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Influence of Process Variable and Physicochemical Properties on the Granulation Mechanism of Mannitol in a Fluid Bed Top Spray Granulator

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ABSTRACT This study investigated the influence of specific process variables, including the hydroxypropyl cellulose (HPC) binder solution atomization, on the fluidized bed top spray granulation of mannitol. Special attention was given to the relationship between wetting and the granule growth profile. The atomization of the HPC binder solution using a binary nozzle arrangement produced droplets of decreasing size as the atomization pressure was increased, while changes in the spray rate had little effect on the mean droplet size. Increasing the HPC binder concentration from 2 to 8% w/w increased the binder droplet size and was most likely attributed to higher solution viscosity. The top spray granulation of mannitol showed induction type growth behavior. Process conditions like high spray rate, low fluidizing air velocity and binder solution concentration that promote the availability of HPC binder solution at the surface of the particles appeared to be key in enhancing nucleation and growth of the granules. Increasing the bed moisture level, up to a certain value, reduced the contribution of attrition to the overall growth profile of the granule and, more significantly, produced less granule breakage on drying. It was observed that the mean granule size could be reduced as much as 40% between the end of granulation and the end of drying for lower initial bed moisture level despite a shorter drying phase. High atomization pressure, especially when maintained during the drying phase, contributed substantially to granule breakage.

KEYWORDS Fluidized bed, Granulation, Agglomeration, Growth mechanisms, Moisture content

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INTRODUCTION

Fluid bed granulation is a process which forms small particles into larger aggregates or granules using a liquid binder sprayed onto the fluidized

TABLE 1 Experimental Test Matrix

	HPC concentration (wt/wt %)	Binder spray rate (g/min)	Binder atomization pressure (psi)	Fluidizing air velocity (m/s)	Dewpoint (°C)
1	8	10	10	8	<2
2	8	10	20	8	<2
3	8	10	30	8	<2
4	8	20	10	8	<2
5	8	20	20	8	<2
6	8	20	30	8	<2
7	8	10	20	4	<2
8	8	5	20	8	<2
9	2	10	20	8	10
10	4	10	20	8	12
11	6	10	20	8	10
12	8	10	20	8	11

particles. The granulation process can generally be viewed as a combination of three rate processes: 1) wetting and nucleation, 2) consolidation and growth, and 3) breakage and attrition (Iveson & Wauters, 2001). Each of them is ruled by the process parameters (Iveson et al., 2001; Jones, 1989; Schaefer & Worts, 1978a, 1978b; Watano & Morikawa, 1996), the physicochemical properties of the binder liquid (Hemati et al., 2003), and the material particles (Abberger, 2001; Hemati et al., 2003) and their relationship (Hemati et al., 2003; Iveson & Wauters, 2001). Consequently, fluid bed granulation is considered a fairly complex process.

In fluid bed granulation, a finely divided binder is sprayed onto fluidized particles. As a result of collisions and coalescence between the surface-wetted powder particles, liquid bridges are formed and nucleation of particles occurs leading to the growth of granules. The availability of the liquid binder at or near the granule surface is thus of great importance in the formation of liquid bridges between particles. W hether or not the liquid binder spreads on the granule surface, evaporates, or is imbibed into the porous powder structure, as well as its ability to migrate to the surface upon collision with other granules, will greatly impact the granulation mechanism and the granule growth profile.

This investigation examined the granulation mechanism of mannitol in a fluidized bed granulator using HPC solution at different concentrations as a liquid binder. Special attention was given to the relationship between wetting and the granule growth profile of the granules especially how fluid bed process parameters, such as binder addition rate, atomization pressure, binder droplet size, and air velocity and the physicochemical properties of the binder solution, impacted the granule growth process and the final physical characteristics of the granules.

MATERIALS AND METHODS

Experimental Test Matrix

The experimental test matrix was set up in order to study how binder spray rate, atomization pressure, fluidizing air velocity, and the binder concentration affect the granule growth mechanism and the physical characteristics of the granules (Table 1). The experimental matrix allowed the isolation of each parameter for evaluation of its effect on the granulation mechanism and final product characteristics.

Preparation of Hydroxypropyl Cellulose (HPC) Solutions

The HPC binder solutions (2, 4, 6, and 8% w/w) were prepared by adding HPC (Klucel LF from Hercules Inc., Hopewell, VA, USA) to deionized water under constant stirring. The solution was allowed to sit overnight to allow hydration and degassing. The solution density was obtained at room temperature by precisely weighing 10 mL of solution using a pycnometer. The surface tension was measured at 25°C using a dynamic contact angle analyzer (DCA-322, Cahn, Madison, WI, USA) and the ring method. A DV-II+

viscometer (Brookfield, Middleboro, MA, USA) equipped with a LV1 spindle was used to measure the viscosity of the different solutions at 25°C (www.herc.com/aqualon/pharm/index.htm).

Characterization of Binder Droplet Size

A Malvern Particle/Droplet Sizer (Malvern Instruments Ltd., Worcestershire, UK) was used to measure liquid binder droplet size obtained under various atomization conditions. The nozzle assembly (Schlick #940) was set vertically at a distance of two inches from the laser beam to reduce droplet interactions and coalescence observed at larger measurement distance. In addition, it mimicked the zone underneath the nozzle where the powder cannot penetrate due to the atomization air (Hemati et al., 2003).

Granulation

Four hundred and twenty grams of mannitol (Pearlitol SD200 from Roquette et Freres, Lestrem, France) was granulated in the Glatt GPCG1 fluid bed granulator (Glatt Air Techniques Inc., Ramsey, New Jersey). The HPC binder solution was sprayed onto the fluidized bed using a Schlick nozzle #940 assembled with a #12 liquid insert (1.2 mm) and a 2 mm air cap flush with the liquid tip. The nozzle was located in the upper port above the bed, facing downward. The binder solution was sprayed until 40 g of HPC was added to obtain a final mass of 460 g. The total quantity of solution added varied with the binder concentration. Spray rate, atomization pressure, and air velocity were set according to Table 1. The inlet air temperature was set to 30°C and the inlet air humidity was not controlled and generally constant with a dew point <2°C, unless mentioned otherwise (Table 1). The inlet air temperature was monitored throughout granulation. Samples were taken at regular intervals in order to measure the granule growth and the bed moisture content as the granulation progressed.

Characterization of Granulation Process

Granulation Wetting Profile

The Mettler DL-37 KF Coulometer (Mettler Toledo, Greifensee, Switzerland) was used to measure the moisture content of each sample taken during the progress of the granulation run. The moisture level was plotted against time to provide the wetting profile of the granulation.

Granule Growth Profile

The growth profile was obtained by plotting the geometric mean diameter of each sample taken during granulation versus time. The geometric mean diameter was determined on a 1 gram sample using a sonic sifter (ATM Corporation, Milwaukee, WI, USA) and six sieves (63, 125, 250, 500, 1000, and 1400 μm). Sonic sifting was also used to determine the extent of granule breakage during the drying phase, i.e., after binder addition was completed.

Final Granule—Size Distribution and Friability

Using a sieve shaker (Model SS-8R Gilson Company Inc., Lewis Center, OH, USA) and a set of 10 sieves (63, 125, 250, 500, 710, 850, 1000, 1400, 1700, and 2000 μm), a 50 g sample of the final product was shaken for 10 min to obtain the size distribution and the geometric mean diameter. To determine the friability of the granules, sieves were shaken for an additional 20 min and the change in mass percentage of fines was measured (Utsumi & Hirano, 2002). For the mannitol lot used in this study, a geometric mean diameter (D_{50}), was measured at 130 μm and the corresponding D_{95} at $\sim$250 μm. Hence, particles that were smaller than 250 μm were considered non-granulated mannitol and reported as fines for the friability measurements.

Bulk and Tapped Densities

Granules were gently poured into a 10.0 mL graduated cylinder. The granule weight and volume were used to calculate the bulk density. Using an automatic tapper (Tap Density Tester, VanKel Technology Group, Cary, NC, USA), the cylinder was tapped 2000 times and the new volume was used to calculate the tapped density. Bulk and tapped densities were used to determine the Carr's index, an empirical value used to categorize powder flow. The Carr's index was calculated according to the equation (Aulton, 1988):

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

TABLE 2 Binder Solution Properties Versus HPC Concentration

HPC concentration (% wt/wt)	Density (g/ml)	Surface tension (dynes/cm)	Viscosity (cP)
0*	0.998*	71.97*	1.0*
2	0.986	41.23	11.6
4	0.963	41.09	50.0
6	0.962	41.94	190.0
8	0.962	43.48	510.0

*From Perry (1997).

RESULTS AND DISCUSSION

Characterization of Atomization Process

To avoid localized wetting, binder solutions are atomized to produce very fine droplets, which are evenly distributed over the powder bed (Iveson et al., 2001). Physicochemical properties of the binder solution and droplet size affect the binder distribution and spreading on the powder and, hence, are controlling factors in the granule nucleation and growth mechanism. Most fluid bed granulation equipment use a binary nozzle assembly, producing atomization of the liquid jet by an air-blast mechanism (Huimin, 2000). For a given atomizer geometry, the droplet size is generally influenced by the air to liquid ratio and the liquid physicochemical properties (density, viscosity, and surface tension), which depend directly on the binder concentration (Huimin, 2000).

Effect of HPC Concentration

Table 2 presents the physicochemical properties of the HPC solutions at different concentrations. The viscosity of the solution was greatly influenced by HPC concentration in agreement with literature (www.herc.com/aqualon/pharm/index.htm). Surface tension was not greatly affected by concentration in the range considered since HPC solution as low as 0.01% w/w produces close to the maximum change in surface tension www.herc.com/aqualon/pharm/index.htm. Similarly, solution density was constant with concentration (Table 2). Therefore, the effect of binder concentration on the atomization quality (i.e., widening of the distribution related to the increase in D_{90} value) observed in Fig. 1 was ascribed to the change in viscosity.

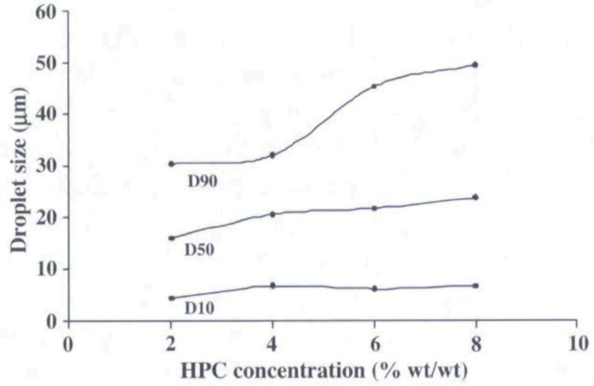

FIGURE 1 Droplet Size Distribution Versus Binder Concentration (Binder Flow Rate=10 g/min and Atomization Pressure=20 psi).

Effect of Atomization Pressure

The kinetic energy (dynamic pressure) of atomization gas is deemed to be a predominant factor determining the atomization quality. Figure 2 depicts the effect of an atomization pressure increase from 10 to 30 psi on the mean droplet size for a 8% w/w HPC binder solution sprayed at 10 g/min and 20 g/min. Increasing pressure, as expected for an air-blast atomization (Huimin, 2000), produced smaller droplets with a narrower distribution.

Effect of HPC Solution Flow Rate

Liquid flow rate is also known to influence the atomization droplet size produced by a high pressure

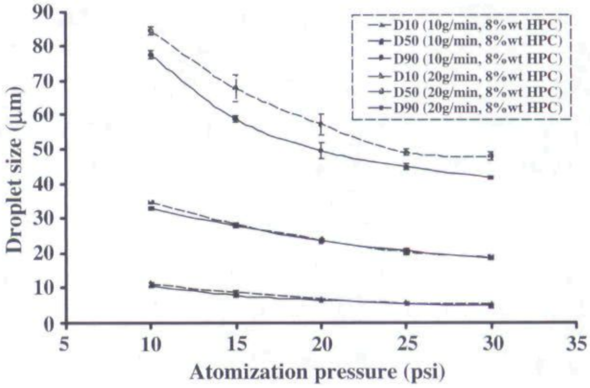

FIGURE 2 Effect of Atomization Pressure and Binder Solution Flow Rate on the Droplet Size for a 8% w/w HPC Solution.

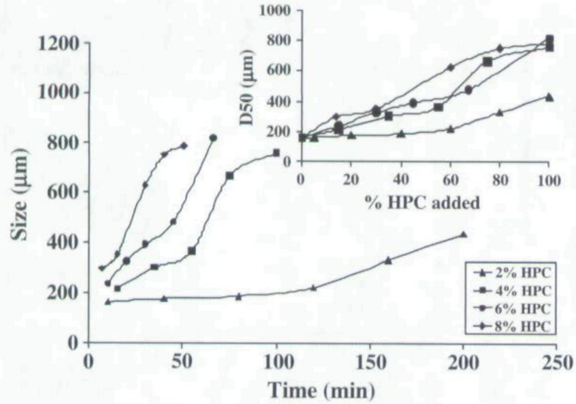

FIGURE 3 D_{50} Versus Time (Insert: Versus % HPC Added) for Different Binder Concentration Runs (Binder Spray Rate=10 g/min and Atomization Pressure=20 psi).

nozzle (Huimin, 2000), by hindering the atomization process through a reduction of the liquid and air velocity ratio. Larger liquid droplets are often observed when the flow rate is increased. However, with the 8% w/w HPC solution, an increase flow rate from 10 g/min to 20 g/min, did not significantly change average droplet size given a constant atomization pressure (Fig. 2). This was attributed to the relatively high viscosity of the solution (510 cp) becoming a dominant factor (Mansour & Chigier, 1995). It was noted, however, that a slight widening of the droplet size distribution is observed with the increased D_{90} value.

Granule Wetting and Growth Rate

Effect of Binder Concentration

Figure 3 presents mannitol SD200 granulation growth behavior when HPC solutions of various concentrations were added to the fluidized bed of particles. The shape of the curves suggest that the granulation proceeded through an induction period of little growth (Iveson & Wauters, 2001), followed by a period of rapid growth. This granulation behavior indicated an induction growth mechanism (Hapgood & Litster, 2003), where pore saturation is not the main factor affecting the granule growth rate, but rather the availability of binder at the surface. The increase in HPC binder concentration decreased the duration of the nucleation period (Fig. 3). This was a predictable behavior as the greater availability of HPC binder solution on the surface allowed formation of strong bonds that resisted the breaking forces encountered during fluidization. Moreover, granulations manufactured with 4% w/w, 6% w/w, and 8% w/w HPC solutions showed similar wetting profiles; the granulations remained relatively dry. This suggested that the solution did not imbibe the particles and partial evaporation occurred, which correlated well with the induction growth observed.

These results also indicate that the growth of granules was dictated mainly by the amount of HPC sprayed independently of the HPC solution concentration. As observed for granulations manufactured with 4%, 6%, and 8% HPC solution (insert on Fig. 3), growth was similar when the amount of HPC added was considered. Moisture level had less impact on the growth profile in this situation. The deviation observed for the 2% w/w HPC solution was ascribed to improve penetration of the less viscous (Table 2) solution into the powder (Abberger & Seo, 2002; Hapgood & Litster, 2002) resulting in reduced availability of HPC binder solution on the surface.

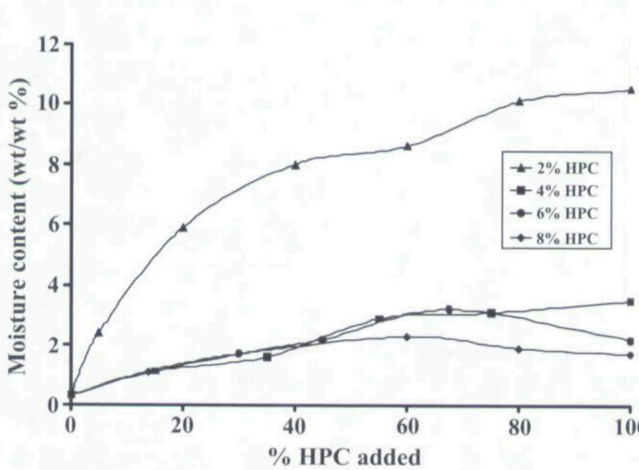

FIGURE 4 Moisture Content as a Function of HPC Added for Different Binder Concentration (Binder Spray Rate=10 g/min and Atomization Pressure=20 psi).

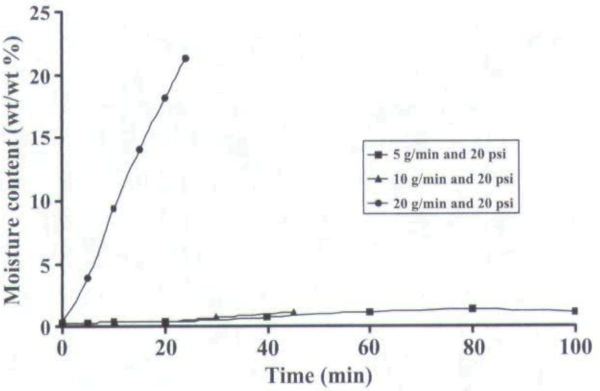

FIGURE 5 Moisture Content Versus Time with Different Spray Rates for 8% w/w HPC Binder Solution.

The increased penetration rate explains the significant increase in wetting observed when the granulation was performed with the 2% w/w HPC solution (Fig. 4). As a result of a the reduced process time, the fact that it practically eliminates the nucleation–induction period, and would also make the comparison of growth rates easier, 8% w/w HPC solutions were used for the remainder of the work.

Effect of Binder Addition Rate

Using the 8% w/w HPC solution, addition rates of 5, 10, and 20 g/min were tested in this experimental section. At the slower addition rates (5 and 10 g/min), it was observed that effective evaporation of the solvent was obtained such that there was little influence on the moisture level of the bed (Fig. 5). At these low wetting levels, the granule growth were primarily controlled by the amount of HPC added (Fig. 6). At the higher addition rate (20 g/min), wetting of the granules was much more apparent (Fig. 5), however it was not reflected in the growth kinetics and the addition of HPC controls granule growth (Fig. 6). This granulation behavior was consistent with the

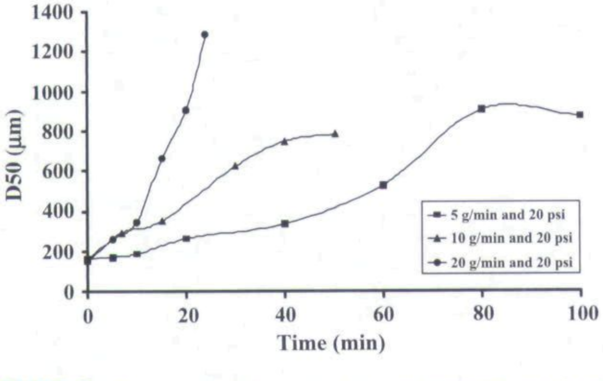

FIGURE 6 D_{50} Versus Time with Different Spray Rates for 8% w/w HPC Binder Solution.

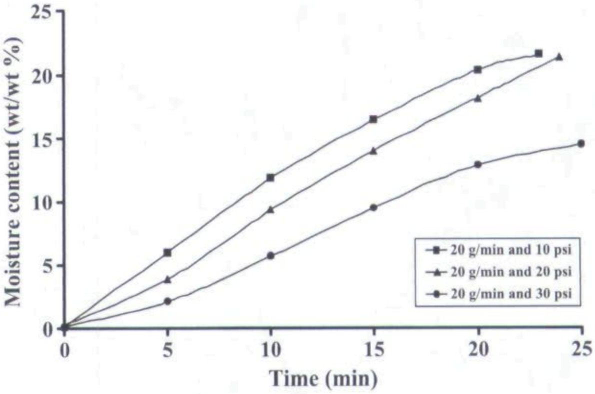

FIGURE 7 Moisture Content Versus Time for Different Atomization Pressures (8% w/w HPC Binder and Air Velocity Set at 8 m/s).

induction growth mechanism (Hapgood & Litster, 2003) observed earlier, where pore saturation was not the main factor affecting the granule growth rate, but rather the binder availability at the surface.

Effect of Atomization Pressure and Binder Droplet Size

Binder droplets have been reported to impact nucleation and growth of granules (Abberger & Seo, 2002; Schaefer & Worts, 1978b). Specifically, two nucleation mechanisms were identified as a function of the droplet and particle size ratio and enhanced moisture penetration into the granule: the immersion mechanism, where binder droplets are bigger than the particles to granulate, and the distribution mechanism, where binder droplets are smaller than the particles. The latter mechanism is generally dominant in fluid bed granulation because of binder atomization, which leads to the formation of nuclei by collisions between the surface-wetted powder particles. Since growth of the mannitol granules with HPC solution had shown an inductive granule enlargement behavior, little effect of the binder droplet size was expected on the granulation growth rate, the larger droplets being compensated by a larger number of the smaller droplets (Farid, 2003). Figures 7 and 8 present the wetting and granulation growth profiles, respectively, for a granulation prepared at 20 g/min and atomization pressures of 10, 20, and 30 psi. It could be observed that while atomization pressure had significant influence on the wetting profile, it had little influence on the granulation mechanism, and the growth profile remain unaffected by atomization pressure or droplet size. The change in wetting

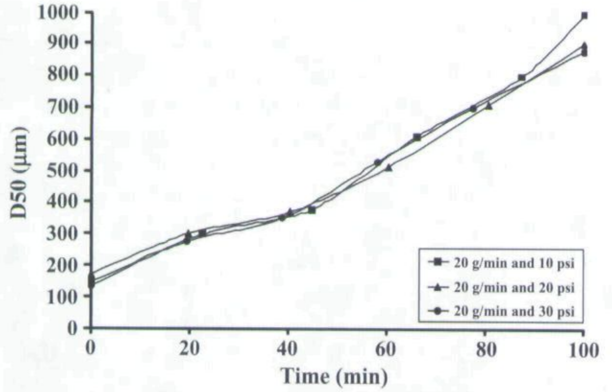

FIGURE 8 D_{50} Versus Time for Different Atomization Pressures at 20 g/min (8% HPC Binder and Air Velocity Set at 8 m/s).

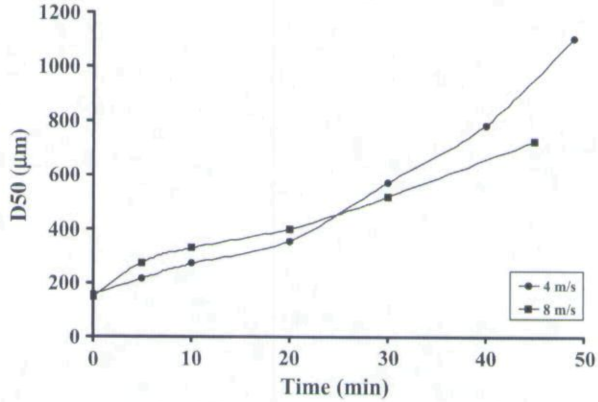

FIGURE 10 D_{50} Versus Time for Different Air Velocities (Binder Spray Rate = 10 g/min and Atomization Pressure = 20 psi, 8% w/w HPC).

behavior could be related to the droplet size. For a given binder solution, larger droplets enhance the moisture penetration into the granule, therefore hindering evaporation (Farid, 2003).

At a reduced binder addition spray rate of 10 g/min, the situation was somewhat reversed, i.e., atomization pressure or droplet size did not have a significant influence on the wetting profile, due to efficient drying, but the increase in pressure was shown to produce a somewhat smaller granule particle size (Fig. 9). As it had already been established that wetting has no influence on the granule growth at binder spray rate varying from 5 g/min to 20 g/min, it was believed that the effect of atomization pressure observed at lower spray rates was not related to wetting (droplet size) of the granules but rather to the increase in shear forces provided by the atomization air (Bemrose & Bridgwater, 1987) accentuating breakage and affecting the granulation growth rate. Moisture levels in the granulation affect the cohesion of the granules and balance the contribution of the granule breakage to the granule growth. This is in agreement with Kristensen et al. (1985) who had shown that moisture level is a controlling factor in final granule size. Liquid penetration increases the plasticity and hardness of the granules thereby reducing the agglomerates tendency to fracture up to a critical liquid saturation, where the moisture creates a lubrication effect that increases the breakage of the granules by attrition (Pepin & Simons, 2001; Takenaka & Kawashima, 1981; Verkoeijen & Gabriel, 2002). The results obtained by Verkoeijen and Gabriel (2002) demonstrated that granules have a critical liquid saturation where they are less affected by the shear forces. This helps to explain the superposition of the growth curves for 20 g/min, where the higher moisture content improved the granules resistance to atomization air shear forces. In comparison, the growth curves for 10 g/min, where the moisture content was at ~1% w/w (i.e., below the critical saturation), showed faster granulation with reduced atomization pressure due to reduced shear force acting on the granules. It should be noted also from Fig. 9 that attrition contribution to the overall growth rate became more important when the granules reached a certain size.

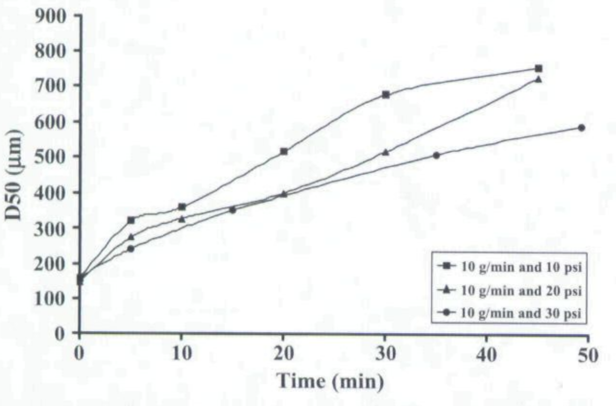

FIGURE 9 D_{50} Versus Time for Different Atomization Pressures at 10 g/min (8% HPC Binder and Air Velocity Set at 8 m/s).

Air Velocity

Figure 10 presents the data collected for granulation performed at a spray rate of 10 g/min and atomized at 20 psi, when the inlet air flow rate was decreased from 8 to 4 m/s. Although the granulation wetting became ~50 times more important on reducing the air velocity (see Tables 1 and 3, exp. #2 and 7), the granule growth profiles were very similar. The slight difference observed at the beginning of the granulation, where the growth rate was higher for the higher

TABLE 3 Summary of Granulation Physical Characteristics for the Different Processing Test

Batch	Total wetting (%)	Granule size-wet (μm)	Granule size-dried (μm)	Breakage on drying (%)	Bulk density (g/mL)	Tap density (g/mL)	Carr's index	Friability (%)
1	0.62	794	725	8.7	0.18	0.25	25.76	0.32
2	0.28	720	610	15.3	0.20	0.29	30.59	1.24
3	0.35	590	375	36.4	0.22	0.35	35.19	1.80
4	23.33	997	849	14.8	0.24	0.31	19.94	0.25
5	22.87	900	819	9.0	0.26	0.31	15.97	0.34
6	16.33	877	724	17.4	0.24	0.30	21.39	0.41
7	15.69	1100	966	12.2	0.23	0.29	21.55	0.66
8	1.13	874	513	41.3	0.25	0.34	24.98	1.72
9	10.167	435	405	6.9	0.28	0.34	19.44	0.28
10	3.2411	760	735	3.4	0.21	0.28	24.87	0.17
11	1.9085	820	710	13.4	0.17	0.26	34.61	0.20
12	1.4069	785	755	3.8	0.20	0.26	22.82	0.15

air velocity, was ascribed to the higher frequency and energy of collisions between granules (Iveson et al., 2001). After this initial growth period, the shear forces provided by process air velocity (Bemrose & Bridgwater, 1987) controls the granulation growth rate. As a result, the lower air velocity resulted in larger granules, similar to the observation made by Nienow and Rowe (1985) for non-deformable and surface-wet granules.

Effect of Inlet Air Dew Point

The inlet air dew point affects the solvent evaporation capacity of the air at constant temperature and has critical importance during the fluid bed granulation process. The effect of inlet air dew point on the mannitol fluid bed granulation wetting profile was significant with moisture level mostly below 0.5% w/w for an inlet air D.P. <2°C, compared to moisture level consistently well above 1% w/w at an inlet D.P. of 11°C (Fig. 11). However, since the granulation moisture content was still relatively low (likely below the above mentioned critical level), the increased moisture level helped to improve the granule plasticity, leading to slightly larger granules (Fig. 12). This was likely the result of a reduced contribution of granule breakage to the overall growth profile.

Breakage of Granules on Drying

Granules can break and wear due to either particle–particle and particle–walls collisions or compaction (Iveson et al., 2001). Jets grinding, bubbling, and splashing of ejected particles are additional factors

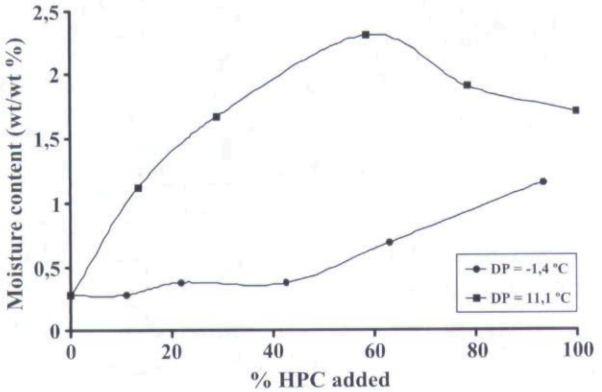

FIGURE 11 Moisture Content Versus HPC Added at Different Dewpoints (Binder Spray Rate=10 g/min and Atomization Pressure=20 psi, 8% w/w HPC).

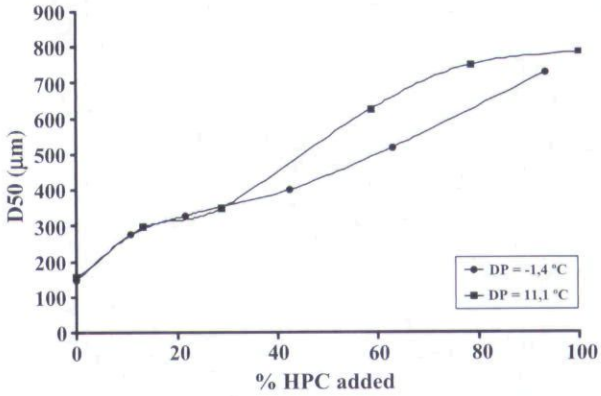

FIGURE 12 D_{50} Versus HPC Added at Different Dewpoints (Binder Spray Rate=10 g/min and Atomization Pressure=20 psi, 8% w/w HPC).

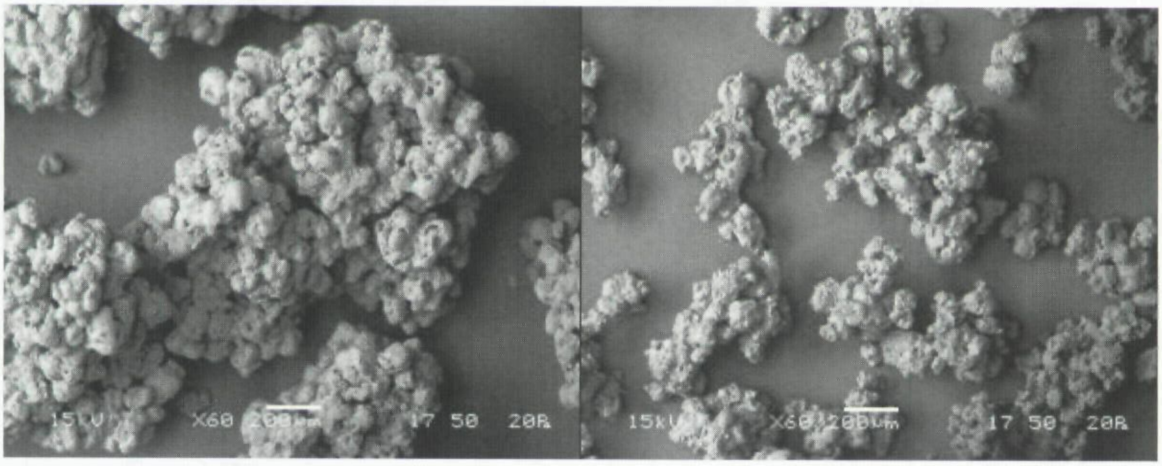

FIGURE 13 SEM Picture of Granules Produced Using a Binder Spray Rate of 20 g/min and 10 g/min, Respectively. Air Velocity 8 m/s, Atomization Pressure 20 psi, and 8% w/w HPC Binder Concentration.

contributing to the breakage of granules in a fluid bed granulator (Kristensen et al., 1985). Table 3 shows the level of breakage on drying (i.e., after the addition of binder solution has been terminated) for the different granulations. Increasing the atomization pressure from 10 to 30 psi (experiment 1 to 3) had a clear effect with the breakage increasing from 8.7% to 36.4%. The comparison of experiment 2 (8 m/s) and 7 (4 m/s) demonstrated that process air flow velocity had a smaller impact on the extent of breakage, 15.3% and 12.2%, respectively. This is in agreement with the results obtained by Werther and Xi that showed bubbling contribution to breakage is negligible when the atomization air velocity is high (Werther & Xi, 1993). Experiment 8 (5 g/min), 2 (10 g/min), and 5 (20 g/min) demonstrated the effect of binder spray rate or wetting on the breakage of agglomerates. These values were 41.3%, 15.3%, and 9.0%, respectively. The granules produced in experiment 8 broke more easily than those from experiment 2, even though the moisture content was relatively similar. Lower spray rate decreased binder availability to form liquid bridges between particles which imply weaker cohesive forces involved in forming the granules (Schaefer & Worts, 1978b) and promote breakage.

Effect of Processing Parameters on Final Granules Characteristics

Friability

Granules must be strong enough to survive handling. One measure of granule strength is friability. Since granule strength tends to increase with the formation of more liquid bridges, conditions that favor the formation of liquid bridges should reduce friability. From experiments described in Table 3, it could be seen that an increased binder spray rate, a decrease in atomization pressure, a decrease in air velocity, and an increase HPC binder concentration were important factors that contribute to reduce granule friability.

Flow Behavior

The Carr's index values provided some indication of the flow behavior of the various granulations obtained during this investigation. For example, granules that were relatively dry during the process (experiments 1, 2, 3, 8, 11, and 12) displayed poor flow as indicated by high Carr indexes values. Granules that were maintained wet during processing (Binder spray rate of 20 g/min, or at lower process air velocity 4 m/s), had improved flow characteristics. This is likely related to the granule size and morphology. Wet granulation conditions provided larger granules that resisted attrition and presented a smoother surface (Fig. 13). The increase in mean diameter of the granules resulting from increasing binder concentration had a predictable improvement on granule flow properties as measured by Carr's Index (Table 3).

Morphology

As mentioned above, granules produced by spraying at 20 g/min appeared much smoother than those produced by spraying at 10 g/min (Fig. 13). This was attributed to the high moisture content of the bed during granulation. At the higher spray rate, granules were evenly coated with the HPC binder solution and more substantial liquid bridges were formed. Granules produced at lower spray rate (10 g/min) had many rough edges, likely because of reduced HPC solution coverage. The different surface aspects likely also contributed to the change in flowability observed.

CONCLUSION

The fluid bed granulation is a fairly complex process that can be divided in three rate steps: 1) wetting and nucleation, 2) consolidation and growth, and 3) breakage and attrition. Process parameters and physicochemical properties of the binder and granule substrate can have significant impact on these rate processes and, consequently, the physical properties of the granules formed. This study investigated the influence of certain process variables and HPC binder solution physicochemical properties on binder atomization processes and fluidized bed granulation of mannitol with special attention to the relationship between wetting and the granule growth profile.

It was shown that the mannitol granules growth present an induction growth mechanism when a viscous and not rapidly absorbed binder (HPC) was used as a binder. The growth mechanism depended mainly on the interrelated contribution of HPC added and bed moisture content. The amount of HPC added via the solution mainly controlled the nucleation and growth process, while the bed moisture level was important in reducing breakage and attrition during both the granulation phase and the drying phase. It is believed that above a certain bed moisture threshold, the granulation process is almost solely controlled by the amount of HPC added, suggesting that processing time can be reduced by increasing the HPC binder concentration of the solution without producing significant variations in the granulation growth rate and final product characteristics. The growth rate, especially below a bed moisture threshold, and more importantly the final granule size, was affected by the granule breakage during granulation and drying. The velocity of atomizing air was identified as the major source of granule breakage and its impact could be reduced by adequate bed moisture level or reducing atomization pressure during operation.

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