Drug Development and Industrial Pharmacy, 27(1), 47–55 (2001)

RESEARCH PAPER

Using Experimental Design to Optimize the Process Parameters in Fluidized Bed Granulation

B. Rambali,[1,*] L. Baert,[2] D. Thoné,[2] and D. L. Massart[1]

[1]*Farmaceutisch Instituut, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium*
[2]*Janssen Research Foundation, Turnhoutseweg 30, 2340 Beerse, Belgium*

ABSTRACT

In this study many parameters were screened for a small-scale granulation process for their effect on the yield of granules between 75 and 500 μm and the geometrical granule mean size (d50). First a Plackett-Burman design was applied to screen the inlet air temperature, the inlet flow rate, the spray rate, the nozzle air pressure, the nozzle spray diameter, and the nozzle position. The Plackett-Burman design showed that the key process parameters were the inlet flow rate and the spray rate and probably also the inlet air temperature. Afterward a fractional factorial design (2^{5-2}) was applied to screen the remaining parameters plus the nozzle aircap position and the spraying time interval. The fractional factorial design showed that the nozzle air pressure was also important. As the target values for the granule yield (between 75 and 500 μm) and the geometric mean granule size (between 300 and 500 μm) were reached during the screening experiments, further optimization was not considered necessary.
KEY WORDS: Granulation process; Fluid bed; Geometric mean granule diameter; Experimental design; Plackett Burman design; Fractional factorial design.

INTRODUCTION

Granulation is the size-enlargement step in the production of tablets in the pharmaceutical industries. During size-enlargement, adhesive forces such as van der Waals forces and the formation of liquid bridges become effective (1). The fluidized bed makes it possible to prepare granules efficiently. The granulation process

*To whom correspondence should be addressed. Fax: +32-14-605333. E-mail: brambali@janbe.jnj.com

in the fluidized bed is however a complex process, because there are many parameters that can influence it. Therefore knowledge about the effects of the granulation process is necessary for controlling the process. During the last years, much effort has been spent to investigate the fluidized granulation process systematically.

The parameters that influence granule properties can be classified as apparatus, process, or product variables (2). The apparatus parameters are typical for the equipment used. Important parameters can be: distribution grid, geometry of the equipment, filter mechanism, and nozzle spray characteristics. The product parameters are related to the formulations used. The effect of the formulation parameters on the wet granulation process has been surveyed extensively by several investigators (2,3,4). The process parameters are related to the procedure used for the preparation of the granules. The process parameters have been studied extensively since the introduction of the fluidized bed. The apparatus and the process parameters become effective when one considers scaling-up the granulation process (5).

Statistical tools have been used for the investigation of the granulation process. The first studies of the granulation process parameters investigated the effect of parameters on the granule properties one at a time (6). In the last two decades experimental design (7–10) have been applied to investigate the effects of the process parameters on the granule properties. Gorodnichev et al. (7) applied a half-fractional (2^{4-1}) factorial design to find optimum conditions in preparing solid dosage form. They investigated the effect of the spray rate, the inlet air temperature, the inlet air flow rate, and the nozzle air pressure. Lipps et al. (8) applied a full factorial design (3^2) to study the effect of the spray rate and the inlet air temperature. Merkku et al. (9) also used a full factorial design (3^3) to investigate the effects of inlet air temperature, nozzle air pressure and the spray solution amount on the flow properties of the granules. Meshali et al. (10) used a quarter fractional (2^{5-2}) factorial design to study the effects of four process parameters (spray rate, the inlet air flow rate, the inlet air temperature, and nozzle air pressure) and one product parameter (binder concentration).

These studies have shown that the main process parameters are the spray rate, the inlet airflow rate, the inlet air temperature, and the nozzle air pressure. The inlet air humidity is also an important parameter, but there are few studies published on the effect of the inlet air humidity (2). Other fluidized granulation process parameters were not investigated systematically. The object of this study was to screen more parameters (process and apparatus). In total we investigated eight parameters, which were more than in any study investigated. In the literature, only four process variables have been investigated simultaneously. The aim was to define the parameter settings of the important process parameters so that they would maximize the yield of granules between 75 and 500 μm (>90% (w/w)), and a geometric mean granule size between 300 and 500 μm would be obtained.

MATERIALS AND METHODS

Experimental

The granules were produced in the fluid bed (GPCG-5, Glatt GmbH, Binzen, Germany). The compositions were 70.7% (w/w) (2803 g) lactose monohydrate 200 mesh (DMV, Veghel, The Netherlands), 27.0% (w/w) (1070 g) corn starch (Cerestar, Sas van Gent, The Netherlands), 2.3% (w/w) (92 g) hydroxypropylmethylcellulose 2910 15 cps (HPMC) (Dow, Midland). The binder solution was prepared by mixing the HPMC with 460 ml of water at >80°C. After mixing for 5 to 10 min, water was added to reach 2300 ml.

The lactose and the corn starch were placed in the fluid bed and were mixed by using air flow (238 m^3/hr) until the setting temperature that was necessary for the granulation cycle was reached. Afterward the binder solution was sprayed on the fluidizing powder bed using a peristaltic pump (ABM, Germany). The spraying process was carried out according to the settings of the process parameters for that specific run. Spraying continued until all the binder solution was used, and afterward 200 ml of water was sprayed to rinse the tubes.

The wetted granules were dried by fluidizing the granules with heated air flow (238 m^3/hr) of 75°C. The drying cycle was terminated when an outlet air temperature of 37°C was reached. After this cycle the granules were collected and sampled for sieve analysis.

Sieve Analysis

The sieve analysis was carried out to determine the granule yield (% (w/w)) between 75 and 500 μm. A set of sieves (75, 150, 250, 500, 850, and 1000 μm) in combination with the Retsch VE 1000 sieve shaker (Retsch, Haan, Germany) was used for this analysis. A 100-g of granule sample was transferred to the preweighed sieves and allowed to shake at amplitude of 1.5 mm for 5 min. The sieves were then reweighed to determine the weight fraction of granules retained on each sieve.

These weights were converted in mass percentage. The granule yield between 75 and 500 μm was obtained by eumulating of the mass percentage from the sieves of 75, 150, and 250 μm. The geometric mean granule size is calculated according to the equation given by Fonner et al. (11).

Design Development and Analysis of Results

The designs have been developed by the graphic software STATGRAPHICS PLUS, version 2.1 (STSC Inc., Rockville, MD). The statistical analyses of the measured response parameters also have been carried out with this software. It enabled ANOVA.

RESULTS AND DISCUSSION

The Granulation Process

Table 1 summarizes some process and apparatus parameters of the granulation process. The granule growth and therefore the granule size depend on the moisture content of the powderbed (3,12,13). The moisture content is the balance between the liquid supply and the evaporation and the outlet of the liquid. The key process parameters that influence the liquid balance are the inlet air humidity and the spray rate, that determine the liquid supply and the inlet air flow rate and the inlet air temperature that determine the evaporation and the outlet of the liquid.

The nozzle air pressure and the spray rate determine mostly the liquid droplet size. As is described by Parikh (12), these liquid droplets form nuclei with powder particles, the size of which depends on the droplet size. Schaefer and Worts (13) have demonstrated that the granule size is affected by the droplet size of the binder solution and therefore by the nozzle air pressure. These five process parameters are usually considered to be the key process parameters for the granule size.

Table 1.

Process Parameters of the Fluidized Bed

Inlet air flow rate
Inlet air temperature
Spray rate of the binder solution
Nozzle air pressure
Nozzle height position
Nozzle aircap position
Nozzle diameter
Inlet air humidity
Filter shaking time interval
Spraying time interval
Batch loading

Other parameters may also have an effect on the granule properties but to a lesser extent than the above-mentioned key parameters. Davies and Gloor (6) investigated the effect of the nozzle position on the granule size. They found that the lower the nozzle was positioned, the larger the average granule size was. The effect of the nozzle diameter has not yet been investigated. However, it is expected that the larger the diameter, the larger the droplet size, and thus larger granules will be obtained. The nozzle aircap position determines the angle in which the binder solution is sprayed on the fluidized powderbed by changing the airflow rate through the nozzle. When the angle is too wide, the binder solution will be sprayed on the sidewall of the expansion chamber. When the angle is too narrow, the spray may approach a straight stream, only wetting a small part of the powder. In this case, local overwetting will be obtained. The angle must be configured in such a way that spraying of the binder solution to the chamber wall or spraying as a spout must be avoided.

The granulation process cycle of the GPCG-5 fluid bed consists of spraying time interval and shaking time interval. During the spraying time interval, the binder solution is sprayed on the fluidized powderbed. The spraying and the air fluidization are stopped during the shaking time interval, and the filters are shaken to release the entrapped particles caught during the spraying. The shaking time interval is fixed at 10 sec during the experiments. This time is considered long enough to release the entrapped particles (15). The shaking time interval effect on the granulation process is therefore considered to be negligible.

In this study, we wanted to investigate many parameters (eight) combining process parameters with apparatus parameters. In this case, full and partially fractional designs would require many experiments. For that reason, first a Plackett-Burman design was applied on the six probable most important parameters to screen the key process parameters. The following process parameters were investigated in this design: the spray rate, the inlet airflow rate, the inlet air temperature, the nozzle air pressure, the nozzle height position, and the nozzle diameter. Afterward, a fractional factorial design (2^{5-2}) was applied on the remaining less important parameters, plus the nozzle aircap position and the spraying time interval. The significance of the effect of these process parameters on the percentage yield of granules between 75 and 500 μm and on the geometric mean granule size (d50) was determined. The d50 is the sieve diameter, that lets through 50% of the granule mass. In this way, many process parameters were screened. The batch loading (3.873 kg) during these experiments was fixed to keep the binder solution amount constant. The inlet air humidity is an

Table 2.

Settings of the Granulation Process Parameters in the Plackett-Burman Screening Design

Process Parameters	Settings
Inlet air flow rate	140–286 m^3/h
Nozzle spray diameter	1.2–2.2 mm
Nozzle height position	1.0–3.0
Nozzle air pressure	1.5–2.5 bar
Inlet air temperature	50–70°C
Spray rate	58.0–135.6 g/min

Note: Nozzle aircap position is fixed (position 5), spraying time is 35 sec, and filter shaking time is 7 sec.

important parameter; however, the equipment cannot condition the inlet air for the humidity. This parameter is therefore noncontrollable during these experiments. To investigate the effect of the inlet air humidity on the granule yield, the inlet air humidity was calculated from the air temperature and the relative air humidity during the experiments. No correlation was found between the inlet air humidity and the granule yield or granule size. Also the replication of the granulation process ($n = 6$) showed that the effect of the inlet air humidity on the granule yield or the granule size was negligible during the experiments.

Plackett-Burman Screening Design

To determine the key parameters, a screening design is applied. The screening design that was used in this study was a Plackett-Burman design. This design is a cyclic permutation of the factor combinations. It consists of 4*m* runs with 4 m > k parameters (m = 1, 2, 3, ... cycles k = number of parameters). In this study, the design involved 12 different experimental runs, combining six process parameters at low and high level for each examined parameter. It had enough runs (5 degrees of freedom) for the estimation of the residual error. With this design, only the main effects could be determined. The settings in the Plackett-Burman design of the process parameters are listed in Table 2. Table 3 lists the runs for the Plackett-Burman design.

Table 3 also shows the results obtained for the 12 runs, the granule yield between 75 and 500 μm, and the geometrical mean granule size. Some runs failed (runs 5, 6, 7, 9) because of overwetting of the powderbed with the binder solution. Because no granules were obtained for the failed runs, the granule yield for these runs was zero, and of course the d50 of the failed runs could not be determined. To perform statistical analyses of the design for the d50, the missing d50 of the failed runs must be estimated. Because the powderbed was overwetted, the granules would be very large. Therefore, the d50 of the failed runs was >694 μm (run 3), and a nonparameteric evaluation of the granulation parameters was recommended.

Table 3.

Plackett-Burman Screening Design of the Process Parameters for the Granulation Process with Fluidized Bed

	Process Parameters						Response	
Run	Air Flow Rate (m^3/hr)	Nozzle Diameter (mm)	Nozzle Height Position	Nozzle Air Pressure (bar)	Inlet Air Temperature (°C)	Spray Rate (g/min)	R^a (%)	D50[b] (μm)
1	140	1.2	3	2.5	70	77.5	81.6	470
2	140	2.2	3	1.5	70	77.5	59.0	602
3	286	2.2	3	1.5	70	135.6	47.4	694
4	286	2.2	1	2.5	70	77.5	90.3	298
5	140	1.2	1	1.5	50	77.5	0.0	>694[c]
6	140	1.2	1	2.5	70	135.6	0.0	>694[c]
7	140	2.2	1	1.5	50	135.6	0.0	>694[c]
8	286	1.2	3	1.5	50	77.5	84.7	457
9	140	2.2	3	2.5	50	135.6	0.0	>694[c]
10	286	1.2	1	1.5	70	135.6	64.8	562
11	286	1.2	3	2.5	50	135.6	2.9	>694[c]
12	286	2.2	1	2.5	50	77.5	97.5	297

[a] Granule yield between 75 and 500 μm [%(w/w)].
[b] Geometric mean granule size (μm).
[c] Failed runs are set to d50 > 694 μm.

An appropriate nonparameteric test is the Mann-Whitney test (16). In this test, first all the d50 values are ranked. Rank 1 is given to the lowest d50, rank 2 to the second lowest, etc. When ties are present, the average of the ranks is given. When n_1 and n_2 are the number of runs at low and high level, respectively, and R_1 and R_2 are the sums of the ranks at these two levels, then

$$U_1 = n_1 n_2 + n_1(n_1 + 1)/2 - R_1$$
$$U_2 = n_1 n_2 + n_2(n_2 + 1)/2 - R_2$$

The Mann-Whitney test in fact compares the median of the two levels. To evaluate whether an effect is significant, a hypothesis test is performed:

$$\mathrm{H}_0 : U_1 = U_2$$
$$\mathrm{H}_1 : U_1 \neq U_2$$

The min (U_1, U_2) of each granulation parameter was compared with tabular critical values for U. If this value was smaller or equal to the critical value, then the parameter was considered to be significant. From Table 4 we indeed conclude that the spray rate and the inlet air flow have a significant effect on the d50.

Table 4 shows the ANOVA for the yield of the granules. Effects that have p values less than 0.05 are considered significant. From Table 4, we again conclude that airflow rate and spray rates have p values less then 0.05, indicating that they have a significant effect on the yield and on the d50 value. Because of the low p value for the inlet air temperature, we cannot discard the possibility that this may be an important factor. The other parameters will, at least temporarily, be considered less important and their value fixed.

It is doubtful whether a statistical interpretation is valid when one fills in zeros for unsuccessful granulations. Indeed, ANOVA can be considered to represent a linear model. When no granules are produced, this indicates a breakdown of the model. The zero values for the yield are only a convenient way of indicating this and should not be considered response values. Therefore, we prefer to consider the Plackett-Burman design as a way of describing the six-variable space and finding a starting point for further experimentation. If we rank the experiments according to quality obtained, we note that the best result is from experiment 12, followed by experiments 4, 8, and 1. These experiments were carried out at diverse parameter settings, except that the spray rate was always 77.5 g/min. This shows that the most important parameter is spray rate and that higher levels of spray rate are not indicated. If further optimization is needed, only lower spray rates should be considered. Because it was possible to work also at a 58.0 g/min spray rate, we carried out a small centered two-level design at this value, including the other two parameters that, from the statistical conclusions of the Plackett-Burman design, appeared important (Table 5). Low yield is obtained for the granules at low airflow rate and at low inlet air temperature (run 4). Run 4 produces coarse granules in excess (granules >500 μm) that make this run resulting in low granule yield and high d50 value. Other combinations of the airflow rate and inlet air temperature give acceptable results for the yield of the granules (yield $\geq$88.8%). The results of run 1, 3, and 5 are comparable with each other (93.6 to 95.4%). However, run 2, with high inlet air flow rate and high inlet air temperature, gives lower yield than do runs 1, 3, and 5, with low/high inlet air flow rate and high/low inlet air

Table 4.

ANOVA for the Granule Yield Between 75 and 500 μm and the Mann-Whitney Test for the Geometric Mean Granule Size (d50) in the Plackett-Burman Screening Design of Table 3

	Granule Yield					d50
Source	Sum of Squares	df	Mean of Squares	F Ratio	p Value	Min (U_1, U_2)
Inlet air flow rate	5079.97	1	5079.97	7.80	0.038	5
Nozzle spray diameter	303.01	1	303.01	0.47	0.525	15
Nozzle height position	45.24	1	45.24	0.07	0.803	17
Nozzle air pressure	21.60	1	21.60	0.03	0.863	16
Inlet air temperature	2088.24	1	2088.24	3.21	0.133	13
Spray rate	7405.30	1	7405.30	11.37	0.020	5
Residual	3255.09	5	651.02	—	—	—
Total (corr.)	18198.4	11				

R-squared = 82.1%.
R-squared (adjusted for d.f.) = 60.6%.
$U_{\mathrm{crit.}(\alpha=0.05, n1=n2=6)} = 5$.

Table 5.

Centered Two-Level Factorial Design of the Inlet Air Flow Rate and the Inlet Air Temperature at a Spray Rate of 58.0 g/min

	Process Parameters		Response	
Run	Inlet Air Flow Rate (m^3)	Inlet Air Temperature (°C)	R^a (%)	D50[b] (μm)
1	286	40	93.6	322
2	286	70	88.8	235
3	213	55	94.1	334
4	140	40	45.8	697
5	140	70	95.4	288

[a] Granule yield between 75 μm and 500 μm (%).
[b] Geometric mean granule size (μm).
Note: Nozzle spray diameter is 1.8 mm, nozzle pressure is 2.5 bar, nozzle height position is 2.

temperature or at their center values. Run 2 produces fines in excess (granules <75 μm). These fine granules are not desirable in the granulation process because such granules lead to poor processing characteristics. It is concluded that the lower limit of the spray rate will be set at 58.0 g/min.

To investigate the upper limits of spray rate a similar factorial design was planned at 96.8 g/min. Because unfavorable results were obtained at the center values (mean granule yield of six measurements was 43.6%), this factorial design was not completed. This does not exclude that at some combinations of other variables, good results would be obtained at this level of spray rate, but makes it less likely. Therefore, the investigation was limited at the spray rate of 77.5 g/min. We can now go back to interpreting the results obtained at 77.5 g/min in the Plackett-Burman design in function of the inlet air flow rate and the inlet air temperature (see Table 3). One concludes that, as for the results at a spray rate of 77.5 g/min, the combination of low flow rate and low inlet temperature yields very unfavorable results (run 5). We also see that some of the parameters, which according to the statistical analysis have no effect (compare runs 8, 12, 1, and 2) should indeed have an effect. For this reason, it was decided to carry out a quarter fractional (2^{5-2}) factorial design (Table 6) on the parameters that were temporarily considered less important in the Plackett-Burman design, and on two additional parameters that at first were not investigated in the Plackett-Burman design. This new factorial design consisted of 12 runs. The central point was replicated four times for the experimental error to evaluate the main effects. The parameters that were most significant in the Plackett-Burman design (the spray rate, the inlet airflow rate, and the inlet air temperature) were fixed in this new design. Because zero-values were no longer present, a valid statistical analysis can now be carried out.

Quarter Fractional Factorial Design (2^{5-2})

From Table 6, we can see that high nozzle air pressure resulted in low d50 values (runs 1, 3, 5, and 7) and low

Table 6.

Centered Quarter Fractional (2^{5-2}) Factorial Design

	Process Parameters					Response	
Run	Nozzle Diam. (mm)	Nozzle Height Position	Nozzle Air Pressure (bar)	Nozzle Aircap Position	Spraying Time Interval (sec)	R^a (%)	D50[b] (μm)
1	2.2	1	2.5	1	70	96.4	348
2	2.2	3	1.5	5	35	82.3	528
3	2.2	3	2.5	5	70	96.7	352
4	1.8	2	2	3	52.5	85.2	494
5	1.2	3	2.5	1	35	94.4	458
6	1.8	2	2	3	52.5	94.7	471
7	1.2	1	2.5	5	35	97.6	355
8	1.8	2	2	3	52.5	93.5	444
9	1.8	2	2	3	52.5	95.4	426
10	1.2	1	1.5	5	70	82.8	504
11	2.2	1	1.5	1	35	57.9	612
12	1.2	3	1.5	1	70	65.2	565

[a] Granule yield between 75 and 500 mm (%).
[b] Geometric mean granule size (μm).
Note: Spray rate was 68 g/min, inlet air flow rate was 213 m^3/hr, and inlet air temperature was 55°C.

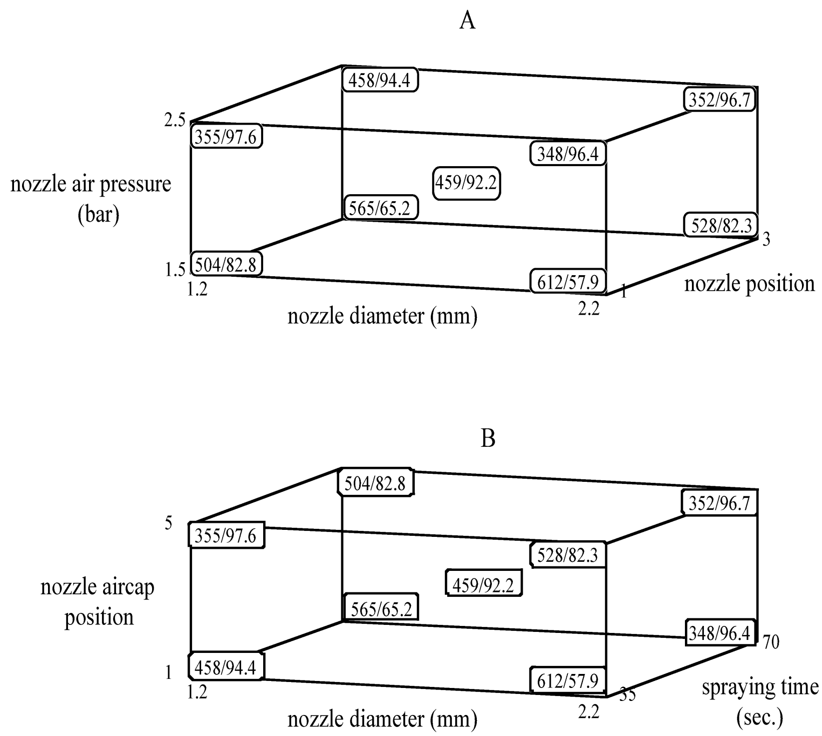

Figure 1. Cube plots of the granule yield [%(w/w)] between 75 and 500 μm in the applied fractional factorial design (2^{5-2}).

nozzle air pressure in high d50 values (runs 2, 10, 11, and 12). This means that increasing the nozzle air pressure decreases the d50 values. The effect of the nozzle air pressure on the d50 value was confirmed by other studies (5,6,9). The liquid droplet size produced by the nozzle depends mainly on the nozzle air pressure, the spray rate, the nozzle diameter, and the nozzle aircap position. The nozzle produced smaller liquid droplets at high nozzle air pressure level, which resulted in lower d50 values of the granules. In Figure 1, we can see the effect clearly. The d50 values at low nozzle air pressure were larger than the desired optimal d50 values between 300 and 500 μm. If we want to produce granules with a desired d50 value between 300 and 500 μm, then the nozzle air pressure must be set at the high level. This means that the nozzle air pressure is an important parameter in operating the fluid bed. In Figure 1, we can see that the nozzle aircap position also had an effect on the d50 value. A high level of the aircap position resulted in lower d50 value than did the low level of the aircap position. The effect of this parameter was not as large as the nozzle air pressure. Both levels of the nozzle aircap position lead to the desired d50 value, thus, we can conclude that this parameter, although significant, was less important. The effect of other parameters on the d50 value is not clear in Figure 1.

In Figure 1, we note that the effects of the nozzle air pressure and aircap position on the granule yield were the opposite of those of the effects on the d50 value. We observe that at a high level of nozzle air pressure, a granule yield of >90% (w/w) was obtained. These results

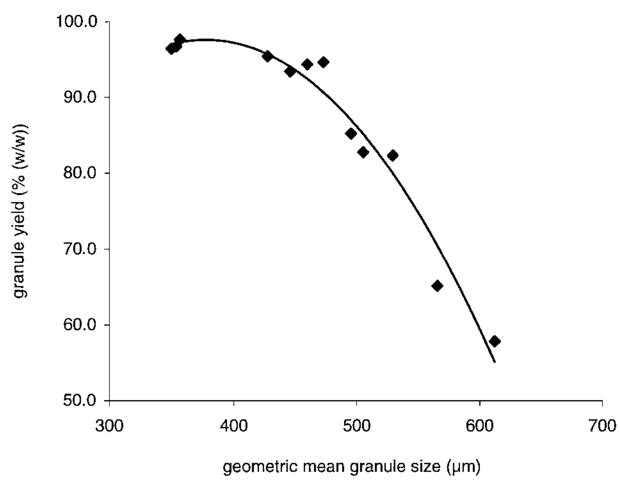

Figure 2. The observed geometric mean granule size versus the granule yield [%(w/w)] between 75 and 500 μm.

Table 7.

ANOVA for the Process Parameters of the Geometric Mean Granule Diameter in the $2^{5\text{-}2}$ Factorial Design

Source	Sum of Squares	df	Mean of Squares	*F* Ratio	*p* Value
Nozzle spray diameter	220.50	1	220.50	0.25	0.654
Nozzle height position	962.67	1	962.67	1.08	0.376
Nozzle air pressure	60552.00	1	60552.00	67.7	0.004
Nozzle aircap position	7442.00	1	7442.00	8.3	0.063
Spraying time	4232.00	1	4232.00	4.73	0.118
Lack of fit	2409.00	3	803.00	0.90	0.534
Residual	2682.75	3	894.25		
Total (corr.)	78500.9	11			

R-squared = 92.9%.
R-squared (adjusted for df) = 87.0%.

confirmed that the optimal setting for the nozzle air pressure was 2.5 bar.

In Figure 2, we observe that the obtained d50 values were inversely proportional to the yield of the granules between 75 and 500 μm, which explained the results reported in Figure 1. Because the granule size weight distribution data describe a log-normal distribution, there exists an optimal d50 value where the granule yield is maximum. D50 values higher or lower than the optimal d50 value will result in a lower granule yield. Figure 2 shows the granule yield at d50 values that were probably equal to or greater than the optimal d50 value.

The four replicates of the center points give a mean of 459 μm for the d50 value, which is close to the mean (466 μm) of the d50 values obtained from the eight runs in the $2^{5\text{-}2}$ factorial design, indicating that the granulation process on a small scale is linear for the parameters investigated. ANOVA (Table 7) of the results of the $2^{5\text{-}2}$ factorial design confirms the nozzle air pressure ($p = 0.004$) has a p value <0.05, indicating that it has a significant effect on the d50 value. Because the main effects are confounded with the interaction effects, we cannot conclude whether the nozzle aircap position ($p = 0.063$) has a significant effect on the d50 value; it is in the zone of doubt. The other parameters in the $2^{5\text{-}2}$ factorial design are not considered important.

CONCLUSIONS

We can conclude from the applied Plackett-Burman design and the quarter fractional factorial design that the key granulation process parameters are the spray rate, the inlet air flow rate, the inlet air temperature, and the nozzle air pressure. The objective was to obtain a high granule yield (>90%) between 75 and 500 μm and a d50 value between 300 and 500 μm. From Table 6, it was observed that runs 1, 3, 5, and 7 comply with the objective. All these runs were performed at a nozzle air pressure of 2.5 bar. The other key parameters were fixed at parameter setting: spray rate of 68.0 g/min, inlet air flow rate of 213 m^3/h, and inlet air temperature of 55°C. These parameter settings are considered as optimal settings for the small scale.

ACKNOWLEDGMENTS

The authors wish to thank Janssen Research Foundation for the financial support, the supply of products, and the use of the equipment. D.L. Massart thanks the Nationaal Fonds voor Wetenschappelijk Onderzoek.

REFERENCES

1. Fonner, D.E.; Anderson, N.R.; Banker, G.S. Granulation and Tablet Characteristics. In *Pharmaceutical Dosage Forms: Tablets*, Vol. 2; Lieberman, H.A., Lachman, L., (Ed.); Marcel Dekker, Inc.: New York, 1981; 186–187.
2. Kristensen, H.G.; Schaefer, T. Granulation. A Review on Pharmaceutical Wet-Granulation. Drug Dev. Ind. Pharm. **1987**, *13*, 803–872.
3. Wan, L.S.C.; Heng, P.W.S.; Muhuri, G. Analysis of Growth of Granules in a Fluidized Bed Granulator. S.T.P. Pharm. Sci. **1992**, *2*, 381–386.
4. Wan, L.S.C.; Lim, K.S. Action of Binders in the Fluidized Bed Granulation of Lactose. S.T.P. Pharm Sci. **1991**, *1*, 248–255.
5. Mehta, A.M. Scale-Up Considerations in the Fluid-Bed Process for Controlled-Release Products. Pharm. Tech. **1988**, *12* (2), 46–52.

6. Davies, W.L. and Gloor, W.T., 1971. Batch production of pharmaceutical granulations in a fluidized bed I: effects of process variables on physical properties of final granulation. J. Pharm. Sci., 60 (12), 1869–1874.
7. Gorodnichev, V.I.; El-Banna, H.M.; Andreev, B.V. The Construction of Uses of Factorial Designs in the Preparation of Solid Dosage Forms. II: Granulation in a Fluidized Bed. Pharmazie **1981**, *36*, 270–273.
8. Lipps, M.; Sakr, A.M. Characterization of Wet Granulation Process Parameters Using Response Surface Methodology. I. Top-Spray Fluidized Bed. J. Pharm. Sci. **1994**, *83*, 937–947.
9. Merkku, P.; Lindqvist, A.-S.; Leiviska, K.; Yliruusi, J. Influence of Granulation and Compression Process Variables on Flow Rate of Granules and on Tablet Properties, with Special Reference to Weight Variation. Int. J. Pharm. **1994**, *102*, 117–125.
10. Meshali, M.; El-Banna, H.M.; El-Sabbagh, H. Use of a Fractional Factorial Design to Evaluate Granulations Prepared in a Fluidized Bed. Pharmazie **1983**, *38*, 323–325.
11. Fonner, D.E.; Anderson, N.R.; Banker, G.S. Granulation and Tablet Characteristics. In *Pharmaceutical Dosage Forms: Tablets*, Vol. 2; Lieberman, H.A., Lachman, L., (Eds.); Marcel Dekker, Inc.: New York, 1981b; 191–194.
12. Parikh, D.M. Theory of Granulation. In *Handbook of Pharmaceutical Granulation Technology*; Parikh, D.M., Ed.; Marcel Dekker, Inc.: New York, 1997, 7–25.
13. Watano, S.; Sato, Y.; Miyanami, K. Application of a Neural Network to Granulation Scale-Up. Powder Technol. **1997**, *90*, 153–159.
14. Schaefer, T.; Worts, O. Control of Fluidized Bed Granulation. IV. Effects of Binder Solution and Atomization on Granule Size and Size Distribution. Arch. Pharm. Chem, Sci. Ed., **1978**, *6*, 14–25.
15. Parikh, D.M.; Bonck, J.A.; Mogavero, M. Batch Fluid Bed Granulation. In *Handbook of Pharmaceutical Granulation Technology*; Parikh, D.M., Ed.; Marcel Dekker, Inc.: New York, 1997, 227–302.
16. Massart, D.L.; Vandeginste, B.G.M.; Deming, S.N.; Michotte, Y.; Kaufman, L. Evaluation of Precision and Accuracy. Comparison of Two Procedures. In *Chemometrics: A Textbook*, Elsevier Science Publishers B.V.: Amsterdam, 1988, 50–51.