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Controlling granule size by granulation liquid feed pulsing

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Abstract

The effects of inlet air humidity, granulation liquid feed rate and granulation liquid feed pulsing on the particle-size distribution of final granules were studied in a laboratory scale fluid-bed granulator using a central composite study design. The factors examined were modelled using three different particle-size measurement techniques (sieve analysis, laser light diffraction and the spatial filtering technique). Best goodness of fit ($R^2 = 0.94$) and goodness of prediction ($Q^2 = 0.90$) values were obtained using particle-size results of the spatial filtering technique. Increasing inlet air humidity and granulation liquid feed rate resulted in greater median granule size, as expected. When pulsing (interruption of granulation liquid feed in predetermined sequences) was used, the median granule size decreased clearly. This effect was strong, especially with high inlet air humidity and rapid liquid feed rate processes. Granulation liquid feed pulsing is an effective way to modify the particle size of final granules. Pulsing can be used as a controlling tool to compensate for excessive moisture content in the granulation process.

Keywords: Fluid-bed granulation; Particle-size distribution; Granule growth; Process analytical technology (PAT)

1. Introduction

The pharmaceutical industry has a growing interest in achieving more robust, efficient and controlled processes in production. Granulation is one of the key unit processes in pharmaceutical solid dosage form production. Among the various granulation techniques, fluid-bed granulation is one of the most frequently used. Mixing, wetting, granule growth and drying all occur in the same equipment and simultaneously. By utilizing design of experimental studies, the effects of critical material and process parameters on critical quality attributes can be understood. This is also encouraged by recent guidelines (International Conference on Harmonisation (ICH) Q8, 2005; Food and Drug Administration (FDA), 2004).

Fluid-bed granulation is a complex process with many interrelated process variables. It is influenced by raw material characteristics, process variables and equipment design. Systematic studies of granule growth mechanisms and the role of different factors in the fluid-bed have been performed since the 1970s (Schæfer and Wørts, 1977, 1978a,b) and complemented quite recently (Wan et al., 1992; Rohera and Zahir, 1993; Watano et al., 1995, 1996; Schaafsma et al., 2000; Bouffard et al., 2005; Abberger, 2001; Hemati et al., 2003; Schinzinger and Schmidt, 2005).

Granule size (GS) is the main characteristic that has been examined (Faure et al., 2001). Previously, sieve analysis was the most frequently used method for determination of the particle size of final granules, but recently laser diffraction and other optical methods have been increasingly utilized. The measuring principle and algorithms used for the particle-size calculation influence the results. The spatial filtering technique (SFT) is a quite new method that determines the chord length of each particle passing through the laser light beam (Petrak, 2001). It is designed mainly for in-line particle-size determination, but it can also be used for rapid at-line or off-line measurement, e.g. for granules.

Sampling can be a major source of error in particle-size results, because the sample volume is usually very small compared with that of the entire batch. In addition, segregation by size difference is very likely to occur in fluid-bed processes, especially when larger granules are present (Wormsbecker et

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al., 2005; Hoffman and Romp, 1990). Hence, most effective practices for sampling and sampling devices should be used for minimizing sampling-related errors (Shekunov et al., 2007).

The fluid-bed granulation process is greatly affected by water in both vapour and liquid form. Wetting of particles is needed to form liquid and solid bonds between the particles that enable the growth of granules (Kristensen and Schaefer, 1987; Kristensen, 1988). However, if the moisture in the process is too high, granule growth can be excessive and in extreme cases the bed can even collapse (Westrup, 1996; Schaafsma et al., 1999), due to the poor fluidizing properties of the over-wetted mass. Lipsanen et al. (2007) recently studied the effects of various relative humidity (RH) levels and fluidization modes on the particle-size of finished granules.

The use of pulsing (i.e. interrupting the granulation liquid feed for predetermined time sequences) in the fluid-bed process has been little addressed, although it influences the moisture level in the process. Schaafsma et al. (1999) found that short spraying periods (3–30 s) affected the bed moisture level but did not influence the final GS of lactose when the same amount of granulation liquid was sprayed.

The aim of the present study was to evaluate whether pulsing of the granulation liquid feed is a process adjustment tool that can be used against excessive moisture levels in the fluid-bed granulation process. In addition, the performance of three particle-size analysis methods was compared for final GS determination.

2. Materials and methods

2.1. Materials

Each batch consisting of 2.0 kg theophylline anhydrate (200 M, BASF Aktiengesellschaft, Ludwigshafen, Germany) and 2.0 kg α-lactose monohydrate (200 M, DMV International GmbH, Veghel, The Netherlands) was granulated, using 2 kg of 7.5% aqueous binder solution of polyvinylpyrrolidone (Kollidon K-30; BASF).

2.2. Manufacturing process

The granulations were performed in an automated bench-scale fluid-bed granulator (Glatt WSG 5; Glatt GmbH, Binzen, Germany). The instrumentation is described in detail by Rantanen et al. (2000). The inlet air RH of the process air was modified using a humidifying system (Defensor Mk4; Brautek Oy, Espoo, Finland). The RH of the inlet air was measured from the inlet air duct before the heating element. The atomization pressure was 0.1 MPa and the nozzle height set to 45 cm from the distributor plate. The inlet air temperature was 40 °C during the mixing and spraying phases and was raised to 60 °C during the drying phase. The inlet airflow rates were adjusted to 0.04 m^3/s and 0.08 m^3/s for the mixing and granulation/drying phases, respectively. A mixing time of 2 min was used in all batches. The final moisture content of the granules, measured by loss-on-drying (Sartorius Thermocontrol MA 100; Sartorius, Göttingen, Germany), was not more than 1.1% in all batches.

Table 1
Design of experiments

Batch	Air humidity	Granulation liquid feed rate	Granulation liquid feed pulsing
1	−1	−1	−1
2	1	−1	−1
3	−1	1	−1
4	1	1	−1
5	−1	−1	1
6	1	−1	1
7	−1	1	1
8	1	1	1
9	−1	0	0
10	1	0	0
11	0	−1	0
12	0	1	0
13	0	0	−1
14	0	0	1
15	0	0	0
16	0	0	0
17	0	0	0

2.3. Experimental design

A central composite face-centred design (CCF) with three mid-point repetitions was used in this study. Inlet RH, granulation liquid feed rate and granulation liquid feed pulsing were studied at three levels as illustrated in Table 1. The inlet air humidity levels were >13 g/m^3 (high), 7–12 g/m^3 (medium) and <6 g/m^3 (low). The granulation liquid feed rate values were 90 g/min, 70 g/min and 50 g/min. Granulation liquid feed pulsing was initiated after half of the total liquid amount (2000 g) was sprayed. The granulation liquid feed was interrupted for 1 min every 2nd minute (50% pause time), every 3rd minute (33% pause time) or not at all (0% pause time). The granulations were performed in randomized order.

2.4. Physical characterisation of granules

After manufacturing, all granules were poured through a 3.15-mm sieve to remove any clumps. All mass was fed through a sample divider (Fritsch Sample Divider Laborette 27, Idar-Oberstein, Germany) and representative samples obtained were used for analyses.

The particle-size distribution determination of the final granules was carried out, using sieve analysis, laser light diffraction and SFT. For sieve analysis, a 50 g sample was vibrated with an automatic sieve shaker (Fritsch analysette, Idar-Oberstein, Germany) for 5 min. The sieve analysis (range 71–2000 μm with $\sqrt{2}$ increment) was performed in triplicate and the mean value for mass median GS was determined.

The volume particle-size distribution was determined with laser light diffractometry (Laser Diffraction Particle-size Analyzer LS13 320; Beckman Coulter Inc., Miami, FL, USA), using Fraunhofer theory. A 20-ml sample was dispersed, using air as the medium in the Tornado Dry Powder System; the dispersion pressure was 4.7 kPa. A mean of three measurements was used for data analyses.

An SFT apparatus (Parsum® IPP 70; Gesellschaft für Partikel-, Strömungs- und Umweltmesstechnik GmbH, Chemnitz, Germany) was installed on a laboratory table and the sample was poured through the orifice (diameter 4 mm), using a funnel. The particles were dispersed by pressurized air. The number particle-size (chord length) distribution was transformed to volume particle-size distribution for data analysis.

Images of the final granules were recorded with a scanning electron microscopy (Zeiss DSM 962, Oberkochen, Germany). The flowability and the apparent volume values were determined according to the European Pharmacopoeia 5th edition. The Carr's Index was calculated from the bulk and tapped density values.

2.5. Data analysis and modelling

The 10% (d_{10}), 50% (d_{50}) and 90% (d_{90}) fractiles from the cumulative particle-size distribution were used for modelling. In addition, sieve fraction calculation was performed for to SFT and laser diffraction results. The independent variables (factors) in the model were: (1) humidity of the inlet air (Air), (2) granulation liquid feed rate (Liq) and (3) relative time of pauses in the granulation liquid feed (Pau). The average inlet air RH values measured during the process were used for the modelling. The responses included the median GS of the final product and the relative width (RW) of the size distribution:

$$\mathrm{RW} = \frac{d_{90} - d_{10}}{d_{50}} \quad (1)$$

Both responses were measured using three techniques. Modelling was performed by Modde for Windows (Version 7.0, Umetrics, Umeå, Sweden), using a stepwise regression technique. The effects of the process variables were then modelled, using a second-order polynomial fitting (Eqs. (2) and (3)). The models were simplified with a multilinear backwards, stepwise regression technique. The least significant terms were excluded from the model as long as the predictive power (Q^2) of the model increased.

$$\begin{aligned}\log[\mathrm{GS}(\mathrm{Air},\mathrm{Liq},\mathrm{Pau})] = {} & a_1 \times \mathrm{Air} + a_2 \times \mathrm{Liq} + a_3 \times \mathrm{Pau} \\ & + a_4 \times \mathrm{Air} \times \mathrm{Liq} + a_5 \times \mathrm{Air} \\ & \times \mathrm{Pau} + a_6 \times \mathrm{Liq} \times \mathrm{Pau} + a_7 \\ & \times \mathrm{Air}^2 + a_8 \times \mathrm{Liq}^2 + a_9 \\ & \times \mathrm{Pau}^2 + a_0 \end{aligned} \quad (2)$$

$$\begin{aligned}\mathrm{RW}(\mathrm{Air},\mathrm{Liq},\mathrm{Pau}) = {} & a_1 \times \mathrm{Air} + a_2 \times \mathrm{Liq} + a_3 \times \mathrm{Pau} \\ & + a_4 \times \mathrm{Air} \times \mathrm{Liq} + a_5 \times \mathrm{Air} \times \mathrm{Pau} \\ & + a_6 \times \mathrm{Liq} \times \mathrm{Pau} + a_7 \times \mathrm{Air}^2 + a_8 \\ & \times \mathrm{Liq}^2 + a_9 \times \mathrm{Pau}^2 + a_0 \end{aligned} \quad (3)$$

3. Results and discussion

3.1. Comparison of particle-size measurement techniques

In general, sieve analysis gave the highest median values and laser diffraction the lowest, while the SFT results were between these values (Fig. 1). The median GS range was 262–1033 μm, 160–863 μm and 106–695 μm for sieve analysis, SFT and laser diffraction, respectively. Batches 4, 8 and 12 had the greatest median values in all techniques, but the order correlation among the remaining batches varied, depending on the technique used. Since there were no substantial size differences between most of the batches, random variation may also have affected the results. For example, the 13 lowest median values measured by laser diffraction were all in the range 106–191 μm. SFT could also differentiate these batches much more clearly.

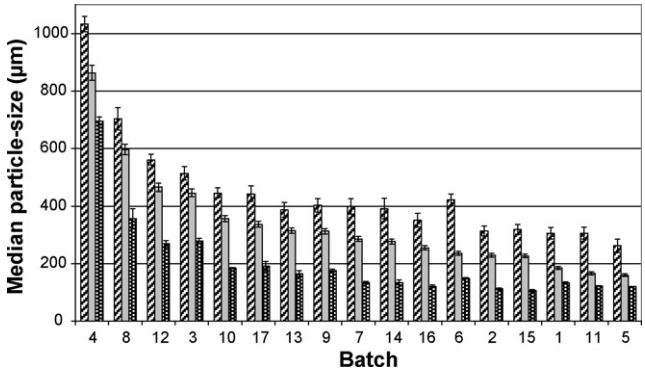

Fig. 1. Median granule size results ($n = 3$) of the batches, measured by sieve analysis (left column), SFT (middle column) and laser diffraction (right column) in descending order.

It was expected that some differences in results would occur among the analytical techniques studied, but the magnitude of the differences was unexpected, which necessitated more detailed evaluation of the particle-size distribution. Evaluation of the size fractions among the three particle-size methods revealed that the amount of particles under 180 μm was clearly smaller in the sieve analysis results and greater in the laser diffraction results than those of the SFT (Fig. 2). The most remarkable difference was obtained in the finest fraction (<90 μm).

The smallest particles were lacking in sieve analysis, probably due to the presence of high static electrical charges and van der Waals forces, which acted on the particles, effectively removing them from analysis. Thus, fine particles can adhere to each other and also to the surfaces of granules and sieve material, suggesting that not all fines pass through the correct sieve size during shaking and the results will be biased. According to SEM images, the granules were very different from batch to batch. For example, the batch 8 consisted of spherical granules, whereas quite loosely bound granules were mainly present in batch 5 (Fig. 3). In order to avoid the disintegration of the loose granules, a relatively short shaking time (5 min) was used.

When sieve analysis is used as a quality control technique, shaking time is usually validated (United States Pharmacopeia (USP) 30, 2007), but in the present type of developmental study it is not feasible because validation should be performed for every batch with a different GS distribution. Finally, sieve analysis gives results presented as a mass distribution, while the results of the other two methods were presented as volume particle-size distributions. The porosity and density of the granules are probably not the same in all size fractions, due to dissolving and recrystallization during the granulation process.

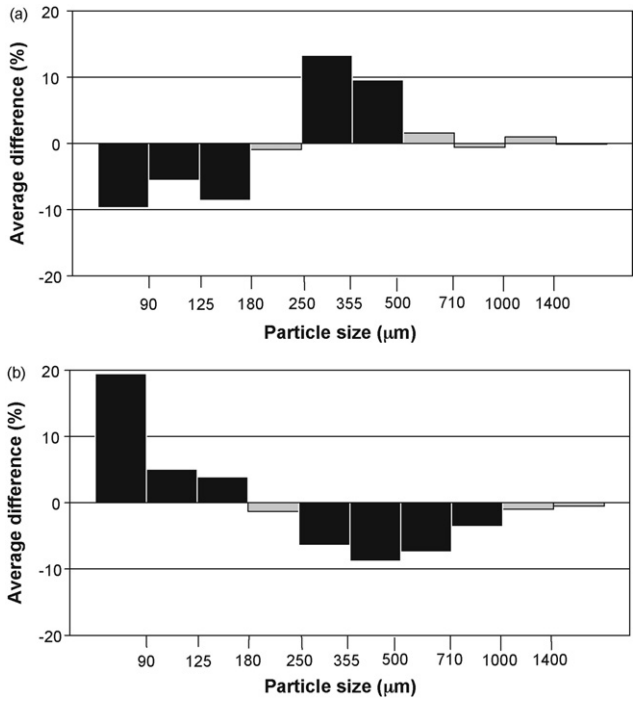

Fig. 2. Average absolute differences (%) of the sieve fractions between sieve analysis and SFT (a) and laser diffraction and SFT (b) of all batches. Black bars indicate the significant difference ($p < 0.05$).

The large number of fines in the laser diffraction results, compared with other techniques, was probably caused by the sample treatment. After dispersing by vacuum air the granules collide with the wall before entering to laser diffraction measuring area. Some granules may break or very fine powder form, due to attrition by these collisions. In SFT, pressurized air is also used as a dispersing agent, but the particles are passed directly through the measuring zone. The effects of mechanical stresses on the granules are probably formulation-dependent and should undergo more systematic future study.

3.2. Effect of the studied factors on particle-size distribution

3.2.1. Model goodness

The median GS and RW distribution values determined with the three techniques were used as responses for the studied factors (air RH, granulation liquid feed rate and granulation liquid feed pulsing). The numerical values of the coefficients, goodness of fit (R^2) and goodness of prediction (Q^2), are shown in Table 2. The SFT results for the median GS model gave the best R^2 and Q^2 values: 0.94 and 0.90, respectively. The R^2 values of the models calculated by sieve analysis and laser diffraction were also favourable, near to 0.9, but the predictive capability of these models was clearly lower than that of the SFT model. With all techniques air RH and granulation liquid feed rate had the strongest influence on the model. The effect of pulsing could also be seen as an important factor in the SFT and laser diffraction models, while its effect was smaller in the sieve analysis model. Only the SFT results gave somewhat acceptable R^2 and Q^2 values for the RW of the size distribution model.

The SFT results were the most consistent in the models and hence were regarded as the most reliable particle-size results among the three techniques studied. Consequently the SFT models were used in more detailed evaluation of the factors.

3.2.2. Effect of inlet air humidity and granulation liquid feed rate

Both air RH and granulation liquid feed rate strongly influenced the median GS, as expected (Fig. 4). When the air RH and/or liquid feed rate increased, larger granules were formed during granulation. This is in good accordance with results obtained in previous studies (Schæfer and Wørts, 1978a; Bouffard et al., 2005). The liquid feed rate can also be utilized for particle-size adjustment; e.g., when a median GS of 300 μm is targeted, the effect of inlet air RH increases from 20% to 70% can be compensated for by decreasing the liquid feed rate from 75 g/min to 60 g/min. The contour lines are slightly curved, which indicates that there is also some interaction between the factors.

3.2.3. Effect of granulation liquid feed pulsing

The effect of granulation liquid feed pulsing on median GS is illustrated in Figs. 5 and 6. When the pulsing is considered together with changing inlet air RH, a linear influence could be seen, whereas pulsing and liquid feed rate interacted slightly. The model offers great potential for GS prediction and adjustment. In Fig. 5 the granulation liquid feed rate is a constant 70 g/min. When inlet air RH is increased from 35% to 55% the median GS can be maintained at a 300-μm level by using pulsing (liquid

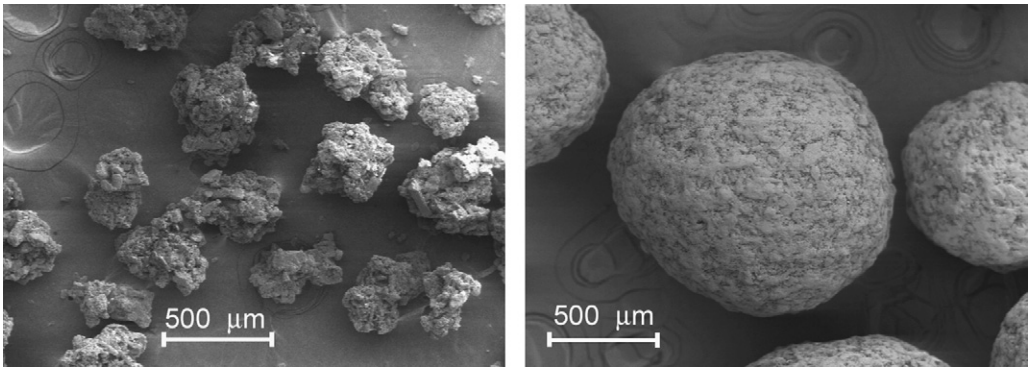

Fig. 3. SEM images of final granules in batches 5 (left) and 8 (right).

Table 2
Coefficients $a_1 \ldots a_{10}$, statistical significance (p), goodness of fit (R^2) and goodness of prediction (Q^2) values of modelling (GS = median granule size, RW = relative width of size distribution, Air = humidity of the inlet air, Liq = granulation liquid feed rate and Pau = relative time of pauses in the granulation liquid feed)

GS	SFT		Sieve analysis		Laser diffraction	
	Coefficient	p	Coefficient	p	Coeffecient	p
Air	0.112	***	0.102	***	0.106	**
Liq	0.101	***	0.138	***	0.187	***
Pau	−0.0480	*	−0.0248	NS	−0.0633	*
Air × Liq	0.0450	NS	0.0423	NS	0.110	*
Air × Pau	–	–	–	–	–	–
Liq × Pau	−0.0378	NS	−0.0439	NS	−0.0866	*
Air × Air	–	–	–	–	–	–
Liq × Liq	–	–	–	–	0.0848	NS
Pau × Pau	–	–	–	–	–	–
a_0	2.49		2.63		2.20	
	$R^2 = 0.94$, $Q^2 = 0.90$		$R^2 = 0.89$, $Q^2 = 0.68$		$R^2 = 0.90$, $Q^2 = 0.76$	

RW	SFT	
	Coefficient	p
Air	−0.169	**
Liq	−0.0390	NS
Pau	0.0930	*
Air × Liq	–	–
Air × Pau	0.0939	NS
Liq × Pau	0.0634	NS
Air × Air	–	–
Liq × Liq	−0.113	NS
Pau × Pau	–	–
a_0	1.70	
	$R^2 = 0.71$, $Q^2 = 0.31$	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; NS = not statistically significant.

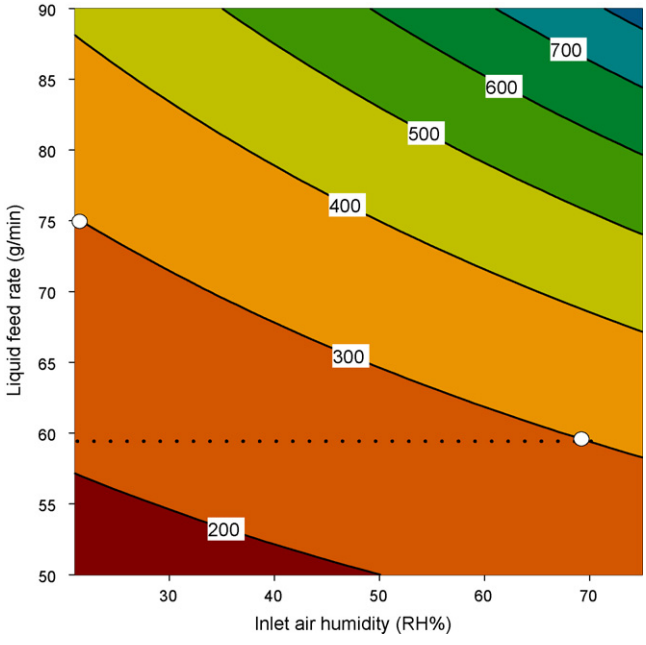

Fig. 4. Effect of granulation liquid feed rate and inlet air humidity on median granule size, using continuous spraying.

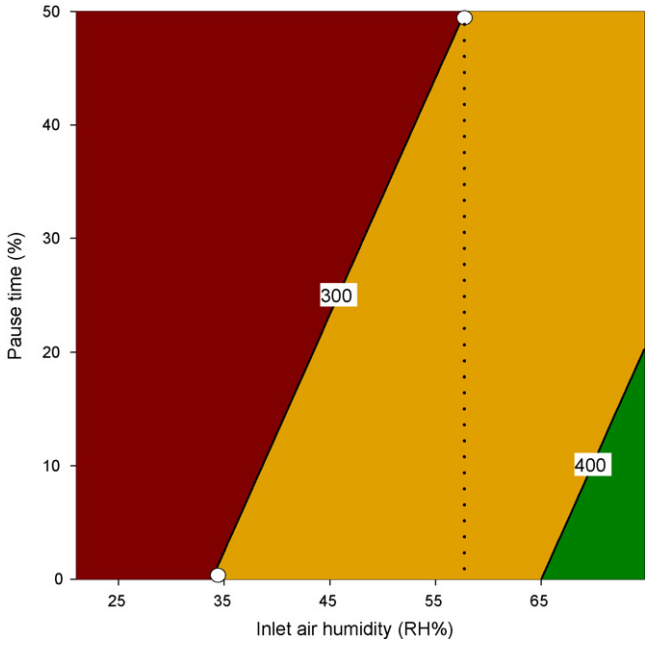

Fig. 5. Effect of granulation liquid feed pulsing and inlet air humidity on median granule size.

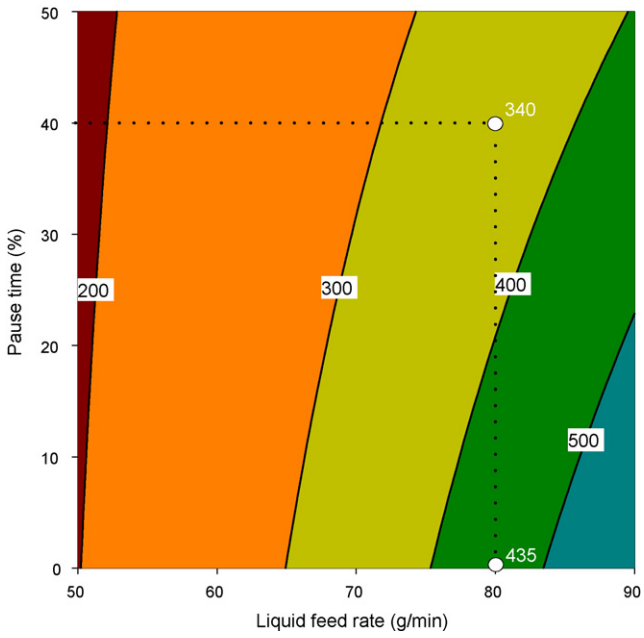

Fig. 6. Effect of granulation liquid feed pulsing and liquid feed rate on median granule size.

feed pause time of 50%). On the other hand, if the incoming air RH is 45% and the feed rate 80 g/min, the median GS could be decreased from 435 μm to 340 μm using a 40% pause time (Fig. 6).

Granulation liquid feed rate pulsing did not influence the bulk and tapped density, Carr's Index, and flowability values of the final granules. However, pulsing broadened the size distribution of the granules (Fig. 7). This broadening effect is probably due to the extended spraying phase time resulting from pulsing (Table 3), which can generate more fines due to attrition of granule surfaces. When the inlet air RH was low (<30%), the total process times also increased, whereas no significant changes were obtained in the drying process times. On the contrary, granulation liquid feed pulsing clearly decreased the drying process times when the inlet air RH was high (>60%), while no major changes were seen in the total process times.

Granulation liquid feed pulsing affected also the fluidising mass temperature. With the driest process (batch 5), the granulation liquid feed pulsing increased the mass temperature level from 20 °C to 28 °C, and the mass temperature fluctuated ±3 °C during the pulsing. The mass temperature increase during the granulation liquid feed pause is similar to the drying phase when there is no free surface water left in the granules. The higher the amount of water in the process, the smaller effect the pulsing had on the mass temperature; e.g. with the batch 8, no temperature effects were obtained due to the pulsing.

When the influence of all factors examined is evaluated together, it is clearly seen that granulation liquid feed pulsing is an efficient and straightforward way to control particle size (Fig. 8). Similar experiments adjusting the particle size of granules and compensating for the excessive moisture produced by pulsing have not previously been reported. We also emphasize that if this study were carried out using sieve analysis as the only technique, the effects of pulsing would have been masked. Sieve analysis is widely used for GS determination, but it is clear that more useful information can be gathered by using more accurate and reproducible analytic methods.

The seasonal effect of the air RH is a significant and uncontrollable variable in the fluid-bed granulation process if no dehumidifying systems for the inlet process air exist. The results of this study suggest that granulation liquid feed pulsing can be used to compensate for the disadvantageous influence of

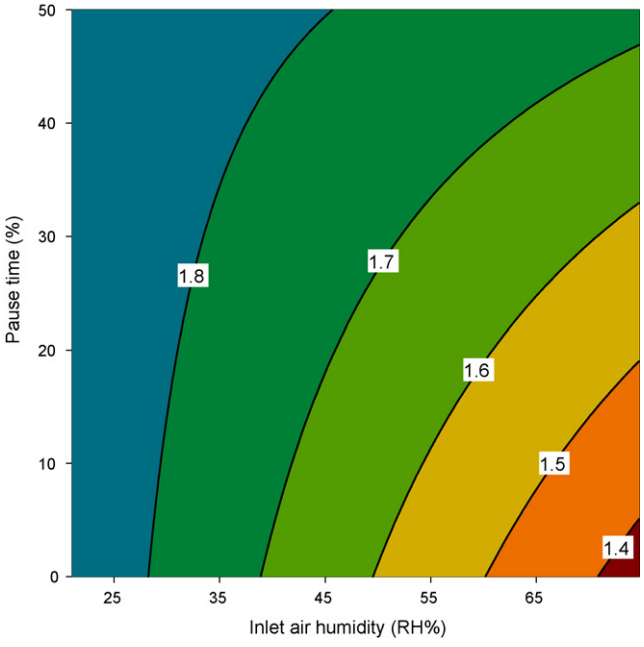

Fig. 7. Effect of granulation liquid feed pulsing and inlet air humidity on relative width of granule size distribution.

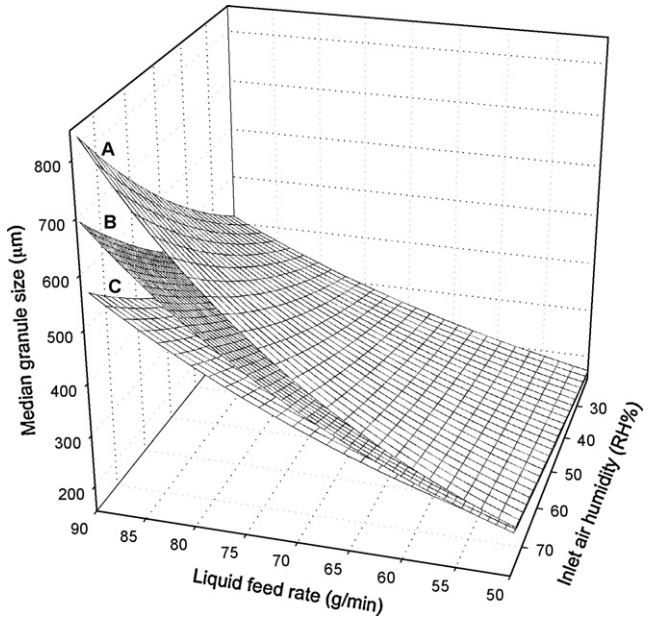

Fig. 8. Effect of all factors on median granule size. Continuous spraying (A), 33% pause time (B) and 50% pause time (C).

Table 3
Process times of the batches manufactured using continuous spraying (Cont.) and using pulsing (50% pause time)

Process variables		Spraying phase		Drying phase		Total process time		
Relative air humidity (%)	Liquid feed rate (g/min)	Cont. (min)	Pulsing (min)	Cont. (min)	Pulsing (min)	Cont. (min)	Pulsing (min)	Change (%)
<30	50	56	74	9	13	65	87	34
<30	90	27	40	14	13	41	53	29
>60	50	55	72	20	8	75	80	7
>60	90	30	41	40	21	70	62	−11

too high a level of moisture in the fluid-bed granulator. Consequently, pulsing is a practical tool for use against seasonal air RH variations.

4. Conclusions

The SFT results were the most consistent of the studied three techniques. The SFT model for median GS had the highest goodness of fit ($R^2 = 0.94$) and goodness of prediction ($Q^2 = 0.90$) values. Granulation liquid feed pulsing decreased the median GS clearly and broadened the size distribution slightly. The study results suggest that granulation liquid feed pulsing is an efficient way to modify the particle-size of final granules. In addition, pulsing can be applied as a controlling tool to compensate for the excessive moisture content in the granulation process, e.g. due to high inlet air RH.

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