THE INFLUENCE OF LIQUID FLOW RATE ON NUCLEUS FORMATION IN HIGH SHEAR GRANULATION

Phung Le[1] and Agba Salman[2]

[1] Department of Chemical and Process Engineering, Ho Chi Minh University of Technology, Ho Chi Minh City, Vietnam, e-mail: phungle@hcmut.edu.vn
[2] Department of Chemigical Engineering, the University of Sheffield, Sheffield , UK

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Abstract

This paper looks at the nucleation stage, which is a fundamental stage of the granulation process. In order to clarify this mechanism the penetration time of the liquid into the powder bed was studied in both the cases of static and moving beds. Then the formation of the nuclei was studied by slowing down the binder addition rate. The effect of binder addition rate and viscosity on the size and binder fraction of the nuclei and granules was also demonstrated in this study. It was revealed that the penetration time is second power of drop size. Linear relationships between nucleus size and drop size onto both a static powder bed and a moving bed have also been found. It was shown the significant effect of the viscosity of binder on the drop sizes in both static and moving bed cases and granules keep their integrity; large nuclei produce large granules.

Keywords: Binder distribution, Coalescence, Consolidation, High shear granulation, Nucleation

Introduction

High shear mixers are widely used in the pharmaceutical industry for wet granulation and many formulation and process variables (properties of primary powder and binder, impeller and chopper speed, massing time, temperature, etc.) can influence the granule properties. The influence of different process variables on the granule characteristics of the final product has been studied by several authors [1-5]. However, it should be noted that those studies is based on measurements done at least one minute after the start of liquid addition. There is no information about the early few seconds of the process. Even though there have been a number of studies on the effect of the binder spray flux on the size of nuclei, no research effort has been encountered in published literature where the effect of changing binder flow rate has been studied using the pour-on binder addition method [6, 7]. The effect viscosity on nuclei size was investiagted by Le et al [8]. Other reseach by Schæfer and Mathiesen.,[9] and van Den Dries and Vromans. [10] showed that increasing viscosity produced the smaller initial granule sizes. It could be argued that studies of different nucleation mechanisms such as melting, pour on or spray on coupled with different impeller speeds amounts to studies of different binder adding rates since, in terms of actual mechanisms; it is the rate of nucleation that changes when the binder addition rate is changed by a process operator. So that, for example, if the impeller speed were increased in order to disperse poured-on binder faster over the powder bed, then not only has the nucleation rate been altered but also the regime within which the aggregative and breakage mechanisms are to proceed as well. Thus, there is much insight to be gained from an explicit study of the binder addition rate. The study of Le at al. [8] showed that the effect of operating conditions on granules properties in the early stages and at the end of the

process is similar. Therefore, further study is required to show how the nuclei are formed so that in future the effect of operating conditions on nucleation at the beginning and granules properties at the latter stages of the process can be quantified.

The aim of this study was to investigate nucleus formation and growth of granules during the liquid addition stage of the granulation process in a high shear mixer. First, the interaction of liquid and powder was evaluated by measuring the penetration time of the liquid into the static and moving powder bed then nucleus formation in the actual process by slowing down the binder addition rate was demonstrated.

Experiment Set-up

Drop Penetration Time and Nucleus Size Measurement

In this experiment, the penetration time and nucleus size of hydroxypropyl cellulose (HPC) solution into the mixture of lactose M200 and starch was measured. This experiment will show the behaviour of liquid-solid interaction and the formation of nucleus size affected by liquid viscosity and droplet size.

The static experiments were set up in a Petri dish and in the low impeller speed moving bed in the mixer. Three aqueous HPC solutions were used with the mass ratio: HPC/water = 0; 0.04; 0.08 with viscosities was measure by rotational viscosimeter with the temperature control. The viscosities were 0.001, 0.017 and 0.104 Pa.s respectively.

A loosely packed powder bed was formed by lightly sieving the powder through a 1000 μm sieve into a Petri dish (85 mm inner diameter) and scraping level with a metal spatula to produce a smooth powder surface. The weight of powder added to the dish was recorded to calculate average porosity. The dish was 17.4 mm deep, which was sufficient to avoid interfering with the drainage process (3 - 4 drop lengths deep).

The average porosity was calculated from the bulk density ρ_{bulk} and particle density $\rho_{particle}$:

$$\phi = 1 - \frac{\rho_{bulk}}{\rho_{particle}} \quad (1)$$

With the experiment done in the mixer, powder mixtures of lactose and starch were premixed for 90 seconds at 250 rpm, before lowering the impeller speed to just 50 rpm to ensure that the drop would not break up during the experiment. More details of the breakage of the nuclei can be found in Figure 4.

In both case, a 100 μL burette with a needle was positioned just above the bed surface (5 mm). This allowed the drop to fully detach from the needle before encountering the powder bed but minimised the height of the fall. Four needles with different size of nozzles were used in this experiment (Table 1). Red dye was added to the binders to assist drop visibility. The drop size of each fluid was estimated at the end of each set of experiments by recording the volume of liquid added using the burette markings dividing by the number of drops with the assume that the drops are spherical.

Table 1. Size of Needles Used in the Penetration Experiment

Name of Needles	Needle 1	Needle 2	Needle 3	Needle 4
Gauge No	14	20	25	32
Outer diameter (mm)	1.6	0.585	0.241	0.089

A Phantom V7 colour high-speed camera operating at 1000 frames/second was used to film a single drop of binder penetrating into the powder surface. A spotlight was used to illuminate the powder bed beneath the drop. The spotlight was turned off between runs to

minimise radiant heating of the fluid, which could potentially and inadvertently affect solution viscosity.

Twenty replicates were performed for each experiment. A number of runs were performed on each dish of powder. Each drop was at least 1 cm from the walls of the Petri dish or the granulator wall and neighbouring drops. The penetration time was determined from the video recording and taken as the number of frames between when the drop hit the powder surface and when the last liquid drained away. As long as a fluid drop is present, a single light source will present a single reflection. Once the fluid drains below the powder surface, the light will be reflected from the rough powder surface and one light source produces several reflections. The appearance of multiple reflections was taken as the point at which drainage was complete.

Once drop penetration time measurements were complete, the nuclei were removed carefully and their sizes measured by image analysis in the microscope. The addition of red dye in the binders allowed visual observations of the saturation of the nuclei.

Granulation Process

To investigate the influence of binder addition rate on the nucleation stage of the granulation process, experiments were carried out in a Roto Junior high shear mixer. During the experimentation, the rotational speeds of the impeller were kept constant at 250 rpm. The 1800 g Lactose and 200 g potato starch powder mixture to be granulated was placed in the bowl. The impeller was started and the powder was mixed for 90 seconds before binder was added.

A 300 g of the binder (aqueous HPC solution) at three different HPC/water ratios (12, 16, and 20) was added to the granulator using a pump at pre-defined constant flow rate 300, 150 and 100 g/min. Owing to the variation in liquid flow rate the time of water addition was different for each of the experiments (1, 2, and 3 minutes respectively). The liquid to solid ratio, L/*S*, is defined by the mass ratio of binder to solid particles and was 0.15 in all cases.

The granulation time was taken from the time of binder addition. Samples of the granulated product were taken at specific time intervals. As the experiments were focused on examining short granulation times, the first samples were taken after 1, 2 and 3 minutes of the binder being added. Further samples were taken 5 minutes and 12 minutes after water addition finished.

Granule samples were sieved after being dried to obtain the granule size distribution. The binder fraction of a group of granules from each of the sieve cuts were measured using UV spectrometry to obtain the binder size distribution for each sample.

Results and Discussion

Drop Penetration Time and Nucleus Size

Due to the difference in surface tension and density, the drop size differs with differing viscosity from the same nozzle. Figure 1 demonstrates the size of drops that were formed by three different viscosities and four needle sizes by image analysis, the size of the drops (r_d) were measured just before the drops came into contact with the powder bed. It was shown that larger drops were formed from the lower viscosity fluids. The error bars indicate the 95% confidence interval of about 20 drops of the same viscosity and needle.

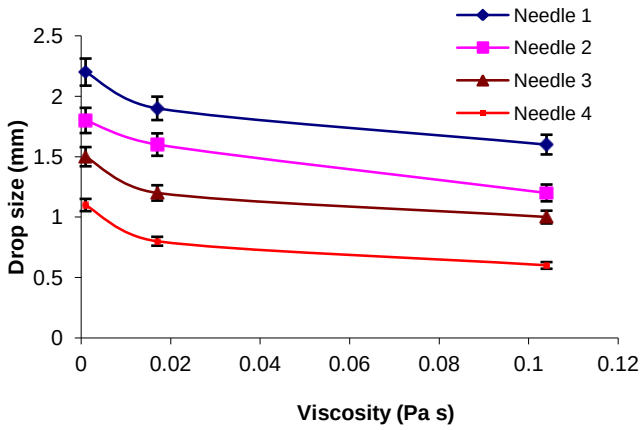


Figure 1. The influence of viscosity on the drop size

The observation of liquid distribution in the powder was done initially to understand the nucleation stage of the granulation process. The results in Figure 2 showed that the viscosity has a dramatic effect on penetration time. The higher viscosity liquids penetrate more slowly than lower viscosity. Imbibitions of a single drop into a porous substrate depends on the structure of the substrate: the porosity, the size of the pores, the orientation of the pores, and the surface chemistry within the bed. The penetration time for a droplet into a porous substrate is determined by [11]:

$$t = 3.55 \frac{r_d^2}{\varepsilon_p^2 R_{pore}} \frac{\mu}{\gamma \cos\theta} \qquad (2)$$

in which R_{pore} is the radius of the capillary (m), γ the liquid surface tension (N/m), θ the contact angle (-), μ the viscosity of the solution (Pa.s), ε_p the porosity of the powder bed (-) and r_d is the radius of the liquid drop covering the powder (m). As shown in Equation 2, under the same experimental conditions, the penetration time is proportional to liquid viscosity and inversely proportional to surface tension. This emphasizes the importance of both wetting thermodynamics and kinetics. Hapgood et al.[6] completed an extensive study of drop penetration into loosely packed powder beds and obtained similar results. Not only the experiment in the Petri dish was done, more single droplet experiments were also investigated on a moving power bed in the high shear granulator. Figure 2 indicates the influence of the drop size on penetration time in both static experiments and on the moving bed experiments. It is shown in the figure that the penetration of the same size of drops in the mixer is shorter than in the powder bed of the Petri dish and there are the second power relation between penetration time and droplet size. Which is similar results was found in the Equation (2), with the same binder and powder properties group $\frac{\mu}{\gamma \cos\theta \varepsilon_p^2 R_{pore}}$, penetration time is a power function of droplet size.

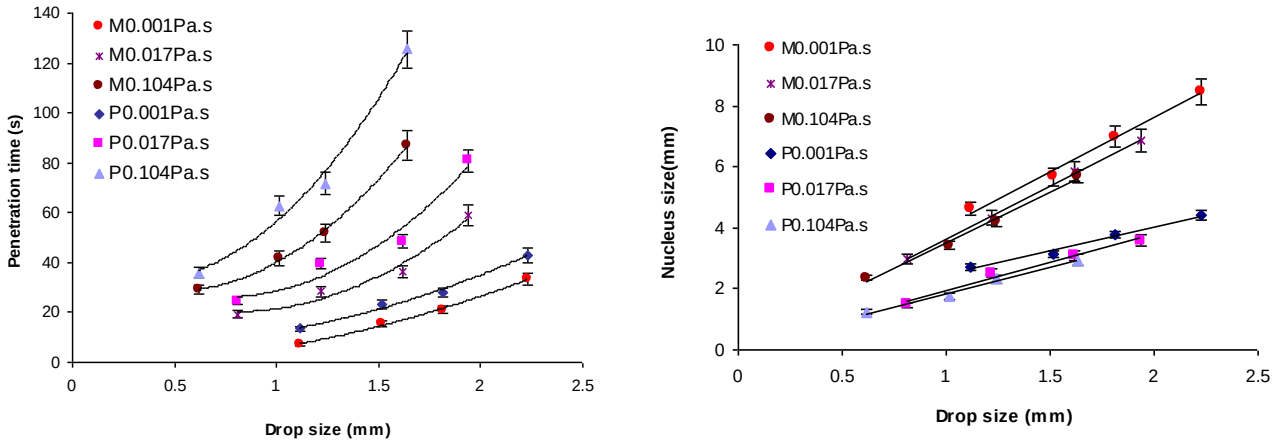


Figure 2. The influence of viscosity and drop size on the penetration time (a) and the nucleus size (b) (Legend note: M: drop in the powder bed inside the mixer; P: drop in powder bed of the Petri dish)

Figure 2b demonstrates that the nuclei size is linear proportional to droplet size. Nuclei formed from the Petri dish are smaller than nuclei formed from the drop into the mixer. The relationship between granule size and droplet size can be estimated by the following equation [10] :

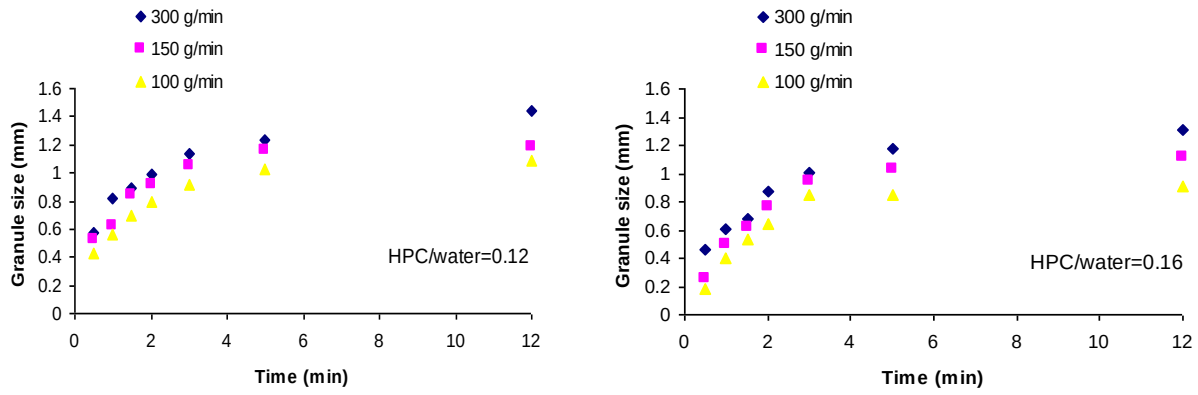
$$r_g = r_d/\varepsilon_g^{1/3} \quad (3)$$

where ε_g is the porosity of the granules. It is reasonable to suggest that porosities of the nuclei formed from the mixer are lower due to the shear stress of impeller and mixer wall. Therefore, with the same size and viscosity of the drop, the nuclei produced from the mixer are larger.

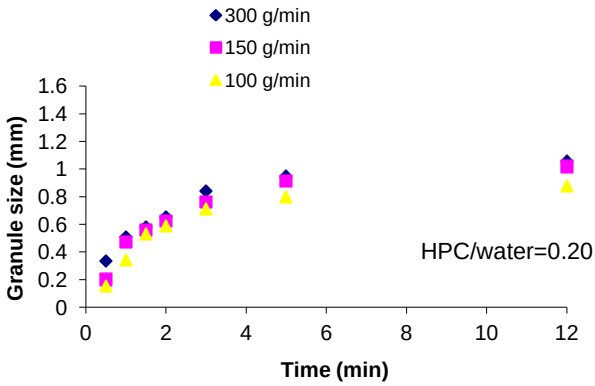
Effect of Nucleation Formation on Granule Size and Binder Distribution

Nuclei and Granule Mean Size

Figure 3 demonstrates the effect of binder flow rate and viscosity on granule mean size during binder addition and granulation process.

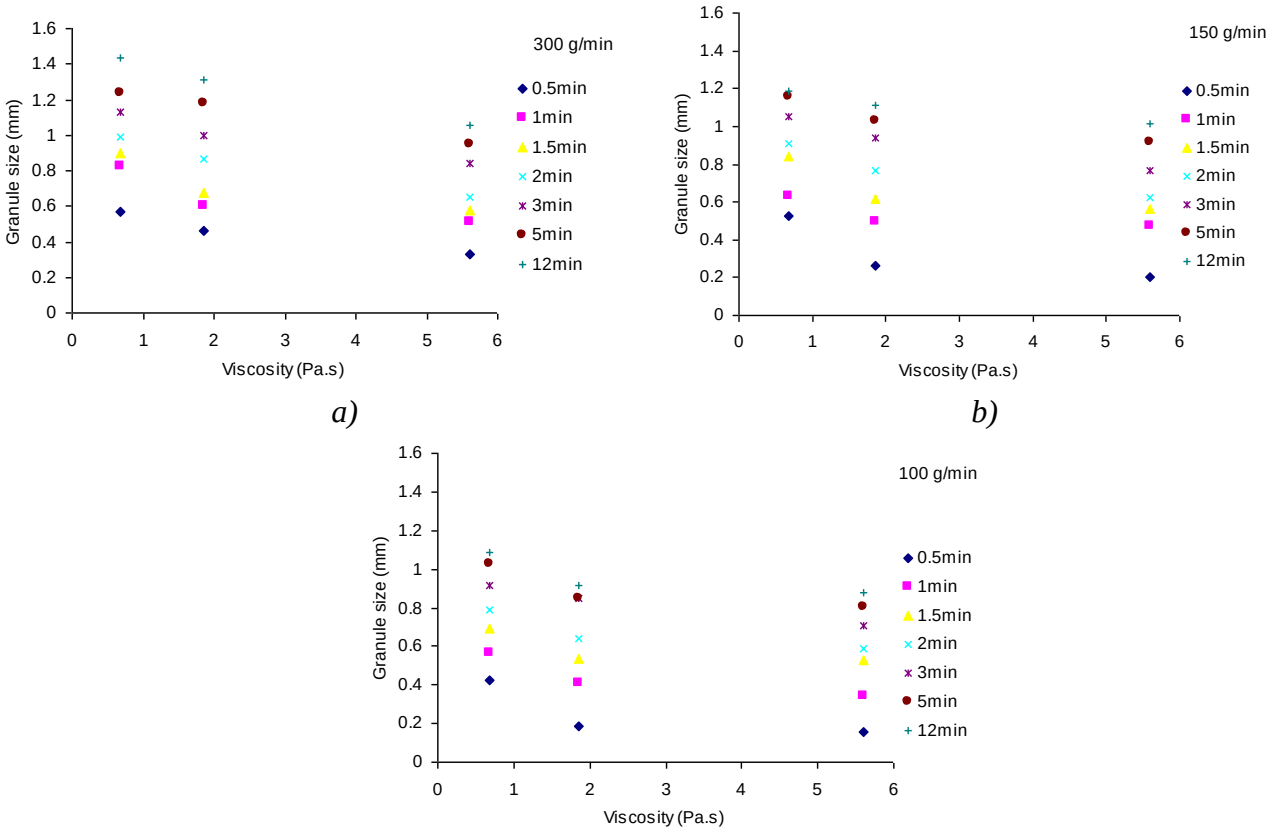


a) *b)*



c)

Figure 3. Influence of binder flow rate on the mean size of the granules; a) HPC/water = 0.12, b) HPC/water = 0.16, c) HPC/water = 0.20



a) *b)*

c)

Figure 4. Influence of viscosity on the mean size of the granules; a) 300 g/min, b) 150 g/min, c) 100g/min

It is shown in Figure 3 a, b, c that the widely different end point values of 4,3 mean size granules were obtained with the altered values of binder flow rate. All the curves were found to be similar principle for all settings. With the same amount of binder loading, slower binder flow rate produces smaller nuclei mean size and the process ended up with

smaller granules. This obviously can be explained based on the size of nuclei formed, at the same powder bed velocity, fast binder flow rate can be produced the larger drop from the "breakage" of the binder which is then formed larger nuclei. Another reason is by the presence of the liquid in the primary powder, with an identical granulation time, more binder present in the powder bed produced more nuclei and therefore less primary powder left in the powder bed. Furthermore, the presenting of more nuclei at the same time makes it easy for them to collide and aggregate to form bigger granules. Mainly these larger granules were produced from the larger nuclei. Once these granules have been formed they keep their integrity. However, it is important to notice there was breakage and re-aggregation of the granules which was shown in the microscopic study of Le at al.[12]. It is also can be seen in Figure 4 a, b, c that high viscosity produced a smaller nuclei mean size throughout the process. It can be easily explained through the static experiment above, that the nuclei size is proportional to the droplet size which is dependent on viscosity. High viscosity liquid produced smaller droplet size and therefore produced smaller size of nuclei. However, it is important to note that this is the pour-on liquid system, where the liquid is poured and breaks to form droplets simultaneously with the penetration of the liquid into the powder bed. The breakage of lower viscosity liquid produces a smaller size of binder droplet at first but eventually larger nuclei are formed because of the faster penetration. In contradiction, the higher viscosity liquid can be dispersed to become larger drops at first but the slower penetration can lead to further dispersion of the liquid, therefore the nuclei produced are of a smaller size. The effect of higher viscosity on nuclei size was also discussed in [8]. The influence of liquid dispersion becomes clearer when comparing granule size distributions for different binder addition rates at an early stage of the granulation process, i.e. during wetting or immediately afterwards. Smaller initial granule sizes at increasing viscosity have also been observed by Schæfer and Mathiesen.,[9] and van Den Dries and Vromans. [10].

Nuclei and Granule Size Distributions

Figures 5a, b, c show the change of the mass cumulative distribution of the granules for liquid addition with the different viscosities. The principal behaviour in the change of granule size distribution with time was found to be similar for all of the binder addition times and viscosities. The broadest particle size distribution and the highest fraction of fines were observed in the early stages in all cases. With increasing binder content and agglomeration time, the fraction of fine granules decreases, and further mixing of the wetted product results in a more narrow size distribution and a growth of median particle size. It indicates in the Figure 5a that at the same binder liquid, the faster binder addition formed larger granules at the early granulation time (0.5 minute) and ended up with larger granules at the end of the process. Similar results were revealed in Figure 5b and 5c. It can be seen by comparing among Figure 5a, 5b and 5c that with the same binder addition rate, high HPC/water ratio produced the larger granules at the early samples and also larger granules at the products.

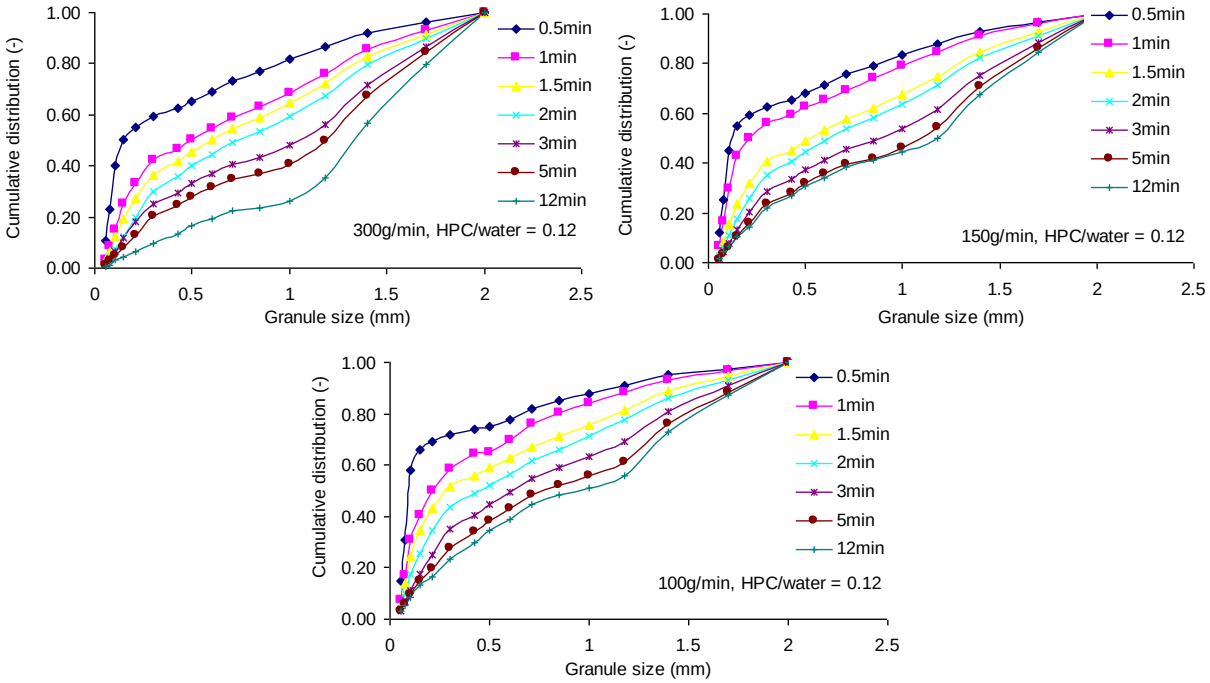


Figure 5a. Cumulative distribution of granule size at different binder flow rate at HPC/water = 0.12

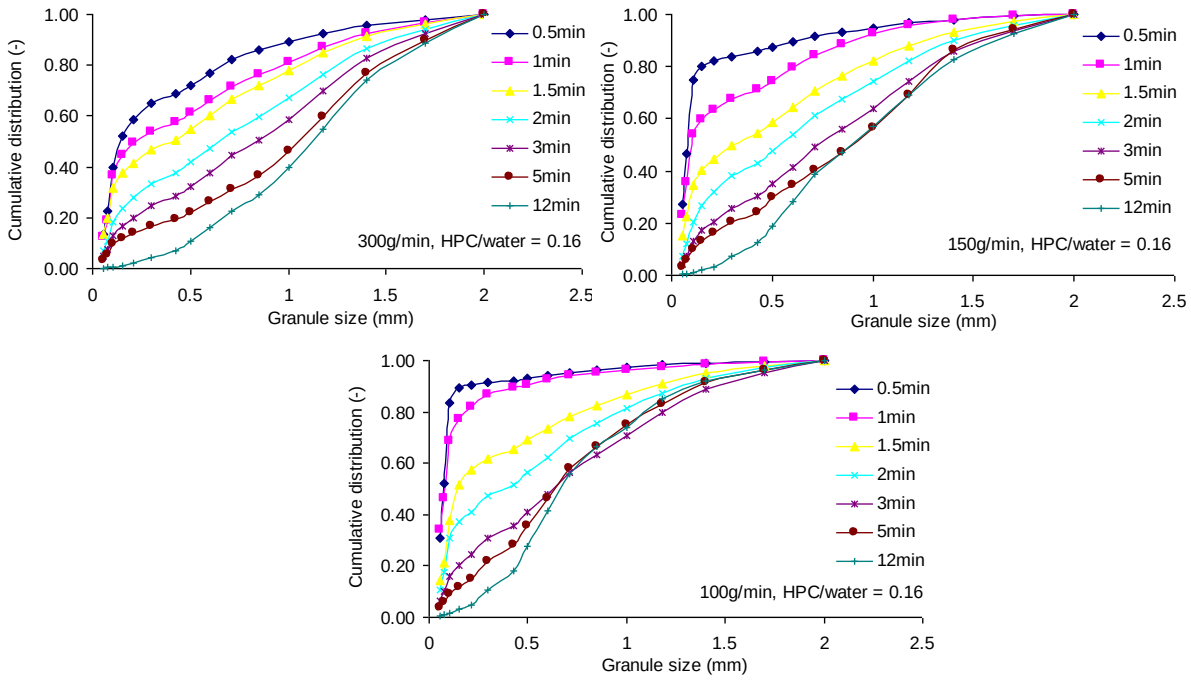


Figure 5b. Cumulative distribution of granule size at different binder flow rate at HPC/water = 0.16

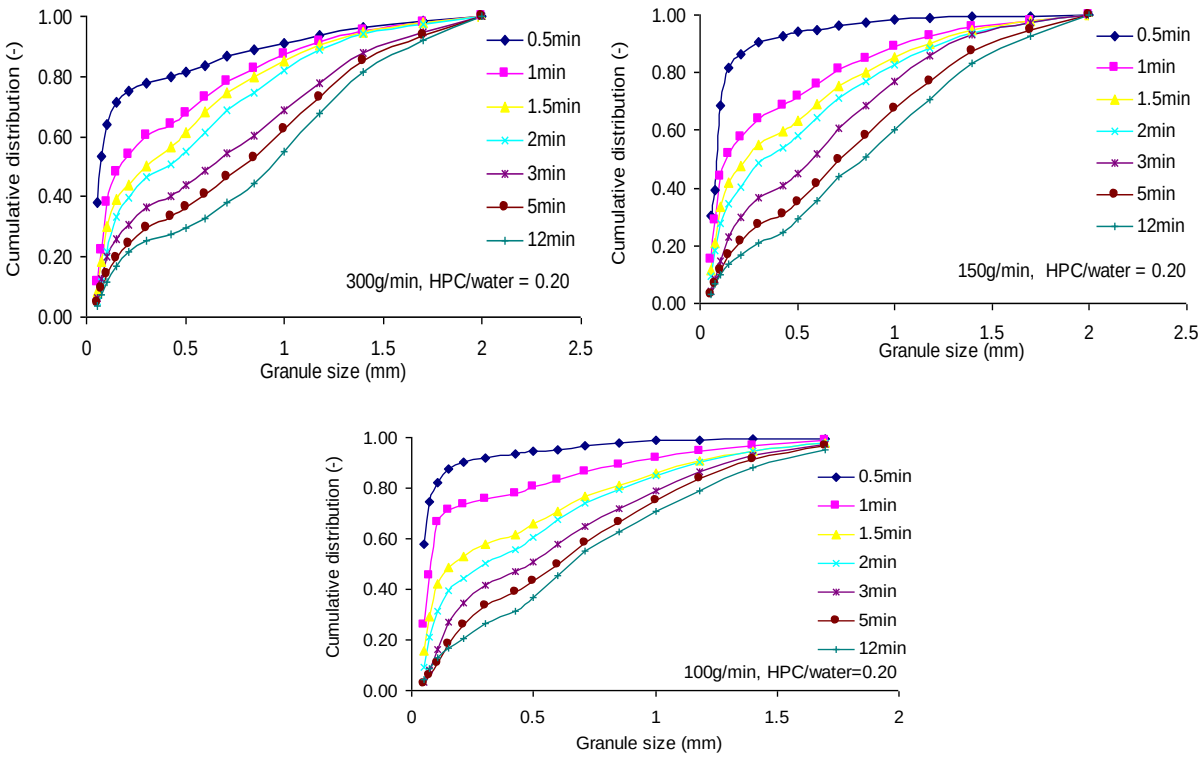
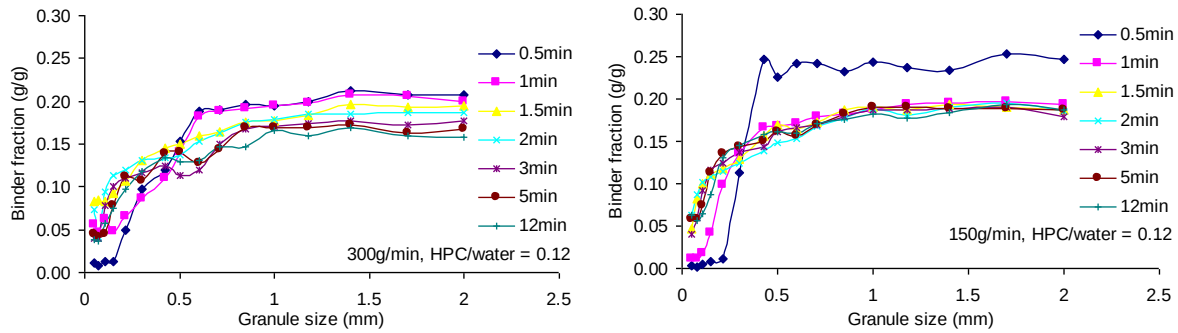


Figure 5c. Cumulative distribution of granule size at different binder flow rate at HPC/water = 0.20

Binder Distribution

Figure 6 a, b and c demonstrates the binder fraction of the granules for different settings. The principal behaviour in the change of binder fraction with time was found to be similar for all binder addition times and viscosities. At 30 seconds of the granulation process, almost all the binder liquid is located in the larger granules (> 300 μm) and contains a larger mass fraction of binder compared to that of the granules in the latter stages of the process.

There was a big difference in the binder content between the large and small granules and almost no binder in the primary powder (< 300 μm) especially at the slow binder addition rate (100 g/min).



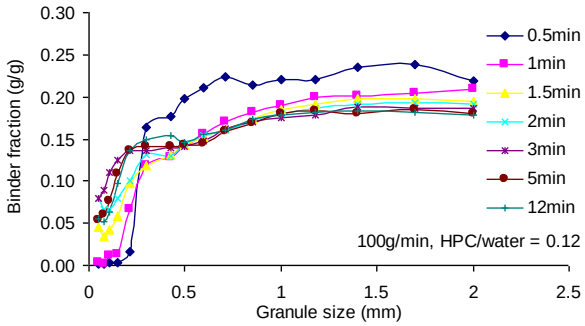


Figure 6a. Influence of binder flow rate on the binder distribution at HPC/water = 0.12

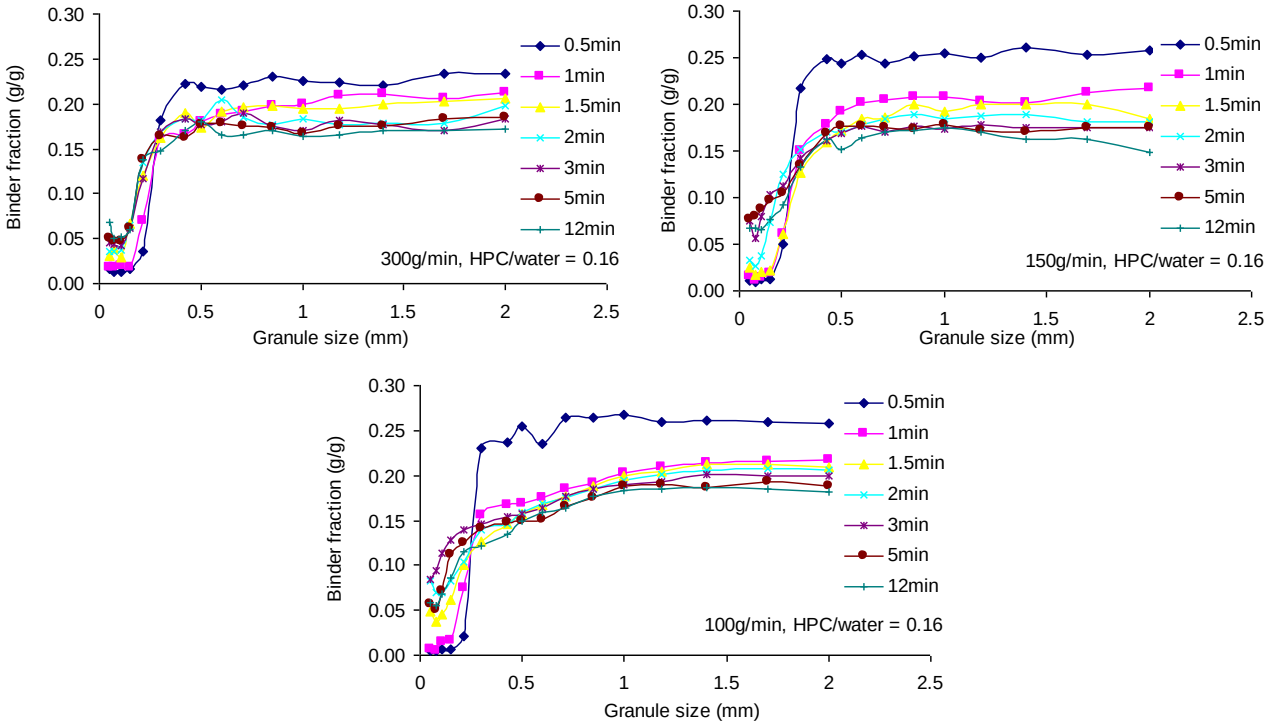
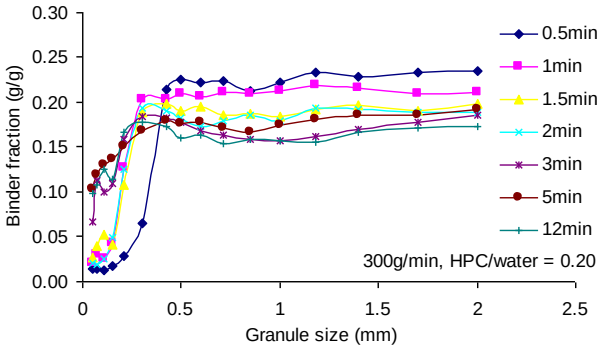


Figure 6b. Influence of binder flow rate on the binder distribution at HPC/water = 0.16



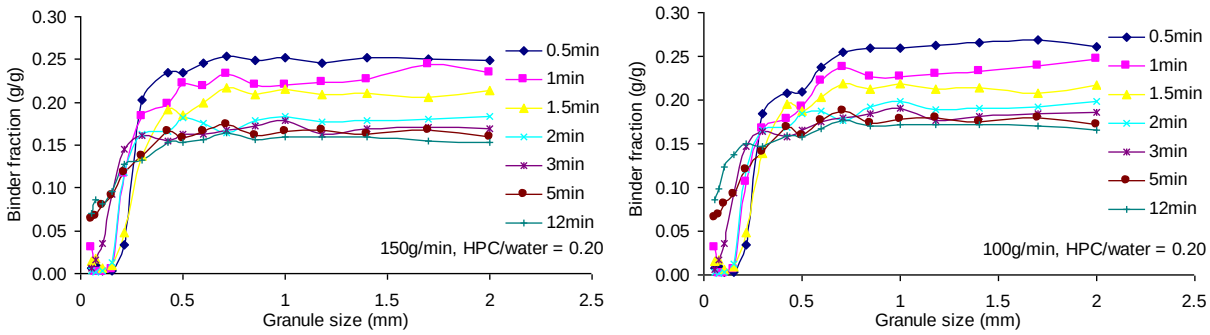


Figure 6c. Influence of binder flow rate on the binder distribution at HPC/water = 0.20

As 300g of binder added in 2000g of powder, the average ratio of the binder liquid and solid should be 0.15 g/g in the case of uniform binder distribution. These results showed that the concentration in the large granules is much higher than this average concentration, while the concentration in the ungranulated powder mass is below average. This indicated that the binder liquid is poorly distributed over the powder mass. The change of binder distribution with time shows that the liquid load in larger particle size fractions decreases with increasing granulation time. This behaviour was also observed by Knight et al.,[4] , Scott et al.,[13] and by Reynolds et al.,[14] . The distribution of the binder could be attributed to the mechanisms of granule formation; when the binder liquid is poured into the high shear mixer, the mechanical agitation is responsible for the dispersion of the liquid into droplets. These droplets become smaller as the process proceeds. Parallel to the binder dispersion process, penetration of these binder droplets into the porous powder bed results in granule formation. On the one hand, when binder dispersion is the dominant process, complete dispersion of the binder will occur. This results in a homogeneous distribution of the binder over the (primary) particles. When the penetration is faster than the binder, dispersion granules are formed. Hardly any binder will then distribute over the primary particles, because the penetration prevents complete binder dispersion. In this case, the binder is mainly present in the (relatively large) granules. A homogeneous distribution is only obtained when these freshly formed granules are broken down again. In fact, the inhomogeneous distribution shown in Figure 6 a, b, c demonstrates that granules are directly formed by liquid penetration. The high viscosity drops, which are slow to penetrate and difficult to be broken, produce nuclei containing a high binder fraction.

Conclusions

Penetration time studies have confirmed penetration time is second power of drop size. Linear relationships between nucleus size and drop size onto both a static powder bed and a moving bed have also been found.

It is great importance to notice that varying viscosity of the binder formed significantlydifferent drop sizes, which is the main reason for the production of different size of nuclei.

The studies on the high shear mixer showed that both the size of the produced granules and their liquid binder content vary with binder addition time and binder viscosity. Pouring liquid binder onto the powder bed at the slowest rate and at low viscosity will produce a smaller droplet size and provide a better distribution of liquid in the samples taken, but the consequence of that will be smaller granules compared to that of the faster binder addition rate.

The final important point is that granules keep their integrity; large nuclei produce large granules. Therefore, the properties of granules can be predicted and controlled from the early stages of the granulation process.

References

[1] H.G. Kristensen, P. Holm, and T. Schaefer, "Mechanical properties of moist agglomerates in relation to granulation mechanisms part II. Effects of particle size distribution," *Powder Technology*, Vol. 44, No. 3, pp. 239-247, 1985.

[2] S.T. Keningley, P.C. Knight, and A.D. Marson, "An investigation into the effects of binder viscosity on agglomeration behaviour," *Powder Technology*, Vol. 91, No. 2, pp. 95-103, 1997.

[3] P.C. Knight, et al., "An investigation into the kinetics of liquid distribution and growth in high shear mixer agglomeration," *Powder Technology*, Vol. 97, No. 3, pp. 246-257, 1998.

[4] P.C. Knight, et al., "An investigation of the effects on agglomeration of changing the speed of a mechanical mixer," *Powder Technology*, Vol. 110, No. 3, pp. 204-209, 2000.

[5] J.S. Fu, et al., "An experimental study of the variability in the properties and quality of wet granules," *Powder Technology*, Vol. 140, No. 3, pp. 209-216, 2004.

[6] K.P. Hapgood, et al., "Drop penetration into porous powder beds," *Journal of Colloid and Interface Science*, Vol. 253, No. 2, pp. 353-366, 2002.

[7] K.P. Hapgood, et al., "Dimensionless spray flux in wet granulation: Monte-carlo simulations and experimental validation," *Powder Technology*, Vol. 141, No. 1-2, pp. 20-30, 2004.

[8] P.K. Le, et al., "Multivariate statistical modelling for granulation of phamarceutical products," *Journal of Science and Tuechnology*, Vol. 47, No. 5A, pp. 21-36, 2009.

[9] T. Schaefer, "Melt pelletization in a high shear mixer VI. Agglomeration of a cohesive powder," *International Journal of Pharmaceutics*, Vol. 132, No. 1-2, pp. 221-230, 1996.

[10] K. van den Dries, and H. Vromans, "Qualitative proof of liquid dispersion and penetration-involved granule formation in a high shear mixer," *European Journal of Pharmaceutics and Biopharmaceutics*, Vol. 58, No. 3, pp. 551-559, 2004.

[11] M. Denesuk, et al., "Capillary penetration of liquid droplets into porous materials," *Journal of Colloid and Interface Science*, Vol. 158, No. 1, pp. 114-120, 1993.

[12] P.K. Le, et al., "A microscopic study of granulation mechanisms and their effect on granule properties," *Powder Technology*, Vol. 206, No. 1-2, pp. 18-24, 2011.

[13] A.C. Scott, M.J. Hounslow, and T. Instone, "Direct evidence of heterogeneity during high-shear granulation," *Powder Technology*, Vol. 113, No. 1-2, pp. 205-213, 2000.

[14] G.K. Reynolds, et al., "Non-uniformity of binder distribution in high-shear granulation," *Powder Technology*, Vol. 140, No. 3, pp. 203-208, 2004.