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Study growth kinetics in fluidized bed granulation with at-line FBRM

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Abstract

In this study, a novel at-line focused beam reflectance measurement (FBRM) technique was developed to investigate granule growth in a fluidized bed granulation (FBG). The chord length distribution (CLD) measured by the FBRM was used to represent granule particle size distribution (PSD). Through a systematic study, it was proved that the trends of the chord length measured by the at-line FBRM technique were identical to those measured by a laser diffraction instrument and sieve analysis in spite of different measurement mechanisms. The portable at-line FBRM technique was successfully applied to a granule growth kinetics study for a fluidized bed granulation performed in a Glatt GPCG-1 granulator. Granule size evolution was clearly exhibited by the at-line FBRM. Spray rate was found to be the most significant factor on the granule growth compared with the other two factors: binder solution concentration and intra- to extra-granular microcrystalline cellulose (MCC) ratio for the formulation studied in this work. The CLD evolution measured by the FBRM confirmed that the granule agglomeration was mainly dominated by the binder on the granule surface. The at-line FBRM enables us to select appropriate process parameters and effectively control the fluid bed granulation process.

Keywords: Fluidized bed granulation; FBRM; Granule growth; Particle size distribution

1. Introduction

Fluidized bed granulation is a process by which granules are produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed. Although the fluidized bed granulation is widely used to produce coarse solid particles in pharmaceutical, food and chemical industries, it continues to be one of the least understood processes like most solid-handling operations (Litster, 2003). The fluidized bed granulation is a complicated process involving multiple process variables and three simultaneous rate processes: (1) wetting and nucleation, (2) consolidation and growth, and (3) breakage and attrition. Hence, the establishment of dynamic granule growth kinetics is essential for gaining an insight into the basic mechanism of the fluidized bed granulation (Menon et al., 1996; Cryer and Scherer, 2003; Hemati et al., 2003). The fluidized bed granulation has been extensively studied and the most widely studied granule properties in the literature are: geometric mean granule size, granule size distribution, angle of repose, loose and tap density, and loss on drying (Wan and Lim, 1991; Gordon, 1994; Lipps and Sakr, 1994; Liu et al., 1994; Merkku et al., 1994; Miyamoto et al., 1995; Vojnovic et al., 1995; Justin and Yliruusi, 1996; Watano et al., 1996a,b,c). There are few studies reported in the literature on the granulation kinetics because of the lack of appropriate techniques. Therefore, a robust and precise granule size monitoring technique is required.

Various techniques such as sieve analysis (Washington, 1992), laser diffraction (Etzler and Sanderson, 1995; Etzler, 2004) and image analysis (Russ, 1999; Laitinent et al., 2003) are available for particle size distribution (PSD) measurement. However, these techniques are offline measurements and require sample preparation. An increasingly popular particle size analysis technique is Mettler-Toledo's focused beam reflectance measurement (FBRM) (Ruf and Worlitschek, 2000; Heath et al., 2002; Worlitschek and Mazzotti, 2003; Kougoulos et al., 2005). The FBRM uses a focused beam of laser light that scans across particles passing in front of the probe window to measure chord length distribution (CLD). The probe is typically immersed in a flowing suspension of particles. When the beam hits a particle, it is reflected and propagated back through the probe. The reflection duration is then processed by the device electronics and the corresponding chord length is calculated as the product of time

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of the beam crossing the particle and the beam velocity. The scan speed of FBRM is adjustable from 2 m/s to 8 m/s, which is very fast and adequate to collect enough chord length data even in a very short time period. Advantages of the technique include ease of use, little maintenance or calibration requirement and capability of on-line and in situ measurements in systems with high solid concentration. The FBRM has a wide range of applications in crystallization (Farrell and Tsai, 1995; Barrett and Glennon, 1999; Worlitschek and Mazzotti, 2003; Kougoulos et al., 2005), flocculation (Williams et al., 1992; Heath et al., 2002), petroleum and grinding (Alfano et al., 2000). Although the FBRM is a relatively straightforward method, no studies on its application to the granulation kinetics have been reported in the literature yet. In the pharmaceutical industry, the recent attempts to use FBRM to monitor granulation in-line were not successful. From our experience, a major obstacle is that the FBRM probe window is very easily fouled by fine powders during spray. To solve this problem, an at-line FBRM technique was developed. Another advantage of the at-line FBRM is that it is portable and can be applied to any granulations without implementation issues.

What the FBRM instrument measures is particle's chord length distribution (CLD), which is a function of the actual particle size distribution. For most applications, the distinction between the particle chord length and actual size is not important. Relevant process variables may be correlated directly with chord length, and the actual particle size is not specially required. Based on this fact, the FBRM can be applied to granulation process studies and the chord length can be used to qualitatively represent the granule size without converting it to the actual particle size.

This work attempts to systemically study the at-line FBRM technique and apply it to a granule growth kinetics study for a fluidized bed granulation process.

2. Experimental

2.1. At-line experimental set-up

A FBRM S400 probe (Mettler-Toledo Inc., Columbus, OH) was used in this study for the at-line granule size measurement. The laser wavelength of the FBRM is 780 nm and the beam spot is approximately 3 μm at the focal point. The schematic of the experimental set-up is shown in Fig. 1. The length of the probe is 20 cm. A small quantity of granule samples (2 g used in the current granulation) withdrawn periodically during the granulations were added to a 100 ml beaker containing 50 ml anti-solvent silicone oil which is also typically used in laser diffraction method for particle size measurement. The probe was put into the suspension at an angle of 45° as shown in Fig. 1. It was found that granules were best presented to the probe window and the optimum signals were obtained at this angle. A 3.5 cm magnetic stir bar was used to gently agitate the suspension composed of silicone oil and the granules. A rotation speed of 15 rpm, at which the granules were not broken down in silicone oil, was used in all measurements. The CLDs of the granules were collected by the FBRM as they passed through the sapphire window of the probe. The granules were suspended

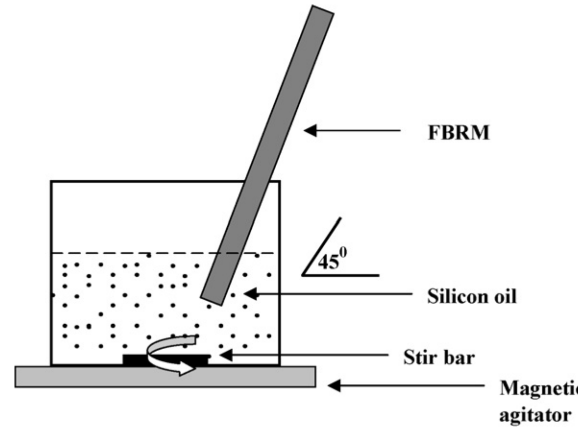

Fig. 1. Schematic of the at-line FBRM set-up for granule size measurement.

and dispersed uniformly in the silicon oil. This was confirmed by the constant CLDs obtained when the probe was placed at different locations in the suspension.

Generally, the reproducibility of FBRM results is satisfactory. To reduce variation and maintain comparable results, the rotation speed of the stir bar and the amount of samples added into silicone oil should be kept constant in measurements. A fast stir bar speed may cause the granules to break down by the aggressive shear forces.

2.2. Methods

The experiments were performed in a 1 kg scale top-spray batch fluidized bed granulator, Glatt GPCG-1 (Glatt Air Techniques Inc., Ramsey, NJ) using a proprietary formulation under development by Johnson and Johnson Pharmaceutical Research and Development (JJPRD). Microcrystalline Cellulose (MCC, Avicel® PH102, FMC BioPolymer, Newark, DE) was used as a filler in the formulation. A binder solution was sprayed onto the powder bed using a Schlick #940 nozzle assembled with a 1.2 mm liquid insert and a 2 mm air cap. The nozzle arm was placed on the upper spray port of the bed, facing downward. The granule samples were removed regularly from the bed during granulations and then rapidly analyzed by the FBRM for particle size distribution analysis. To validate the FBRM results, samples were also taken for laser diffraction and sieve analysis measurement. To study the relationship between the granule size and moisture, samples were taken for loss on drying (LOD) measurements by a Computrac moisture analyzer (Model MA-5, Arizona Instrument, Phoenix, AZ) as well.

The granule growth of the formulation used in this study was studied by the at-line FBRM technique. The effects of spray rate, binder solution concentration and intra- to extra-granular MCC ratio were primarily investigated because, for this new formulation, their effects on product quality were unknown. In this study, the efforts were focused on their effects on the granule growth kinetics and size. For this purpose, a two-level full factorial experimental matrix design was generated by a commercial DOE software, Design-Expert ®7.0 as shown in Table 1. This

Table 1
Three factors two-level full factorial design and responses

Run	Std.	Binder concentration[a] (%)	Spray rate[b] (ml/min)	MCC ratio[c]	Mean chord length at the end of spray (μm)	Mean chord length at the end of dry (μm)	LOD at the end of spray (%)
1	4	10	25	0	305.93	322.95	10.87
2	2	10	15	0	243.01	196.00	1.86
3	12	5	15	0	231.04	181.40	2.47
4	1	5	15	0	235.72	187.48	2.69
5	9	7.5	20	0.5	237.11	224.48	10.93
6	11	10	15	1	253.93	154.57	3.71
7	6	10	15	1	220.94	175.91	3.75
8	5	5	15	1	221.22	152.92	3.62
9	8	10	25	1	284.32	272.00	13.86
10	7	5	25	1	256.35	209.15	14.68
11	13	10	25	0	281.75	282.86	9.31
12	10	10	15	0	252.95	239.94	2.47
13	3	5	25	0	271.05	262.24	12.37

[a] Binder concentration: high = 10%; low = 5%.
[b] Spray rate: high = 25 ml/min; low = 15 ml/min.
[c] Intra- to extra-granular MCC ratio: high = 1:1; low = 0:1.

experimental matrix allows isolating the effects of each parameter. Four replicates were included in the current DOE design, allowing us to see the reproducibility of batches. The experiments were carried out sequentially based on the above design. The other process parameters including airflow rate, inlet air temperature, inlet air relative humidity, nozzle port size, nozzle position and atomization pressure were kept constant through the entire DOE study, as illustrated in Table 2.

3. Results and discussion

3.1. Evaluation of FBRM results

3.1.1. The CLD measured by FBRM

Fig. 2 is a typical CLD evolution measured by the at-line FBRM. Each CLD curve corresponds to the sampling time interval during the granulation. Fig. 2 (a) and (b) depicts the cumulative and frequency curves of the chord length of Run 1, respectively. It is evident that the CLD shifts to the right direction gradually, indicating the continuous granule growth. Diameters D_{10}, D_{50} and D_{90} obtained from Fig. 2(a) are presented in Fig. 3, clearly showing the granule growth kinetics. For Run 1, the similarity between the CLD at the end of dry (EOD) and at the end of spray (EOS) indicates that the granule strength was high and the granules were not broken down by attrition and collision during the drying stage.

Table 2
The controlled fluidized bed granulation process parameters in DOE study

Process parameter	Value
Loading in the bed	1 kg
Airflow rate	4.0 m/s
Inlet air temperature	60 °C
Inlet air humidity	35%
Atomization pressure	2 bar
Nozzle size	1.2
Nozzle type	Schlick (two-fluid)
Nozzle position	High
Shaking interval	30 s
Shaking period	7 s

The square weighted mean chord length is used by the FBRM to indicate the mean particle size, which is defined as

$$\bar{C} = \frac{\sum_{i=a}^{b} n_i M_i^3}{\sum_{i=a}^{b} n_i M_i^2}$$

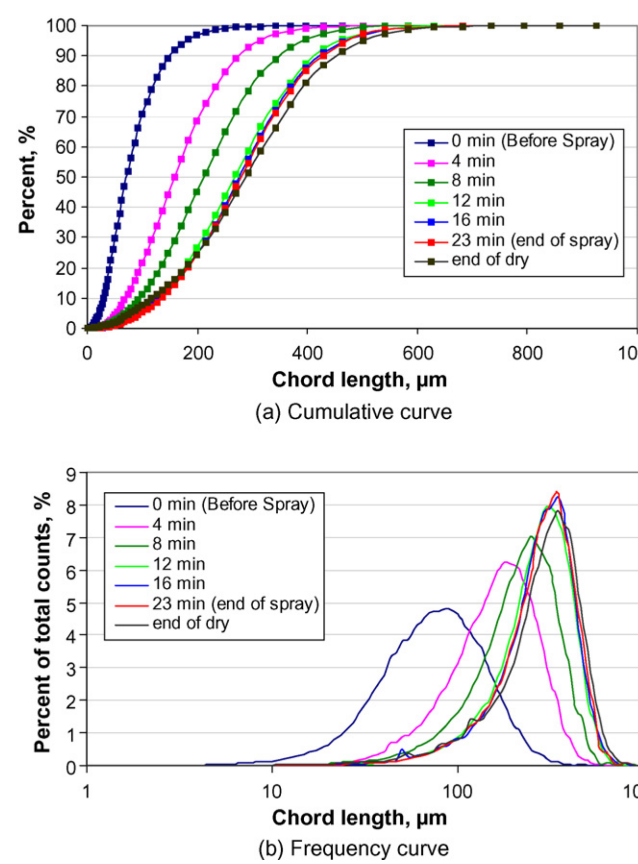

Fig. 2. CLD evolution measured by the at-line FBRM (Run 1).

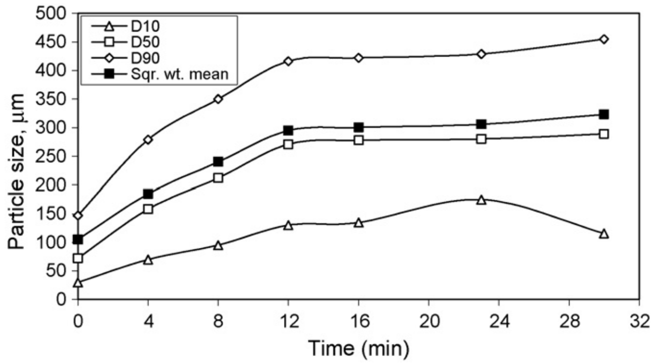

Fig. 3. D_{10}, D_{50}, D_{90} and square weighted mean chord length determined by the at-line FBRM (Run 1).

where $\bar{C}$ is the square weighted mean chord length; n_i the unweighted counts and M_i is the value of the midpoint of each channel. The square weighted mean chord length, depicted in Fig. 3, is different from the D_{50}, but they are similar in value and identical in trend. It should be noted here that the nomenclatures as chord length or mean particle size measured by FBRM used in this study, refer to the squared weighted mean chord length.

The at-line FBRM clearly presented the granule growth kinetics during the spray. This process knowledge provides not only the fundamental kinetics of granule agglomeration but also the possibility to effectively control the granule size by adjusting process parameters promptly.

3.1.2. Comparison of FBRM results with those of laser diffraction and sieve analysis

Fig. 4 compares the D_{10}, D_{50} and D_{90} measured by the FBRM with those measured by a laser diffractometer Coulter LS instrument (Model 13-320, Beckman Coulter Inc., Fullerton, CA). It was clearly demonstrated that, in spite of the difference in measurement mechanism, the trends of granule growth measured by both methods were identical. The FBRM measures the chord length of particles passing through a rotation beam whereas the Coulter LS instrument measures the diffraction patterns generated by laser light scattered by suspended particles. The distinctions in particle size value measured by these two methods were due to different mechanisms (Barrett and Glennon, 1999; Etzler and Sanderson, 1995; Heath et al., 2002). However, the trends of the particle size measured by them were similar by comparing the results of all batches in this study.

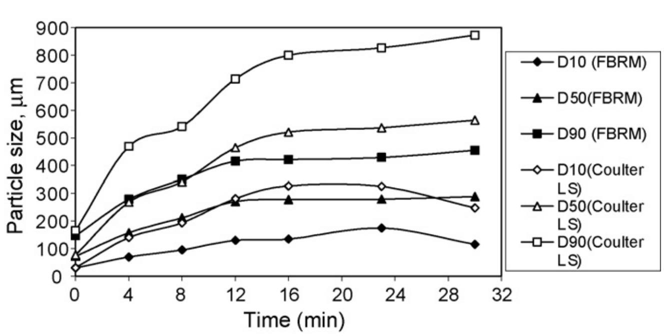

Fig. 4. Granule sizes measured by the FBRM and Coulter LS.

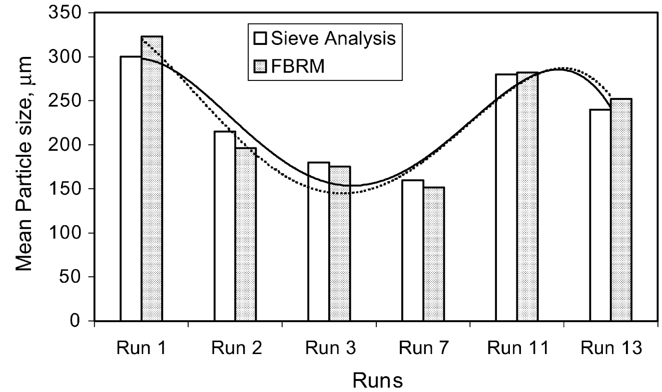

Fig. 5. Mean particle size of dry granulation measured by the FBRM and sieve analysis.

Fig. 5 compares the D_{50} obtained from a sieve analysis and the square weighted mean particle size measured by the FBRM. The results of dry granules of several batches were compared because sieve analysis only measures dry particles. The results shown in Fig. 5 are from different batches presented in Table 1. An identical trend in particle size was observed from the FBRM and sieve analysis results. The FBRM is based on a particle counting method, which assesses the size of individual particles and assembles the particle size distribution of a population from a large number of such measures. The sieve analysis belongs to an ensemble method, which assesses the properties of the entire distribution without considering individual particles. These two methods are based on different particle-sizing mechanisms; nevertheless the identical trend in particle size was obtained.

The actual particle size is very difficult to be expressed due to irregularity in particle shape and differences in measurement mechanisms. In this case, where precision is more important than accuracy, the CLD measurements are adequate to monitor the dynamic granule growth during granulation. In comparison to the Coulter LS method and sieve analysis, it was confirmed that the at-line FBRM is a sensitive and reliable qualitative technique in wet and dry particle size measurement.

3.2. Parameter effects on granulation

3.2.1. Effects of spray rate

The spray rate, a critical parameter to the formulation, affects granule size, bed moisture and product quality. Generally, increasing the spray rate enhances granule growth. However, Hemati et al. (2003) reported that the spray rate had no effects on the granule growth when it was lower than a critical value. For the current formulation, the effects of the spray rate and its significance compared with the other two factors needed to be investigated. Fig. 6 compares the granule growth of the two runs with the same binder concentration and intra- to extra-granular MCC ratio but with different spray rate. FBRM results revealed that, in both cases, the granule growth was obvious by comparing the CLDs before and after spray. For the run at the lower spray rate, the granule growth ended in 12 min. However, at the higher spray rate, the granule growth was continuous and sustained

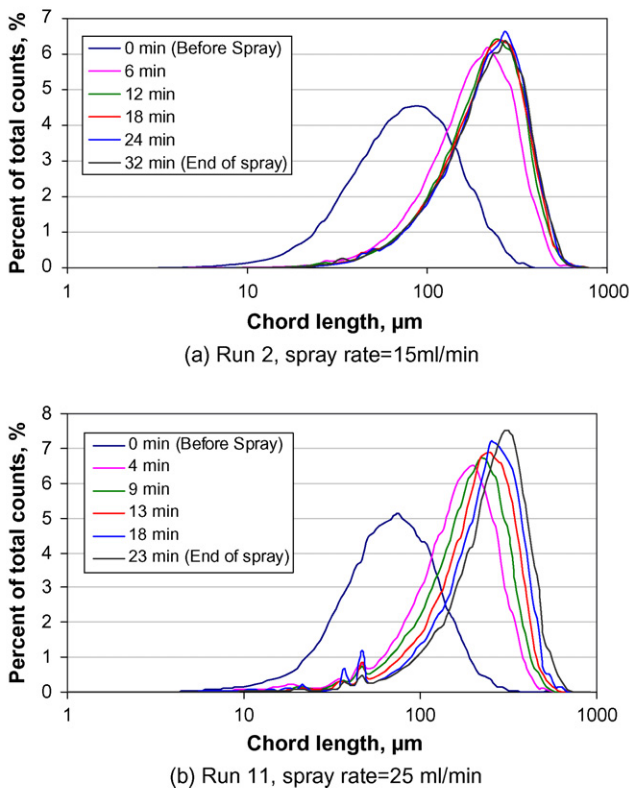

Fig. 6. Effects of the spray rate on the granule growth binder concentration = 10%; intra- to extra-granular MCC ratio = 0:1.

through the entire spray period and larger granules resulted, as shown in Figs. 6 and 7. Generally, the granule growth increased with the spray rate because of its significant enhancement on droplet size and moisture content.

Granule growth rate, which is usually used to express the growth, is defined as

$$X\ (\%) = \frac{d_t - d_0}{d_0} \times 100 \quad (1)$$

where d_t and d_0 are the granule size at time t and the initial average particle size, respectively. The granule growth rate is presented in Table 3, from which it can be seen clearly that a period of rapid growth, followed by a period of little growth. As shown in Table 3 and Fig. 6, the granule agglomeration occurred

Table 3
The granule growth rate at two spray rates

Time period	High spray rate (25 ml/min)	Low spray rate (15 ml/min)
<16 min	1.72	1.54
>16 min	0.147	0.061
Entire spray	2.12	1.71

primarily prior to 12 min in the spray, exhibited by a significant shift of the CLD to the right direction in Fig. 6 and a greater growth rate presented in Table 3. Thereafter, the CLD changed slightly and the growth rate was very small, indicating no significant growth. From the CLD evolution, it appeared that this was true at both high and low spray rates for the current formulation. The explanation to this phenomenon is that the binder was wet, spreading on the granule surface at the beginning of the spray, so the growth was significant. As the granulation progressed, it is assumed that the surface of the granules became dry because the binder was deposited into the pores inside the granules. In addition, the granules became large and were more easily broken down by attrition (Reynolds et al., 2005). These two factors made the granule size enlargement not evident in the latter period. This granulation behavior indicated that the binder on the granule surface was the governing factor on the granule growth rate.

Fig. 8 shows the profiles of the granule moisture content and mean granule size. The left and right vertical axis stands for the mean chord length and moisture content LOD, respectively. The point at which the LOD starts to decrease is the end of spray (EOS). As demonstrated in Fig. 8, the granule growth increased with the granule moisture content. For Run 2 (at the lower spray rate), both granule size and moisture did not increase significantly after 12 min. The attrition during the drying led the granule size to decrease further. For Run 11 (the higher spray rate), the granule moisture kept increasing and resulted in the larger granule size. The granules were not crushed to a smaller size by the attrition and collision during the drying.

3.2.2. *Effects of intra- to extra-granular MCC ratio*

MCC is widely used in wet-granulations where it prevents overrunning granulation end-point. Increasing the intra-granular

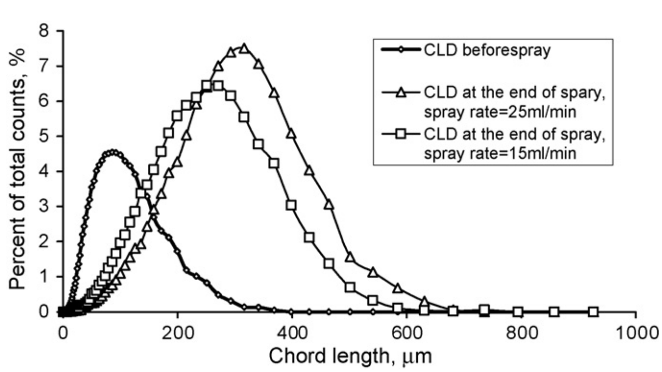

Fig. 7. Effects of the spray rate on the CLD of granules at the end of spray (EOS) (Run 2 and Run 11).

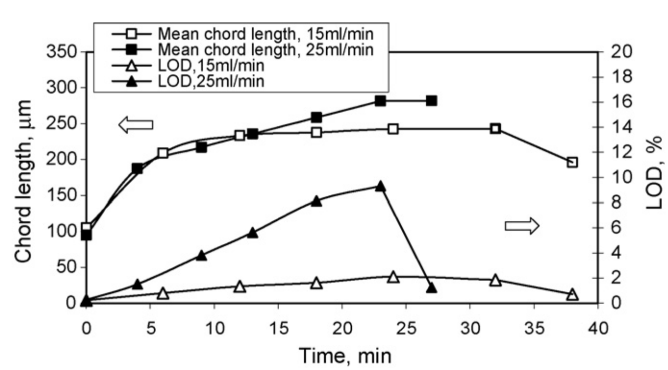

Fig. 8. Effects of the spray rate on the mean chord length $\bar{C}$ and moisture (LOD) (Run 2 and Run 11).

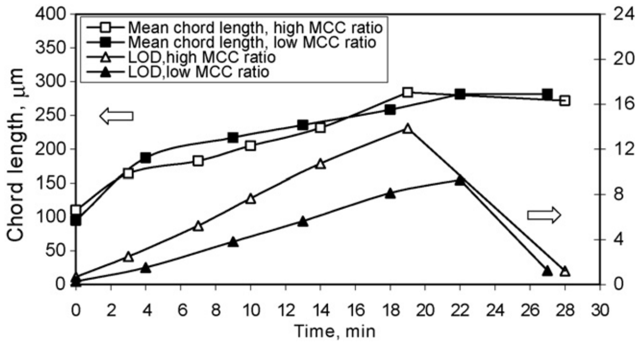

Fig. 9. Effects of the intra- to extra-granular MCC ratio on the mean chord length $\bar{C}$ and moisture (LOD) (Run 9 and Run 11).

MCC ratio can reduce the possibility of the segregation occurred in blending and compression steps, but the compactibility of tablets is generally decreased. For the current formulation, it is critical to determine how to distribute MCC intra-granularly and extra-granularly and investigate the effects of the intra- to extra-granular MCC ratio on the granule size. Fig. 9 shows the effects of the intra- to extra-granular MCC ratio on the granule size and moisture content. The experiments were performed with different MCC ratios but at the same spray rate (25 ml/min) and binder concentration (10%). Both runs revealed similar granule growth kinetics and size. As shown in Fig. 9, increasing the intra-granular MCC significantly increased the granule moisture because water could be easily absorbed by the MCC. Usually, the granule growth is governed by the moisture content. However, in this case, the higher moisture content did not contribute to the granule growth. An explanation could be that the moisture absorbed by the MCC may have penetrated into the pores of granules and did not spread on the granule surface to form nuclei. This fact disclosed that pore saturation was not the main factor affecting the granule growth rate, but rather the availability of binder on the surface (Hapgood et al., 2003).

3.2.3. Effects of binder concentration

Fig. 10 shows the granule growth and moisture content of the two runs with different binder concentrations but the same spray rate and intra- to extra-granular MCC ratio. The kinetics of the granule growth and moisture content were similar under both binder solution concentrations. In the current work, the binder solution concentration was found not as influential as the spray rate on the granule growth. The binder solution concentration has profound effects on the granule growth by affecting moisture content, droplet size distribution and the stickiness of the binder. Theoretically, increasing the binder solution concentration decreases the granule moisture content and increases the droplet size. Decreasing the granule moisture reduces the granule size whereas increasing the droplet size promotes the granule size. These two opposite factors acting together determine the effects of the binder solution concentration on the granule growth. Bouffard et al. (2005) pointed out that the granule growth rate was dictated mainly by the amount of binder solution independent of binder solution concentration. For the current formulation, this was true at a lower spray rate. From Fig. 10, the granule size and growth were independent of binder solution concentration at a lower spray rate. However, the CLD results showed that the binder solution concentration influenced the granule size at a higher spray rate, but not as significantly as the spray rate did. As shown in Fig. 11, the higher binder concentration increased the granule size at a higher spray rate 25 ml/min by comparing Run 9 and Run 10.

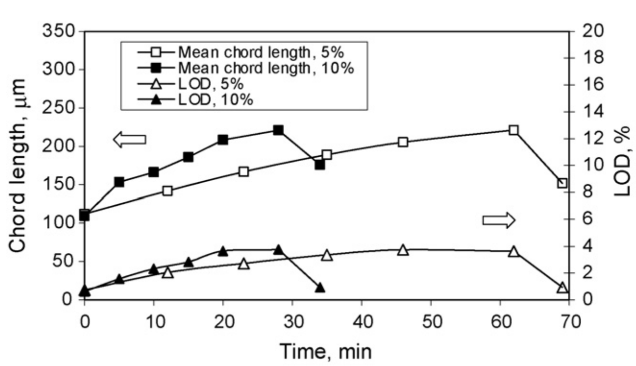

Fig. 10. Effects of the binder concentration on the mean chord length $\bar{C}$ and moisture (LOD) (Run 7 and Run 8).

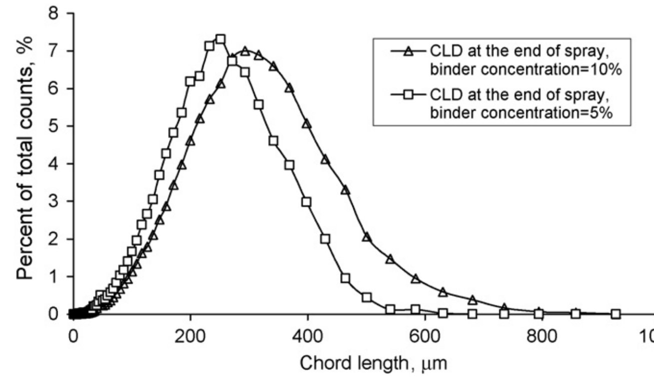

Fig. 11. Comparison of the CLD at the EOS at the spray rate of 25 ml/min (Run 9 and Run 10).

3.2.4. ANOVA analysis

The above discussions have isolated the effects of each factor. For the statistical significance, an analysis of variance (ANOVA) was performed. All the responses including the mean chord length and LOD at the EOS, and the chord length at the EOD is listed in Table 1. Fig. 12 shows the Pareto chart, illustrating the relative significance of factors on the granule size at the

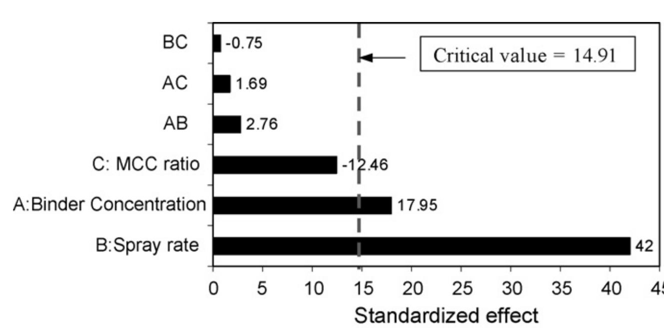

Fig. 12. Standardized Pareto chart for the granule size of the EOS.

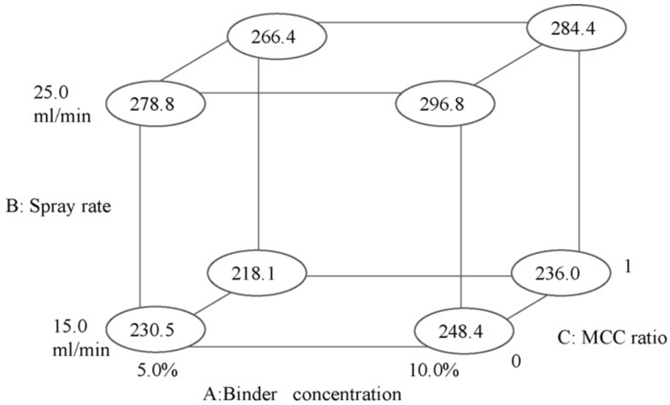

Fig. 13. Cubic graph of the effects of the binder concentration solution, spray rate and the intra- to extra-granular MCC ratio on the mean chord length $\bar{C}$ at the EOS.

end of spray. The negative value means that the granule size decreases with that factor. The vertical dashed line represents the critical *t*-value at the $P = 0.05$ significance level. The effects above this line are regarded as significant. The effects that fall below this line are not considered significant. Pairs of letters represent the interaction between process variables. Three two-way interactions were found to be no statistical significance. The Pareto analysis revealed that the spray rate was the most significant factor on the granule size at the EOS. Although the binder concentration was also considered as a significant factor, it was not as influential as the spray rate. *P*-value calculated by ANOVA represents the level of significance. Sensitive process parameters are those whose *P*-values are small ($P \leq 0.05$). The *P*-values of the spray rate, binder concentration and intra- to extra-granular MCC ratio obtained from ANOVA were 0.0004, 0.0259 and 0.0976, respectively. Therefore, the spray rate was the most significant factor on the granule size.

Fig. 13 is the cube plot of the predicted granule size (chord length) as a function of the three factors. The height, length and width of the cube stand for the spray rate, binder solution concentration, and intra- to extra-granular MCC ratio, respectively, as shown in Fig. 13. Based on ANOVA analysis, the combinational effects of these three factors on the granule chord length are exhibited by this cube plot. Given a certain spray rate, binder solution concentration and intra- to extra- granular MCC ratio, the corresponding chord length of granules can be easily determined from Fig. 13. For the current formulation, the granule size can be predicted and effectively controlled based on this cube plot.

4. Conclusions

Through systematic study, the portable at-line FBRM technique developed in this study was proved to be a useful technique in granulation kinetics measurement. By comparing with the Coulter LS and sieve analysis methods, the CLD measured by the FBRM could qualitatively represent actual particle size. Although distinctions in the expression of the actual particle size existed, the particle size distributions measured by these three methods were identical in trend.

The at-line FBRM has been successfully applied to the granule growth study for a new formulation. The effects of the three critical parameters on the granule growth were clearly presented by the CLD evolution measured by the at-line FBRM. Through an ANOVA analysis, it was found that the spray rate was the most significant factor on the granule growth. The binder solution concentration also presented influence on the granule growth, but, statistically, not as significant as the spray rate. The intra- to extra-granular MCC ratio increased the granule moisture significantly but played no influence on the granule growth. The CLD evolution demonstrated that, in most cases, a period of rapid granule growth was followed by a slight growth period. This phenomenon confirmed that the granule growth mechanism was dictated by the binder on the granule surface, not by the pore moisture.

As a PAT tool, the portable and non-process-invasive at-line FBRM technique can be applied to high shear granulations and other wet and dry powder size characterizations as well. The at-line FBRM technique supplies more process knowledge immediately and provides the opportunity to effectively control the granule growth.

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