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Effect of Amount and Composition of Granulating Solution on Physical Characteristics of Tablets

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KEYWORDS

Tablets, Disintegration Time, Hardness, Computer Optimization, Multiple Regression Analysis, Experimental Design, Response Surface, Granulating Solution

ABSTRACT

The effect of granulating solution on the physical characteristics and physical stability of tablets was studied based on the response surface methodology. The amount of granulating solution, X1 and its composition ratio, X2, were selected as independent variables. The tablets (100 mg) were manufactured by compressing the mixture of each granule with disintegrant (4 %) and lubricant (0.5 %). A rotary tabletting machine was used. Several characteristics of tablets were well expressed as a quadratic function of X1 and X2 in coded levels. A computer optimization method was applied to the data generated, and a good agreement was observed between the predicted and experimental results in the optimal formula.

INTRODUCTION

The physicochemical characteristics of tablets, are often affected by the mean particle size and its distribution (1), shape (2), hardness (3), surface condition (4) density and water content (5) of granules in addition to the manufacturing conditions (6,7) for tabletting. We have previously reported that the amount and composition of the granulating solution were closely related to the particle size and distribution of the granules (8). In addition, the mean particle size and its distribution could be expressed as a quadratic function of causal factors such as the amount of granulating solution and its composition ratio(8).

In this study, the effect of granulating solution on the physical characteristics of tablets was investigated by means of the response surface methodology. A computer program, NOPCON (9), was applied to the results measured in this study in order to find the optimal conditions for preparing tablets by wet granulation.

EXPERIMENTAL

Materials

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

Equipments

T.K.Fielder (Nara machinery Co., Ltd.), a high-speed mixer granulator, was employed for granulation. A Fitz mill (The Fitzpatrick Co.) was used for dry sizing of granules. Cleanpress 12KAWC equipped with 6.35 mm flat face punches and dies (Kikusui Co., Ltd) was used as the tabletting machine.

Tablet Preparation

Wet granules for tabletting were manufactured using nine experimentally designed granulating solutions in accordance with the procedures reported in a previous paper (8). Two factors, the amount of granulating solution and its composition ratio, were chosen as independent variables. The experimental design for two factors in coded levels and in physical units employed in this study is listed in Tables I and II, respectively. Tablets (100 mg) were prepared by compressing each wet granule (95.5 mg) with PVPP (4.0 mg) and magnesium stearate (0.5 mg) using the same process and conditions, using a rotary tabletting machine at the batch size of 4 kg.

Measurement of Physical Characteristics

The disintegration time (DI) was measured in accordance with the J.P.XI test method. The hardness (HD), thickness (TN) and weight (WT) of tablets were measured by conventional methods.

Physical Stability Measurement

As the result of the swelling of disintegrant incorporated into tablets by moisture uptake, the decrease in hardness and the increase in thickness under storage are often observed. Therefore, the stabilities of the hardness and thickness of tablets were measured under the various relative humidities (RHs), 10, 33, 51 and 75%, at 25°C. RHs were adjusted by the constant humidity solution method. S_{HD} and S_{DM} values were calculated as the indices of physical stability of the tablets. The both indices are defined by *Eqs. 1* and *2*.

$$S_{HD} = \{(HD_5-HD_0)/HD_0\}^2_{10\%RH/25^\circ C} + \{(HD_5-HD_0)/HD_0\}^2_{33\%RH/25^\circ C} + \{(HD_5-HD_0)/HD_0\}^2_{51\%RH/25^\circ C} + \{(HD_5-HD_0)/HD_0\}^2_{75\%RH/25^\circ C} \quad \text{---}Eq.\ 1$$

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

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

$$S_{DM} = \{(TN_5-TN_0)/TN_0\}^2_{10\%RH/25°C} + \{(TN_5-TN_0)/TN_0\}^2_{33\%RH/25°C} + \{(TN_5-TN_0)/TN_0\}^2_{51\%RH/25°C} + \{(TN_5-TN_0)/TN_0\}^2_{75\%RH/25°C}$$

---*Eq. 2*

where, S_{HD} and S_{DM} are indices for the stability of hardness and thickness, respectively. HD_0 and HD_5 are hardness at initial time and after storage for 5 days under various humidity conditions, respectively. TN_0 and TN_5 are thickness at initial time and after storage for 5 days under various humidity conditions, respectively.

Response Surface Analysis

A second order polynomial regression model was applied to the prediction of the variable responses, as shown in *Eq. 3*.

Table III. Parameters for Particle Size Profiles of Granules, Physical Characteristics and Physical Stability of Tablets

Form.	Physical Characteristics[a)] HD (kg)	DI (min)	TN (mm)	WT (mg)	Physical stability[b)] SHD	SDM ($X10^{-2}$)
1	5.5	3.98	2.38	100.2	0.5032	0.573
2	7.0	8.33	2.36	99.2	0.3762	0.524
3	5.2	3.40	2.38	99.8	0.5106	0.722
4	6.3	5.87	2.38	100.4	0.4127	0.509
5	6.5	7.25	2.37	99.6	0.3476	0.475
6	7.9	8.05	2.36	100.0	0.2928	0.373
7	4.9	3.62	2.39	100.2	0.5239	0.627
8	4.6	3.97	2.38	99.4	0.4397	0.587
9	7.5	8.35	2.36	99.8	0.3603	0.555

Compression pressure; a) 1300 kg/cm^2, b) 1000 kg/cm^2
HD; hardness (n=5), DI; disintegration time (n=6), TN; thickness (n=5), WT; weight (n=5), SHD; stability of HD (n=5), SDM; stability of dimension (n=5)

$$Yi = b0 + b1X1 + b2X2 + b3X1^2 + b4X2^2 + b5X1X2 \quad \text{---Eq. 3}$$

where, *Yi* is the level of the response, *bi* is the regression coefficient, and *Xi* is the coded level of the independent variables.

The optimum formula was estimated by using a computer program, NOPCON, based on the response surface method (9).

RESULTS AND DISCUSSION

Characteristics of Tablets

Physical characteristic values for nine tablet formulations are listed in Table III. The amount of granulating solution and its composition, X1 and X2, strongly affected the response variables, hardness (HD) and disintegration time (DI), though the values of thickness (TN) and total weight (WT) of the tablets were scarcely changed by these factors. Both HD and DI showed a wide range from 4.6 to 7.5 kg and from 3.62

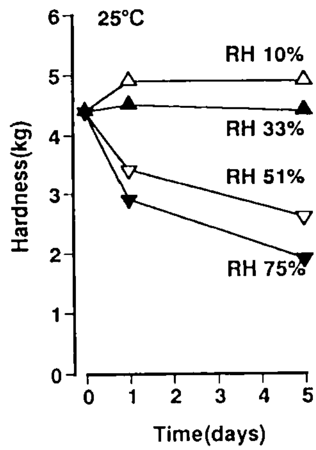

Fig. 1. Change of Hardness in The Formulation No. 1 under Various Humidities at 25°C

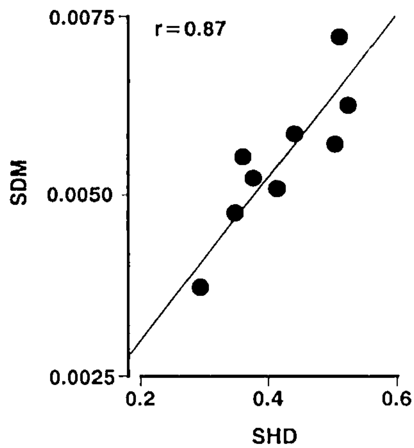

Fig. 2. Relationship between Indices SDM and SHD

to 8.35 min, respectively. These tablet parameters are well known to be affected by shape, particle size, its distribution, etc. of the wet granules for tabletting (10). We have already reported the particle size and its distribution of the wet granule system under test could be controlled by the amount and composition of granulating solution (8). This fact may suggest that the physical characteristics of tablets can be expressed quantitatively as a function of X1 and X2.

Figure 1. shows the change of hardness in the formulation No. 1. under various relative humidities (RH) at 25°C. The hardness was stable at RH below 33%, while unstable at 51 and 75%RH. Change of thickness depicts a similar tendency to that of hardness. Based upon these data, S_{HD} and S_{DM} were calculated according to *Eqs.1* and *2*, respectively, as parameters evaluating the physical stability of tablets (Table III). Strong correlation between S_{HD} and S_{DM} was recognized as shown in Fig. 2.

Table IV. Optimum Regression Equation for Each Parameter determined by Multiple Regression Analysis

Constants	Physical Characteristics HD (μm)	DI (min)	Physical stability S_{HD}	S_{DM}
b0	6.156	7.250	0.378	0.00496
b1	0.708	1.103	-0.031	-0.00055
b2	-0.784	-1.689	0.057	0.00045
b3	---	-0.738	---	---
b4	---	-0.783	0.046	0.00061
b5	---	-0.471	---	-0.00041
r	0.900	0.978	0.910	0.921
s	0.592	0.742	0.043	0.00054
F	12.752	12.941	8.008	5.578

HD; hardness, DI; disintegration time, TN; thickness, WT; weight, S_{HD}; stability of hardness, S_{DM}; stability of dimension, r; multiple correlation coefficient, s; standard deviation, F; observed F value
$Y = b0 + b1X1 + b2X2 + b3X1^2 + b4X2^2 + b5X1X2$

Regression Equation for Each Parameter

The functional relationship between the dependent variables (parameters) measured and the independent variables, amount (X1) and composition ratio (X2) of granulating solutions, were estimated 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 the correlation coefficient which was doubly adjusted with degrees of freedom (11).

The optimum regression equations were listed in Table IV. Two physical characteristics (HD and DI) and the stability indices of physical characteristics (S_{HD} and S_{DM}) could be predicted quantitatively by using a second-order polynomial model (*Eq. 3*). Multiple regression analysis for the thickness and the total weight of the tablets was not performed because the values of these characteristics were invariable for these formulations.

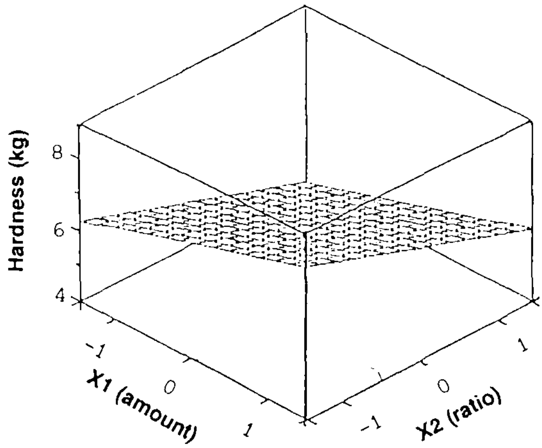

Fig. 3. Three-dimensional Plot of Hardness of Tablets as a Function of X1 and X2

Response Surface

Three-dimensional graphs (response surfaces) are useful to elucidate the significance of each regression equation. Figs. 3-6 show the response surfaces as a function of X1 and X2 for HD, DI, S_{HD} and S_{DM}, respectively. In this study, as each experiment was carried out using a two factor composite experimental design, the functional relationship between a response and the independent variables can be expressed clearly by using three-dimensional diagrams, as shown in Figs. 3-6. The hardness (HD) of tablet is depicted as a plane surface composed of X1 and X2 suggesting that the HD increased with an increase in X1 and with decrease in X2 (Fig. 3). The HD of tablets is known to be strongly affected by the binding ability and strength of granules prepared. X1 and X2 contribute to the modification of the binding ability and strength of granules by affecting the disposition of binder.

The disintegration time (DI) can be described as a convex function of X1 and X2, and has a maximum value within the experimental area (Fig. 4). DI increased with an increase of X1, with a decrease of X2. This

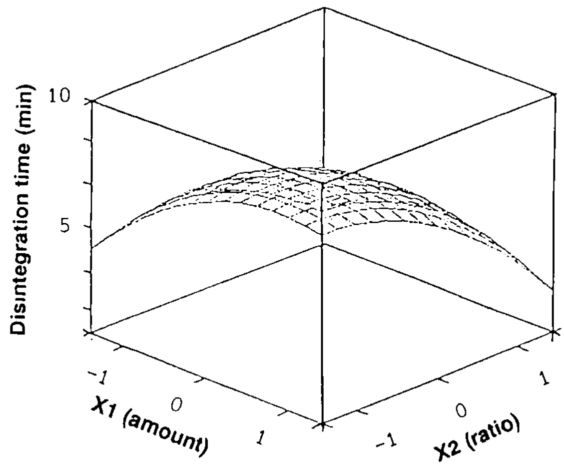

Fig. 4. Three-dimensional Plot of Disintegration Time of Tablets as a Function of X1 and X2

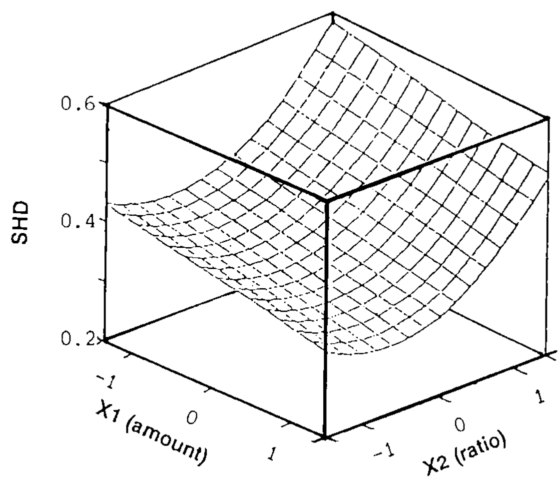

Fig. 5. Three-dimensional Plot of Stability of Hardness (SHD) of Tablets as a Function of X1 and X2

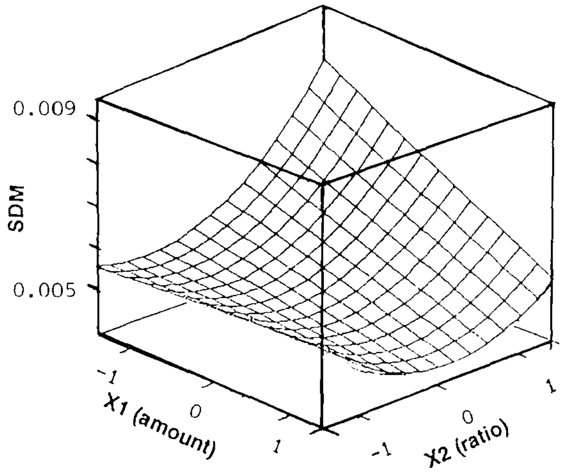

Fig. 6. Three-dimensional Plot of Stability of Dimension (SDM) of Tablets as a Function of X1 and X2

tendency is similar to that of hardness. The S_{HD} value of tablets decreased linearly with an increase of X1, and a parabolic relation was obtained as a function of X2 (Fig. 5). A similar tendency was obtained for the S_{DM} value, as shown in Fig. 6. The reduction in DI and the increase in S_{HD} and S_{DM} were considered to be mainly caused by the swelling of PVPP following the penetration of moisture into the tablet. Accordingly, a formulation with rapid disintegration is physically unstable, as shown in Figs. 4-6. If we design a rapid disintegrating tablet in this system, they might have low hardness and an undesirable physical stability (Figs. 3-6).

Optimum Formulation Analysis

Adjustments in physical characteristics are often carried out by means of modification in the ingredients or granulating solutions at the final step of dosage form design. To search for the optimal formula, a computer optimization technique was applied. In the formulation design of rapid release tablets, PVPP was

Table V. Experimental and Predicted Values

Distribution parameter	Experimental	Predicted
Hardness (kg)	7.19	7.40
Disintegration time (min)	7.28	6.93
Stability of hardness (S_{HD})	0.325	0.321

incorporated as an effective disintegrant into the granules. The lowering of hardness in storage was considered to be a side-action by the incorporation of PVPP. The S_{HD} is a parameter for describing the lowering of hardness. The smaller the value of S_{HD}, the more stable are the physical characteristics. The hardness and disintegration time desired for this formulation are not less than 5.5 kg and not more than 8.0 min, respectively.

To solve the optimum proposition described above, S_{HD} was selected as objective function to minimize under the constraints of $HD-5.5 \geq 0$, $8.0-DI \geq 0$, $2-X1^2 \geq 0$ and $2-X2^2 \geq 0$. These conditions mean the search for the formulation which provides the minimum values of S_{HD}, stability of hardness, under the constraints of not less than 5.5 kg of HD and not more than 8 min of DI in experimental area. Thus, the experimental unit $(X1, X2)_{e.u.} = (1.4142, -0.3155)_{e.u.}$ was obtained as the optimal condition which gave the minimum value of S_{HD}, namely gave the highest stability of hardness under the constraints given above. The experimental unit $(1.4142, -0.3155)_{e.u.}$ can be translate into the physical unit $(X1(\text{amount; ml}), X2(\text{ratio}))_{p.u.} = (880, 0.268)_{p.u.}$ based on the Table II.

Table V shows the predicted values and experimental ones of each parameter of the optimum formulation. Experimental values of these parameters showed good agreement with predictions.

Conclusions

Physical characteristics such as HD, DI, S_{HD} and S_{DM} of tablets were strongly affected by the amount and composition of granulating solution in preparation of tablet granules by the wet granulation. A computer optimization technique applied in this work was quite useful in searching for the optimal condition of the granulating process.

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