Optimization of the Granulation Process for Designing Tablets

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A computer optimization technique based on surface response methodology was applied to optimize the wet granulation process for designing tablets. Physical properties (mean granule size, granule size distribution, compressibility, granule strength) of a model granule formulation containing ethenzamide were accurately described by a second polynomial equation based on two independent variables (amounts of binder and binder solution). This regression equation also gave a good correlation for three physical properties of tablets (disintegration time, compactibility, compression force variance), but the correlation for tablet hardness and weight variation was poor. These results imply that not only the above physical properties of granules but also the rheological behavior and porous structure of granules are closely related to tablet properties. Using an optimization of five tablet properties using the generalized distance function, the predicted values of the physical properties of both granules and tablets agreed well with experimental values. This agreement indicates that the computer optimization technique is useful for optimizing the granulation process for designing tablets.

Key words computer optimization; tablets; surface response method; granulation

Tablets are widely accepted as the preferred dosage form among patients and progress in tabletting technology has produced several types such as chewable, effervescent, and multilayer tablets. Despite technical progress, however, the pharmaceutical properties of tablets are still controlled by the powder and/or granules used in the formulation. In general, it is difficult to use powders without pretreatment because of their poor physical properties (flowability, compressibility, *etc.*) exhibited in the tabletting process. The granulation process is an effective means of improving these unfavorable properties of powders. However, the physical properties of granules required for designing tablets are not necessarily the same as those required for granule formulation. Granule flowability and compressibility, for example, are critical properties for tablets but uniformity of granule size is more important for the design of granules. A number of studies on the granulation process for designing tablets have been reported with respect to the optimization of formulation and operational conditions.[1] For example, Shiraishi *et al.*[2—4] reported in a series of studies that the inner structure of granules plays an important role in controlling the physical properties of the final tablets. Similar results with tablets consisting of lactose granules were obtained by Zuurman *et al.*[5] and Horisawa *et al.*[6] discussed the relationship between granule and tablet strengths.

In the last few decades, computer optimization has been found useful for studying pharmaceutical granulation.[7,8] Miyamoto *et al.*[9,10] investigated the critical factors for determining granule properties in the manufacturing process and applied this technique to describe an explosive growth of particles in the granulation process. Scale-up problems in the wet granulation process were discussed by Ogawa *et al.*[11] Several studies have been performed on the optimization of granule formulation from the viewpoint of tablet design. For example, Chowhan and Amaro[12] used a computer-optimized experimental design to optimize four physical tablet properties by controlling in-process variables in granulation. Lipps and Sakr[13] applied response surface methodology to evaluate the correlation between granule characteristics and drug dissolution from tablets while Yajima *et al.*[14] tried to optimize granule size distribution for designing tablets.

In the present study, a computer optimization technique based on surface response methodology was applied to investigate the relationship between the physical properties of granules and tablets. Four properties (granule strength, compressibility, granule size, granule size distribution) of granules were selected as factors predominantly influencing the physical properties of tablets. In addition, tablet hardness, disintegration time, weight and compression force variance in the tabletting process and compactibility, obtained as a slope of the plot of tablet hardness *versus* compression force, were evaluated as physical properties of the tablets obtained.

Experimental

Materials Ethenzamide, the model drug, was purchased from Iwaki Co., Ltd. Lactose, cornstarch and hydroxypropyl cellulose (HPC-L) were obtained from De Melkindustrie Veghel bv, (Netherlands), Nihon Shokuhin Kako Co., Ltd. and Shinetsu Chemical Co., Ltd., respectively. Crystalline cellulose, marketed as Avicel PH101, was purchased from Asahi Kasei Industries, Co., Ltd. and magnesium stearate from Taihei Chemical Co., Ltd. Other chemicals were of reagent grade.

Granule Formulation Ethenzamide was selected as a model drug with poor compressive properties for this study. Granule formulation is shown in Table 1. The amount of HPC-L used as binder was varied from 0.07 to 5.7% in order to change the physical properties of the granules. Binder solution was obtained by dissolving HPC-L in purified water. In the tabletting process, magnesium stearate was added 1.0% to the granules as lubricant.

Granulation and Tabletting 1) Preparation of Granules: Granules were prepared using a high-speed mixer granulator (VG-10, Powrex Co., Ltd.). Binder solution was added to the powder mixture after pre-mixing ethenzamide, cornstarch, lactose and crystalline cellulose for 3 min in the granulator. The operational conditions of the granulation process were as follows: blade rotation speed: 450 rpm; chopper rotation speed: 1450 rpm; granulation time: 10 min. Wet granules obtained were then dried in a fluid-bed dryer (FLO-5, Freund Industry, Ltd.) at 70 °C air temperature for 15 min. The granules obtained were spherical in shape.

2) Preparation of Tablets: A rotary tablet press (HT-AP15, Hata Iron Factory) with a flow feeder was employed to prepare tablets after granules were

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mixed with magnesium stearate in a planetary mixer (5DMr, Dalton Corporation). The operational conditions of the mixing process were controlled so that they were identical (beater rotation speed; 63 rpm, mixing time; 1 min) for all granules. The weight of each tablet and rotating speed of the tablet press were adjusted to 120 mg/tablet and 35 rpm, respectively. The tablet diameter and radius of curvature was 7.0 and 5.6 mm, respectively. The compression force during the tabletting process was recorded by strain gauges attached to the upper and lower punches. These conditions were kept constant in order to prevent the operational conditions of the press from affecting the physical properties of the tablets.

In addition, an eccentric tablet press (N-30E, Okada Seiko Co., Ltd.) with an 11.3 mm diameter flat face punch was also used to prepare tablets (tabletting rate: 30 tablets/min) and evaluate the effect of granule properties on tablet hardness.

Experimental Design As reported in our previous study,[9] the formulation of binder solution plays a critical role in controlling the physical properties of the granules obtained during wet granulation, so the amounts of purified water (X_1) and HPC-L (X_2), presented in coded form in Table 2, were selected as independent variables. Six physical properties (Y_1: geometrical mean granule size (μm); Y_2: granule size uniformity calculated as the geometrical standard deviation; Y_3: granules larger than 500 μm (%); Y_4: granules smaller than 106 μm (%); Y_5: compressibility (%); Y_6: granule strength (g/mm^2)) were determined as response variables. A total of 10 experiments were performed according to a spherical central composite experimental design (Table 3) to obtain the regression function of each response variable.

Tablet hardness (Yt_1; N), disintegration time (Yt_2; minute), weight variance (Yt_3; %), compression force variance (Yt_4; kg), and compactibility (Yt_5) were evaluated as physical tablet properties.

Determination of Physical Properties 1) Physical Properties of Granules: The geometrical mean granule size (Y_1) and geometrical standard deviation (Y_2) were calculated using Eqs. 1 and 2 from a plot of the cumulative residual % of granule weight left on each sieve against the granule diameter represented by the aperture of the sieve.[15] This procedure was described in detail in a previous paper.[9]

$$f(\ln d)=\frac{\Sigma n}{\ln \sigma g\sqrt{2\pi}}\exp\left\{-\frac{(\ln d-\ln dg)^2}{2\ln^2 \sigma g}\right\} \quad (1)$$

where dg and $f(\ln d)$ are the 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 represents the diameter differential.

The geometrical standard deviation (Y_2) of the granule size was defined as σg in Eq 2.

$$\sigma g=\frac{\text{a granule diameter equivalent to } 80\% F(\ln d)}{\text{a granule diameter equivalent to } 50\% F(\ln d)} \quad (2)$$

The compressibility (Y_5) of granules was measured using a 100 ml cup attached to the powder tester (PT-D, Hosokawa Powder Technology Co., Ltd.) and calculated from Eq. 3.[16]

$$\text{compressiblity } (Y_5:\%)=\frac{(\text{tapped density}-\text{fluff density})}{\text{tapped density}}\times 100 \quad (3)$$

Granule mechanical strength (Y_6) was calculated from Eq. 4.[17]

$$\text{granule strength } (Y_6:\text{g/mm}^2)=\frac{4P}{\pi D^2} \quad (4)$$

where D and P are the diameter of the granule (mm) and crushing strength (g), respectively. In this equation, the granule crushing strength (P) was determined using a particle hardness tester (Grano, Okada Seiko Co., Ltd.).

An air comparison pycnometer (Model 930, Beckman Co., Ltd.) was used to measure granule density.

2) Physical Properties of Tablets: Tablet hardness (Yt_1) was determined as the average hardness from 10 measurements using a hardness tester (PTB 301, Pharm Test). The disintegration time (Yt_2) was determined by the method described in the Japanese Pharmacopeia XII using water at 37 °C. The weight variance(Yt_3) was obtained as the standard deviation of tablet weights based on 50 measurements. The compression force variance (Yt_4) was calculated as the difference between the maximum and minimum compression forces of the upper punch based on 500 measurements. The tablet compactibility (Yt_5), which was evaluated as an index of tablet formation ability of granules, was defined as the slope obtained from a plot of tablet hardness *versus* compression force.

Regression Analysis and Optimization Procedure A second-order polynomial equation (Eq. 5) was used to predict the response variables.

$$Y=b_0+\sum_{i=1}^{n} b_i X_i+\sum_{i=1}^{n}\sum_{j=1}^{n} b_{ij} X_i X_j \quad (5)$$

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

Table 1. Granule Formulation

Ingredient	(g)	%
Ethenzamide	560.0	28.0
Lactose	855.4—968.6	42.8—48.4
Cornstarch	392.0	19.6
Crystalline cellulose	78.0	3.9
HPC-L	1.4—114.6	0.07— 5.7
Total	2000.0	100.0

In the tabletting process, 1.0% magnesium stearate was added to granules as a lubricant.

Table 2. Level of Independent Variables (X_1 and X_2) in Physical Units

Independent variable	Level in coded form				
	$-\sqrt{2}$	−1	0	1	$\sqrt{2}$
X_1 (Purified water, ml)	300	330	400	470	500
X_2 (HPC-L, g)	1.4	18	58	98	114.6

Table 3. Experimental Design and Values of Six Response Variables (Y_1, Y_2, Y_3, Y_4, Y_5, Y_6) Obtained for Granules

Experiment number	X_1[a]	X_2[b]	Y_1[c] (μm)	Y_2[d]	Y_3[e] (%)	Y_4[f] (%)	Y_5[g] (%)	Y_6[h] (g/mm^2)
1	1	1	785.3	2.58	56.5	1.4	5.0	665.80
2	1	−1	394.5	2.37	48.8	9.0	7.4	330.60
3	−1	1	186.1	2.27	7.8	21.9	11.9	480.36
4	−1	−1	93.1	2.39	2.0	56.7	22.3	471.95
5	0	0	265.2	2.08	10.7	9.9	5.5	464.51
6	0	$\sqrt{2}$	474.3	2.50	27.1	0.1	3.6	600.35
7	$\sqrt{2}$	0	460.4	2.61	50.9	8.5	2.5	504.06
8	0	$-\sqrt{2}$	207.8	2.89	18.6	29.0	16.5	260.10
9	$-\sqrt{2}$	0	120.4	2.15	3.8	48.2	16.4	457.05
10	0	0	261.2	2.05	9.5	11.1	6.8	447.67

a) Volume of binder solution. *b*) Amount of binder. *c*) Geometrical mean size of particles. *d*) Geometrical standard deviation. *e*) Yield of granules more than 500 μm. *f*) Yield of granules less than 106 μm. *g*) Compressibility. *h*) Granule strength.

Table 4. Optimum Regression Equation for Six Response Variables of Granules

Coefficient	Regression coefficient value					
	Y_1 [a] (μm)	Y_2 [b]	Y_3 [c] (%)	Y_4 [d] (%)	Y_5 [e] (%)	Y_6 [f] (g/mm²)
b_0 (constant)	292.7410	2.0650	10.0989	10.4998	6.1494	450.3880
b_1 (X_1 [g])	172.6960	0.1176	20.2655	−15.5443	−5.1817	13.8224
b_2 (X_2 [h])	107.5950	—	3.1904	−10.4096	−3.8751	103.106
b_{11} (X_1^2)	—	0.1237	9.5460	9.1270	2.1388	22.3249
b_{22} (X_2^2)	40.1171	0.2813	7.2954	2.2250	2.4139	—
b_{12} (X_1X_2)	74.4500	0.0825	—	6.8000	1.9875	81.6975
r [i]	0.9594	0.8898	0.9831	0.9970	0.9842	0.98032
r^2 [j]	0.8568	0.6253	0.9397	0.9865	0.9296	0.92985
s [k]	79.1324	0.1621	5.1590	2.2593	1.7609	30.6800
F_0 [l]	14.46[m]	4.7545	36.07[m]	132.46[m]	24.77[m]	30.83[m]

a) Geometrical mean size of particles. *b*) Geometrical standard deviation. *c*) Yield of granules more than 500 μm. *d*) Yield of granules less than 106 μm. *e*) Compressibility. *f*) Granule strength. *g*) Volume of binder solution. *h*) Amount of binder. *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.

The optimization procedure using a generalized distance function (Eq. 6) is described in our previous paper.[10]

$$S(X)=\left[\sum_{i=1}^{n}|w_i\{FD_i(X)-FO_i(X)\}|^p\right]^{1/p} \quad (6)$$

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

Results and Discussion

Regression Analysis of Six Response Variables of Granules The experimental values of six response variables are summarized in Table 3. Based on these data, the results of the multiple regression analysis shown in Table 4 indicate that the values of r^2 (doubly adjusted correlation coefficient with degrees of freedom) were high enough to predict response variables by Eq. 5. Contour diagrams of six response variables as a function of X_1 and X_2 are shown in Fig. 1. As clearly depicted in the figure, mean granule size (Y_1), granules larger than 500 μm (Y_3) and granule strength (Y_6) tend to increase with an increase in X_1 and X_2. However the compressibility (Y_5) and granules smaller than 106 μm (Y_4) are liable to increase with a decrease in X_1 and X_2. From this trend, it seems reasonable to assume that increases in the amount of HPC-L as binder increase granule strength and that the total amount of binder solution used in the process results in an accelerated formation of agglomerates. Further, the values (less than 20%) of granule compressibility, except in experiment No. 4 indicate that the flowability of the granules could be classified as "good".[15] The spherical shape of the granules is thought to account for their good flowability. On the other hand, there are optimal values of X_1 and X_2 to give good granule size uniformity (Y_2). This result suggests that both the acceleration of granulation due to an excess of binder solution and the incomplete granulation due to insufficient binder solution resulted in high Y_2 values (low uniformity of granule size).

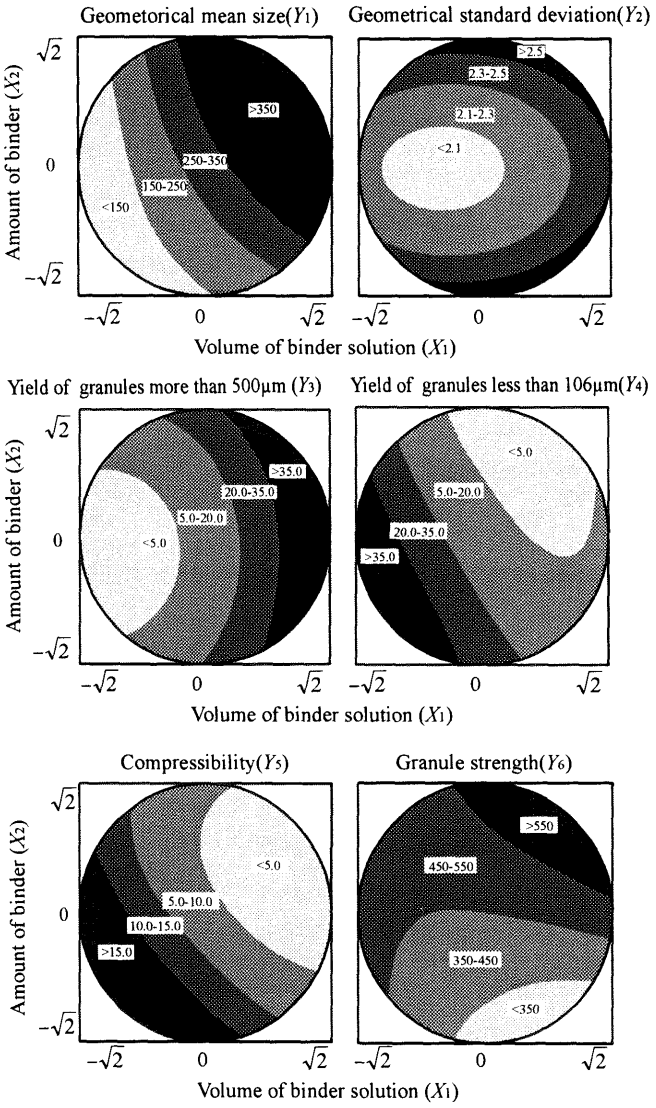

Fig. 1. Contour Diagrams of Y_1, Y_2, Y_3, Y_4, Y_5 and Y_6 as a Function of X_1 and X_2

Regression Analysis of Five Response Variables of Tablets The experimental values of five response variables and the results of the multiple regression analysis are shown in Tables 5 and 6, respectively. Contour diagrams of the response variables as a function of X_1 and X_2 are illustrated in Fig. 2. As clearly shown, values of r^2 are relatively low for all response variables compared with those observed in granules. The r^2-values of tablet hardness (Yt_1) and weight variance (Yt_3) were 0.3493 and 0.2031, respectively. Contour diagrams of Yt_1 and Yt_3 are also shown in the figure as a refer-

Table 5. Experimental Design and Values of Five Response Variables (Yt_1, Yt_2, Yt_3, Yt_4, Yt_5) Obtained for Tablets

Experiment number	X_1[a]	X_2[b]	Yt_1[c] (N)	Yt_2[d] (min)	Yt_3[e] (%)	Yt_4[f] (kg)	Yt_5[g]
1	1	1	50.7	30.0	1.20	330	0.0064
2	1	−1	27.7	1.6	1.82	360	0.0035
3	−1	1	26.5	1.3	0.88	210	0.0045
4	−1	−1	21.4	0.3	0.87	180	0.0041
5	0	0	25.7	1.3	1.20	210	0.0049
6	0	$\sqrt{2}$	24.5	30.0	0.96	300	0.0043
7	$\sqrt{2}$	0	30.4	2.7	1.00	330	0.0043
8	0	$-\sqrt{2}$	19.2	0.3	0.89	150	0.0036
9	$-\sqrt{2}$	0	28.5	1.1	0.63	180	0.0051
10	0	0	30.1	0.9	1.77	330	0.0049

a) Volume of binder solution. *b*) Amount of binder. *c*) Hardness. *d*) Disintegration time. *e*) Weight variance. *f*) Compression force variance. *g*) Tablet compactibility.

Table 6. Optimum Regression Equation for Five Response Variables of Tablets

Coefficient	Regression coefficient value				
	Yt_1[a] (N)	Yt_2[b] (min)	Yt_3[c] (%)	Yt_4[d] (kg)	Yt_5[e]
b_0 (constant)	28.4700	1.4687	1.4849	258.0000	0.00487
b_1 (X_1[f])	4.1490	4.0372	0.2242	64.0222	
b_2 (X_2[g])	4.4500	8.9221	—	26.5165	0.00054
b_{11} (X_1^2)	—	—	−0.2544	—	—
b_{22} (X_2^2)	—	6.8364	−0.1993	—	−0.00039
b_{12} (X_1X_2)	4.4750	6.8575	—	—	0.00063
r[h]	0.7525	0.9552	0.7344	0.8270	0.8645
r^2[i]	0.3493	0.8421	0.2031	0.5936	0.6211
s[j]	6.9306	4.8367	0.3253	50.3560	0.0005
F_0[k]	2.6106	13.00[l]	2.3412	7.5737	5.9179

a) Hardness. *b*) Disintegration time. *c*) Weight variance. *d*) Compression force variance. *e*) Tablet compactibility. *f*) Volume of binder solution. *g*) Amount of binder. *h*) Multiple correlation coefficient. *i*) Doubly adjusted r^2 with degrees of freedom. *j*) Standard deviation. *k*) Observed F value. *l*) $p<0.01$. — This factor is not included in the optimum regression equation.

ence. No apparent trend was observed in the present study because the value of Yt_3 lay within a narrow range (2%) due to good flowablity. The low r^2-values of Yt_1 are probably due to the complexity of the tabletting process. In brief, some physical properties are not simply controlled by those of the granules but by the mechanical structure and operational conditions of the tablet press. For this reason, the effect of granule properties on tablet hardness was also evaluated using an eccentric tablet press. We prepared tablets with curvature in order to simulate the actual tabletting process in a rotary tablet press machine. A flat face punch with a diameter of 11.3 mm was employed in the preparation of tablets in the eccentric press because the curvature of the tablet might influence tablet hardness. Although Heckel's equation[18] is generally used to evaluate the tablet formation ability of granules, tablet compactibility (Yt_5) was introduced to avoid the effect of compression force because tablet hardness is evaluated during the manufacturing process. The values of the correlation coefficient (ranging from 0.993 to 1.000) showed good linearity between tablet hardness and compression force. The result of the multiple regression analysis of Yt_5, shown in Table 6, indicates that the r^2-value was improved to 0.6211. The contour diagram of Yt_5 depicted in Fig. 2, showed that tablet hardness tended to increase in regions of high X_1 and X_2. In particular, a high X_2 value seems to be necessary to increase tablet hardness. As already shown, granule strength was also high in this region. Granule strength is considered to have an effect on the plastic deformation/brittle fracture of granules during the tabletting process, in that plastic deformation/brittle fracture of granules will not occur effectively at low pressure. However, this is not consistent with the results obtained here. During the compacting process, not only plastic deformation/brittle fracture but also elastic deformation is responsible for tablet hardness. As shown in Fig. 3, marked elastic deformation was observed in the determination of granule strength. In addition, the density of granules determined by pycnometer was almost the same (1.29—1.33 g/ml) for different granules although tapped (0.67—0.83 g/ml) and fluff densities (0.59—0.73 g/ml) were dependent on the granule formulation. The tapped density decreased with an increase in fluff density and exhibited a reverse relationship to granule compressibility. This implies that granules with a porous structure tend to increase tablet hardness. The compacting pressure employed here and/or this elastic behavior of granules could account for the results obtained in this study. Unlike tablet hardness, disintegration time (Yt_2) tends to increase in the region of high X_1 and X_2. Values of Yt_4 were found to be lower in the region of low X_1 and X_2, suggesting that the relatively high compression force needed to press granules produces high Yt_4-values.

Correlation between Physical Properties of Granules and Tablets To discuss the relationship between physical properties of granules and tablets in detail, the correlation coefficients of the response variables of tablets and granules are summarized in Table 7. Granule strength was found to

have a positive relationship with tablet hardness (Yt_1) and disintegration time (Yt_2), and geometrical mean granule size (Y_1) also had a positive relationship with both tablet properties in this analysis. On the other hand, compressibility (Y_5) of granules and geometrical mean granule size (Y_1) exhibit negative and positive relationship with compression force variance (Yt_4), respectively. These results also suggest that granule size distribution significantly influences Yt_4. This could be explained by considering physical processes such as plastic and elastic deformation involved in the tabletting process. As mentioned above, granules in the die were pressed into tablets in five steps (filling the die in cascaded fashion, rearrangement, elastic deformation, plastic deformation/brittle fracture and fusion) by Carstensen.[15] If a suitable amount of lubricant is added to granules, the effect of steps 1—2 is minimal. This means that the effect of granule preparation on steps 3 and 4 will control the physical properties of tablets. Granule strength, elastic properties and size are very likely to control these steps, and low values of granule compressibility would be responsible for lowering the compacting force variance.

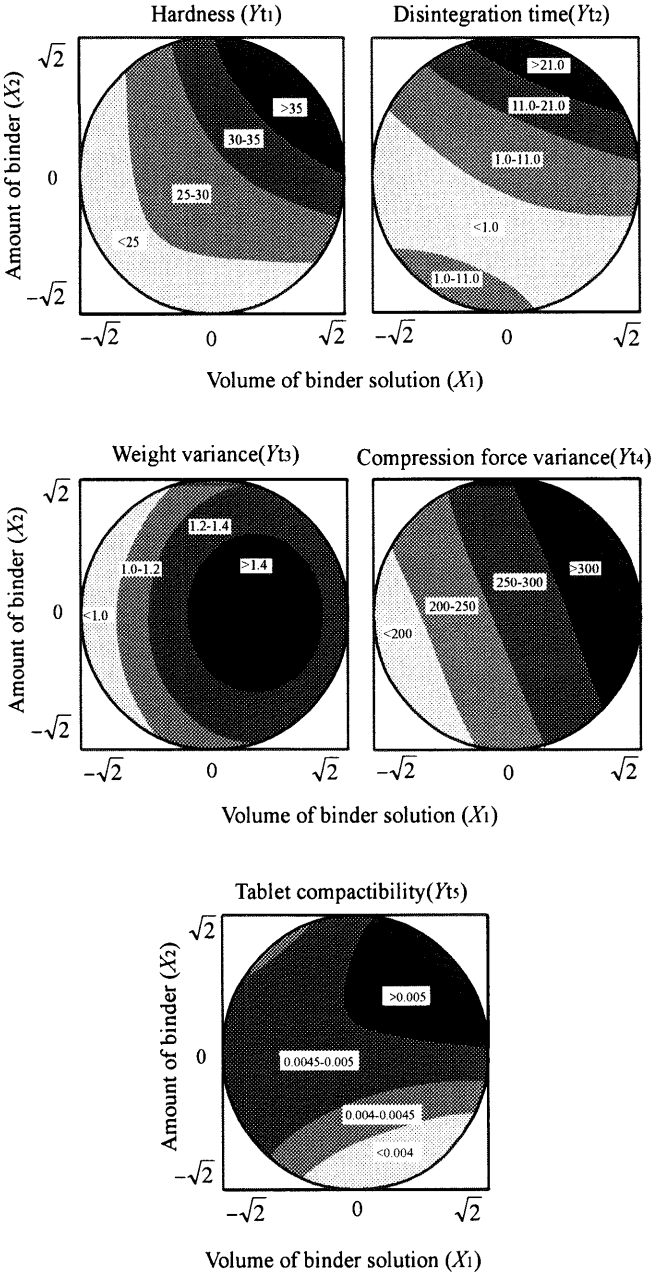

Fig. 2. Contour Diagrams of Yt_1, Yt_2, Yt_3, Yt_4 and Yt_5 as a Function of X_1 and X_2

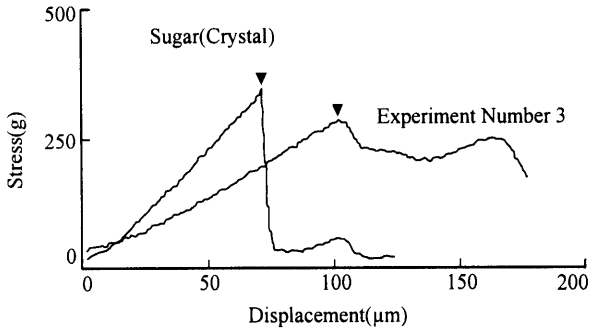

Fig. 3. Relationship between Stress and Displacement in the Determination of Granule Strength

Optimization of Granulation and Tabletting Process

Optimized conditions of granulation, in which tablets have a high degree of hardness, short disintegration time, and low weight and compacting force variances, were calculated using the generalized distance function and are summarized in Table 8. The universal optimal conditions (shown as the small open circle in Fig. 4) obtained were $X_1=-0.758$ and $X_2=0.400$. These results were compared with experimental data obtained for newly prepared granules and tablets (summarized in Tables 8 and 9). As clearly shown, predicted values agree well with experimental results for the physical properties of both tablets and granules. In spite of the low r^2 values of Yt_2 and Yt_3, the agreement between predicted and experimental values was also good. The results obtained here suggest that the computer optimization technique is useful for analyzing the tabletting process and optimizing the granulation process for designing tablets. These data will also be

Table 7. Correlation between Physical Properties of Granules and Tablets

Response variable	Definition	Yt_1 (N)	Yt_2 (min)	Yt_3 (%)	Yt_4 (kg)	Yt_5
		Hardness	Disintegration time	Weight variance	Compression force variance	Tablet compactibility
Y_1 (μm)	Geometrical mean size of particles	0.7978**	0.7917**	0.2954	0.7257*	0.4915
Y_2	Geometrical standard deviation	0.0061	0.2985	−0.2758	−0.0373	−0.2700
Y_3 (%)	Yield of granules more than 500 μm	0.6112	0.4904	0.3552	0.7486*	0.1367
Y_4 (%)	Yield of granules less than 106 μm	−0.4527	−0.5394	−0.5364	−0.7529*	−0.2135
Y_5 (%)	Compressibility	−0.4691	−0.4758	−0.4656	−0.7836**	−0.2785
Y_6 (g/mm^2)	Granule strength	0.6585*	0.7635*	−0.1719	0.3581	0.7436*

Significant *: $p<0.05$, **: $p<0.01$.

Table 8. Predicted and Experimental Values for Response Variables (Y_1, Y_2, Y_3, Y_4, Y_5, Y_6) of Granules

Response variable	Definition	Granule	
		Predicted	Experimental
Y_1 (μm)	Geometrical mean size of particles	188.8	197.4
Y_2	Geometrical standard deviation	2.09	1.77
Y_3 (%)	Yield of granules more than 500 μm	2.7	3.3
Y_4 (%)	Yield of granules less than 106 μm	21.6	27.5
Y_5 (%)	Compressibility	9.5	10.5
Y_6 (g/mm^2)	Granule strength	469.4	463.4

Table 9. Predicted and Experimental Values for Response Variables (Yt_1, Yt_2, Yt_3, Yt_4, Yt_5) of Tablets

Response variable	Definition	Tablet	
		Predicted	Experimental
Yt_1 (N)	Hardness	25.7	30.4
Yt_2 (min)	Disintegration time	1.0	1.0
Yt_3 (%)	Weight variance	1.13	0.99
Yt_4 (kg)	Compression force variance	220	225
Yt_5	Tablet compactibility	0.0048	0.0044

useful for validating the tabletting process.

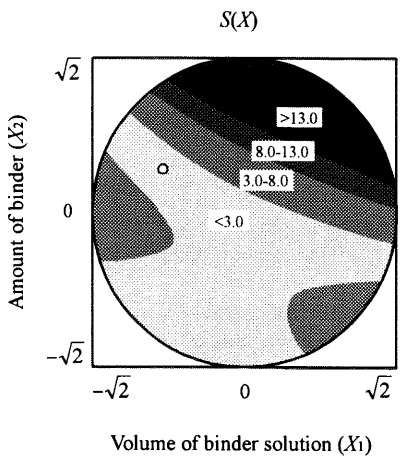

Fig. 4. Contour Diagram of Generalized Distance Function $S(X)$ as a Function of X_1 and X_2 at $P=2$
○: Optimal condition.

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