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Research paper

Influence of the centrifugal granulating process on the properties of layered pellets

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Abstract

Drug-layered pellets based on microcrystalline cellulose (MCC) beads as substrates were prepared using a laboratory-scale centrifugal granulator. The effect of three independent process parameters (rotor rotation speed, slit air flow rate, and spray air rate) on responses describing the amount of drug loss during the process, amount of agglomerates, bulk density, flowability, friability, shape, and surface roughness were studied using a 3^3 full factorial experimental design. The variables studied were found to have a significant influence on the responses evaluated. Rotor rotation speed and slit air flow rate had a significant positive influence on the amount of drug loss during the process and the amount of agglomerates, whereas rotor rotation speed and spray air rate had the same effect on the bulk density, flowability, and the roundness of the pellets. The amount of agglomerates and the roundness value of the pellets were negatively affected by the spray air rate while the slit air flow rate showed the same effect on the bulk density and flow rate of the pellets. In addition to the main effects, there were some significant paired interactions between slit air flow rate and spray air rate as well as rotor rotation speed and slit air flow rate. Based on the results, the significance of these three parameters should be considered carefully for quality pellet preparation by the centrifugal granulating technique using MCC beads as substrates.

Keywords: Drug-layered pellets; Centrifugal granulation; Microcrystalline cellulose bead; Process parameters; Flowability; Friability; Roundness

1. Introduction

Pelletization by a centrifugal drug-layering process is an advanced technique for preparing controlled-release multiple-unit oral drug products. Being a multivariate process, it is important to identify and control the process variables and conditions. There are only a few studies on the effects of process variables on the properties of beads or pellets. Most of them were confined to the utilization of non-pareils as substrates (sugar and starch beads) and to the effects of three process parameters (spray rate of the binding solution, powder flow rate, and rotor rotation speed) [1–3]. The powder flow rate and the binder spray rate were found to be critical parameters affecting the properties of sugar pellets.

In our previous study, five process variables of potential importance were studied using the 2^{5-2} fractional factorial design in order to observe their effects on the properties of microcrystalline cellulose (MCC) initial beads [4]. Rotor rotation speed, slit air flow rate, and spray air rate were found to be the most significant factors influencing the yield and the properties of the MCC beads produced. The initial beads were prepared by using the same type of centrifugal granulator as was used for the subsequent drug layering, but the methods of preparation were different.

The aim of the present study was to characterize the effects of three process variables, i.e. rotor rotation speed, slit air flow rate, and spray air rate, on the properties of the drug-layered pellets prepared with MCC beads as substrates. The responses studied were the amount of drug loss during the process, the amount of agglomerates, bulk density, flowability, friability, as well as the shape and surface roughness of the pellets.

2. Materials and methods

2.1. Materials

MCC beads (500–800 μm) previously prepared in our laboratory were used as substrates for drug layering. Plasdone K-25 (ISP Technologies Inc., Wayne, NY) was used as an aqueous binding agent at a concentration of 18% (w/w).

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Table 1
Operating parameter settings

Parameter	Setting
Spray air pressure (kg/cm^2)	1.2
Spray rate (g/min)[a]	3.1–5.2
Filler dropping rate (g/min)	6.3
Inlet temperature (°C)	28–30
Outlet temperature (°C)	20–22
Spray nozzle distance from bottom plate (cm)	4.0

[a] The rate was 5.2 g/min for the first 25.5 min, and subsequently 3.1 g/min for 1.0 min.

Purified water (Ph. Eur.) and micronized caffeine anhydrate (Ph. Eur.) were used as solvent and active ingredient, respectively.

2.2. Preparation of pellets

A 3^3 full factorial design was used for preparing pellets by a laboratory-scale centrifugal granulator (Freund CF-360EX, Freund Industries Co. Ltd., Tokyo, Japan). A schematic diagram of the equipment was presented in our previous paper [5]. The levels of the operating parameter settings during the preparation of pellets are shown in Table 1.

In each experiment, 151.43 g (equivalent to approximately 150.0 g of caffeine) of a mixture of micronized caffeine anhydride and colloidal silicon dioxide (0.5%) was used as a filler. A total of 306.0 g of MCC beads (equivalent to 300.0 g anhydrous MCC beads) was placed in the processing chamber and allowed to tumble for 1.0 min before spraying the binder solution. After spraying the binder solution for 0.5 min, the filler was added to the wetted mass at a screw rate of 5.0 rpm (8.0 rpm at 13.0 min), keeping all the process parameters constant. At 24.5 min, the addition of the filler was finished and the spraying was continued at the same rate for another minute. At 25.5 min, the spraying was continued at a rate of 3.1 g/min. After the addition of 136.0 g of binder, the final pellets were taken out at 26.5 min and dried at room temperature (23 ± 2°C) for 48 h.

The three process parameters studied were rotor rotation speed X1, slit air flow rate X2 and spray air rate X3 (Table 2).

2.3. Evaluation of pellets

The pellets were evaluated with respect to the amount of agglomerates (i.e. oversized pellets larger than 1000 μm in diameter), drug loss during the process, bulk density, flowability, roundness, roughness, and friability. The amount of agglomerates (>1000 μm) in each experiment was determined by sieve analysis (Fritsch Analysette, Germany). The amount of pellets in the fraction 500–1000 μm was used to evaluate the bulk density, flowability, roundness, roughness, and friability.

The percentage of drug loss during the process and the percentage of oversized pellets (agglomerates) were calculated by using the following formulas

$$\text{Drug loss during the process } (\%) = (1 - (\text{AT}/\text{AM})) \times 100 \quad (1)$$

$$\text{Oversized pellets } (\%) = (O/M) \times 100 \quad (2)$$

where M is the amount of total material used excluding moisture content, O is the total amount of oversized pellets in the product excluding moisture content, AT is the amount of drug present in the total product, and AM is the total amount of drug used.

The amount of oversized pellets including agglomerates in the product was determined by sieve analysis (Fritsch Analysette, Germany). The percentage of drug loss during the process was determined spectrophotometrically at a wave length of 273 nm.

The moisture content of the starting materials and the product (total product, oversized pellets) were measured as a loss of weight using an infrared dryer (Sartorious Thermocontrol YTC OIL, Sartorious GmbH, Germany). A 2.0 g sample was heated up to 120°C until the loss of weight was less than 0.1 mg in 50 s.

The bulk density of the pellets was determined by pouring 50 g of material into a 250 ml graduated glass cylinder which was kept at an angle of 45° to horizontal while pouring. The cylinder was straightened up and the volume occupied by the material was read to the nearest 1 ml. The bulk density was calculated by dividing the weight by the volume occupied. The measurements were made in triplicate.

The flowability of the pellets was measured by a flow-time and cone-angle testing instrument (Pharma Test Ptg, Germany) with a 8 mm orifice. The flow rate was calculated by dividing the bead weight (50 g) by the flow time.

The shape and the roughness of the pellets were characterized by using an optical microscopic image analysis system (Leach MZ6, Leica Imaging Systems Ltd., UK). The image analysis procedure has been described previously [6]. The characteristics measured from each pellet were area, perimeter (perim), and convex perimeter (cperim). From the measured data, roughness and roundness (shape parameter) were derived as follows

$$\text{Roundness} = (\text{perim})^2/(4\pi \times \text{area} \times 1.064) \quad (3)$$

$$\text{Roughness} = \text{perim}/\text{cperim} \quad (4)$$

The shape and surface roughness of the pellets were studied by scanning electron microscopy (SEM) (Jeol JSM-840A, Jeol, Japan). Before taking the micrograph, the sample of the materials was coated with gold in an argon atmosphere by an ion sputter coater (SDOO4, Balzers Union, Liechtenstein).

The friability of the pellets was determined by weighing 10.0 g of initial beads and 10.0 g of glass beads (diameter of about 2 mm) in a 100 ml container. The pellets were mixed with the glass beads in a turbula mixer (System Schatz, W.A. Bachofen, Switzerland) for 10 min and then sieved

Table 2
Matrix of the full factorial design (3^3) and results (mean ± SD)

	Process parameters[a]			Responses[b]					
	X1	X2	X3	A	B	C	D	E	F
1	−1	−1	−1	4.90	10.9	0.633 (0.016)	6.94	1.123 (0.031)	0.72 (0.02)
2	−1	0	0	5.32	10.1	0.630 (0.012)	6.85	1.114 (0.022)	0.93 (0.06)
3	0	0	−1	7.78	23.2	0.654 (0.009)	7.04	1.139 (0.042)	0.62 (0.02)
4	0	1	0	10.77	21.5	0.654 (0.012)	7.25	1.126 (0.024)	0.66 (0.04)
5	0	−1	1	5.13	4.9	0.676 (0.012)	7.69	1.101 (0.020)	0.99 (0.03)
6	1	0	1	7.82	14.1	0.690 (0.009)	7.58	1.103 (0.021)	0.89 (0.05)
7	1	1	−1	10.25	41.0	0.661 (0.010)	7.04	1.119 (0.026)	0.36 (0.02)
8	−1	1	1	10.57	10.1	0.647 (0.013)	6.95	1.128 (0.029)	0.96 (0.07)
9	1	−1	0	6.00	17.0	0.692 (0.011)	7.39	1.111 (0.024)	0.64 (0.04)
10	0	−1	−1	4.00	22.0	0.685 (0.009)	7.46	1.115 (0.025)	0.63 (0.03)
11	0	0	0	7.84	14.9	0.667 (0.009)	7.32	1.107 (0.022)	0.78 (0.04)
12	1	0	−1	9.30	32.8	0.668 (0.007)	7.25	1.115 (0.023))	0.56 (0.02)
13	1	1	0	10.63	29.9	0.664 (0.005)	7.58	1.111 (0.022)	0.49 (0.02)
14	1	−1	1	5.71	8.1	0.690 (0.010)	7.81	1.104 (0.021)	0.91 (0.05)
15	−1	0	1	5.56	8.0	0.658 (0.009)	7.25	1.088 (0.019)	1.22 (0.10)
16	−1	1	−1	6.21	35.0	0.617 (0.004)	6.58	1.153 (0.045)	0.65 (0.05)
17	0	1	1	10.85	16.0	0.658 (0.016)	7.35	1.122 (0.026)	0.79 (0.04)
18	−1	−1	0	4.32	6.0	0.630 (0.004)	7.04	1.117 (0.024)	1.35 (0.08)
19	1	−1	−1	5.91	26.0	0.694 (0.009)	6.85	1.126 (0.026)	0.58 (0.04)
20	1	0	0	8.53	27.1	0.690 (0.009)	7.46	1.110 (0.020)	0.65 (0.01)
21	−1	0	−1	4.85	17.0	0.627 (0.012)	6.76	1.131 (0.030)	0.68 (0.04)
22	−1	1	0	9.67	20.0	0.622 (0.005)	6.76	1.127 (0.026)	0.89 (0.06)
23	−1	−1	1	5.00	4.0	0.649 (0.017)	7.14	1.122 (0.024)	2.56 (0.01)
24	0	0	1	8.27	12.5	0.666 (0.009)	7.35	1.111 (0.022)	0.88 (0.03)
25	0	1	−1	9.97	38.8	0.649 (0.008)	6.94	1.144 (0.042)	0.61 (0.03)
26	1	1	1	10.05	19.2	0.678 (0.011)	7.46	1.117 (0.023)	0.86 (0.05)
27	0	−1	0	6.31	12.0	0.646 (0.019)	6.94	1.104 (0.020)	0.77 (0.06)
28	−1	−1	1	4.10	5.2	0.661 (0.010)	7.14	1.105 (0.020)	2.26 (0.12)
29	1	1	1	7.50	17.6	0.682 (0.011)	7.58	1.113 (0.023)	0.71 (0.02)
30	−1	1	1	7.14	12.5	0.655 (0.013)	7.04	1.122 (0.026)	1.27 (0.08)

[a] X1, rotor rotation speed (rev./min) 150, 200, 250; X2, slit air flow rate (l/min) 100, 200, 300; X3, spray air rate (l/min) 10, 16, 22.
[b] A, drug loss during the process (%); B, agglomerates (%); C, bulk density (g/cm^3); D, flow rate (g/s); E, roundness; F, friability (%).

through a 450 μm sieve. The percentage weight loss was then calculated [7]. The measurements were made in triplicate.

2.4. Statistical analysis

Statistical evaluation was made using the Windows version of Systat 5.0. Modelling was performed by Modde for Windows (Version 3.0, Umeå, Sweden). The effects of the process variables were modelled using a second-order polynomial fitting. The models were simplified by the normal stepwise regression technique [8]. Terms were included in the model so that the maximum value for the prediction power Q^2 was obtained.

3. Results and discussion

The feasibility of the centrifugal granulating process for preparing drug-layered pellets using MCC beads as substrates and a sparingly water soluble drug as filler has been reported in our previous paper [9]. In this study, three process variables which were found to have a significant effect on the quality of the MCC beads prepared in the same equipment were studied using a 3^3 full factorial design. The results are presented in Table 2. A summary of the fitted models and statistical analysis with estimated effects are shown in Table 3.

3.1. Drug loss during the process

The main ingredients used in the dry condition for the preparation of pellets were powdered drug and MCC beads. There is no possibility of loss of MCC beads due to leakage through the opening of the processing chamber except if they adhere to the body of the chamber, whereas drug loss likely occurred by both ways. The drug loss during the process could be reduced by controlling the process parameters. In the literature, yields of 90% are regarded as acceptable in a corresponding drug-layering process [10]. In our study, the drug loss was 5–10%.

The statistical analysis shown in Table 3 indicates that the rotor rotation speed ($P < 0.01$) and slit air flow rate ($P < 0.001$) were important parameters affecting the drug loss during the process. Both parameters had a positive

Table 3
Statistical analysis of results, quadratic terms and estimated effects of interactions between process parameters; coefficients for the coded factors and level of significance[a]

Response	Independent variables			Interactions			Quadratic terms			
	X1	X2	X3	X1X2	X1X3	X2X3	$X1^2$	$X2^2$	$X3^2$	Constant
Agglomerates	5.332 (<0.001)	6.546 (<0.001)	−8.476 (<0.001)	–	−1.311 (NS)	−2.531 (<0.01)	–	–	–	18.494
Drug loss	1.103 (<0.01)	1.903 (<0.001)	–	–	–	–	–	–	–	7.188
Friability	−0.250 (<0.001)	−0.127 (NS)	0.290 (<0.001)	–	–	−0.168 (<0.05)	0.168 (NS)	–	–	0.749
Roundness	−4.356e-03 (<0.05)	0.008 (<0.001)	−0.009 (<0.001)	–	–	–	–	–	–	1.118
Bulk density	0.021 (<0.01)	−0.006 (<0.01)	0.008 (<0.001)	−0.006 (<0.05)	−3.576e-03 (NS)	0.005 (<0.05)	–	–	–	0.660
Flowability	2.458e-01 (<0.001)	−7.043e-02 (NS)	2.122e-02 (<0.001)	–	–	–	–	−9.206e-02 (NS)	–	7.262

[a] *P* Values are in parentheses. NS, not significant.

effect on the drug loss. The effect of the slit air was more potent than that of the rotor rotation speed.

3.2. Formation of agglomerates

Agglomeration is a common processing problem in preparing pellets by the drug-layering technique. Generally, the problem of agglomeration could be minimized by controlling the critical process parameters. The statistical analysis shown in Table 3 indicates that all three parameters studied (rotor rotation speed ($P < 0.001$), slit air flow rate ($P < 0.001$), and spray air rate ($P < 0.001$)) had a significant influence on the formation of agglomerates during the pellet preparation. As shown in Fig. 1, the amount of agglomerates was positively affected by the rotor rotation speed and the slit air flow rate, and negatively affected by the spray air flow rate. As the rotor rotation speed and the slit flow air rate were increased from the lower to the higher level, the amount of agglomerates increased. Increasing the spray air rate from the lower to the higher level resulted in a decreased amount of agglomerates. An obvious explanation is that as the rotor rotation speed and slit air flow rate were higher, the initial beads used were wetted more due to the leakage of fine filler drug powder through the opening of the processing chamber. While increasing the spray air rate the overwetting of the pellets decreased. Some paired interactions can be seen between the process parameters tested (Table 3). Slit air flow rate and spray air rate were shown to have a significant interaction with the formation of agglomerates.

3.3. Bulk density

The process parameters affecting the bulk densities of the pellets were rotor rotation speed ($P < 0.01$), slit air flow rate ($P < 0.01$), and spray air rate ($P < 0.001$) (Table 3). The rotor rotation speed and the spray air rate had a positive effect and the slit air flow rate a negative effect on the bulk densities of the pellets. Of the process parameters studied, the rotor rotation speed was dominant.

The effect of the spray air rate on the bulk density of the pellets was inverse to that found with the MCC beads [4]. The reasons could be that in the case of the preparation of MCC beads only water was used as a wetting agent without any binder, and MCC could not agglomerate until it was fully wet and had achieved plastic properties. The wetter the MCC powder was, the denser and rounder were the beads obtained. In the preparation of drug-layered pellets, layering of drug powder over the initial beads depends mainly on the binding capacity of the binder. Overwetting of the surface of the initial beads with the binder solution enhances their agglomeration, resulting in irregular and rough pellets. As the spray air rate was increased, overwetting of the surface of the pellets decreased, and obviously this resulted in smoother and rounder pellets. As seen in Table 3, significant paired interactions related to bulk density were also found between the process parameters tested.

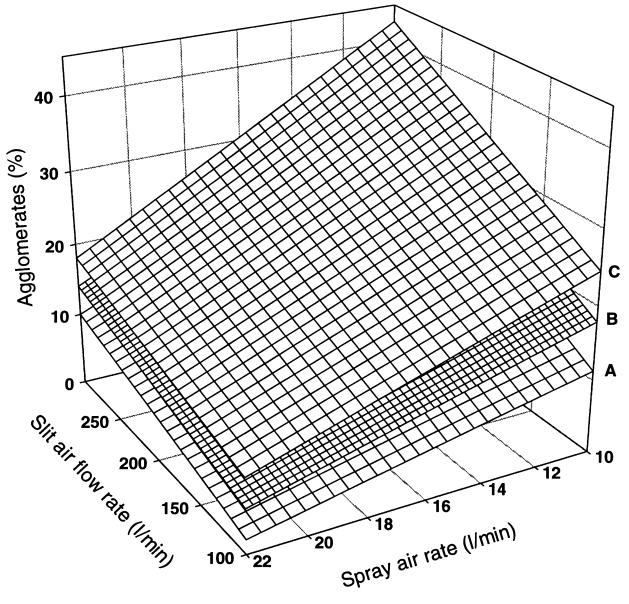

Fig. 1. Surface plots representing the effects of slit air flow rate and spray air rate on the amounts of agglomerates. The rotor rotation speeds are 150 rpm (A), 200 rpm (B), and 250 rpm (C).

3.4. Pellet flow rate

As seen in Tables 2 and 3, both rotor rotation speed ($P < 0.001$) and spray air rate ($P < 0.001$) had a significant positive effect on the flow rate of the pellets. Increasing the rotor rotation speed and the spray air rate resulted in an increased flow rate.

3.5. Shape and surface morphology

One of the main goals in pellet preparation is to produce spherical round particles, which contribute to successful coating and thus are optimal for controlled-release products. Good flow characteristics of particles during coating and accurate metering of granules, e.g. in capsule filling, are clearly dependent on the roundness of the particles. Roundness is often defined by Eq. (3). By this definition for a perfectly round particle the roundness value is 1. For the MCC beads the value was 1.061. Concerning the quantitative values of roundness, the rotor rotation speed ($P < 0.05$) and spray air rate ($P < 0.001$) had a negative effect, and the slit air flow rate ($P < 0.001$) had a positive effect (Table 3 and Fig. 2). This means that by increasing the rotor rotation speed and spray air rate, and by decreasing the slit air flow rate, more spherical and rounder pellets could be prepared. In this case, the effect of the spray air rate on the roundness was opposite to that on the shape of the MCC beads. The reasons could be the same as for the bulk density of the pellets.

The surface roughness properties of the pellets measured by image analysis exhibited no significant differences. However, the SEM micrographs representing the pellets of the corner points of the full 3^3 factorial design shown in

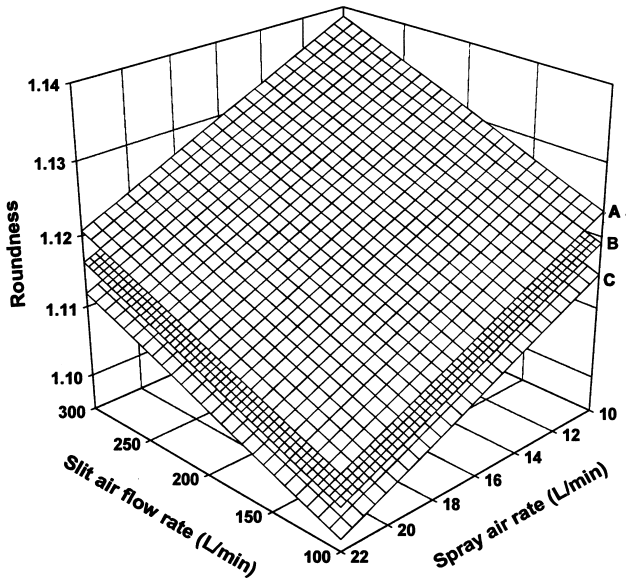

Fig. 2. Surface plots representing the effects of slit air flow rate and spray air rate on the roundness of the pellets. The rotor rotation speeds are 150 rev./min (A), 200 rev./min (B), and 250 rev./min (C).

Figs. 3 and 4 indicate that pellets with a rounder shape had a relatively smoother surface than the less round ones.

3.6. Friability

As seen in Table 3 and Fig. 5, both the rotor rotation speed ($P < 0.001$) and the spray air rate ($P < 0.001$) had statistically significant effect on the friability of the pellets. The rotor rotation speed had a negative effect and the spray air rate had a positive effect on the friability. At the highest rotor rotation speed, however, the spray air rate had virtually no effect on the friability (Fig. 5). A change in the spray air rate at the lower level of the rotor rotation speed influenced the friability to a greater extent than the respective change at the higher speed. This can be explained by the fact that as the rotor rotation speed is higher the initial beads become wetter due to the loss of the drug and thus nullify the effect of the spray air. The present results also show a significant interaction between the slit air flow rate and the spray air rate affecting friability (Table 3).

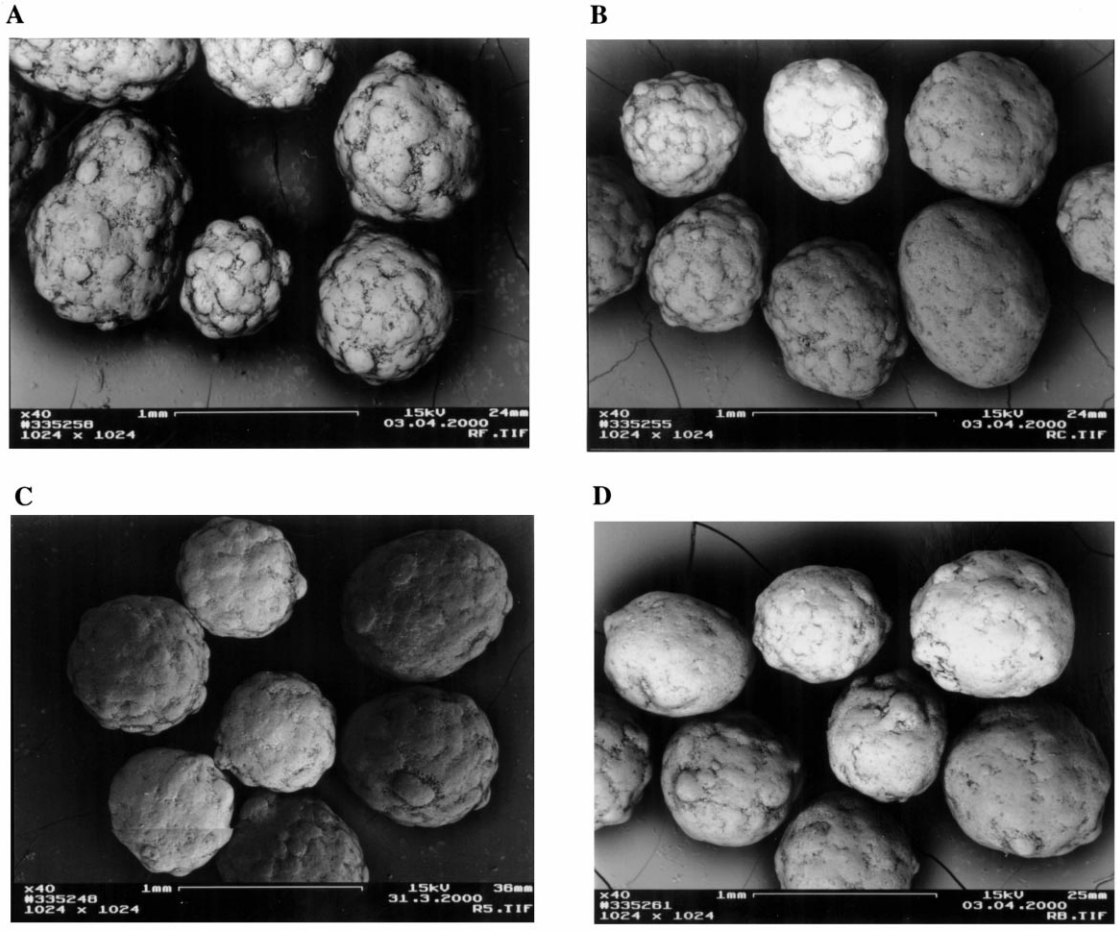

Fig. 3. SEM micrographs of experiments (A: −1, 1, 1), (B: 1, 1, 1), (C: −1, −1, 1), and (D: 1, −1, 1) representing the upper corner points of the experimental design (X3, the spray air rate is 22 l/min).

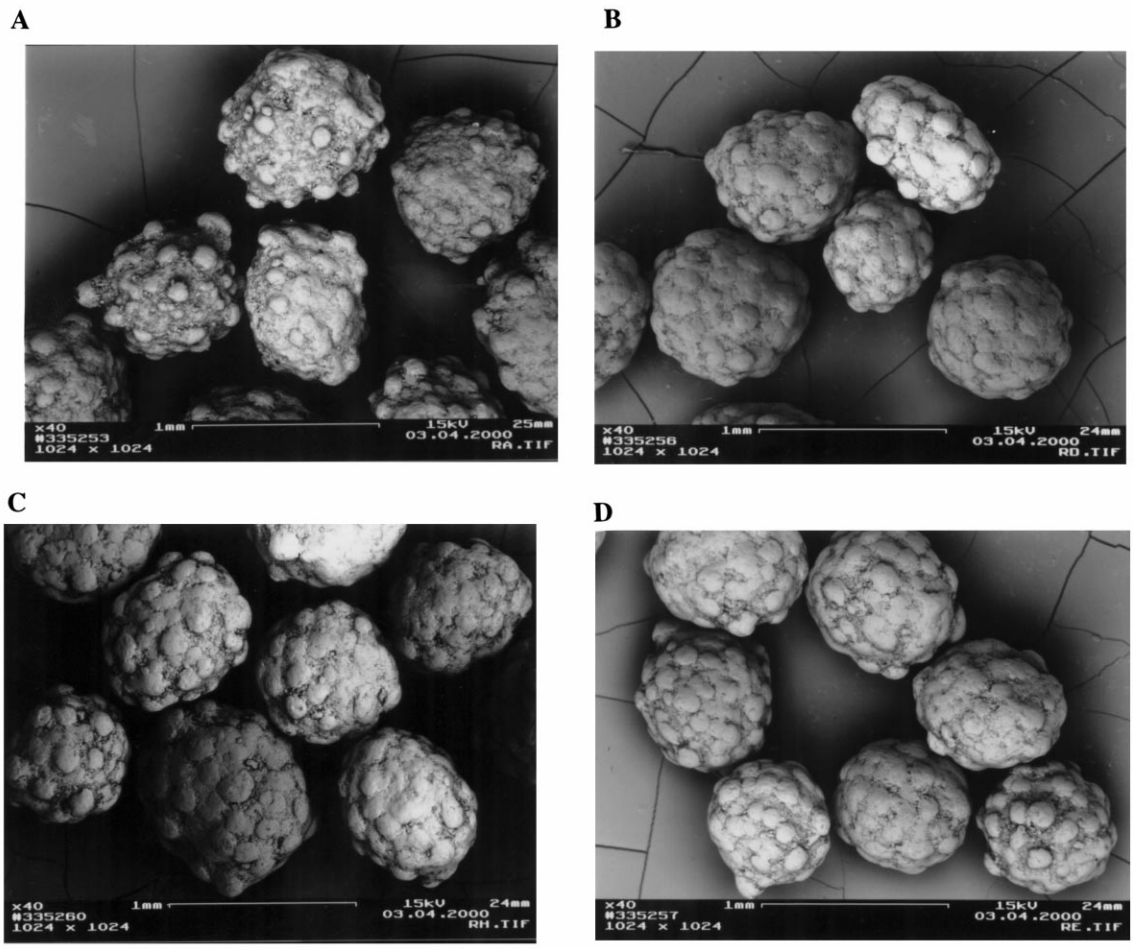

Fig. 4. SEM micrographs of experiments (A: −1, 1, −1), (B: 1, 1, −1), (C: −1, −1, −1), and (D: 1, −1, −1) representing the lower corner points of the experimental design (X3, the spray air rate is 10 l/min).

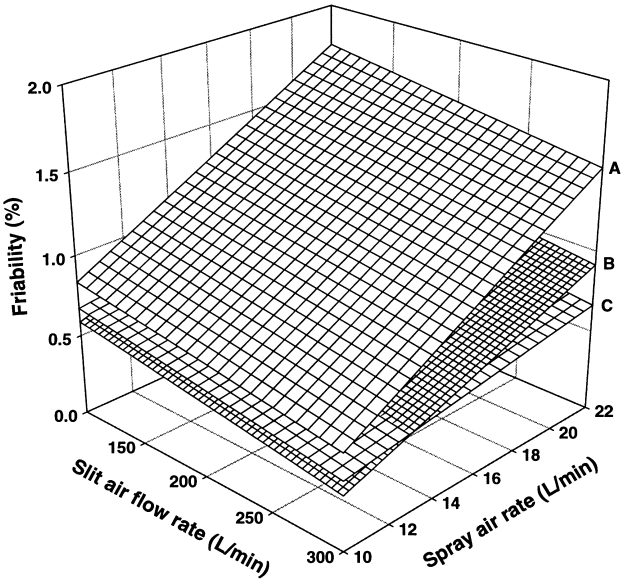

Fig. 5. Surface plots representing the effects of slit air flow rate and spray air rate on the friability of the pellets. The rotor rotation speeds are 150 rev./min (A), 200 rev./min (B), and 250 rev./min (C).

4. Conclusions

Rotor rotation speed, slit air flow rate and spray air rate are important process factors affecting the characteristics of the pellets prepared by a centrifugal drug-layering technique. As regards drug loss and agglomeration, the rotor rotation speed and slit air rate seem to be the most critical process parameters. Slit air flow rate and spray air rate are the potent parameters affecting the roundness and the bulk density of the pellets. Spray air rate, especially at lower rotation rotor speeds, should be considered in respect to the friability of pellets.

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