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RESEARCH PAPER

Simultaneous Optimization of Wet Granulation Process Involving Factor of Drug Content Dependency on Granule Size

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ABSTRACT

Computer optimization technique was applied to the simultaneous optimization of wet granulation process by a high-speed mixer granulator. Four pharmaceutical properties, including yield, drug content uniformity, geometrical mean diameter of granules, and uniformity of granule size, were selected to evaluate the quality of the granules. In particular, dependence of drug content uniformity on granule size was investigated using two model drugs, ascorbic acid and ethenzamide. An appreciable dependence of ascorbic acid content on granule size was not observed in model formulations. On the other hand, ethenzamide was contained more in small-size granules, and its content was decreased with an increase in amounts of hydroxypropyl cellulose (HPC-L; used as a binder) and binder solution. These observations suggested that drug content uniformity is influenced not only by drug solubility in the binder solution, but also by the use of HPC-L. A simultaneous optimal point incorporating four pharmaceutical properties was obtained using the generalized distance function. The experimental values of the four response variables obtained

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in newly prepared granules were found to correspond well with the predicted values of both granules containing ascorbic acid and ethenzamide. These results suggested that computer optimization would benefit the wet granulation process even if drug content segregation was involved in the process. Further, data obtained from computer optimization, in particular the contour diagram, will be valuable in the process validation.

INTRODUCTION

In the design of pharmaceuticals, wet granulation is a very effective procedure for improving such physical properties of powders as flowability, compressibility, and hydrophobic surface character. High-speed mixers are widely used for wet granulation because they provide short granulation times, high-density and high-strength granules, and easy machine handling. However, the quality of granules is strongly influenced by the mechanical structure of the granulator and its operating conditions. A number of studies have been published describing the effect of operating conditions on granule quality and the optimization of the process (1–3). For example, Schafer et al. investigated the effects of nine different high-speed mixers on the porosity and size distribution of granules (4). Ogawa et al. applied a computer optimization technique based on response surface methodology to scale-up the wet granulation process (5). Shirakura et al. (6) and Miyamato et al. (7,8) discussed factors critical to obtaining granules with desirable physical properties in granulation by the high-speed mixer. Terashita et al. (9,10) and Holm et al. (11) evaluated the granulation end point from the perspective of power consumption change. On the other hand, it is well known that the drug content is liable to affect granule size during wet granulation (12). Nishimura et al. (13–15) and Higashide et al. (16) have reported on the problems experienced in wet granulation using an oscillating granulator and the fluidized-bed granulators, respectively. But, few studies have reported on wet granulation using high-speed mixer granulators (17). In general, analysis and resolution of such segregation phenomena is rather difficult owing to the participation of the multiple factors involved in the wet granulation process.

In the present study, a computer optimization technique based on well-designed experiments, which is useful for analyzing pharmaceutical phenomena involving multiple factors, was applied to describe the dependence of drug content uniformity on granule size in wet granulation using a high-speed mixer granulator. Model formulations containing ascorbic acid and ethenzamide were employed to evaluate the effect of their physicochemical properties on the drug content uniformity, and simultaneous optimization of four physical properties during the wet granulation process was achieved by minimizing a generalized distance function.

MATERIALS AND METHODS

Materials

Ascorbic acid (Japanese Pharmacopeia grade) and ethenzamide were purchased from Daiichi Seiyaku Company, Limited (Japan) and Iwaki Company, Limited (Japan), respectively. Crystalline cellulose, marketed as Avicel PH101, was obtained from Asahi Kasei Industries, Company, Limited (Japan). Lactose and cornstarch were purchased from De Melkindustrie Veghel bv (Netherlands) and Nihon Shokuhin Kako Company, Limited (Japan). Hydroxypropyl cellulose (HPC-L) was from Shinetsu Chemical Company, Limited (Japan). Other chemicals were of reagent grade.

Formulation and Preparation of Granules

Formulations of granules investigated in the study are shown in Table 1. Because of a close relationship between drug content segregation and drug solubility in

Table 1

Granule Formulation (Ascorbic Acid and Ethenzamide)

Ingredient	(g)	W/W (%)
Ascorbic acid or 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

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[a] (ascorbic acid, ml)	208	220	250	280	292
X_1[a] (ethenzamide, ml)	300	330	400	470	500
X_2 (HPC-L, g)	1.4	18	58	98	114.6

[a]Total volume of binder solution (purified water).

binder solution (12), ascorbic acid and ethenzamide were selected as a high- and low-soluble drug, respectively. In addition, our previous study indicated that binder solution played a critical role in determining the physical properties of granules prepared by a high-speed mixer granulator (7). Total volume of binder solution (purified water) and amount of HPC-L as binder used in the process were selected as independent variables. Granules A and B in this report represent the granules containing ascorbic acid and ethenzamide, respectively.

Table 3

Experimental Design and Obtained Values of Response Variables (Y_1, Y_2, Y_3, and Y_4) for Ascorbic Acid Granule

Experimental Number	X_1[a]	X_2[b]	Y_1[c] (%)	Y_2[d] (%)	Y_3[e] (μm)	Y_4[f]
1	1	1	8.8	97.53	3485.4	5.26
2	1	1	11.9	97.27	2451.5	3.90
3	1	−1	79.8	95.76	268.8	2.01
4	1	−1	81.6	96.52	245.1	2.00
5	−1	1	83.7	86.24	200.9	1.98
6	−1	1	82.6	86.24	195.1	2.01
7	−1	−1	62.9	102.32	104.5	2.63
8	−1	−1	64.5	101.93	108.5	2.55
9	0	0	85.9	99.50	258.5	1.82
10	0	0	85.6	79.80	252.6	1.85
11	0	$\sqrt{2}$	20.8	94.07	1304.1	2.85
12	0	$\sqrt{2}$	19.6	95.33	1337.4	2.83
13	$\sqrt{2}$	0	28.1	102.40	720.0	2.93
14	$\sqrt{2}$	0	27.5	104.02	729.3	2.90
15	0	$-\sqrt{2}$	81.1	98.94	184.2	2.10
16	0	$-\sqrt{2}$	82.0	100.42	180.6	2.07
17	$-\sqrt{2}$	0	83.0	96.05	159.4	1.94
18	$-\sqrt{2}$	0	81.2	96.43	149.7	1.99
19	0	0	85.0	99.49	258.2	1.82
20	0	0	84.3	99.99	266.8	1.85

[a]Volume of binder solution.
[b]Amount of binder.
[c]Yield of granules.
[d]Content of ascorbic acid.
[e]Geometrical mean size.
[f]Geometrical standard deviation.

Table 4

Experimental Design and Values Obtained for Response Variables (Y_1, Y_2, Y_3, and Y_4) for Ethenzamide Granule

Experimental Number	X_1[a]	X_2[b]	Y_1[c] (%)	Y_2[d] (%)	Y_3[e] (μm)	Y_4[f]
1	1	1	43.0	93.7	785.3	2.58
2	1	1	43.9	95.0	796.4	2.57
3	1	−1	47.3	81.2	394.5	2.37
4	1	−1	46.5	87.7	390.5	2.42
5	−1	1	85.8	95.2	186.1	2.27
6	−1	1	86.6	95.3	183.3	2.26
7	−1	−1	58.6	93.5	93.1	2.39
8	−1	−1	59.5	89.0	93.4	2.38
9	0	0	85.7	100.4	265.2	2.08
10	0	0	86.7	99.3	269.2	2.04
11	0	$\sqrt{2}$	72.7	95.5	474.3	2.50
12	0	$\sqrt{2}$	74.7	96.0	466.9	2.52
13	$\sqrt{2}$	0	45.0	103.3	460.4	2.61
14	$\sqrt{2}$	0	41.3	96.6	440.1	2.63
15	0	$-\sqrt{2}$	66.0	84.9	207.8	2.89
16	0	$-\sqrt{2}$	66.1	81.1	205.1	2.92
17	$-\sqrt{2}$	0	75.3	97.0	120.4	2.15
18	$-\sqrt{2}$	0	76.1	99.6	120.5	2.10
19	0	0	86.5	102.3	261.2	2.05
20	0	0	86.0	101.2	268.0	2.05

[a]Volume of binder solution.
[b]Amount of binder.
[c]Yield of granules.
[d]Content of ethenzamide.
[e]Geometrical mean size.
[f]Geometrical standard deviation.

All ingredients were mixed for 3 min in the high-speed mixer granulator (VG-10, Powrex Co., Ltd., Japan), and then binder solution was added to the powder mixture. Wet granules were dried in a fluid-bed dryer (FLO-5, Freund Industry, Ltd., Japan) at 70°C air temperature for 15 min.

Experimental Design

The influences of two independent variables (X_1, total volume of binder solution; X_2, amount of HPC-L) on four pharmaceutical properties selected as response variables were evaluated for describing drug content segregation. The four pharmaceutical properties were yield Y_1, obtained as weight of granules in the size range 75–500 μm as a percentage of total granule weight; drug content in granules in the size range 75–500 μm (Y_2) as an index of the dependence of drug content uniformity on granule size; geometrical mean granule size Y_3; and granule size uniformity Y_4, estimated as geometrical standard deviation. Physical values of the independent variables represented as the coded forms are shown in Table 2. Sample measurement was repeated under each condition to evaluate experimental error. A total of 20 experiments according to the spherical central composite experimental design for each drug were performed to obtain the regression function of each response variable (Tables 3 and 4) (18).

Pharmaceutical Properties of Granules

Granule size distribution was estimated using eight different size sieves (aperture size: 75, 106, 150, 180, 250, 355, 500, and 1000 μm) in a vibrating shifter (Electromag, Itoh, Japan). Granules in 20-g samples were introduced into the sieves, and the weight of granules left on each sieve was measured after 10 min of vibration.

The results were analyzed on the basis of the log-normal distribution described as Eq. 1.

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

where d is granule diameter represented a aperture of the sieve, and dg and $f(\ln d)$ are geometrical mean granule size and the number of granules having a diameter between $\ln d$ and $\ln d + \Delta(\ln d)$, respectively. In this distribution, the standard deviation of granule size (σ_g was defined by Eq. 2:

$$\sigma_g = \frac{\text{A diameter of granule equivalent to 84\% of } F(\ln d)}{\text{A diameter of granule equivalent to 50\% of } F(\ln d)} \quad (2)$$

where $F(\ln d)$ is the cumulative residual percentage of granule weight left on the sieve.

From the plot of $F(\ln d)$ against the logarithm of granule diameter d, yield of granules Y_1 was determined as the percentage of granule weight left on sieves from 75 to 500 μm in size against total granule weight. Geometrical mean size of granules Y_3 was obtained as the granule size equivalent to 50% of $F(\ln d)$ from the plot.

On the other hand, drug content per unit weight of granules should be constant independent of granule size if the drug disperses uniformly among different granule sizes. Accordingly, drug content in the granules size range from 75 to 500 μm (Y_2) is evaluated as a quantitative index of the segregation of the drug content uniformity. At the same time, drug contents in granules over 500 μm and less than 75 μm are also discussed in this report. Y_2 is presented as the percentage of theoretical drug content calculated from the total amount of drug in all granule sizes and the weight of granules in the size range from 75 to 500 μm. As a result, the value of Y_2 should be 100% if no segregation phenomenon occurs.

Determination of Ascorbic Acid and Ethenzamide in Granules

Ascorbic acid was assayed by the titration method according to the assay of ascorbic acid powder in the *Japanese Pharmacopoeia XIII*. On the other hand, a high-performance liquid chromatography (HPLC) method was employed to determine ethenzamide in granules. Granules were dispersed in purified water and then filtrated (0.45 μm; Toyo Roshi, Japan). Sample solution for the assay was prepared after adding hydroxypropiophenone solution as an internal standard into the filtrated solution. Operational conditions for HPLC were as follows: HPLC was performed on an LC10A (Shimadzu, Japan); the column was an s4.6 × 15 cm TSK-80TS (Toso Co., Ltd., Japan); column temperature was 40°C, mobile phase was 40% methanol–0.05 M KH_2PO_4 (pH 4.5); flow rate was 1.0 ml/min; and detection wavelength was 280 nm.

Simultaneous Optimization Procedure

The second-order polynomial equation (Eq. 3) was employed for predicting the four response variables.

$$Y = b_0 + \sum_{i=1}^{n} b_i X_i + \sum_{i=1}^{n} \sum_{j=1}^{n} b_{ij} X_i X_j \quad (3)$$

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

Although several methods have been proposed for the optimization procedure (19–22), the objective functions for each response variable have to be incorporated into a single function in the case of simultaneous optimization for several variables. In the present study, the generalized distance function $S(\mathbf{X})$ introduced by Takayama and Nagai was used to obtain a simultaneous optimum condition (23).

$$S(\mathbf{X}) = \left[\sum_{i=1}^{n} |w_i\{FD_i(\mathbf{X}) - FO_i(\mathbf{X})\}|^p\right]^{1/p} \quad (4)$$

where w_i is the weight coefficient defined as $1/FD_i(\mathbf{X})$, and $FD_i(\mathbf{X})$ is the ideal value of each objective function.

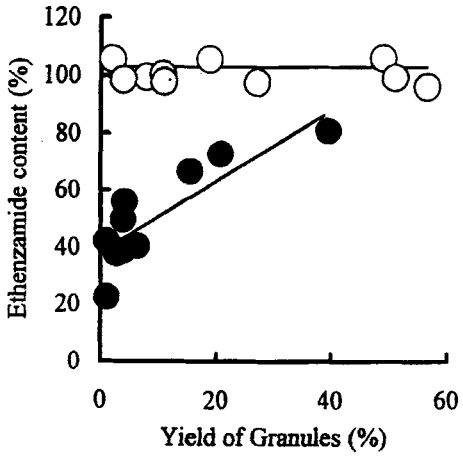

Figure 1. Relationship between the yield of granules and the content of ethenzamide; O, granule size more than 500 μm; ●, granule size less than 75 μm.

Table 5

Optimum Regression Equation for Four Response Variables of Ascorbic Acid

Coefficient	Regression Coefficient Value			
	Y_1[a] (%)	Y_2[b] (%)	Y_3[c] (μm)	Y_4[d]
b00 (constant)	85.1980	99.6959	258.9390	1.8349
b01 (X_1[e])	−16.5750	1.8791	465.9480	0.4180
b02 (X_2[f])	−17.2087	− 2.7088	551.6620	0.3810
b011 (X_1^2)	−13.4850	− 0.7309	162.0760	0.3879
b022 (X_2^2)	−15.5231	− 1.9988	318.1100	0.3992
b012 (X_1X_2)	−22.4500	4.2863	655.0000	0.7925
r[g]	0.9811	0.9262	0.9190	0.9361
r^2[h]	0.9492	0.8071	0.7891	0.8320
s[i]	6.6410	2.0569	408.6350	0.3498
F_0[j]	72.058[k]	16.901[k]	15.218[k]	19.823[k]

[a]Yield of granules.
[b]Content of ascorbic acid.
[c]Geometrical mean size of particles.
[d]Geometrical standard deviation.
[e]Volume of binder solution.
[f]Amount of binder.
[g]Multiple correlation coefficient.
[h]Doubly adjusted r^2 with degrees of freedom.
[i]Standard deviation.
[j]Observed F value.
[k]$p < 0.01$

In this study, the values of $FD_i(\mathbf{X})$ for Y_1, Y_2, Y_3, and Y_4 were 100%, 100%, 250 μm, and 1.0, respectively. $FO_i(\mathbf{X})$ is the simultaneous optimum value of each objective function. Impartiality among the values of the four response variables is adjusted by employing a parameter p ($p>1$).

RESULTS AND DISCUSSION

Influences of Independent Variables on Response Variables

Experimental values of the four pharmaceutical properties of granules prepared under various conditions are summarized in Tables 3 and 4 for ascorbic acid granule (granule A) and ethenzamide granule (granule B); they show a strong dependence of these properties on two of the independent variables. As clearly shown, experimental error was very small, except for Y_3 of granule A at $X_1 = 1$ and $X_2 = 1$. Regarding Y_1, Y_3, and Y_4, this dependence particularly seems to be more evident for granule A compared to granule B. For example, the values of Y_1 in granule A and granule B range from 8.8% to 85.9% and from 41.3% to 86.7%, respectively. On the other hand, the variation range of Y_2 values in granule B is larger than that in granule A. Though the experimental values are not shown here, ethenzamide was contained less in small-size granules (<75 μm). The reverse tendency, in which ethenzamide was contained more in small-size granules and ascorbic acid was contained less in these granules, was reported by Suzuki et al. (17). In general, drug granulation with good wettability may proceed faster than that with low wettability since the formation of agglomerate in the granulation process is considered to occur through the wetting of powders. This means that the relatively low value of Y_1 and small variations of Y_3 and Y_4 in granule B seem to be due to the low solubility of ethenzamide in binder solution. However, HPC-L was used as a binder in the formulation, which compensated for the low solubility of ethenzamide in the formation of agglomerate in the granulation process. Based on the results in Table 4, the yield and the content of ethenzamide in granule sizes less than 75 μm and more than 500 μm are shown in Fig. 1; they indicate that the content of ethenzamide obviously increases with the yield of granules less than 75 μm. On the other hand, no

Table 6

Optimum Regression Equation for Four Response Variables of Ethenzamide

Coefficient	Regression Coefficient Value			
	Y_1[a] (%)	Y_2[b] (%)	Y_3[c] (μm)	Y_4[d]
b00 (constant)	86.2267	100.8010	292.2590	2.0543
b01 (X_1[e])	−12.6176	—	171.4930	0.1281
b02 (X_2[f])	4.3153	3.9917	107.9300	−0.0624
b011 (X_1^2)	−14.8412	−1.5692	—	0.1242
b022 (X_2^2)	−9.6146	−6.4456	39.7888	0.2933
b012 (X_1X_2)	−7.6500	1.4750	76.7250	0.0744
r[g]	0.9818	0.9087	0.9559	0.9185
r^2[h]	0.9509	0.7794	0.8907	0.7877
s[i]	3.8196	3.0648	67.3911	0.1237
F_0[j]	74.639[k]	17.777[k]	39.715[k]	15.098[k]

[a]Yield of granules.
[b]Content of ethenzamide.
[c]Geometrical mean size of particles.
[d]Geometrical standard deviation.
[e]Volume of binder solution.
[f]Amount of binder.
[g]Multiple correlation coefficient.
[h]Doubly adjusted r^2 with degrees of freedom.
[i]Standard deviation.
[j]Observed F value.
[k]$p < 0.01$
—This factor is not included in the optimum regression equation.

increase or decrease of ethenzamide content in granule sizes more than 500 μm was observed over the yield obtained. High yield by granules less than 75 μm indicates an incomplete formation of agglomerates. Bearing this in mind, the content of ethenzamide in granules less than 75 μm in size decreased as granulation progressed.

Contrary to these results, granulation of ascorbic acid with the good wettability (soluble in binder solution) was well distributed among granules so that no significant difference in content among granules with different sizes was observed. However, agglomerate formation was strongly affected by the amount of binder solution and HPC-L used in the process. That is why large variations in Y_1, Y_3, and Y_4 were obtained. A relatively high value of Y_1 in granule A compared with that in granule B was a result of the solubility of ascorbic acid in binder solution.

Regression Analysis of Response Variables

Based on the results shown in Tables 3 and 4, optimal regression coefficients of Eq. 3 composed of a combination of statistically significant independent variables are shown in Tables 5 and 6 for granules A and B, respectively. The optimal equation was judged using the coefficient of determination doubly adjusted with degrees of freedom (24). The multiple correlation coefficient r was found to be high enough to predict each response variable in both granules A and B.

In order to describe the relation between each response variable and independent variables based on the optimal regression equation, the contour diagrams for the four response variables are illustrated in Figs. 2 and 3 for granules A and B, respectively, as functions of X_1 and X_2 under the restriction of the experimental region. The region giving a high yield value for granule A is located at a specific combination of X_1 and X_2. In particular, Y_1 tends to be lower in the region where both X_1 and X_2 are rather high, and Y_3 in this region becomes large, as shown in Fig. 2. This result indicates that Y_1's decrease in that region is due to the growth of granules caused by the use of large amounts of binder solution and HPC-L.

Corresponding to this result, granule size uniformity is also lower in the high X_1 and X_2 region. Ascorbic acid

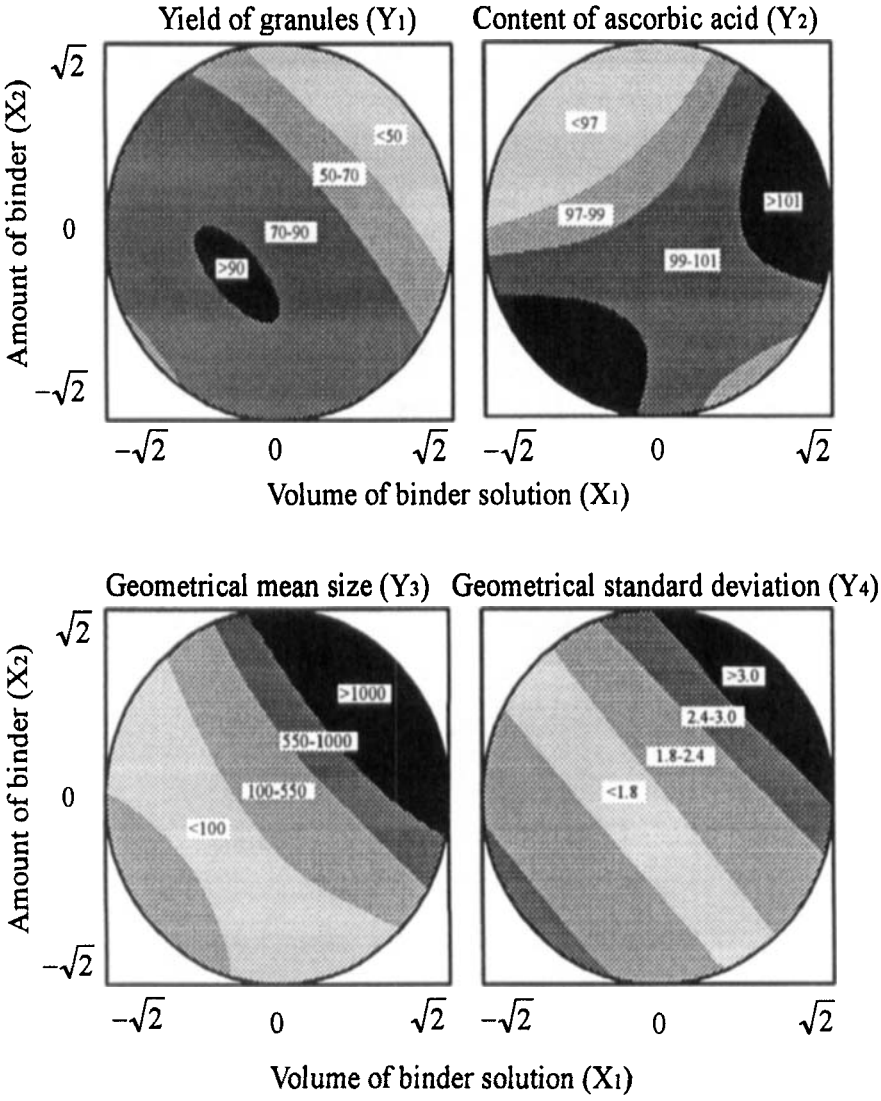

Figure 2. Contour diagrams of Y_1, Y_2, Y_3, and Y_4 for granule A as a function of X_1 and X_2.

content was found to be higher in the low X_1 and X_2 region and the high X_1 and X_2 region and to be lower in the high X_1 and the low X_2 region. Further, Y_2 tended to be lower in inverse proportion to Y_3 and Y_4. The range of variation of Y_2 among different conditions, however, was relatively small, as shown in Table 3. These results suggested that ascorbic acids' solubility in binder solution allowed it to be easily distributed into granules, thus giving small variations of Y_2 among different granule sizes. As already discussed, the formation of agglomerates in granulation is strongly influenced by X_1 and X_2, so Y_1, Y_2, and Y_3 varied depending on these two factors.

On the other hand, the region giving high Y_1 in granule B tends to be located in the high X_1 region, particularly $Y_1 > 90\%$ exists at $-0.76 < X_1 < -0.42$ and $0.2 < X_2 < 0.82$. The values of Y_3 in granule B increased with both X_1 and X_2, but its rate of increase was low compared with that of granule A. For example, $Y_3 > 1000$ μm was not obtained in granule B. The superior granule uniformity is considered to be due to the incomplete formation of agglomerates. On the other hand, the region of high Y_2 value is located around the center of the diagram.

Since ethenzamide is contained less often in small-size granules, the contour diagram of ethenzamide con-

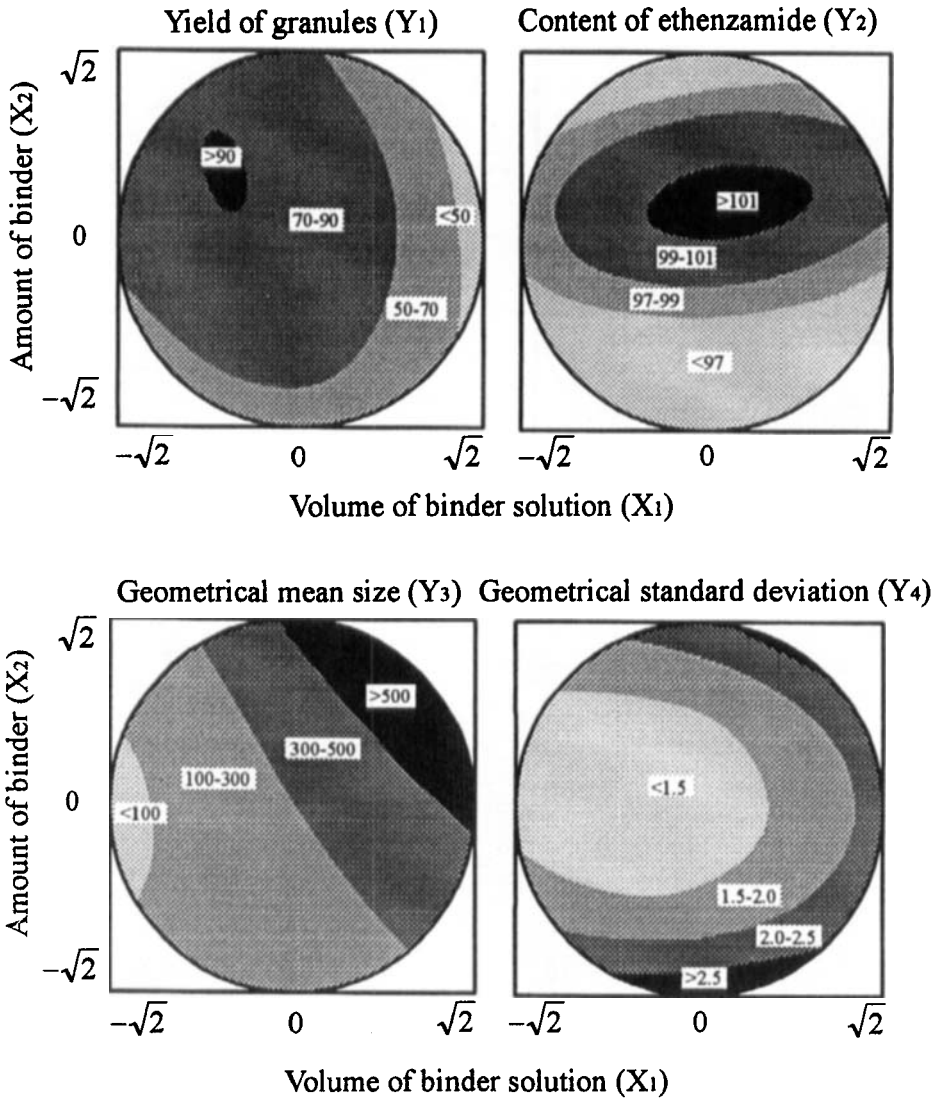

Figure 3. Contour diagrams of Y_1, Y_2, Y_3, and Y_4 for granule B as a function of X_1 and X_2.

tent in granule sizes less than 75 μm is illustrated in Fig. 4 to describe the relation between drug content and independent variables. The figure clearly shows that less binder solution and HPC-L resulted in a high ethenzamide content. This is due to the influence of ethenzamide's low solubility in binder solution on content uniformity at relatively low X_1 and X_2 in spite of the addition of HPC-L. This result also agrees with the observation reported by Suzuki et al. (17).

The diagram of Y_2 in Fig. 3 also supports that the amount of HPC-L is very important in determining the content of ethenzamide. A certain amount of binder solution, of course, is necessary in the granulation process, but the formation of agglomerate containing ethenzamide is considered to be controlled mainly by HPC-L, not by binder solution. The ethenzamide content in granule sizes larger than 1000 μm (data not shown) was not dependent on X_1 and X_2.

Optimization

Based on Eq. 4, the contour diagrams of the generalized distances of ascorbic acid and ethenzamide are depicted in Fig. 5. The simultaneous optimal point is pre-

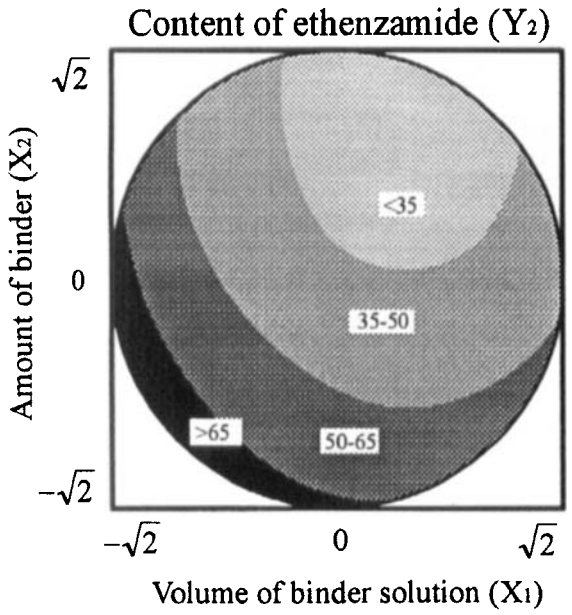

Figure 4. Contour diagram of the content of ethenzamide in granule sizes less than 75 μm as a function of X_1 and X_2.

sented as the open circle in the diagrams. The conditions for simultaneous optimization were found to be similar for both granules, although the influences of the two drugs' physical properties on the four response variables were different. The values of X_1 and X_2 at the simultaneous optimal point are $X_1 = -0.373$ and $X_2 = 0.274$ for granule A and $X_1 = -0.423$ and $X_2 = 0.199$ for granule B; their physical values are summarized in Table 7.

Based on these optimizations, the predicted values of four response variables were compared with those of the experimental values, which were obtained with newly prepared granules under the corresponding optimal condition. The results of this comparison are also summarized in Table 7, indicating that both predicted and experimental values were in close agreement for both granules A and B. This agreement indicates that computer optimization is useful in granulation optimization involving the dependence of drug content uniformity on granule size. In addition, a contour diagram will be also useful in ascertaining granulation validation.

CONCLUSION

A computer optimization technique was applied to the optimization of wet granulation involving the factor of drug content dependency on granule size. The content uniformity of ascorbic acid and ethenzamide used as model drugs affected granule size differently. No appreciable dependence was observed in granules containing ascorbic acid, but high ethenzamide content was obtained in granules with sizes less than 75 μm. This difference

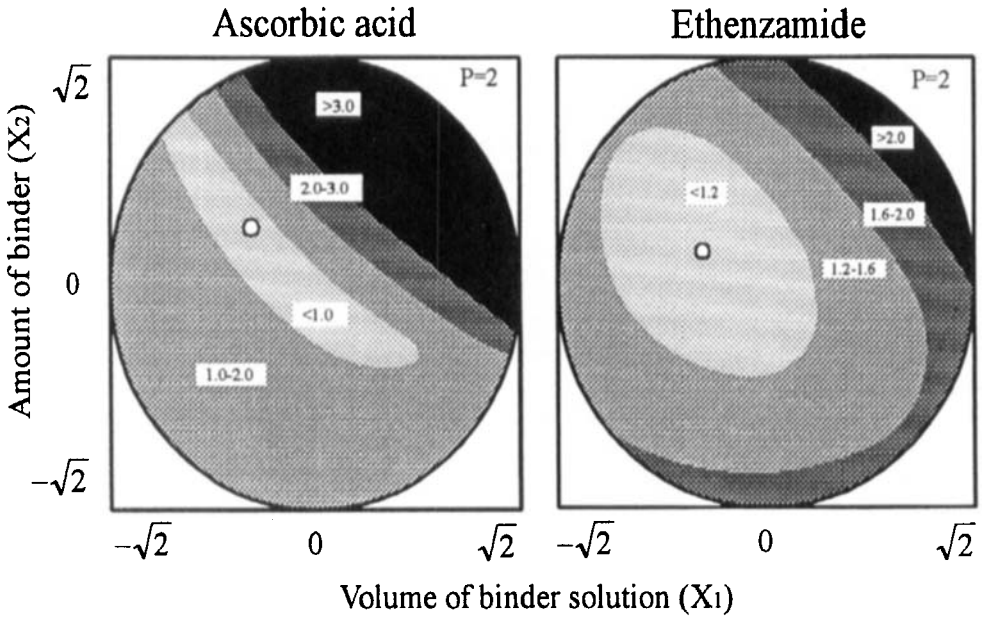

Figure 5. Contour diagrams of generalized distance function as a function of X_1 and X_2; O, optimum formulation.

Table 7

Predicted and Experimental Values of Response Variables (Y_1, Y_2, Y_3, and Y_4)

Response Variable	Definition	Ascorbic Acid		Ethenzamide	
		Predicted	Experimental	Predicted	Experimental
Y_1 (%)	Yield of granules	85.9	90.7	90.0	90.6
Y_2 (%)	Content of ascorbic acid or ethenzamide	97.6	98.4	100.9	100.6
Y_3 (μm)	Geometrical mean size	215.6	215.4	236.3	236.6
Y_4	Geometrical standard deviation	1.8	2.0	2.0	1.9

can be explained by the difference in solubility of the two model drugs in binder solution and the use of HPC-L as a binder. Further, the agreement between the predicted values of the four response variables obtained from minimization of the generalized distance function and the experimental values under optimal conditions suggested that computer optimization would be useful to optimize wet granulation even if problems associated with drug content uniformity due to the drug's physicochemical properties were involved. In addition, a contour diagram, in which the influence of independent variables on response variables can be visually represented, will also be useful in validation of the granulation process.

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