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Using experimental design to optimize the process parameters in fluidized bed granulation on a semi-full scale

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Abstract

A face-centered central composite design was applied in order to optimize the granulation process on a semi-full scale (30-kg batch) for the geometric mean granule size. The granulation process variables investigated were: inlet air temperature, inlet airflow rate, spray rate and inlet air humidity. Based on the process variables, the theoretical powder bed moisture content after the spraying process and a measure for the droplet size were determined. Multiple regression modeling was used to develop two models for the granule size: an empirical model, based on the four process parameters, and a fundamental model, based on the balance between the granule growth affected by the theoretical powder bed moisture content and the droplet size and the breakage effect of the airflow rate. These regression models were used to optimize the granulation process to obtain a granule size between 300 and 500 μm. Additional experiments confirmed that these models were valid. Other granule properties, namely the geometric standard deviation, the Hausner index, the angle of repose and the moisture content, were evaluated at the optimal operation conditions. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Granulation process; Granule properties; Fluid bed; Central composite design; Optimization; Regression model

1. Introduction

The granulation process in a fluidized bed is a complex process. There are many process variables (spray rate, inlet airflow rate, inlet temperature, inlet air humidity, nozzle air pressure, nozzle height, etc.) (Mehta, 1988) that can influence the granule properties. These variables have been studied extensively (Gorodnichev et al., 1981; Wan and Lim, 1991; Lipps and Sakr, 1994; Merkku et al., 1994; Miyamoto et al., 1995; Vojnovic et al., 1995; Juslin and Yliruusi, 1996; Watano et al., 1996a,b,c). The most widely studied granule properties in the literature are: geometric mean granule size, granule size distribution, angle of repose, loose and tap density (Hausner index), granule flow rate (angle of repose), and loss on drying (Gorodnichev et al., 1981; Meshali et al., 1983; Acarturk, 1989; Wan and Lim, 1991; Gordon, 1994; Lipps and Sakr, 1994; Liu et al., 1994; Merkku et al., 1994;

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Dussert et al., 1995; Miyamoto et al., 1995; Vojnovic et al., 1995; Juslin and Yliruusi, 1996; Watano et al., 1996a,b,c).

In earlier experiments the granulation process on a small scale (3.87 kg batch) was investigated (Rambali et al., 2001). In that study, it was shown that the inlet air temperature, the inlet airflow rate, the spray rate and the nozzle air pressure were the key process variables determining the granule size. An increase in inlet temperature, airflow rate or nozzle air pressure reduced granule size whilst the spray rate increased it. The effect of inlet air humidity was not studied in the earlier experiment, because the equipment did not allow it. The effect of the inlet air humidity on the granule size has not been investigated much yet. One expects that an increase of the inlet air humidity will increase the granule size, because it decreases the water evaporation capacity of the inlet air and increases the powder bed moisture content. The latter depends on the equilibrium between liquid supplied by the spray rate and the inlet air humidity and the evaporation of liquid by the inlet airflow rate and the inlet air temperature (Scott et al., 1964; Watano et al., 1996a,b,c). Watano et al. (1996a,b,c) showed that the granule size depends on the powder bed moisture content. If too much liquid is added or the evaporation of the liquid is not adequate than this results in an increase of the powder bed moisture content. Above a certain powder bed moisture content the powder bed becomes overwetted and defluidizes (Schaefer and Worts, 1978a; Parikh et al., 1997). At an increased inlet airflow rate, the powder bed defluidizes at higher moisture content due to the increased deformation force on the agglomerated granules exercised by the airflow.

When the evaporation of the liquid is excessive because of high inlet flow rate and/or high inlet air temperature or low supply of liquid by the spray rate, the powder bed moisture content will be low and a spray dry process will be obtained where the granule size depends essentially on the droplet size of the binder (Schaefer and Worts, 1978b. The droplet size is mainly dependent on the nozzle air pressure and the spray rate. Therefore, the granule size is affected by the following fundamental variables: powder bed moisture content, droplet size of the binder solution and the deformation force exercised by the airflow. These variables must be controlled between certain ranges in order to produce granules of a desirable size.

In this study the granulation process was optimized on semi-full scale (30-kg batch) by developing an empirical model and a fundamental model for the granule size. In view of the small-scale results, the following variables were investigated in the design: spray rate, inlet airflow rate, inlet air temperature and, additionally, the inlet air humidity. The nozzle air pressure was kept constant during the experiments and the droplet size of the binder solution depended mainly on the spray rate. The process was optimized with the target of a geometric mean granule size between 300 and 500 μm.

Other granule properties [granule size distribution, angle of repose, loose and tap density (Hausner index), angle of repose, and loss on drying] were also considered here in order to evaluate the granules.

Because of the complexity of the granulation process, experimental design was an appropriate way to investigate it. Experimental designs are widely used in pharmaceutical science (Doornbos, 1981). Experimental designs dealing with the granulation process have been applied in several studies (Gorodnichev et al., 1981; Meshali et al., 1983; Gordon, 1994; Lipps and Sakr, 1994; Merkku et al., 1994; Dussert et al., 1995; Miyamoto et al., 1995; Vojnovic et al., 1995).

2. Materials and methods

2.1. Granulation process

The granules were produced in the GPCG-30 fluid bed (Glatt GmbH, Binzen, Germany). The compositions were: 70.7% (w/w) (21.020 kg) lactose monohydrate (200 mesh, DMV, Veghel, Netherlands), 27.0% (w/w) (8.025 kg) corn starch (Cerestar, Sas van Gent, Netherlands), 2.3% (w/w) (690 g) hydroxypropylmethyl-cellulose 15 cps 2910 (HPMC)(Dow, Midland, USA). The binder solution was prepared by mixing the HPMC with

4.0 l water at 81°C. After mixing for 5–10 min, water was added to 17.25 l. The lactose and the corn starch were placed in the fluid bed and were mixed by using air, conditioned for the specific run at a flow rate at 500 Nm^3/h, for 5–6 min. Afterwards the binder solution was sprayed on the fluidizing powder bed using a peristaltic pump (adjusting the spray rate, using a micro motion system). The spraying process was carried out according to the settings of the process variables for the specific run. Spraying was continued until all the binder solution was used and afterwards 0.5 l of water was sprayed in order to rinse the tubes. The wetted granules were dried by fluidizing them with an inlet air temperature of 75°C. The drying cycle was terminated when an outlet air temperature of 35°C was reached, indicating that the granules were dried sufficiently. After this cycle, a 250-g sample was taken from the top, middle and the bottom of the powder bed and stored in an airtight plastic bag for the determination of the granule properties.

2.2. Physical characteristics of the granules

2.2.1. Granule size

The granule size distribution was measured according to the methods described by Rambali et al. (2001). A set of sieves (75, 150, 250, 500, 850 and 1000 μm) in combination with the Retsch VE 1000 sieve shaker (Retsch, Haan, Germany) were used for this analysis. A 100-g granule sample was transferred to the pre-weighed sieves and shaken at an amplitude of 1.5 mm for 5 min. The sieves were then re-weighed to determine the weight fraction of granules retained on each sieve. These weights were converted in mass percentage. The geometric mean granule size was calculated from these mass fractions according to Fonner et al. (1981).

2.2.2. Loss on drying

A 10-g sample of the granules was dried at 105°C for 15 min in a Mettler LP 16 (Mettler-Toledo, Swiss), immediately after the granulation process. This time setting was sufficient to reach a constant mass. The loss in weight after 15 min gave the loss on drying (LOD) (%, w/w).

2.2.3. Hausner index

The Hausner index is the ratio of the bulk density and the tapped density of the granules. A 100-g granule sample was weighed and poured into a graduated 250-ml cylinder. The volume of the granules in the cylinder was read and the bulk density was determined in g per ml. The cylinder was tapped 500 times on a tapping device (J. Engelsmann AG, Ludwigshafen a. Rh., Germany) and the tapped density was determined in g per ml. The tap settings were sufficient to reach a constant volume.

2.2.4. Angle of repose

The angle of repose was determined by an angle of repose tester (Janssen Pharmaceutica, Beerse, Belgium). A ±145-ml granule sample was allowed to flow through a 4.6-cm orifice. The granules formed a pile on a 5.0-cm circular platform. The instrument measured the height of this granule pile. The arctangent of the height and the radius of the platform determined the angle of repose.

2.3. Statistical analysis

The designs have been developed by the graphic software 'STATGRAPHICS PLUS' version 3.3 (STSC Inc., Rockville, MD, USA). The statistical analyses were also carried out by this software. It enabled the multiple regression modeling.

2.4. Design development

For the optimization of the granulation process a face-centered central composite design (FcCCD) was applied. For practical reasons it was preferred to the more usual spherical central composite design, because the axial points yield variable combinations, that would lie outside the equipment performance. This involved $(2^k + 2k + 1)$ experimental measurements with $k = 4$ variables at low, central and high level for each examined variable. The central point was replicated six times for the determination of the experimental error. The Fc-CCD consisted of 30 runs. The runs were randomized in order to exclude block effects. The settings of the process variables are listed in

Table 1. These settings were based on the settings applied on a small scale (Rambali et al., 2001). Mehta (1988) proposed two alternatives for scaling-up the settings from the small to the medium scale.

Method 1

$$A_1/A_2 = S_1/S_2 \quad (1)$$

Method 2

$$V_1/V_2 = S_1/S_2 \quad (2)$$

where

- A_1 = cross-sectional area of the distributor plate in the small scale;
- A_2 = cross-sectional area of the distributor plate in the medium scale;
- S_1 = spray rate in the small scale;
- S_2 = spray rate in the medium scale;
- V_1 = inlet airflow rate in the small scale; and
- V_2 = inlet airflow rate in the medium scale.

In the small scale the optimal settings obtained (Rambali et al., 2001) for the inlet airflow rate were 207 Nm^3/h at a spray rate of 69.0 g/min and an inlet air temperature of 55°C. The cross-sectional areas were 0.049 m^2 and 0.197 m^2 in the small and the medium scale, respectively. Using these values in the above equation, the inlet airflow rate should be 831 Nm^3/h and the spray rate should be 277 g/min in the medium scale. These variable settings of the spray rate and the inlet airflow rate were in the range of settings applied in the design. The temperature settings used here were the same as in the small scale. The inlet air humidity settings reflected the absolute ambient air humidity. At high levels of airflow rate the high level of the inlet air humidity could not be achieved, due to equipment performance.

Table 1
Process variables and settings in the face centered central composite design

Process variable	Level		
	Low	Central	High
Inlet air flow rate (Nm^3/h)	500	800	1100
Inlet air temperature (°C)	40	55	70
Spray rate (g/min)	240	290	340
Inlet air humidity (g/kg)	6	10	14

In Table 2 the design is displayed. Multiple regression modeling was used in order to find those variable combinations that give granules with optimal geometric mean size. The optimum desired was between 300 and 500 μm.

3. Results and discussion

3.1. Granule size

The granule size results are given in Table 2.

The six replicates of the central point gave results between 484 and 585 μm with a S.D. of 7.7%. The replicate run 22 gave a high value (585 μm) compared to the other replicates. This run was subjected to an outlier test (Dixon's test, $\alpha = 0.05$). This test showed that run 22 could not be considered an outlier ($Q_{n=6,\alpha=0.05} = 0.48 < Q_{\text{crit.}} = 0.56$). Therefore this run was included for the statistical analysis.

Runs 1, 6, 20, 21, 25, and 26 did not succeed, because the powder bed was overwetted. Because of the results of these runs, it was decided not to perform runs 5 and 24, which certainly would also result in overwetting. Almost all runs that did not succeed have a low level of inlet airflow rate and/or of inlet air temperature and/or high level of spray rate in their variable combinations (see the cube plots, Fig. 1) and high powder bed moisture content (Table 2). These process variables interact resulting in high powder bed moisture content and therefore also in overwetted powder beds.

The results obtained from the previous study on a small scale were confirmed in the sense that the largest granules (runs 2, 12, 18, 23) are obtained at high levels of spray rate. The high spray rate promotes granule growth via excessive liquid supply and large droplet size. Almost all acceptable granules were obtained at low level of spray rate (runs 3, 9, 14–16, 27, 28). These results show that the spray rate had a profound effect on the granule size. From the results it was clear that the granule size was affected also by the other three process variables. Small granules were obtained at high airflow and inlet air temperature settings. The four process variables determine the powder

Table 2
Face-centered central composite design and the granule properties

Run	Process variables					Response			
	Inlet air flow rate (Nm^3/h)	Inlet air temperature (°C)	Spray rate (g/min)	Inlet air humidity (g/kg)	Powder bed moisture content (%)	Granule size (μm)	LOD (%)	Hausner index	a.o.r (°)
1	500	70	340	6.01	28.6	[b]			
2	1100	40	340	6.01	27.0	592	2.81	1.17	31.58
3	1100	40	240	6.01	13.6	432	2.44	1.22	33.42
4	800	55	290	10.03	20.3	497[a]	2.89	1.19	34.66
5	500	40	340	14	47.6	[c]			
6	500	40	240	6.01	38.0	[b]			
7	800	55	290	10.03	20.3	484[a]	2.65	1.21	33.81
8	800	55	290	14	22.7	572	2.93	1.20	33.67
9	1100	70	240	6.01	0.0	336	2.57	1.24	40.36
10	500	70	240	14	16.1	584	2.86	1.19	32.79
11	1100	70	340	6.01	0.0	518	3.37	1.21	35.04
12	1100	40	340	12.23	33.4	811	2.88	1.15	
13	800	55	290	10.03	20.3	493[a]	2.71	1.19	33.28
14	1100	40	240	12.23	22.6	429	2.99	1.20	34.42
15	500	70	240	6.01	15.7	421	2.82	1.22	35.22
16	1100	70	240	12.23	0.0	342	2.91	1.21	40.05
17	800	70	290	10.03	4.6	478	3.19	1.18	35.97
18	1100	70	340	12.23	0.0	610	3.65	1.16	36.06
19	800	55	290	6.01	17.2	533	2.59	1.19	33.92
20	500	70	340	14	28.9	[b]			
21	500	55	290	10.03	34.5	[b]			
22	800	55	290	10.03	20.3	585[a]	2.93	1.16	32.31
23	800	55	340	10.03	26.1	736	2.72	1.18	33.25
24	500	40	340	6.01	44.3	[c]			
25	500	40	240	14	42.7	[b]			
26	800	40	290	10.03	35.1	[b]			
27	1100	55	290	10.03	6.2	409	3.27	1.21	36.64
28	800	55	240	10.03	12.2	414	2.79	1.20	33.50
29	800	55	290	10.03	20.3	537[a]	2.72	1.18	34.22
30	800	55	290	10.03	20.3	487[a]	2.57	1.19	34.25

[a] Replicates.
[b] Overwetted.
[c] Not performed. LOD, loss on drying; aor, angle of repose.

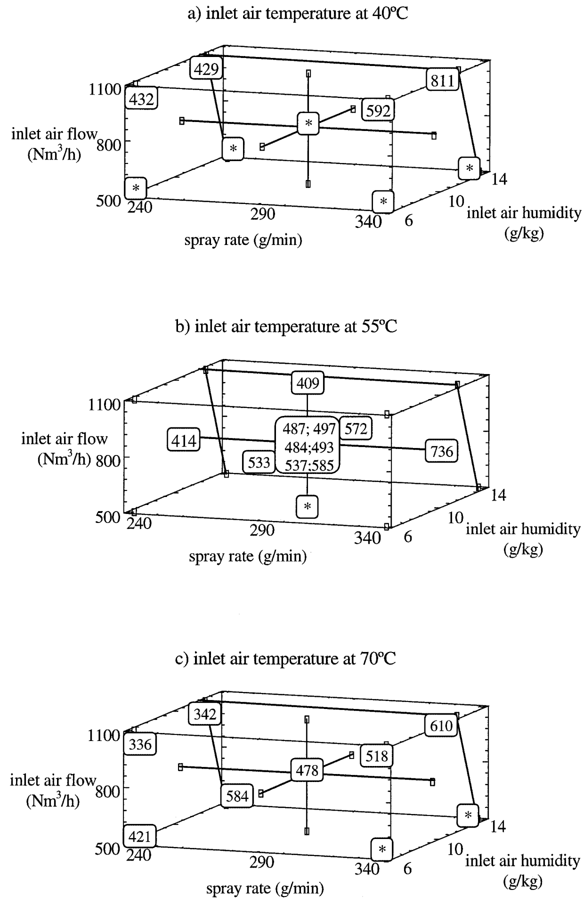

Fig. 1. Cube plots of the observed granule size (μm) in the face-centered central composite design at different settings of process variables. (* indicates that these factor combinations did not succeeded).

bed moisture content and the droplet size of the binder solution, thus, more fundamentally, the granule size was affected by the powder bed moisture content and the droplet size.

Table 2 shows that the granule size increased proportionally with the powder bed moisture content, except for some runs (runs 11 and 18). These runs were carried out at a high spray rate level, indicating that the relatively large granule size was caused by large droplets.

The granulation in run 12 was successful, in spite of its high powder bed moisture content, which was comparable with the overwetted runs. Run 12 was carried out at a high airflow rate, which exercised an enhanced deformation force on the agglomerated granules and prevented overwetting of the powder bed. The granulation results confirmed that the granule size is a result of equilibrium between the granule growth (powder bed moisture and droplet size) and the deformation force exercised on the agglomerated granules (airflow rate) (Sherrington and Oliver, 1981).

It was decided to develop two models for the granule size, an empirical model based on the four adjustable process parameters and a fundamental model based on the powder bed moisture content, the droplet size and the airflow rate.

3.1.1. Empirical model

A quadratic model was proposed for the granule size. As missing data occurred, the usual analysis of variance was not appropriate and therefore a multiple regression analysis in order to evaluate the variables was recommended (Montgomery, 1997). The quadratic polynomial model is:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{14}X_1X_4 + b_{23}X_2X_3 + b_{24}X_2X_4 + b_{34}X_3X_4 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 + b_{44}X_4^2 + e \quad (3)$$

where Y is the estimated response, X_i is the scaled independent process variable (-1 = low level, 0 = central level and $+1$ = high level) and b_i represents the model coefficient for variable i and e, is the error term, the difference between the predicted and the observed value.

A stepwise regression (hierarchical) was applied, which means that non-significant interaction effects were sequentially eliminated and only significant interaction coefficients ($P < 0.05$) were retained. The resulting regression model based on the scaled variables is:

$$\text{granule size}(\mu\text{m}) = 521 - 0.8361A - 54.61T + 130.41S + 49.72H + 77.91S^2 \quad (4)$$

where coefficients are given for the scaled independent variables: A is airflow rate, T is inlet air temperature, S is spray rate and H is inlet air humidity.

In order to evaluate the adequacy of the empirical model, an analysis of the residuals was performed. Fig. 2 shows the analysis of the residuals obtained from the difference between the predicted granule size in Eq. (4) and the observed granule size. The residuals were normally distributed. It can therefore be concluded that the model proposed in Eq. (4) fits the observed granule size adequately.

Fig. 3 shows the contour plots of the granule size as a function of the actual process variable values obtained from Eq. (4). The optimization goal was set to a granule size between 300 and 500 µm. The contour plots showed that the conditions of Fig. 3 d, g, h give the best results for the optimal process settings.

3.1.2. Fundamental model

In order to develop a fundamental model, the powder bed moisture content at the end of the spraying process and the droplet size must be known for each run.

The powder bed moisture content can be determined from the liquid mass balance, if the liquid supply and the water evaporation is known (Ormos et al., 1973; Watano et al., 1996a,b,c). The liquid mass balance can be calculated from the empirical variable settings:

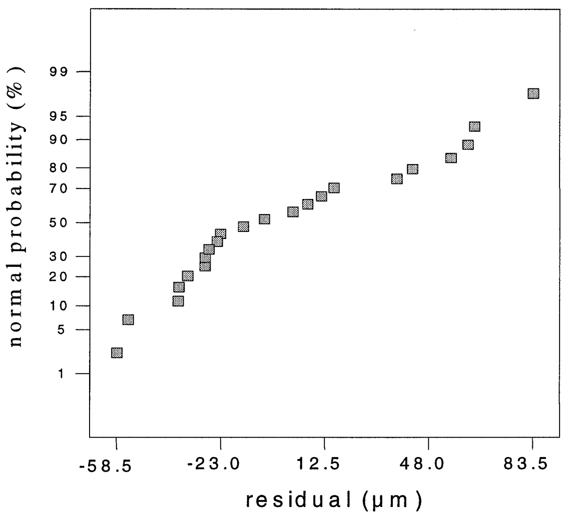

Fig. 2. Normal probability plot of the residuals obtained from the empirical model for the granule size.

$$S(1-C)t - A_i(H_o - H_i)t - A_n(H_n - H_o) = MP \tag{5}$$

where S is the average spray rate (g/min), C is the binder solution concentration (kg/kg), t is the spraying cycle (min), A_i and A_n are average inlet airflow rate (kg/min) and nozzle airflow (kg/min), respectively, H_o, H_i, H_n are the outlet air humidity, the inlet air humidity and nozzle air humidity (g/kg), respectively, M is the powder bed moisture content (kg/kg) and P is batch size (kg).

The outlet air humidity was determined from the inlet air temperature and the inlet air humidity with a Mollier diagram. Indeed, an adiabatic drying process was assumed and Ormos et al. (1973) have shown for the same type of process that a large part of the measured outlet air humidity was within 10% (w/w) of the saturated outlet air humidity. The nozzle inlet air humidity was zero.

The theoretical powder bed moisture content was calculated for each run according to Eq. (5). A powder bed moisture content of zero was assigned to runs 9, 11, 16 and 18 with a spray drying process.

The droplet size depends mainly on the spray rate and the nozzle air pressure, given that other parameters are kept constant. According to the nozzle manufacturer, the droplet size depends on the ratio of the spray rate (S) and the nozzle airflow rate (A_n):

$$R = S/A_n^2 \tag{6}$$

Schaefer and Worts (1978a) have shown that the granule size increases when the droplet size increases. The ratio, R, is used as a measure for the droplet size. The larger the R ratio, the larger the droplet size will be and therefore the larger the granule size.

The following quadratic fundamental model was postulated for the geometric granule size based on the powder bed moisture content, a measure for the droplet size and the airflow rate:

$$Y = b_0 + b_1M + b_2R + b_3A + b_{12}MR + b_{13}MA + b_{23}RA + b_{11}M^2 + b_{22}R^2 + b_{33}A^2 + e \tag{7}$$

where Y is the geometric granule size, M is the scaled powder bed moisture content, R is the scaled measure for the droplet size, A is the scaled airflow rate, b_i and b_{ij} are the coefficients of the

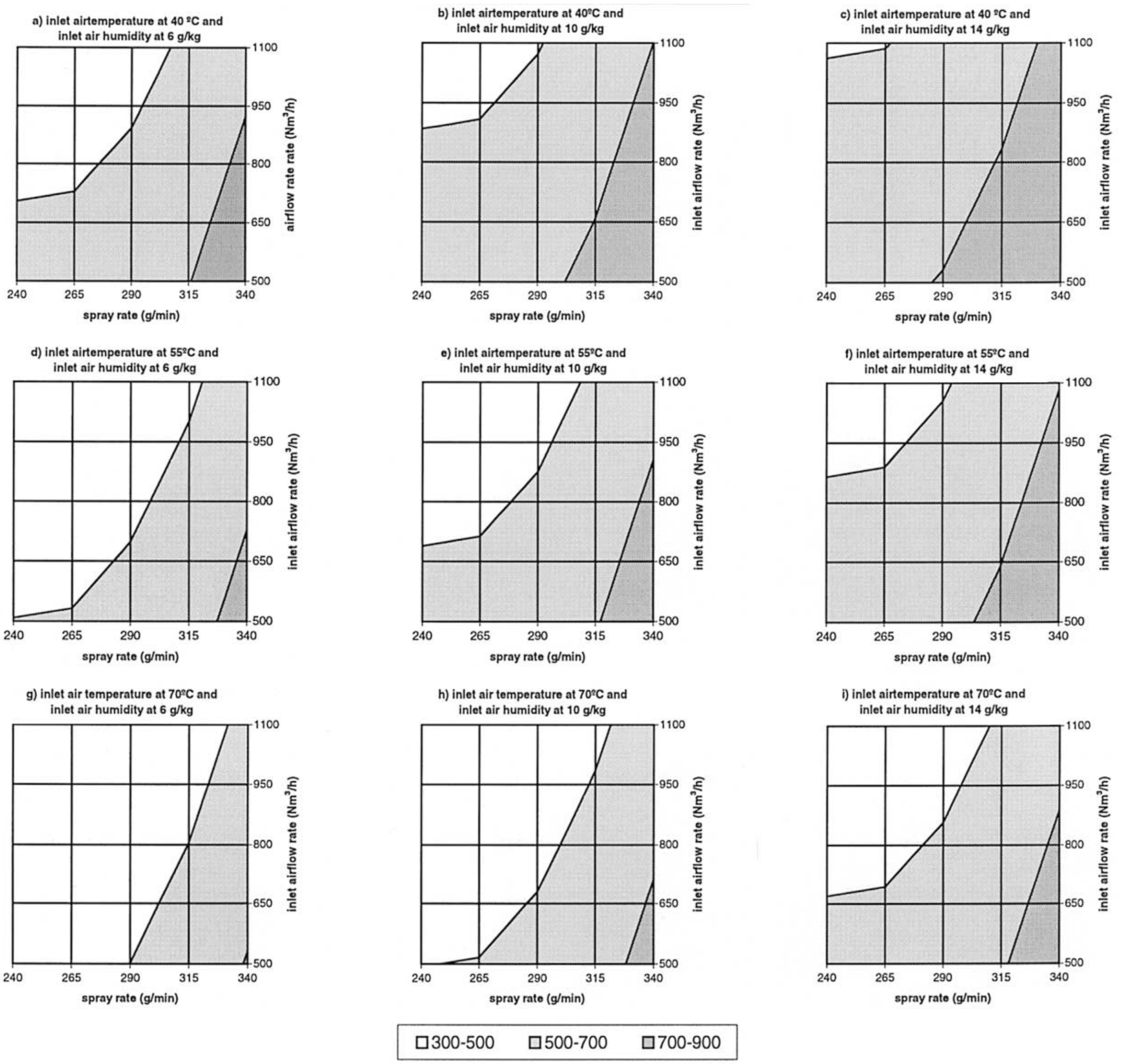

Fig. 3. Contour plots of the predicted granule size based on the empirical model of the process variables.

variables and e is the error term (the difference between the predicted and the observed response).

Since both Eqs. (5) and (6) contained the spray rate (S), the powder bed moisture content and the ratio for the droplet size are correlated. Using strongly correlated variables can lead to numerical instability. However, the correlation coefficient between these parameters was found to be only -0.38.

In the polynomial model [Eq. (7)] the same stepwise regression modeling (hierarchical) was performed as for the empirical model. The regression model, based on the scaled variables is:

$$\text{Granule size} = 540.53 + 101.99M + 113.05R - 38.55A + 62.83R^2 + 14.78MA \quad (8)$$

Fig. 4 shows the analysis of the residuals obtained from the difference between the granule size predicted by Eq. (8) and the observed granule

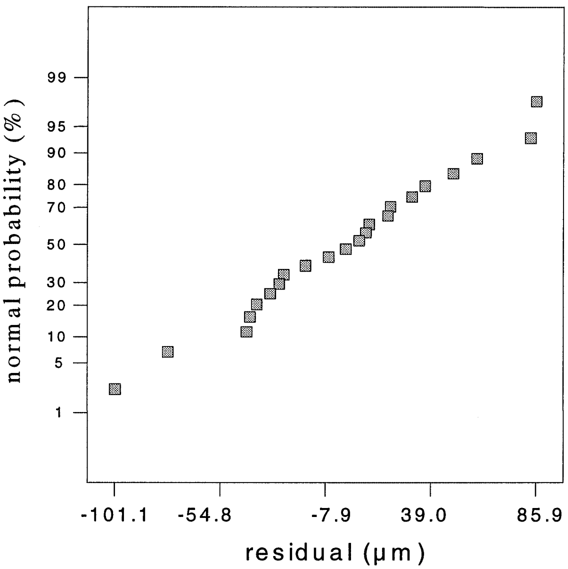

Fig. 4. Normal probability plot of the residuals obtained from the fundamental model for the granule size.

size. The residuals were normally distributed. It can therefore be concluded that the model proposed in Eq. (8) fitted the observed granule size adequately.

Fig. 5 shows the contour plots of the granule size as a function of the actual powder bed moisture content and the ratio for droplet size at different airflow rates, obtained from Eq. (8). These plots show that optimal granule size was obtained at low powder bed moisture content, low to central level of the ratio for the droplet size and at a central and high level of airflow rate. At higher airflow rates, the granulation is successful at larger powder bed moisture contents, due to the enhanced deformation force by the airflow rate.

3.1.3. Selection of optimal parameter settings for the granule size

The selection of the optimal parameter settings was based on the contour plots of the empirical model.

Fig. 5. Contour plots of the granule size predicted from the fundamental model of the powder bed moisture content, the ratio for the droplet size and the airflow rate.

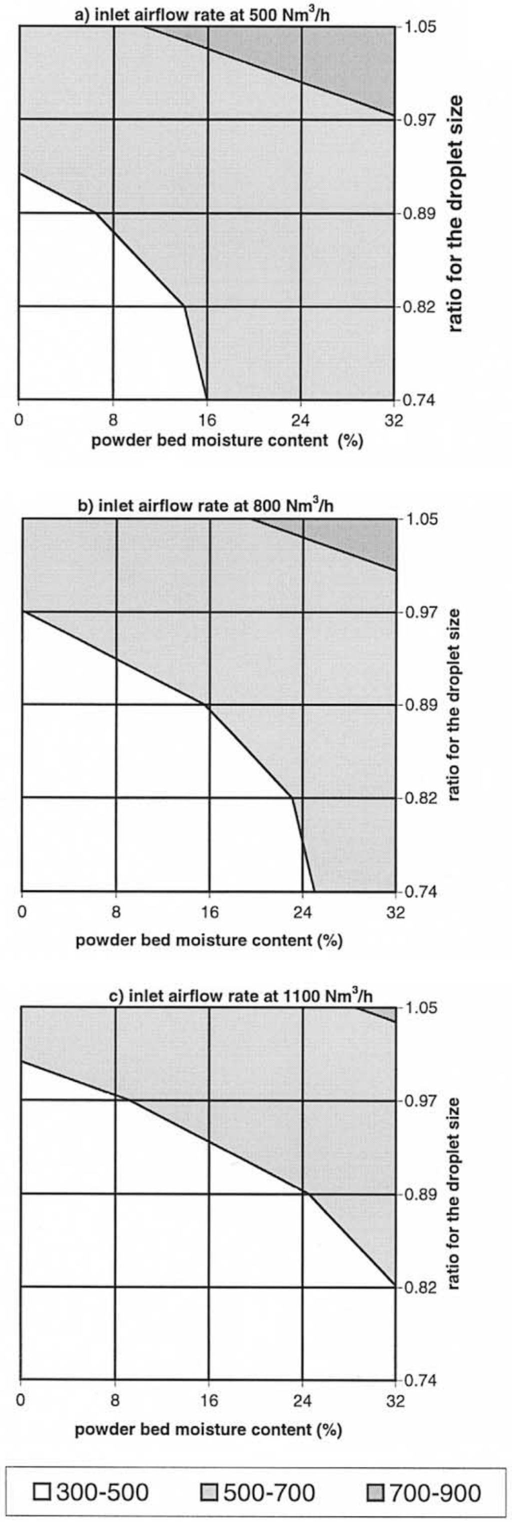

Fig. 5. (*Continued*)

They showed that the best conditions for the optimal granule size were found in Fig. 3d, g, h. In Fig. 3d the inlet temperature setting was at a central level and in Fig. 3g, h it was at a high level. It is preferred to keep the inlet air temperature at relatively low levels in order to obtain granules of better quality (less friability, less fine and better flow properties) (Parikh et al., 1997). Therefore, it was decided to select the optimal parameter setting from Fig. 3d. The selected optimal selected parameter settings are given in Table 3. These optimal parameter settings yielded according to the empirical model a granule size of 448 ± 111 μm and according to the fundamental model a granule size of 427 ± 149 μm. Two runs were performed at these parameter settings, resulting in a mean granule size of 404 μm, which was within the confidence interval of both models.

An additional run at a higher inlet air temperature (70°C), airflow rate (950 Nm^3/h), at central spray rate level (290 g/min) and low inlet air humidity level (6 g/kg) was performed in order to validate the regression model. The empirical and the fundamental model predicted granule sizes of 375 ± 116 μm and 412 ± 140 μm, respectively. A granule size of 394 μm was observed at these parameter settings, which was within the predicted granule size, thereby confirming the validity of the models.

In a previous study (Rambali et al., 2001), the small fluid-bed scale with the same ratio between the spray rate and the airflow rate as on this medium scale (Mehta, 1988) resulted in granule sizes between 348 and 458 μm (at an inlet air temperature of 55°C), which was in good agreement with the granule sizes found for the chosen optimal condition on a medium scale.

3.2. Other granule physical properties

The granule size is the most important variable for the evaluation of the granulation process. Besides the particle size, other granule characteristics also determine the granule quality. This means that these granule characteristics must be acceptable at the optimal operating conditions of the fluid bed. Therefore, it was investigated whether these granule characteristics complied with the criteria.

3.2.1. Loss on drying (LOD)

The LOD is a measure of the drying ability of the granulation process. LOD values less than 3.5% (w/w) were considered to be acceptable for the subsequent tabletting process. Table 2 summarizes the LOD of the runs. Almost all runs complied with the objective. Only run 18 gave a slightly higher LOD [3.65% (w/w)]. Because almost all the runs resulted in an acceptable LOD, it was concluded that a Granule size between 300 and 500 μm would result in an acceptable LOD. This was confirmed by the two runs performed at the chosen variable combination, which resulted in LOD values of 2.53% and 2.40%, respectively.

3.2.2. Hausner index

The Hausner index gives a measure of the packing of the granules. Smaller granules tend to have greater cohesiveness due to high surface-to-

Table 3
Observed granule size and predicted by the empirical and fundamental models of the optimal and variable runs

	Predicted granule size (μm)		Observed granule size (μm)
	Empirical model	Fundamental model	
Optimal[a]			
Run 1	448 ± 111	427 ± 149	363
Run 2			445
Variable run[b]	375 ± 116	412 ± 140	394

[a] Air temperature (55°C), airflow rate (885 Nm^3/h), spray rate (290 g/min) and inlet air humidity (6 g/l).
[b] Air temperature (70°C), airflow rate (950 Nm^3/h), spray rate (290 g/min) and inlet air humidity (6 g/l).

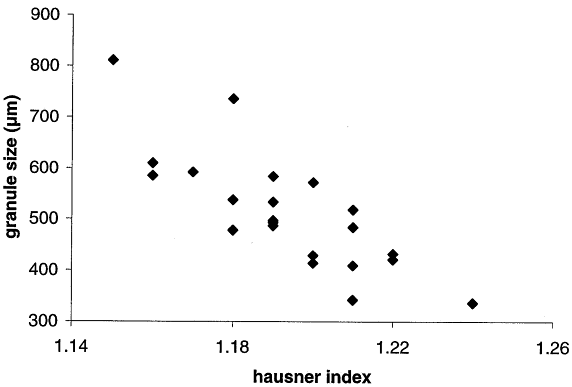

Fig. 6. The observed granule size as a function of the observed Hausner index.

mass ratio and result in greater bulk density (Fonner et al., 1981). Therefore, the Hausner index tends to increase with smaller granule size. The Hausner index of the runs is summarized in Table 2. The Hausner index was highly correlated with granule size ($P < 0.0001$) (Fig. 6). Hausner indices lower than 1.22 were considered to be acceptable, because the granules are then considered to be free-flowing (Fonner et al., 1981). Except for run 9, all the runs resulted in acceptable Hausner indices, which means that granule sizes between 300 and 500 µm will probably result in an acceptable Hausner index. This was confirmed by the two runs performed under the chosen variable combination, which resulted in Hausner indices of 1.18 and 1.17, respectively.

3.2.3. Angle of repose

The angle of repose (aor) is used to characterize the granule flow. Small granules tend to have high surface-to-mass ratio, which results in low viscosity. The aor of the runs are summarized in Table 2. Fig. 7 confirms that the aor decreases when the granule size increases. Angles of repose less than 400 were considered to be acceptable (Fonner et al., 1981). All the runs complied with the objective. The two runs performed under the chosen variable combination also complied with the objective for the aor. The values obtained for the aor for the two runs were 35.7 and 34.8, respectively.

4. Conclusions

This study shows that experimental design was an appropriate method to optimize the granulation process on the medium scale. It was shown in this study that granule size of the granulation could be optimized empirically, by considering the process variables. Optimal granules were obtained at low and central levels of the spray rate and inlet air humidity and central or high levels of the inlet air temperature and airflow rate.

However, the granule size is the result of the balance between granule growth affected by the powder bed moisture content and the droplet size and the deformation force affected by the airflow rate. Therefore, the granule size could also be optimized by a fundamental model, based on the three fundamental variables, the powder moisture content, the droplet size and the airflow rate. An optimal granule size was obtained at low levels of the powder bed moisture content and at low and central levels of the droplet size and at central and high levels of the airflow rate.

Additional experiments performed at the optimal variable settings confirmed the validity of the proposed models. Other granule properties were shown to be within the desired limits of the variable settings, optimal for granule size.

The granule size found at optimal variable settings were comparable with the granule size found at the small scale with the same ratio between the

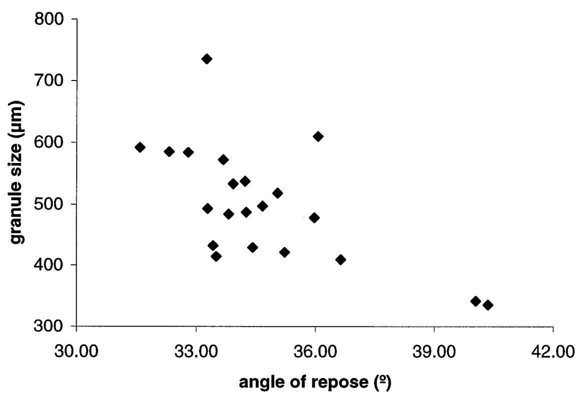

Fig. 7. The observed granule size as a function of the observed angle of repose.

spray and airflow rates. Using this ratio for scaling-up the granulation process is therefore useful.

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