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

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DOI 10.1002/aic.14717
Published online January 8, 2015 in Wiley Online Library (wileyonlinelibrary.com)

The two available wetting methods for twin screw granulation, namely foam delivery and liquid injection, were studied in detail by examining granule development along the screws as powder formulation and screw design were varied. Granulation profiles were determined by particle size analysis of samples along the screws collected using the "screw pullout" technique. Analysis of the particle size and porosity of produced granules revealed only minor differences between the two methods of wetting despite the larger dropsize of liquid injection compared to foam delivery. Excipients like microcrystalline cellulose or hydroxypropyl methyl cellulose with poor spreading properties, quantified by their specific penetration time and nucleation ratio, made the differences more apparent. The general similarities in granulation independent of wetting method implied that binder dispersion in an extruder was dominated by mechanical dispersion. Screw design (i.e., location of kneading block) had the dominant effect on the granulation process in this study. © 2015 American Institute of Chemical Engineers *AIChE J*, 61: 780–791, 2015
Keywords: continuous manufacturing, wet granulation, foam delivery, twin screw extruder

Introduction

The rapid and uniform wetting of powder excipients and active pharmaceutical ingredients is considered to be one of the more pressing challenges to developing a stable, consistent continuous wet granulation processes with twin screw machinery.[1–3] In twin screw granulation all steps of wetting, granule growth (i.e., layering and coalescence), compression and comminution must occur within a very short period of time (i.e., seconds) and must do so sequentially for the most part.[4–6] The process demands that the liquid distribution within all powders be as uniform as possible prior to compression or else the final product will likely consist of a high fines content. In addition, inadequate lubrication of conveyed powders against interior metal surfaces while being compressed will often result in material overheating, motor surging, and considerable variation in the final particle size.[2,7] The main complication to uniformly wetting any powder within the extruder is the enclosed flow path, which is generally beneficial as it provides a uniform shear history, but also dictates where and how the binding liquid may be added. Issues of poor wetting are expected to occur more often in larger machines where the relative wetting area is normally well below unity and that area diminishes as the screw diameter of the machine increases; the relative wetting area is defined by the fluid cross-sectional area exiting an injection port vs. the surface contact area of powders within the screw channels underneath said port..

The necessary quantity of liquid for granulation that satisfies pendular saturation[8] is normally added at a single port in the extruder (close to the powder feed opening) to minimize equipment and operational costs but the high volumetric flow rate that it enters at unfortunately creates local regions in the feed powder that can be severely oversaturated initially. Adding the same quantity of liquid over two or three ports spaced down the length of the process minimizes the state of initial oversaturation,[1] but complicates the steps of granule growth and demands more equipment (which includes higher maintenance and control requirements).

In high shear batch mixers or fluidized beds, increasing initial binder dispersion within powders is achieved by spraying whereby the reduced droplet size relative to feed particles leads to consistency in size and porosity among the developing granules.[9–11] However, insufficient clearance in an extruder negates this as a feasible solution for liquid addition. The staggering of injection sites down the length of the extruder proposed by Shah,[1] as mentioned above, seems the best solution currently disclosed in the literature to directly injecting the binding liquid when a process encounters surging and poor granulation. Alternatively, a new method was introduced recently where the binding liquid is delivered to the process as a semi-rigid, unstable foam with the consistency of shaving cream. The technique is known as foam granulation, named by its inventors.[12] Foam granulation has

This contribution was identified by William Ketterhagen (Pfizer Inc.) as the Best Presentation in the session "Applications of Continuous Processing in Manufacture of Pharmaceuticals: Drug Product" of the 2012 AIChE Annual Meeting in Pittsburgh, PA.

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Table 1. Properties of the Formulation Powders

Formulation	Bulk Density (kg/m^3)*	Tap Density (kg/m^3)*	d_{10} (μm)†	d_{50} (μm)†	d_{90} (μm)†
Lactose	646 ± 1.1%	737 ± 1.1%	125	150	180
20% HPMC	570 ± 0.3%	660 ± 0.4%	50	125	180
50% MCC	491 ± 0.3%	589 ± 0.8%	125	150	250

*Included stated uncertainty, RSD (%).
†Particle size data determined by sieving using different screens with nominal opening width of 500, 300, 250, 180, 150, 125, and 75 μm and a bottom pan.

been demonstrated to be a robust technique for the wetting of either batch[13,14] or continuous processes.[2,15] Similar to its benefits in the textile industry, introducing a foamed binder into granulation processes allow the liquid to be spread over a larger relative wetting area than possible by liquid injection (LI) without oversaturation of the initially contacted powder. A review of foam delivery (FD) vs. LI in a twin screw granulator was recently given[16] with pros and cons stated for each. This article probes in greater detail the differences between the two methods of binder addition to granule development when using a twin screw granulator.

It is the purpose of this article to present results on granule size and porosity based on different operating parameters and different powder formulations which are characteristic of the pharmaceutical industry. The study uses a screw pull-out technique disclosed in a recent paper to directly access particles along the process length of the extruder,[5] providing an understanding of how granule growth can differ based on the chosen method of wetting, that is, FD vs. LI.

Experimental

Materials

Three formulations were examined in this study using powders commonly used in the pharmaceutical industry for solid oral dosage forms. The simplest formulation consisted solely of Flowlac® 100 spray-dried α-lactose monohydrate (Meggle Pharma, Germany). The second formulation consisted of 42.25% microcrystalline cellulose (MCC; Avicel® PH101, FMC Biopolymer; Newark, NJ), 15% ibuprofen USP (Spectrum Chemical; Gardena, CA), 42.25% α-lactose monohydrate and 0.5% fumed amorphous silica (Sigma-Aldrich; Toronto, ON); this formulation is denoted as 50% MCC due to the ratio of MCC to lactose. MCC is a fine powder with strong water absorption capacity and improves the fracture strength of produced granules. The third formulation consisted of 20% METHOCEL™ E3PLV hydroxypropyl methylcellulose (The Dow Chemical Company; Midland, MI) blended with α-lactose monohydrate; this formulation is denoted as 20% HPMC. This grade of hydroxypropyl methylcellulose has minimal controlled release properties but gels on contact with water and improves the fracture strength of granules produced. None of these formulations granulated within the extruder without addition of a liquid binder. Powder properties of the formulations used in the study are summarized in Table 1.

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

Twin screw granulator

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

Two screw designs were examined in the study, both primarily composed of conveying elements but including a 10-disc 60° offset kneading block that spanned 2 L/D in length. In one design, the kneading block was located at barrel zone Z8 to be closer to the die (denoted as screw design #1) while the other design had the kneading block at zone Z4 to be closer to the site of binder addition (denoted as screw design #2). Screw design #1 allowed a comparatively longer duration for binder dispersion throughout the powder by shear-induced particle collisions prior to compression in the nonconveying zone containing the kneading block. The kneading block provided both compaction and comminution to the wet granulation process which has been reported to reduce granule friability and improve binder dispersion.[4–6,17,18] By moving the kneading block to zone Z4 in screw design #2, the heterogeneity in binder dispersion produced by a selected method of wetting was hoped to be better revealed. Both screw designs and the barrel configuration denoting the zone numbering are shown in Figure 1. In this study, flow rate and screw speed were kept constant at 10 kg/h and 220 RPM, respectively.

The characteristic residence time (RT) for the process was estimated for these two screw design using the 50% MCC formulation and a procedure outline in a previous study.[5] The procedure described in the briefest sense used a tracer of cocoa powder introduced as a pseudo dirac pulse which was monitored for its exit age distribution with a video recorder.

Methods of liquid binder delivery to the extruder

For LI, the binding solution was directly metered into the extruder at barrel zone Z2 from a pair of interlinked ISCO 260D high pressure syringe pumps (Teledyne-ISCO Inc.; Lincoln, NE) configured for continuous flow; accuracy of the pumps was ±0.01 mL/min. The injector stem had an exit diameter of 1.5 mm. For FD, a mechanical foam generator supplied by The Dow Chemical Company (Midland, MI) was used to entrain air into the binding liquid to yield an 85% foam quality (FQ); FQ refers to the volume fraction of air in the produced foam. The foam was continuously metered into the extruder using a side stuffer (American Leistritz Extruder Corporation; Somerville, NJ) mounted at barrel zone Z2.[2] The equivalent diameter of the opening into

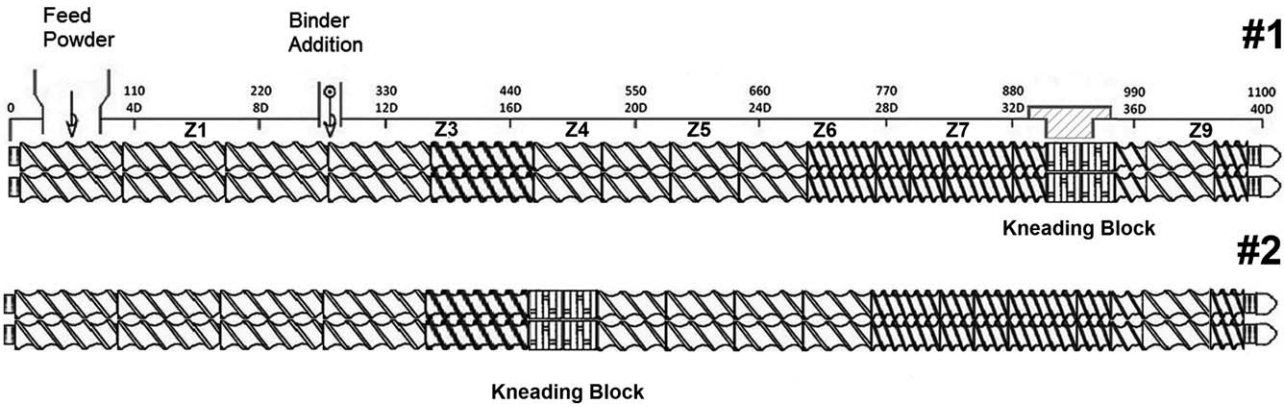

Figure 1. Comparison of the two screw designs examined in the study with the nonconveying kneading block located at barrel zone Z8 (#1) or zone Z4 (#2).

Top screw design include the nine barrel zones and their spatial locations relative to the start of the feed zone (Z0) with values quoted in mm (upper) and L/D (lower).

the extruder for the side stuffer was 32 mm calculated for its dual annular flow areas.

The liquid-to-solids (L/S) ratio was optimized from preliminary studies with the LI method and screw design #1 at 220 RPM and 10 kg/h for each formulation to achieve exiting particles in the size range of 0.5–2 mm which is desirable for tableting. The meant that overgranulation occurred for several of the tested conditions but at least ensured the system never operated in too dry of a state to lock up the motor. The L/S ratios required for successful granulation were 8% for pure lactose, 16% for the 20% HPMC formulation and 60% for the 50% MCC formulation. It is not the intention of this article to make direct comparisons between the different formulations and hence the use of different L/S did not influence the discussion. The use of common pharmaceutical ingredients with different wetting behaviors relative to water, and needing different amounts of water to develop cohesive properties was simply meant to perturb the granule development profile in the extruder and offer the most insights into how the method of wetting impacted granulation.

Process analysis by screw pullouts

To directly observe granulation within the extruder, a technique known as "screw pullouts" was used in this work. The extruder after running at steady state for a minimum of 5 min was stopped in such a manner that screw rotation was abruptly halted (i.e., an emergency stop condition), preventing the drive controller from gradually slowing the motor. This best preserved the granules as being representative of the steady state process. The screws were then pulled from the barrel with an extraction device, withdrawn one zone (11 cm) at a time, to visually inspect the granules present and collect all material in the exposed section for subsequent particle characterization; all materials collected from said zone were combined together to create a large enough sample for size analysis by sieving. The highly compacted mass in the kneading block was not analyzed as in many cases it had to be pried off the screws with a tool. Screw extraction in this stepwise manner was continuously done until reaching the zone where the binder was added (i.e., Z2). An intact example of a screw pull out where the particles were not removed but left in place is shown in Figure 2.

Samples collected from along the screws and at the exit of the machine were air-dried for 48 h in a lab held at 23°C and 35% relative humidity, and then stored in sealed plastic bags for later characterization. Residual moisture content was below 1% once dry except for the 50% MCC samples which were higher at $1.8\% \pm 0.3\%$, as determined using a Mettler-Toledo HG63 moisture analyzer.

Particle size analysis

The particle-size distribution (PSD) was determined using a Ro-Tap RX-29 sieve shaker (W.S. Tyler; Mentor, OH) using different screens with nominal openings of 2100, 1180, 850, 500, 250, 125, and 75 μm, as well as a bottom pan. The amount of sample used for PSD characterization was approximately 5 g per zone of the screw and 100 g for the collected material at the extruder exit, which was sieved by mechanical agitation for 5 min. The uncertainty in the analysis varied based on the size fraction being largest on the 2100 μm screen at 6.4% RSD based on measured samples from duplicate trials for the MCC-containing formulation.

Porosity, pore size, and fracture strength characterization

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

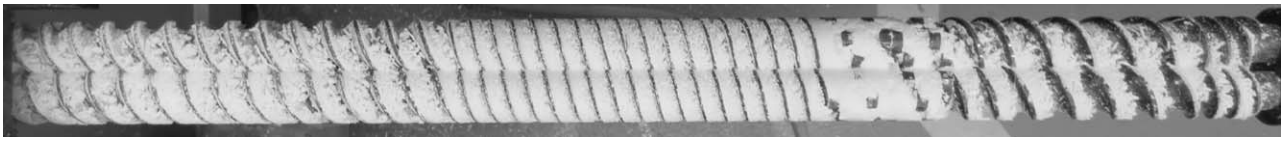

Figure 2. Photograph of a screw pull out for the 50% MCC formulation at 10 kg/h and 220 RPM with the kneading block located at zone Z8.

The screw is oriented such that zone Z2 is to the far left and zone Z9 is to the far right.

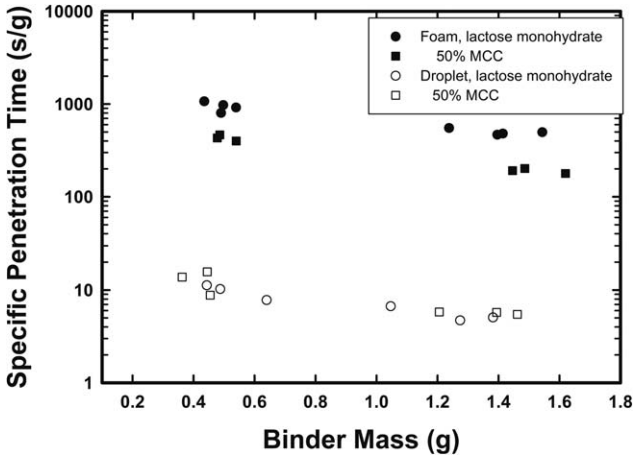

Figure 3. Specific penetration time relative to the binder atop a static bed of lactose monohydrate and the 50% MCC formulation compared based on wetting method.

uncertainty was 3%RSD. No values were reported before the kneading block (zone Z3) on screw design #2 as many of the specimens lacked integrity and readily fell apart.

Characteristic fracture strength of granules exiting the process was determined by confined uniaxial compression of a sample initially screened to consist of 500–850 μm particles. The value for fracture strength was calculated according to the equation and method described by Adams.[19] A mass of 0.60 g was introduced into a die press described in[20] and compressed to maximum load of 4200 N at a crosshead speed of 3.5 mm/min, consistent with Adams. Between samples the die press was lubricated with magnesium stearate.

Binder penetration time

Each formulation was first sieved through a 300 μm screen. A sample of the powder ($\sim$100 g) was then poured through a funnel suspended 5 cm above a glass petri dish (10 cm in diameter and 1.5-cm deep). A ruler was used to carefully spread the powder evenly around the perimeter of the dish and then drawn across the top of the dish to create a flat surface for the bed; preparation of the powder bed was done in this manner to minimize differences in porosity between repeats. Variation in the porosity by this method of filling was 1.89% RSD. Differing masses of foam or liquid were added atop the powder bed. The dispensed liquid was monitored visually till it had fully penetrated into the bed. The binder-saturated powder bed was left for 48 h to air dry before the resulting granule nuclei were isolated by inverting the dish above a 300 μm screen and then were weighed. The specific penetration time (t_p) was defined as the elapsed time till the binder had fully penetrated normalized with respect to the binder mass whereas the nucleation ratio (K_m) referred to the mass of the resulting granule nuclei relative to the binder mass. This method of quantifying binder penetration corresponds to the approach devised by Hapgood and coworkers.[21,22]

Results

Characteristic saturation behavior of the different formulations

To understand how liquid penetrates into the different tested formulations, based on wetting method, and under more controlled circumstances than within the extruder, a binder penetration test was used according to the method set out by Hapgood and coworkers.[21,22] The specific penetration times for lactose and the 50% MCC formulation are shown in Figure 3, although no data could be provided for the 20% HPMC formulation; the uncertainty in the time measurement was 6.6% RSD by foam and 17.1% RSD by drop addition. In the case of the latter formulation, the binding solution never fully saturated the powder by either droplet or foam as the HPMC immediately gelled on wetting, forming a barrier which prevented the remaining liquid from penetrating into the bed. The other two formulations provided reasonable results, allowing the binder to fully penetrate into the powder. The passage of liquid through the bed, based on specific penetration time, was longer for FD with pure lactose compared to the 50% MCC formulation but no difference was noted with LI. The difference between lactose and MCC is consistent with results reported in an earlier study.[7] As previously found by Hapgood,[21,22] the smaller the dispensed binder mass atop of the powder the longer the time to fully penetrate, by either method of wetting, which relates to the state of powder saturation as it affects liquid mobility. The difference in the specific penetration time between foam vs. droplet was significant, taking almost two orders of magnitude longer to fully penetrate the powder by the former approach. This is attributed to the fact that liquids drain from a semi-rigid foam slowly, following a tortuous path along the boundaries (i.e., plateau borders and film walls) of its numerous gas bubbles rather than allowing all of its retained liquid to be immediately available like a droplet.[12]

The nucleation ratio which represents the spread of binder in a powder system was measured from each penetration test, with average values reported in Table 2. The wetted mass was more than 300% larger for pure lactose as it has less tendency to absorb the water unlike HPMC or MCC, allowing it to spread further within the interstitial regions of the powder.[7] The results for the 20% HPMC formulation did not properly convey the wetting nature of this powder as most of the liquid was unable to penetrate the bed due to rapid gelation of the cellulose ether ingredient, as mentioned above. The 50% MCC formulation generated much smaller K_m values (for example, $K_m = 1.14$ vs. $K_m = 4.63$ with lactose for the foam case) due to its high water absorbing capacity retarding interstitial distribution of the binder. Comparing the state of saturation based on these selected wetting methods found that granule nuclei were consistently 20% larger by foam vs. droplet; a result consistent with other studies comparing the two wetting methods looking at lactose[22] or a glass ballotini/salicylic acid blend.[14] The higher spread-to-soak characteristic of foam vs. a droplet that produced these larger nuclei in the tests was predominantly related to the larger contact area made with the powder bed; the larger relative wetting area is due to the occupied volume by foam being much larger than the

Table 2. Nucleation Ratio (K_m)

	State of the Binding Liquid	
	Foam, 85% Foam Quality	Droplet
Formulation	K_m	K_m
Lactose monohydrate	4.63 ± 0.21	3.79 ± 0.20
20% HPMC	1.57 ± 0.07	0.80 ± 0.23
50% MCC	1.14 ± 0.03	0.95 ± 0.01

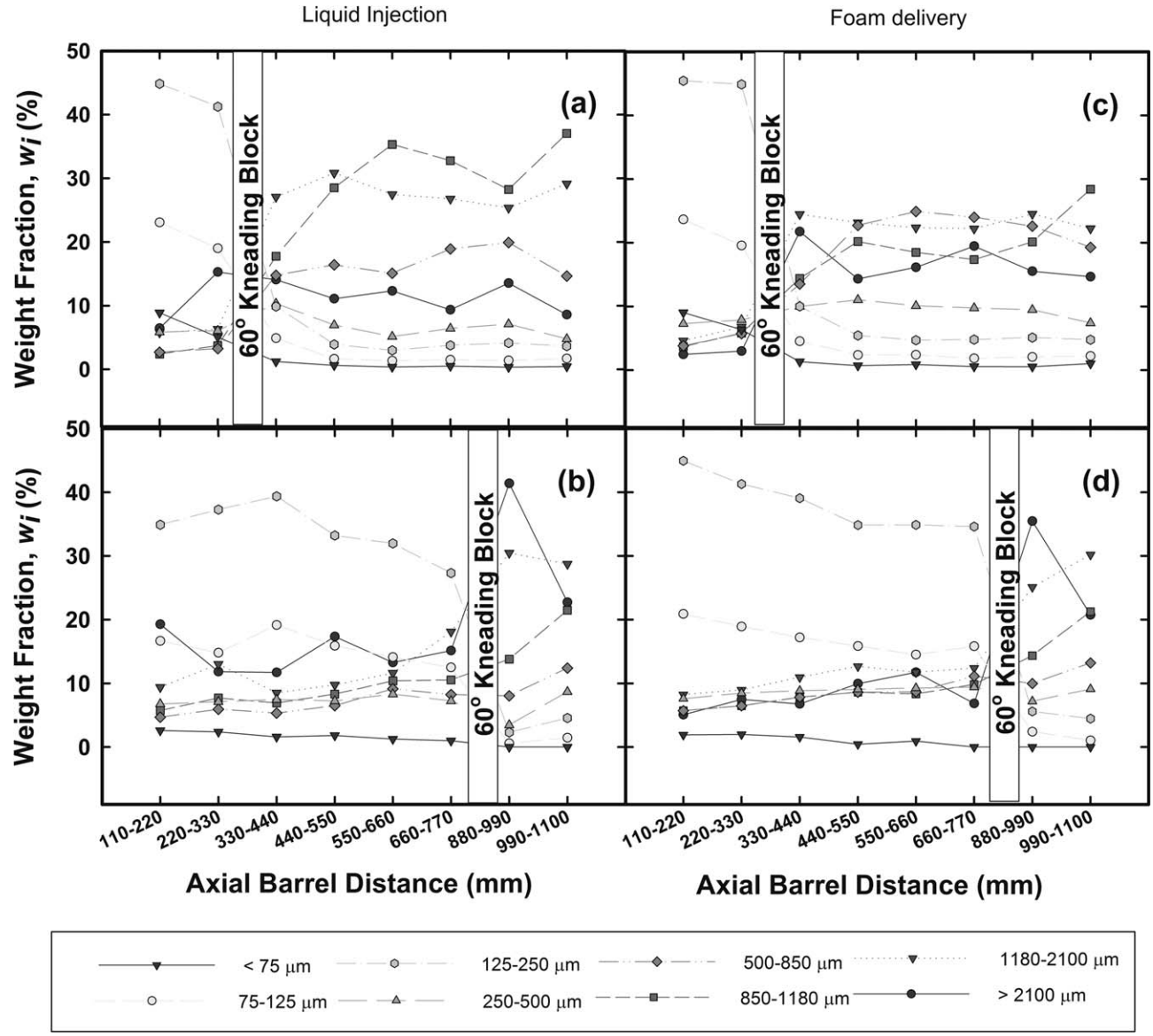

Figure 4. Granulation profile for α-lactose monohydrate comparing results on screw design #2 (a,c) vs. #1 (b,d).

Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).

liquid on account of its high volume fraction of entrained air (85% v/v in this case).

Granulation profiles for α-lactose monohydrate

Figure 4 presents granulation profiles corresponding to the wetted length of the screws (i.e., from zone Z2 to Z9) for pure lactose monohydrate using the two screw designs and operating conditions of 10 kg/h and 220 RPM. The plots for both wetting methods are shown. By either screw design or wetting method the profiles showed little granulation in the upstream conveying zones prior to the kneading block, with fines ($<250\,\mu$m) being predominant in the screws ($F_{<250\,\mu\text{m}} = 66\%$ for foam and $F_{<250\,\mu\text{m}} = 54\%$ for LI at zone Z2). The only difference seen by wetting method was a higher content of lumps (>2 mm) being immediately formed on binder addition by LI (10–20% vs. <5% with foam), retained up to the kneading block. For screw design #1, the kneading block brought about an increase in the weight fraction of large particles (>850 μm) by either method of wetting. The lumps produced by the kneading block subsequently fragmented in the downstream conveying zone, showing less stability than in screw design #2. For screw design #2, the downstream granule profiles showed greater sensitivity based on the method of wetting. By FD, the content of lumps significantly increased ($F_{>2100\,\mu\text{m}} = 3\% \rightarrow 21\%$) across the kneading block, although to a lesser degree than previously found with screw design #1 ($F_{>2100\,\mu\text{m}} \sim 40\%$). With LI more lumps were present before the kneading block yet that weight fraction did not change through the kneading block ($F_{>2100\,\mu\text{m}} = 15\% \rightarrow 14\%$). Between the two methods, the lactose showed more change in granule size along the longer downstream conveying zone by LI than by FD—possibly reflecting the greater need to distribute the liquid after initially being highly segregated. The early kneading block made the system more sensitive to binder distribution although eventual growth/attrition balanced out the differences between the two wetting methods.

The exiting cumulative PSDs from the extruder are shown in Figure 5 with the top plot corresponding to the lactose samples. Granulation of lactose produced only monomodal

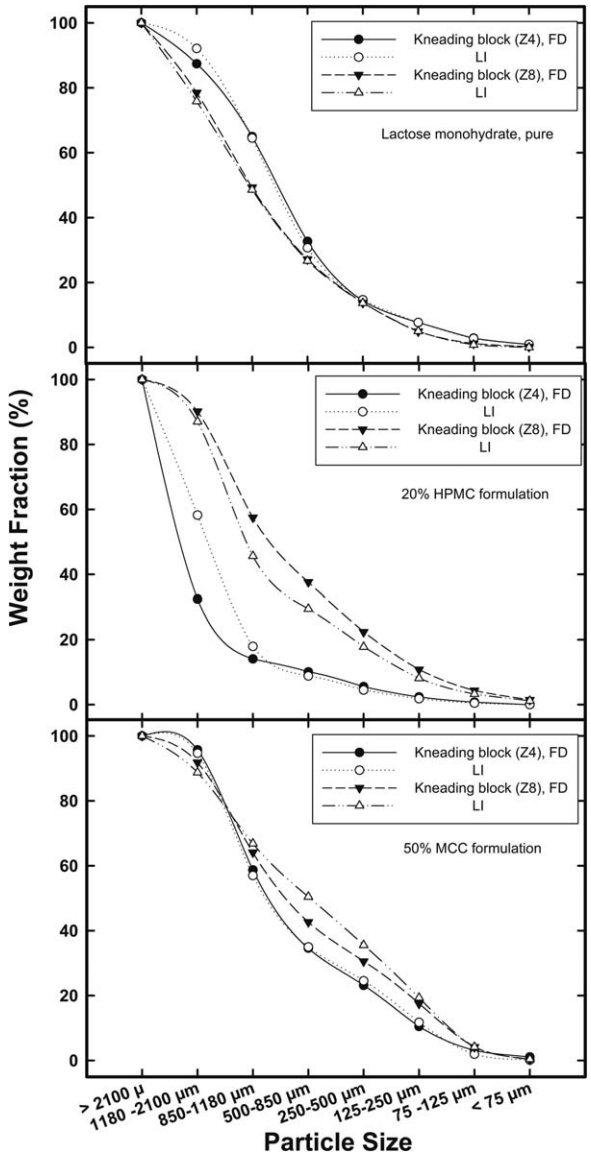

Figure 5. Cumulative PSDs for the three formulations on exiting the extruder, showing results for the two screw designs and two method of wetting.

size distributions in this study. The nominal particle size was larger with the kneading block in zone Z8 ($d_{50} = 870$ μm vs. $d_{50} = 700$ μm, zone Z4) yet identical based on the method of wetting.

To examine changes in the granule structure based on the wetting method and screw design selected, samples were analyzed for their porosity and fracture strength. Table 3 presents the porosimetry results for granules of lactose monohydrate before and after the kneading block. In general, porosity and pore size of granules decreased from compression in the kneading block of either screw design. Based on the method of wetting, bulk porosity was lower by LI. Pore size was smaller by LI but that could only be conclusively stated in the case of screw design #1. The fracture strength of exiting particles from the extruder were 13.5 ± 1.6 MPa and 12.3 ± 0.3 MPa for FD and LI, respectively, with screw design #1 and, 12.4 ± 0.5 MPa and 10.5 ± 0.3 MPa for FD and LI, respectively, with screw design #2. In general, the results indicate comparable compaction between the two screw designs and wetting methods.

Selected particles (found on the 850 μm sieve) from granulation with screw design #1 were analyzed by SEM. Figure 6 included images of lactose particles based on the method of wetting; there was no notable difference in average particle shape (for any of the formulations actually) and so the particles shown should not be construed to be indicating a shape dependency based on wetting. The lactose particles showed no discernable difference in their structure based on wetting. They appeared well agglomerated and dense in structure.

Granulation profiles for the 20% HPMC formulation

The granulation profiles presented in Figure 7 for the formulation containing 20% HPMC showed more sensitivity to the tested factors than previously seen with purely lactose, more so to screw design than the wetting method. Using LI with screw design #1, only 37% fines were present after wetting in zone Z2 (110–220 mm) with the rest being 0.25–2 mm in size. A progressive increase in the content of 0.25–2 mm particles was noted after zone Z2 along the upstream conveying zone while fines content was reduced. Conversely, by FD the profile on screw design #1 showed higher fines ($F_{<250\,\mu m} = 55\%$) and a substantial quantity of lumps ($F_{>2100\,\mu m} = 25\%$) in the wetting zone by its higher relative wetting area. Those lumps decreased to a stable content of $\sim$18% while still upstream of the kneading block with a corresponding increase in fines suggesting the lumps were quite friable. Compaction in the kneading block left less than 10% fines and coarse particles similar in size distribution to pure lactose by either wetting method. The exiting cumulative PSDs for this screw design, included in Figure 5, showed a similar nominal size from foam wetting ($d_{50} = 730$ μm) to the lactose trials although by LI, the nominal size was larger ($d_{50} = 950$ μm). The distributions had a Gaussian shape which was similar to the lactose samples. The particles prepared with 20% HPMC on this screw, as visually shown in Figure 6, looked slightly looser in composition with more and larger pores by LI in comparison to foam wetting (although porosity measurements below do not corroborate this observation).

Moving the kneading block close to the site of liquid addition (i.e., screw design #2) for this formulation had the most dramatic effect on granulation seen in this study compared to the other two formulations. In the upstream conveying section, the differences for zones Z2–Z3 were minor

Table 3. Granule Porosity for Samples of Lactose Monohydrate Across the Kneading Block

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

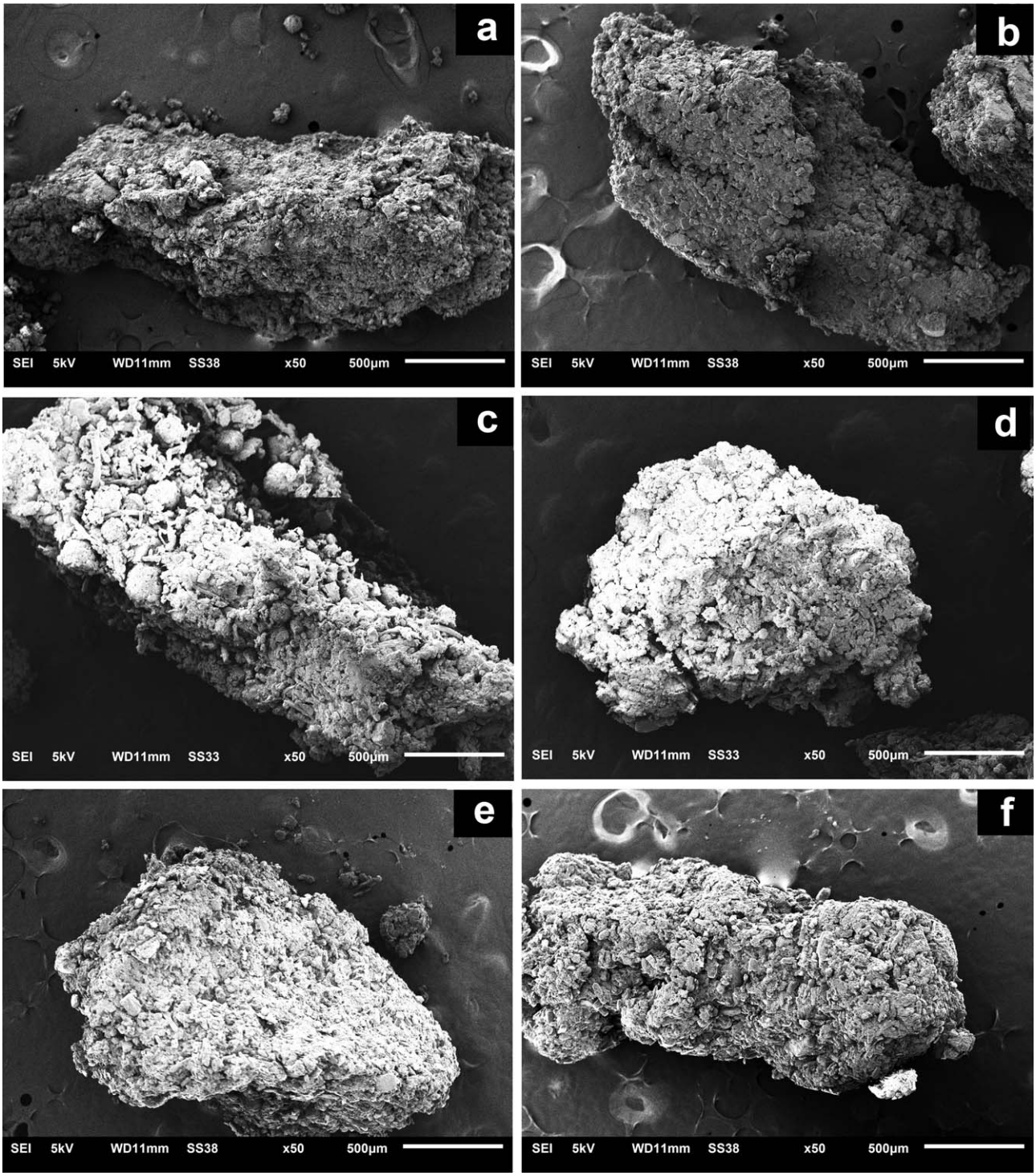

Figure 6. Micrographs for granules of lactose (a,b), 20% HPMC (c,d), and 50% MCC (e,f) produced at 10 kg/h and 220 RPM on screw design #1.

Particles on the left produced by liquid injection (a,c,e) vs. on the right by foam delivery (b,d,f).

compared to the same zones in screw design #1 but much different after the kneading block. Exiting the kneading block, there was an excessive amount of lumps generated—more than double what was found with screw design #1 and this occurred by either wetting method ($F_{>2100\,\mu m} = 60\%$ for foam and $F_{>2100\,\mu m} = 70\%$ for LI). The lumps readily fracture passing through the most immediate conveying elements after the kneading block (zones Z4–Z6) resulting in an increase of particles that were 1–2 mm in size. The only difference downstream between the two wetting methods was that the lumps began to increase in content again, after zone Z6 for FD but not until zone Z8 by LI, consuming the particles of 1–2 mm in size to grow. The final cumulative particle distributions shown in Figure 5 revealed the samples from this screw were comprised of coarser particles than seen in screw design #1, but more so with foam ($d_{50} = 1420\,\mu m$) than by LI ($d_{50} = 1120\,\mu m$). Neither product was considered desirable based on the excessive fraction of

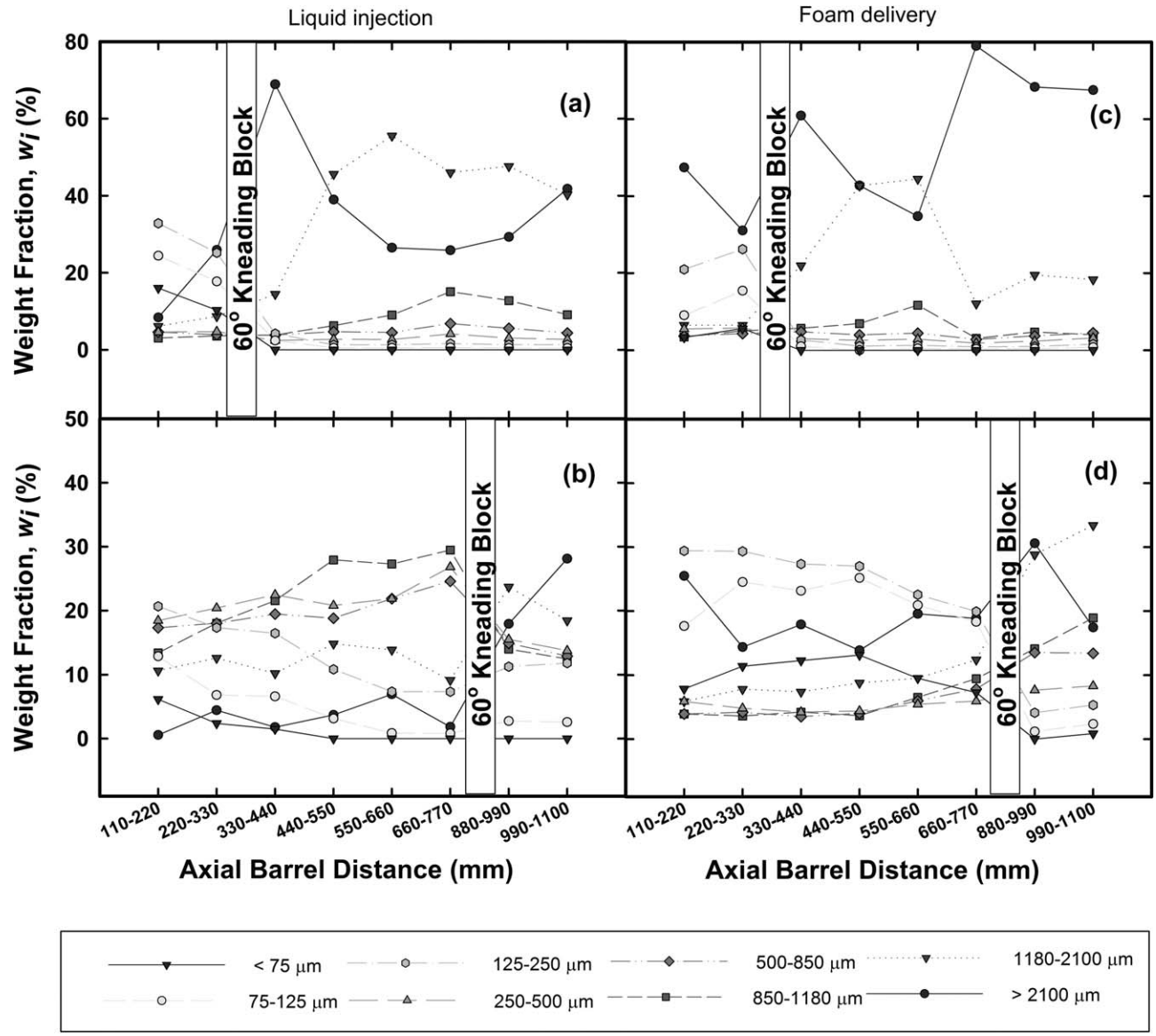

Figure 7. Granulation profile for the 20% HPMC formulation comparing results on screw design #2 (a,c) vs. #1 (b,d).

Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).

lumps present; however, it should be noted that the L/S ratio had been optimized in our pretrial experiments with screw design #1 not #2.

The porosity and pore size results across the kneading block for the 20% HPMC formulation are listed in Table 4. Across the kneading block both pore size and porosity decreased, as seen previously with pure lactose. Differences based on the method of wetting were negligible for screw design #1 with similar pore size ($\sim$0.31 μm) and bulk porosity ($\sim$41%) observed after the kneading block. However, having the kneading block closer to the wetting zone produced significantly denser granules with a bulk porosity now of apprximately 31% by either wetting method. The fracture strength of granules exiting the process were 15.5 ± 0.3 MPa and

Table 4. Granule Porosity for the 20% HPMC Formulation*

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

*Operating condition, 10 kg/h and 220 RPM, particle size 850–1180 μm.

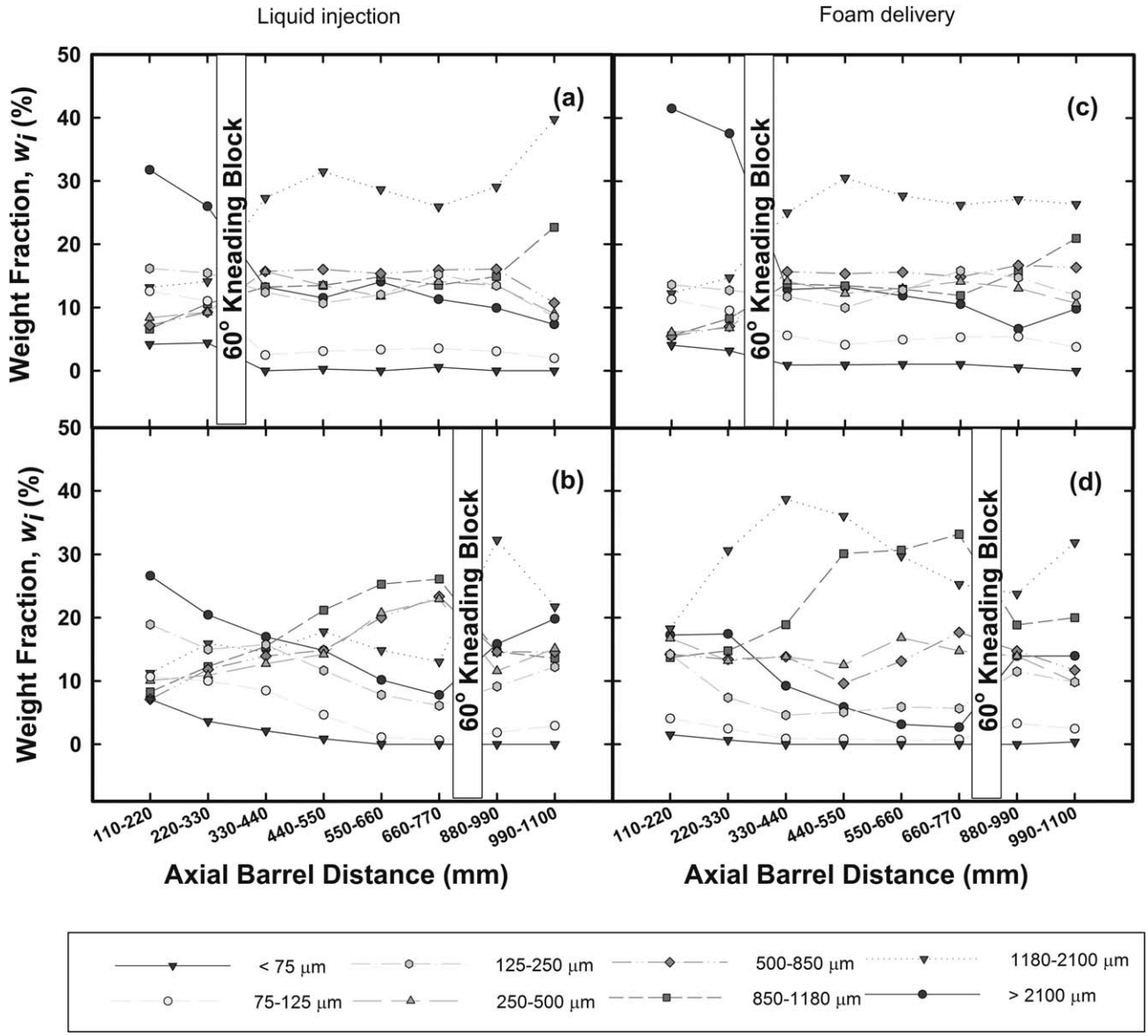

Figure 8. Granulation profile for the 50% MCC formulation comparing results on screw design #2 (a,c) vs. #1 (b,d).

Results produced at 10 kg/h, 220 RPM. Wetting method used: liquid injection (a,b) vs. foam delivery (c,d).

17.8 ± 1.9 MPa for foam and LI, respectively, on screw design #1, and were 5.0 ± 1.4 MPa and 7.5 ± 1.0 MPa for foam and LI, respectively, on screw design #2. The fracture strength values for screw design #2 seemed unusually low and were not considered accurate as granules larger than 850 μm had to be tested in this case as there was insufficient product collected in the 500–850 μm range for testing and these lumps made for difficulties filling of the die press cavity.

Granulation profiles for the 50% MCC formulation

Granulation profiles for the 50% MCC formulation are presented in Figure 8 for the two screw designs and by both methods of wetting. With screw design #1, lumps were found in the screws at zone Z2 on initial wetting by LI ($F_{>2100\,\mu m} \sim 28\%$) while their content was less (~19%) for FD. Few fines were present on wetting ($F_{<250\,\mu m} = 37\%$ for LI and $F_{<250\,\mu m} = 20\%$ for foam). By either method, the fraction of lumps decreased steadily along the conveying zones upstream of the kneading block, suggesting a weak and friable nature. Using FD, the fragmentation of lumps was progressive, with particles of 1–2 mm being generated in the earlier zones (Z2–Z4) and subsequently decreasing to 0.8–1 mm sized particles along zones Z4–Z7. Some of similar aspects of that progressive fragmentation was also seen by LI but in that case, granules of 0.8–1 mm and smaller resulted. By both wetting methods, minor granule growth resulted from compression in the kneading block ($F_{>2100\,\mu m} = 3\% \rightarrow 14\%$ for foam and $F_{>2100\,\mu m} = 8\% \rightarrow 16\%$ for LI) but this change was less than observed with the other formulations for this screw design. It was the particles of 1–2 mm size, rather than lumps, that experienced the most significant increase in content on exiting the kneading block. The nominal particle size at the exit (referring to Figure 5) was significantly smaller by LI ($d_{50} = 490$ μm) in comparison to FD ($d_{50} = 620$ μm). Selected particles analyzed by SEM from these samples visually seen in Figure 6 showed the granules were distinctly more porous when prepared by FD.

Examining results when the kneading block was moved to zone Z4 revealed this formulation was the only case in the study where lumps were reduced by going through the

Table 5. Granule Porosity for the 50% MCC Formulation*

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

*Operating condition, 10 g/h and 220 RPM, particle size 850–1180 μm.

kneading block. Before the kneading block, lumps dominated the solids composition yet a considerable amount of fines remained. The PSD appeared similar with either method of wetting although more lumps were present by FD ($F_{>2100\ \mu m} \sim 38\%$ vs. $\sim$30% by LI). After the kneading block, the granules were predominantly 1–2 mm in size ($F_{1180–2100\ \mu m} \sim 30\%$) by either method of wetting although all other size fractions, 125 μm and above, remained significantly present (around 10% for each fraction). Most granule sizes remained constant in their weight fraction along the downstream conveying zones; such stabilization in size was similarly noted with pure lactose. The small difference in particle size seen in zones Z8–Z9 between the two wetting methods was not observed in the exiting samples from the process. The cumulative PSDs of collected samples from the machine exit are given in Figure 5 and appeared identical based on wetting method ($d_{50} = 730\,\mu$m for both cases). The exit PSDs remained bimodal as found with screw design #1 but the nominal particle size was much larger with screw design #2.

The porosity and pore size results for the 50% MCC formulation across the kneading block are listed in Table 5. With screw design #1, there was no change in porosity (43%) or pore size ($\sim$0.36 μm) by passage through the kneading block for foam wetted granules. The granules upstream of the kneading block had a higher bulk porosity by LI (48%) and comparable porosity after compression to FD but much lower pore size (0.22 μm). The fracture strength of granules exiting the machine with this screw design was 27.8 ± 0.4 MPa and 40.2 ± 1.5 MPa for foam and LI, respectively. For screw design #2, similar granule structures were noted after the kneading block for the two wetting methods with identical pore size measurements (0.25 μm) although porosity was slightly higher by LI. The fracture strength values of exiting granules were 30.8 ± 1.6 MPa and 30.0 ± 0.7 MPa for foam and LI, respectively, with screw design #2.

Discussion

The binder droplet size contacting these dry formulations differed from 1.5 mm by LI to 120 μm by FD; the estimated droplet size for LI was based on the internal diameter of the injector whereas for foam, it was calculated based on the diameter of plateau borders along bubble boundaries, using an equation for foam drainage corresponding to channel-dominated flow[23] and foam drainage results presented in an earlier study.[15] The overall similarity in granule development seen in this study between the two methods of wetting, despite their seemingly different state of nuclei saturation based on powder-to-droplet size, implied that binder distribution was dominated by mechanical dispersion.[10] This conclusion was hypothesized in an earlier work by the authors[15] although now reaffirmed based on a more detailed analysis of the process. The alternative mechanism for binder dispersion, drop controlled,[10] where spreading dictates growth rather than agitation, seems unlikely as the penetration times presented in Figure 3 suggested the time scale of the process ($\sim$22 s) was too short for nucleation, growth, and stabilization to all occur; RT corresponded to the extruder operating for 220 RPM and 10 kg/h and was found to have no observable difference between FD vs. LI with regards to both peak RT and mean RT. Much of the results in the granulation profiles showed that nuclei formed rapidly and changed little in size along the subsequent conveying zones, indicating the timescale for nucleation must have been smaller than the RT of 22 s and much smaller than the penetration times reported in Figure 3. The dominance of mechanical dispersion in an extruder for granule development implied a certain degree of robustness toward either choice of wetting method as shear should dictate the ultimate distribution of liquid in a powder bed rather than how it was initially added; later discussion will review the influence of formulation on binder distribution. However, for twin screw granulation it is not just granule growth which should concern an operator in regards to the wetting method but also the state of powder lubrication on reaching a nonconveying zone. The state of lubrication must occur quickly before a kneading block (or other nonconveying screw element) else negatively influence the process stability and material temperature.[2,7] As the exiting temperature of granules were within 30–36°C for all experiments and motor load was constant, there were no concerns of poor lubrication in the study despite the early position of the kneading block in screw design #2. To highlight how quickly the liquid dispersed within the powder by either method of wetting, higher flow rates were tested with lactose

Table 6. Influence of Flow Rate on the Operating Conditions for Lactose Monohydrate

	Liquid Injection			Foam Delivery		
Screw Design/ Flow Rate	Motor Load (Amp)	Exiting Temperature (°C)	Nominal Particle Size, d_{50} (μm)	Motor Load (Amp)	Exiting Temperature (°C)	Nominal Particle Size, d_{50} (μm)
#1/10 kg/h	4	30–31	1040	6	29–30	1030
#1/30 kg/h	7	35	1190	8	35–36	1460
#2/10 kg/h	4	29	870	4	29	860
#2/30 kg/h	12	37	1370	12	37	1610

monohydrate and the results form 30 kg/h vs. 10 kg/h are shown in Table 6. Temperature and motor load increased with flow rate yet not based on the method of wetting. The data in the table also shows a point that was observed in the granulation profiles although not well distinguished, that particle size is generally larger by FD for all formulations, a result previously reported.[2,24] The method generally requires less liquid for granulation and creates granules of near identical porosity. Certainly from the perspective of drying time downstream of the granulation unit operation, less liquid present can mean lower overall energy requirements and potential less of a bottleneck in operating rates.

Each formulation tested represents a different wetting situation for granulation to differentiate the influence of the method of wetting. Lactose monohydrate is representative of powders with a low capacity to absorb water, leaving most at the periphery of the granules[25] and hence required a low L/S to produce reasonably sized granules. The penetration trials indicated that liquid spreading with that excipient required mechanical action, else under static conditions there was too little time for binder dispersion in the extruder (which may be why only feed particles were predominately seen before the kneading block). Only the compressive force of the kneading block appeared sufficient to significantly improve binder dispersion within lactose such that granules developed to an appropriate size and strength. This reliance on mechanical force for binder dispersion meant that the wetting method had no impact on granulation.

The 50% MCC formulation included ibuprofen which as an ingredient has a lower affinity to water compared to the other powders in the mixture, but as the penetration times decreased for this blend compared to pure lactose, the water absorption characteristics of MCC will be considered more relevant in this discussion of wetting. The relatively high water absorption capacity of MCC meant a higher L/S ratio was required for granulation before adequate surface water was present for bridging particles.[25] This formulation exemplifies conditions opposite to lactose as the liquid is internally absorbed[8] and less able to develop bridges between particles during granulation (as noted by the low nucleation ratio values seen in the penetration test) and hence resulted in smaller granules. Granule nucleation displayed no sensitivity to the wetting method as the amount of liquid required (i.e., L/S = 60%) was very high for addition at a single site, as evident by the large amount of lumps created initially by foam or LI. However, the greater initial dispersion of liquid by FD must be seen as beneficial as granule growth occurred more quickly and much fewer fines were present, most notably observed in a long conveying zone prior to a kneading block (i.e., screw design #1). Moving the compression zone closer to the wetting zone similarly reduced the fines content; in fact, the process could be made quite short in length if this approach is chosen.

Finally, the nature of HPMC as a powder excipient dramatically hinders binder dispersion, as indicated by the poor results in the penetration test. Like MCC, this excipient absorbed the added liquid but in this case formed a viscous gel[26] with adhesive properties to bind with local particles (i.e., layering). Assuming that adhesion rather than liquid bridging was the dominant form of agglomeration, this would explain the largely different results between LI and FD seen for the 20% HPMC formulation. The large contact area of the foam, despite its smaller droplet size, immediately created a large content of lumps whereas the larger droplet size yet relatively smaller contact area by LI produced fewer lumps but more particles in the 0.5–1 mm range. Other particles unable to contact the adhesive gel remained in their original powder state. The granules entering the kneading block largely resembled their nuclei size distribution. Larsson et al.,[26] have reported that HPMC creates a segregated binder distribution inside a bed of powder which often results in a bimodal size distribution. The results with HPMC also displayed the strongest influence of screw design among the tested formulations. The close proximity of the nonconveying zone to the site of wetting in screw design #2 presented little time for layering to distribute the liquid, meaning that the HPMC in the produced lumps would have been so highly plasticized with water that it plastically deform when compacted,[27] flowing to the periphery such that larger lumps formed.

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

Conclusions

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

Acknowledgments

The authors would like to extend their thanks to the Natural Sciences and Engineering Research Council of Canada for their funding of this project and to The Dow Chemical Company for their technical advice and donation of materials. The SEM micrographs were conducted at the Canadian Centre of Electron Microscopy (CCEM).

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Manuscript received July 11, 2014, and revision received Oct. 9, 2014.