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Particle Size Design Using Computer Optimization Technique

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ABSTRACT

The effect of binder solution (amount and composition) on the mean particle size and its distribution of granule was investigated by using a computer optimization technique. The granules were manufactured by two continuous processes, granulating and sizing using a high-speed mixer granulator and a hammer mill, respectively. The particle size distribution pattern of granules was markedly varied with the change in the amount and composition of the binder solution. The distribution pattern could be well expressed by the log-normal distribution model. For designing the optimal particle, a computer optimization technique was applied to the experimental results obtained in this study. The technique was found to be useful for searching the optimal formula in the practical scale.

KEYWORDS

Computer Optimization, Granules, Particle Size Distribution, Binder Solutiuon, Experimental Design, Regression Analysis, Response Surface, High-Speed Granulator

INTRODUCTION

Although granulation is the most important process in manufacturing powder dosage forms of drugs, its formulation and manufacturing conditions consist of many processes tinged with empirical coloring. As the formulation optimizing step requires a considerable effort and large amount of materials, compromised formula and its manufacturing conditions were often taken as final ones from the results on sets of single factor experiments. The formula obtained, however, was not always optimal, because the combined effects among factors are not considered. Therefore, a more suitable and systematic methods for solving the optimizing problems should be conducted.

The response surface method first reported by Box and Wilson (1) has been applied to dosage form design for various kinds of drugs by many researchers (2-10). Usefulness of this method has been confirmed in many cases, but our knowledge has been used infrequently in development of the particle design using manufacturing facilities.

In this study, the computer optimization technique based on the response surface method was applied to the particle design of granules which were manufactured by two continuous processes, granulating and sizing using a high speed mixer granulator and a hammer mill, respectively.

EXPERIMENTAL

Materials

Lactose (150 mesh), Avicel PH101, citric acid monohydrate and butylated hydroxyanisol used were of J.P. XI grade. Starch 1500 was purchased from Colorcon Japan Ltd. Byco C, a hydrolyzed gelatin, was supplied by Croda Japan Co., Ltd. Other chemicals used were of reagent grade.

Table I. Experimental Design for Two Factors

Form No.	X1	X2
1	1	1
2	1	-1
3	-1	1
4	-1	-1
5	0	0
6	1.414	0
7	0	1.414
8	-1.414	0
9	0	-1.414

X1: total amount of ethanol and water
X2: volume ratio of ethanol to water

Equipments

T.K.Fielder (Nara machinery Co., Ltd.), a high-speed mixer granulator, was employed for particle preparing. A Fitz mill (The Fitzpatric Co.) was used for dry sizing of granules. A vibrating shaker (Tsutsui rikagakukikai Co. Ltd.) equipped with sieves (mesh size; 0, 44, 74, 149, 297 and 590 μm) was adopted to the particle size classification.

Granules Preparation

The granulating solutions consisted of ethanol and water are shown in Tables I and II. They contained a constant amount of Byco C (binder, 0.16 kg), citric acid and butylated hydroxyanisol. With continuous mixing, the solution was sprayed on the powder mixture (total 3.61 kg; lactose, Avicel PH101 and starch 1500) through a schlick nozzle (2.5 mm diameter, 60° spray angle) at a pressure of 2.4 bar. The mixture was granulated for 3 min after all the solution was added. The each granule was dried under 50 °C forced air condition for 5 h. The dried granules (0.8-2.5 %, loss on drying; 105 °C, 15 min) were passed through a #2 screen of a Fitz mill, operating on medium speed with knives forward. The particle size distribution pattern

Table II. Translation of Experimental Condition to Physical Units

Factor	1.414	1	0	-1	-1.414
X1 (ml)	880	851	780	709	680
X2	0.4414	0.4	0.3	0.2	0.1586

X1; total amount of ethanol and water, X2; volume ratio of ethanol to water

and physical characteristics of the sized granules were evaluated by standard methods described below.

The total volumes (X1; E+W) of ethanol (E) and water (W) and the ratio (X2; E/W) of volume of ethanol to that of water were selected as independent variables. Nine experiments were performed according to the central composite experimental design (1), as shown in Table I. The experimental unit was translated to physical unit as summarized in Table II. Other factors in sample preparation were kept constant throughout the experiment.

Particle Size Classification

Particle size classification was performed using a vibrating shaker equipped with sieves. The weight distribution of the particle size of the samples (10 g) was measured after vibrating for 5 minutes. To evaluate the mean particle size and its distribution, the following parameters were calculated from equations 1-5 as dependent variables shown below;

Normal distribution equation

$$F(d)=\frac{\Sigma\, n}{\sigma\ 2\ \pi}\ exp\{-\ \frac{1}{2}(\frac{d\ -\ d'}{\sigma})^{2}\} \qquad \text{---Eq. 1}$$

$$\sigma=\frac{\Sigma\ [n(d\ -\ d')^{2}]}{\Sigma\ n} \qquad \text{---Eq. 2}$$

Log-normal distribution equation

$$F(d)=\frac{\Sigma\ n}{log\ \sigma g\quad 2\ \pi}exp\{-\ \frac{(log\ d\ -\ log\ dg')^{2}}{2log^{2}\sigma g}\} \text{--Eq. 3}$$

$$log\ \sigma g=\frac{\Sigma\{n(log\ d\ -\ log\ dg')^{2}\}}{\Sigma\ n} \qquad \text{---Eq. 4}$$

Rosin-Rammler distribution equation

$$\log (2 - \log R) = \log (a \log e) + b \log d \quad \text{---Eq. 5}$$

where d is the particle size (μm), d' is the arithmetic mean of size (μm), dg' is the geometric mean of size (μm), σ is the standard deviation (μm), σg is the geometric standard deviation (μm), $F(d)$ is cumulative residual % by weight on the sieve of mesh size d, and R is cumulative residual % by weight, a and b are constant, and e is the base of natural logarithm.

Physical Parameter Measurement

Loss on drying (LOD) of the sample at 105°C for 15 min, density after tapping 1500 times and compression ratio (% decrease of volume by tapping) were measured as physical parameters.

Response Surface Analysis

A second order regression model was employed for predicting the responses in the form shown in equation 6.

$$Yi = b0 + b1X1 + b2X2 + b3X1^2 + b4X2^2 + b5X1X2 \text{---Eq. 6}$$

where, Yi is the level of the response, bi is the regression coefficients, and Xi is the coded level of the independent variable.

The optimal formula was predicted by using a computer program based on the response surface methods described in the previous paper(11).

RESULTS AND DISCUSSION

Particle Size Distribution and Physical Properties

Figs. 1, 2 and 3 show the normal distribution plot, the log-normal distribution plot, and the Rosin-Rammler distribution plot for particle size of formulation No.

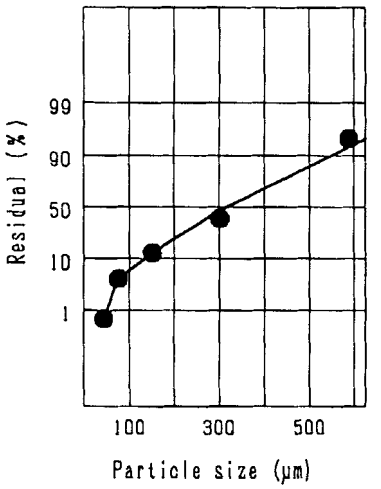

Fig. 1. Normal Distribution Plot of Perticle Size Classification Data for Formulation No. 1

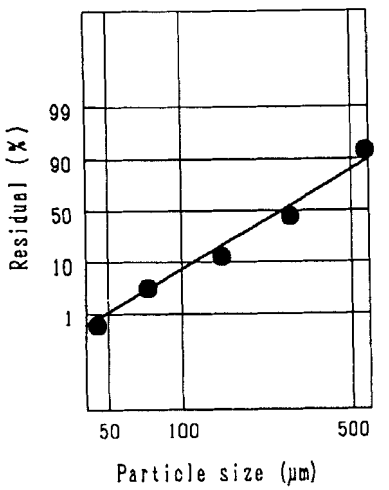

Fig. 2. Log-Normal Distribution Plot of Particle Size Classification Data for Formulation No. 1

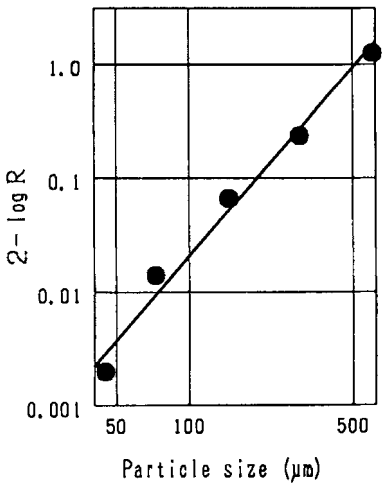

Fig. 3. Rosin-Rammler Distribution Plot of Particle Size Classification Data for Formulation No.1

1, respectively. The distribution parameters and three physical parameters evaluated for formulation No. 1-9 are listed in Table III. The distribution parameters of the dry-sized granules could be well expressed by the log-normal distribution model (r=0.981-0.997). Rosin-Rammler distribution model was also useful for the prediction of distribution parameters (r=0.975-0.997). The parameters varied markedly with the change in the amount and composition of binder solution. In the case of physical parameters, deviation among the formulations in LOD was larger than that in density and compression rate, as shown in Table III. It appears Table IV that the binder solution also affected density as much as LOD. Thus, binder solution (amount and composition) affected particle size distribution parameters and LOD and density of the sized granules.

Regression Equation for Each Parameter

Functional relationships between the variable (each parameter) measured and the independent variables for

Table III. Parameters for Particle Size and Its Distribution

Form.	Parameters						
	log-normal[a]		Rosin-Rammler[b]		Physical		
	D50% (um)	σg	log a[c]	b	LOD (%)	Density (g/ml)	Comp. rate (%)
1	261	0.533	-6.053	2.372	1.08	0.829	18.5
2	361	0.368	-4.183	1.560	1.16	0.848	18.5
3	196	0.612	-6.940	2.829	0.79	0.825	21.0
4	283	0.541	-6.575	2.559	0.89	0.825	20.0
5	295	0.464	-5.193	1.998	1.43	0.817	20.0
6	357	0.401	-4.604	1.726	2.44	0.828	20.0
7	225	0.587	-6.791	2.710	1.61	0.842	18.0
8	199	0.588	-6.790	2.753	1.03	0.831	17.0
9	421	0.323	-3.865	1.419	1.71	0.861	21.5

a) correlation coefficients of log-normal plots; 0.981-0.997
b) correlation coefficients of Rosin-Rammler plots; 0.975-0.997
c) translated to logarithmic form for enhancing the statistical significance

Table IV. Optimum Regression Equation for Each Particle Size Parameters Determined by Multiple Regression Analysis

Constant	Log-normal		Rosin-Rammler		Physical		
	D50% (μm)	σg	log a[a]	b	LOD (%)	Density (g/ml)	Compr. rate (%)
b0	306.182	0.4716	-5.666	2.111	1.349	0.823	19.955
b1	45.806	-0.0646	0.796	-0.363	0.319	—	—
b2	-58.024	0.0762	-0.797	0.363	—	-0.006	—
b3	-19.705	0.0216	—	0.116	—	—	—
b4	—	—	—	—	—	0.012	—
b5	—	0.0235	-0.376	0.136	—	—	-0.636
r	0.965	0.969	0.948	0.968	0.619	0.824	0.337
s	25.748	0.0369	0.491	0.194	0.433	0.009	1.484
F	22.935	15.435	14.802	14.969	4.347	6.323	0.899

a) translated to logarithmic form for enhancing the statistical significance
r; multiple correlation coefficient, s; standard deviation, F; observed F value
$Y = b0 + b1X1 + b2X2 + b3X1^2 + b4X2^2 + b5X1X2$

amount (X1) and composition (X2) of binder solution were obtained using a multiple regression analysis. The best combination of independent variables for the prediction of each parameter was selected from among all combinations by using a correlation coefficient which was doubly adjusted with degrees of freedom (12) as an index. The optimum regression equations are listed in Table IV. The parameters of particle size distribution could be predicted statistically by using second order regression model as a function of independent variables. On the other hand, physical parameters could not be expressed closely by the second order regression model. To evaluate the particle size distribution, the log-normal model was preferable to the Rosin-Rammler model in the mean of correlation coefficients of 9 formulations designed. The distribution parameters such as D50% and σg, of the log-normal model were represented as a function of X1 and X2. Therefore, it might be considered that the contribution of the amount and composition of binder solution to particle size distribution was large.

Response Surface

Three-dimensional graphs (response surface) were useful to elucidate the significance of regression equation. Figs. 4 and 5 show the response surfaces as a function of X1 and X2 for D50% and σg, respectively. In this study the experiment was done with two factor composite experimental design, therefore the functional relationship between response variable for each parameter and independent variables can be expressed clearly by using a three dimensional graph, as shown in Figs. 4 and 5. For instance, if a smaller size of particles is desirable, the combination of smaller value of X1 and a larger value of X2 should be taken as the preparative condition. However, this condition may lead to a large deviation of particle size. Thus existence of the optimal point can be grasped geometrically by superimposing these graphs.

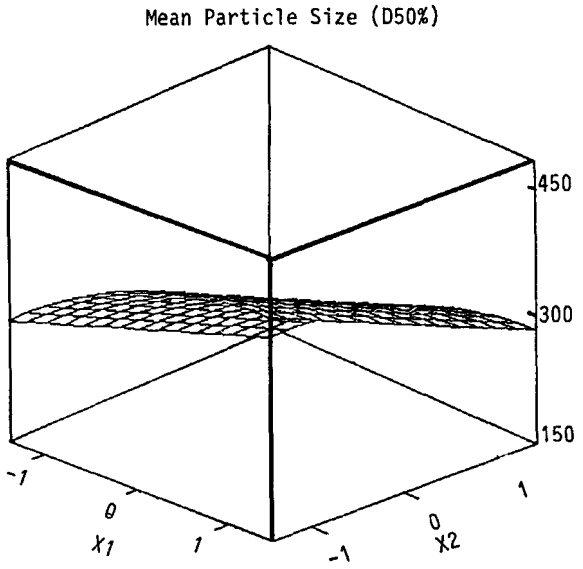

Fig. 4. Three-dimensional Plot of Mean Particle Size of Granules as a Function of X1 and X2

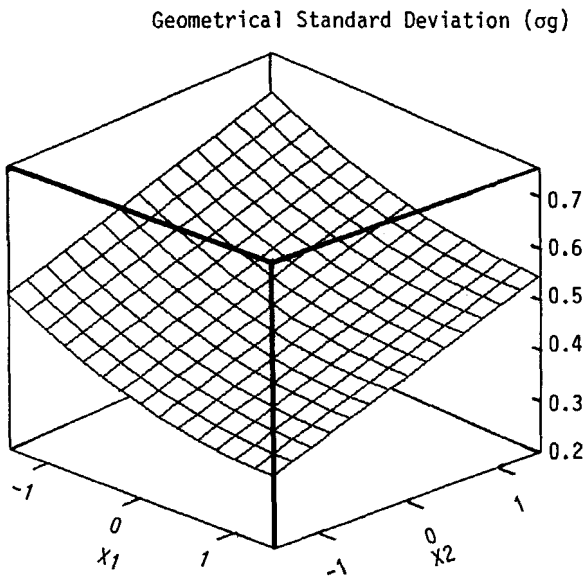

Fig. 5. Three-dimensional Plot of Geometrical Standard Deviation of Granules as a Function of X1 and X2

Table V. Experimental and Predicted Values of Each Parameters of Optimum Formulation

Distribution parameter	Proposition	Experimental	Predicted
D50%[a] (μm)	300-350	358	350
σg[b]	minimization	0.381	0.389
D50%[a] (μm)	300-350	312	300
σg[b]	maxmization	0.531	0.520

a) geometrical mean particle size
b) geometrical standard deviation

Optimum Formulation Analysis

The necessity of precise control of physical characteristics such as particle size distribution of granules has been increased with enhancing the qualitative requirement in formulation design.

As an example of application of a computer optimization technique to pharmaceutical process design and/or formulation design, developing the optimum formulation of binder solution giving maximum or minimum particle size distribution with 300-350 μm mean particle size was approached in this study. Employing a broad particle size distribution of granules is effective for obtaining the high hardness of tablets, while a narrow one has often been designed for the core of film coated granules and the carrier of drug delivery system.

To solve the optimum problem described above, the following equations were given as objective function and constraints: objective function (σg: minimization or maximization) and constraints ($350 - D50\% \geq 0$, $D50\% - 300 \geq 0$, $2 - X1^2 \geq 0$, $2 - X2^2 \geq 0$). These conditions mean the search of the formulation which provides the minimum or maximum values of σg, geometrical standard deviation, under the constraints of the mean particle size of 300 - 350 μm in experimental area. The optimization was performed using the method reported by

Takayama et al (11). Thus, X1=1.4142; X2=-0.3179 and X1=-1.2518; X2= -1.4138 were obtained as the optimal conditions which gave the minimum and maximum values of σg under the constraints of D50% of 300-350 μm, respectively. Table V shows the predicted value and experimental value of each parameter of the optimum formulation. Experimental values of these parameters showed good agreement with predictions.

Thus, the computer optimization technique was considered to be useful in the search of the optimum formulation in practical scale in which manufacturing conditions are not always controllable as well as in laboratory scale.

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