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RESEARCH PAPER

Effects of Process Variables on the Size, Shape, and Surface Characteristics of Microcrystalline Cellulose Beads Prepared in a Centrifugal Granulator

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ABSTRACT

Preparation of microcrystalline cellulose (MCC) beads with a laboratory-scale centrifugal granulating apparatus was studied, and the pharmaceutical quality of the beads was characterized with respect to the subsequent drug layering. Five process parameters of potential importance, including rotor rotation speed X_1*, slit air* X_2*, spray air pressure* X_3*, spray air rate* X_4*, and height of nozzle setting* X_5*, were evaluated using a fractional factorial design (FFD* 2^{5-2}*) as the experimental design. The responses evaluated were expected yield, mean size, size distribution, shape characteristics (including roundness, circularity, elongation, rectangularity, and modelx), and friability. All five process parameters studied were found to have an influence on the selected properties of the beads, but the effects of rotor rotation speed, slit air flow rate, and spray air rate were statistically significant (*$p < .05$*). The effect of the rotor rotation speed was found to be the most potent on all the responses studied. The results also show some significant interactions between the parameters tested. The most significant interactions were between rotor rotation speed and slit air, rotor rotation speed and spray air, and slit air and spray air.*

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INTRODUCTION

The centrifugal type of equipment is commonly regarded as one of the most advanced ways of producing drug-layered pellets. The major advantages of the centrifugal granulator and its recent modifications over the conventional pan coating systems include lower manufacturing cost, flexibility in operation, coat uniformity, and ease of automation (1).

In our previous paper (2), the suitability of the centrifugal granulating process for the preparation of microcrystalline cellulose (MCC) beads was studied. The main aim of the study was to develop a sugar-free substitute for the traditionally used nonpareils (sugar-starch beads) as a substrate for drug layering. The results suggested that substrates of high pharmaceutical quality could be prepared using different MCC grades as starting materials in a centrifugal granulator. Furthermore, it was observed that the spray rate and the powder flow rate have an obvious influence on the process and the final quality of the beads.

In the literature, there are only few studies on the effects of process variables on the properties of the beads or pellets made by a multivariate centrifugal granulating process (3–6). Gajdos (3) studied the effects of three process parameters (i.e., spray rate of the binding solution, addition of powder, and rotation speed) on the physical properties of sugar pellets. The powder flow rate was found to be the most critical parameter affecting the yield of the sugar pellets, while the increase in the spray rate had only a minor positive effect on the yield. So far, virtually no studies have been made systematically to identify and characterize the potential important process variables related to the preparation of MCC beads with a centrifugal technique.

The aim of the present study was to investigate the effects of five selected process variables on the physical properties of the MCC beads prepared by a centrifugal granulating technique. A fractional factorial design (FFD) was used to identify the critical parameters. A major advantage of using this kind of experimental design is that information on the main effects and lower-order interactions of interest may be obtained by less work than by running the complete factorial design (7).

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (EMCOCEL 90M and 50M, Edward Mendell Co., Finland) was used as a basic ingredient and purified water (Ph. Eur.) as a wetting agent.

Preparation of Beads

Beads were prepared by a laboratory-scale centrifugal granulator (Freund CF-360EX, Freund Industries Co. Ltd., Tokyo, Japan). The schematic diagram of the equipment was presented in our previous paper (2). Five process parameters of potential importance with respect to the pharmaceutical quality of the beads were evaluated. The parameters studied were rotor rotation speed X_1, slit air X_2, spray air pressure X_3, spray air rate X_4, and height of nozzle setting X_5 (Table 1). A fractional factorial design (FFD 2^{5-2}) was used as the experimental design (Table 2). In each experiment, 500 g MCC (EMCOCEL 90M) was placed in the processing chamber and allowed to wet for 21.2 min. During the first 10 min, the rotor rotation speed was kept at 100 rpm and was then set to the respective level of the experiments. After 21.2 min of wetting, the filler (EMCOCEL 50M) was added in the wetted mass. The final product was taken out at 36.0 min after finishing the addition of the filler and dried at 60°C in a fluidized bed dryer for 40 min.

Evaluation of Spherical Beads

The spherical beads were evaluated with respect to expected yield percentage, mean diameter, bulk density,

Table 1

Levels of Process Variables (Fractional Factorial Design, FFD 2^{5-2})

Process Parameter	Level (−)	Level (+)
X_1, rotor rotation speed (rpm)	180	280
X_2, slit air flow rate (L/min)	140	240
X_3, spray air pressure (kg/cm^2)	0.6	1.4
X_4, spray air rate (L/min)	10	16
X_5, spray nozzle distance from bottom plate (cm)	5.0	7.0

Table 2

Matrix of Fractional Factorial Design (2^{5-2}) and Results

	Process Parameter					Response								
Experiment	X1	X2	X3	X4	X5	A	B	C	D	E	F	G	H	I
1	−	−	−	−	+	82.0	620	0.667	1.101	0.853	1.198	1.196	0.771	0.05
2	+	−	−	−	−	3.3	870	0.694	1.082	0.869	1.127	1.149	0.773	<0.05
3	−	+	−	−	−	94.0	485	0.641	1.103	0.852	1.221	1.207	0.772	0.05
4	+	+	−	−	+	31.2	790	0.694	1.089	0.863	1.155	1.166	0.771	<0.05
5	−	−	+	−	−	84.0	580	0.673	1.098	0.856	1.184	1.189	0.770	<0.05
6	+	−	+	−	+	2.0	880	0.704	1.088	0.864	1.141	1.157	0.774	<0.05
7	−	+	+	−	+	94.4	440	0.649	1.108	0.848	1.189	1.196	0.769	0.1
8	+	+	+	−	−	33.7	780	0.699	1.084	0.867	1.139	1.156	0.772	<0.05
9	−	−	−	+	−	91.6	550	0.667	1.099	0.855	1.177	1.184	0.771	<0.05
10	+	−	−	+	+	13.2	860	0.709	1.084	0.867	1.148	1.159	0.774	<0.05
11	−	+	−	+	+	90.0	385	0.629	1.118	0.841	1.217	1.216	0.768	0.05
12	+	+	−	+	−	70.8	670	0.694	1.093	0.860	1.171	1.176	0.773	<0.05
13	−	−	+	+	+	89.8	540	0.658	1.103	0.852	1.192	1.195	0.769	<0.05
14	+	−	+	+	−	40.6	770	0.704	1.089	0.863	1.163	1.169	0.773	<0.05
15	−	+	+	+	−	94.4	395	0.625	1.123	0.837	1.215	1.220	0.767	0.1
16	+	+	+	+	+	62.2	680	0.694	1.086	0.865	1.161	1.167	0.773	<0.05

A = expected yield (%); B = mean diameter (μm); C = bulk density (g/cm^3); D = roundness; E = circularity; F = elongation; G = modelx; H = rectangularity; I = friability (%).

shape (roundness, circularity, elongation, rectangularity, modelx), roughness, and friability. The expected yield of the beads in each experiment was determined by a sieve analysis method. The fraction (250–1000 μm) was used to evaluate the shape, surface roughness, bulk density, and friability. The bulk density and friability were determined by the same methods as used in our previous paper (2). The shape and surface roughness of the beads were characterized using an optical microscopic image analysis system (Leach MZ6, Leica Imaging Ltd., Cambridge, England), and the results are given in Table 2.

The image analysis procedure is described elsewhere (8). The characteristics measured from each core were area, minimum and maximum diameter (d_{min} and d_{max}), perimeter (*perim*), and convex perimeter (*cperimeter*). From the measured data, the roughness and the shape parameters were derived. The shape parameters include sphericity (roundess and circularity) and oblongation (elongation, rectangularity, modelx). These parameters are shown below (Eqs. 1–6).

$$\text{Circularity} = 4 * \pi * area/(perim)^2 \quad (1)$$

$$\text{Roundness} = (perim)^2/(4 * \pi * area * 1.064) \quad (2)$$

$$\text{Elongation} = d_{max}/d_{min} \quad (3)$$

$$\text{Rectangularity} = area/d_{min} * d_{max} \quad (4)$$

$$\text{Modelx} = perim * d_{max}/4 * area \quad (5)$$

$$\text{Roughness} = perim/cperim \quad (6)$$

Statistical evaluation was made using the Windows version of Systat 5.0. Modeling was performed by Modde for Windows (Version 3.0, Umetri AB, Umeå, Sweden). The effects of the process variables were modeled using the following polynomial equation:

$$\begin{aligned} y = {} & a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_4X_4 \\ & + a_5X_5 + a_6X_1X_2 + a_7X_1X_3 \\ & + a_8X_1X_4 + a_9X_1X_5 + a_{10}X_2X_3 \\ & + a_{11}X_2X_4 + a_{12}X_2X_5 + a_{13}X_3X_4 \\ & + a_{14}X_3X_5 + a_{15}X_4X_5 \end{aligned}$$

Only terms significant at the level of $p < .05$ were included in the final model.

RESULTS AND DISCUSSION

The suitability of the centrifugal granulating process for preparing MCC beads was preliminarily studied in our previous paper (2). It was found mainly by trial and error that if the process parameters are precisely set and controlled, it is possible to prepare MCC beads as substrates for drug layering without any remarkable problems relating to the quality of the product and the process. In this study, five process variables of potential importance were systematically studied using a 2^{5-2} fractional

Table 3

Summary of Fitted Models and Adjusted R^2 *Values*

Fitted Model	Significance	R^2 Value
Yield: $y = 61.075 - 28.950X_1 + 10.263X_2 + 8.000X_4 + 7.088X_1X_2 + 6.575X_1X_4$	.05	.957
Mean diameter: $y = 643.125 + 144.375X_1 - 65.625X_2 - 37.500X_4$	.05	.974
Bulk density: $y = 0.6751 + 0.0239X_1 - 0.0094X_2 - 0.0026X_4 + 0.0057X_1X_2 + 0.0038X_1X_4 - 0.0026X_2X_4$	.05	.985
Roundness: $y = 1.0970 - 0.0099X_1 + 0.0037X_2 + 0.0026X_4 - 0.0026X_1X_2$	.05	.858
Circularity: $y = 0.8571 + 0.0077X_1 - 0.0029X_2 - 0.0021X_4 + 0.0019X_1X_2$	.05	.905
Elongation: $y = 1.175 - 0.024X_1 + 0.009X_2$	.05	.827
Modelx: $y = 1.181 - 0.0190X_1 + 0.0066X_2 + 0.0044X_4$	.05	.912

factorial design. The results are shown in Table 2. The summary of the fitted models (and adjusted R^2 values) and statistical analysis with estimated effects are presented in Tables 3 and 4, respectively.

Main Effects

Expected Yield and Mean Diameter

The statistical analysis shown in Table 4 demonstrates that the rotor rotation speed ($p < .001$), the slit air flow rate ($p < .01$), and the spray air rate ($p < .05$) are important parameters affecting the expected yield. As shown in Fig. 1, the rotor rotation speed had a clear negative effect on the expected yield (the higher the rotor rotation speed, the lower the response), while the slit air flow rate (also spray air rate) had a positive effect. When the rotor rotation speed was increased from 180 rpm to 280 rpm, the relative change of expected yield was in the range of −(32.4–90.3)%. As the levels of slit air flow rate and spray air rate were increased from the lower to the higher,

Table 4

Statistical Analysis of Results: Values for Estimated Main Effects (%) and Levels of Significance

Process Parameter	Response						
				D			
	A	B	C	1	2	3	4
X_1, rotor rotation speed (rpm)	− (32.4–90.3)***	+58.3***	+ (36.3–84.1)***	− (44.6–76.9)***	+ (45.3–75.9)***	−72.7***	−63.3***
X_2, slit air flow rate (L/min)	+ (6.7–36.7)***	−26.5***	− (3.0–31.6)***	+ (6.9–39.2)**	− (7.9–38.4)**	+27.3*	+22.1**
X_3, spray air pressure (kg/cm^2)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
X_4, spray air rate (L/min)	+ (3.0–30.9)**	−15.2***	− (3.3–22.5)**	+16.1*	−16.2*	n.s.	+14.6*
X_5, spray nozzle distance from bottom plate (cm)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

A = expected yield; B = mean diameter; C = bulk density; D = shape: (1) roundness, (2) circularity, (3) elongation, (4) modelx.
n.s. = not significant; *$p < .05$; **$p < .01$; ***$p < .001$.

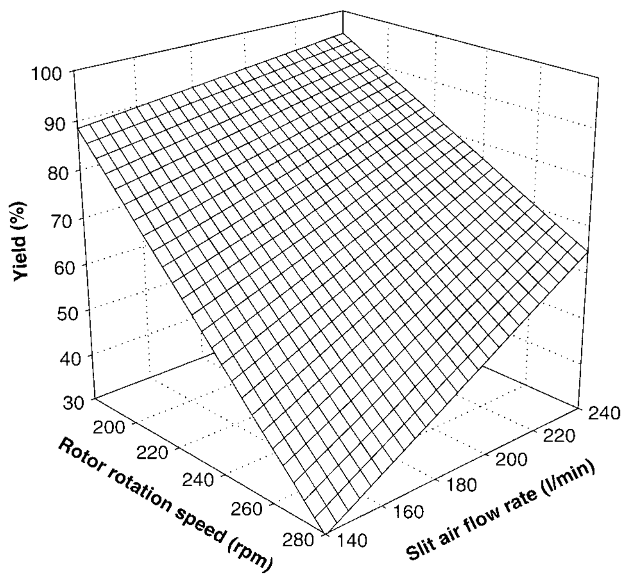


Figure 1. Three-dimensional surface plot representing the effect of rotor rotation speed and slit air rate on the expected yield.

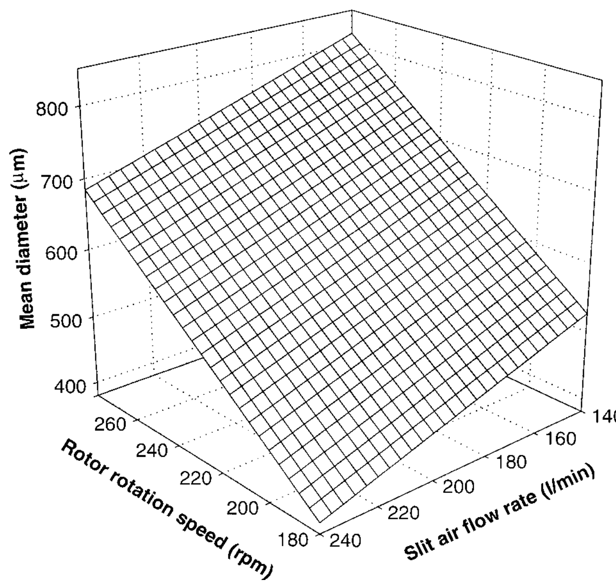


Figure 2. Three-dimensional surface plot representing the effect of rotor rotation speed and slit air rate on the mean diameter of the beads.

the relative changes of the expected yield were in the ranges of +(6.7–36.7)% and +(3.0–30.9)%, respectively.

The rotor rotation speed ($p < .001$), the slit air flow rate ($p < .001$), and the spray air rate ($p < .001$) were also found to be critical parameters affecting the mean diameter (Table 4). As seen in Fig. 2, the effect of the rotor rotation speed was the most potent on this response. Increasing the rotor rotation speed from 180 rpm to 280 rpm resulted in a relative change of +58.3% of mean diameter, while increasing the slit air flow rate from 140 L/min to 240 L/min (and spray air rate from 10 L/min to 16 L/min) resulted in a relative change of −26.5% (and −15.2%), respectively.

The models estimating the effects of rotor rotation speed and slit air flow rate on the expected yield and mean diameter were found to approximate well the true response surface (Table 3, Figs. 1 and 2). The R^2 values for the models on expected yield and mean diameter were 0.957 and 0.974, respectively.

Bulk Density

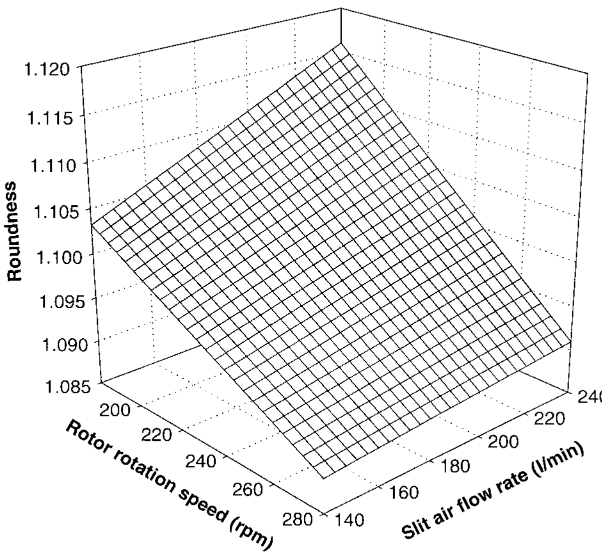
Bulk density is indicative of the packing properties of the particles, and the bulk densities of the pellets are proportional to the bulk densities of the starter seeds (1). The process parameters statistically affecting the bulk densities of the beads were the rotor rotation speed ($p <$ .001), slit air flow rate ($p < .001$), and spray air rate ($p < .01$) (Table 4). The rotor rotation speed had a positive effect, and the slit air flow rate and the spray air rate a negative effect on the bulk densities of the beads.

Shape and Surface Morphology

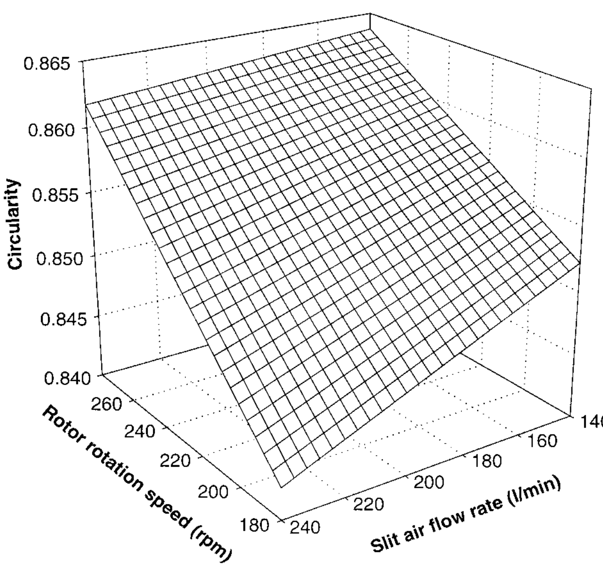
The effects of the process parameters on the bead shape were characterized by measuring the sphericity (roundness and circularity) and oblongation (elongation, rectangularity, and modelx) of the beads. For a perfectly round particle (bead), the concerned values are 1.

As regards quantitative values of roundness (sphericity), the rotor rotation speed ($p < .001$) had a negative effect, and the slit air flow rate ($p < .01$) and spray air rate ($p < .05$) had a positive effect (Table 4, Figure 3a). As regards values of circularity (sphericity), the rotor rotation speed ($p < .001$) had a positive effect, and the slit air flow rate ($p < .01$) and spray air rate ($p < .05$) had a negative effect (Table 3, Figure 3b). This means that, by increasing the rotor rotation speed and by decreasing the slit air flow rate and the spray air rate, more-spherical beads can be produced.

In case of oblongation, the rotor rotation speed and slit air flow rate had statistically significant effects on the elongation and modelx, but not on the rectangularity of the beads (Table 4). Rotor rotation speed ($p < .001$) had



a



b

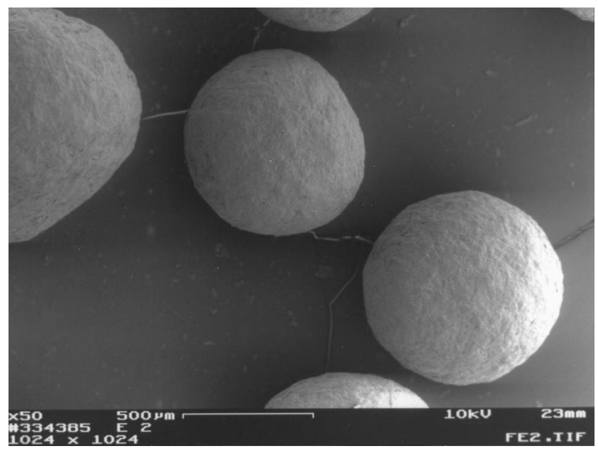
Figure 3. Surface plots illustrating the effects of the main variables, rotor rotation speed and slit air flow rate, on the shape parameters: (a) roundness; and (b) circularity.

a clear negative effect, and slit air flow rate ($p < .05$) had a positive effect on the elongation. The main parameters affecting the modelx values of the beads were the rotor rotation speed, the slit air flow rate, and the spray air rate. The rotor rotation speed ($p < .001$) had a negative effect, and the slit air flow rate ($p < .01$) and the spray air rate ($p < 0.05$) had a positive effect on the modelx values. Consequently, increasing the rotor rotation speed resulted in a decrease of the elongation and modelx values, thus producing rounder beads. Conversely, increasing the slit air flow rate and the spray air rate resulted in an increase of the modelx values, thus making less-round beads. The differences in the rectangular and roughness values of the beads within the 16 experiments were negligible in order to calculate any statistical significance.

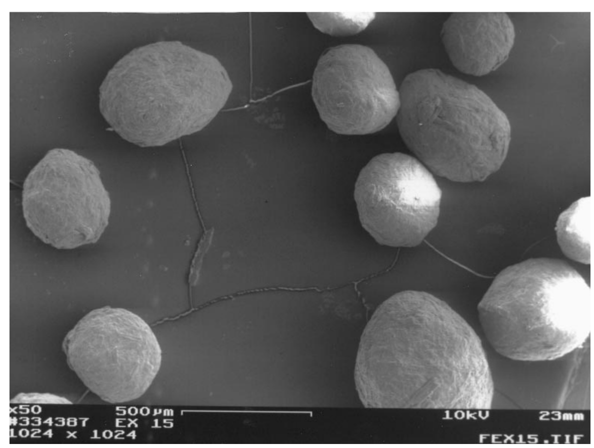
The SEM micrographs representing beads having the least- and the most-round shapes (experiments 2 and 15) are shown in Figs. 4a and 4b, respectively.

Friability

Cores require a certain resistance to friability to withstand further processing, including drug layering and



a



b

Figure 4. SEM micrographs of (a) experiment 2 and (b) experiment 15, representing the most- and the least-round beads, respectively.

Table 5

Statistical Analysis of Estimated Effects of Interactions Between Process Parameters (Levels of Significance)

	Response						
			C				
Interaction	A	B	1	2	3	4	D
Rotor rotation speed X_1 and slit air flow rate X_2	**	n.s.	*	*	n.s.	n.s.	***
Rotor rotation speed X_1 and spray air rate X_4	**	n.s.	n.s.	n.s.	n.s.	n.s.	***
Slit air flow rate X_2 and spray air rate X_4	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	**
Spray air pressure X_3 and spray air rate X_4	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	***

A = expected yield; B = mean diameter; C = shape: (1) roundness, (2) circularity, (3) elongation, (4) modelx; D = bulk density.
n.s. = not significant; *$p < .05$; **$p < .01$; ***$p < .001$.

coating. As seen in Table 2, the friability of the cores in all 16 experiments was highly uniform and satisfactory.

Interactions

One additional contribution of using the FFD is that possible low-order interactions between the factors of interest can be identified. The present results show some significant low-order interactions between the process parameters tested. Rotor rotation speed and slit air flow rate were shown to interact with the yield and sphericity (roundness and circularity) (Table 5; Figs. 1, 3a, and 3b). This means that the effects of changes in rotor rotation speed on the above-mentioned responses varied significantly depending on the slit air flow rate and vice versa. As seen in Figs. 1, 3a, and 3b, a change in rotor rotation speed clearly influenced the responses to a greater extent at the low level of slit air flow rate than the respective change in rotor rotation speed at the high level of slit air flow rate. Other significant interactions were found between rotor rotation speed and spray air rate affecting yield and bulk density. Furthermore, potential low-order interactions were found between slit air flow rate and spray air rate and between spray air pressure and rate; these were related to bulk density.

CONCLUSIONS

In conclusion, the effects of some other process variables in addition to the previously established powder and binder solution flow rates, including rotor rotation speed, slit air (fluidized air) flow rate, and spray air (atomizing air) rate, should be taken into account in preparing acceptable MCC beads in a centrifugal granulator. Based on the limited range of variable levels used in this experimental design, the effects of the spray air pressure and height of nozzle setting seem to be of minor importance. It is evident that significant interactions between rotor rotation speed and some other parameters do exist.

REFERENCES

1. I. Ghebre-Sellassie, *Pharmaceutical Pelletization Technology*, Marcel Dekker, New York, 1989, pp. 136–137, 241–243.
2. H. A. Rashid, J. Heinamaki, and J. Yliruusi, STP Pharma Sci., 8(3), 163–168 (1998).
3. B. Gajdos, Drugs Made in Germany, 27, 30–36 (1984).
4. G. Agyilirah, P. Bullens, J. Lee, L. DiMemmo, and T. Wheatley, Pharm. Res., 12(9), 149 [abstract] (1995).
5. L. Maggi, A. Bonfanti, P. Santi, G. Massimo, P. L. Catellani, A. Bellotti, P. Colombo, and A. Zanchetta, Pharm. Technol. Eur., 82–90 (October 1996).
6. J. Vertommen and R. Kinget, STP Pharma. Sci., 6 (5), 335–340 (1996).
7. D. C. Montgomery, *Design and Analysis of Experiments*, John Wiley and Sons, Singapore, 1983, pp. 325–356.
8. L. Hellen, Doctoral thesis, University of Helsinki, Yliopistopaino, p. 56, 1992.