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An application of the computer optimization technique to wet granulation process involving explosive growth of particles

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Abstract

The computer optimization technique based on well-designed experiments is applied to optimize the wet granulation process in which an explosive growth of particles is involved. Total volume of binder solution used in the process (X_1), power consumption (X_2) of the blade and the interaction between X_1 and the blade rotation speed (X_3) were found to have strong influence on the granulation process based on the analysis of variance. Further, scraping off of powder adhered to the vessel wall by the blade could play a critical role in such explosive growth of particles. In scale-up studies (1.2 kg and 3.0 kg scale), an optimization incorporating scale effect of three response variables (geometrical mean size of granules, the portion of granules passed through 75 μm, and granulation time) which have high correlation coefficients in regression analysis was possible by using an integrated optimization function, T(**X**). A universal optimal condition unaffected by manufacturing scale is obtained by the minimization of T(**X**). Experimental values of these three response variables of granules prepared under the universal optimal condition agreed well with the predicted values in two manufacturing scales, suggesting that the computer optimization technique would be useful to optimize and visualize the process of wet granulation involving the explosive growth of particles. © 1997 Elsevier Science B.V.

Keywords: Computer optimization; Wet granulation; Scale-up; Response surface; Well-designed experiment

1. Introduction

Wet granulation is a very effective procedure used in the pharmaceutical industry to improve the physical properties of powders such as poor-

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flowability and compressibility. A high-speed mixer granulator, in particular, is often employed for this process because it enables a short granulation time, high-density and strength granules, and easy machine handling. A number of studies concerning wet granulation have been published describing optimization of operational conditions (Holm et al., 1983, 1984; Aoki et al., 1993), analyses of the granulation process based on energy consumption (Terashita et al., 1985, 1987, 1990) and the process validation (Wehrle et al., 1993; Miyamoto et al., 1995). However, kinetic evaluation of the granulation process has been little discussed because of the complicated interaction between the physical properties of powders and operational conditions. In general, it is easy to specify operational conditions for a high-speed mixer granulator if granulation observed as growth of particles proceeds at a constant rate. However, explosive growth of particles from a certain stage is often observed in the process and causes difficulties in controlling product quality. This phenomenon could depend strongly on the physical properties of powders employed in the process, but what factor actually causes such explosive growth of particles has not been explained. An elucidation of the mechanism of this process is of importance to control the granulation process and improve product quality.

The computer optimization technique based on well-designed experiments has been recognized as a useful technique for specifying and optimizing various pharmaceutical processes. This method is particularly valuable for analysing pharmaceutical processes involving multiple factors and for evaluating the relative influence of each factor on experimental results. For example, Takayama and othres applied this technique to determine optimal formulation with desired pharmaceutical properties in transdermal delivery systems (Hirata et al., 1992) and sustained release dosage forms (Takayama and Nagai, 1989). Fonner et al. (1970) and Schwartz et al. (1973) used this technique in the formulation design of tablets. Optimization of the wet granulation process for manufacturing fine granules has been investigated based on the methodology of Shirakura et al. (1991). Ogawa et al. (1994) have evaluated the application of this technique to the scale-up problem in the granulation process.

In the present publication, the computer optimization technique based on well-designed experiments is applied to analyze the wet granulation process, which involves the explosive growth of particles. Scale-up of this type of granulation process is also investigated at two different manufacturing scales (1.2 and 3.0 kg scales). A universal optimal condition unaffected by manufacturing scale is sought by minimizing an integrated optimization function. Model formulation consisting of Flost sugar, calcium silicate, lactose and crystalline cellulose was employed in this study.

2. Materials and methods

2.1. Materials

Flost sugar (FS-2) and lactose were obtained from To-han (Japan) and De Melkindustrie Veghel BV, (Netherlands), respectively. Crystalline cellulose, marketed as Avicel PH101, was purchased from Asahikasei Industries (Japan). Calcium silicate, marketed as Florite-RE, was supplied by Eisai (Japan). All other chemicals were of reagent grade.

2.2. Model formulation

Liver hydrolysis products are known empirically to show explosive growth of particles in their granulation process. In the present study, a model formulation having such characteristics (shown in Table 1) was employed to evaluate the influence of process variables on the pharmaceutical properties of granules obtained.

Table 1
Formulation of granule and manufacturing scale

Ingredient	w/w (%)	VG-10 (g)	VG-25 (g)
Flost sugar	50.0	600.0	1500.0
Calcium silicate	25.0	300.0	750.0
Crystal line cellulose	10.0	120.0	300.0
Lactose	15.0	180.0	450.0

Table 2
Orthogonal arrays of $L_8(2)^4$ experimental design and obtained values of four response variables (Y_1, Y_2, Y_3 and Y_4)

Experimental number	Array number							Response variables			
	1	2	3	4	5	6	7	Y_1^b (%)	Y_2^c (μM)	Y_3^d	Y_4^e (s)
1	1	1	1	1	1	1	1	37.0	63	3.258	1127
2	1	1	1	2	2	2	2	35.6	46	3.218	688
3	1	2	2	1	1	2	2	64.2	153	2.662	1086
4	1	2	2	2	2	1	1	0.0	4738	1.710	923
5	2	1	2	1	2	1	2	52.0	63	2.679	492
6	2	1	2	2	1	2	1	59.9	142	2.896	417
7	2	2	1	1	2	2	1	0.0	5921	1.864	688
8	2	2	1	2	1	1	2	60.2	119	2.903	418
Factor[a]	X_1	X_2	A	X_3	B	C	X_4				

[a] $A = X_1 * X_2$, $B = X_1 * X_3$, $C = X_2 ** X_3$.
[b] Yield of granule.
[c] Geometrical mean size of granules.
[d] Geometrical standard deviation.
[e] Granulation time.

2.3. Evaluation of process variables and experimental design

The influence of four process variables (X_1: amount of binder solution used in granulation process; X_2: power consumption of the blade obtained as change in electric current; X_3: blade rotation speed; X_4: amount of powder supplied into the granulator) on four pharmaceutical properties were evaluated by employing an L_8 (2^4) fractional factorial experimental design based on the table of orthogonal arrays. In the study, power consumption of the blade is selected as an important process variable because power consumption changes depending on the condition of granulation even under the constant rotation speed of the blade. Four pharmaceutical properties were yield (Y_1) as fine granules defined in Japanese Pharmacopoeia XII, geometrical mean size of granules (Y_2), uniformity of granule size (Y_3) calculated as geometrical standard deviation, and granulation time (Y_4). The assignment of process variables and their interactions described as factors to the table of orthogonal arrays is shown in Table 2, in which interactions consisting of more than three factors are ignored. Each process variable expressed in coded form was studied at two levels in physical units as shown in Table 3. The granulator used in the study was a high-speed mixer granulator (VG-10, Powrex, Japan). Results obtained were analyzed by the method of analysis of variance, known as ANOVA (Taguchi, 1976).

2.4. Scale-up study

The influence of manufacturing scale on the granulation process was investigated using two different sizes of high-speed mixer granulator (VG-10 and VG-25, Powrex, Japan). The total volume (3.0 kg) of powder supplied into the VG-25 type high-speed mixer granulator is 2.5 times

Table 3
Level of independent variables in physical unit

Independent variables	Level in coded form	
	1	2
Total volume of binder solution (X_1)[a]	50 v/w%	60 v/w%
Power consumption of blade (X_2)	4.5 A	5.0 A
Blade rotation speed (X_3)	400 rpm	500 rpm
Amount of powder supplied into the granulator (X_4)	0.78 kg	1.30 kg

[a] X_1 is represented as volume percent against powder weight.

Table 4
Spherical central composite experimental design and obtained values of five response variables (Y_1, Y_2, Y_3, Y_4 and Y_5)

Experimental number	X_1^a	X_2^b	Z^c	Y_1^d (%)	Y_2^e (μM)	Y_3^f	Y_4^g (min)	Y_5^h (%)
1	1	1	−1	39.8	63	3.764	4.05	54.7
2	1	−1	−1	61.1	170	2.908	9.27	25.0
3	−1	1	−1	41.1	119	3.677	9.92	34.5
4	−1	−1	−1	0.0	413	1.436	21.45	0.8
5	0	0	−1	58.3	139	3.072	8.40	32.0
6	0	0	−1	54.5	136	3.202	8.93	24.3
7	$\sqrt{2}$	0	−1	52.0	101	3.247	3.72	46.0
8	0	$\sqrt{2}$	−1	37.8	95	4.034	4.78	46.1
9	$-\sqrt{2}$	0	−1	50.9	226	3.140	15.35	11.4
10	0	$-\sqrt{2}$	−1	1.7	945	3.877	16.20	0.2
11	1	1	1	52.5	120	3.059	6.87	29.8
12	1	−1	1	68.1	217	2.208	14.38	6.4
13	−1	1	1	56.9	158	2.711	13.00	22.0
14	−1	−1	1	62.0	337	1.755	26.92	0.2
15	0	0	1	61.9	140	2.593	13.23	22.0
16	0	0	1	52.7	124	2.809	12.45	30.6
17	$\sqrt{2}$	0	1	53.6	114	3.016	7.90	30.3
18	0	$\sqrt{2}$	1	50.5	128	4.060	7.20	30.0
19	$-\sqrt{2}$	0	1	65.5	174	2.402	17.75	15.0
20	0	$-\sqrt{2}$	1	11.3	643	1.620	21.40	0.0

[a] Total volume of binder solution (ml).
[b] Blade rotation speed (rpm).
[c] Manufacturing scale.
[d] Yield of granule.
[e] Geometrical mean size of granules.
[f] Geometrical standard deviation.
[g] Granulation time.
[h] Portion of granules less than 75 μm.

larger than that supplied into the VG-10 type high-speed mixer granulator. The studies were performed to obtain the regression functions of five response variables (pharmaceutical properties) shown in Table 4, according to the spherical central composite experimental design. In addition to the four response variables in Table 2, the portion of granules less than 75 μm (Y_5) was also evaluated in scale-up study. Factors employed were selected on the basis of the results obtained in ANOVA. The amount of binder solution used in the VG-25 type granulator was 2.5 times that used in the VG-10 type granulator and the blade rotation speed in two granulator was adjusted to have the same lap speed. In Table 4, manufacturing scale is coded as $Z = -1$ for the VG-10 type granulator and $Z = 1$ for the VG-25 type granulator.

The optimization procedure has been proposed by Takayama and Nagai (1991), Khuri (1980) and Derringer and Suich (1980). In the present study, an optimal condition of the granulation process at each scale was determined by minimizing the multi-objective function, S(**X**), described in Eq. (1).

$$S(\mathbf{X}) = \left[\sum_{i=1}^{n} |w_i\{FD_i(\mathbf{X}) - FO_i(\mathbf{X})\}|^p \right]^{1/p} \quad (1)$$

$FD_i(\mathbf{X})$ and $FO_i(\mathbf{X})$ are the optimum value of each objective function optimized individually over the experimental region and the simultaneous optimum value of each objective function. Impartiality between response variables is adjusted by employing a parameter p. The weighting coefficient, w_i, is defined as $1/FD_i(\mathbf{X})$.

Based on the experiments at each scale, a universal optimal condition unaffected by manufacturing scale was obtained using an integrated optimization function (Eq. (2)) introduced in our previous study (Ogawa et al., 1994).

$$\mathrm{T}(\mathbf{X}) = \mathrm{SS}(\mathbf{X}) + \mathrm{SL}(\mathbf{X}) + \mathrm{PN}(\mathbf{X}) \quad (2)$$

$$\mathrm{PN}(\mathbf{X}) = \left[\sum_{i=1}^{n} |w_i\{\mathrm{FS}_i(\mathbf{X}) - \mathrm{FL}_i(\mathbf{X})\}|^p \right]^{1/p} \quad (3)$$

where SS(**X**) and SL(**X**) are multi-objective functions for 1.2 kg scale and for 3.0 kg scale, respectively. PN(**X**) is a penalty function described in Eq. (3). The reciprocal of the mean FS(**X**) and FL(**X**) was employed as w_i.

2.5. Preparation of granules

All ingredients of the granule formulation in Table 1 were mixed for 3 min in the granulator, then binder solution was added to the powder mixture at once, followed by granulation for a predetermined time. Wet granules were dried in a fluid-bed dryer (FLO-5, Freund Industry, Japan) at 70°C air temperature for 15 min.

2.6. Physical properties of granules

Yield of granules (Y_1) was determined as weight of granules in the range of 75 to 500 μm as a percent of total granule weight. Granule size distribution was determined using different size sieves (Aperture size; 75, 106, 150, 180, 250, 355, 500 and 1000 μm) in a vibrating sifter (Electromag, Itoh, Japan). Twenty g of sample granules was introduced into the sieves and the weight of granules left on each sieve was measured after 10 min of vibration. Results obtained were analyzed according to the log-normal distribution described in Eq. (4), in which geometrical mean size of granules (Y_2) was calculated as the granule size equivalent to 50% of the cumulative residual % of granule weight ($F(\ln d)$) left on the mesh plotted as a function of the logarithm of granule diameter (d) (Carstensen, 1980).

$$f(\ln d) = \frac{\sum n}{\ln \sigma_g \sqrt{2\pi}} \exp\left\{ -\frac{(\ln d - \ln dg)^2}{2 \ln^2 \sigma_g} \right\} \quad (4)$$

where dg and $f(\ln d)$ are geometrical mean granule size and the number of granules having diameters (d) between $\ln d$ and $\ln d + \Delta(\ln d)$, respectively. The symbol Δ presents differential with diameter.

Uniformity of granule size (Y_3) is obtained as the standard deviation of granule size (σ_g) defined in Eq. (5).

$$\sigma_g = \frac{\text{A diameter of granule equivalent to 84\% of } F(d)}{\text{A diameter of granule equivalent to 50\% of } F(d)} \quad (5)$$

The portion of granules passed through 75 μm (Y_4) was used as a response variable to evaluate progress in the granulation process because more than 90% of the powders used in the model formulation were less than 75 μm. Further, granulation time (Y_5) was defined as the time that an electric current imposed on the blade achieves 5.0 A and 6.8 A in VG-10 and VG-25 type granulators, respectively, since the explosive granulation was found to occur when the electric current of the blade was over those values. Granulation time would be an important factor in controlling the terminal point of wet granulation in pharmaceutical plants.

2.7. Prediction of each response valuable

A second-order polynomial equation (Eq. (6)) including a scale variable, Z, is used to predict each response value.

$$Y = b_{00} + \sum_{i=1}^{n} b_{0i}X_i + \sum_{i=1}^{n}\sum_{j=1}^{n} b_{0ij}X_iX_j + b_{10}Z + \sum_{i=1}^{n} b_{1i}X_iZ + \sum_{i=1}^{n}\sum_{j=1}^{n} b_{1ij}X_iX_jZ \quad (6)$$

where Y is the response variable, b is the regression coefficient, and X and Z are the independent variable in coded form.

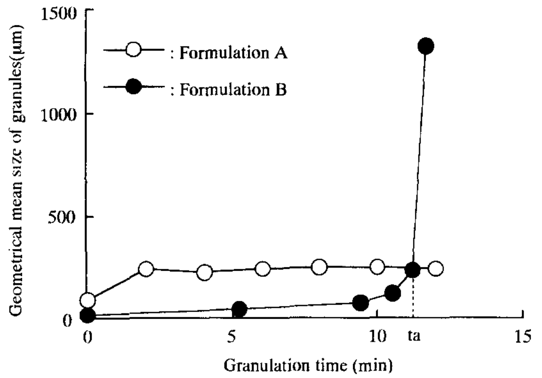

Fig. 1. Relationship between geometrical mean size of granules and granulation time.

3. Results and discussion

3.1. Evaluation of process variables

Fig. 1 shows the relationship between geometrical mean size of granules and granulation time in two different formulations, A and B. The physical properties of formulation A, which consisted of ascorbic acid (28.0 w/w%), lactose (45.6 w/w%), cornstarch (19.6 w/w%), crystalline cellulose (3.9 w/w%) and hydroxypropylcelluose (2.9 w/w%), were investigated in detail in our previous publication (19). Formulation B, described in Table 1, is the model formulation employed in the present study. As clearly shown in Fig. 1, explosive growth of granules occurred at and after granulation time $t = 11$ min with Formulation B. Control of particle size was extremely difficult in this case. On the other hand, the size of granules in Formulation A gradually increased with the increase in granulation time, so determining optimum granulation time was relatively easy.

In order to evaluate which process variables would have strong influence on such explosive growth of particles, the effects of four process variables (shown in Table 2) on four physical properties of the obtained granules were estimated using an L_8 (2^4) fractional factorial experimental design. Assignment of process variables to orthogonal arrays and the results of physical properties are summarized in Table 2, showing that granule yield (Y_1) was almost zero in experiments 4 and 7. This indicates that explosive growth of particles were completed under those experimental conditions. Furthermore, the values of four physical properties were found to vary widely and to be significantly influenced by the process variables. As an example, analysis of the geometrical mean size of granules (Y_2) by ANOVA is summarized in

Table 5
The analysis of variance for geometrical mean size of granules (Y_2)

Source of variance	Degree of freedom	Sum of squares	Mean squares	F^a	S'^b	Contribution[c] ratio (ρ) (%)
X_1	(1)	(388129)				
X_2	1	28164249	28164249	240.1**	28046935	33.6
X_3	(1)	(332929)				
X_4	1	27478564	27478564	234.2**	27361250	32.8
X_1*X_2	(1)	(276676)				
X_2*X_3	(1)	(409600)				
X_1*X_3	1	26471025	26471025	225.6**	26353711	31.5
S.e[d]	(8)	(434)				
(e)	12	1407768	117314		1759710	2.1
Total	15	83521606			83521606	100.0

Sum of squares in the parentheses are pooled as error.
[a] Mean square of each factor/Error.
[b] Revised sum of squares.
[c] Revised sum of square/Total sum of squares.
[d] Sampling error estimated from repeated experiments.
** $F > F0.01(1,12) = 9.33$.

Table 5. According to the analysis, three factors—power consumption of blade (X_2), amount of powder (X_4) supplied into the granulator and an interaction ($X_1 \times X_3$) between total volume of binder solution used in the process (X_1) and blade rotation speed (X_3)—had significantly high contribution ratios (ρs). Similar results are also obtained in other three physical properties (Y_1, Y_3 and Y_4). For example, ρs of X_1, X_2, X_4 and $X_1 \times X_3$ in Y_1 are 3.1, 9.4, 34.7 and 46.9%, respectively. On the other hand, ρs of X_1, X_2, X_3, X_4 and $X_1 \times X_3$ are 0, 45.1, 0, 15.6 and 26.6% for uniformity of granule size (Y_3) and 70.8, 3.2, 19.4, 4.7 and 1.4 for granulation time (Y_4). These results suggest that four factors (X_1, X_2, X_4 and $X_1 \times X_3$) possess critical influence on the granulation process of the model formulation.

With the elapse of granulation time, powder tended to adhere to the lower part of the vessel wall and accumulate there (the space between rotating blade and the vessel wall). This adhered powders finally reached to the maximum amount and extra powder then began to be scraped off by the blade. The occurrence of this phenomenon is designated as the point ta, in the abscisa of Fig. 1. Once the granulation process went through this point, growth of granules accelerated and resulted in an explosive increase in mean granule size. Further, an electric current imposed on the blade when the scraping of powders started was found to be almost constant at the same manufacturing scale even if operational conditions were different. This value was 5.0 A at the 1.2 kg scale and 6.8 A at the 3.0 kg scale. On the other hand, no adhesion or accumulation of powder on the vessel wall was observed with Formulation A (Fig. 1).

This phenomenon is supposed to be caused by a power balance among several forces acting on powders, such as the forces among powders, the force between powders and the wall, the centrifugal force, the centripetal force and gravity. The binder solution used in the process, physico-chemical properties of powder and structural features of the granulator such as the shape of the blade, could be critical factors in controlling the magnitude of these forces. The adhesion of powder on the wall and the centrifugal force would be strong enough to cause such a phenomenon and the explosive growth of particles under the operational conditions employed in the present study. Thus, the scraping of powder could be the determining step for such characteristic granulation.

In spite of the results of ANOVA, X_1 and X_3 were selected as process variables for scale-up studies because of the difficulty of controlling X_2 value in small range and the existence of a suitable amount of supplied powder for each granulator under the actual production in the plant. Although Terashita and co-workers used X_2 for determining the terminal point of granulation process (Terashita et al., 1985, 1987, 1990), our results suggested that their idea would be effective in the present case.

3.2. Scale-up and optimization

We have already reported the usefulness of the computer optimization technique on scale-up of the wet granulation process (Ogawa et al., 1994). However, the formulation evaluated in the study had granulation behaviour shown as Formulation A in Fig. 1, so the applicability of this technique to a granulation process involving explosive growth of particles, shown as Formulation B in Fig. 1, is unclear. On the basis of the observation in the above section, this evaluation was conducted by using the model formulation for the granulation process until the electric current of the blade reached 5 A for the 1.2 kg scale and 6.8 A for the 3.0 kg scale.

The experimental design and results of response variables are summarized in Table 4. Based on these results, an optimal regression equation for each response variable was obtained according to Eq. (6), and the regression coefficients of the equations composed of a combination of statistically significant variables are shown in Table 6. The coefficient of determination doubly adjusted with degrees of freedom was employed as a judgment standard for determining the optimal equation (Haga et al., 1976). As clearly indicated, the multiple correlation coefficient, r, was high enough to predict each response variable except Y_1 and Y_3. Thus, Y_2, Y_4 and Y_5 were used to optimize the process. Contour diagrams for Y_2, Y_4 and Y_5 are provided in Fig. 2, showing that the

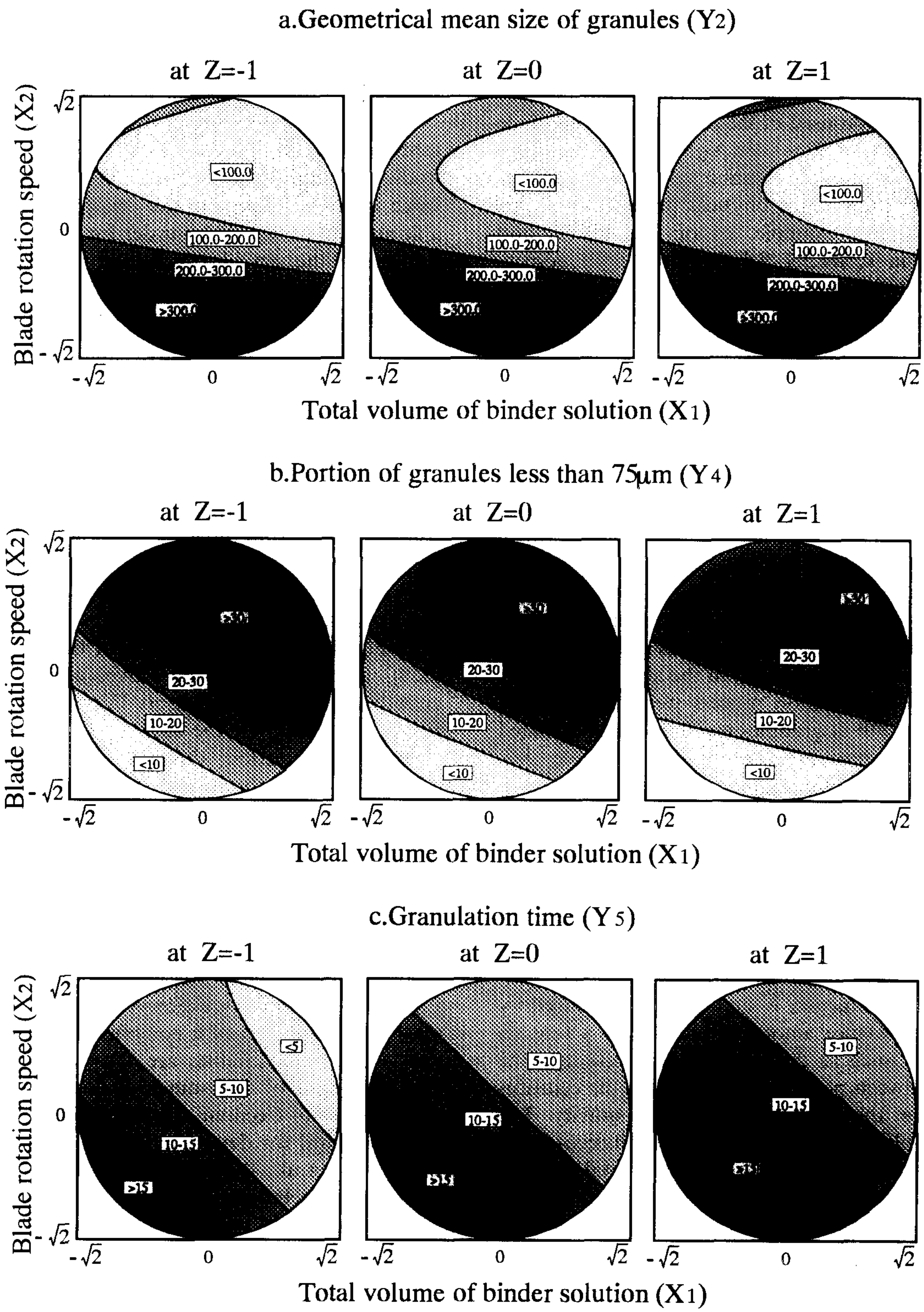

Fig. 2. Contour diagrams of three response variables: (a) geometrical mean size of granules (Y_2), (b) portion of granules less than 75 μm (Y_4), and (c) granulation time (Y_5)) as a function of Z.

Table 6
Optimum regression equation for five response variables

Coefficient	Regression coefficient value				
	Y_1^a (%)	Y_2^b (μm)	Y_3^c	Y_4^d (%)	Y_5^e (min)
b_{00} (constant)	58.15770	115.9980	2.92950	26.13970	10.75210
b_{01} $(X_1)^f$	—	−44.9187	0.21125	8.06113	−4.19393
b_{02} $(X_2)^g$	6.59938	−162.9690	0.53609	13.49720	−4.65112
b_{011} (X_1^2)	—	—	—	—	0.57531
b_{012} (X_1X_2)	−9.11250	—	—	—	1.59000
b_{022} (X_2^2)	−14.43680	140.1490	—	−3.84398	1.18299
b_{10} $(Z)^h$	6.89000	—	−0.30620	−3.13161	1.95150
b_{11} (X_1Z)	−4.78085	—	—	−3.60618	—
b_{12} (X_2Z)	—	37.4238	—	−2.54305	−0.53826
b_{111} (X_1^2Z)	—	—	—	—	—
b_{112} (X_1X_2Z)	6.48750	—	—	—	—
b_{122} (X_2^2Z)	—	—	—	−1.62949	—
r^i	0.83992	0.88837	0.80053	0.98231	0.99137
r^{2j}	0.44655	0.68213	0.51258	0.92598	0.96371
s^k	13.10280	111.6000	0.50173	3.83371	1.03946
F_0^l	5.18972[m]	14.0398[m]	9.51645[m]	47.17980[m]	98.01590[m]

[a] Yield of granule (%).
[b] Geometrical mean size of granules.
[c] Geometrical standard deviation.
[d] Portion of granules less than 75 μm.
[e] Granulation time.
[f] Total volume of binder solution.
[g] Blade rotation speed.
[h] Manufacturing scale.
[i] Multiple correlation coefficient.
[j] Doubly adjusted r^2 with degrees of freedom.
[k] Standard deviation.
[l] Observed F value.
[m] $P<0.01$.
—, This factor is not included in the optimum regression equation.

area giving a low Y_2 value is relatively wide at $Z = -1$ and becomes smaller with the increase of manufacturing scale, however the area giving a high Y_2 value ($Y_2 > 300$) did not change. In Fig. 2, the contour diagram at $Z = 0$ was added although experiments were not conducted. On the other hand, the area showing high Y_4 values is seen to narrow with the increase of manufacturing scale. Granulation time (Y_5) tends to be prolonged with the increase of manufacturing scale. Force imposed on powder in the vessel is proportional to the square of angular velocity and the radius of the blade. The magnitude of force imposed on powder increases with the increase of the angular velocity, since the rotation speed of the blade was adjusted to be the same as the lap speed in the present study. This force is higher in the VG-10 type granulators than in the VG-25 type granulators, and this difference could explain the results obtained in Fig. 2.

Based on Eq. (1), contour diagrams for $Z = -1$ and for $Z = 1$ are depicted in Fig. 3, and optimal conditions, shown as small open circle in the figure, are obtained as $X_1 = -0.4800$ and $X_2 = -0.0792$ for $Z = -1$ and $X_1 = 1.3259$ and $X_2 = -0.4920$ for $Z = 1$, respectively. The optimal condition at $Z = -1$ is certainly different from that at $Z = 1$, indicating that this granulation process is strongly influenced by manufacturing scale. This seems to be a reasonable

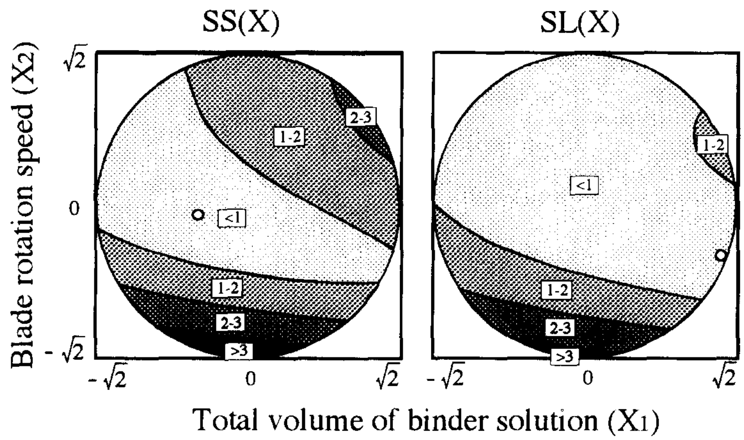

Fig. 3. Contour diagrams of generalized distance functions, SS(**X**) and SL(**X**) as functions of X_1 and X_2 at $P = 2$. (○) Optimal condition of each scale.

conclusion because of the strong influences of rotation speed and energy consumption of the blade on response variables mentioned in the above section. However, the area giving small values of SS(**X**) and SL(**X**) are located at similar conditions. The universal optimal condition, depicted as the small open circle in Fig. 4, was found to be $X_1 = -0.4536$ and $X_2 = -0.0569$.

To evaluate the usefulness of this method, the predicted values of Y_1, Y_2, Y_3, Y_4 and Y_5 at the universal optimal conditions ($X_1 = -0.4536$ and $X_2 = -0.0569$) were compared with those of experimental results which were obtained with newly prepared granules at 1.2 and 3.0 kg scales. The results (summarized in Table 7) indicate that both predicted and experimental values agree well at the two manufacturing scales. These coincidences were also good for Y_1 and Y_3, for which the correlation coefficient was not high enough in regression analysis. This means that the computer optimization technique could be useful for obtaining the optimal condition in the wet granulation process even if the process involves the explosive growth of particles.

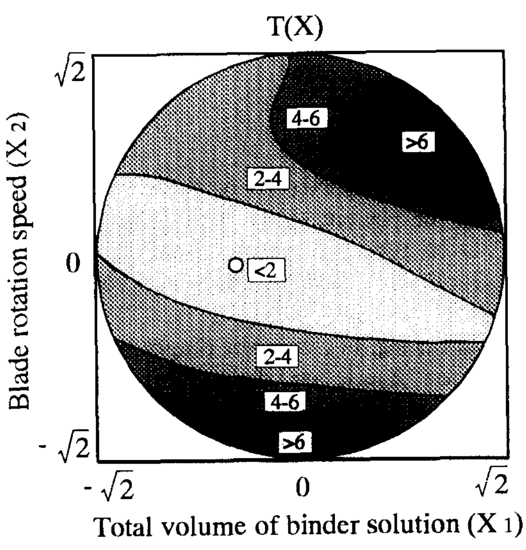

Fig. 4. Contour diagram of integrated optimization function, T(**X**), as a function of X_1 and X_2 at $P = 2$. (○) Optimal condition of T(**X**).

4. Conclusion

In the wet granulation process involving explosive growth of particles, four factors (binder solution, power consumption of blade, the powder supplied into the granulator, and the interaction between binder solution and blade rotation speed) were found to have strong influence on the physical properties of granules. Such growth of particles seemed to be caused by the scraping off of powder adhered to the wall of the granulator by the blade. A scale-up study of this granulation process was conducted employing the computer

Table 7
Predicted and experimental values of response variables (Y_1, Y_2, Y_3, Y_4 and Y_5)

Response variable	1.2 kg scale		3.0 kg scale	
	Predicted	Experimental[a]	Predicted	Experimental[a]
Y_1^b (%)	48.3	61.7	66.7	68.1
Y_2^c (μm)	148	154	144	147
Y_3^d	3.1	2.9	2.5	2.5
Y_4^e (%)	23.1	22.0	20.3	22.2
Y_5^f (min)	11.1	12.0	15.0	14.7

[a] Each scale of experimental data obtained from two granulation batches.
[b] Yield of granules.
[c] Geometrical mean size of granules.
[d] Geometrical standard deviation.
[e] Portion of granules less than 75 μm.
[f] Granulation time.

optimization technique. An optimal condition unaffected by manufacturing scale was obtained by minimizing the integrated optimization function. Experimental and predicted values of three response variables agreed well, so the computer optimization technique may be useful and applicable for optimizing the wet granulation process even if explosive growth of granules is involved.

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