DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(19), 2213-2225 (1995)

AN EVALUATION OF PROCESS VARIABLES IN WET GRANULATION

Y. Miyamoto[a], S. Ogawa[a], M. Miyajima[a*], H. Sato[a], K. Takayama[b], and T. Nagai[b]

[a]Central Research Laboratories, Zeria Pharmaceutical Co., Ltd.
2512-1 Oshikiri, Konan-machi, Osato-gun, Saitama 360-01 Japan
[b]Department of Pharmaceutics, Hoshi University,
Ebara 2-4-41, Shinagawa-ku, Tokyo 142 Japan

ABSTRACT

In wet granulation, determining the process variables which play an essential role in granule quality is crucial for optimizing the manufacturing process. An L16(2^5) fractional factorial experimental design using the table of orthogonal arrays was employed in order to estimate the relative intensity of the influences of five process variables on granule quality in wet granulation using a high-speed mixer granulator. Total volume and formulation of binder solution, blade rotation speed, granulation time, and amount of powder supplied into the granulator were selected as decisive process variables in the

Address reprint requests to: Masaharu Miyajima; Central Research Laboratories; Zeria Pharmaceutical Co., Ltd.; 2512-1 Oshikiri, Konan-machi; Osato-gun, Saitama 360-01; Japan

formation of granules. Granule yield, geometrical mean granule size and uniformity of granule size were evaluated as representative properties of granule quality. Experimental results were analyzed according to the analysis of variance (ANOVA).

The results of significance test and contribution ratio in ANOVA indicated that, within the experimental region, only binder solution had a critical effect on the three physical properties of the obtained granules. The effects of other variables were found to be minimal. Further, the contribution of sampling error to total variance was quite small.

INTRODUCTION

Wet granulation has been widely employed to improve unfavorable properties of powders such as poor-flowability in the manufacturing of pharmaceuticals. However, physical properties of granules obtained are significantly influenced by a number of process variables such as formulation of binder solution (1-2), type and operational condition of apparatuses (3-4), etc. Evaluation of the influences of these process variables on granule quality is therefore important to optimize the manufacturing process, in particular at the scale-up stage of the process (5-6). Generally, the effect of one or two process variables on granule quality has been evaluated at constant values of other variables in the studies. The process variables, however, might interact with each other to determine the quality of granules, so from the experiments mentioned above it is very difficult to estimate which process variables play an essential role in the formation of high-quality granules.

Well-designed experiments (i.e. experiments with a particular structure) are required to evaluate the intensity of the influence of each independent variable on experimental results (7). Utilization of the table of orthogonal arrays is particularly effective for reducing the number of experiments and for estimating the chief determining factor and interaction between independent variables. Basic idea of experimental design was applied in the optimization studies (8-10), but there are a few studies on an application of this valuable method to analyze pharmaceutical phenomenon (11-12). In addition, the data obtained in the designed experiments are analyzed by the method of analysis of variance, known as ANOVA.

In the present study concerning wet granulation, an L16(2^5) fractional factorial experimental design was employed to evaluate the relative intensity of the influences of five process variables on granule quality as characterized by three physical properties: yield, geometrical mean size, and uniformity of size. The five process variables were total volume of binder solution used in the process, formulation of binder solution expressed as volume percent of ethanol, blade rotation speed of a high-speed mixer granulator, granulation time, and amount of powder supplied into the granulator.

MATERIALS

Crystalline cellulose, marketed as Avicel PH 101, was purchased from Asahi Kasei Industries, Co., Ltd.(Japan). Hydroxypropyl Cellulose (EF-P) and ascorbic acid (Japanese Pharmacopoeia grade) were obtained from Shinetsu Chemical Co., Ltd. (Japan) and Daiichi Seiyaku Co., Ltd. (Japan), respectively. Lactose and cornstarch were purchased from De Melkindustrie Veghel bv, (Netherlands) and Nihon Shokuhin Kako Co., Ltd. (Japan). Other chemicals were of reagent grade.

METHODS

Experiment Design

Using the table of orthogonal arrays (13), an L16 (2^5) fractional factorial experimental design was employed to evaluate the influence of five process variables (X_1: total volume of binder solution used in the granulation process; X_2: formulation of binder solution; X_3: granulation time; X_4: blade rotation speed; X_5: amount of powder supplied into the granulator) on granule quality. The binder solution was made up of a mixture of water and ethanol. Table 1 shows the assignments of process variables and their interaction to the table of orthogonal arrays. Although interactions consisting of more than three factors are generally ignored with this method, all process variables and their interactions could be assessed independently because of the table of orthogonal arrays. In Table 1, process variables and their interaction were expressed as factors. Each process variable described in coded form was studied at two levels. Physical units of the coded values were shown in Table 2.

Experimental conditions according to the L16 (2^5) fractional factorial experimental design are presented in Table 3, so sixteen experiments were conducted. Further, measurements of physical properties were repeated to estimate sampling error.

Preparation of Granules

All ingredients of granule formulation shown in Table 4 were mixed for 3 minutes in a high-speed mixer granulator (VG-10, Powrex Co., Ltd., Japan). Binder solution was then added to the powder mixture, followed by granulation for a predetermined time. Wet granules were dried in a fluid-bed dryer (FLO-5, Freund Industry, Ltd., Japan) at 70 °C air temperature for 15 minutes.

Evaluation of Granule Quality

Three physical values (granule yield, geometrical mean granule size, and uniformity of granule size) were selected for the evaluation of granule quality: 1) Yield of granule (Y1) was obtained as weight of granules in the size range of 75 to 500 μm as a percent of total granule weight. 2) Granules size distribution was assumed to be log-normally distributed by weight so that geometrical mean granule size (Y2) was determined 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). Log-normal distribution is described as Equation 1 (14). Weight distribution of 20 g granules was measured after 10 minutes of vibration in

TABLE 1 Table of the Orthogonal Arrays of $L_{16}(2^5)$ Experimental Design

Experimental Number	Array Number														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2
3	1	1	1	2	2	2	2	1	1	1	1	2	2	2	2
4	1	1	1	2	2	2	2	2	2	2	2	1	1	1	1
5	1	2	2	1	1	2	2	1	1	2	2	1	1	2	2
6	1	2	2	1	1	2	2	2	2	1	1	2	2	1	1
7	1	2	2	2	2	1	1	1	1	2	2	2	2	1	1
8	1	2	2	2	2	1	1	2	2	1	1	1	1	2	2
9	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
10	2	1	2	1	2	1	2	2	1	2	1	2	1	2	1
11	2	1	2	2	1	2	1	1	2	1	2	2	1	2	1
12	2	1	2	2	1	2	1	2	1	2	1	1	2	1	2
13	2	2	1	1	2	2	1	1	2	2	1	1	2	2	1
14	2	2	1	1	2	2	1	2	1	1	2	2	1	1	2
15	2	2	1	2	1	1	2	1	2	2	1	2	1	1	2
16	2	2	1	2	1	1	2	2	1	1	2	1	2	2	1
Factor [a]	X1	X2	A	X3	B	C	D	X4	E	F	G	H	I	J	X5

[a] A=X1*X2, B=X1*X3, C=X2*X3, D=X4*X5, E=X1*X4, F=X2*X4, G=X3*X5, H=X3*X4, I=X2*X5, J=X1*X5
Symbol (*) indicates an interaction between factors.

TABLE 2 Level of Independent Variables in Physical Unit

Independent variables	Level in coded form	
	1	2
X1 (%)[a]	12	17
X2 (V/V %)	30	70
X3 (minutes)	5	15
X4 (rpm)	300	600
X5 (Kg)	1.5	2.5

[a] X1 was represented as volume percent against powder weight.

TABLE 3 Experimental Design and Obtained Values of Three Physical Properties

No.	X1	X2	X3	X4	X5	Y1 (%)		Y2 (μm)		Y3	
1	1	1	1	1	1	41.3	42.7	47.9	57.7	5.9	5.2
2	1	1	1	2	2	60.2	56.2	60.0	48.0	3.7	4.4
3	1	1	2	1	1	42.9	44.7	34.9	41.1	6.7	6.0
4	1	1	2	2	2	40.9	45.0	22.6	32.3	8.6	6.6
5	1	2	1	1	1	43.1	43.7	42.6	43.8	6.0	5.9
6	1	2	1	2	2	38.2	36.5	17.9	15.6	10.4	11.7
7	1	2	2	1	1	39.3	42.3	20.0	26.9	9.7	7.8
8	1	2	2	2	2	38.7	40.5	16.8	22.3	10.7	8.8
9	2	1	1	1	2	80.1	79.8	185.8	187.1	1.7	1.7
10	2	1	1	2	1	88.1	87.5	217.2	241.2	1.5	1.5
11	2	1	2	1	2	77.8	77.6	168.3	171.3	1.8	1.8
12	2	1	2	2	1	50.2	46.8	257.6	281.5	1.7	1.6
13	2	2	1	1	2	61.0	60.2	87.0	86.9	3.2	3.2
14	2	2	1	2	1	81.8	80.8	165.6	162.0	1.8	1.9
15	2	2	2	1	2	60.7	58.2	88.9	84.0	3.1	3.3
16	2	2	2	2	1	62.6	65.4	91.3	102.2	3.0	2.8

TABLE 4 Formulation of Granule

Ingredient	W/W(%)
Ascorbic Acid	28.0
Lactose	45.6
Cornstarch	19.6
Crystalline Cellulose	3.9
Hydroxypropylecellulose	2.9
Total	100.0

the vibrating sifter (Electromag, Itoh Co., Ltd., Japan) equipped with sieves (size; 1000, 500, 355, 250, 180, 150, 106, and 75 μm).

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

where dg is geometrical mean granule size, f (ln d) is the number of granules having diameters d between ln d and ln d + Δ (ln d). The symbol Δ presents differential with diameter. σ g calculated from Equation 2 is geometrical standard deviation of granule size. 3) Uniformity of granule size (Y3) is expressed as σg.

$$\sigma g = \frac{\text{Diameter of granule equivalent to 84 \% of F(ln d)}}{\text{Diameter of granule equivalent to 50 \% of F(ln d)}} \qquad \text{Equation 2}$$

RESULTS AND DISCUSSION

Granule Size Distribution and Physical Properties

Size distribution of granules was described well by the log-normal distribution equation as illustrated in Figure 1. This relation was confirmed to be maintained in all experiments (r > 0.98-0.96). According to the procedure explained in the Evaluation of Granule Quality, geometrical mean granule size (Y2) and geometrical standard deviation (Y3) in Figure 1 were calculated as 47.9 μm and 5.9, respectively. The results of three physical values are summarized in Table 3.

The results clearly indicated that granule qualities varied greatly with change in experimental conditions. For example, the value of Y2 was changed in the size range of 16.7 to 269.5 μm, and that of Y1 from 36.5 to 88.1 %. However, it was difficult to confirm specific relationships between changes in the three properties and experimental conditions.

Analysis of Variance(ANOVA)

Results of ANOVA for Y1 are summarized in Table 5, in which the sum of squares with small values were pooled as an error term.

Further, the revised sum of squares (S') obtained by subtracting of the mean square of the error term from the mean square of each factor was used to estimate a contribution ratio. Ten factors including seven interactions were found to be significant at α=0.05 in this analysis, in particular the F-value of total volume of binder solution (X1) used in the process, which was extremely high compared with that of other factors. Further, the results of the contribution ratio, which refers to the proportion of each factor's variance to

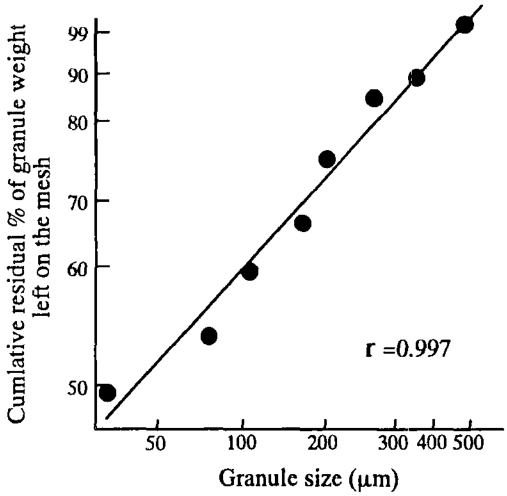

FIGURE 1

Log-normal Distribution Plot of Granule Size at X1=1, X2=1, X3=1, X4=1 and X5=1.

TABLE 5 Analysis of Variance for Yield of Granule (Y1)

Source of variance	Degrees of Freedom	Sum of Squares	Mean Square	F [a]	S' [b]	Contribution Ratio (%) [c]
X1	1	5575.68	5575.68	1570.61**	5572.13	63.5
X2	1	369.92	369.92	104.20**	366.37	4.1
X3	1	680.80	680.80	191.77**	677.25	7.7
X4	(1)	(18.00)				
X5	(1)	(0.13)				
X1*X2	(1)	(0.98)				
X1*X3	1	266.80	266.80	75.15**	263.25	3.0
X1*X4	(1)	(2.20)				
X1*X5	1	228.98	228.98	64.50**	225.43	2.6
X2*X3	1	163.80	163.80	46.14**	160.25	1.8
X2*X4	1	72.00	72.00	20.28**	68.45	0.8
X2*X5	1	210.13	210.13	59.19**	206.58	2.4
X3*X4	1	534.65	534.65	150.61**	531.10	6.1
X3*X5	1	598.58	598.58	168.61**	595.03	6.7
X4*X5	(1)	(12.50)				
Sampling error [d]	(16)	(40.64)				
Error	21	74.45	3.55		109.95	1.3
Total	31	8775.79			8775.79	100.0

** $F > F_{0.01}(1,21) = 8.017$

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] Estimated from repeated experiments

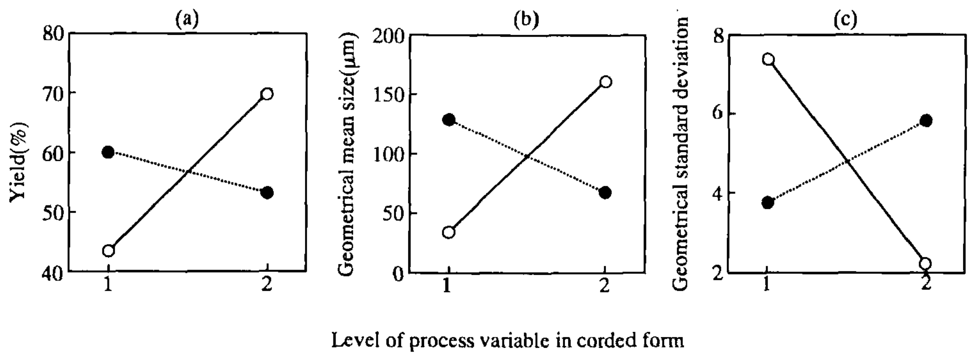

FIGURE 2

Schematic Representations of the Effects of Binder Solution on Three Physical Properties.

(a): Relation between granule yield and binder solution

(b): Relation between geometrical mean granule size and binder solution

(c): Relation between geometrical standard deviation of granule size and binder solution

(O): Total volume of binder solution used in the process

(●): Formulation of binder solution

total variance, indicated that 63.5 % of variance in experiments could be explained by X1. On the other hand, the contribution of interactions of factors were relatively small, although F-values were significant. Furthermore, sampling error was very small. These results suggested that X1 is the critical factor in the yield of granules in the wet granulation process and that the other four factors make only a minor contribution. Based on this result, the relations between X1 or X2 and Y1 are shown in Figure 2(a), indicating that an increase in binder solution used in the process would lead to a decrease in granule yield, and a decrease in the percentage of ethanol would lead to an increase in the yield.

TABLE 6 Analysis of Variance for Geometrical Mean Granule Size (Y2)

Source of variance	Degree of Freedom	Sum of Squares	Mean Squares	F [a]	S' [b]	Contribution Ratio (%) [c]
X1	1	128461.13	128461.13	2312.53**	128405.58	65.2
X2	1	30055.39	30055.39	541.05**	29999.84	15.2
X3	1	1304.33	1304.33	23.48**	1248.78	0.6
X4	1	4510.13	4510.13	81.19**	4454.58	2.2
X5	1	3114.58	3114.58	56.07**	3059.03	1.6
X1*X2	1	15466.01	15466.01	278.42**	15410.46	7.8
X1*X3	(1)	(26.10)				
X1*X4	1	9068.68	9068.68	163.25**	9013.13	4.6
X1*X5	1	995.70	995.70	17.92**	940.15	0.5
X2*X3	1	558.62	558.62	10.06**	503.07	0.3
X2*X4	1	728.67	728.67	13.12**	673.12	0.3
X2*X5	(1)	(51.77)				
X3*X4	(1)	(0.20)				
X3*X5	(1)	(147.49)				
X4*X5	1	1671.87	1671.87	30.10**	1616.32	0.8
Sampling error [d]	(16)	(885.42)				
Error	20	1110.98	55.55		1722.03	0.9
Total	31	197046.09			197046.09	100.0

$^{**}F > F_{0.01}(1,20) = 8.096$

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] Estimated from repeated experiments

Table 6 and Table 7 summarize the results of ANOVA for Y2 and Y3, respectively. Of both properties, only X1 had a significantly high F-value (α=0.05), and the contribution ratio results indicated that more than 80% of variance observed in the experiments could be attributed to X1 and X2.

The relations between physical property and process variable shown in Figure 2(b) and (c), in which an increase in X1 was resulted in an increase in geometrical mean granule size and an improvement in the uniformity of granule size. On the other hand, an increase in X2 leaded to a decrease of geometrical mean granule size and a lowing in the uniformity of granule size. These results imply that an increase in the volume of binder solution used in the process would accelerate the growth of granules and decrease the

TABLE 7 Analysis of Variance for Uniformity of Granule Size (Y3)

Source of variance	Degree of Freedom	Sum of Squares	Mean Squares	F [a]	S' [b]	Contribution [c] Ratio (%)
X1	1	212.95	212.95	308.62**	212.26	69.5
X2	1	34.01	34.01	49.29**	33.32	10.9
X3	1	6.67	6.67	9.67**	5.98	1.9
X4	(1)	(1.84)				
X5	1	7.52	7.52	10.90**	6.83	2.2
X1*X2	1	7.02	7.02	10.17**	6.33	2.1
X1*X3	(1)	(2.54)				
X1*X4	1	7.87	7.87	11.41**	7.18	2.3
X1*X5	1	4.17	4.17	6.04*	3.48	1.1
X2*X3	(1)	(0.50)				
X2*X4	(1)	(3.17)				
X2*X5	(1)	(0.72)				
X3*X4	(1)	(0.01)				
X3*X5	1	7.17	7.17	10.39**	6.48	2.1
X4*X5	(1)	(1.65)				
Sampling error [d]	(16)	(7.50)				
Error	23	17.93	0.78		24.17	7.9
Total	31	305.31			305.31	100.0

** $F > F_{0.01}(1,23) = 7.881$, *$F > F_{0.05}(1,23) = 4.279$

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] Estimated from repeated experiments

proportion of fine granules, with improved uniformity of granule size as the result.

CONCLUSION

Although a number of process variables have been considered to influence granule quality in the wet granulation process, only binder solution was found to be a determining factor among the three physical properties of model granules in the present study. It is, of course, difficult to apply this result in different situations, such as when granules have different formulations. However, determining the critical factor in obtaining granules with desired properties is an extremely important problem in the manufacturing process as well as in expanding the process. Well-designed experiments such as employed in this study are of maximum efficiency in estimating the main effects and interactions of factors with a minimum number of experiments. Using the table of orthogonal arrays is a particularly useful and effective method for investigating of pharmaceutical problems.

REFERENCES

1. H. G. Kristensen, P. Holm, A. Jaegerskou and T. Schaefer, Pharm. Ind., 46,763 (1984).
2. O. Shirakura, M. Yamada, M. Hashimoto, S. Ishimaru, K. Takayama and T. Nagai, Drug Dev. Ind. Pharm., 17, 471 (1991).
3. P. Holm, O. Jungensen, T. Schaefer and H. G. Kristensen, Pharm. Ind., 45, 806 (1983).
4. T. Schaefer, P. Holm and H. G. Kristensen, Pharm. Ind., 52, 1147 (1990).
5. G. K. Bolhuis, S. W. De Jong, H. V. Vankamp and H. Deffemers, Pharm. Technol., 11, 36 (1987).
6. S. Ogawa, T. Kamijima, Y. Miyamoto, M. Miyajima, H. Sato, K. Takayama and T. Nagai, J. Pharm. Sci., 83, 439 (1994).
7. S. Bolton, "Pharmaceutical Statistics, Practical and Clinical Applications," Marcel Dekker, Inc., New York, 1984, pp. 258-280.
8. D. Fonner,Jr., J. R. Buck and G. S. Banker, J. Pharm. Sci., 59, 1587 (1970).
9. K. Takayama and T. Nagai, Chem. Pharm. Bull., 37, 160 (1989).
10. M. Matsumura, H. Nakagami, T. Yamao, K. Takayama and T. Nagai, Chem. Pharm. Bull., 42, 1902 (1994).
11. N. -O. Lindberg and C. Jonsson, Drug Dev. Ind. Pharm., 11, 387 (1985).
12. H. Lindner and P. Kleinebudde, J. Pharm. Pharmacol., 46, 2 (1994)

13. G. Taguchi, "Jikken Keikakuhou," Maruzen, Tokyo, 1976.

14. J. T. Carstensen, "Solid Pharmaceutics: Mechanical Properties and Rate Phenomena," Academic Press, New York, 1980, pp. 34-42.