Formulation Optimization of Sustained-Release Tablet of Chlorpheniramine Maleate by Means of Extreme Vertices Design and Simultaneous Optimization Technique

Meiko HIRATA, Kozo TAKAYAMA,* and Tsuneji NAGAI

Department of Pharmaceutics, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan. *Received September 14, 1991*

Formulation optimization of sustained-release tablet of chlorpheniramine maleate (CPM) was performed by means of an extreme vertices design and simultaneous optimization technique. Polyvinylpyrrolidone, carboxyvinyl polymer and crystalline cellulose were used as excipients of the tablet. Mixing ratios of these polymers were selected as formulation factors. In addition, the tablet diameter was employed as an independent process variable. Release parameters of CPM in the model formulations were estimated by using an exponential model for the drug diffusion. These parameters were selected as response variables and optimized by the simultaneous optimization technique. Response variables predicted with the optimum formulations agreed well with the experimental results, suggesting usefulness and reliability of the computer optimization method based on the extreme vertices design and simultaneous optimization technique.

Keywords computer optimization; extreme vertices design; simultaneous optimization; formulation factor; process factor; tablet diameter; sustained-release; chlorpheniramine maleate; polyvinylpyrrolidone; carboxyvinyl polymer

Introduction

An interpolymer complex of polyvinylpyrrolidone (PVP) with carboxyvinyl polymer (CP), crosslinked polyacrylic acid, has been reported to be applicable for obtaining the sustained-release of drugs in the pharmaceutical field.[1,2] Recently, we have investigated the mechanism of this polymer–polymer interaction based on turbidity measurement, a binding isotherm study and Fourier-transform infrared spectroscopy.[3] It was confirmed that the interpolymer complex of PVP with CP was formed in the unit molecular ratio of 1 : 1 under ideal conditions in which hydrogen bonding was considered to have an important role. Drug release behaviors from the compressed tablet which consisted of a simple blend of drugs, PVP and CP were also investigated considering the relation to the complex formation in the tablet.[3] As a result, the drug release was observed to be significantly dependent on the mixing ratio of PVP and CP.

In this study, with a view to a practical application of this phenomenon, a computer optimization technique was applied to the formulation design of a sustained-release tablet which consisted of PVP, CP and crystalline cellulose (MCC) as excipients. Chlorpheniramine maleate (CPM) was selected as a model drug. Seeking the optimal mixing ratio of these excipients was thought to be valuable for the accurate control of drug release from the tablet.

With regard to the optimization of pharmaceutical formulations, statistical experimental designs such as factorial design,[4-9] central composite design[10-22] and simplex lattice design[23,24] have been widely used for dealing with several causal factors simultaneously. In these experimental designs, the levels of each factor were independent of those of all other variables. However, these experimental designs can not be applied when all the components in the formulation are selected as causal factors because their levels are not independent of those of all other factors. Namely, an increase of levels of one factor leads to a decrease of levels of other factors since the total amount of factor levels is always constant. Furthermore, in practical cases, the levels of each factor are often associated with lower and upper constraints. The extreme vertices design[25] can be applied to the optimization problem in such mixture experiments.[26-28] In this study, we have investigated an optimization of the sustained-release tablet formulation based on the extreme vertices design and simultaneous optimization technique.[29,30] In addition, a method to incorporate an independent process variable to the mixture experiments was investigated by the modification of the extreme vertices design.

General Concept In the mixture experiments, the restrictions on the levels of each factor are expressed as follows.

$$\sum_{i=1}^{q} X_i = 1 \tag{1}$$

$$0 \le L_i \le X_i \le U_i \le 1 \qquad i = 1, 2, 3, \ldots, q \tag{2}$$

where X_i is the proportion of the ith component in the mixture where the number of components is q. L_i and U_i are the lower and upper bounds on the levels of each component, respectively. Due to the restrictions given in Eqs. 1 and 2, the feasible experimental region is a geometrical shape of a convex polyhedron. Extreme vertices, midpoints of edges, centroids of faces and overall centroid are usually taken as primary experimental points. In order to predict response variables, $F(X)$, by the combination of factors, the following canonical models can be used.

$$F(X) = \sum_{i=1}^{q} b_i X_i \tag{3}$$

$$F(X) = \sum_{i=1}^{q} b_i X_i + \sum\sum_{i<j}^{q} b_{ij} X_i X_j \tag{4}$$

$$F(X) = \sum_{i=1}^{q} b_i X_i + \sum\sum_{i<j}^{q} b_{ij} X_i X_j + \sum\sum\sum_{i<j<k}^{q} b_{ijk} X_i X_j X_k \tag{5}$$

where, b_i, b_{ij} and b_{ijk} represent regression coefficients of each monomial. Equations 3, 4 and 5 represent linear, quadratic and special cubic models, respectively. The special cubic model is desirable to predict response variables when the interaction term among the factors is thought to be important, though relatively many experimental points are required to use this model. To include the independent process variable, Z, into the extreme vertices design, the same experimental points have to be taken in each level of the process factor. If the process factor has two levels (low and high levels), the special cubic model given in Eq. 5 can

be modified as follows.

$$F(X)=\sum_{i=1}^{q} b_{0i}X_i+\sum\sum_{i<j}^{q} b_{0ij}X_iX_j+\sum\sum\sum_{i<j<k}^{q} b_{0ijk}X_iX_jX_k + \sum_{i=1}^{q} b_{1i}X_iZ+\sum\sum_{i<j}^{q} b_{1ij}X_iX_jZ+\sum\sum\sum_{i<j<k}^{q} b_{1ijk}X_iX_jX_kZ \quad (6)$$

Predicted equations for each response variable are, then, assembled as multi-objective optimization problems.[29,30]

When the optimization problem includes several objectives, response variables should be incorporated into a single function in order to consider all the responses simultaneously. Khuri and Conlon introduced a novel method to combine plural objective functions based on the generalized distance between the predicted value of each response and the optimum one that was obtained individually.[29]

$$S(X)=\left(\sum_{i=1}^{n}[w_i\{FD_i(X)-FO_i(X)\}]^2\right)^{1/2} \quad (7)$$

where, n is the number of response variables (objective functions), $S(X)$ is the distance function generalized by the weighting coefficient, w_i, $FD_i(X)$ is the ideal value of each objective function, $F_i(X)$, optimized individually under the restrictions of the experimental region and $FO_i(X)$ is the predicted value of $F_i(X)$. Simultaneous optima for all the responses can be obtained by minimizing $S(X)$ under the constraints of the experimental region. As a proper and significant way to determine the w_i values, the following equation was employed.[30]

$$w_i=RA_i/SD_i \quad (8)$$

where RA_i is the coefficient of determination which was adjusted with degrees of freedom and SD_i is the standard deviation of observed values of each response variable. Further improvement of the distance function given in Eq. 7 can be made available as follows.[30]

$$S(X)=\left[\sum_{i=1}^{n}\{w_i|FD_i(X)-FO_i(X)|\}^P\right]^{1/P} \quad (9)$$

where P is a parameter relating to the impartiality among the response variable ($P\geq 1$). Increasing the P values leads to an enlargement in the importance of the response of which deviation from the optimum value was greater than that of the other responses. Thus, the user's preferability can be incorporated into the multi-objective function to a certain extent as a function of the P values.

Experimental

Materials CP, marketed as Hiviswako 104, and CPM were purchased from Wako Pure Chemical Industries, Ltd. PVP, marketed as Povidone K-90, was purchased from Tokyo Chemical Industrial Co., Ltd. MCC, marketed as Avicel PH 102, was purchased from Asahi Kasei Industries, Co., Ltd. Other chemicals used were of reagent grade.

Experimental Points and Preparative Method for Tablet The proportions of MCC (X_1), CP (X_2) and PVP (X_3) in the three-component mixture were selected as formulation factors. In view of drug release behaviors in the preliminary experiments, the lower and upper bounds in the levels of each factor were set as follows.

$$0.05\leq X_1\leq 0.40 \quad (10)$$

$$0.20\leq X_2\leq 0.70 \quad (11)$$

$$0.20\leq X_3\leq 0.70 \quad (12)$$

Consequently, the feasible experimental region was a convex hexagonal shape as shown in Fig. 1, and six vertices, six midpoints of edges and one overall centroid were selected as experimental points. To investigate the effect of a tablet diameter on the drug release, two levels of diameter (6 mm and 8 mm) were selected as an independent process variable, Z. As a corded form, $Z=-1$ means 6 mm of the diameter and $Z=1$ means 8 mm, respectively. The centroid experiment was repeated three times to evaluate experimental error. Model formulations employed in this study are listed in Table I. To the excipient mixtures, 8% of CPM and 1% magnesium stearate were added and mixed thoroughly. A flat-faced tablet with a diameter of 6 mm or 8 mm was prepared by compressing 100 mg of the mixture at a pressure of 40 kg/cm^2 using a Shimadzu hydraulic press.

Determination of Release Profiles Release profiles of CPM from the tablet were determined by using a paddle method. The procedure and apparatus described in dissolution test No. 2 (paddle method) in JP XII were employed. Taking account of the movement of the tablet in the gastrointestinal tract, the release behavior of CPM was measured during the initial 2 h in 500 ml of disintegration fluid No. 1 (pH 1.2) in JP XII at 37 °C under 100 rpm of the paddle rotation speed, then the tablet was transferred to 500 ml of disintegration fluid No. 2 (pH 6.8) in JP XII and the release test was continued at 37 °C under 100 rpm of the paddle rotation speed. At appropriate intervals, 5 ml of aliquots were taken and the volume of dissolution medium was kept constant by adding the same amount of fresh dissolution medium at the same temperature. The concentration of CPM was determined spectrophotometrically at 255 nm by using a Jasco

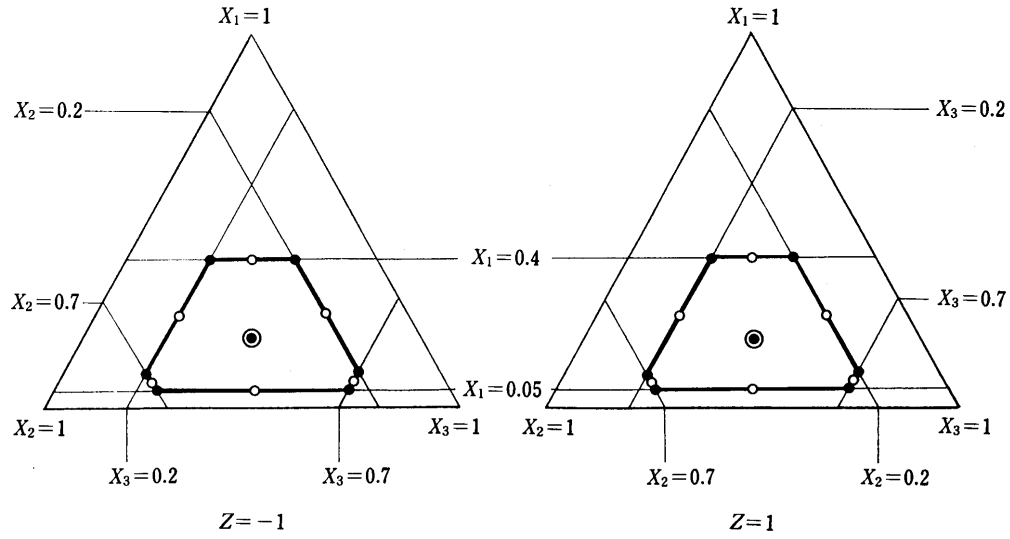

Fig. 1. Geometrical Representation of Extreme Vertices Design for Three Components and One Process Factor

●, extreme vertex; ○, midpoint of edges; ⊙, overall centroid.

TABLE I. Extreme Vertices Design for Three Formulation Factors and One Process Factor

Formulation	Formulation factor			Process factor
	MCC (X_1)	CP (X_2)	PVP (X_3)	Diameter (Z)
1	0.400	0.400	0.200	−1
2	0.100	0.700	0.200	−1
3	0.050	0.700	0.250	−1
4	0.050	0.250	0.700	−1
5	0.100	0.200	0.700	−1
6	0.400	0.200	0.400	−1
7	0.250	0.550	0.200	−1
8	0.075	0.700	0.225	−1
9	0.050	0.475	0.475	−1
10	0.075	0.225	0.700	−1
11	0.250	0.200	0.550	−1
12	0.400	0.300	0.300	−1
13	0.184	0.408	0.408	−1
14	0.184	0.408	0.408	−1
15	0.184	0.408	0.408	−1
16	0.400	0.400	0.200	1
17	0.100	0.700	0.200	1
18	0.050	0.700	0.250	1
19	0.050	0.250	0.700	1
20	0.100	0.200	0.700	1
21	0.400	0.200	0.400	1
22	0.250	0.550	0.200	1
23	0.075	0.700	0.225	1
24	0.050	0.475	0.475	1
25	0.075	0.225	0.700	1
26	0.250	0.200	0.550	1
27	0.400	0.300	0.300	1
28	0.184	0.408	0.408	1
29	0.184	0.408	0.408	1
30	0.184	0.408	0.408	1

Ubest-30 spectrophotometer (Japan Spectroscopic Co., Ltd.).

Computer Programs The computation was carried out on a desktop digital computer (PC-9801 RX, NEC Corp.). The computer programs, written by the authors, were used for the regression analysis, the contour diagrams and the simultaneous optimization for multi-objective functions under the constraints.[30]

Results and Discussion

Prediction of Response Variables In order to analyze the release behaviors of drugs from solid dosage forms, an exponential model is frequently applied to the initial portion (amount released $\leq 60\%$) of the release data.[31]

$$M_t = kt^n \tag{13}$$

where M_t is the amount of drug (%) released at time t (h), n is a diffusional exponent and k is the apparent release rate constant (%/h^n). The release parameters, k and n, can be obtained by a linear least-squares fitting using a logarithmic transformation of Eq. 13.

$$\log M_t = \log k + n \log t \tag{14}$$

In the case of insoluble and non-swellable polymer matrix, the drug release has generally been expressed by a Fickian diffusion mechanism, that is a time-dependence of the square-root of time ($n=0.5$ in Eq. 14). If the n value is close to 1, the drug release can be regarded as following an apparent zero-order mechanism.

The parameters, k and n, determined from the initial portion ($M_t \leq 60\%$) of the release data of CPM are summarized in Table II. The k values were widely varied from 17.3 (formulation 3) to 41.5 (formulation 21). A large deviation was also observed in the n values among the formulations ($n=0.321$ at formulation 21; $n=0.740$ at formulation 3). Therefore, the release characteristics of CPM were greatly affected by the change of the levels of the formulation factors, X_1, X_2 and X_3. The effect of the tablet diameter on the release parameters was also observed. When the tablet diameter is small ($Z=-1$; formulations

TABLE II. Experimental Values of Response Variables

Formulation	$k^{a)}$ (%/h^n)	$n^{b)}$
1	29.6	0.438
2	19.9	0.620
3	17.3	0.740
4	29.3	0.417
5	36.2	0.365
6	38.2	0.365
7	20.9	0.580
8	21.4	0.553
9	20.2	0.523
10	34.3	0.395
11	33.9	0.398
12	31.0	0.397
13	20.0	0.510
14	22.7	0.517
15	23.3	0.468
16	32.2	0.455
17	19.7	0.573
18	22.4	0.532
19	33.1	0.411
20	35.1	0.378
21	41.5	0.321
22	29.8	0.451
23	24.0	0.534
24	24.3	0.461
25	34.7	0.426
26	42.7	0.367
27	32.3	0.392
28	24.5	0.457
29	25.3	0.484
30	28.3	0.433

a) Apparent release rate constant. *b*) Diffusional exponent.

TABLE III. Regression Equation for Each Response Variable

Coefficient	Regression coefficient value	
	$k^{a)}$ (%/h^n)	$n^{b)}$
b_{01} (X_1)	24.0	0.186
b_{02} (X_2)	21.4	0.721
b_{03} (X_3)	44.4	0.325
b_{012} (X_1X_2)	88.8	−0.143
b_{013} (X_1X_3)	146	−0.243
b_{023} (X_2X_3)	−38.8	−0.0602
b_{0123} ($X_1X_2X_3$)	−604	1.76
b_{11} (X_1Z)	−64.1	0.492
b_{12} (X_2Z)	−13.1	0.0399
b_{13} (X_3Z)	−15.6	0.195
b_{112} (X_1X_2Z)	190	−1.34
b_{113} (X_1X_3Z)	200	−1.82
b_{123} (X_2X_3Z)	73.2	−0.719
b_{1123} ($X_1X_2X_3Z$)	−520	4.90
$r^{c)}$	0.979	0.944
$RA^{d)}$	0.926	0.804

a) Apparent release rate constant. *b*) Diffusional exponent. *c*) Multiple correlation coefficient. *d*) Adjusted r^2 with degrees of freedom.

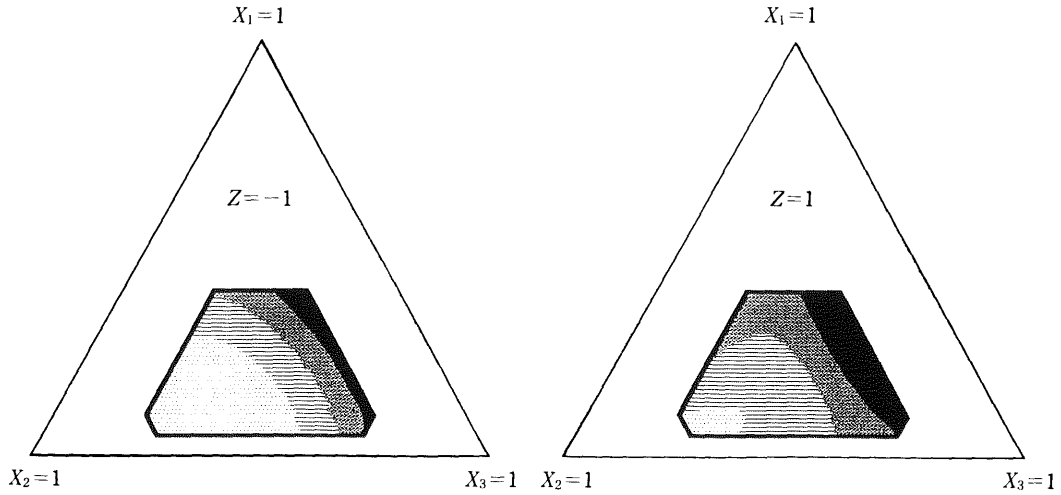

Fig. 2. Contour Diagrams for Apparent Release Rate Constant, k, as a Function of X_1, X_2, X_3 and Z

□, <23; ▤, 23—28; ▦, 28—33; ■, >33.

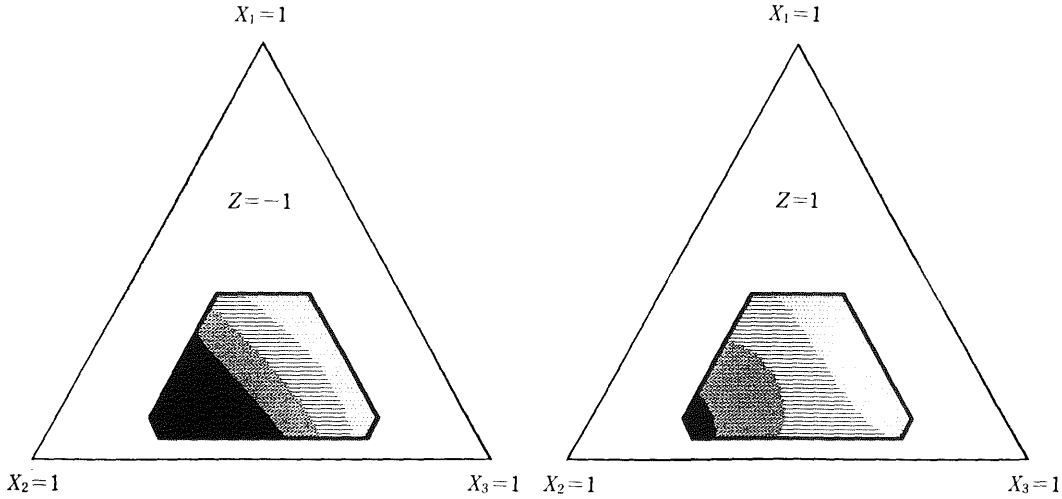

Fig. 3. Contour Diagrams for Diffusional Exponent, n, as a Function of X_1, X_2, X_3 and Z

□, <0.42; ▤, 0.42—0.47; ▦, 0.47—0.52; ■, >0.52.

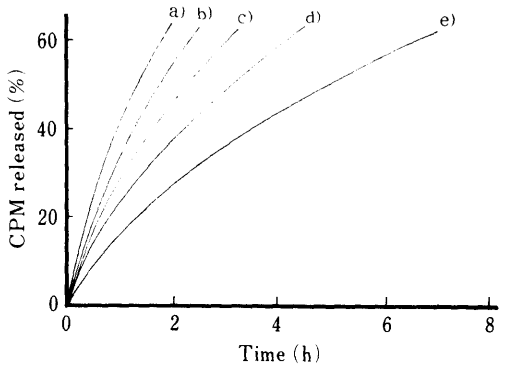

Fig. 4. Release Profiles of CPM from Tablets Simulated as a Function of k Values ($n=0.643$)

a) $k=42$, b) $k=36$, c) $k=30$, d) $k=24$, e) $k=18$.

1—15), the k values were relatively smaller than those of the large diameter tablets ($Z=1$; formulation 16—30). On the other hand, the n values observed in the tablets with a small diameter were greater than those of the large tablets. An increase of the tablet surface may lead to an increase of the effective release area of CPM and a decrease of diffusion distance of drug molecules in the tablet. This might be a possible mechanism of the considerable difference which was brought about by the tablet diameters.

Regression equations for each release parameter were determined by means of multiple regression analysis. Estimated values of each coefficient are summarized in Table III. Each parameter was predicted accurately by the modified special cubic model (Eq. 6) with sufficiently high values of the multiple correlation coefficient, r. Figures 2 and 3 show the contour diagrams of k and n as a function of X_1, X_2, X_3 and Z, respectively. It was obvious that both k and n values were significantly affected not only by the mixing ratio of three components but also by the tablet diameter.

Mathematical Optimization In order to estimate the ideal release profiles of CPM from the tablets, the release behavior was simulated by using the parameters, k and n, in Eq. 13. Results are shown in Fig. 4. The maximum value of n, which was determined under the restrictions of the experimental region, was employed as the ideal one ($n=0.643$), because the zero-order release is considered to be desirable in the formulation design of a sustained-release tablet. Thus, the release curves shown in Fig. 4 were expressed as only a function of k values. When the k values

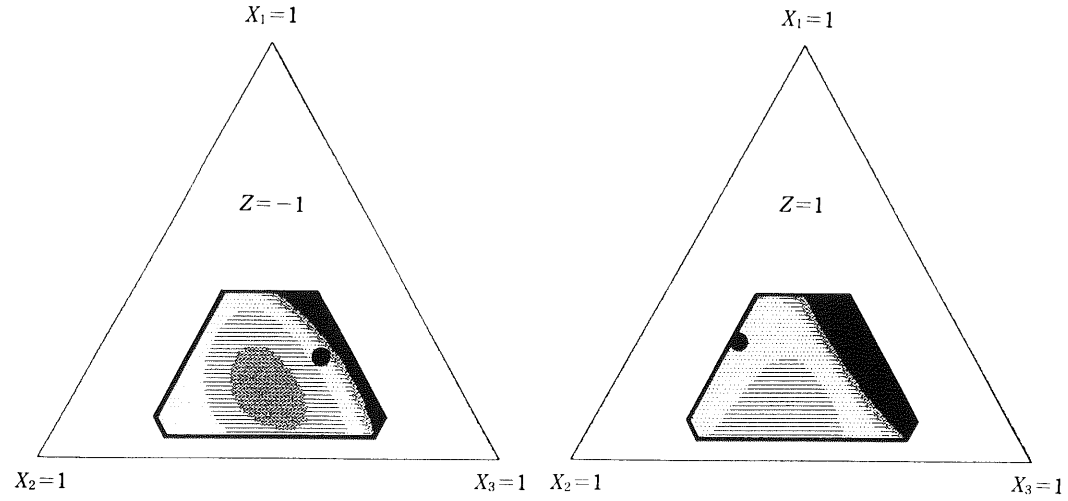

Fig. 5. Contour Diagrams of Combined Objective Function, $S(X)$, as a Function of X_1, X_2, X_3 and Z at $P=1$
●, optimum point of $S(X)$. ⬚, <2.1; ▤, 2.1—2.3; ▦, 2.3—2.5; ■, >2.5.

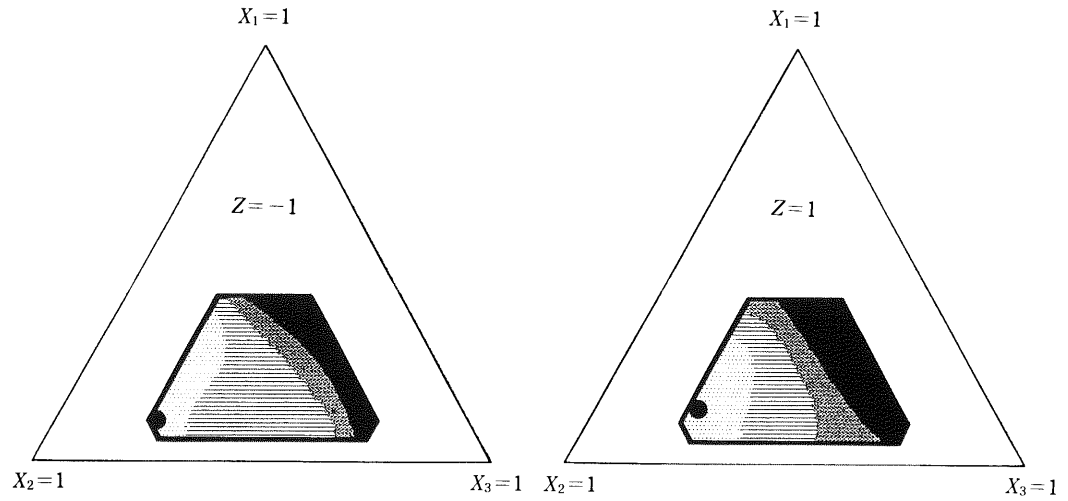

Fig. 6. Contour Diagrams of Combined Objective Function, $S(X)$, as a Function of X_1, X_2, X_3 and Z at $P=2$
●, optimum point of $S(X)$. ⬚, <1.6; ▤, 1.6—1.8; ▦, 1.8—2.0; ■, >2.0.

TABLE IV. Optimum Mixing Ratio of Three Components

P value[a]	Diameter (mm)	MCC (X_1)	CP (X_2)	PVP (X_3)
1	6	0.201	0.257	0.542
	8	0.290	0.510	0.200
2	6	0.100	0.700	0.200
	8	0.140	0.660	0.200

a) Impartiality parameter given in Eq. 9.

TABLE V. Release Parameters of the Optimum Formulations

P value[a]	Diameter (mm)	Parameter	Predicted	Experimental[b]
1	6	k (%/h^n)	30.0	32.7±1.0
		n	0.421	0.424±0.006
	8	k (%/h^n)	30.0	29.2±3.0
		n	0.468	0.460±0.015
2	6	k (%/h^n)	20.0	20.7±2.2
		n	0.636	0.552±0.017
	8	k (%/h^n)	24.8	21.0±1.4
		n	0.528	0.540±0.018

a) Impartiality parameter given in Eq. 9. *b*) Mean±S.D. for three determinations.

are relatively large ($k=36$ and $k=42$), the release of CPM was too rapid. On the other hand, when the small k values were used ($k=18$ and $k=24$), the release of CPM was rather slow. Then, $k=30.0$ and $n=0.643$ were selected as the acceptable ideal values, though the desirable release profiles of CPM should be decided based on the pharmacokinetic or pharmacodynamic investigations.

The optimization was performed according to the method described above. The regression equation for k and n summarized in Table III were combined into generalized distance function, $S(X)$, given in Eq. 9. The independent process factor, Z, was fixed to be -1 or 1 since the level of this factor was not given as the continuous data. In this study, the effect of impartiality parameter, P, in Eq. 9 on the optimum solutions was investigated in detail. Figures 5 and 6 show the contour diagrams of $S(X)$ as a function of X_1, X_2, X_3 and Z at $P=1$, and $P=2$, respectively. The simultaneous optimum at $P=1$ was found to be close to the ideal point of k, but very far from that of n. When $P=2$ was employed, the optimum point greatly changed to the position which was close to the ideal point of n. A further

increase of the P values (*e.g.*, $P=3$ or $P=4$) resulted in a small change of the simultaneous optima. The optimum formulations obtained at $P=1$ and $P=2$ were listed in Table IV. The predicted values of the release parameters coincided well with the experimental data, as summarized in Table V. The release profiles of CPM from the optimum formulations were satisfactorily predicted in spite of the fact that the functions for predicting the release parameters, k and n, were composed of a simple combination of factors. These results strongly suggest usefulness and reliability of the computer optimization method based on the extreme vertices design and simultaneous optimization technique. The independent process variable could reasonably be incorporated in the mixture experiments by a little modification of the extreme vertices design.

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