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Evaluation and simultaneous optimization of some pellets characteristics using a 3^3 factorial design and the desirability function

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Abstract

A 3^3 full factorial design study has been employed in order to investigate the effect of three variables on size, size distribution and three shape parameters, namely roundness, elongation and e_R, of pellets prepared in a fluid bed rotor granulator with the wet granulation technique. The first variable was a formulation variable, the % w/w content of microcrystalline cellulose (MCC) and the other two variables were processing variables, the temperature of inlet air and the spray rate of the granulation liquid. The analysis of variance showed that the three variables had a significant effect ($P < 0.05$) on pellet size and the shape factors, while only the spray rate influenced the particle size distribution. Significant interactions between the factors, for the size and the shape, were also found. The multiple regression analysis of the results led to equations that adequately describe the influence of the independent variables on the selected responses. Furthermore, the desirability function was employed in order to optimize the process under study. It was found that the optimum values of the responses could be obtained at the low levels of the % w/w content of MCC and temperature of inlet air and at the high level of the spray rate.

Keywords: Pellets; Size; Shape parameters; Factorial design; Optimization; Desirability function

1. Introduction

Among the pelletization techniques available at present, fluid bed granulation is a production method of a great interest as it offers the advantage of combining various wet granulation steps (e.g. mixing, spraying, drying etc.) in single equipment. In this way, dust problems and contamination risks can be avoided, while equipment and energy can be saved. Two types of production machinery are used for ‘single pot’ pellet production: high-shear mixer granulators and rotary processors. In this study a fluid bed rotor granulator was used.

The production of pellets in a fluid bed is a multivariable process. There are many process and formulation variables that influence the quality characteristics of the produced pellets e.g. spray

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rate, temperature of inlet air, atomizing air pressure, air flow rate, amount of granulation liquid, excipients etc. (Rambali et al., 2001a). The knowledge of the influence of these variables is essential in achieving a controlled process.

Experimental design techniques such as factorial design and optimization are useful tools in the characterization of pharmaceutical processes by studying the effects of variables affecting them and their possible interactions (Armstrong and James, 1990).

The objective of this study was to determine the effect of the % w/w content of microcrystalline cellulose (MCC), the temperature of inlet air and the spray rate on the size, the size distribution, and three shape parameters, namely roundness, elongation and e_R of the pellets, using a 3^3 factorial design.

Furthermore the desirability function (Lewis et al., 1999) was employed for the optimization of the process under study.

2. Materials and methods

2.1. Materials

MCC (Avicel®, type PH 101, FMC, Cork, Ireland, Lot 6907c) and α-Lactose monohydrate (Pharmatose®, type 150M, DMV, Veghel, The Nederlands, Lot Z0032) were used for the production of the pellets. Deionized water was used as granulation liquid.

A commercial pellet product, Sporanox® (Janssen Pharmaceutica Inc, Titusville, New Jersey, Lot 0111508) and Werner's® sugar nonpareils (Harms G. Werner GMBH and C.O., Tornesch, Germany) were used for comparison purposes during the Image analysis measurements.

2.2. Preparation of pellets

The pellets were prepared in a fluid bed rotor granulator Glatt GPCG3 (Glatt GmbH, Binzen, Germany). MCC and α-Lactose were adequately mixed at several proportions (Table 1) and 1 kg of the mixture was loaded into the product chamber of the machine. The mixture was fluidized for 3 min and then the water was sprayed at different spray rates, while the inlet air temperature was varied according to the design (Table 1). The amount of the water sprayed was 800 ml and kept constant for every batch. During the experiments all the other processing variables were kept constant: the atomizing air pressure was fixed at 2.5 bar, the rotor speed was at 1200 rpm/min and the exhaust air flap at 20%. Once all the water was sprayed, the pellets were dried for 15 min at 55 °C.

Table 1
Factorial 3^3: factors and their levels

Factors	Low level	Middle level	High level
A: MCC (%)	25	30.0	35
B: Temperature (°C)	28	30.5	33
C: Spray rate (ml/min)	28	30.5	33

2.3. Evaluation of pellets

The purpose of a pelletization process is to produce spherical particles of acceptable size and size distribution. The most common way for the delivery of the pellets is by filling them in hard gelatin capsules. Also they may be coated to produce controlled release dosage forms. For the above mentioned reasons it is important to determine the size, the size distribution and the shape of the pellets, as these parameters determine the quality of the produced pellets, the uniform filling in hard gelatin capsules, and the successfulness of the coating procedure.

The pellets were evaluated using the Image Analysis System (Leica Qwin, Leica Imaging Systems Ltd., Cambridge, UK). Two hundred pellets from every batch were collected, analyzed and the measurements were used to calculate the size and the shape parameters of the pellets.

2.3.1. Determination of the size and size distribution

The image analysis system gives the possibility to calculate the equivalent spheres diameter of the pellets. The evaluation of these results showed that the equivalent spheres diameter of the produced pellets didn't follow a normal distribution so a log–probability plot was used to determine their geometric mean diameter (d_g) and geometric standard deviation (σ_g). The analysis was carried out by the statistical software package, SIGMA PLOT® 2000, SPSS Inc., Chicago, USA. As d_g was regarded the particle size equivalent to 50% of the probability scale, and as σ_g was regarded the ratio 50% size/16% undersize (Martin et al., 1993).

2.3.2. Determination of the shape

A variety of factors have been used to determine the shape of the pellets. In this study the roundness, elongation and e_R factors were selected for the characterization of the shape of the pellets. These shape parameters were calculated by using the following equations (Leena and Jouko, 1993; Podczeck and Newton, 1994, 1995; Vertommen et al., 1997; Ericsson et al., 1997):

$$\text{Roundness} = \frac{\text{area}}{\pi(d_{\max}/2)^2} \qquad (1)$$

$$\text{Elongation} = \frac{\text{max feret diameter}}{\text{min feret diameter}} \qquad (2)$$

$$e_R = \frac{v2\pi r_e}{pf} - \left[1 - \left(\frac{\text{breadth}}{\text{length}}\right)^2\right]^{1/2} \qquad (3)$$

The factor f is a correction factor (Podczeck and Newton, 1995):

$$f = 1.008 - 0.231\left[1 - \left(\frac{\text{breadth}}{\text{length}}\right)\right] \qquad (4)$$

The area, the length, the breadth, the r_e of the pellets and the elongation factor are calculated directly by the Image analysis software. Feret diameter is the distance between two tangents on opposite sides of the particle, parallel to some fixed direction (Martin et al., 1993). In Eq. (3) the factor P is the perimeter of the sphere and r_e is the equivalent radius of the sphere.

The shape factor e_R considers both the geometrical shape and the surface texture of spherical agglomerates. It was found (Podczeck et al., 1999) that the strength of this shape factor is its sensitivity to very small deviations in shape, which are not discovered using the roundness or elongation factors.

2.4. Factorial design and the desirability function

Factorial design is a useful tool in order to characterize multivariable processes. It gives the possibility to separate the important factors from those, which are not, and identifying any possible interactions between them.

In this study a 3^3 full factorial design was used to determine the effect of the % w/w content of MCC, the temperature of inlet air and the spray rate on the geometric mean diameter, the geometric standard deviation, and shape parameters of the pellets. Before the application of the design a number of preliminary trials were conducted to determine the conditions at which the process resulted to pellets. The levels of the factors were also determined by this procedure. The factors and their levels are shown in Table 1.

The different formulations of the factorial design consisted of all possible combinations of all factors at all levels and were conducted in a fully randomized order. The matrix of the experiments and the results of the responses for every experiment are listed in Table 2. To determine the experimental error, the experiment at the center point was replicated five times at different days. The mean diameter of these experiments was 335.3 μm ± 7.4, the mean value of σ_g was 1.23 ± 0.01, the mean value of roundness was 0.784 ± 0.005, the mean value of elongation was 1.236 ± 0.01, the mean value of e_R was 0.367 ± 0.005, The above-mentioned values show good reproducibility of the process. The statistical evaluation of the results was carried out by analysis of variance (ANOVA) using a commercially available statistical software package (DESIGN EXPERT V 6.0.4, Minneapolis, USA). The quadratic model was selected for this analysis.

Finally the desirability function was used for the optimization of the process. During the optimization of a multivariable process, such as pelletization, the responses have to be combined in order to produce a product of desired characteristics. The application of the desirability function combines all the responses in one measurement (Lewis et al.,

Table 2
Factorial 3^3: matrix of the experiments and results for the measured responses and the desirability

Factors/levels						Responses			Overall desirability
ES[a]	MCC (%)	Temperature (°C)	Spray rate (ml/min)	d_g	σ_g	Roundness	Elongation	e_R	
3	25	28.0	28.0	726.5	1.25	0.841	1.171	0.433	0.715
30	25	28.0	30.5	924.7	1.20	0.854	1.137	0.448	0.821
2	25	28.0	33.0	1325.1	1.29	0.886	1.115	0.502	1.000
28	25	30.5	28.0	258.3	1.30	0.776	1.217	0.356	0.326
19	25	30.5	30.5	443.3	1.29	0.791	1.207	0.371	0.421
27	25	30.5	33.0	583.1	1.30	0.830	1.175	0.423	0.669
1	25	33.0	28.0	376.4	1.25	0.783	1.237	0.349	0.290
21	25	33.0	30.5	269.2	1.26	0.785	1.214	0.371	0.393
4	25	33.0	33.0	611.1	1.28	0.828	1.193	0.419	0.623
20	30	28.0	28.0	312.2	1.31	0.789	1.212	0.357	0.368
24	30	28.0	30.5	441.0	1.30	0.806	1.195	0.385	0.515
14	30	28.0	33.0	832.5	1.23	0.859	1.147	0.467	0.846
25	30	30.5	28.0	234.5	1.26	0.763	1.243	0.334	0.170
9	30	30.5	30.5	337.0	1.22	0.782	1.234	0.369	0.340
15	30	30.5	33.0	482.6	1.27	0.815	1.202	0.407	0.557
22	30	33.0	28.0	211.8	1.21	0.757	1.262	0.334	0.104
26	30	33.0	30.5	228.5	1.30	0.771	1.234	0.353	0.270
16	30	33.0	33.0	317.4	1.33	0.805	1.208	0.392	0.497
7	35	28.0	28.0	239.2	1.22	0.777	1.250	0.361	0.266
23	35	28.0	30.5	382.4	1.34	0.794	1.189	0.371	0.457
8	35	28.0	33.0	518.6	1.29	0.833	1.186	0.426	0.659
29	35	30.5	28.0	179.4	1.21	0.755	1.233	0.329	0
18	35	30.5	30.5	310.0	1.24	0.776	1.233	0.348	0.278
17	35	30.5	33.0	289.0	1.28	0.802	1.213	0.387	0.469
5	35	33.0	28.0	171.0	1.21	0.752	1.269	0.323	0
31	35	33.0	30.5	261.2	1.25	0.793	1.226	0.372	0.391
6	35	33.0	33.0	292.8	1.30	0.792	1.229	0.369	0.378

[a] ES, experimental sequence.

1999), and gives the possibility to predict the optimum levels for the independent variables.

The combination of the responses in one desirability function requires the calculation of the individual desirability functions.

In this particular study there were not special requirements for the geometric mean diameter of the optimum formulation, so the range of the values of the produced formulations was selected.

The optimum formulation of this study should have a geometric mean diameter ranging between 200 and 1325.1 μm, with maximum roundness and e_R and minimum elongation. The individual desirability for each response was calculated using the following methods (Lewis et al., 1999).

For the geometric mean diameter the formulations that have a d_g value within the range 200–1325.1 μm have a desirability function of 1, while the formulations that have values out of this range have a desirability value of 0. These can be described by the following equations:

$$d_1 = 0 \quad \text{for} \quad Y_i < Y_{\min} \tag{5}$$

$$d_1 = 1 \quad \text{for} \quad Y_{\min} < Y_i < Y_{\max} \tag{6}$$

$$d_1 = 0 \quad \text{for} \quad Y_i > Y_{\max} \tag{7}$$

where d_1 is the individual desirability of the geometric mean diameter.

The roundness and the e_R value were maximized in the optimization procedure, as spherical particles have high values of this parameter. The desirability functions of these parameters were calculated by using the following equation:

$$d_2 \text{ or } d_3 = \frac{Y_i - Y_{\min}}{Y_{\max} - Y_{\min}} \tag{8}$$

where d_2 is the individual desirability of roundness d_3 is the individual desirability of e_R.

The values of $Y_{\max}$ and $Y_{\min}$ for roundness are 0.886 and 0.752 and the values of $Y_{\max}$ and $Y_{\min}$ for e_R are 0.502 and 0.323 and Y_i is the experimental result.

The elongation value was minimized in the optimization procedure, as spherical particles have low values of elongation parameters. The calculation of the desirability function was carried out using the equation:

$$d_4 = \frac{Y_{\max} - Y_i}{Y_{\max} - Y_{\min}} \tag{9}$$

where d_4 is the individual desirability of elongation.

The $Y_{\max}$ and $Y_{\min}$ values are 1.269 and 1.115 and Y_i is the experimental result.

The overall desirability values were calculated from the individual values by using the following equation:

$$D = (d_1 d_2 d_3 d_4)^{1/4} \tag{10}$$

3. Results and discussion

3.1. Main effect of the factors

3.1.1. Geometric mean diameter

From the Table 3 it can be concluded that the main effects of the three factors on the geometric mean diameter were found statistically significant ($P < 0.05$). The results obtained from the Table 2 show that the largest pellets were obtained at the high level of the spray rate. Especially the batch of the largest pellets was produced when the high level of the spray rate was followed by low levels of the other two factors (experiment 2). The high spray rate promotes granule growth because of excessive liquid supply and larger droplet size. It has been reported (Rambali et al., 2001b), that the spray rate has a profound effect on the granule size, as it determines the bed moisture content and the droplet size of the binder solution. The same result was found in another study (Vertommen et al., 1996).

Table 3
ANOVA results (P values): effect of the variables on d_g and σ_g

d_g			σ_g	
Factors	Coefficient	P	Coefficient	P
A	−158.7	< 0.0001*	−0.0061	0.4944
B	−164.6	< 0.0001*	−0.0022	0.8028
C	140.3	< 0.0001*	0.0210	0.0256*
A^2	62.3	0.0620	0.000002	0.9923
B^2	106.1	0.0034*	0.0018	0.2778
C^2	29.0	0.3774	0.0003	0.6679
AB	108.7	0.0002*	−0.0120	0.2906
AC	−55.4	0.0350*	0.0160	0.1561
BC	−78.0	0.0046*	0.0180	0.1188
Constant	302.1	–	–	–
$r^2_{\text{adj.}}$	0.88	–	–	–

Regression coefficients. *, Statistically significant ($P < 0.05$).

The increase in the temperature of inlet air decreased the size of the produced pellets as the moisture content of the fluid bed was also decreased, due to evaporation of the granulation liquid. It is obvious that the increase in temperature had the opposite effect on size than the effect of the spray rate. It was found (Menon et al., 1996) that granule growth was directly proportional to the spray rate and inversely proportional to the inlet air temperature.

The increase in MCC content led to pellets with smaller particle size. MCC has the ideal physical properties, including moisture retaining and distributing ability and is widely used as pelletization aid because of the favorable rheological properties of its wet mass (Shah et al., 1995). In a previous study (Vertommen and Kinget, 1997) the increase in the content of MCC led to bigger and more spherical pellets when it was sufficiently wetted. This did not happen in this study as the increase in the content of MCC was not followed by an increase in the water added, and that led to pellets of low sphericity when MCC was at its high level.

3.1.2. Geometric standard deviation

The geometric standard deviation was used to evaluate the particle size distribution of the pellets.

As can be seen from Table 3 only the spray rate had a significant effect on the particle size distribution.

As explained previously, the increase in the spray rate of the granulation liquid resulted to an increase in the size of the produced pellets. The increase in the spray rate had the same effect on the size distribution of the pellets. The high spray rates of a granulation process leads to uncontrollable growth of the particles as an equal spreading of the liquid was not ensured, leading to local over-wetting and pellets with less equal size were produced (Vertommen and Kinget, 1997).

It can be seen also, that the increase in the content of the MCC led to a narrower distribution of the pellets. However, this effect was not found statistically significant.

An increase in the temperature of inlet air decreased the size distribution of the pellets but this effect was also not significant.

3.1.3. Shape factors

The three factors had significant influence on the shape of the pellets (Table 4). An increase in MCC content decreased the values of the shape parameters. MCC is a material widely used for the production of pellets as it has good plastic properties. To obtain its plastic properties should be sufficiently wetted (Vertommen et al., 1997). In this study the increase in the content of MCC was not followed by an increase of the added water and so the shape parameters were decreased. An increase in spray rate led to more spherical pellets. The increase in the spray rate increased the plasticity of the formulations, as the MCC was sufficiently wetted, and spherical pellets were produced. The increase in the temperature of inlet air decreased the moisture content of the mixture and the sphericity was also decreased.

3.2. Interactions between the factors

An interaction is the failure of a factor to produce the same effect on the response at the different levels of the other factor (Montgomery, 1999). The ANOVA results (Tables 3 and 4) showed that the interaction AB had significant influence on the geometric mean diameter and the shape parameters of the pellets. Especially this interaction was synergistic, as it led to an increase in the size and the sphericity. The interactions BC and AC, were also found to have significant influence on the geometric mean diameter.

The analysis of the results of the Table 2 by multiple regression analysis leads to equations that adequately describe the influence of the selected factors on the size and the shape of the pellets. In the Tables 3 and 4 regression coefficients of these equations are presented.

Table 4
ANOVA results (P values): effect of the variables on the shape factors

Factors	Roundness		Elongation		e_R	
	Coefficient	P	Coefficient	P	Coefficient	P
A	−0.0170	<0.0001*	0.0200	<0.0001*	−0.0210	<0.0001*
B	−0.0210	<0.0001*	0.0260	<0.0001*	−0.0260	<0.0001*
C	0.0250	<0.0001*	−0.0240	<0.0001*	0.0340	<0.0001*
A^2	0.0070	0.0420*	−0.0130	0.0066*	0.0070	0.1501
B^2	0.0160	<0.0001*	−0.0160	0.0001*	0.0190	0.0005*
C^2	0.0060	0.0866	−0.0020	0.7030	0.0090	0.0783
AB	0.0100	0.0008*	−0.0100	0.0051*	0.0130	0.0021*
AC	0.00004	0.9933	0.0020	0.6547	−0.0030	0.3978
BC	−0.0030	0.1954	0.0040	0.2430	−0.0060	0.1174
Constant	0.78	–	1.23	–	0.36	–
$r^2_{adj.}$	0.93	–	0.90	–	0.91	–

Regression coefficients. *, Statistically significant ($P < 0.05$).

3.3. Reliability of the image analysis measurements

As it was shown previously, the calculation of the shape parameters was carried out using the Eqs. (1)–(3). The theoretical values of these factors for a perfect sphere are 1. From Table 2 it is evident that the values of the roundness factors of the factorial experiments range from 0.752 to 0.886, the elongation factors range between 1.115 and 1.269 and the e_R values range between 0.323 and 0.502. It is obvious that there is a deviation from the value that describes a perfect sphere. In order to confirm that these values describe a formulation of acceptable sphericity two other commercially available pellets products were measured at the Image Analysis system. Five samples from the same batch of the Sporanox® and three formulations of Werner's®, with different size of pellets, were analyzed. The results of this analysis are presented in Table 5.

The analyzed samples of Sporanox®, had a mean value of roundness 0.889, a mean value of elongation 1.107 and e_R value 0.5. Similar values were also obtained from the analysis of the sugar nonpareils. It is clear that these values are in good agreement with the experimental values (Table 2, experiment 2) of the studied formulations that showed good sphericity. In a previous study (Podczeck et al., 1999), values of 1.1 for elongation and 0.6 for e_R were suggested for pellets of good sphericity.

3.4. Optimization of the process using the desirability function

Generally the aim of the optimization of pharmaceutical formulations is to find the optimum levels of the variables, which affect a process, where a product of good quality characteristics could be produced. During the optimization procedure, all the measured responses that may affect the quality of the product should be taken into consideration. Some of these responses have to be minimized and some have to be maximized, in order to produce a product of desired characteristics. Using the desirability function, all the selected responses were combined in one overall response, the overall desirability. As it has been already discussed the overall desirability response was calculated from the individual desirability of each of the responses using the Eqs. (5)–(10). The results of each of these overall desirability responses are included in the optimization procedure and an equation that describes the influence of the factors on the overall desirability was found. The equation was as follows (coded factors):

$$\begin{aligned} D = {} & 0.33 - 0.13A - 0.15B + 0.19C + 0.043A^2 \\ & + 0.12B^2 + 0.006C^2 + 0.051AB + 0.023AC \\ & - 0.004BC \quad (r^2_{adj.} = 0.95, \\ & P = 0.0001) \end{aligned} \tag{11}$$

In Figs. 1–3 the response surface plots that describe the influence of the factors on the overall desirability are presented.

The study of these plots showed that the highest values for the desirability could be obtained at low values of MCC content and inlet air temperature and at high values of the spray rate. Especially the analysis of the Eq. (11) by the previously mentioned statistical software package resulted to the optimum combination of the independent variables where a product of desired characteristics

Table 5
Results for the shape parameters of Sporanox® commercial product, and Werner's®, sugar nonpareils

Products	Mean diameter (μm)	Shape parameters		
		Roundness	Elongation	e_R
Sporanox	936.2	0.889	1.107	0.501
Werner's 1	326.3	0.818	1.191	0.428
Werner's 2	855.9	0.889	1.110	0.522
Werner's 3	1162.2	0.900	1.098	0.526

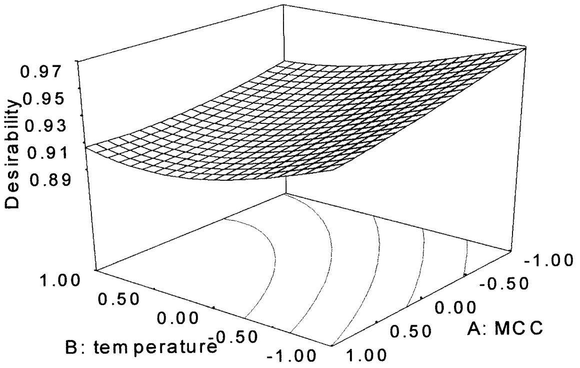

Fig. 1. Influence of the % MCC and temperature on the overall desirability. (Spray rate = 1.0).

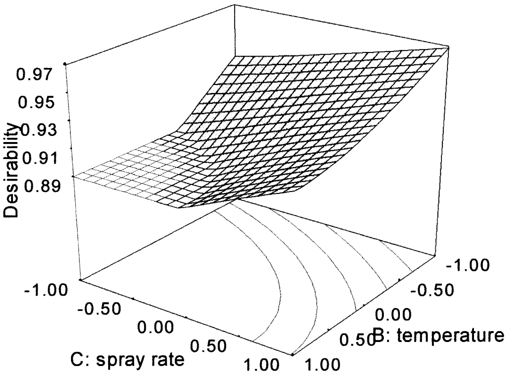

Fig. 2. Influence of temperature and spray rate on the overall desirability. (MCC = −1.0).

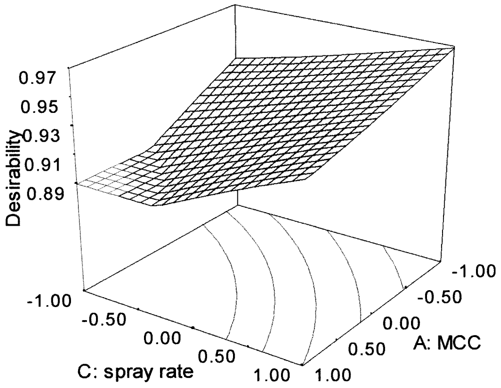

Fig. 3. Influence of the % MCC and Spray rate on the overall desirability. (Temperature = −1.0).

may occur. The results of this analysis are shown in Table 6.

3.5. Evaluation of the equations that describe the influence of the factors on the pellets characteristics

In order to assess the reliability of the equations that describe the influence of the factors on the pellets characteristics, five additional experiments were conducted by varying the three independent variables. For each of these test formulations the responses were estimated by using the equations and the experimental procedure. In Table 7 the comparison between the experimental and predicted values of the responses for the additional experiments is presented. It can be seen that in all cases there was a reasonable agreement between the predicted and the experimental values, since low values of the bias were found. For this reason it can be concluded that the equations describe adequately the influence of the selected independent variables on the responses under study.

4. Conclusions

The spray rate, temperature of inlet air and the % w/w content of MCC affect the mean diameter and the shape factors (roundness, elongation, e_R) of the pellets. Interactions between these factors were also found to be statistically significant. Particle size distribution is only affected by the spray rate of the granulation liquid.

The multiple regression analysis of the results led to equations that describe adequately the influence of the selected variables on the responses under study.

Table 6
Optimum levels for the independent variables

Independent variables	Optimum values
MCC content	25% w/w
Inlet air temperature	28 °C
Spray rate	33 ml/min
Overall desirability	0.969

Table 7
Comparison between predicted and experimental values for the test formulations

Responses	Test	Factors/levels			Predicted values	Experimental values	Bias%*
		A	*B*	*C*			
Geometric mean diameter (μm)	1	−1	+1	+1	512.4	582.2	13.6
	2	+1	−1	+1	559.8	609.1	8.8
	3	0	0	+1	471.4	520.4	10.4
	4	−0.6	0.2	0.6	483.2	446.7	7.6
	5	−0.4	0.6	−0.2	267.1	262.7	1.8
Roundness	1	−1	+1	+1	0.817	0.831	1.7
	2	+1	−1	+1	0.831	0.835	0.4
	3	0	0	+1	0.865	0.844	2.3
	4	−0.6	0.2	0.6	0.805	0.811	0.7
	5	−0.4	0.6	−0.2	0.774	0.779	0.6
Elongation	1	−1	+1	+1	1.193	1.179	1.2
	2	+1	−1	+1	1.177	1.188	0.5
	3	0	0	+1	1.206	1.197	0.8
	4	−0.6	0.2	0.6	1.204	1.211	0.6
	5	−0.4	0.6	−0.2	1.234	1.232	0.2
e_R	1	−1	+1	+1	0.408	0.414	1.5
	2	+1	−1	+1	0.424	0.439	3.5
	3	0	0	+1	0.403	0.378	6.2
	4	−0.6	0.2	0.6	0.393	0.356	9.4
	5	−0.4	0.6	−0.2	0.350	0.354	1.1
Overall desirability	1	−1	+1	+1	0.591	0.629	6.4
	2	+1	−1	+1	0.685	0.678	1.1
	3	0	0	+1	0.526	0.529	0.6
	4	−0.6	0.2	0.6	0.507	0.467	7.9
	5	−0.4	0.6	−0.2	0.294	0.303	2.4

*, Bias was calculated using the equation: [(predicted value − experimental value)/predicted value] × 100.

The optimization of the process using the desirability function resulted to the optimum values of the factors at which the goal of the production of pellets with acceptable characteristics could be fulfilled.

Finally it is clear that the applications of experimental design techniques are useful tools for the characterization and optimization of this pelletization process.

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