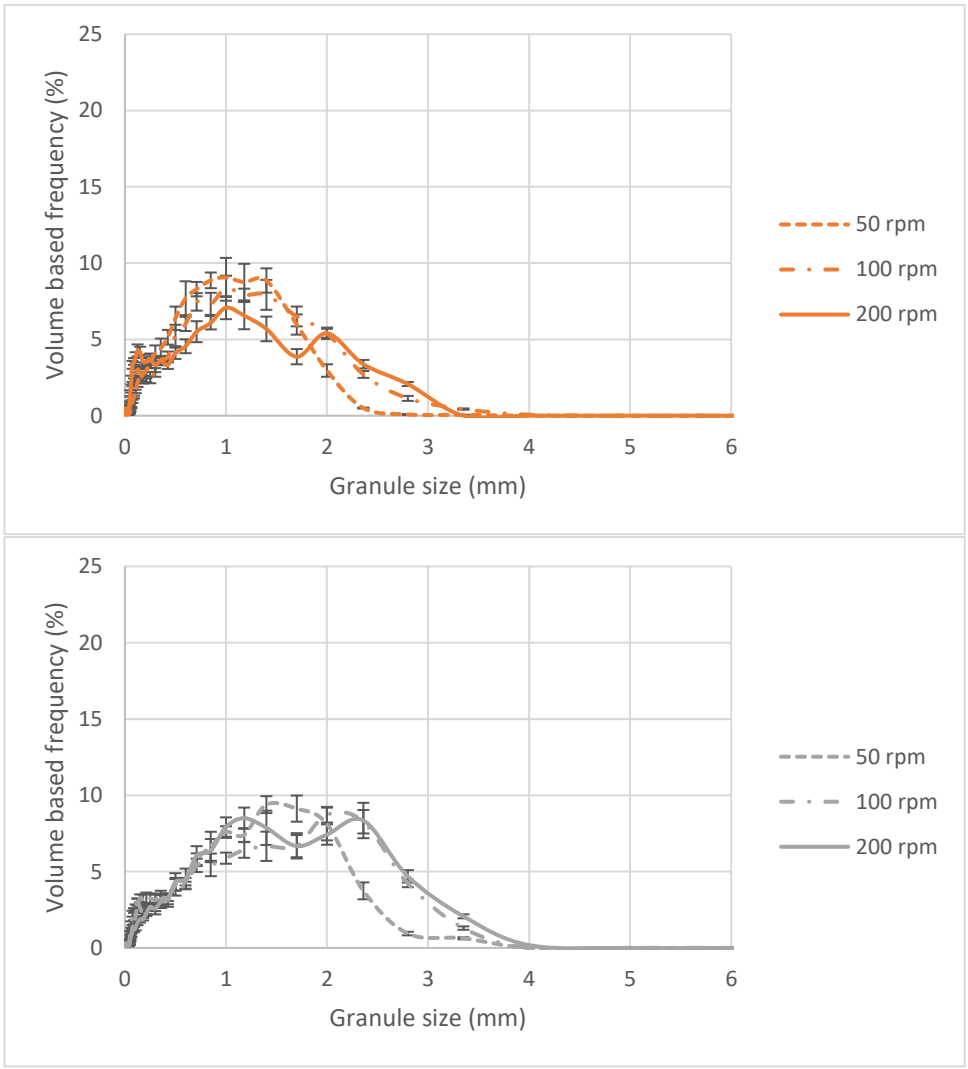


Figure 8-5. Lactose granule size distributions at different screw speeds with a controlled BL (g) and set 1 screw configuration using HPC solid binder (2 & 4%).

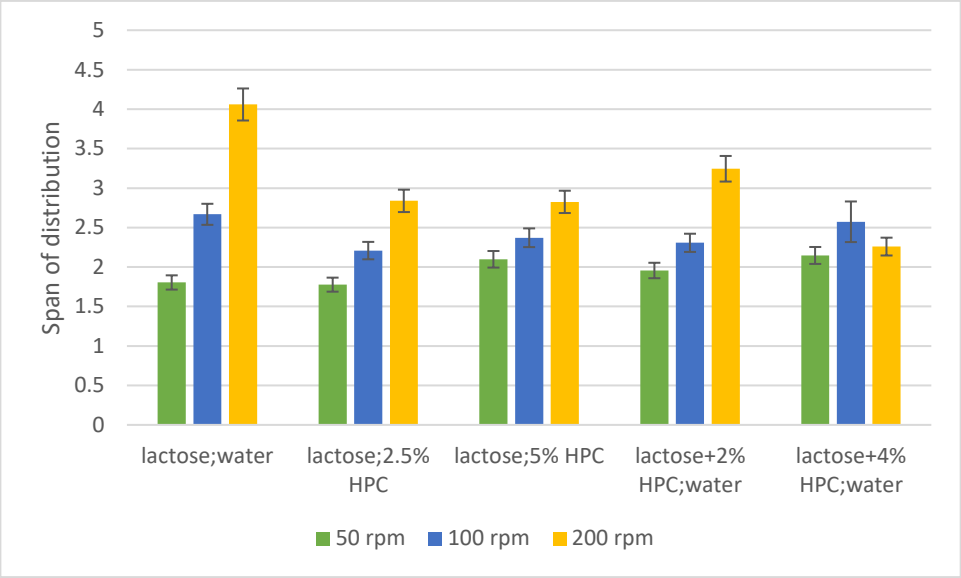


Figure 8-6. Span of distribution for Figure 8-4 and Figure 8-5.

Lactose based formulation with kneading elements using HPC in both forms were granulated and the size distribution is shown in Figure 8-7 and Figure 8-8, respectively. The use of HPC leads to increases in large granules. In terms of the effect of screw speed, different from the use of conveying elements shown in Figure 8-4 and Figure 8-5, the use of higher screw speed (200 rpm) produces fewer lumps. It indicates that although a high screw speed reduces the residence time which makes the mixture has less time for mixing and granulation, the intensive mixing and cutting capability from higher screw speed using kneading elements could compensate the loss in residence time and leads to a better mixing.

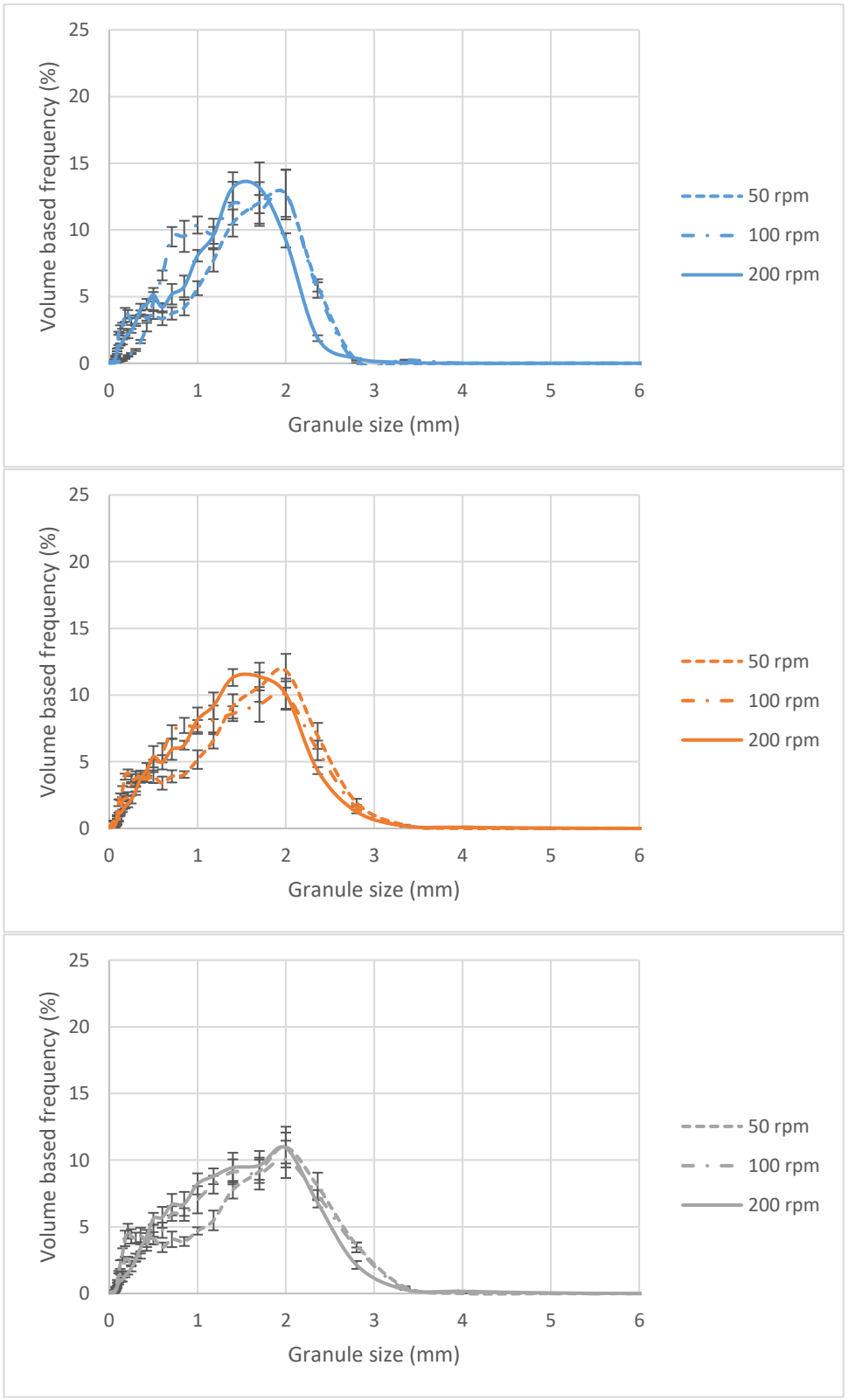


Figure 8-7. Lactose granule size distributions at different screw speeds with a controlled BL (g) and set 2 screw configuration using water and HPC (2.5%, 5% HPC) solution.

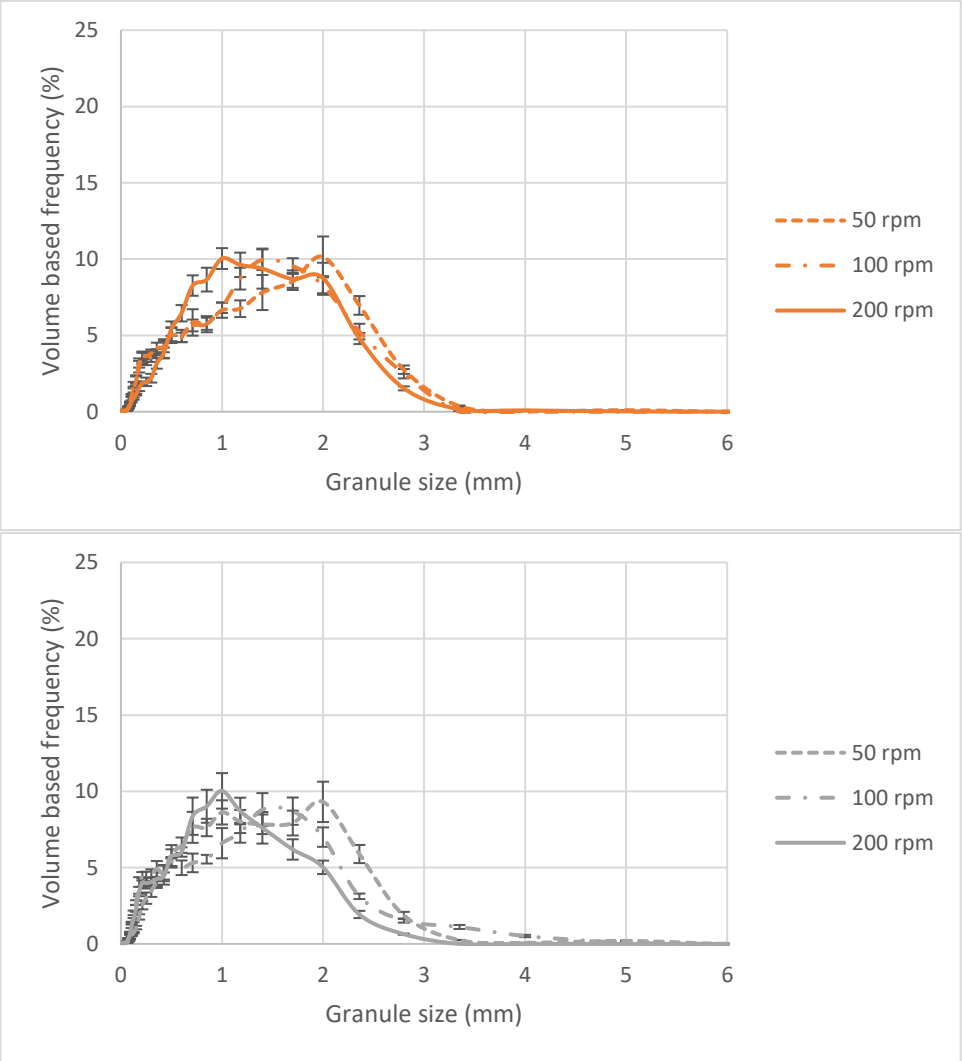


Figure 8-8. Lactose granule size distributions at different screw speeds with a controlled BL (g) and set 2 screw configuration using HPC solid binder (2 & 4%).

The span of distribution is illustrated in Figure 8-9. Comparing with the use of conveying elements, the span is smaller, which indicates the use of kneading elements could enhance the liquid-powder mixing and produce the granule with a narrower size distribution. In addition, Figure 8-9 suggests that at high screw speed (200 rpm), the span is relatively smaller comparing with low speed (50 rpm), generally. The use of HPC was

found to increase the span of distribution (Figure 8-9) when comparing to that without HPC, indicating a poorer liquid-powder mixing when HPC was used. To quantify the effect of screw speed on the span of distribution, it was found in Figure 8-10 that for most cases, increases in screw speed could reduce the span of distribution in different extents, indicating that using a higher screw speed could effectively promote the liquid distribution and produce narrower granule size distribution. However, using 4% HPC solid binder at 100 rpm showed opposite effects. It might due to the clear relationship in span of distribution at corresponding condition, which may be resulted from the operating error. In general, using 200 rpm gave more stable reductions of span for all cases and the reduction is between 0 to about 22.1%.

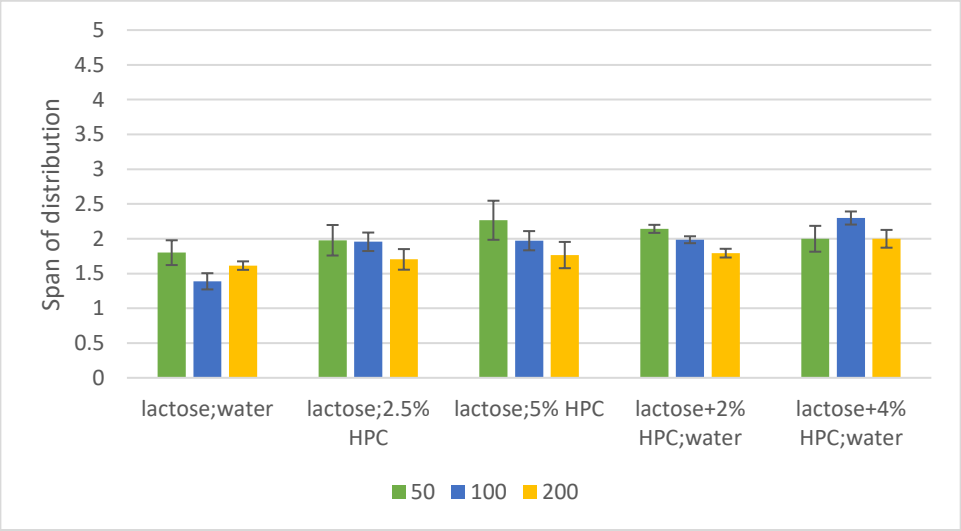


Figure 8-9. Span of distribution for Figure 8-7 and Figure 8-8.

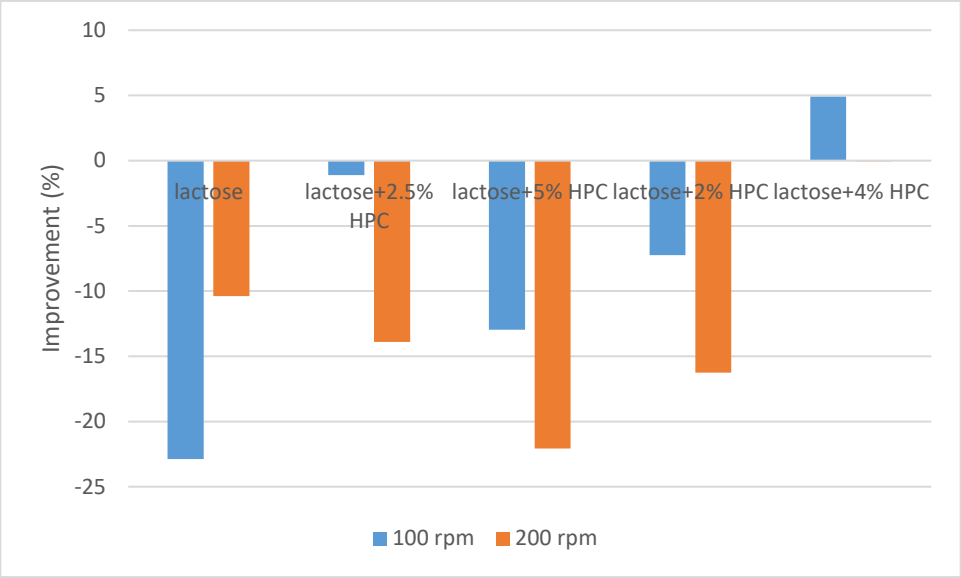


Figure 8-10. Improvement of span of distribution.

Figure 8-11 and Figure 8-12 illustrate the MCC granule size distribution using conveying elements with the addition of water and HPC in liquid form and solid form, respectively. When HPC was used, larger granules would be obtained. In terms of the effect of screw speed, a higher speed makes the granule size distribution more bimodal, which indicates poorer liquid-powder mixings. The span of distribution shown in Figure 8-13 also shows that a higher screw speed leads to a higher span. As was mentioned, it is because of insufficient residence time when conveying elements were used, especially if the screw speed is high. Comparing with that of lactose, it could be observed that higher proportions of fines could be produced. It is because MCC could swallow water, leaving less amount of liquid to bond particles.

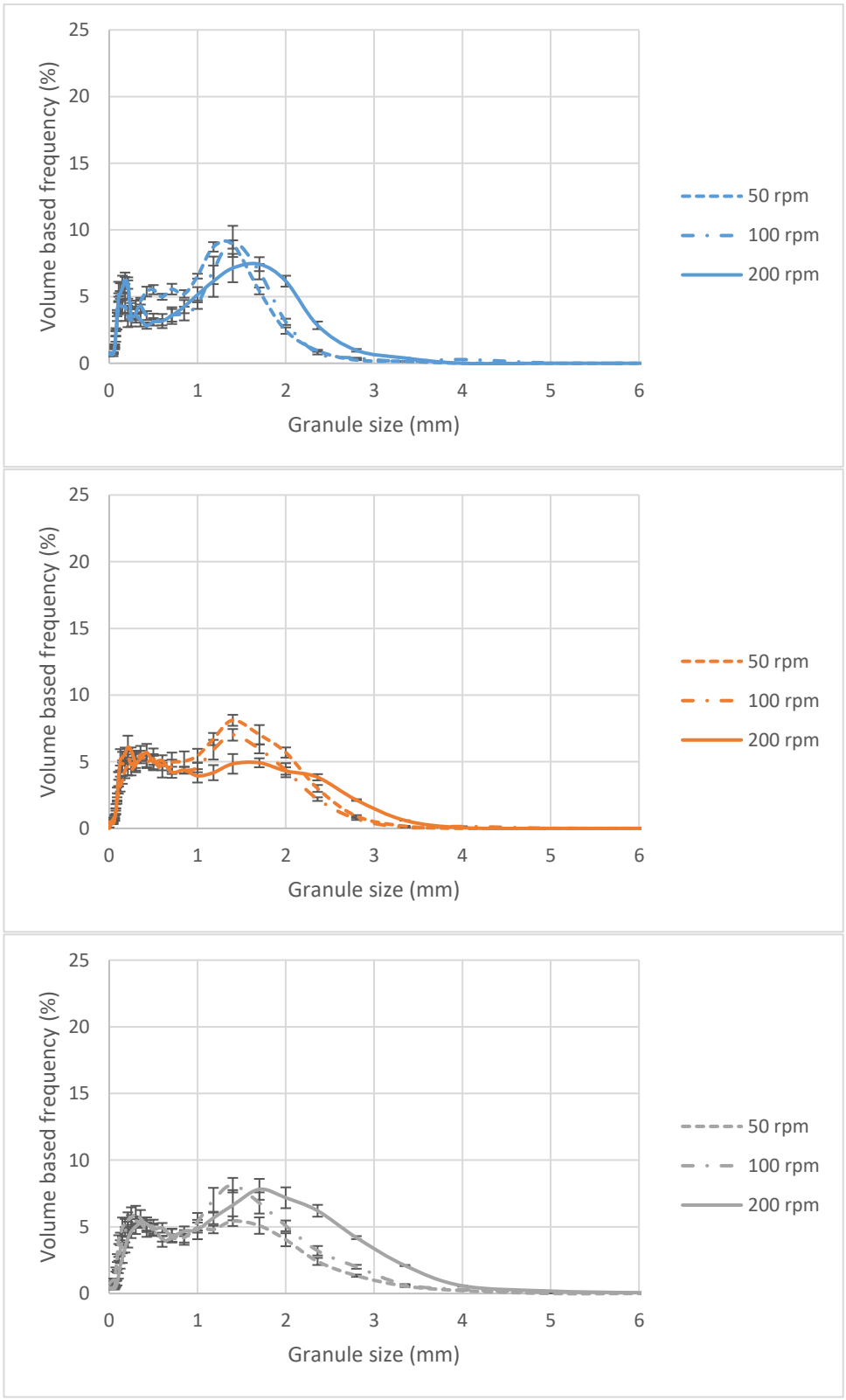


Figure 8-11. MCC granule size distributions in different screw speeds with a controlled BL (g) and set 1 screw configuration using water and HPC (2.5%, 5% HPC) solution.

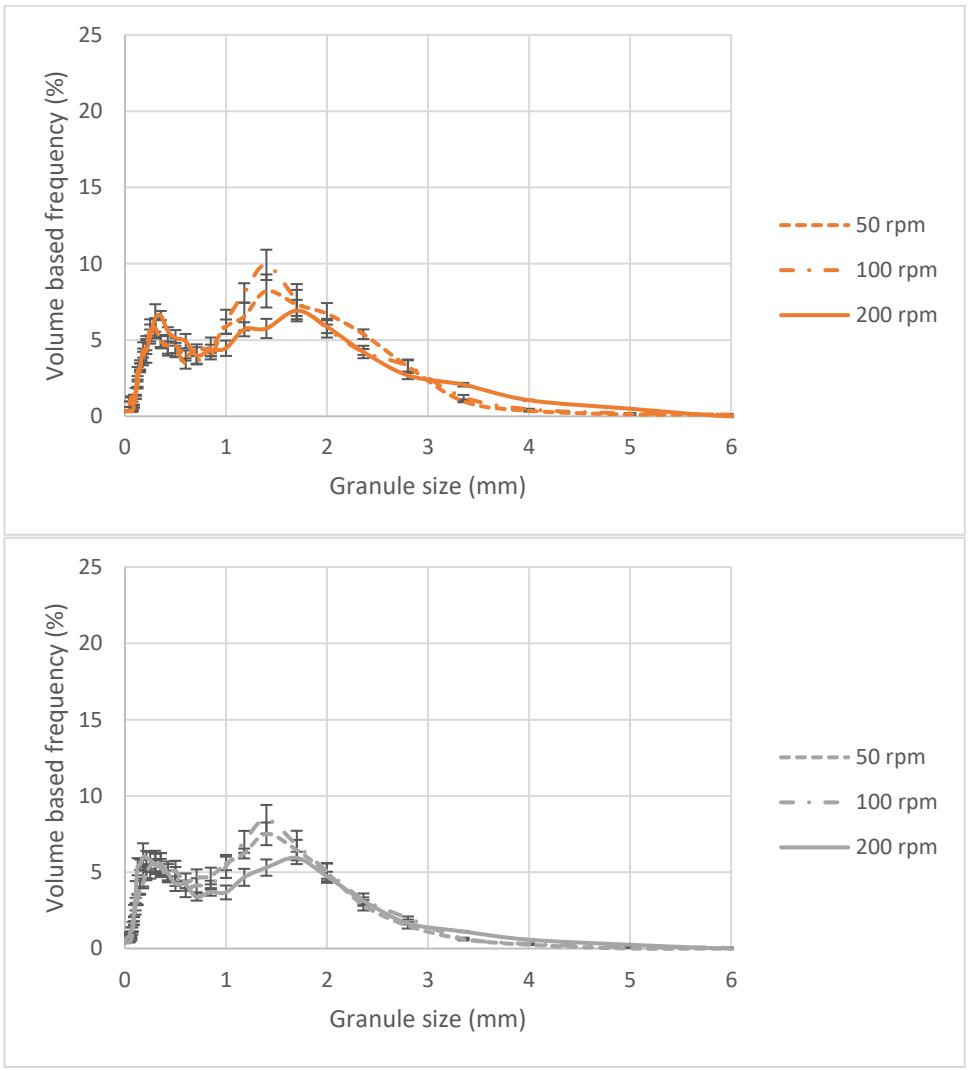


Figure 8-12. MCC granule size distributions in different screw speeds with a controlled BL (g) and set 1 screw configuration using HPC solid binder (2 & 4%).

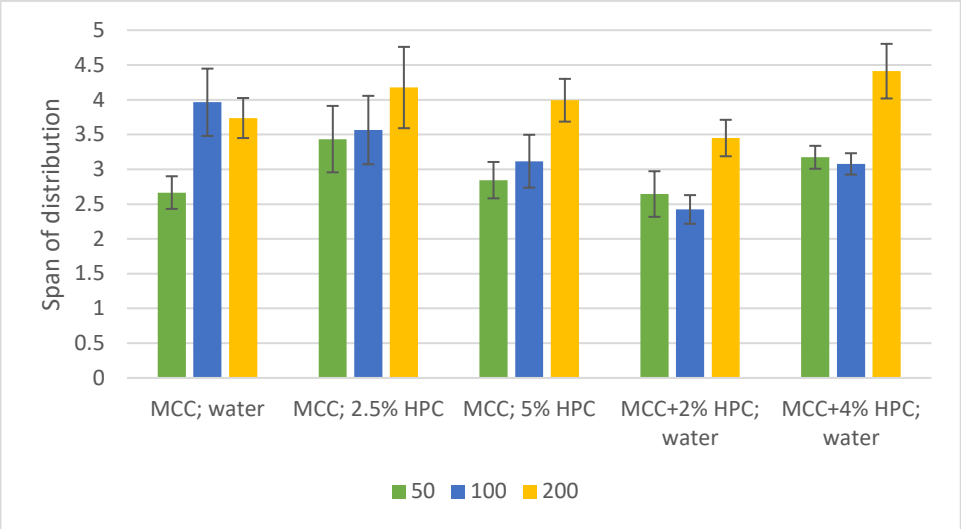


Figure 8-13. Span of distribution for Figure 8-12 and Figure 8-13.

When kneading elements are used, Figure 8-14 and Figure 8-15 are the size distribution and MCC granule size distribution. Firstly when HPC solution was used, a higher concentration produced larger granules. In addition, use of HPC in liquid forms produces more fines than that when HPC particles were used. Whilst, an increase in solid HPC particles shows unclear effect on the granule size distribution. Figure 8-16 shows the span of distribution for Figure 8-14 and Figure 8-15. It shows that the use of HPC in solid form shows smaller spans than the use of HPC in solution, which is agreed with the observation from Figure 8-14 and Figure 8-15. Comparing with Figure 8-11 and Figure 8-12, the use of high screw speed shows a different effect on granule size distribution. Specifically, a high screw speed generates a wider span of distribution and poorer liquid-powder mixing when conveying elements were used, whilst a higher screw speed tends to produce the granule with narrower size distributions. It indicates that the effect of screw speed is different based on the specific configuration applied. For conveying elements only, the screw speed is mainly related to the conveying speed, as conveying elements are weaker in mixing but good as transporting materials. When kneading elements are

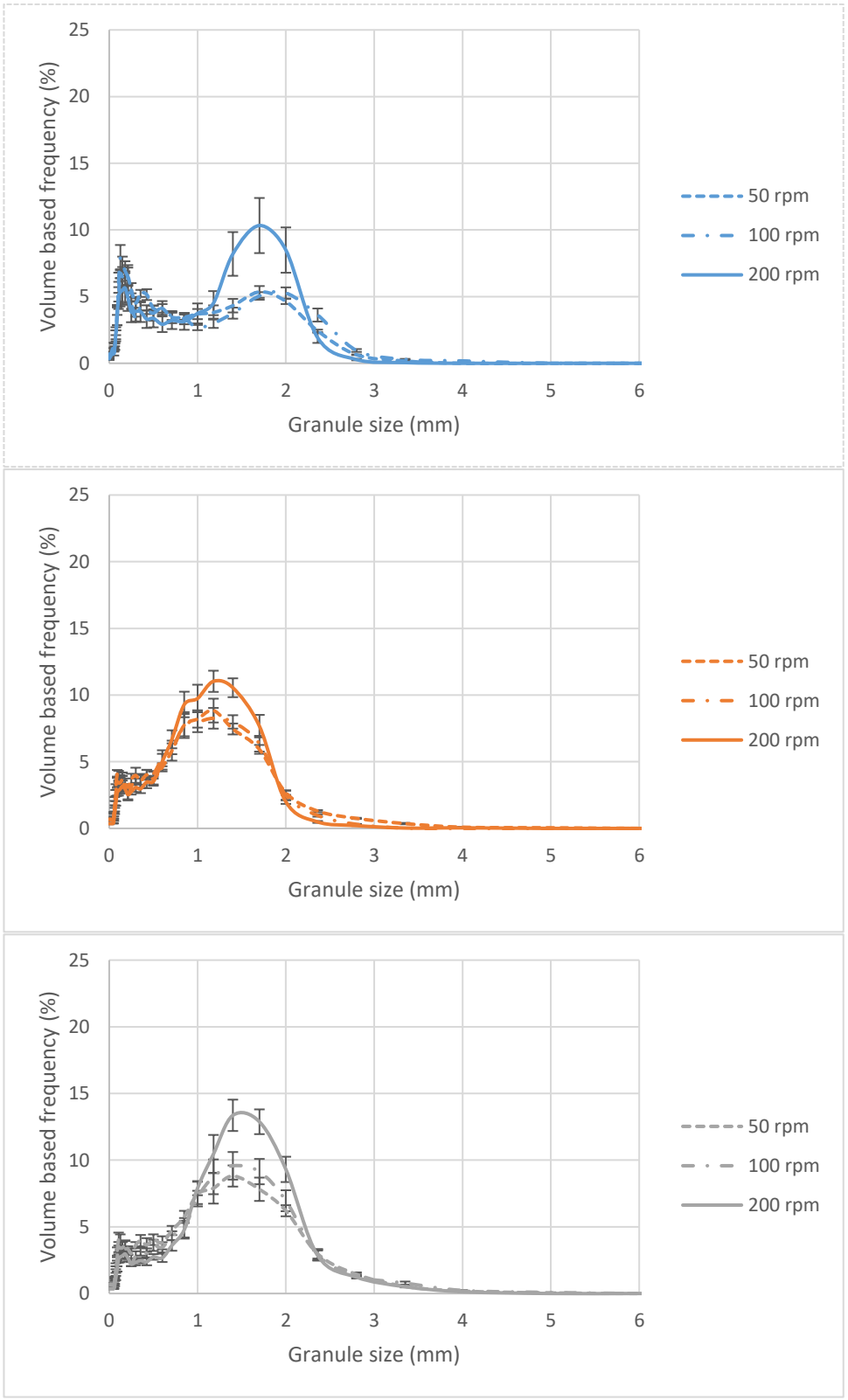


Figure 8-14. MCC granule size distributions in different screw speeds with a controlled BL (g) and set 2 screw configuration using water and HPC (2.5%, 5% HPC) solution.

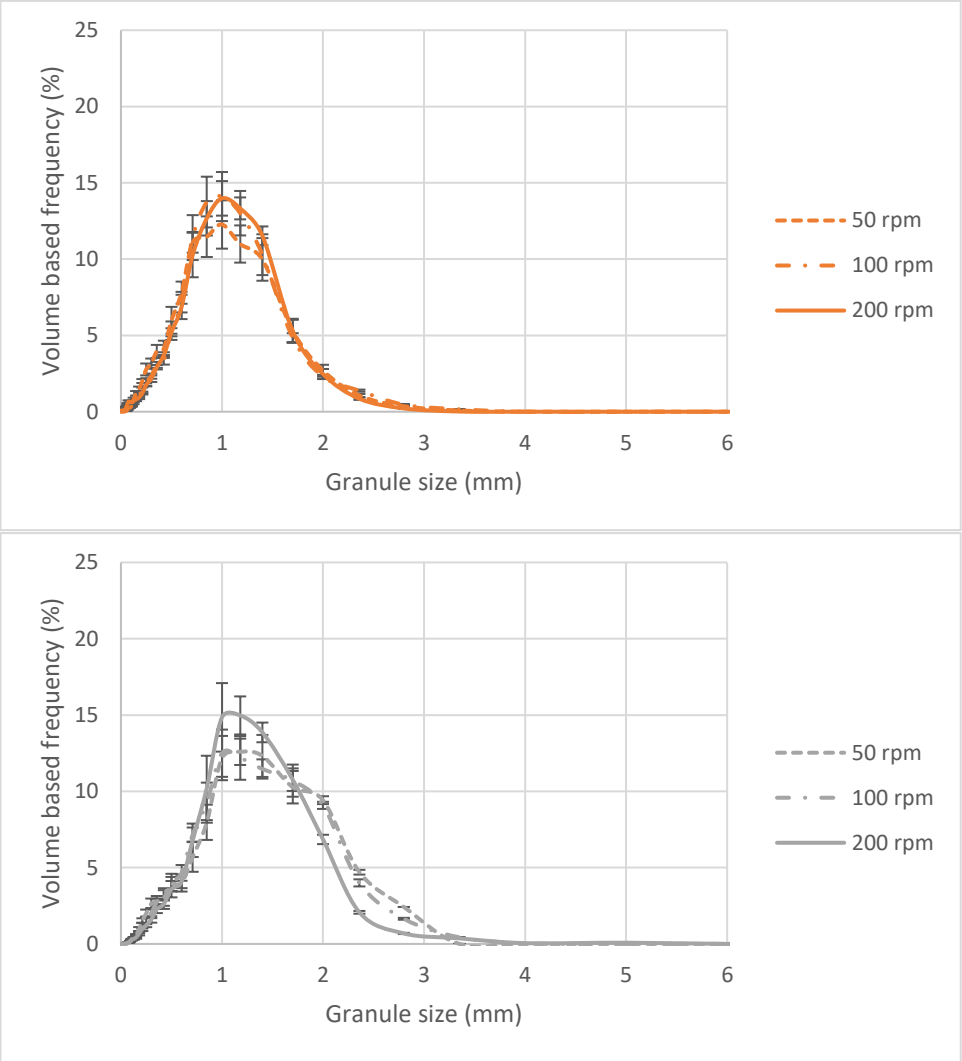


Figure 8-15. MCC granule size distributions in different screw speeds with a controlled BL (g) and set 2 screw configuration using HPC solid binder (2 & 4%).

used, although higher screw speed would reduce the residence time, the more intensive mixing from a higher screw speed could compensate the loss in residence time.

Figure 8-17 quantifies the effect of screw speed on the span of distribution. Apart from the first column, it was found that using higher speeds could reduce the span of distribution in different extents. The reason why the first column showed opposite result was because Figure 8-17 was calculated based on the average span value and could not

make the error bar into consideration. In general, using 200 rpm shows more stable effects on reducing the span of distributions more than 20 %.

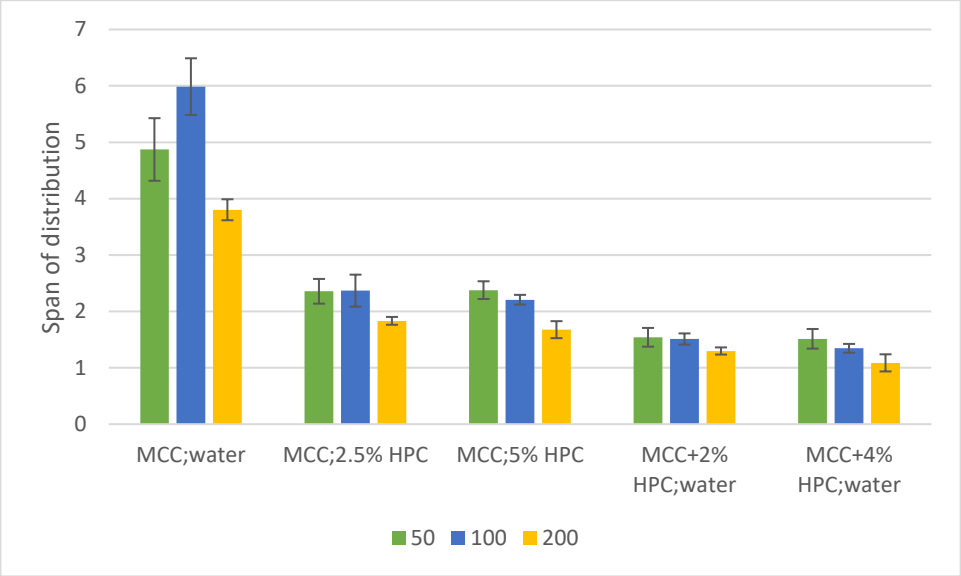


Figure 8-16. Span of distribution for Figure 8-14 and Figure 8-15 (*different scale in y-axis*).

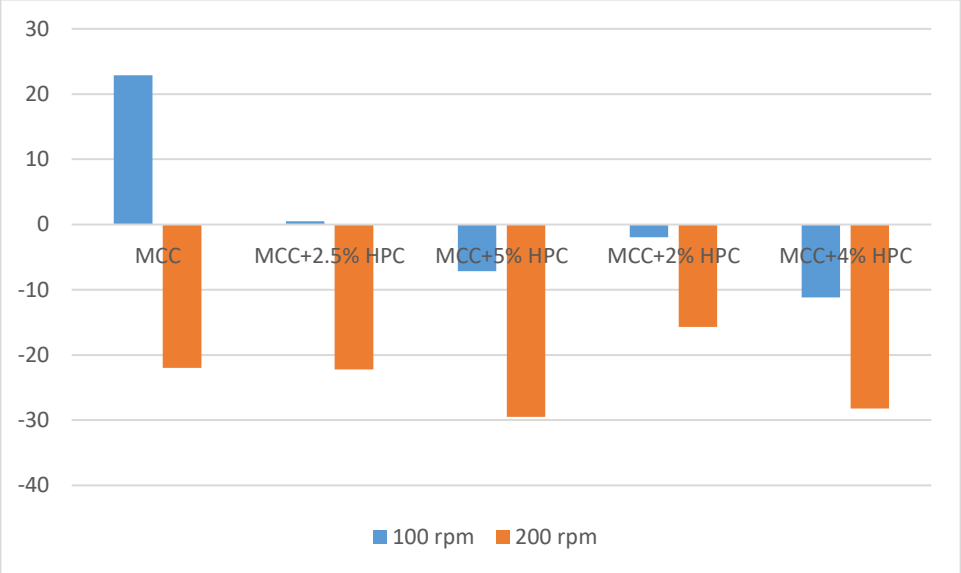


Figure 8-17. Improvement of span of distribution.

When comparing the span of distribution from the previous chapter at 200 rpm, it could be seen from Figure 8-18 that by controlling FL, the span of distribution could be improved in most cases, which indicates a more even liquid distribution when FL was controlled. Figure 8-18 quantify these variation and was found that for most cases, the use of FL could effectively narrow the granule size distribution by reducing the span of distribution. The reason why lactose with 4% HPC solid binder showed opposite result may due to the large error bar produced from the corresponding column in Figure 8-18. Comparing the difference between different binder delivery methods, it was found that the use of liquid binder shows more obvious improvement when controlling FL. Using HPC solution could achieve an improvement of about 19.7%, whilst the use of solid binder could only achieve the maximum improvement of about 2.7%, showing that a controlled FL could significantly enhance the liquid distribution even the liquid was quite viscous.

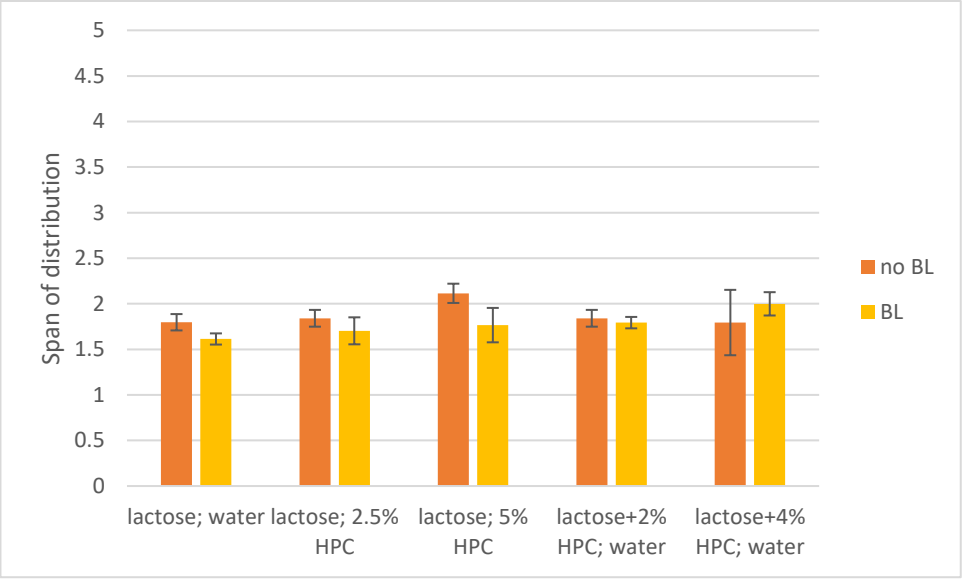


Figure 8-18. Comparison of the span of distribution using lactose based materials with a screw speed of 200 rpm.

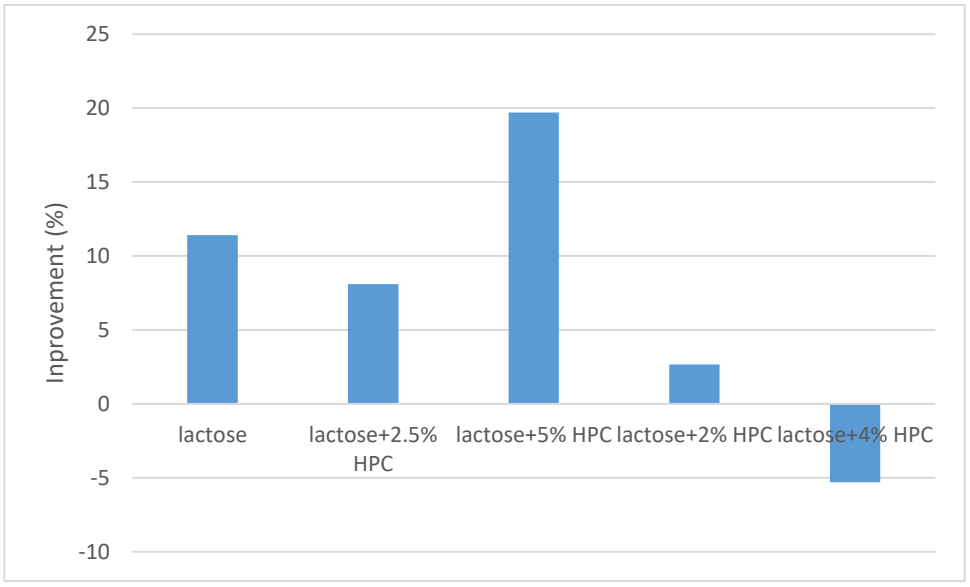


Figure 8-19. Improvement of span of distribution.

Figure 8-20 compared the span of distributions between weather the BL was controlled or not. In general, the span of distributions are much larger comparing with that of lactose shown in Figure 8-18. It is mainly because MCC is insoluble and thus a higher proportion of fines were produced, making the span of distribution larger. When comparing the different between controlling FL or not, it was found that the using Fl could effectively narrow the granule size distribution by reducing the span of distribution. Normally, the span of distribution that twin screw granulation could achieved is in a range of 1.5 to 4.5. It could be seen that with the use of FL, using HPC solid binder could even reach a span close to 1.0, which represents quite excellent liquid distribution and granule size distribution. Figure 8-21 quantifies the improvements from using FL and was found that much more obvious improvements could be achieved comparing that with lactose. It might because using a FL could increase the corresponding fill level in the barrel, which would increase the stress faced by the liquid-powder mixture. As MCC is considered as porous sponge material. Specifically, when pressure applied, the free water could be

squeezed out; when the pressure is removed, MCC would absorb water and expand back to its original shape and size (Fielden et al., 1988). Therefore, increased pressures with a control of FL could squeeze more liquid out and the liquid could be used to form more liquid bridges to agglomerate particles. Consequently, controlling FL would make the water distribution more evenly and the granule size distribution would be narrower. This reaction of MCC could be used to further explain why using HPC particles shows better improvement than that of HPC solution. As more liquid was squeezed out, liquid between particle would have more time to interact with the solid HPC particles. As a result, more HPC would be dissolved in the liquid comparing that if BL was not controlled and thus a much obvious improvement could be achieved.

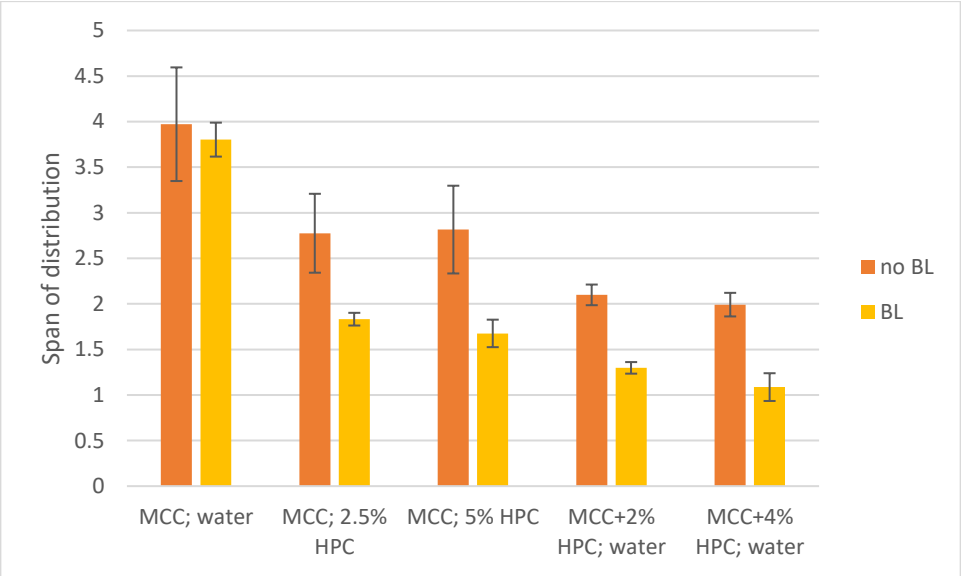


Figure 8-20. Comparison of the span of distribution using MCC based materials with a screw speed of 200 rpm.

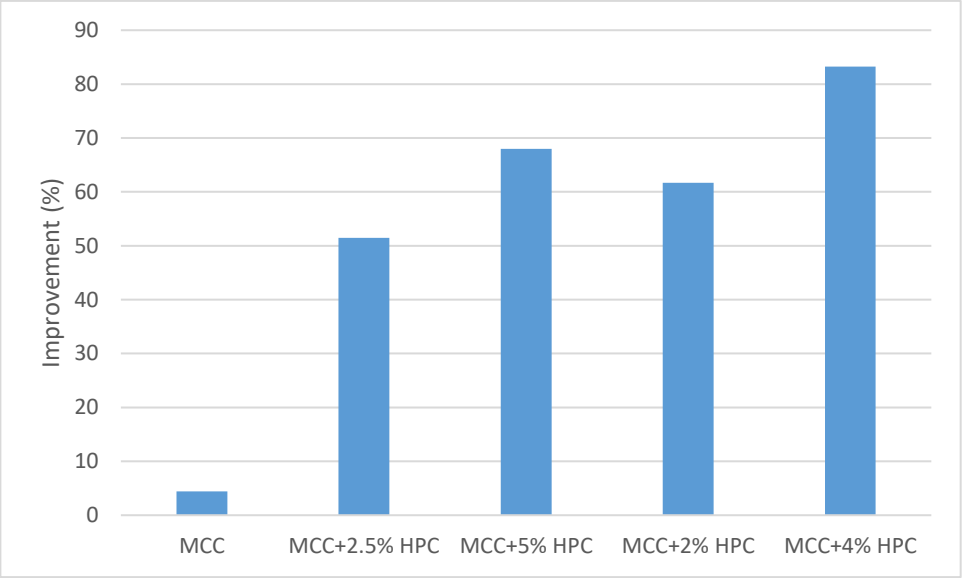


Figure 8-21. Improvement of span of distribution.

8.3.3. Effect of screw speed and configurations on granule strength

Figure 8-22 and Figure 8-23 shows the relationship between granule bulk strength and screw speed under different binder delivery methods using conveying elements and kneading elements, respectively. In general, use of kneading elements could produce stronger granules.

When HPC was added, an increase in granule strength could be observed in both Figure 8-22 and Figure 8-23. When conveying elements were used, HPC solution produced stronger granules than the use of HPC particles. It is probably due to insufficient stress and agitation applied could not dissolve the HPC particle efficiently, which is agreed with the observation on the compact powder bed that the use of solid HPC could not enhance the nucleus hardness. In addition, the insufficient residence time may not allow the liquid-powder being mixed properly. When kneading elements were applied, the use of HPC in both addition method led to more obvious increases in granule strength, which due to intensive stress realised by kneading elements. In addition, the longer

residence time offers sufficient time for the material to achieve an even liquid distribution and also dissolve more portions of soluble materials to enhance the strength. While comparing different HPC delivery methods, it could be seen in the use of solid binder produce the strongest granule. It might be because that when HPC particle is used, the intensive agitation and stress could accelerate the dissolution of the binder particle.

In Figure 8-22, the increase in screw speed produces stronger granules when HPC solution was used. However, when HPC particles were used, no obvious effects could be seen. It is probably because that when conveying elements were used only the screw rotation is incapable to provide enough mixing.

As is known, a industrial standard screw configuration is normally consist of two zone of kneading elements. Therefore, kneading elements were used and the granule bulk strength were evaluated, followed by a quantative comparison of bulk strength improvements between different experiments.

If kneading elements were applied (Figure 8-23), clearer increasing could be observed in all cases, indicating a positive correlation between screw speed and granule strength. In general, all granule bulk strength is in the allowed range (larger than 0.1 MPa) (Dhenge et al., 2012d, Dhenge et al., 2013, Saleh et al., 2015). Specially, the use of solid binder produces stronger granules, which indicate that the use of kneading elements could accelerate of the dissolution of HPC particles. Comparing with the use of conveying elements shown in Figure 8-22, the granule bulk strength from kneading elements were much stronger. It is because the use of kneading elements could provide much stronger stress to the material, which could significantly promote the consolidation process and strengthen the granules. Figure 8-24 quantifies the variation of granule bulk strength. It

could be seen that the use of higher screw speed could enhance the granule strength in all cases. It was reported that at least 5% difference in granule strength could be clear effects on granular properties (tablet tensile strength, etc.)(Horisawa et al., 1995). Therefore, the variation of screw speed could effectively affect the tablet properties. Comparing the improvements using different binder delivery methods, it was found that using solid binder could achieve a better improvement (more than 20%), indicating that solid binder delivery is preferred when a stronger granule was required. It might because the use of kneading elements could provide intensive mixing environment and thus accelerate the dissolution of solid binder, making higher proportions of HPC participate in binding and granule strength enhancement.

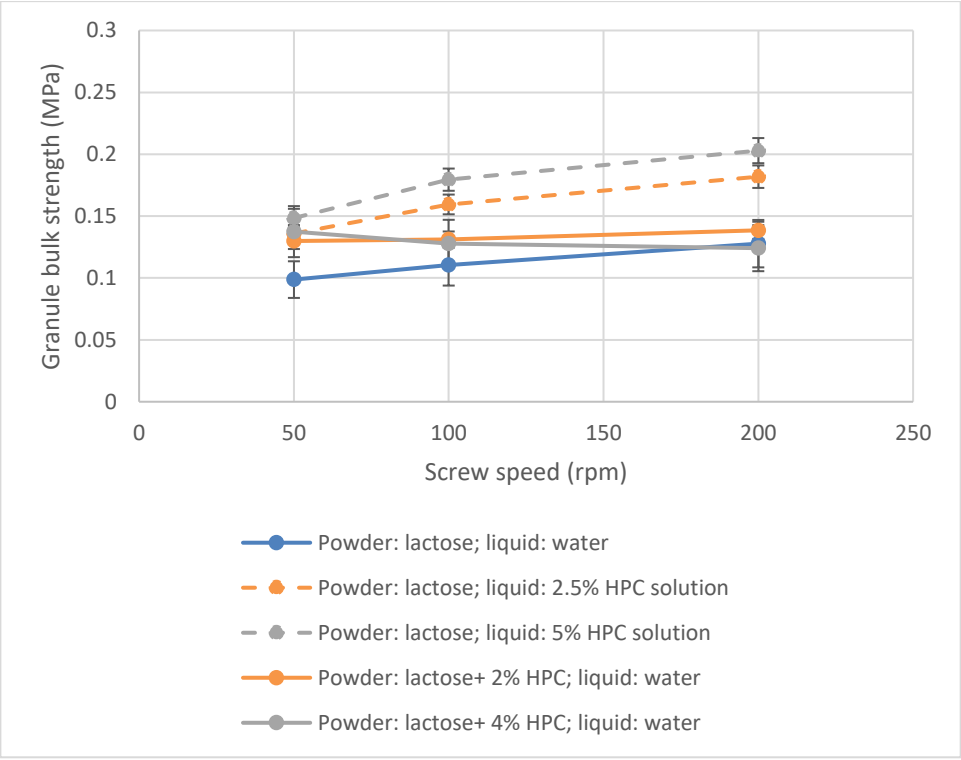


Figure 8-22. Lactose granule bulk strength for conveying elements.

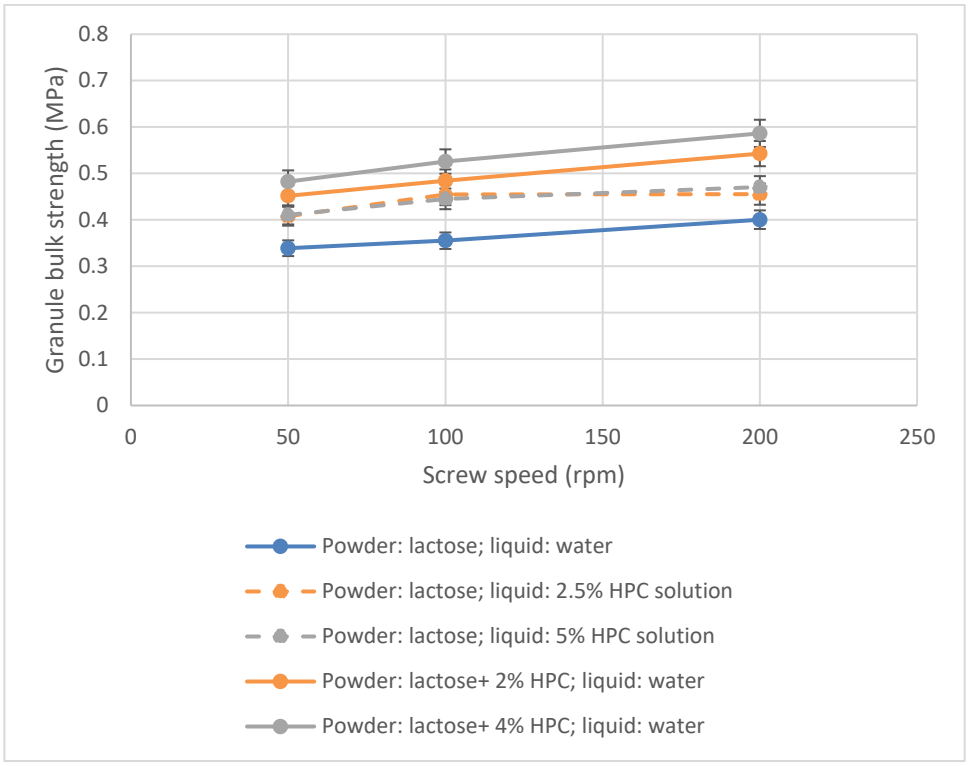


Figure 8-23. Lactose granule bulk strength for kneading elements.

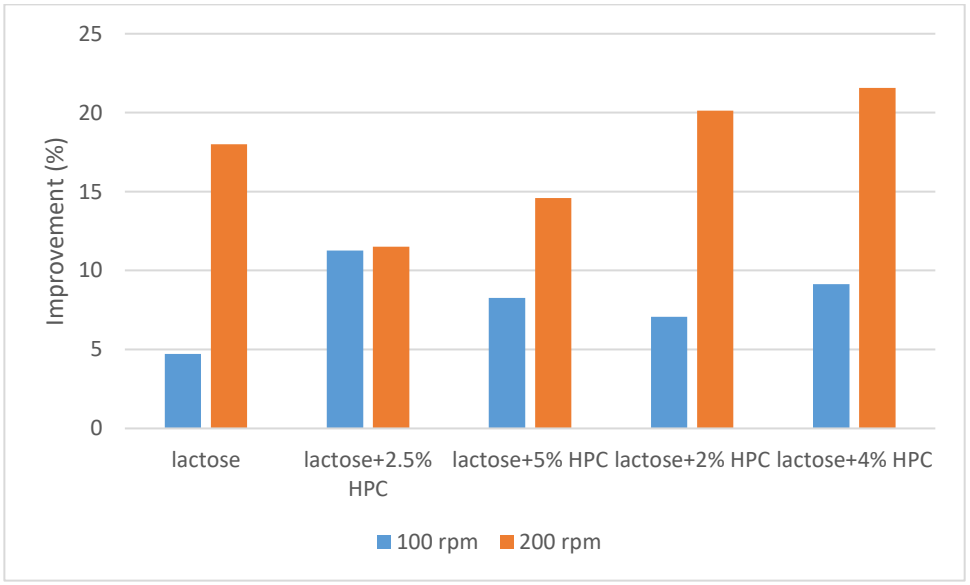


Figure 8-24. Improvement of granule bulk strength.

Figure 8-25 and Figure 8-26 illustrate the relationship between MCC granule strength and screw speed using two screw configurations under different binder delivery methods. Generally, all granule strength are in the allowed range (larger than 0.1 MPa) and use of kneading elements produces stronger granules (Dhenge et al., 2012d, Dhenge et al., 2013, Saleh et al., 2015).

When conveying elements were used only, the use of HPC solution produced the strongest granules. It might be due to insufficient mixing capability from conveying elements and also agreed with the single drop study that the use of HPC solution is easier to form strong nuclei. Whereas, when kneading elements were used, the intensive agitation could accelerate the solid HPC dissolution and produce stronger granules. Nevertheless, the use of HPC solution could still produce stronger granules, which may due to the fact that MCC could swallow liquid into its structure.

Concerning about the effect of screw speed, it could be seen that as the screw speed increases, an increase in granule bulk strength could be more clearly obtained when kneading elements were used. As a comparison, the effect of screw speed was unclear when conveying elements were applied.

Figure 8-27 quantifies the improvement of granule bulk strength between different speeds and binder delivery methods. Comparing with that of lactose, the improvements are much milder, as MCC is insoluble and the increase in stress resulted form the use of kneading elements could not vary the dissolution of MCC particles. As a result, variation of screw speed shows less obvious effect on granule strength. As was reported, more than 5% difference in granule bulk strength could obviously affect the tablet properties. Therefore, the improvement using 100 rpm was incapable to effectively influence the

following product properties. When 200 rpm was used, clearer improvement could be achieved by about 15%.

In general, for both lactose and MCC, the granule strength was measured. Lactose, as a soluble material, could dissolve in the water and increase the strength of bonds between particles. Whereas, the added liquid for MCC granulation would be partially stored into the MCC inner structure, which only leaves less proportions of liquid to form liquid bridges. Therefore, comparing to the insoluble material (MCC), lactose produces stronger granules. In addition, it was found that for both material, using HPC in solid form could produce stronger granule than that of HPC solution.

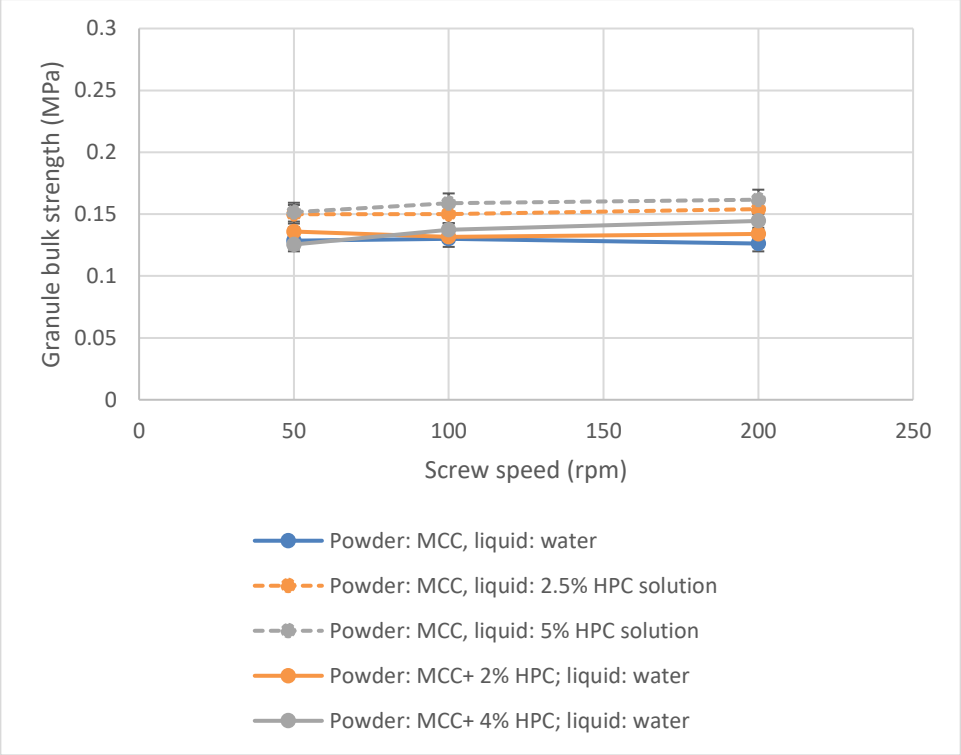


Figure 8-25. MCC granule bulk strength for convey.

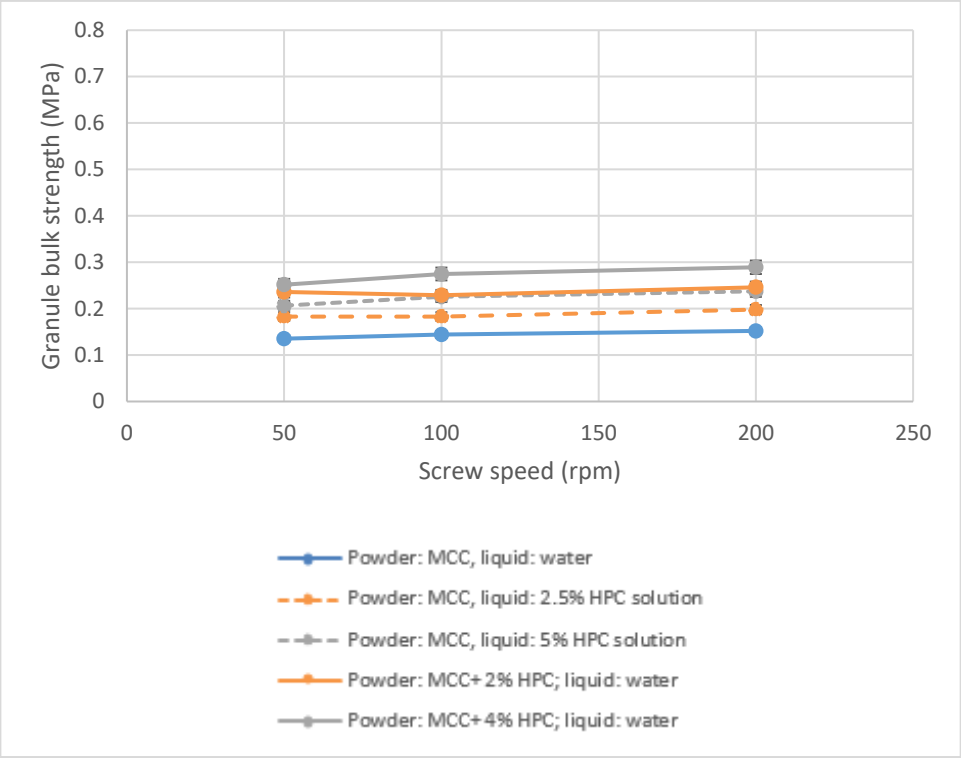


Figure 8-26. MCC granule bulk strength for kneading elements.

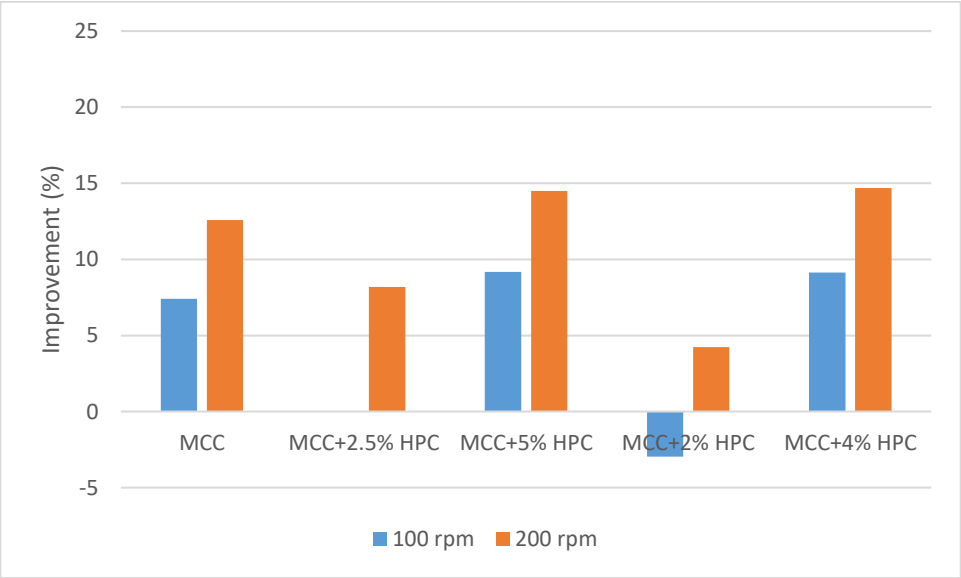


Figure 8-27. Improvement of granule bulk strength.

8.4. Conclusion

In this chapter, processing parameters including screw speed and configuration were studied with a controlled material loads in the barrel (Barrel loading, g), in order to improve the granule yields and strength with different binder delivery method. Different from the typical fill level (powder feed rate/screw speed), the BL considered the effect of liquid binder and different conveying capability between conveying and kneading elements. The study of screw speed and configuration with a constant BL could reveal their effects on granule properties without the distorting from the variation in fill level.

When conveying elements were used, the increase in screw speed would increase the conveying capability of the screw, making the liquid and powder have less time in mixing and produce the granule with a wide span of distribution. While kneading elements were used, the increase of screw speed would help to intensify the mixing and stress acting on the material, which enhances the breakages and coalescence, giving a more even liquid-powder mixing. In addition, with a controlling of BL, using kneading elements could reduce the span of distribution up to 19.7% for lactose and 83.3% for MCC, which significantly improve the liquid distribution and narrow the granule size distribution. In addition, the use of kneading elements could also accelerate the dissolution of solid HPC particles, and enhance its binding capability. For lactose, the enhancement on granule bulk strength could achieve as much as 21.6%, whilst only 14.7% enhancement could be achieved if MCC was used.

Chapter 9. Conclusion and future work

9.1. Conclusion

In twin screw granulation process, narrower granule size distributions (control dosage) and stronger granule strength (avoid breakage) are normally required in granule property designs. Therefore, the research focused on formulation development and process optimisation were carried out, in order to improve the granule properties and process in the pharmaceutical industry.

In **Chapter 4**, single drop study on the compact powder bed was carried out to mimic the twin screw granulation process, in order to understand the liquid-powder interaction in twin screw granulation with the presence of the binder (HPC) in different forms (solution and particle). Through the study of droplet behaviour and nucleus properties, it was found that liquid would keep distributing even after the penetration finished (liquid post-penetration migration) and clear differences between the liquid maximum spreading and nucleus surface diameter would be obtained. This phenomenon becomes less obvious when HPC solution is used. This finding suggests that the nucleus size could not be simply determined by the liquid spreading and the horizontal liquid migration should be considered when studying the liquid-powder interaction on the powder bed and the previous nucleation study (e.g. nucleation regime map) should fully consider the liquid migration in the powder bed rather than only the droplet behaviour. Besides, the single drop study agrees with the fact that the use of HPC solution is more difficult in spreading and distribution in the powder bed and the nucleus produced is much smaller. However, it is also noticed that some of the large HPC particles could not dissolve properly and the actual usage efficiency would be quite low.

In this chapter, the theory and knowledge of liquid-powder interaction under different compression stresses and binder delivery methods were established and learnt. It inspired the following chapters about how to proceed the research to improve the granule properties from the perspectives of formulation and process parameters, respectively.

As the liquid-powder interaction on the compact powder bed could mimic the twin screw granulation process, a miniaturized approach to predict the optimal L/S ratio in twin screw granulation (conveying elements only) using the compact powder bed was developed in **Chapter 5**. By calculating the mass ratio of droplet and dry nucleus, a powder bed based "L/S ratio" was obtained. This value was consistent with the optimal amount of liquid required to produce granules with desired particle size distribution using a twin screw granulator. This approach could locate the suitable L/S ratio before the twin screw granulation process and reduce the trial and error during formulation development.

As the optimal L/S ratio could produce the highest proportion of granules within the required size range and the granules produced at the optimal L/S ratio are normally stronger, this new approach actually give predictions about at which L/S ratio the granulation process could provide a batch of granule with narrowest size distribution and stronger granule strength. Therefore, this new approach was found to be effective to predict the optimal L/S ratio and consequently guide the granulation process to produce the granules with a narrower size distribution and stronger strength, which met the objective of the research.

Apart from the prediction of L/S ratio using a small scaled powder bed, in **Chapter 6**, a new binding excipient was firstly examined and used in twin screw granulation process, to enhance the liquid distribution and granule bulk strength. By evaluating the granule size distribution using micronized lactose, it was found that small amounts of micronized lactose (5% & 10%) have positive effects (about 9.0% & 9.4%) with lactose granule size distributions. However, if 15% micronized lactose was added, wider granule size distribution would be obtained and the span of distribution would be increased (about 10.4%). For MCC, an increase in micronized lactose from 5% to 15% would cause a reduction in the span of distribution of about 26.6% to 54.5%. Through a comparison with literature, it was found that such improvements were capable to distinctively affect the granular product properties.

By comparing the granule bulk strength between micronized lactose was added or not, it was found that using micronized lactose could significantly influence the granule bulk strength. For lactose, the addition of micronized lactose (from 5% to 10%) could enhance the granule strength from about 12.7% to almost 40.0%; for MCC the improvements are from about 14.5% up to about 100.0%. Such improvements on granule bulk strength through using micronized lactose indicate that micronized lactose was able to enhance the granule bulk strength and was capable to be used as a solid binder for both soluble and insoluble materials.

Micronized lactose was proved to be an effective solid binder for twin screw granulation and provides an alternative when selecting solid binder for granulation in the pharmaceutical industry. By using it, granules with narrower size distributions and stronger strength could be produced, which met the objective of research.

The previous chapter (Chapter 5 and Chapter 6) developed new approaches to improve the granule properties from a perspective of formulation development (Chapter 5: optimizing the moisture/liquid content in the formulation; Chapter 6: evaluating a novel binding excipient premixed with powder). In the following two chapters, different approaches from a perspective of process optimization were carried out.

In **Chapter 7**, temperature as an independent variable is investigated. HPC was prepared in two forms: dissolved in water as a solution and premixed with granulation powders. It was found that using a higher temperature (especially at 60 ºC in this chapter) could effectively reduce the span of distribution for both lactose and MCC. For liquid binder delivery, using HPC solution at 60 ºC could decrease the span of distribution by about 42.5% for lactose and 30.5% for MCC, respectively. When solid HPC was premixed, using a formulation of HPC particles premixed at 60 ºC could reduce the span of distribution by about 37.4% for lactose and 28.6% for MCC, respectively. In general, it was found that using a high temperature is capable to effectively affect the granular product properties.

Using a higher temperature could also enhance the granule strength in a certain extent and such enhancements were more effective when HPC solid binder was used. It was found that for when solid HPC was used at 60 ºC, the maximum improvement in granule strength could be as much as 45.88% for lactose and 72.2% for MCC, whilst only 45.9% for lactose and 16.8% for MCC could be achieved when HPC solution was used. Therefore, by reference to the literature, such improvements were identified as effectively affect the tablet properties and following granular products.

In this chapter, using a higher temperature was considered to be a useful way to narrow the granule size distribution and enhance the granule strength. In the application, it is recommended to granulate material in a higher temperature, as the improvements in granule properties could significantly save the expensive API materials and the benefits obtained are more than what it would be costs in rising temperature. What is necessary to be mentioned is that such increase in granulation temperature is limited by the maximum tolerance temperature of the active materials (API).

In **Chapter 8**, processing parameters including screw speed and configuration were adjusted to maintain a controlled material loads in the barrel (Barrel loading, g), in order to improve the granule yields and strength with different binder delivery method. By controlling BL as a constant, the twin screw granulation process could be performed in more steady environment. Owing to a relatively higher level of material in the barrel, less free space would be left and consequently higher compression stress would be maintained. Higher compression reduces the distance between particles and thus enhance the capillary action and thus enhance the liquid distribution.

While kneading elements were used, the increase of screw speed would help to intensify the mixing and stress acting on the material, which enhances the breakages and coalescence, giving a more even liquid-powder mixing. In addition, with a controlling of BL, using kneading elements could reduce the span of distribution up to 19.7% for lactose and 83.3% for MCC, which significantly improve the liquid distribution and narrow the granule size distribution. In addition, use of kneading elements could also accelerate the dissolution of solid HPC particles, and enhance its binding capability. For lactose,

enhancement on granule bulk strength could achieve as much as 21.6%, whilst only 14.7% enhancement could be achieved if MCC was used.

In this chapter, a constant barrel loading was maintained to provide a more steady granulation environment. It was found that when BL was maintained, using kneading elements at 200 rpm could produce granules with a narrower size distribution and stronger strength, which met the research objective. This chapter suggested that with a controlled BL, using kneading elements at a higher screw speed could improve the granule properties and enhance the usage efficiency in pharmaceutical industries.

9.2. Future work

Compact powder bed could be used to predict the optimal L/S ratio before granulation. However, current approach could be only applicable when conveying elements are used. It is necessary to extend this study and link the miniaturized droplet study on the compact powder bed to the real granulation process. In twin screw granulation process, the use of kneading elements could enhance the granule breakages and coalescence, which is not easy to be linked with the current compact powder bed. Therefore, further improvements are still needed to reform the study on the compact powder bed, in order to realize a more accurate prediction for the real granulation process.

To improve this approach, stresses acting along the twin screw barrel should be examined and studied at first. It could be either obtained through the Discrete Element Modeling (DEM), or from the experiment about the material property variation under stress in the twin screw barrel.

In a wet granulation process, particle dissolution and the primary particle hardness are the most important parameters which could affect the granule properties. The dissolution of particles would affect the liquid viscosity and the quality of liquid bridges, which directly affect the liquid distribution and granule strength. The primary particle hardness is related to the deformation and interlocking of the material and also the main parameter to reflect the effect of stress. Microscopic method would be needed to record the particle dissolution. In terms of the particle hardness, nano-indentation would be needed. The study of particle dissolution and hardness could enhance the understanding about the physical reaction occurs in the twin screw barrel. Most importantly, it could provide the essential knowledge to improve the study on the compact powder bed and the approach to prediction the optimum parameter including L/S ratio, stress, etc.

Chapter 10. Reference

ADAMS, M., MULLIER, M. & SEVILLE, J. 1994. Agglomerate strength measurement using a uniaxial confined compression test. *Powder Technology,* 78**,** 5-13.

AI, Q., DHENGE, R. M., HOUNSLOW, M. J. & SALMAN, A. D. 2016. Developing a miniaturized approach for formulation development using twin screw granulation. *Powder Technology*.

AINSWORTH, P., IBANOGLU, S. & HAYES, G. D. 1997. Influence of process variables on residence time distribution and flow patterns of tarhana in a twin-screw extruder. *Journal of Food Engineering,* 32**,** 101-108.

ALVAREZ-LORENZO, C., GOMEZ-AMOZA, J., MARTıNEZ-PACHECO, R., SOUTO, C. & CONCHEIRO, A. 2000. Evaluation of low-substituted hydroxypropylcelluloses (L-HPCs) as filler-binders for direct compression. *International journal of pharmaceutics,* 197**,** 107-116.

AULTON, M. & BANKS, M. 1979. The measurement of spray droplet size distributions. *Journal of Pharmacy and Pharmacology,* 31**,** 102P-102P.

BARRASSO, D., WALIA, S. & RAMACHANDRAN, R. 2013. Multi-component population balance modeling of continuous granulation processes: a parametric study and comparison with experimental trends. *Powder Technology,* 241**,** 85-97.

BUCKTON, G. & NEWTON, J. 1985. Assessment of the wettability and surface energy of a pharmaceutical powder by liquid penetration. *Journal of pharmacy and pharmacology,* 37**,** 605-609.

BUCKTON, G. & NEWTON, J. 1986. Assessment of the wettability of powders by use of compressed powder discs. *Powder technology,* 46**,** 201-208.

CHARLES-WILLIAMS, H. R., WENGELER, R., FLORE, K., FEISE, H., HOUNSLOW, M. J. & SALMAN, A. D. 2011. Granule nucleation and growth: Competing drop spreading and infiltration processes. *Powder Technology,* 206**,** 63-71.

CHIRANGANO, M. 2009. *Granulation and Tabletting: Effect of Process Variables on Mechanical Properties.* Ph.D., University of Sheffield.

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,* 438**,** 20-32.

DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2012b. Twin screw granulation: steps in granule growth. *International journal of pharmaceutics,* 438**,** 20-32.

DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2012c. Twin screw wet granulation: Effects of properties of granulation liquid. *Powder Technology,* 229**,** 126-136.

DHENGE, R. M., 2012d. *Twin screw granulation: A detailed study.* Ph.D., University of Sheffield.

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.

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.

EMADY, H. N., KAYRAK-TALAY, D., SCHWERIN, W. C. & LITSTER, J. D. 2011. Granule formation mechanisms and morphology from single drop impact on powder beds. *Powder Technology,* 212**,** 69-79.

ENNIS, B. J., TARDOS, G. & PFEFFER, R. 1991. A microlevel-based characterization of granulation phenomena. *Powder Technology,* 65**,** 257-272.

FIELDEN, K., NEWTON, J. M., O'BRIEN, P. & ROWE, R. C. 1988. Thermal studies on the interaction of water and microcrystalline cellulose. *Journal of pharmacy and pharmacology,* 40**,** 674-678.

FOWKES, F. M. 1964. Attractive forces at interfaces. *Industrial & Engineering Chemistry,* 56**,** 40-52.

GAMLEN, M. & EARDLEY, C. 1986. Continuous extrusion using a raker perkins MP50 (multipurpose) extruder. *Drug Development and Industrial Pharmacy,* 12**,** 1701-1713.

GIRY, K., PéAN, J. M., GIRAUD, L., MARSAS, S., ROLLAND, H. & WüTHRICH, P. 2006. Drug/lactose co-micronization by jet milling to improve aerosolization properties of a powder for inhalation. *International Journal of Pharmaceutics,* 321**,** 162-166.

GORRINGE, L. J., KEE, G. S., SALEH, M. F., FA, N. H. & ELKES, R. G. 2017. Use of the channel fill level in defining a design space for twin screw wet granulation. *International Journal of Pharmaceutics,* 519**,** 165-177.

HANSFORD, D. T., GRANT, D. W. & NEWTON, J. 1980. The influence of processing variables on the wetting properties of a hydrophobic powder. *Powder Technology,* 26**,** 119-126.

HANSSON, H. & LINDNER-OLSSON, E. 2004. Granulation process. Google Patents.

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.
HOLM, P., JUNGERSEN, O., SCHAEFER, T. & KRISTENSEN, H. 1983. Granulation in high speed mixers. I: Effects of process variables during kneading. *Pharmazeutische Industrie,* 45**,** 806-811.
HORISAWA, E., KOMURA, A., DANJO, K. and OTSUKA, A., 1995. Effect of granule strength on compressed tablet strength. *Chemical and pharmaceutical bulletin*, 43(12), pp.2261-2263.
IVESON, S. & LITSTER, J. 1998. Growth regime map for liquid-bound granules. *AIChE journal,* 44**,** 1510-1518.
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.
JOHN, F. P. & CHARLES, H. 2002. Taste masking pharmaceutical composition. Google Patents.
KARUNANITHY, C. & MUTHUKUMARAPPAN, K. 2011. Optimization of switchgrass and extruder parameters for enzymatic hydrolysis using response surface methodology. *Industrial Crops and Products,* 33**,** 188-199.
KATO, H., ONO, Y., YONEZAWA, Y. & SUNADA, H. 2006. The effect of binder particle size on granule and tablet properties in high shear and extrusion granulation. *Journal of drug delivery science and technology,* 16**,** 461-466.
KAYRAK-TALAY, D. & LITSTER, J. D. 2011. A priori performance prediction in pharmaceutical wet granulation: testing the applicability of the nucleation regime map to a formulation with a broad size distribution and dry binder addition. *International journal of pharmaceutics,* 418**,** 254-264.
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. 2004. Twin screw granulation as a simple and efficient tool for continuous wet granulation. *International journal of pharmaceutics,* 273**,** 183-194.
KOHLGRüBER, K. 2012. *Co-rotating twin-screw extruder,* Carl Hanser Verlag GmbH Co KG.
KOKUBO, H. & SUNADA, H. 1996. Effect of process variables on the properties and binder distribution of granules prepared by a high-speed mixer. *CHEMICAL AND PHARMACEUTICAL BULLETIN-TOKYO-*, 44**,** 1546-1549.
KOLTER, K., KARL, M., GRYCZKE, A. & LUDWIGSHAFEN AM RHEIN, B. 2012. *Hot-melt extrusion with BASF pharma polymers: extrusion compendium*, BASF.
KUMAR, A., VERCRUYSSE, J., BELLANDI, G., GERNAEY, K. V., VERVAET, C., REMON, J. P., DE BEER, T. & NOPENS, I. 2014. Experimental investigation of granule size and shape dynamics in twin-screw granulation. *International journal of pharmaceutics,* 475**,** 485-495.
LANGMUIR, I. & SCHAEFER, V. J. 1937. The effect of dissolved salts on insoluble monolayers. *Journal of the American Chemical Society,* 59**,** 2400-2414.
LE, P. K., AVONTUUR, P., HOUNSLOW, M. J. & SALMAN, A. D. 2011. A microscopic study of granulation mechanisms and their effect on granule properties. *Powder Technology,* 206**,** 18-24.

LEE, K. T., INGRAM, A. & ROWSON, N. A. 2013. Comparison of granule properties produced using Twin Screw Extruder and High Shear Mixer: A step towards understanding the mechanism of twin screw wet granulation. *Powder Technology,* 238**,** 91-98.

LI, H., THOMPSON, M. & O'DONNELL, K. 2014a. Understanding wet granulation in the kneading block of twin screw extruders. *Chemical Engineering Science,* 113**,** 11-21.

LI, H., THOMPSON, M. R. & O'DONNELL, K. P. 2014b. Understanding wet granulation in the kneading block of twin screw extruders. *Chemical Engineering Science,* 113**,** 11-21.

LI, J., TAO, L., DALI, M., BUCKLEY, D., GAO, J. & HUBERT, M. 2011. The effect of the physical states of binders on high-shear wet granulation and granule properties: A mechanistic approach toward understanding high-shear wet granulation process. part II. granulation and granule properties. *Journal of pharmaceutical sciences,* 100**,** 294-310.

LITSTER, J. & ENNIS, B. 2013. *The science and engineering of granulation processes*, Springer Science & Business Media.

LIU, Y., THOMPSON, M., O'DONNELL, K. & GRASMAN, N. 2016. Effect of temperature on the wetting behavior of hydroxypropyl methylcellulose in a twin-screw granulator. *Powder Technology,* 302**,** 63-74.

LUTE, S. V., DHENGE, R. M., HOUNSLOW, M. J. & SALMAN, A. D. 2016. Twin screw granulation: Understanding the mechanism of granule formation along the barrel length. *Chemical Engineering Research and Design,* In Press, Accepted Manuscript.

LUUKKONEN, P., MALONEY, T., RANTANEN, J., PAULAPURO, H. & YLIRUUSI, J. 2001. Microcrystalline cellulose-water interaction—a novel approach using thermoporosimetry. *Pharmaceutical research,* 18**,** 1562-1569.

MANIRUZZAMAN, M., NAIR, A., RENAULT, M., NANDI, U., SCOUTARIS, N., FARNISH, R., BRADLEY, M.S., SNOWDEN, M.J. AND DOUROUMIS, D., 2015. Continuous twin-screw granulation for enhancing the dissolution of poorly water soluble drug. *International journal of pharmaceutics*, 496(1), pp.52-62.

MEIER, R., MOLL, K.-P., KRUMME, M. & KLEINEBUDDE, P. 2017. Impact of fill-level in twin-screw granulation on critical quality attributes of granules and tablets. *European Journal of Pharmaceutics and Biopharmaceutics,* 115**,** 102-112.

MEIRON, T. S., MARMUR, A. & SAGUY, I. S. 2004. Contact angle measurement on rough surfaces. *Journal of Colloid and Interface Science,* 274**,** 637-644.

NOWAK, E., KOVALCHUK, N. M., CHE, Z. & SIMMONS, M. J. H. 2016. Effect of surfactant concentration and viscosity of outer phase during the coalescence of a surfactant-laden drop with a surfactant-free drop. *Colloids and Surfaces A: Physicochemical and Engineering Aspects,* 505**,** 124-131.

NYSTRöM, C. & GLAZER, M. 1985. Studies on direct compression of tablets. XIII. The effect of some dry binders on the tablet strength of compounds with different fragmentation propensity. *International journal of pharmaceutics,* 23**,** 255-263.

NYSTRöM, C., MAZUR, J. & SJöGREN, J. 1982. Studies on direct compression of tablets II. The influence of the particle size of a dry binder on the mechanical strength of tablets. *International Journal of Pharmaceutics,* 10**,** 209-218.

OSBORNE, J. D., SOCHON, R. P. J., CARTWRIGHT, J. J., DOUGHTY, D. G., HOUNSLOW, M. J. & SALMAN, A. D. 2011. Binder addition methods and binder distribution in high shear and fluidised bed granulation. *Chemical Engineering Research and Design,* 89**,** 553-559.

PICKER-FREYER, K. M. & DüRIG, T. 2007. Physical mechanical and tablet formation properties of hydroxypropylcellulose: in pure form and in mixtures. *AAPS PharmSciTech,* 8**,** 82-90.

RAJKUMAR, A. D., REYNOLDS, G. K., WILSON, D., WREN, S., HOUNSLOW, M. J., & SALMAN, A. D. (2016). Investigating the effect of processing parameters on pharmaceutical tablet disintegration using a real-time particle imaging approach. *European Journal of Pharmaceutics and Biopharmaceutics,* 106, 88-96.

REIS, N. C., GRIFFITHS, R. F. & SANTOS, J. M. 2004. Numerical simulation of the impact of liquid droplets on porous surfaces. *Journal of Computational Physics,* 198**,** 747-770.

REITZ, E., VERVAET, C., NEUBERT, R. H. & THOMMES, M. 2013. Solid crystal suspensions containing griseofulvin–preparation and bioavailability testing. *European Journal of Pharmaceutics and Biopharmaceutics,* 83**,** 193-202.

SAKAI, T. & NAKAMURA, A. M. 2005. Quantification of porosity and surface roughness in laboratory measurements of the bidirectional reflectance of asteroid surface analogues. *Earth, planets and space,* 57**,** 71-76.

SALEH, M. F., DHENGE, R. M., CARTWRIGHT, J. J., HOUNSLOW, M. J. & SALMAN, A. D. 2015. Twin screw wet granulation: Binder delivery. *International Journal of Pharmaceutics,* 487**,** 124-134.

SALMAN, A., HOUNSLOW, M. & SEVILLE, J. 2007. Handbook of Powder Technology, Vol. 11: Granulation. Elsevier Publishing, Amsterdam.

ŠANTL, M., ILIĆ, I., VREČER, F. & BAUMGARTNER, S. 2012. A compressibility and compactibility study of real tableting mixtures: the effect of granule particle size. *Acta pharmaceutica,* 62**,** 325-340.

SCHæFER, T. & MATHIESEN, C. 1996. Melt pelletization in a high shear mixer. IX. Effects of binder particle size. *International journal of pharmaceutics,* 139**,** 139-148.

SEEM, T. C., ROWSON, N. A., INGRAM, A., HUANG, Z., YU, S., DE MATAS, M., GABBOTT, I. & REYNOLDS, G. K. 2015. Twin screw granulation—a literature review. *Powder Technology,* 276**,** 89-102.

THOMPSON, M. & SUN, J. 2010. Wet granulation in a twin-screw extruder: Implications of screw design. *Journal of pharmaceutical sciences,* 99**,** 2090-2103.

TU, W.-D., INGRAM, A. & SEVILLE, J. 2013. Regime map development for continuous twin screw granulation. *Chemical Engineering Science,* 87**,** 315-326.

UNLU, E. & FALLER, J. F. 2002. RTD in twin-screw food extrusion. *Journal of Food Engineering,* 53**,** 115-131.

VAN DER WATT, J. 1987. The effect of the particle size of microcrystalline cellulose on tablet properties in mixtures with magnesium stearate. *International journal of pharmaceutics,* 36**,** 51-54.

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., BURGGRAEVE, A., FONTEYNE, M., CAPPUYNS, P., DELAET, U., VAN ASSCHE, I., DE BEER, T., REMON, J. P. & VERVAET, C. 2015. Impact of screw configuration on the particle size distribution of granules produced by twin screw granulation. *International Journal of Pharmaceutics,* 479**,** 171-180.

VERCRUYSSE, J., CóRDOBA DíAZ, D., PEETERS, E., FONTEYNE, M., DELAET, U., VAN ASSCHE, I., DE BEER, T., REMON, J. P. & VERVAET, C. 2012a. Continuous twin screw granulation: Influence of process variables on granule and tablet quality. *European Journal of Pharmaceutics and Biopharmaceutics,* 82**,** 205-211.

VERCRUYSSE, J., DíAZ, D. C., PEETERS, E., FONTEYNE, M., DELAET, U., VAN ASSCHE, I., DE BEER, T., REMON, J. P. & VERVAET, C. 2012b. Continuous twin screw granulation: influence of process variables on granule and tablet quality. *European Journal of Pharmaceutics and Biopharmaceutics,* 82**,** 205-211.

VONK, P., GUILLAUME, C., RAMAKER, J., VROMANS, H. & KOSSEN, N. 1997. Growth mechanisms of high-shear pelletisation. *International Journal of Pharmaceutics,* 157**,** 93-102.

WEATHERLEY, S., MU, B., THOMPSON, M.R., SHESKEY, P.J. AND O'DONNELL, K.P., 2013. Hot-melt granulation in a twin screw extruder: effects of processing on formulations with caffeine and ibuprofen. *Journal of pharmaceutical sciences*, 102(12), pp.4330-4336.

YOUNG, T. 1805. An essay on the cohesion of fluids. *Philosophical Transactions of the Royal Society of London,* 95**,** 65-87.

YUAN, Y. & LEE, T. R. 2013. Contact angle and wetting properties. *Surface science techniques.* Springer.

A. Appendix: nucleus hardness test for Chapter 4

a. Solid binder delivery

i. Wet nucleus hardness

In this section, a series of indentation experiments were carried out in order to study the effect of compression stress on nuclei hardness. Figure A-1 and Figure A-2 show the hardness of wet powder bed nuclei on lactose and MCC based powder bed. It can be seen that an increase in the compression stress led to an increase in the hardness of both wet powder bed nuclei. In case of wet powder bed nuclei it may be attributed to an increase in the formation of liquid bridges requiring less amount of liquid as the powder particles come closer during the compression compared to that with relatively loose powder bed (at low compression stress). Therefore, it can be deduced that if a granulator can exert more stress on powder, stronger granules are more likely to be produced.

Besides, an increase of HPC can also affect the powder bed nuclei hardness. For a constant compression stress, the variation of powder bed nuclei hardness could indirectly reflect the strength of bridges between the particles among different materials. An increase in the amount of HPC was expected to increase the hardness of wet powder bed nuclei formed as more binding capability was introduced. However, the results obtained seemed not to agree with this assumption. According to Figure A-1, the addition of HPC did not enhance the hardness of wet powder bed nuclei but in fact weaken it. Based on the previous study of the liquid behaviour and nucleus weight, some HPC particles, especially large sized particles, could not dissolve properly to enhance the strength between particles. Therefore, in comparison with powder beds containing solid binder,

liquid on powder beds of pure lactose could wet more material and stay on the powder bed for a longer time to dissolve more lactose and form stronger liquid bridges.

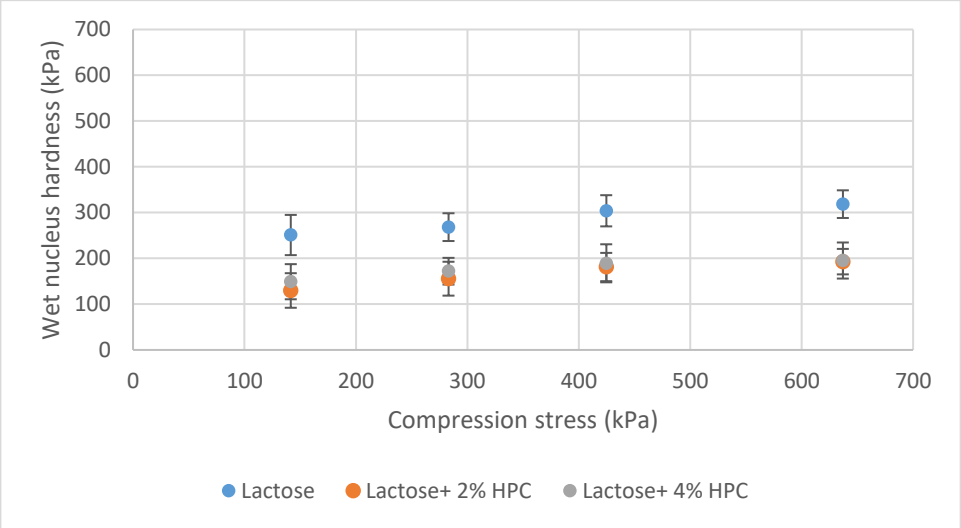


Figure A-1. Wet lactose nucleus hardness under different proportions of HPC.

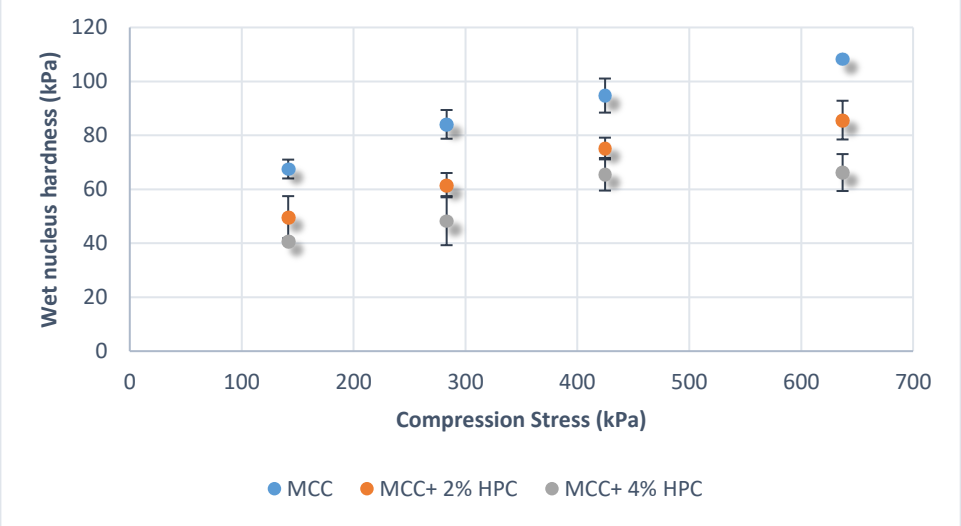


Figure A-2. Wet MCC nucleus hardness under different proportions of HPC.

As a comparison, the addition of HPC showed further less effect on the hardness of wet MCC nuclei compared to that in case of lactose, indicating that HPC could not enhance the strength of bonds among MCC particles. This may be attributed to the fact that MCC consumes more water during powder bed nucleation by its own swelling behaviour and consequently less water was left to interact with HPC particles. For this reason, the addition of HPC had limited influence on liquid-powder interaction in a powder bed of MCC.

ii. Dry nucleus hardness

Figure A-3 and Figure A-4 show the dry nucleus hardness on the lactose and MCC based powder bed with premixing of HPC particles. For both materials, the hardness of dry nuclei was found to increase with an increase in compression stress to produce powder beds. It was probably because of the formation of solid bridges between particles (i.e. after drying the liquid bridges between particles in wet powder bed nuclei turned into solid bridges).

When mixed with HPC solid binder in powder beds, the hardness of dry powder bed nuclei showed similar tendencies as when these powder bed nuclei were wet, i.e. the addition of HPC as a solid binder did not increase the hardness of powder bed nuclei as expected. As mentioned earlier the powder bed made of only lactose might have led to the formation of more viscous liquid compared to that with lactose with HPC by wetting more material and staying longer for dissolution in the powder bed. Thus more viscous liquid might have resulted in stronger liquid bridges and thus form stronger solid bridges between particles (Dhenge et al., 2013). In terms of MCC, due to it could swallow liquid, less liquid was left to interaction with HPC. As a result, it is less sensitive to the addition of HPC.

It was noted that the hardness of dry powder bed nuclei of MCC was much lower than that of lactose shown in Figure A-3. It was probably because, the bridges between lactose particles were made of dried out dissolved lactose, whilst the bridges between MCC particles may have mainly resulted from the physical inter-locking between swelled particles.

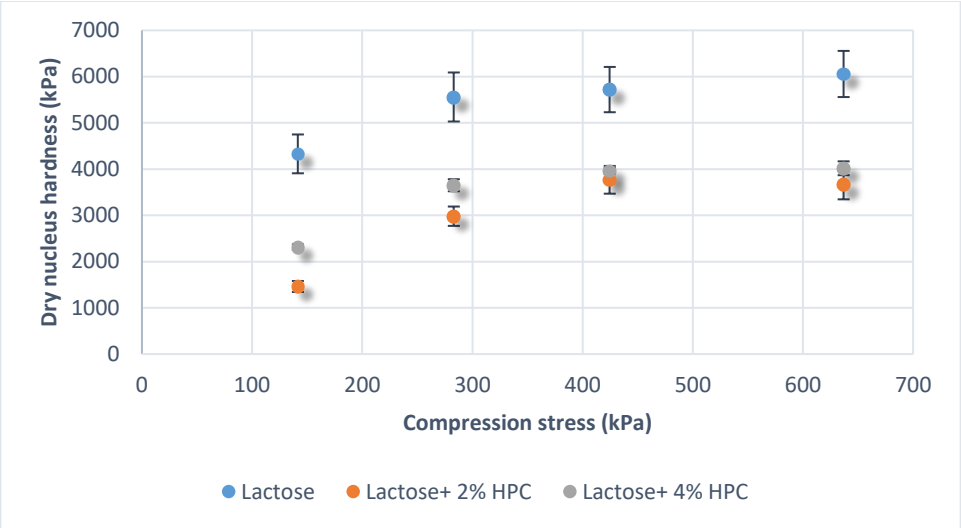


Figure A-3. Dry lactose nucleus hardness under different proportions of HPC (solid form).

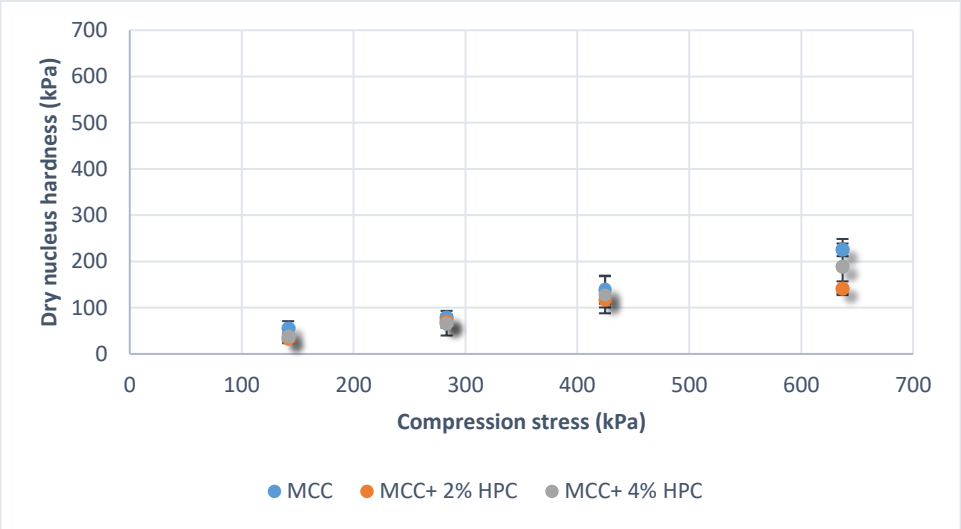


Figure A-4. Dry MCC nucleus hardness under different proportions of HPC (solid form).

b. Liquid binder delivery

i. Wet nucleus hardness

Figure A-5 and Figure A-6 show the wet nucleus hardness on the lactose and MCC based powder bed with the addition of HPC solution. Similar to what was shown in Figure A-1 and Figure A-2, an increase in compression stress reduces the distant between particles and consequently makes it easier for liquid to form liquid bonds. Therefore, the nucleus hardness increases with the increase of compression stress for both material.

Furthermore, the use of HPC solution shows little effects on the strength of liquid bonds. As is known, the HPC solution has a higher viscosity and theoretically could enhance the strength of liquid bonds. The reason why the use of HPC solution could not enhance the nucleus hardness is probably due to its poor flowability that makes the binder solution over-concentrated in the nucleus area (Figure 5-7 and Figure 5-8). Consequently,

the gap between particles would be full of liquid, which could reduce the friction and behave as a lubricant (Tu et al., 2013). As a result, an increase in liquid bonding capability was compensated by the loss of friction.

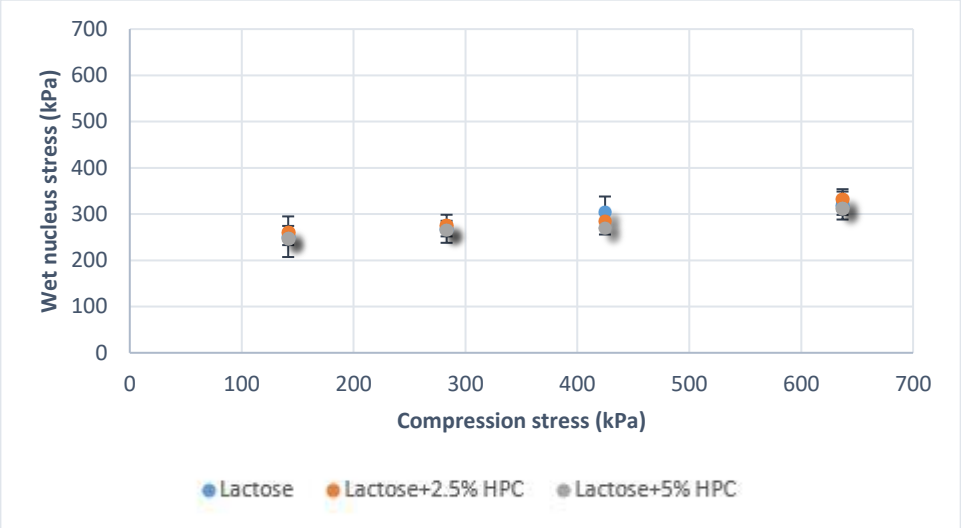


Figure A-5. Wet lactose nucleus hardness under different proportions of HPC (liquid form).

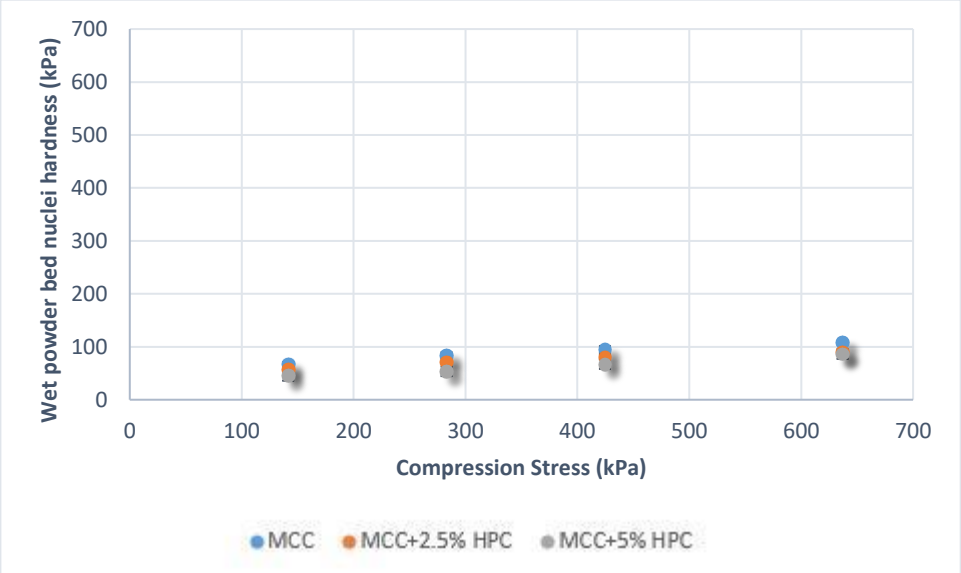


Figure A-6. Wet MCC nucleus hardness under different proportions of HPC (liquid form).

ii. Dry nucleus hardness

Figure A-7 shows the nucleus hardness affected by the compressions stress and HPC concentration in a liquid solution. It could be seen that an increase in compression stress leads to an increase in nucleus hardness. In addition, the nucleus produced using HPC solution is much stronger in nucleus hardness than the one produced using water. Comparing with the use of HPC particles shown in Figure A-3, the use of HPC solution could successfully enhance the bonds strength between particles on the static powder bed. It could be inferred that the use of HPC solution has wider applicability in bond enhancement if there is insufficient agitation during twin screw granulation process.

Similar effects are also available if MCC are used (Figure A-6). In addition, because MCC is insoluble, the nucleus hardness was much lower.

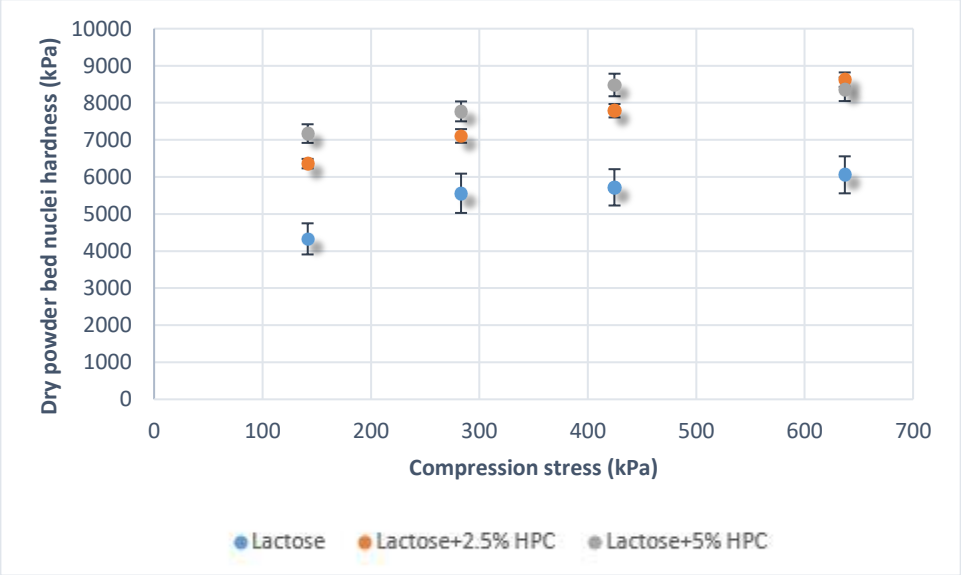


Figure A-7. Dry lactose nucleus hardness under different proportions of HPC (liquid form).

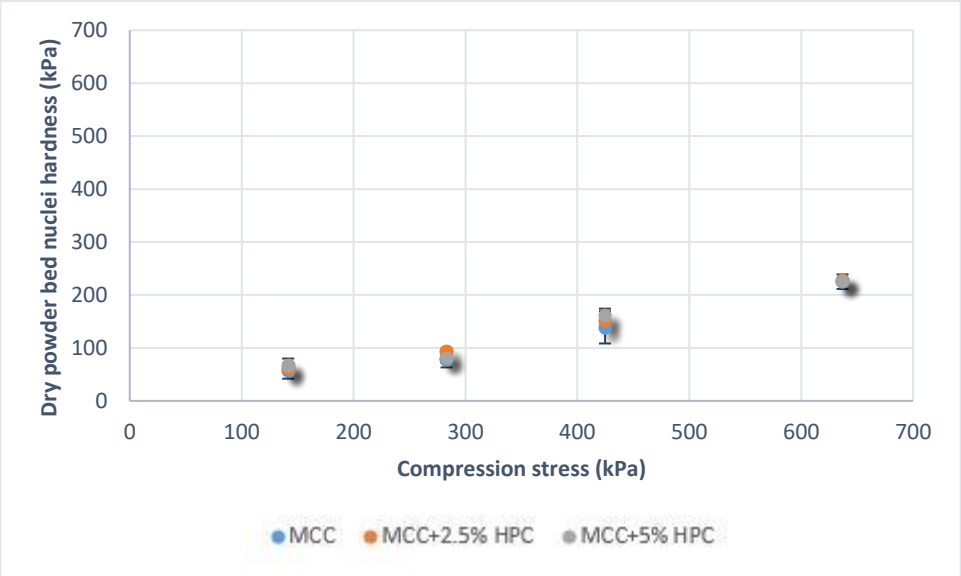


Figure A-8. Dry MCC nucleus hardness under different proportions of HPC (liquid form).

B. Appendix: nucleus hardness for Chapter 6

From the single drop study, it is known that the large HPC particles may not dissolve properly to enhance the nucleus hardness. Therefore, HPC was sieved into two different size classes (<53 μm, d_{10} and > 150 μm, d_{50}) and the normal HPC particle was used as a comparison. It could be seen in Figure B-1 that the use of large HPC particles reduces the nucleus hardness and the small HPC enhance it. As the wet nuclei hardness indirectly reflect the strength of liquid bridge, Figure B-1 indicated that a reduction in HPC particle size could enhance the strength of liquid bridges and this enhancement is applicable for all of the compression stress provided. Similar effect was also shown in MCC based powder bed (Figure B-2).

When the nucleus is dried out, the addition of small sized HPC particle consistently produced stronger nuclei than large HPC for both lactose and MCC based compact powder beds (Figure B-3 and Figure B-4). It indicates that smaller HPC leads to stronger bonds between particles and causes an increase in nucleus hardness.

However, such enhancement in nucleus hardness is still quite limited. Therefore, a new binding excipient micronized lactose was used and evaluated in Chapter 6 and its hardness test was also carried out.

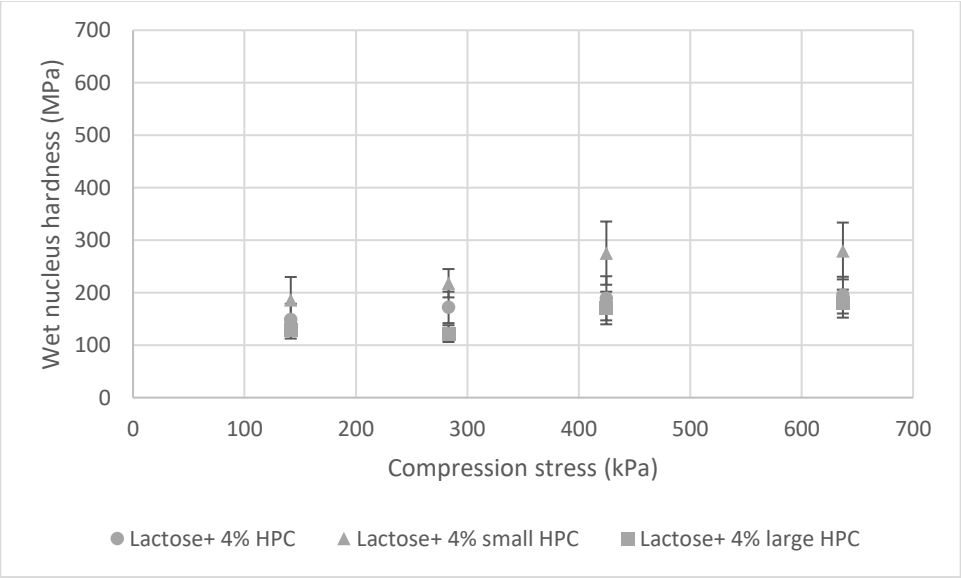


Figure B-1. Wet lactose nucleus hardness using different sized HPC (4%, large: > 150 μm; small: <53 μm)

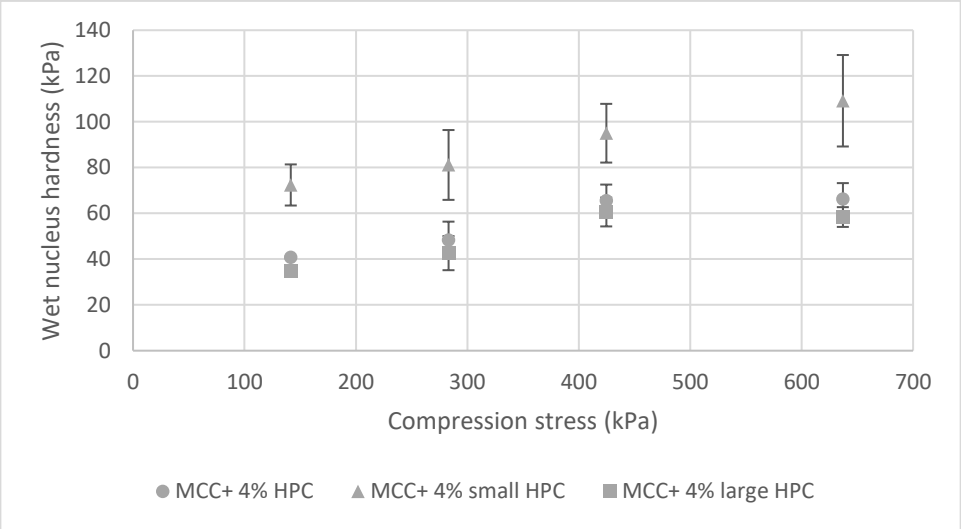


Figure B-2. Wet MCC nucleus hardness using different sized HPC (4%, large: > 150 μm; small: <53 μm).

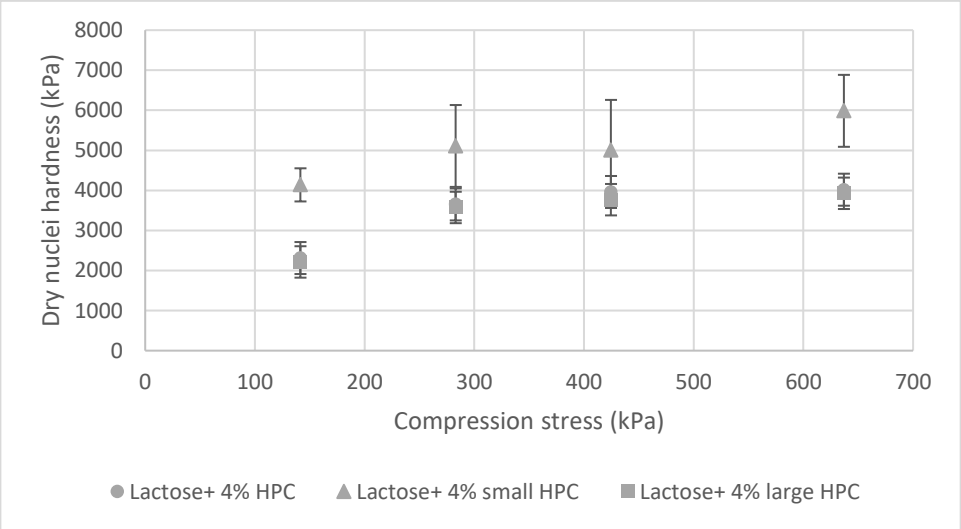


Figure B-3. Dry lactose nucleus hardness using different sized HPC (4%, large: > 150 μm; small: <53 μm).

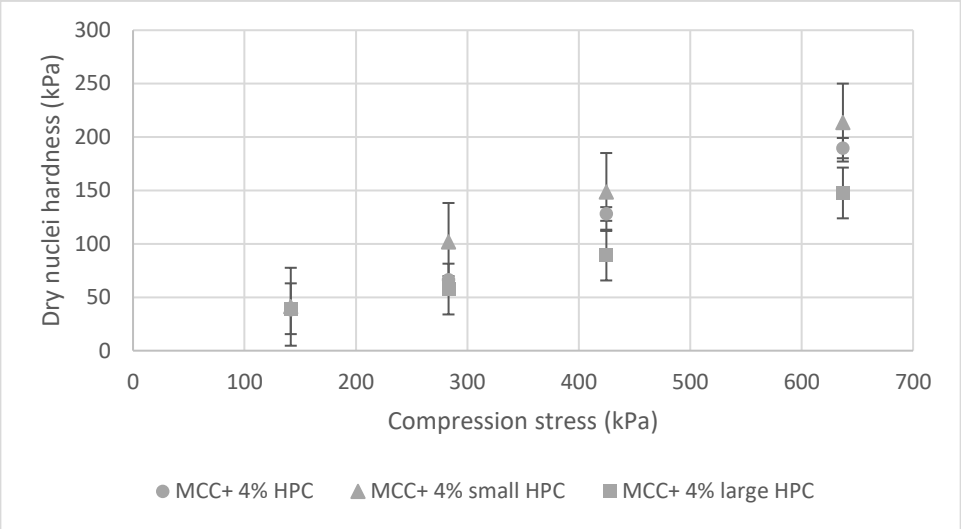


Figure B-4. Dry MCC nucleus hardness using different sized HPC (4%, large: > 150 μm; small: <53 μm).

To evaluate the binding capability of micronized lactose, indentation experiment that was regarded as a method for material hardness testing were carried out. In the experiment, the "nucleus" was formed at which the material was wetted in the compacted powder bed. In Figure B-5, the formulation with a higher proportion of micronized lactose tended to produce a harder nucleus. It indicated that a higher proportion of micronized lactose led to an increase in the strength of liquid bridge. However, the addition of solid binder does not show an obvious different on MCC nuclei hardness, shown in Figure B-6. Basically, it is because the instant dissolved micronized lactose would be carried by the water and swallowed into the MCC particles. Therefore, the remained liquid between particles are insufficient to affect the strength of liquid bonds.

Figure B-7 and Figure B-8 illustrated the relationship between the hardness of dried nucleus and the variation of powder formulations in a series of compression stresses. It

could be seen that the addition of micronized lactose would enhance the hardness of nuclei for both of lactose and MCC. An increase in the proportion of micronized lactose leads to an increase in the hardness of nuclei, indicating that the addition of micronized lactose was capable to strengthen the bonds between particles. In addition, from Figure B-7 and Figure B-8, with the increase in compression stress, increases in nucleus hardness could be observed. It was probably because the increase of compression stress made the powder bed more compacted. Hence, it would become easier for water to form liquid bridges and bond particles.

Upon comparing Figure B-7 with Figure B-3 and Figure B-8 with Figure B-4, it could be seen that the addition of micronized lactose showed a much better capability in enhancing nuclei hardness. Even adding 5% of micronized lactose could produce stronger nuclei compared to HPC. The comparison indicates that micronized lactose was capable to enhance the bond strength between particles and the efficiency is higher than HPC.

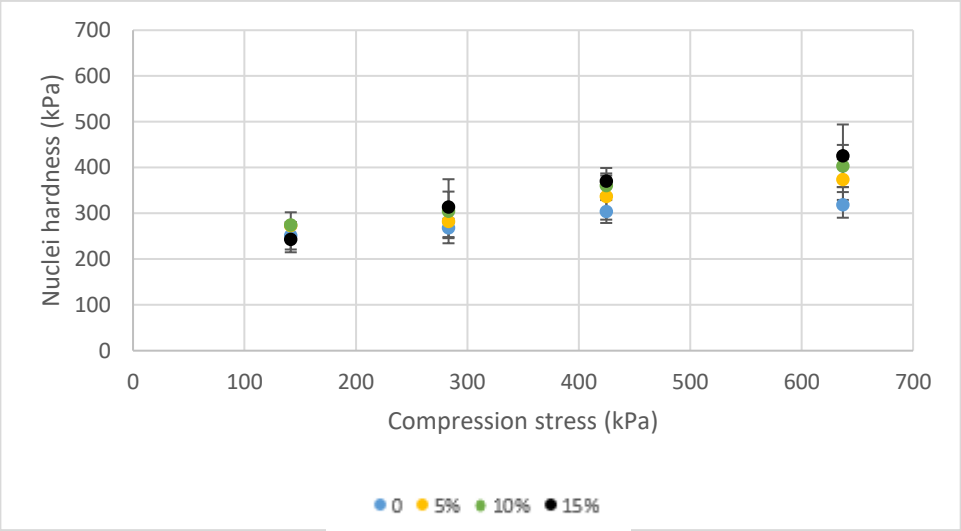


Figure B-5. Hardness of wet nucleus with different proportions of micronized lactose (0, 5, 10 and 15% w/w) on lactose compacted powder bed in different compression stresses.

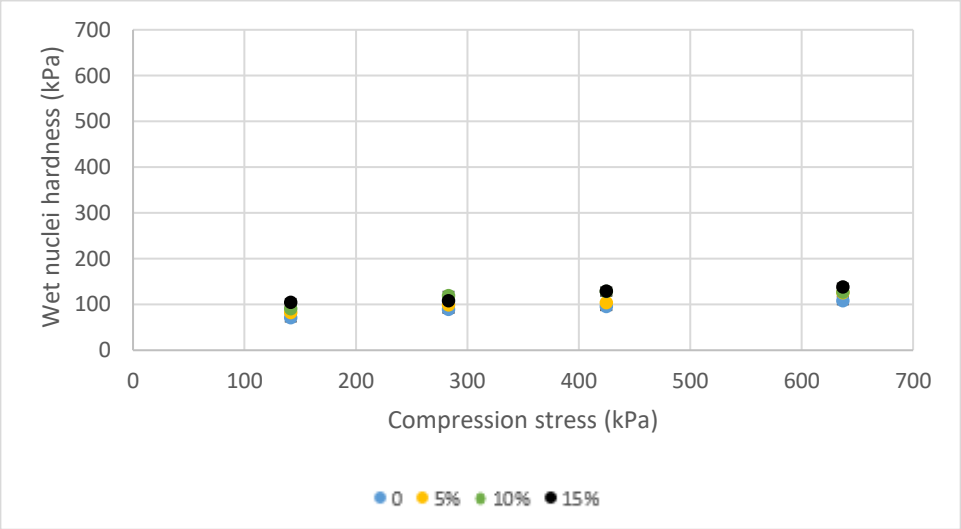


Figure B-6. Hardness of wet nucleus with different proportions of micronized lactose (0, 5, 10 and 15% w/w) on MCC compacted powder bed in different compression stresses.

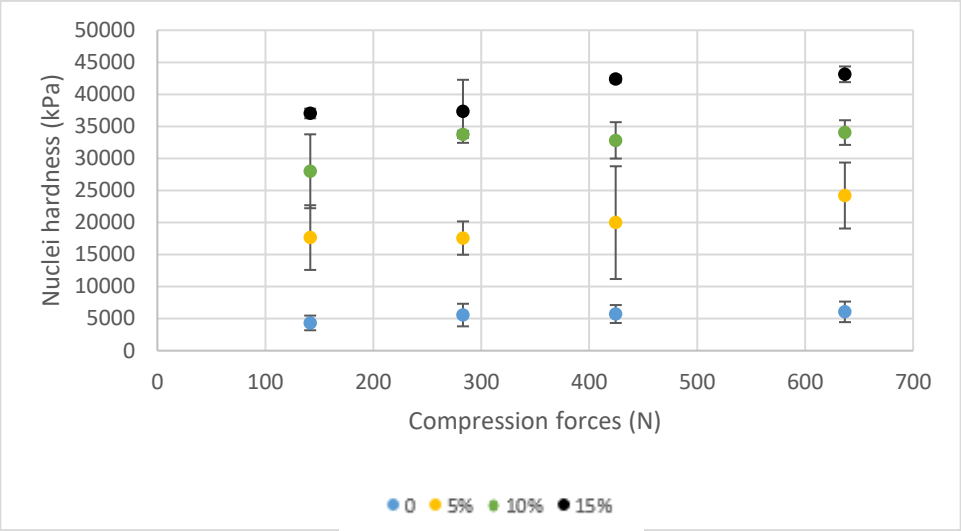


Figure B-7. Hardness of dry nucleus with different proportions of micronized lactose (0, 5, 10 and 15% w/w) on lactose compacted powder bed in different compression stresses.

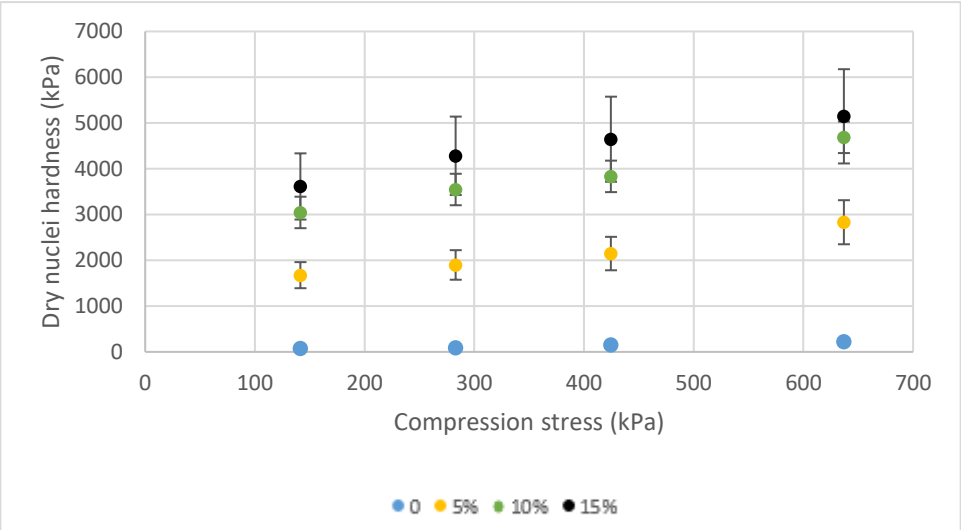
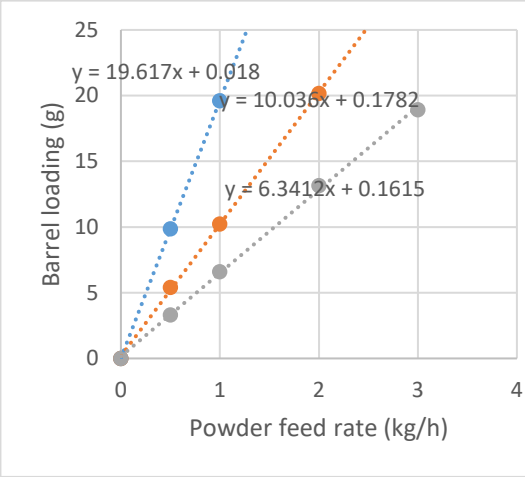
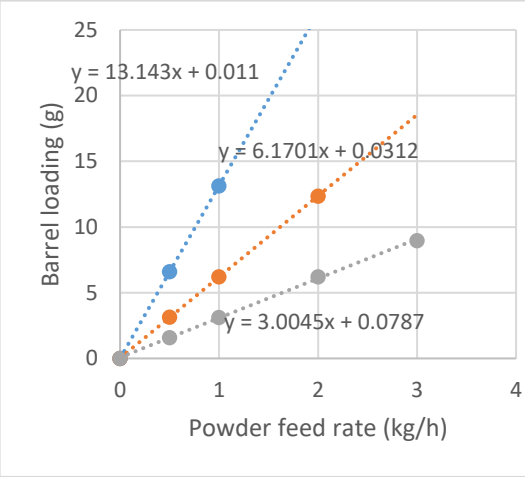


Figure B-8. Hardness of dry nucleus with different proportions of micronized lactose (0, 5, 10 and 15% w/w) on MCC compacted powder bed in different compression stresses.

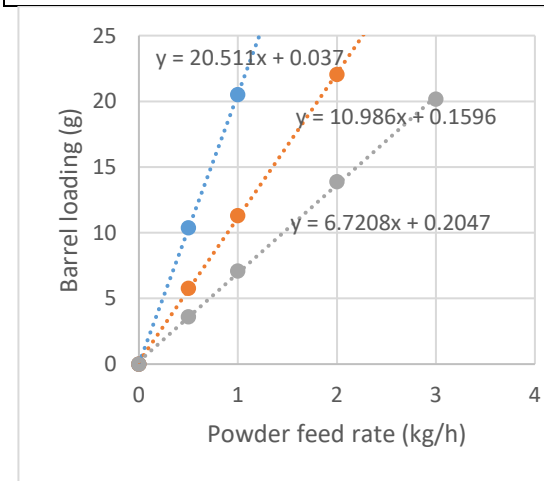
C. Appendix: BL vs powder feed rate for lactose and MCC



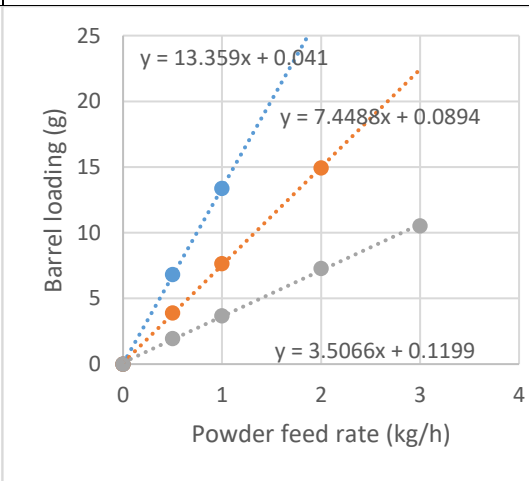
Conveying: lactose; water



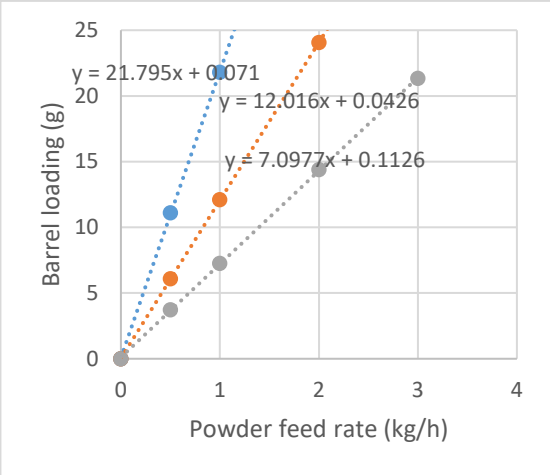
Kneading: lactose; water



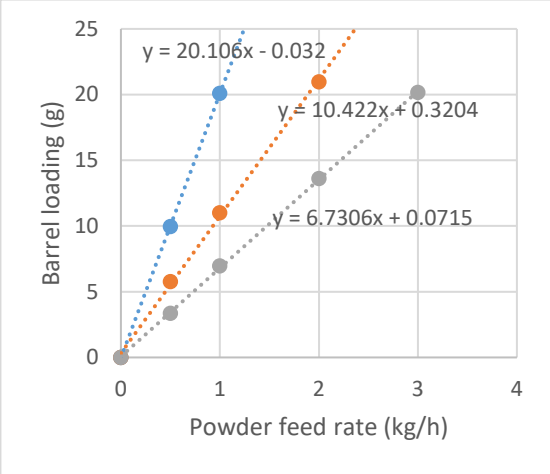
Conveying: lactose; 2% HPC solution



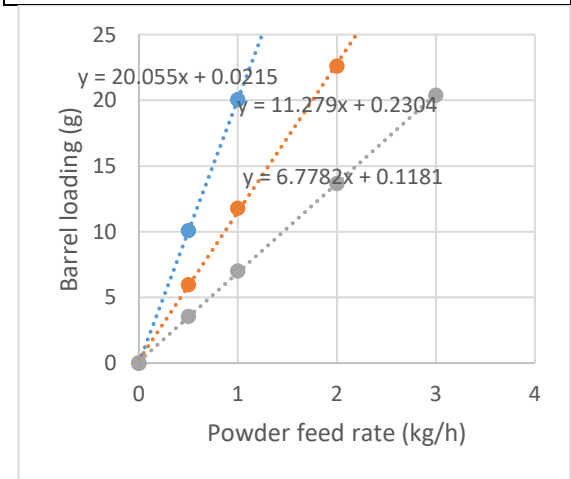
Kneading: lactose; 2% HPC solution



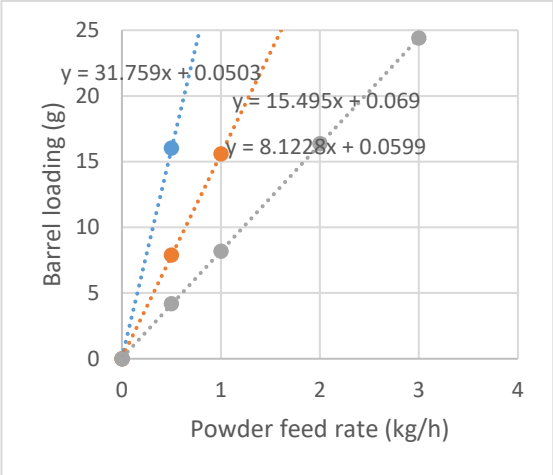
Conveying: lactose; 4% HPC solution	Kneading: lactose; 4% HPC solution



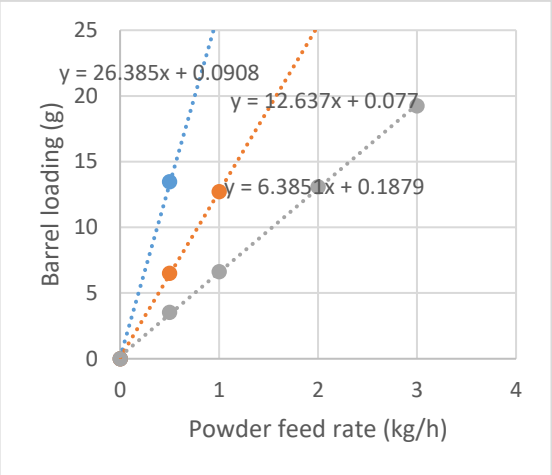
Conveying: lactose; 2% HPC particles	Kneading: lactose; 2% HPC particles



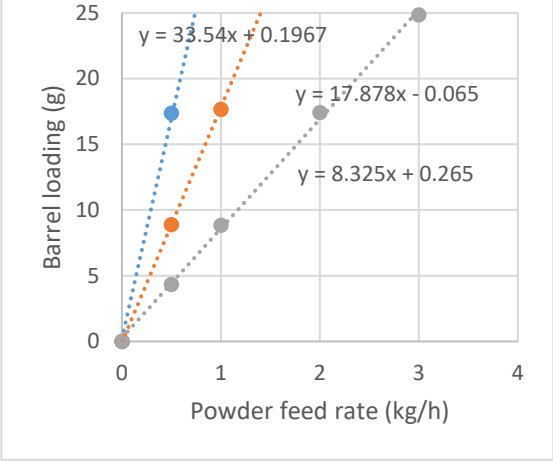
Conveying: lactose; 4% HPC particles	Kneading: lactose; 4% HPC particles



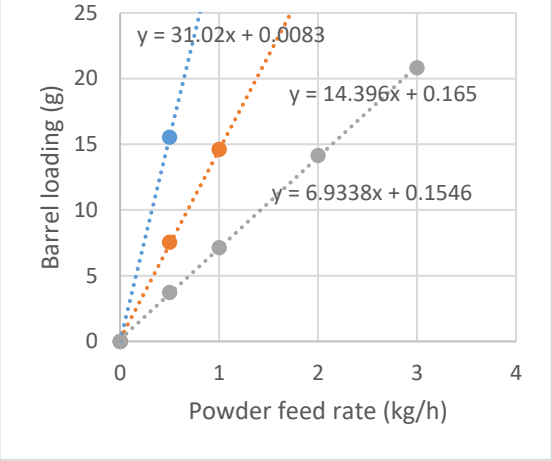
Conveying: MCC; water



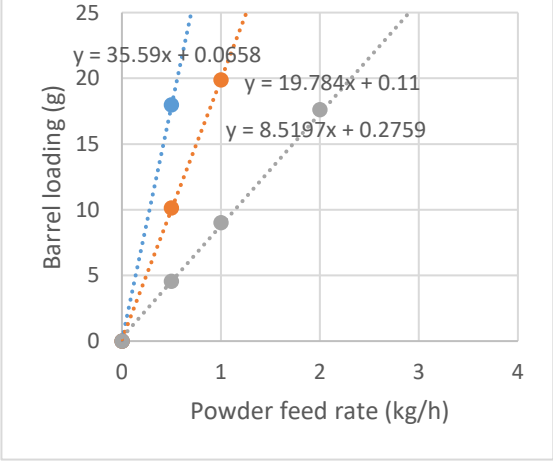
Kneading: MCC; water



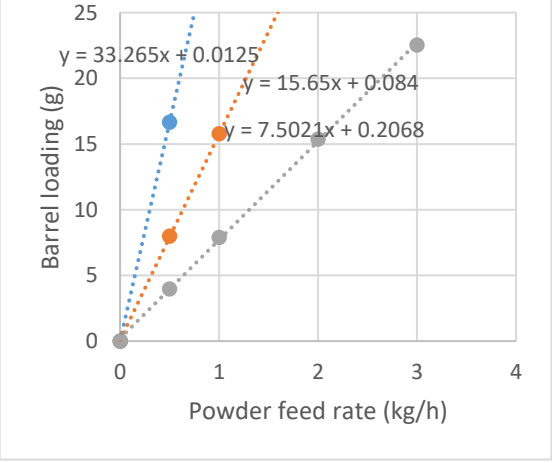
Conveying: MCC; 2% HPC solution



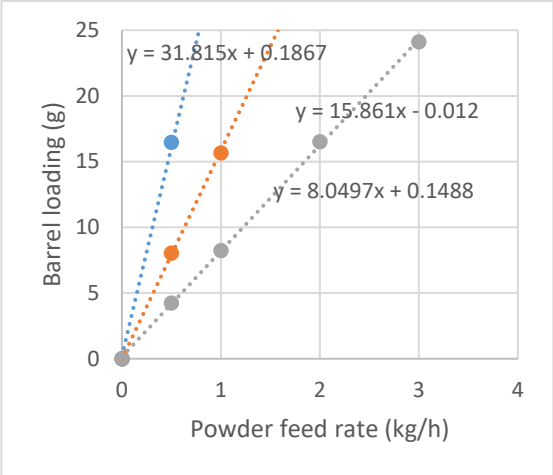
Kneading: MCC; 2% HPC solution



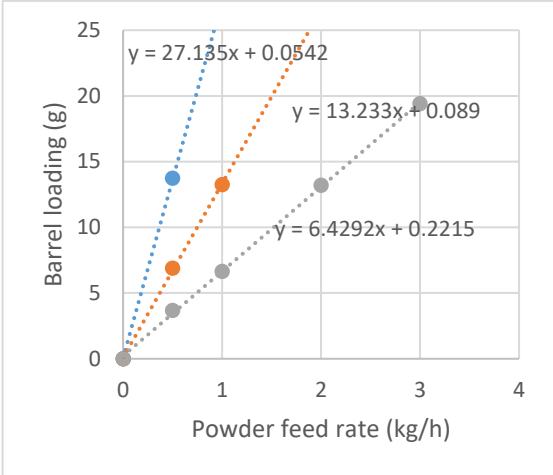
Conveying: MCC; 4% HPC solution



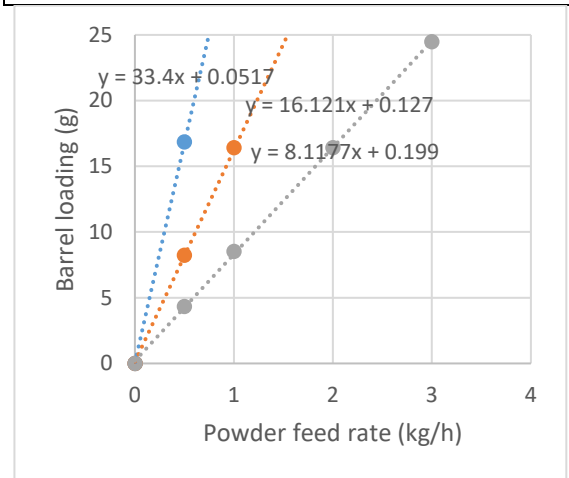
Kneading: MCC; 4% HPC solution



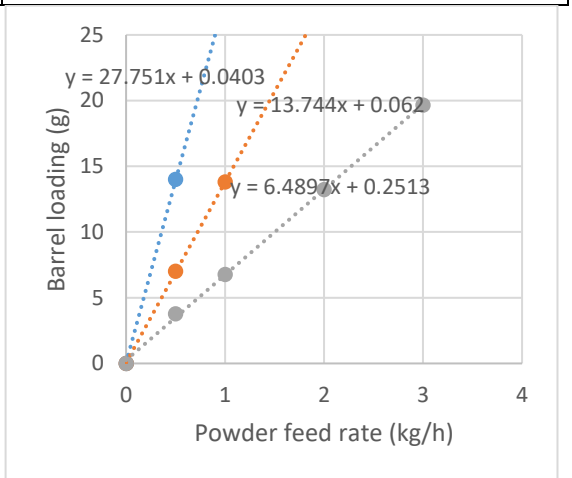
Conveying: MCC; 2% HPC particles



Kneading: MCC; 2% HPC particles

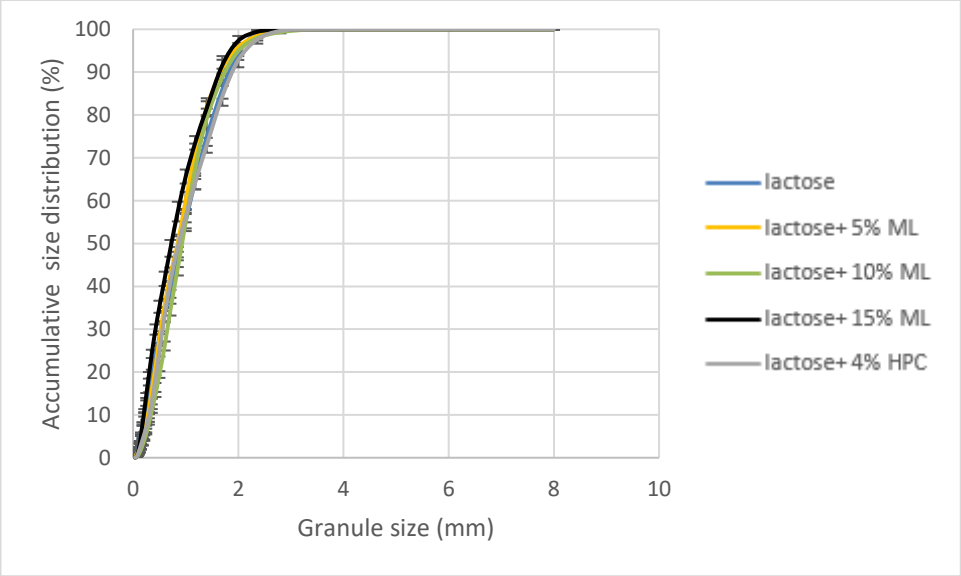


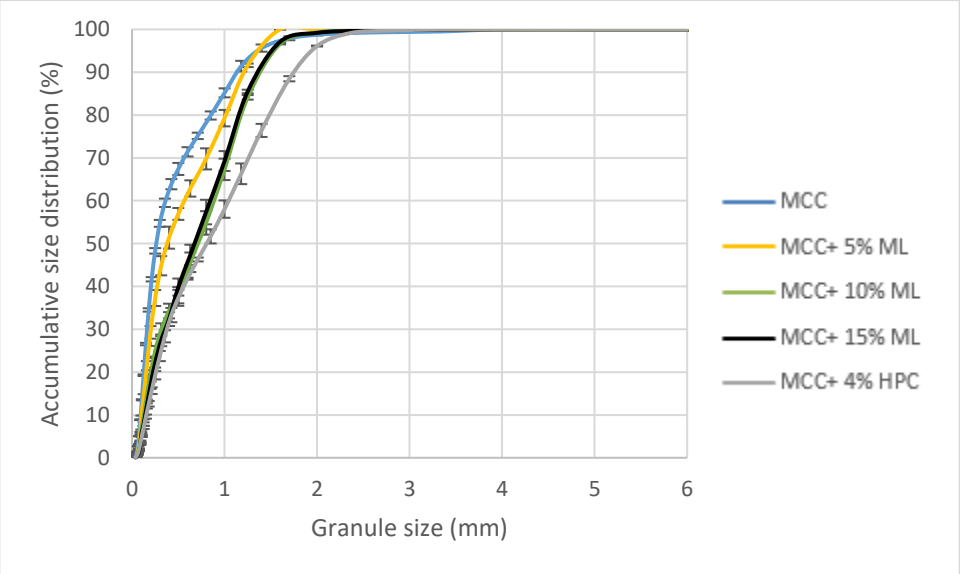
Conveying: MCC; 4% HPC particles



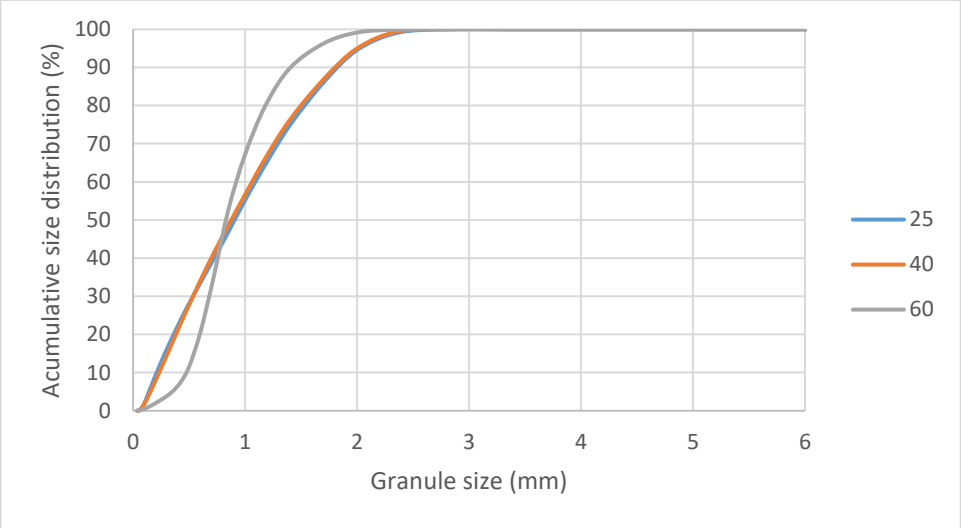
Kneading: MCC; 4% HPC particles

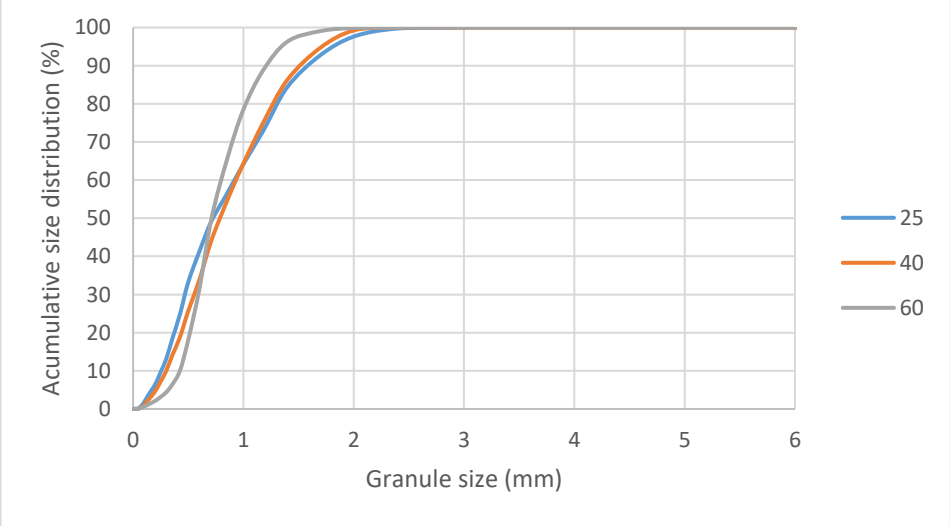
D.Appendix Accumulative distribution curves for Chapter 6





D. Appendix. Accumulative distribution curves for Chapter 7





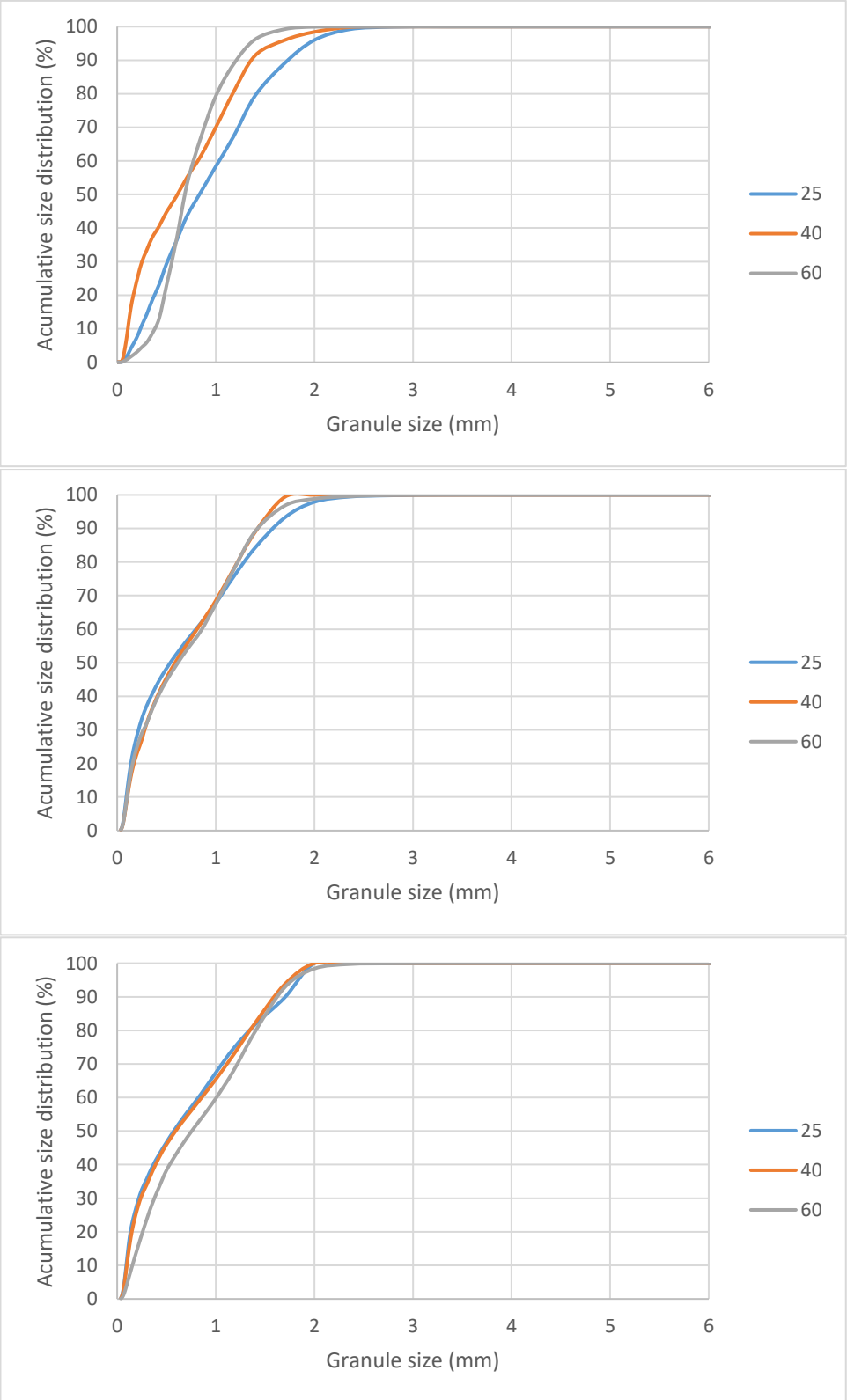


Figure D-1. Accumulative distribution curves for Figure 7-1

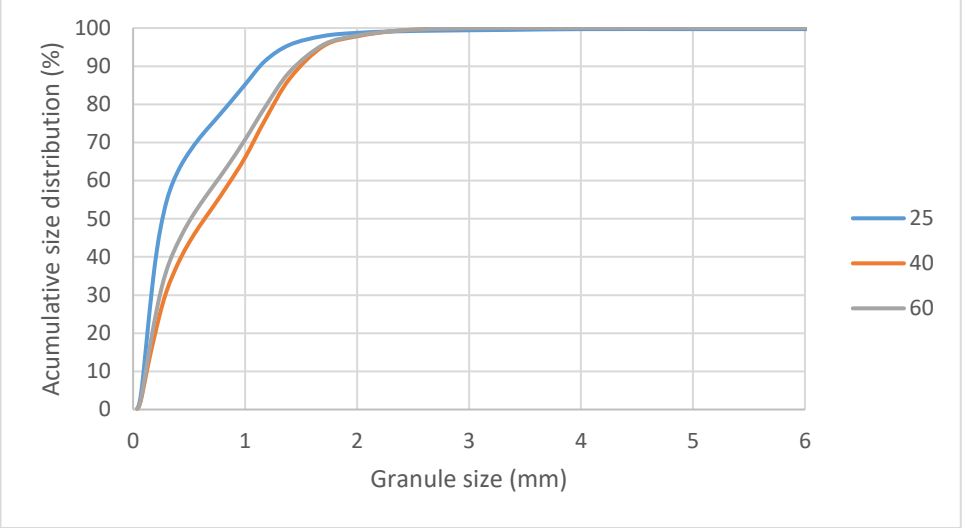
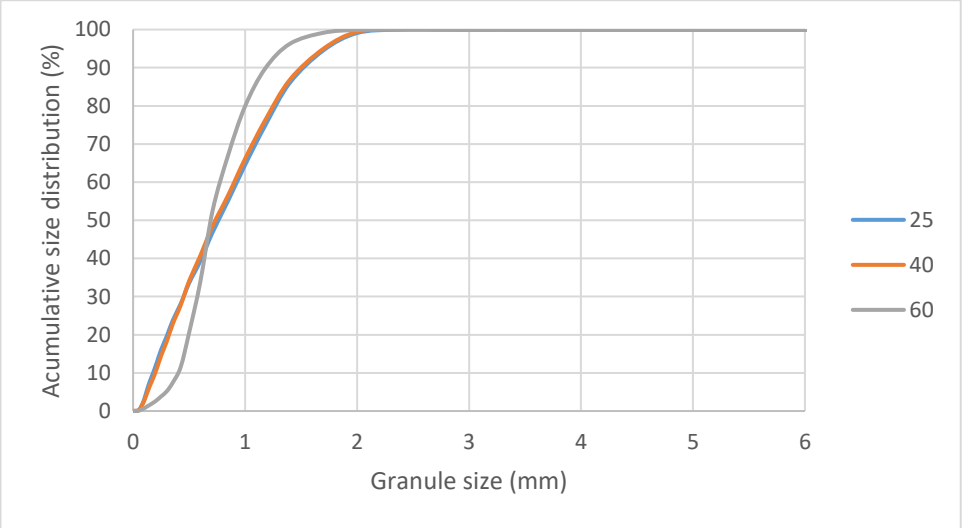


Figure D-2. Accumulative distribution curves for Figure 7-4.



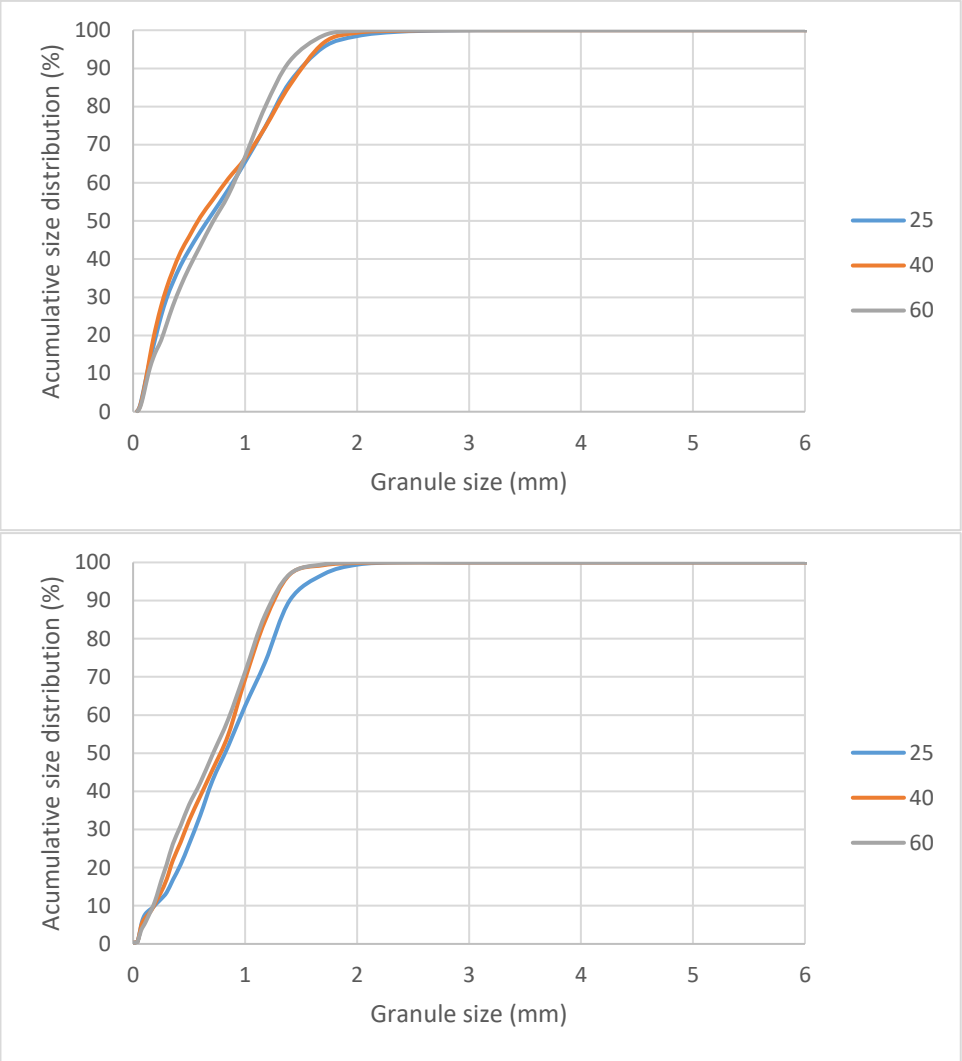
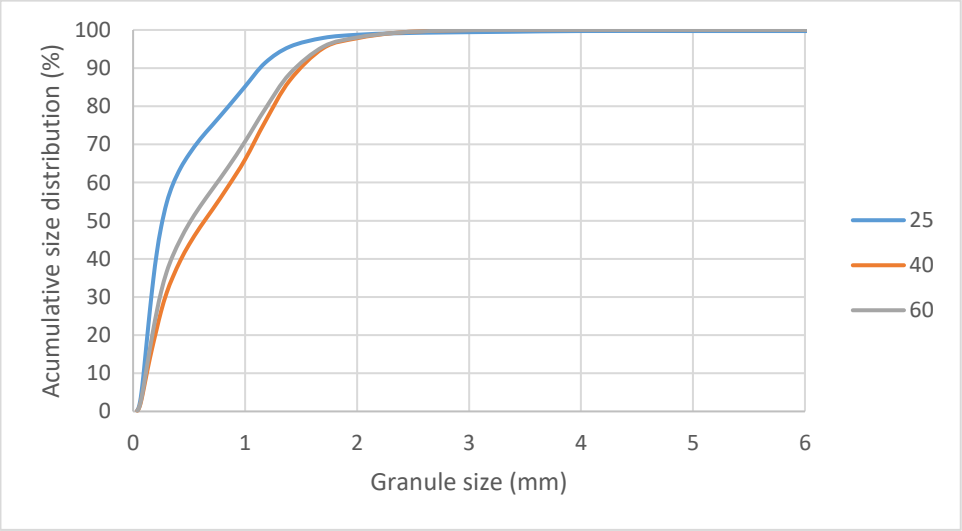


Figure D-3. Accumulative distribution curves for Figure 7-7



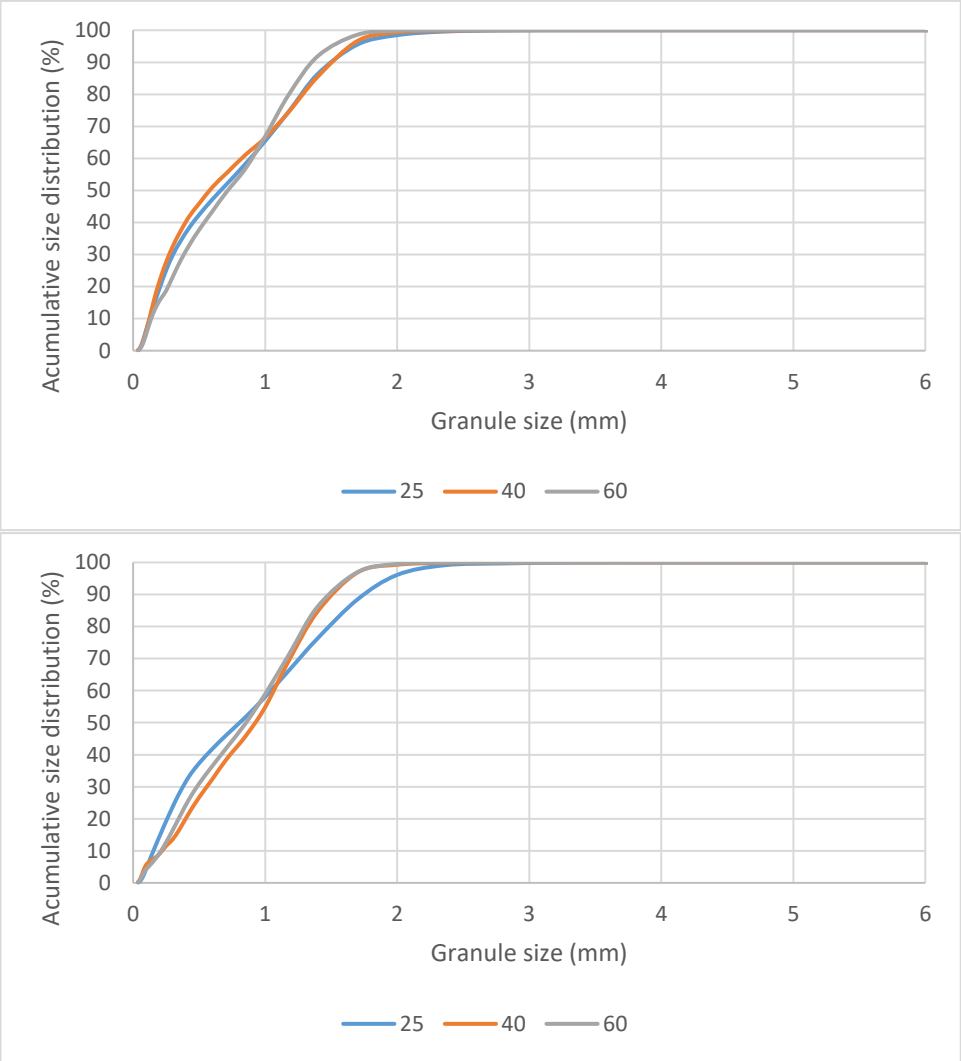
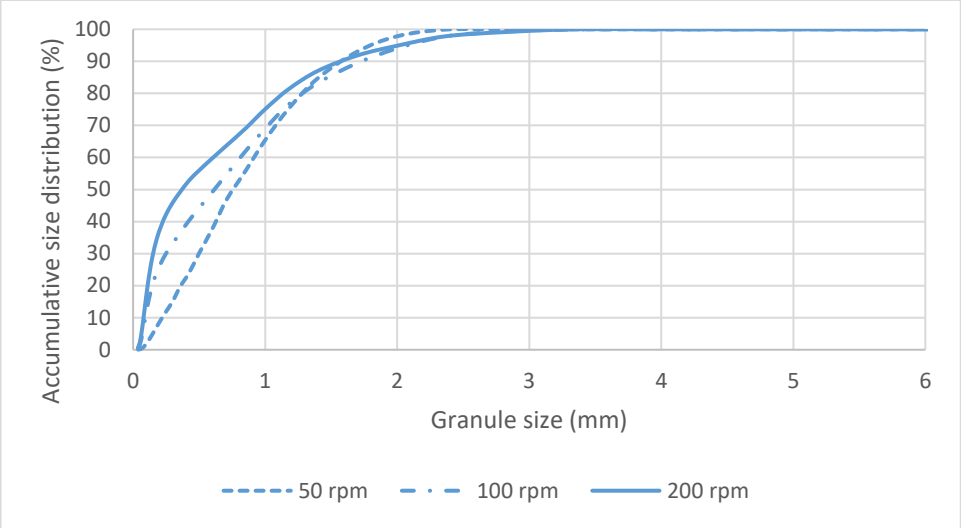
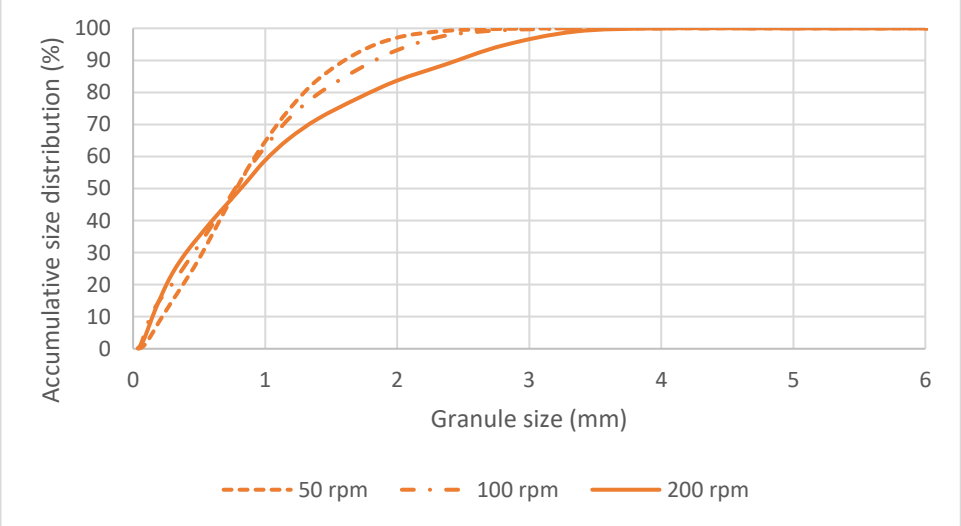


Figure D-4. Accumulative distribution curves for Figure 7-10

E. Appendix: Accumulative distribution curves for Chapter 8





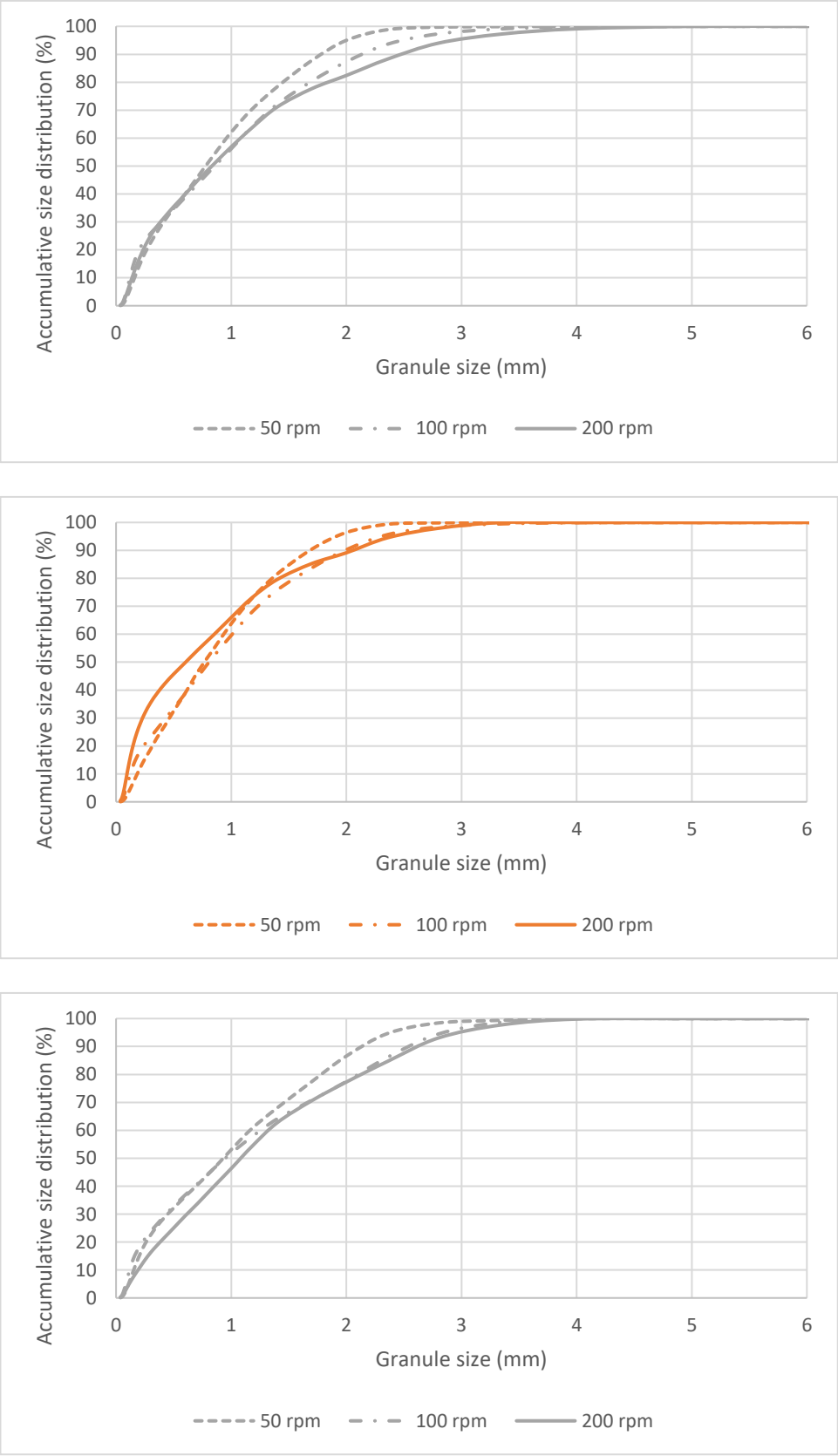
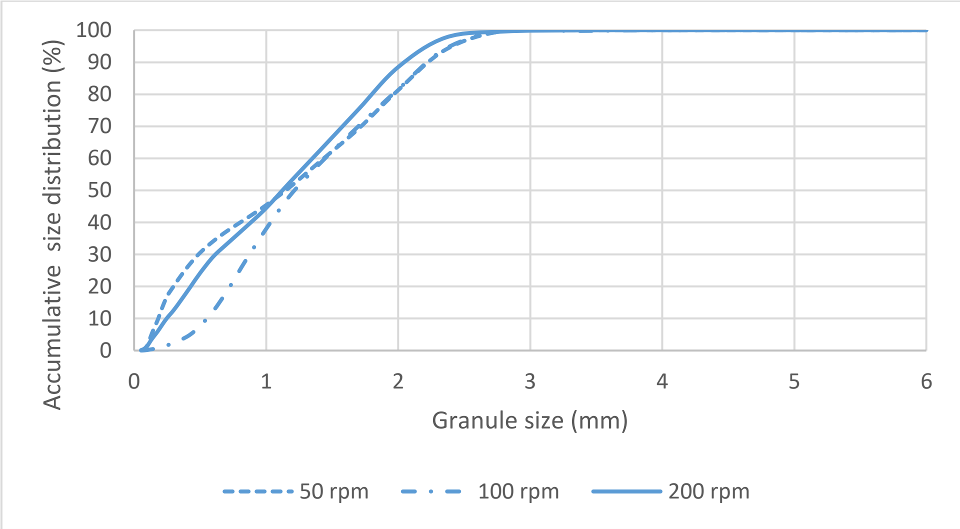
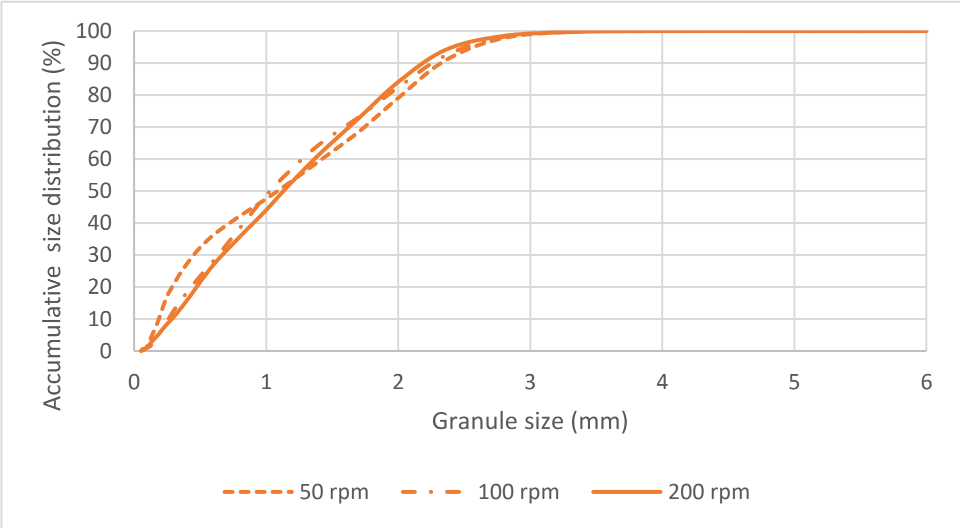
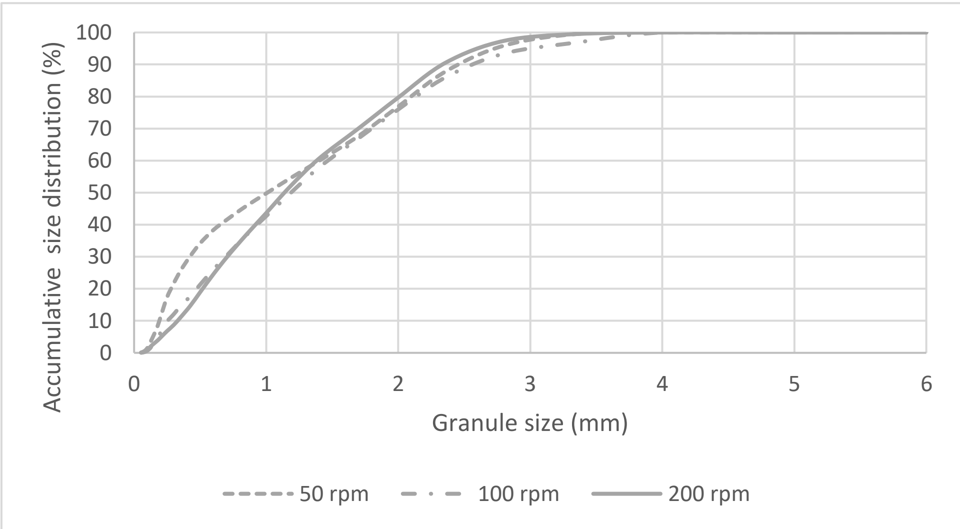
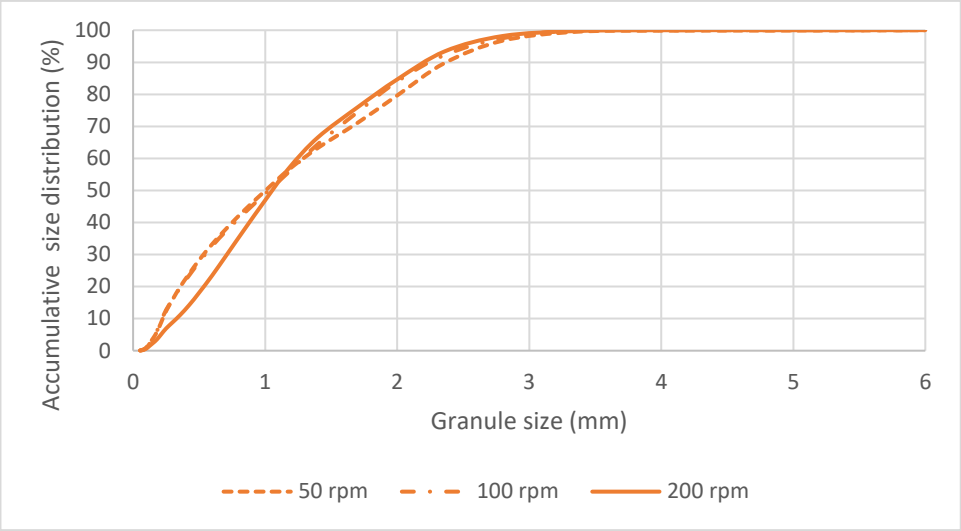


Figure E-1. Accumulative distribution curves for Figure 8-4 and Figure 8-5.


Accumulative size distribution (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Granule size (mm)
50 rpm
100 rpm
200 rpm


Accumulative size distribution (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Granule size (mm)
50 rpm
100 rpm
200 rpm


Accumulative size distribution (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Granule size (mm)
50 rpm
100 rpm
200 rpm



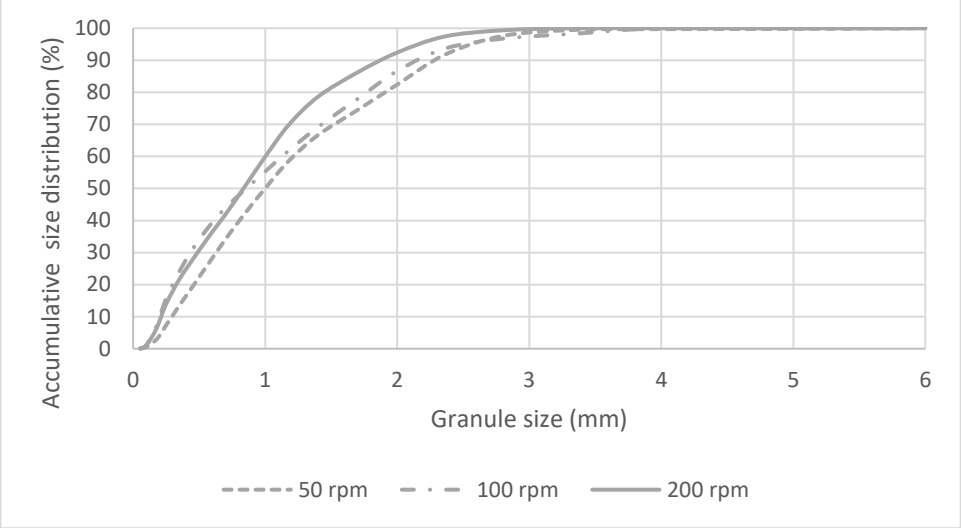
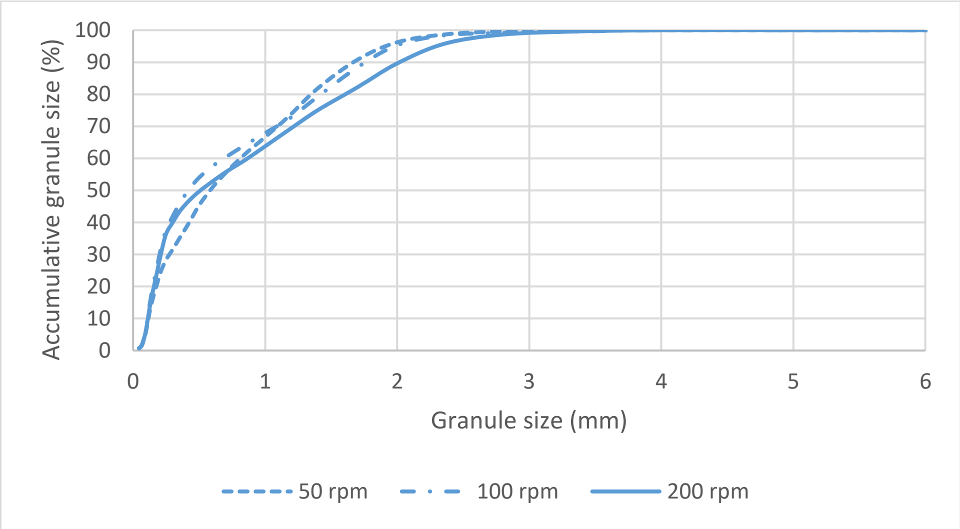
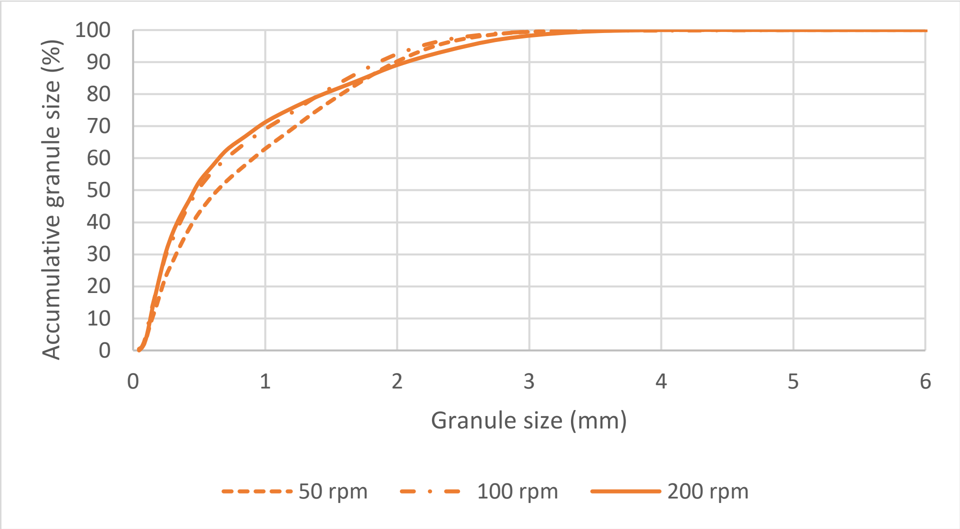
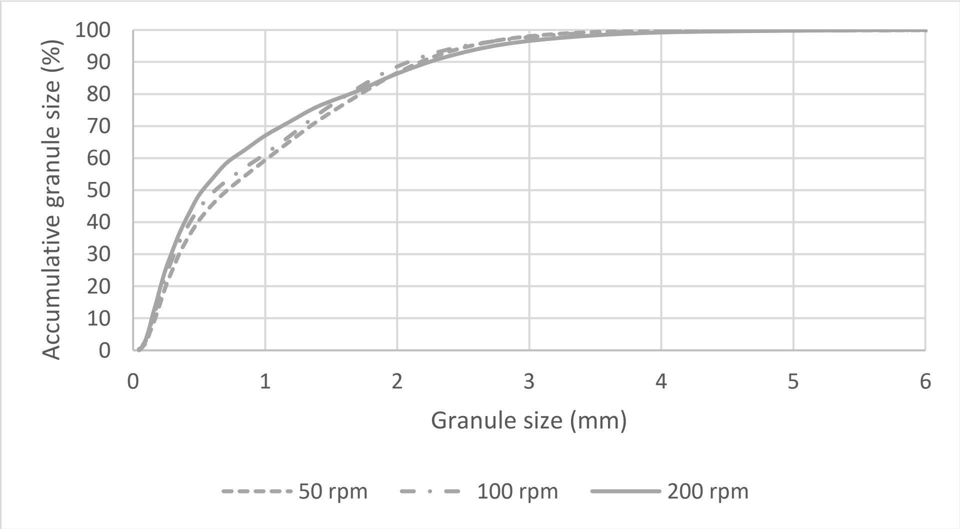
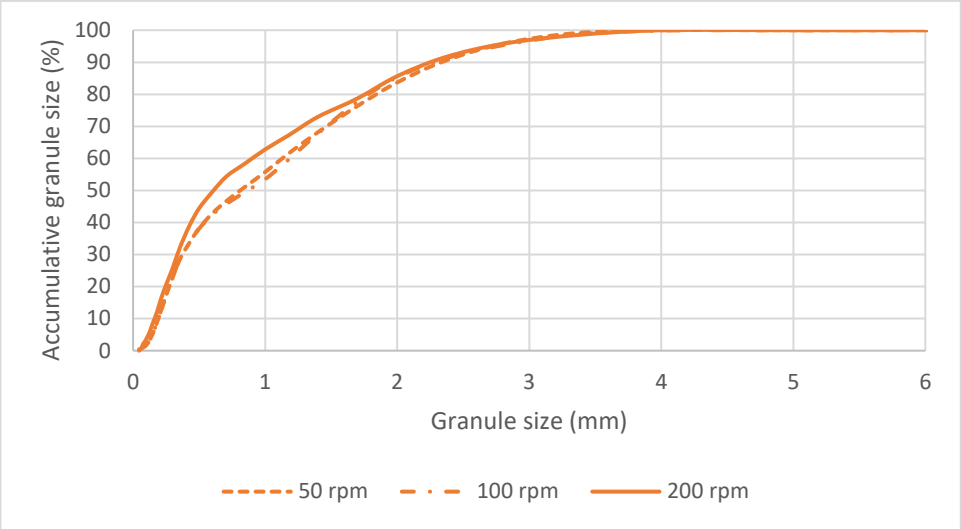


Figure E-2. Accumulative distribution curves for Figure 8-7 and Figure 8-8.


Accumulative granule size (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Granule size (mm)
50 rpm
100 rpm
200 rpm


Accumulative granule size (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Granule size (mm)
50 rpm
100 rpm
200 rpm


Accumulative granule size (%)
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Granule size (mm)
50 rpm
100 rpm
200 rpm



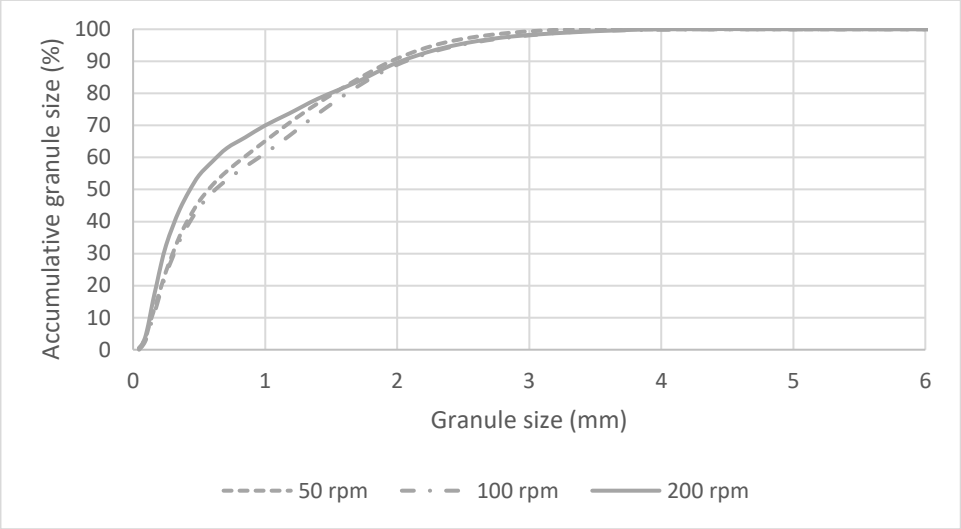
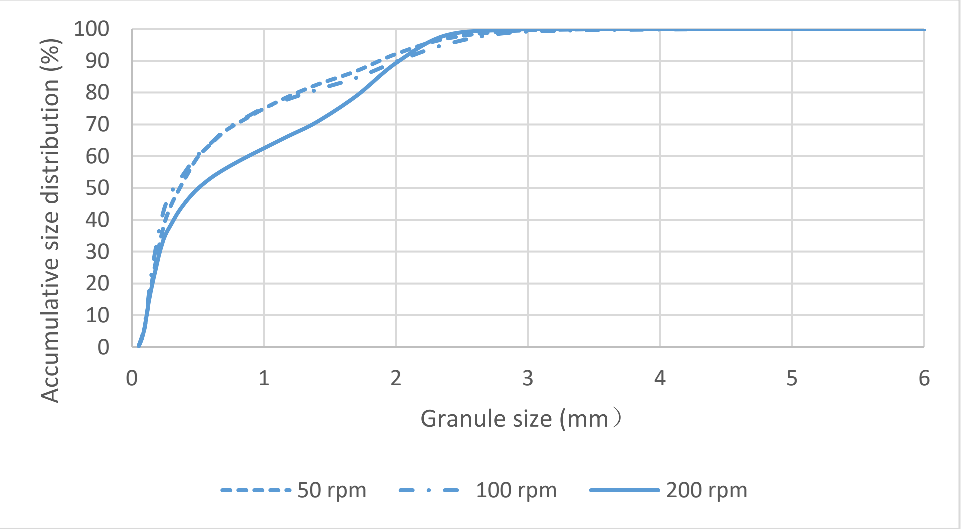
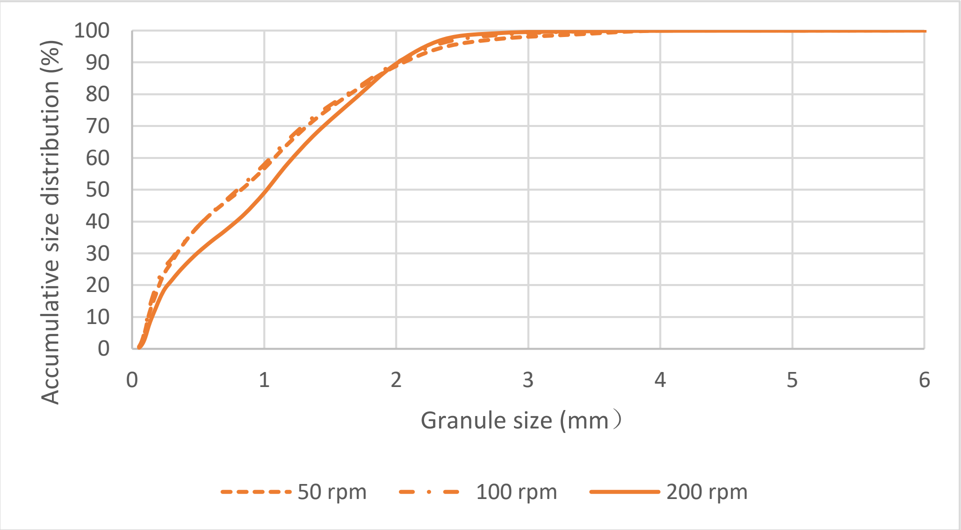
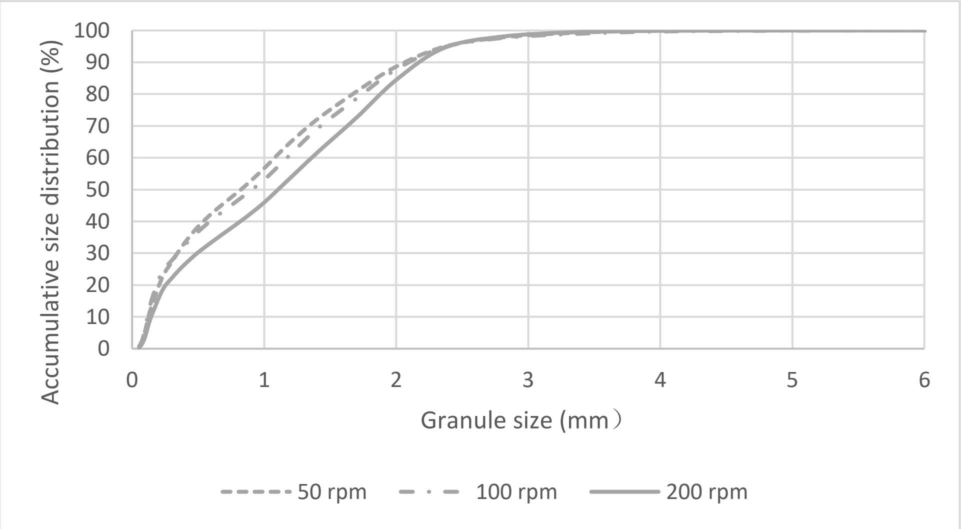
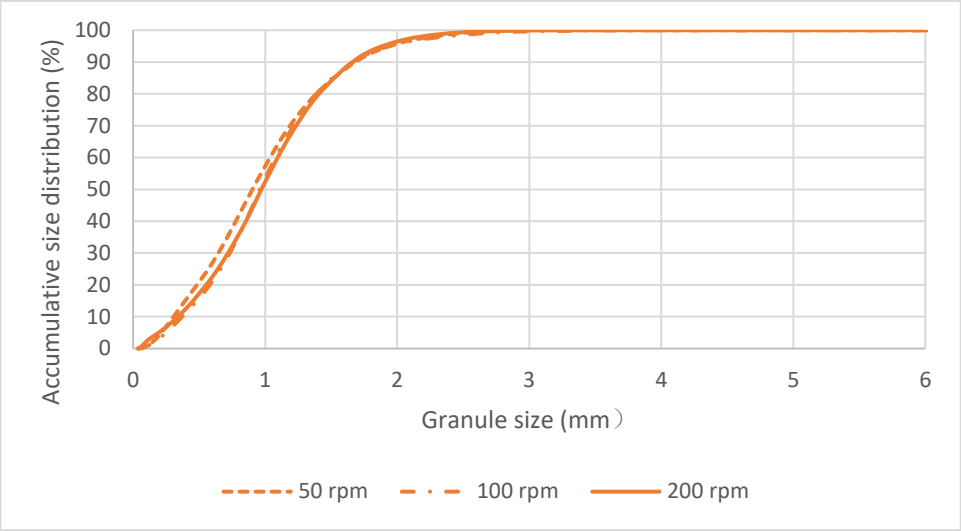


Figure E-3. Accumulative distribution curves for **Error! Reference source not found.** and Figure 8-12.


100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Accumulative size distribution (%)
Granule size (mm）
50 rpm
100 rpm
200 rpm


100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Accumulative size distribution (%)
Granule size (mm）
50 rpm
100 rpm
200 rpm


100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
Accumulative size distribution (%)
Granule size (mm）
50 rpm
100 rpm
200 rpm



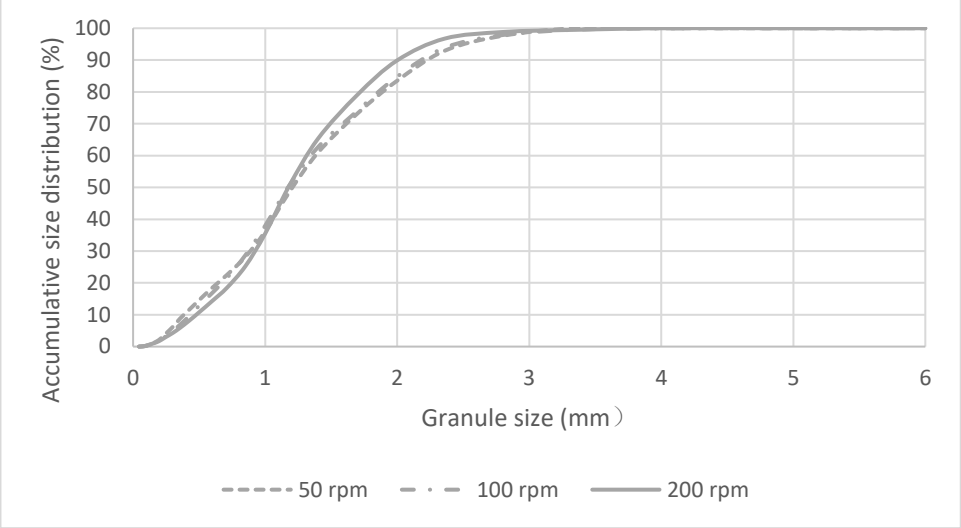


Figure E-4. Accumulative distribution curves for Figure 8-14 and Figure 8-15.

F. Appendix: Residence time

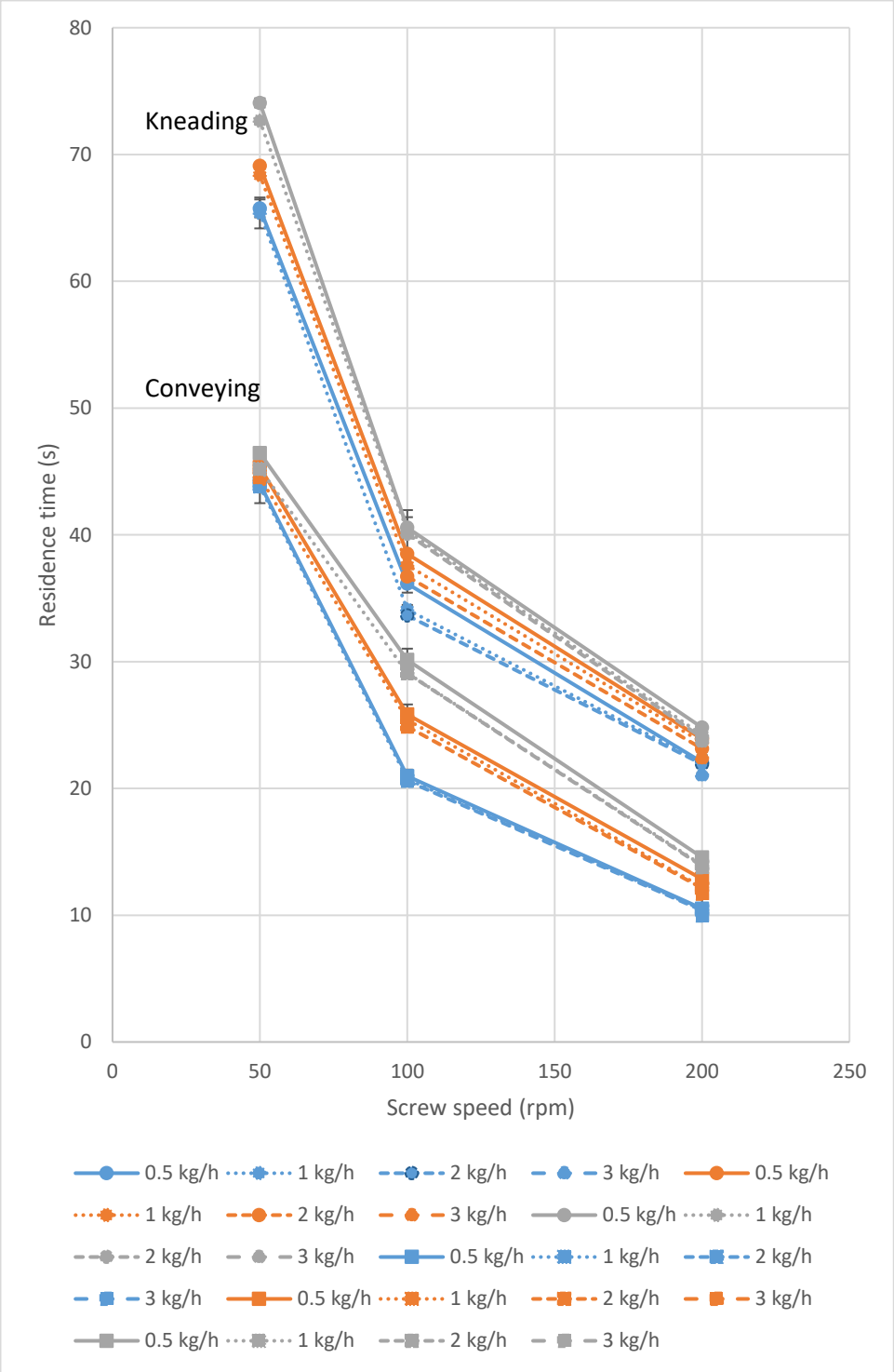


Figure F-1. Residence time for lactose based material in different powder feed rate, configurations and using water and HPC solution (blue: lactose and water; orange: lactose and 2.5% HPC solution; grey: lactose and 5% HPC solution).

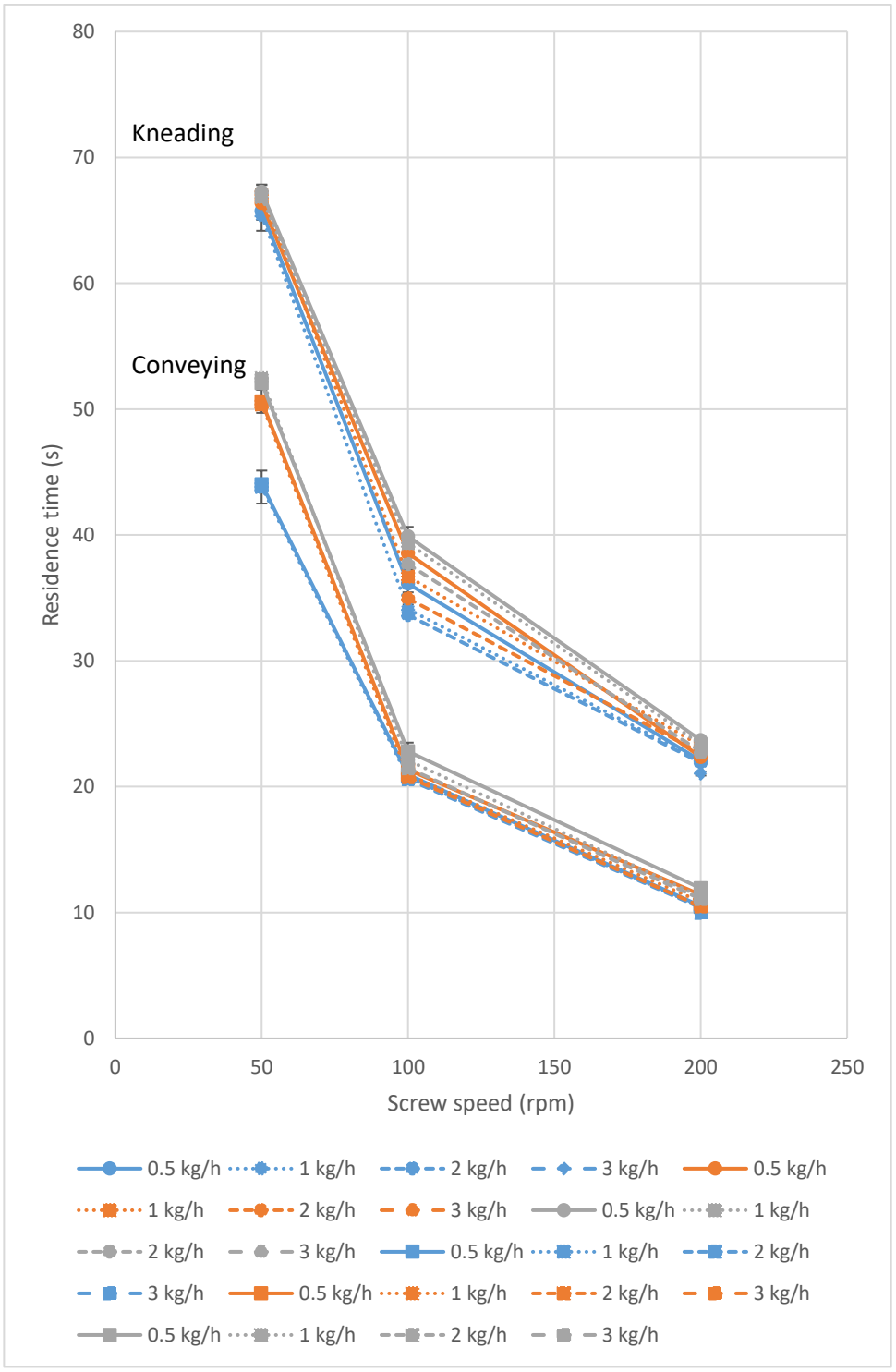


Figure F-2 Residence time for lactose based material in different powder feed rate, configurations and HPC particles (blue: lactose and water; orange: lactose and 2% HPC particles; grey: lactose and 4% HPC particles).

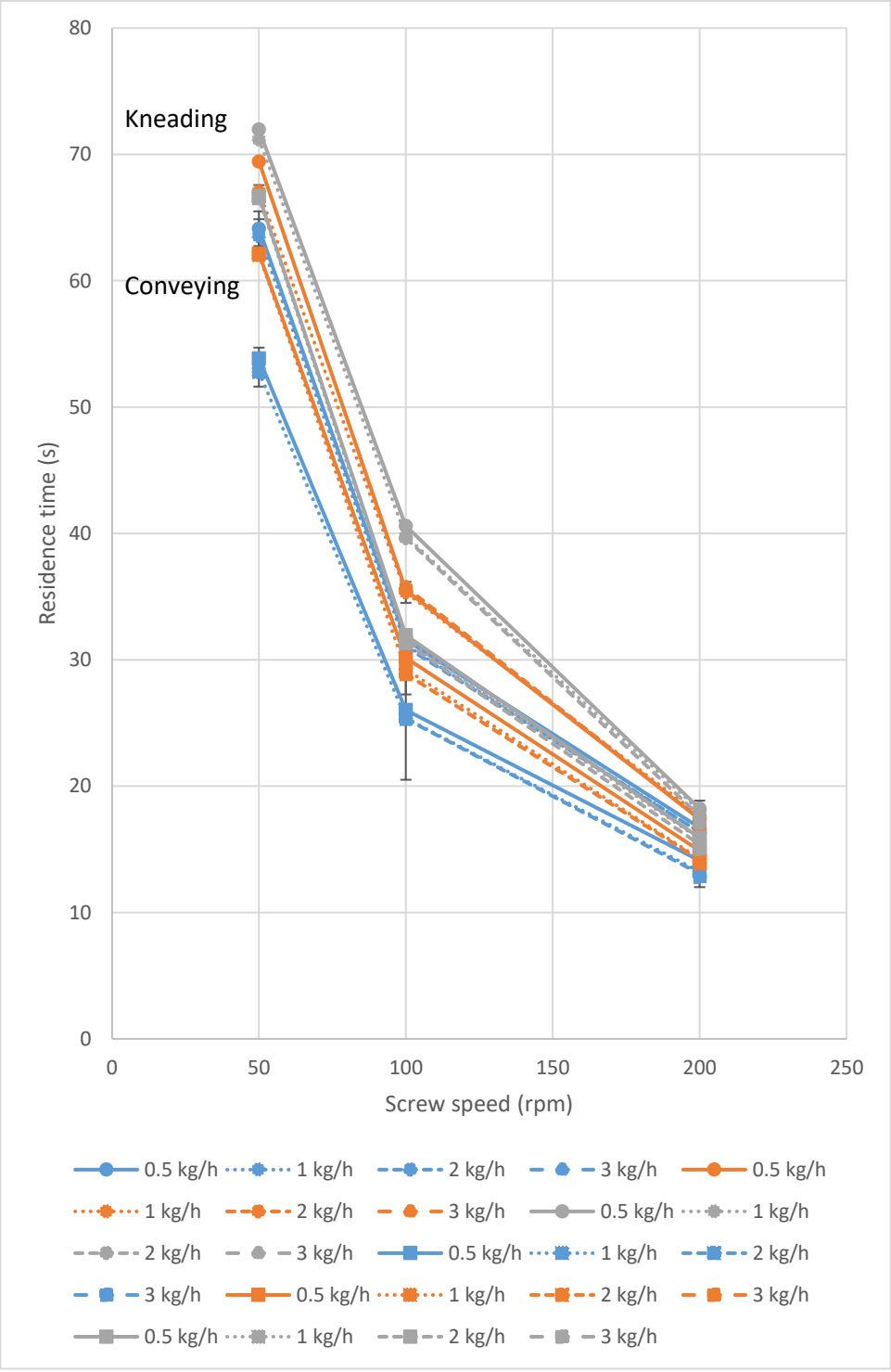


Figure F-3. Residence time for MCC based material in different powder feed rate, configurations and using water and HPC solution (blue: lactose and water; orange: lactose and 2.5% HPC; grey: lactose and 5% HPC).

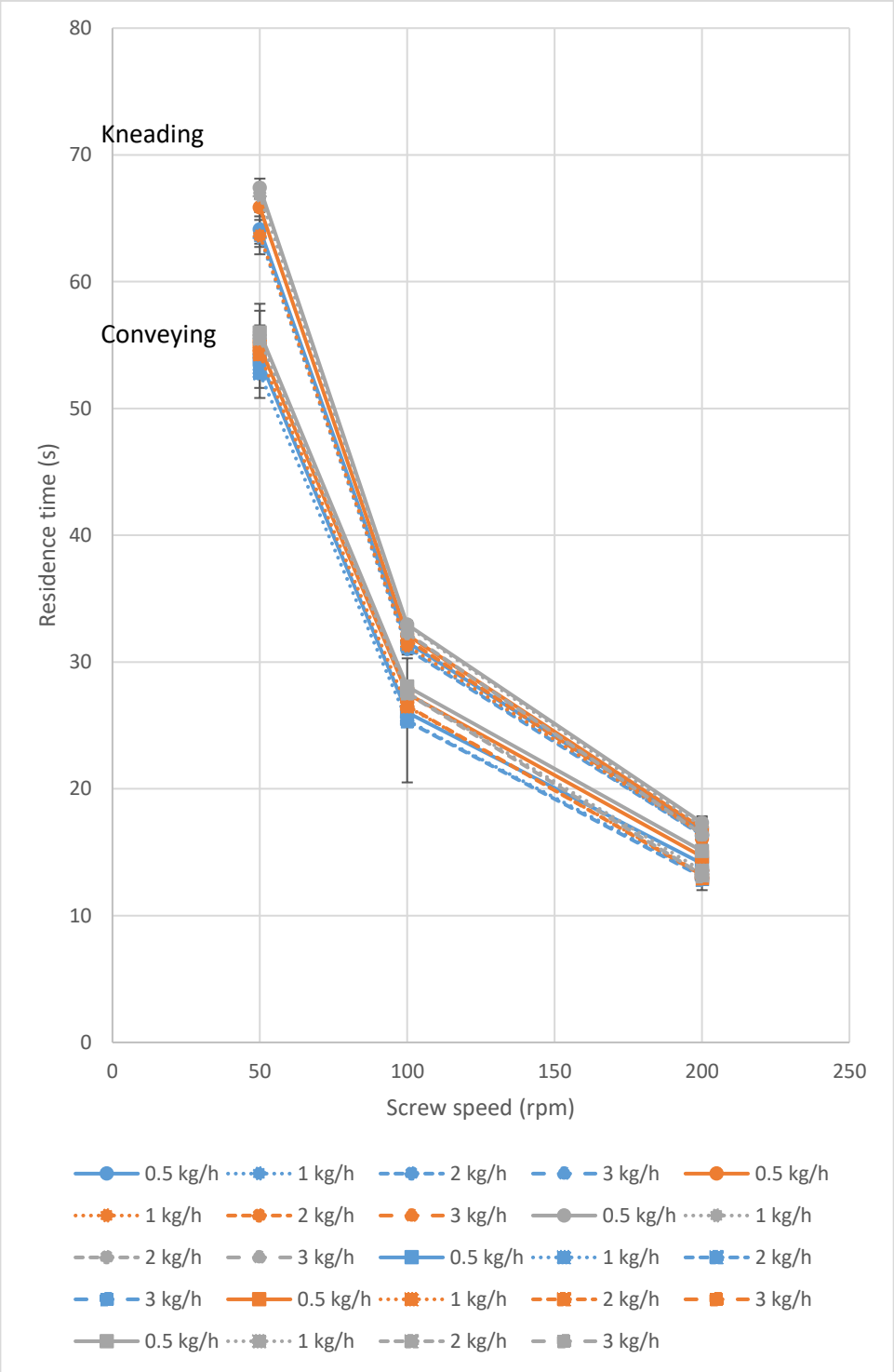


Figure F-4. Residence time for MCC based material in different powder feed rate, configurations and HPC particles (first: kneading; second: conveying; blue: lactose and water; orange: lactose and 2% HPC particles; grey: lactose and 4% HPC particles).