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Scaling up of the fluidized bed granulation process

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Abstract

The scaling up of a fluidized bed granulation process from small scale to production scale is often done empirically in the pharmaceutical industry. In this study, a more practical and systematic method was developed in order to achieve a similar granule size in the scaled up fluid bed. The scaling up is based on the relative droplet size, and the powder bed moisture content at the end of the spraying cycle. The present study describes the scaling up of the fluidized granulation process from small (5 kg scale) to medium (30 kg scale) and to production fluid bed scale (120 kg scale). The granulation process is scaled up with as target a geometric mean granule size of 400 μm. First, the effect of the relative droplet size on the granule size was investigated in the different fluid beds. The effect of the change in relative droplet size on the granule size was different for each fluid bed. Second, experimental design is applied on the small and the medium fluid scale, and regression models for the granule size are proposed in order to scale up the granulation process on the small to medium scale. The granulation process was also successful by scaling-up to the large fluid bed, considering only the relative droplet size.

Keywords: Granulation process; Fluid bed; Granule size; Scaling up; Experimental design

1. Introduction

The fluidized granulation process is a complex process, influenced by several process variables (Rambali et al., 2001a). Due to this complex process, it is difficult to scale-up the granulation process based only on the process variables. The scaling-up of the fluidized granulation process from small scale to production scale is often done empirically in the pharmaceutical industry. Mehta (1988) recommended the scaling-up of the process by increasing the spray rate proportionally with the inlet air volume or the cross-sectional area of the air-distributor plate. However, this method will not always yield acceptable results, since the granule size also depends on more fundamental parameters (Rambali et al., 2001b), such as the droplet size (Schaefer and Worts, 1978) and the powder bed moisture content (Watano et al., 1996a,b,c). Therefore, these parameters must also be considered during scaling-up. The droplet size mainly depends on the spray rate and the nozzle settings. The powder bed moisture content depends on the balance between liquid evaporation and liquid supply. The fundamental parameters are affected by the process variables. It is desirable that process variables are chosen in such a way that the fundamental variable droplet size and the moisture content are kept constant in the different fluid bed scales. Although the theoretical base for granule growth in the fluid bed granulation is known (Sherrington and Oliver, 1981; Schaafsma,

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2000), few studies have been published on scaling-up of the fluid bed granulation based on the moisture content (Watano et al., 1996a,b,c) and the droplet size (Schaefer and Worts, 1977). The present study describes the scaling up of the fluidized granulation process from small (5 kg scale) to medium (30 kg scale) and to production fluid bed scale (120 kg scale). In this study, a more practical and systematic method is applied in order to achieve a similar granule size in the scaled up fluid bed. The scaling-up of the fluidized granulation process was investigated using a calculated measure of relative droplet size, and the powder bed moisture content. The granulation process was scaled up with as target a geometric mean granule size of 400 μm. First, the effect of the relative droplet size on the granule size will be investigated in the different fluid beds. This selected granule size was successfully scaled-up to larger scales (medium and production scales) based on the moisture content of the bed and the relative droplet size.

2. Materials and methods

2.1. Equipment

Three sizes of fluid beds were used: small fluid bed (5 kg batch size, GPCG-5), medium fluid bed (30 kg batch size, GPCG-30) and large fluid bed (120 kg batch size, WSG-120). The geometrical dimensions of the fluid beds are given in Table 1. The fluid beds were manufactured by Glatt GmbH (Binzen, West-Germany). Although, the same manufacturer produced the fluid beds, the granulation process cycle differs between the fluid beds. The granulation process cycle in the small and large fluid bed is discontinuous; it consists of a spraying time interval and a shaking time interval. During the spraying time interval, the binder solution is sprayed on the fluidized powder bed. The spraying and the air fluidization are stopped during the shaking time interval, and the filters are shaken in order to release the entrapped particles caught during spraying. The spraying interval and the shaking time interval were fixed at 35 and 7 s, respectively. The granulation process in the medium fluid bed is continuous; the spraying and the air fluidization are not stopped during the shaking of the filter. Both filters were shaken alternately during 7 s and the spraying interval was 35 s. Furthermore, the inlet air of the small fluid bed could not be conditioned for the inlet air humidity and therefore the inlet air humidity depended on the weather conditions. The inlet air humidity in the small fluid bed was registered before each experiment and was used to adjust the granulation process settings, such as the powder bed moisture content (Rambali et al., 2001b). The medium fluid bed enabled the conditioning of the inlet air humidity and therefore the inlet air humidity could be set precisely. The inlet air of the large fluid bed was dehumidified to 4 g/kg dry air and was constant during the process.

The nozzle type (model 942, Düsen-Schlick, Untersiemau, Germany) with one nozzle head was the same in the small and medium fluid beds. A different nozzle type (model 937, Düsen-Schlick, Untersiemau, Germany) with three nozzle heads was used in the large fluid bed.

Table 1
The geometrical dimensions of the three fluid beds

	Fluid beds		
	GPCG-5	GPCG-30	WSG-120
Batch size (kg)	5	30	120
Area distributor (m^2)	0.04	0.2	0.636
Volume container	22	100	420
Volume expansion chamber (m^3)	0.19	1.42	1.14
Nozzle orifice (mm)	1.8	1.8	3 × 3.0
Nozzle height (m)	0.74	0.81	1.02

GPCG-5 is small scale, GPCG-30 is medium scale and WSG-120 is large scale.

2.2. Granulation process

The granules were produced in three fluid bed scales (small (laboratory, 3.965 kg), medium (laboratory, 29.735 kg) and large (production, 119.96 kg)). The composition of the powder bed at the start of the granulations was: 70.7% (w/w) lactose monohydrate 200 mesh (DMV, Veghel, The Netherlands), 27.0% (w/w) corn starch (Cerestar, Sas van Gent, The Netherlands), 2.3% (w/w) hydroxypropylmethylcellulose 2910 15 cps (HPMC) (Dow, Midland, USA). The quantity for each fluid bed is given in Table 2.

A 4% (w/w) HPMC binder solution was prepared by mixing HPMC with 1/4 of the water at >80 °C.

Table 2
Compositions (in kg) of the powder bed

	Fluid beds		
	GPCG-5	GPCG-30	WSG-120
Lactose monohydrate 200 mesh	2.803	21.02	84.8
Corn starch	1.07	8.025	32.4
HPMC	0.092	0.69	2.76

HPMC: hydroxypropylmethylcellulose 2910 15 cps. GPCG-5 is small scale, GPCG-30 is medium scale and WSG-120 is large scale.

After mixing for 5–10 min, the rest of the water at room temperature was added. The binding solution was cooled off overnight and was used within 24 h after preparation. The lactose and the cornstarch were placed in the powder bed container of the fluid bed and mixed by using airflow (see Table 3) till the inlet air temperature was reached necessary for the spraying cycle. During the spraying cycle, the binder solution was sprayed on the fluidizing powder bed (top spray). The spraying process was carried out according to the settings of the process parameters for that specific granulation run. Spraying continued until all the binder solution was used and afterwards water was sprayed for ±1 min in order to rinse the tubes. During the spraying process, every 10 min, ±10 g samples were taken from the powder bed for moisture content determination. The moisture content was determined according to the method used by Rambali et al. (2001b). The wetted granules were dried by fluidizing with heated air of 75 °C; the drying airflow rates is given in Table 3. The drying cycle was terminated when the outlet air temperature reached 35 °C. After this cycle, the granules were collected and sampled for sieve analysis. The sieve analysis was carried according to the method used by Rambali et al. (2001a).

Table 3
Process settings for the investigation of the ratio on the granule size

	Fluid beds		
	GPCG-5	GPCG-30	WSG-120
Mixing air flow rate (m^3/h)	143	500	1500
Spray rate (g/min)	78	290	965
Spraying inlet air temperature (°C)	70	70	70
Drying air flow rate (m^3/h)	200	885	2950

GPCG-5 is small scale, GPCG-30 is medium scale and WSG-120 is large scale.

2.3. Scaling-up principles

Two systems are geometrically similar when the ratio of the linear dimensions of the small and the scaled-up system are constant (Leuenberger, 1983). It is obvious from Table 1 that the fluid beds are not geometrically similar to each other. The volume of the expansion chamber and the area of the air-distributor plate do not increase proportionally with the batch size from small fluid bed scale to the medium scale and to large scale. If the granulation process was scaled up by the batch size then the inlet airflow rate in the large fluid bed scale would be too large and the powder particles would become entrapped in the filter. A better approach is to scale up by the air-distributor area, in order to have a similar fluidizing profile in all fluid beds. This will result in a constant air velocity through the air-distributor. However, the drying capacity of the air per kilogram powder will be relatively lower (at constant inlet air condition) in the larger fluid bed scale compared to small fluid bed. In order to keep evaporation of liquid constant, the spray rate must be corrected by the airflow rate and the batch size. Furthermore, the droplet size must be similar in the different fluid beds. Mehta (1988) used an approximation for the scaling-up of the spray rate by using the ratio of the cross-sectional areas of the air-distributor plates. When the spray rate is known, then the droplet size in the scaled fluid bed can be adjusted by the nozzle airflow rate.

In this study the scaling-up of the fluidized granulation process from small fluid bed scale to medium and large fluid bed scales was investigated by looking at the effect of the powder bed moisture content at the end of the spraying process and the droplet size on the granule size. The calculation of powder bed moisture content was performed according to the equation proposed by Rambali et al. (2001b). The airflow velocity through the air distributor will be kept as much as possible constant in the three fluid beds, in order to have a constant airflow profile and to have approximately similar breaking force effect on the granules.

The droplet size is calculated by taking the mass ratio of the air-to-liquid in the nozzle (Schaefer and Worts, 1977). The droplet production by the nozzle is based on a binary system of air and liquid; pressurized air is used to disperse the liquid binder solution into droplets. According to the information supplied by the manufacturer of the nozzle, the droplet size is proportional to the ratio of the liquid-mass to the quadratic of the air mass in the nozzle:

$$R \sim \frac{S}{V^2} \tag{1}$$

where R is the ratio, S is the spray rate (g/min) and V is the airflow through the nozzle (g/min).

In the large fluid bed scale the ratio was calculated for one nozzle head and was assumed to be the same for the other heads.

The ratio in Eq. (1) is used in this work to provide a relative estimate of the droplet size.

2.4. Experimental design and analysis of results

The experimental designs were developed by the graphic software "STATGRAPHICS PLUS" version 2.1 (STSC Inc., Rockville, MD, USA). The statistical analyses of the measured response parameters were also carried out with this software.

3. Results and discussion

3.1. The effect of the droplet size on the scaling-up

The effect of the droplet size on the granule size was investigated by varying the relative droplet size (R) in the three fluid beds. The relative droplet size was varied by adjusting the airflow rate through the nozzle. The other process variables settings were kept constant during these experiments (Table 3). The inlet airflow rate was adjusted by taking similar air velocity through the air distributor in the different fluid bed scales (1.25–1.29 m/s). A high spraying inlet air temperature (70 °C) was used in order to achieve a spray drying process. The high temperature minimizes the effect of the powder bed moisture content on the granule size and the granule growth was considered to be small (Schaafsma, 2000). The moisture content was always around 5% (w/w) (Fig. 1) after spraying.

Fig. 2 shows the effect of the relative droplet size (R) on the granule size. In all fluid beds, the granule

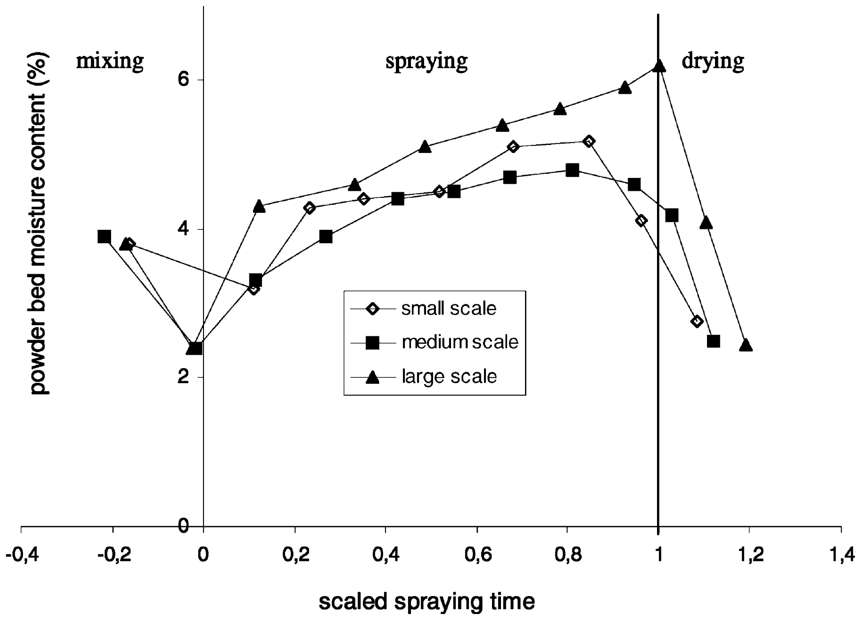

Fig. 1. The powder bed moisture content in function of the scaled spraying time for different fluid bed scales (mixing period ends at time 0, spraying starts at time 0 and ends at time 1 and drying period begins at time 1).

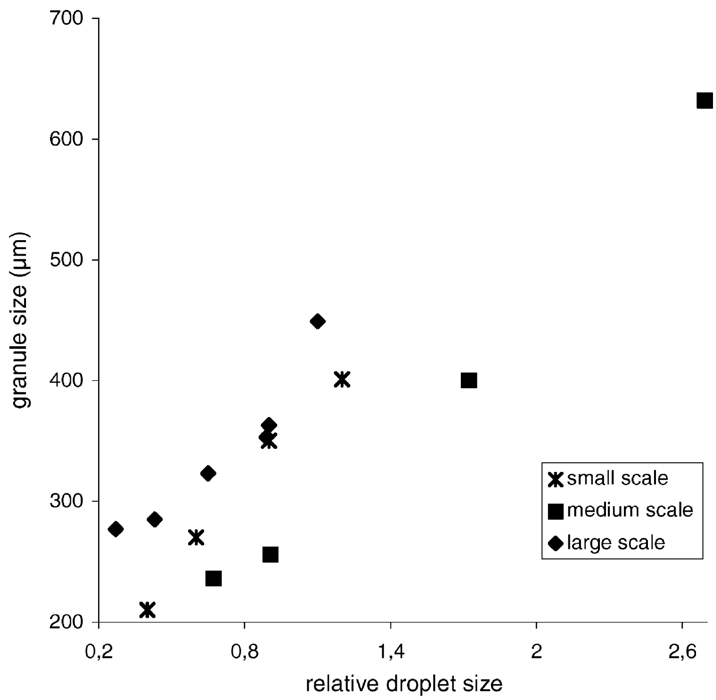

Fig. 2. The effect of the relative droplet size on the granule size in the various fluid bed scales.

size was correlated with *R*. The results summarized in that figure show that the effect of *R* on the granule size shifted towards the right with increasing fluid bed scale. Although the same nozzle type was used in both the small and medium fluid bed scale, the effect of *R* on the granule size was not the same. The granules tend to become smaller in the larger fluid beds than in the small fluid bed at the same setting of *R*. This difference should probably be attributed to the disproportional increase of the batch loading compared to the spray rate. The ratio spray rate to batch size in the small fluid bed (20.9 g/min/kg) was more than twice as large as in the medium fluid bed (9.98 g/min/kg/min) and in the large fluid bed (8.2 g/min/kg). Therefore, relatively more droplets are available in the small fluid bed than in the medium and large fluid beds. Also the attrition effect on the granules becomes higher with increasing fluid bed scale, due to the increased batch size (Parikh et al., 1997). Therefore, these cause the granules to decrease with increasing fluid bed scales at the same fundamental fluid bed settings.

Furthermore, the different nozzle type (with three heads) in the large fluid bed scale and the larger nozzle orifice may explain the different effect of *R* on the granule size in the large fluid bed. The granule size of the granules produced at a ratio of ±0.9 by the small scales was comparable to the size of the granules produced by the large fluid bed scale at a ratio of ±1.7.

3.2. Optimization of the granulation process on the small scale

The granulation process on the small scale was optimized by the calculated relative droplet size® and the powder bed moisture content. A granule size of 400 μm was the target granule size. In the previous section, it was shown that the relative droplet size has a significant effect on the granule size, if the moisture content of the bed was around 5% (w/w). A powder bed moisture content higher than ±15% (w/w) could lead to uncontrollable granule growth (Holm et al., 1983; Kristensen, 1988) and fluidization of the powder bed would become difficult. Therefore, the moisture content of the bed was varied between a spray drying process (5 and 15% (w/w)). The lower limit of *R* was set to 0.5, because previous results for granulation at different ratios showed that a ratio of 0.43 resulted in too small granule size (229 μm). The upper limit of R was set to 1.1, because an upper limit for R of 1.2 could be achieved by the small scale equipment.

Based on an earlier developed model (Rambali et al., 2001b) for the granule size on the medium fluid bed, the following quadratic model was proposed for the granule size on the small scale:

$$\text{Granule size} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + e \quad (2)$$

where β's are the coefficients of the model, X_1 is the powdered moisture content (Mp), X_2 is the relative droplet size (R) and e is the residual error.

A three level factorial design was proposed in order to estimate the parameters of the model proposed in Eq. (2). This design is equivalent to a central composite design with two variables (Montgomery, 1997). This sort of designs is convenient to perform, because only three variable levels are present. Other central composite designs (orthogonal), which contain five levels, are difficult to perform considering the granulation experimental settings. The settings of the design are given in Table 4. Because the humidity of the inlet air could not be conditioned, the powder bed moisture content level in the design could not be set precisely. The powder bed moisture content was calculated before the experiment was performed according to the equation mentioned previously (Rambali et al., 2001b). The actual values varied somewhat around the intended setting in the design. It means that the conventional experimental design analysis was not suitable and regression analysis has to be applied. Table 5 shows the design with the results. From results in this table it can be concluded that the relative droplet size has the largest effect on the granule size. As expected, large binder droplets produce large granules. The powder bed moisture content did not have such a large effect on the granule compared with R. The high level of the moisture content was chosen such that ball growth would be prevented. This could explain the small effect of the powder bed moisture content on the granule size. The granule size results in Table 5 show that the effect of the powder bed moisture content on the granule size was more pronounced at high level of moisture content. Therefore, it seems reasonable to use a moisture content of around 10% (w/w) for scaling-up purposes, as the effect of the moisture content at this level on the granule size is less pronounced.

Table 4
Settings of the factorial design applied on the small fluid bed

	Settings		
	Low (−1)	Central (0)	High (+1)
Powder bed moisture content (%)	5	10	15
Relative droplet size	0.5	0.8	1.1

Table 5
Runs of the factorial design applied on the small fluid bed

Run	Ratio[a]	Powder bed moisture content (%)[b]	Granule size (μm)
1	1.1	15.9	520
2	1.1	16.3	510
3	1.1	12.7	491
4	1.1	8.1	469
5	0.8	13.8	439
6	0.8	9.0	390
7	0.8	12.0	428
8	0.8	9.5	388
9	0.8	8.8	385
10	0.8	12.2	438
11	0.8	6.7	378
12	0.5	10.5	312
13	0.5	5.2	270
14	0.5	12.6	371

[a] Relative droplet size.
[b] Moisture content at the end of the spraying cycle.

A multiple regression analysis was applied on the results in order to develop a model for the granule size. The following model was obtained at the small scale:

$$\text{Granule size } (\mu\text{m}) = 402.81 + 47.60\text{Mp} + 76.78R - 18.75 \times \text{Mp} \times R \quad (3)$$

where Mp is the scaled powder bed moisture content and R is the scaled relative droplet size.

In order to evaluate the adequacy of the model, an analysis of the residuals was performed. Fig. 3 shows the normal probability plot of the studentized residuals. The residuals were normally distributed. It can therefore be concluded that the model proposed in Eq. (3) fitted the observed granule size adequately.

The contour plot based on Eq. (3) is given in Fig. 4. From the contour plot in Fig. 4 it can be observed that at the chosen optimal powder bed moisture content

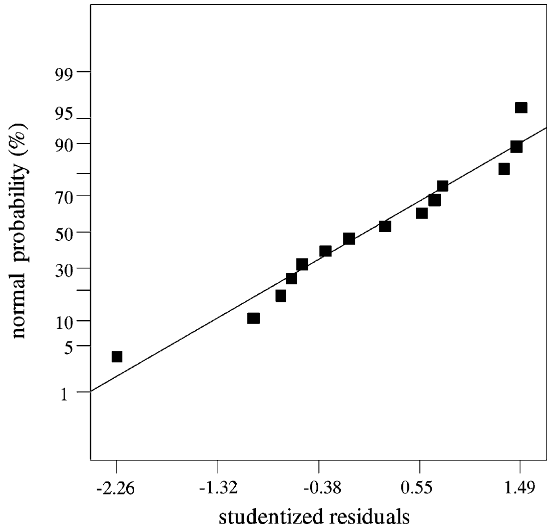

Fig. 3. Normal probability plot of the studentized residuals obtained from the regression model for the granule size of the small fluid bed.

(10% (w/w)), the optimal granules (±400 μm) were obtained for droplet sizes around 0.9.

The contour plot in Fig. 4 is analogous to the plot obtained for the medium fluid bed in a previous study (Rambali et al., 2001b). Comparing both contour plots, it seems possible to scale up the granulation process from small scale to the medium scale.

3.3. Scaling-up of the granulation process

Four runs were performed on the medium fluid bed, in order to evaluate the regression model for the granule size of the small fluid bed for scaling-up purposes. The granule size predicted by the regression model of the small fluid bed and the observed granule sizes obtained by the medium fluid bed are given in Table 6. Only the observed granule size of run 1 was within the confidence limit of the predicted granule size by the model for the granule size of the small fluid bed. The observed granule size of the other runs was considerable smaller than the predicted granule size. These results confirmed that the granule growth is different in the medium fluid bed scale compared with that in the

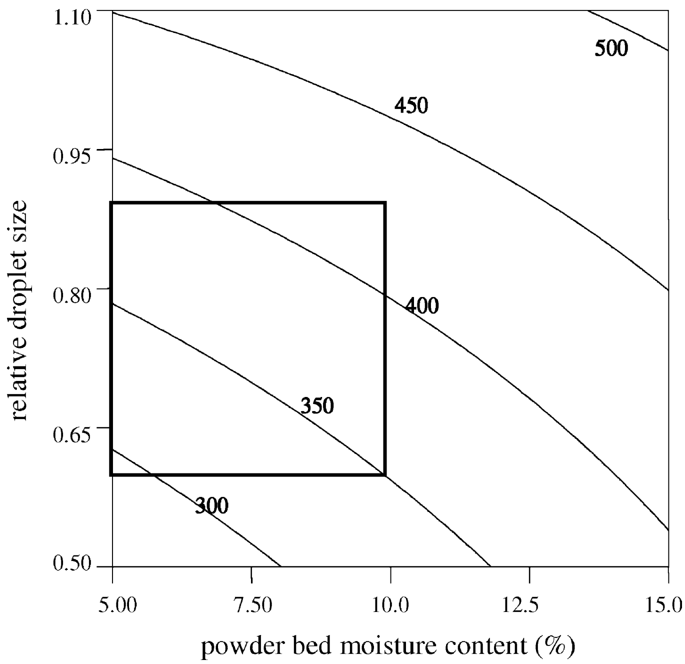

Fig. 4. Contour plot of the granule size (μm) in function of the powder bed moisture content and the relative droplet size of the small fluid bed scale (the runs represented by the vertices of the rectangular were performed on the medium fluid bed scale).

Table 6
Predicted and observed granule size for the medium fluid bed based on the model for the granule size of the small fluid bed

Run	Parameter setting		Granule size (μm)	
	Mp	R	Predicted	Observed
1	−1.07	−0.67	288 ± 30	270
2	−0.85	0.33	394 ± 29	310
3	0.22	−0.67	365 ± 26	302
4	0.28	0.33	441 ± 24	350

Mp: scaled moisture content of powder bed at the end of the spraying cycle; R: scaled relative droplet size.

small fluid bed scale. Possible reasons for this growth difference were explained in a previous section. The different results could be due to the different granulation process in the fluid beds (continuous versus discontinuous granulation process) and by the differences in droplet size as was confirmed in Fig. 2. The results from the four runs confirmed that the model for the granule size of the small scale is inadequate to predict the granule of the medium scale. Therefore a separate model for the granule size of the medium fluid bed scale was developed. We performed additional runs to the four performed runs on the medium fluid bed, such that a factorial design with three levels is obtained (Table 7). The range of the droplet size was adjusted for the equipment constraints of the medium fluid bed and was enlarged to obtain a similar range used in a previous study (Rambali et al., 2001b). The range of the powder bed moisture content was similar to the range used on the small fluid bed scale (Table 5). Table 7 shows the applied factorial design with the results.

Table 7
Factorial design applied on the medium fluid bed

Run	Ratio[a]	Moisture content (%)[b]	Granule size (μm)
1	0.6	14.8	299
2	1.2	6.1	401
3	0.6	11.1	302
4	0.6	4.7	270
5	0.9	5.8	310
6	0.9	11.4	350
7	1.2	15.0	506
8	0.9	14.7	360
9	1.2	10.8	438

[a] Relative droplet size.
[b] Moisture content at the end of the spraying cycle.

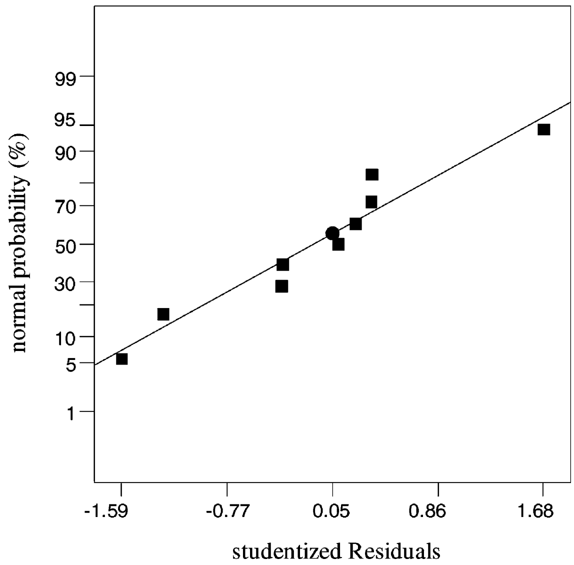

Fig. 5. Normal probability plot of the studentized residuals obtained from the regression model for the granule size of the medium fluid bed.

A quadratic model was proposed for the granule size based on the powder bed moisture content and the relative droplet size. The following model was proposed for the granule size:

$$\text{Granule size }(\mu\text{m}) = 332.50 + 37.17\text{Mp} + 78.41R + 21.69 \times \text{Mp} \times R + 27.06R^2 \quad (4)$$

where Mp is the scaled powder bed moisture content and R is the scaled relative droplet size.

The analysis of the residuals (Fig. 5) of the proposed model, showed that the residuals were distributed normally. It can therefore be concluded that Eq. (4) fits the observed granule size adequately.

The proposed regression model for the granule size of the small fluid bed was compared to the proposed model of the medium fluid bed. This comparison was performed by plotting the predicted granule sizes at similar fundamental granulation process settings (Fig. 6). When the models are equivalent to each other, then the predicted granule size by each model should be comparable. From the results in Fig. 6 it can be concluded that the predicted granule size by both models are highly correlated. However, the predicted granule size of the small fluid bed was systematically

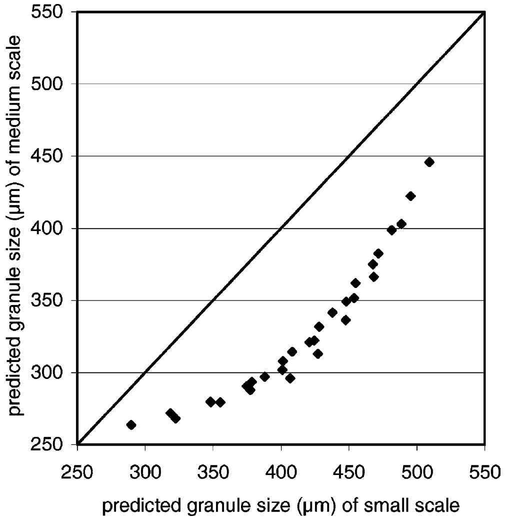

Fig. 6. Predicted granule size by the regression model of medium fluid bed scale in function of the predicted granule size by the regression model of the small fluid bed scale.

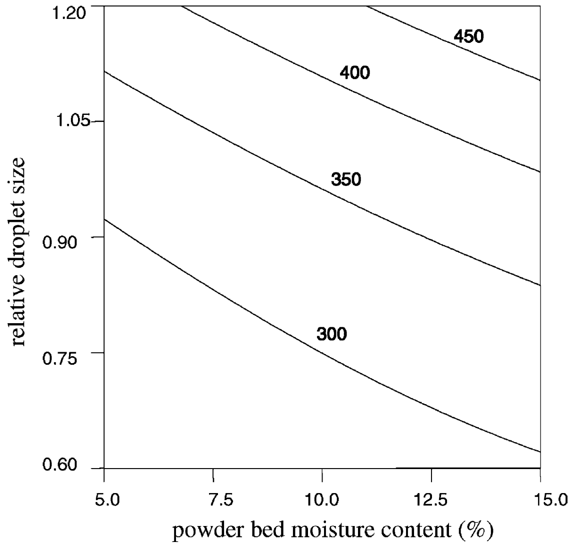

Fig. 7. Contour plot of the granule size (µm) in function of the powder bed moisture content and the relative droplet size of the medium fluid bed scale.

higher than the predicted granule size of the medium fluid at similar fundamental granulation process settings. The high correlation between the predicted granule sizes of both fluid bed scales seems to indicate that the proposed model for the granule size of the small fluid bed could be used to estimate the granule size on the medium fluid bed by adding a correction factor.

The contour plot based on Eq. (4) is given in Fig. 7. This contour plot is analogous to the contour plot previously obtained from the theoretical model (Rambali et al., 2001b), but is shifted towards the right in function of the powder bed moisture content. This is due to difference in definition for the powder bed moisture content in both models. In the current model is the powder bed moisture content the actual values as measured by loss on drying and in the previous model the calculated powder bed moisture content was used.

From the contour plot in Fig. 5 it can be observed that at the chosen optimal powder bed moisture content (10% (w/w)) in the small fluid bed, the optimal granules (±400 µm) are obtained at droplet sizes around 1.1 in the medium fluid bed. These process settings will be used for scaling-up purposes. For example, the optimal granulation process settings of the small fluid bed (10% (w/w) powder bed moisture content at droplet size of 0.9 (Fig. 3)) would give the same granule size on the medium fluid bed at the same powder bed moisture level, but at a larger droplet size (around 1.1, see Fig. 7). By scaling the granulation process to the large fluid bed the same principle could be applied. Based on the granule size in function of the relative droplet size (Fig. 2), the granulation process was scaled-up to the large fluid bed scale in the same way. The powder bed moisture content was set at 10% and the relative droplet size was set at 1.5 (in order to correct the spray dried granulation process mentioned in Fig. 2 for the 10% (w/w) moisture powder bed content). In Table 8, the scaling-up results are given. They are comparable to each other, thereby confirming that the granulation process can

Table 8
Scaling-up of the granulation process

Fluid bed	Parameter setting		Granule size (µm)	
	Mp	*R*	Predicted	Observed
Small scale	9.5	0.9	424 ± 25	428
Medium scale	10.8	1.1	406 ± 23	390
Production scale	10.6	1.5	375[a]	424

Mp: moisture content of powder bed (% (w/w)); *R*: relative droplet size.

[a] Estimated from a spray dried process (Mp is ±5% (w/w)) with *R* is 1.5 (see Fig. 2).

be scaled-up by considering only the powder bed moisture content and the relative droplet size.

4. Conclusions

The scaled-up fluid bed granulation process was based on the relative droplet size and the powder bed moisture content after the spraying cycle. Although the nozzles of the small and the medium scale were the same, different granule size were obtained at the same fundamental granulation process settings. By proposing regression models for the granule size produced in the small and medium fluid beds, the granulation process could be scaled up. The granulation process was also successful by scaling-up to the large fluid bed, considering only the relative droplet size. In this study the scaling up was restricted only to the granule size and other important granule properties, such as the granule porosity and flowability, were not taken in account. We acknowledge that these granule properties are also important when scaling up the granulation process. This study was meant as a guide to scale-up the granulation process using fundamental variables by application of experimental design.

References

Holm, P., Schaefer, T., Kristensen, H.G., 1983. Granulation in high speed mixers. Part 1. Effects of process variables during kneading. Pharm. Ind. 45, 806–811.

Leuenberger, H., 1983. Scale-up of granulation processes with reference to process monitoring. Acta Pharm. Technol. 29, 274–280.

Kristensen, H.G., 1988. Agglomeration of powders. Acta Pharm. Suec. 25, 187–204.

Mehta, A.M., 1988. Scale-up considerations in the fluid-bed process for controlled-release products. Pharm. Tech. 12, 46–52.

Montgomery, D.C., 1997. Design and Analysis of Experiments. Wiley, Singapore, pp. 276–281.

Parikh, D.M., Bonck, J.A., Mogavero, M., 1997. Batch fluid bed granulation. In: Parikh, D.M. (Ed.), Handbook of Pharmaceutical Granulation Technology. Marcel Dekker, New York, pp. 227–302.

Rambali, B., Baert, L., Thoné, D., Massart, D.L., 2001a. Using experimental design to optimise the granulation process in fluid bed. Drug Dev. Ind. Pharm. 27, 53–61.

Rambali, B., Baert, L., Thoné, D., Massart, D.L., 2001b. Using experimental design to optimize the process parameters in fluidized bed granulation on semi full scale. Int. J. Pharm. 220, 149–160.

Schaafsma, S.H., 2000. Down-scaling of a fluidised bed agglomeration process. Ph.D. dissertation of Rijksuniversiteit Groningen, 159 pp.

Schaefer, T., Worts, O., 1977. Control of fluidized bed granulation. II. Estimation of droplet size of atomized binder solutions. Arch. Pharm. Chemi. Sci. Ed. 5, 178–193.

Schaefer, T., Worts, O., 1978. Control of fluidized bed granulation. IV. Effects of binder solution and atomization on granule size and size distribution. Arch. Pharm. Chemi. Sci. Ed. 6, 14–25.

Sherrington, P.J., Oliver, R., 1981. Granulation. Heyden & Son Ltd., London, pp. 7–60.

Watano, S., Morikawa, T., Miyanami, K., 1996a. Mathematical model in the kinetics of agitation fluidized bed granulation. Effects of humidity content, damping speed and operation time on granule growth rate. Chem. Pharm. Bull. 44, 409–415.

Watano, S., Fukushima, T., Miyanami, K., 1996b. Heat transfer and granule growth rate in fluidized bed granulation. Chem. Pharm. Bull. 44, 572–576.

Watano, S., Takashima, H., Sato, Y., Yasutomo, T., Miyanami, K., 1996c. Measurement of humidity content by IR sensor in fluidized bed granulation. Effects of operating variables on the relationship between granule humidity content and absorbance of IR spectra. Chem. Pharm. Bull. 44, 1267–1269.