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Optimal conditions to prepare fine globular granules with a multi-functional rotor processor

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ABSTRACT

The optimal manufacturing conditions to obtain fine globular granules with a narrow size of particle distribution were investigated for a multi-functional rotor processor. A fractional factorial design analysis was undertaken to find out the significant operational conditions influencing the following physical characteristics of the obtained granules: size distribution, roundness and water content. Operational conditions tested were binder flow rate, atomization pressure, slit air flow rate, rotating speed and temperature of inlet air. It was observed that: the proportion of fine particles (106–212 μm) was positively affected by the atomization pressure, while negatively affected by the slit air flow rate; and roundness and water content were positively affected by the binder flow rate. Furthermore, the multiple regression analysis enabled the identification of an optimal operating window for production of fine globular granules. Therefore, the present study demonstrated that the combination of experimental design and multiple regression analysis allows a better understanding of complicated granulating process of multi-functional rotor processor to obtain fine globular granules.

Technology for manufacturing spheroids are crucially important in controlling drug release from functional granules, e.g., sustained release or taste-masking granules. As manufacturing processes for spherical granules, extrusion-spheronization, centrifugal granulation, and fluidized bed rotogranulation have been applied (Vervaet et al., 1995). Extrusion-spheronization and centrifugal granulation require generally long operation time, and material handling is rather complicated. Fluidized bed rotogranulation frequently causes particle aggregation, suggesting that the resultant particle diameter is larger than that designed for a product (Bouffard et al., 2007). And, also for smaller particles than 100 μm, uniform film coating is difficult due to the frequent particle aggregation. Therefore, in the pharmaceutical industry, the preparation of 100–200 μm particles with a narrow particle distribution is desired.

To overcome the disadvantages of the above mentioned granulating methods, we have studied feasibility of a unique multi-functional rotor processor, the "Granurex®" (GX-20, Freund, Japan), which allows one-step coating, spheronization, granulation, and powder layering processes, including fluid bed rotogranulation. Recently, Myo and Tanai succeeded in preparing fine particles with a smooth surface and a mean diameter of 193 μm using the Granurex® (Myo and Tanai, 2003). In addition, the particles with a mean diameter of 106 μm called Nonpareil 108, which is constructed only from D-mannitol, have been commercially marketed from Freund. However, little fundamental information regarding the manufacturing process and operational condition are available. In the present study, using a 2^{5-1} fractional factorial design, we examined the relationships between operational conditions of the multi-functional rotor processor and the physical characteristics of the obtained granules, and tried to optimize the manufacturing conditions for producing fine globular granules.

The multi-functional rotor processor is equipped with a rotor, which is inclined at 30 degrees to the horizontal plane, and an up-and-down drying device (MOV-A-BLO), giving it multi-functionality. The manufacturing process and operational conditions of the equipment are presented in Fig. 1. Four hundred and twenty grams of lactose monohydrate (Pharmatose®, type: 200 M, DMV INTERNATIONAL, Co., Ltd., Netherlands) and 180 g of corn starch (Nihon Shokuhin Kakou Co., Ltd., Japan) were used as fillers, and 220 g of 5% water solution of hydroxylpropylcellulose (HPC-L®, Nippon Soda Co., Ltd., Japan) was used as a binder. The process parameters of this study are presented in Table 1 along with their respective operating limits. The fractional factorial design was chosen because it provides sufficient degrees of freedom to statistically discriminate the effects of main factors and binary interactions in about one-half the experiments required for

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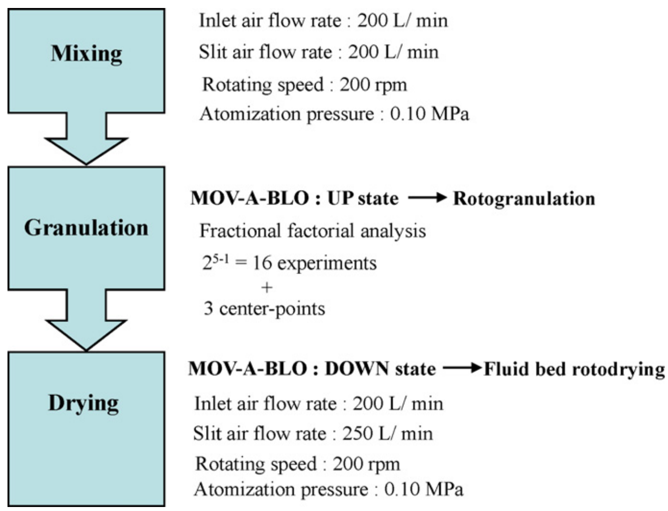

Fig. 1. Manufacturing processes and operational conditions of the multi-functional rotor processor.

Table 1
Process parameters and operating limits range.

Parameters	Low (−1)	High (+1)
X1 Binder flow rate (g/min)	6	10
X2 Atomization pressure (MPa)	0.14	0.20
X3 Slit air flow rate (L/min)	280	380
X4 Rotating speed (rpm)	200	380
X5 Slit and inlet temperature (°C)	45	60

a full factorial design. The coded values of "−1", "1" and "0" denote the lower, higher and average levels of each factor, respectively (Table 2). Therefore, sixteen experiments were carried out, which corresponds to two levels for the five process parameters with three

Table 2
Experimental design of 2^{5-1} fractional factorial design.

Batch no.	Parameter				
	X1	*X2*	*X3*	*X4*	*X5*
1	−1	−1	−1	−1	−1
2	−1	−1	−1	+1	+1
3	−1	−1	+1	−1	+1
4	−1	−1	+1	+1	−1
5	−1	+1	−1	−1	+1
6	−1	+1	−1	+1	−1
7	−1	+1	+1	−1	−1
8	−1	+1	+1	+1	+1
9	+1	−1	−1	−1	+1
10	+1	−1	−1	+1	−1
11	+1	−1	+1	−1	−1
12	+1	−1	+1	+1	+1
13	+1	+1	−1	−1	−1
14	+1	+1	−1	+1	+1
15	+1	+1	+1	−1	+1
16	+1	+1	+1	+1	−1
17–19	0	0	0	0	0

center points. The particle size distribution was determined according to the JP15 sieved method (Tsutsui Rikagaku Kikai Co., Ltd., Japan). The shapes of the granules were determined by image analysis of size fraction ranging from 106 to 212 μm using WinROOF image analysis software (Version: 5.5, MITANI Co., Ltd., Japan). The surface structures of the granules with sizes of 106–212 μm were morphologically assessed using a scanning electron microscope (SEM) (Model: JSM-5310LV, Make: JEOL, Japan). To determine the water content, the samples were dried in an oven at 70 °C for 24 h, and then the water content was calculated on a dry mass basis.

To determine the significance of each main factor as well as their interactions on the granule characteristics, the statistical analysis was performed using the Computer programs ALCORA

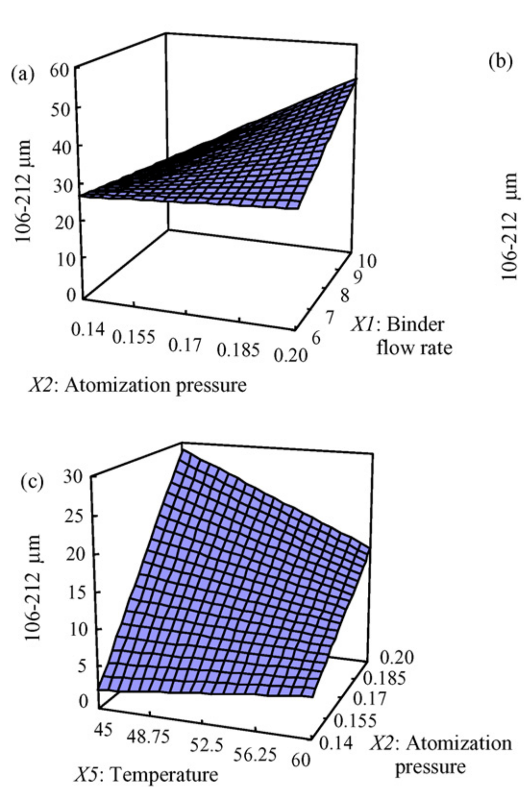

Fig. 2. Response surface plots of the proportion of fine particles (106–212 μm) as a function of binder flow rate (*X1*) and atomization pressure (*X2*) (a), of slit air flow rate (*X3*) and rotating speed (*X4*) (b), and of atomization pressure (*X2*) and temperature (*X5*) (c).

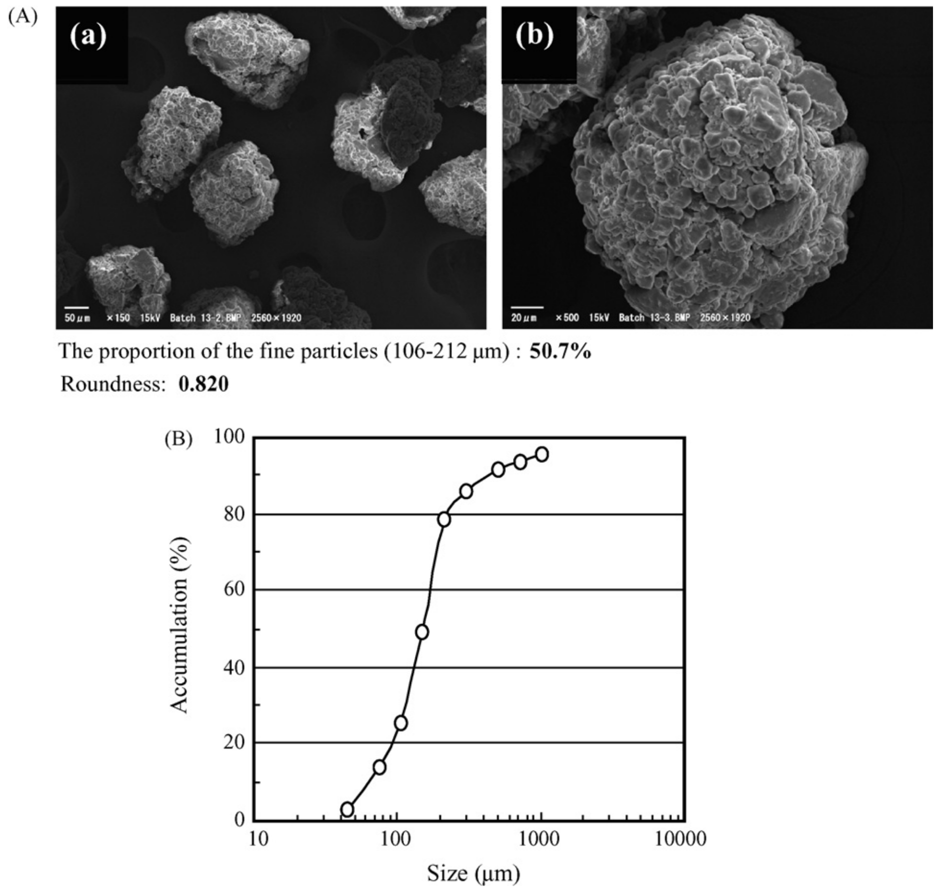

Fig. 3. Granular morphology (A) and particle size distribution (B) in the optimal run. (a) Magnification 150 and (b) magnification 500 (note the different scale bars).

(Takayama et al., 1990). The relationships linking the main factors and interactions with the response were determined and presented as quadratic equations of the general form in the following equation:

$$Y = \text{intercept} + \sum \text{main effect} + \sum \text{interactions}$$

The equation coefficients were calculated using the coded values, thus the various terms can be compared directly regardless of their magnitude. The linear regression equation for the proportion of fine particles (106–212 μm) in terms of the coded factor was:

The proportion of fine particles (106–212 μm) = $21.38 + 0.68 \times X1 + 2.72 \times X2 - 3.64 \times X3 - 1.24 \times X4 - 1.62 \times X5 + 6.34 \times X1X2 - 2.39 \times X1X3 + 0.38 \times X1X4 - 1.12 \times X1X5 - 0.46 \times X2X3 - 0.86 \times X2X4 - 3.86 \times X2X5 + 3.43 \times X3X4 + 0.91 \times X3X5 + 0.48 \times X4X5$ (R^2: 0.951).

In particular, the proportion of fine particles increased when the atomization pressure (*X2*) increased ($P = 0.014$) or the slit air flow rate (*X3*) decreased ($P = 0.006$). In addition, some positive interactions between the binder flow rate and the atomization pressure (*X1X2*; $P = 0.001$, Fig. 2a), and between the slit air flow rate and rotating speed (*X3X4*; $P = 0.007$, Fig. 2b) were observed. On the other hand, a negative interaction between the atomization pressure and temperature (*X2X5*; $P = 0.005$, Fig. 2c) was also observed. In addition, from the multiple regression analysis for granular roundness and water content (data not shown), these parameters increased when the liquid binder flow rate increased ($P = 0.032$ for granular roundness; $P = 0.003$ for water content). Throughout our study of granulation, it was found that three process parameters are dominant: the liquid binder flow rate, atomization pressure, and slit air flow rate.

After generating the polynomial equations relating the dependent and independent variables, operational conditions were optimized using the following criteria: the proportion of the fine particles (106–212 μm) is higher than 50% and the roundness factor must be superior to 0.75. The optimization was performed using the Computer programs OPTIM which was also donated by Kozo Takayama (Hoshi University), and optimized operational conditions were decided as follows: *X1* = 10 g/min, *X2* = 0.20 MPa, *X3* = 280 L/min, *X4* = 200 rpm, *X5* = 45 °C. As result, the proportion of the fine particles (106–212 μm) and the roundness were 50.7% and 0.820, respectively, indicating that each characteristic value complied with the desired product criteria. In addition, it was found that the fine globular granules with a narrow size of particle distribution were obtained from the optimal batch, presented in Fig. 3A and B, demonstrating the success of the optimization procedure.

In conclusion, using combination of experimental design and multiple regression analysis, fine globular granules could be prepared with the multi-functional rotor processor.

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References

Bouffard, J., Dumont, H., Bertrand, F., Legros, R., 2007. Optimization and scale-up of a fluid bed tangential spray rotogranulation process. Int. J. Pharm. 335, 54–62.

Myo, N., Tanai, I., 2003. Application of the centrifugal rotating disc processor to granulation and coating. J. Jpn. Soc. Pharm. Mach. Eng. 12, 189–196.

Takayama, K., Okabe, H., Obata, Y., Nagai, T., 1990. Formulation design of indomethacin gel ointment containing *d*-limonene using computer optimization methodology. Int. J. Pharm. 61, 225–234.

Vervaet, C., Baert, L., Remon, J.P., 1995. Extrusion–spheronization: a literature review. Int. J. Pharm. 116, 131–146.