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Mathematical Optimization of Formulation of Indomethacin/Polyvinylpolypyrrolidone/Methyl Cellulose Solid Dispersions by the Sequential Unconstrained Minimization Technique[1,2]

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A mathematical optimization technique was applied to obtain a formulation of indomethacin (IMC)/polyvinylpolypyrrolidone/methyl cellulose solid dispersion with a high dissolution rate and high stability of IMC. Model formulations were prepared according to a composite spherical experimental design based on the simplex method. The dissolution rate and chemical stability of IMC were determined as response variables for deciding an optimum formulation. These response variables were predicted by the second-order polynomial regression model of formulation and process factors.

In order to optimize the formulation, regression equations of each response were mathematically structured as a constrained nonlinear optimization problem. The solution was obtained by application of the sequential unconstrained minimization technique. Experimental results obtained for the optimum formulation agreed well with the predictions.

Keywords——sequential unconstrained minimization technique; composite spherical experimental design; simplex method; optimum formulation; indomethacin; polyvinylpolypyrrolidone; methyl cellulose; dissolution rate; stability of dissolution profile, chemical stability

Mathematical optimization techniques in pharmaceutical formulations, based on factorial experimental design, have been proved to afford a useful approach for controlling the pharmaceutical properties of tablets,[5-7] capsules,[8] suspensions[9] and solid dispersions.[10] In these studies, the optimization of formulation has been done by means of the following steps. First, model formulations are prepared according to statistically designed experiments. Next, response variables such as the dissolution rate and stability which will decide the optimum formulation are predicted quantitatively from the combination of formulation and process factors. A second-order polynomial regression equation is usually applied for the prediction of the response variables.[6] Finally, the formulation which gives the optimum value of each response might be predicted within the constant limit values of factors. However, as is typical in optimization problems, the best formulations for different response variables are not the same. For example, the tablet formulation with the highest dissolution rate has relatively low hardness.[7] Thus, the optimum formulation has to be taken as an acceptable formulation which will sufficiently satisfy the primary objective under a set of various constraints.

The purpose of the present study was to evaluate the composite experimental design based on a simplex method[11] and constrained mathematical nonlinear optimization method[12] as a technique for seeking the optimum formulation. Indomethacin (IMC)/polyvinylpolypyrrolidone (PVPP)/methyl cellulose (MC) solid dispersions were selected as a model formulation for the optimization problem. PVPP was used as a carrier of solid dispersions and MC was added as a stabilizing agent for dissolution.[10] As the dissolution rate of IMC was considered to be of primary interest, the objective was to increase the dissolution rate without adversely changing other properties of the solid dispersions.

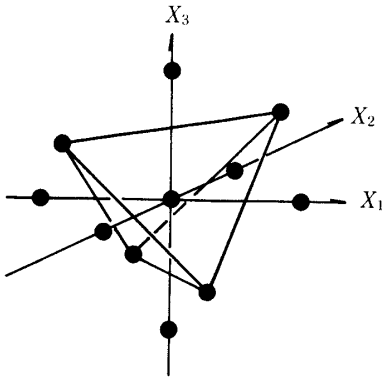

Fig. 1. Geometrical Illustration of the Composite Spherical Experimental Design Based on the Simplex Method for Three Factors

TABLE I. Experimental Design for Three Factors

Formulation	Factor level in coded form		
	X_1	X_2	X_3
1	−1	−1	1
2	1	−1	−1
3	−1	1	−1
4	1	1	1
5	$-\sqrt{3}$	0	0
6	$\sqrt{3}$	0	0
7	0	$-\sqrt{3}$	0
8	0	$\sqrt{3}$	0
9	0	0	$-\sqrt{3}$
10	0	0	$\sqrt{3}$
11	0	0	0

The composite spherical experimental design for three factors at five levels,[11] which was used in this study, is illustrated geometrically in Fig. 1 and a set of experiments based on Fig. 1 is listed in Table I in coded form. This design demands at least eleven experiments, but the number of experiments is the smallest in comparison with other experimental designs. All of the experimental points are placed at the same distance from the center in the spherical design, as shown in Fig. 1. Multiple regression analysis was applied to predict each response from the combination of factors. Regression equations of each response were mathematically structured as a constrained nonlinear optimization problem, and the optimum formulation of IMC/PVPP/MC solid dispersions was obtained by the application of the sequential unconstrained minimization technique (SUMT).[12,13]

Experimental

Materials——IMC was purchased from Sigma Chemical Co., Ltd. PVPP was generously supplied by BASF Japan Ltd. MC with a viscosity of 80—120 cP in 2% aqueous solution at 20 °C was purchased from Tokyo Kasei Industrial Co., Ltd.

Preparation Method for Solid Dispersions——The preparation method for IMC/PVPP/MC samples powders is shown in Chart 1.

The amounts of PVPP (X_1), MC (X_2) and ethanol (X_3) were selected as factors (ethanol is the solvent for the preparation of solid dispersions). Both X_1 and X_2 are formulation variables, while X_3 is a process variable. The experiments listed in Table I in coded form were transformed to the physical units in an empirical way as summarized in Table II.

Determination of Response Variables——The dissolution rate of IMC from samples, the stability of the

IMC 1 g
(1) dissolve in ethanol (31—169 ml)
(2) add PVPP (1.27—4.73 g)
(3) add MC (26.8—373 mg)
(4) agitate well for 5 min
(5) remove the solvent *in vacuo* at 70°C
(6) dry *in vacuo* at room temperature for 24 h
(7) grind in a mortar
(8) sieve (100—200 mesh)
sample

Chart 1. Method for Sample Powder Preparation

TABLE II. Level of Factors in Physical Units

Factor	Factor level in coded form				
	$-\sqrt{3}$	-1	0	1	$\sqrt{3}$
X_1: PVPP (g)	1.27	2	3	4	4.73
X_2: MC (mg)	26.8	100	200	300	373
X_3: Ethanol (ml)	31	60	100	140	169

dissolution profile of IMC and the chemical stability of IMC in samples were selected as response variables.

a) Dissolution Rate: A paddle method was applied to the sample powders. The procedure and apparatus described in dissolution test No. 2 (paddle method) in JPX were applied. A certain amount of sample powder containing 62 mg of IMC was weighed accurately, and dispersed in 900 ml of 1/15 M phosphate buffer solution (pH 6.4) at 37 °C at a paddle rotation speed of 50 rpm. At appropriate intervals, 1 ml aliquots of the solution were taken, and the volume was kept constant by adding the same amount of fresh dissolution medium at the same temperature. The concentration of IMC was determined by the ultraviolet absorption method. In order to determine the stability of the dissolution profile, the dissolution test was also applied to samples which had been kept for 30 d at 40 °C under 75% relative humidity (R. H.).

b) Chemical Stability: For the study of the chemical stability of IMC in solid dispersions to heat and moisture, the residual amount of IMC in each sample was measured after storing them for 30 d at 60 °C under 75% R.H. A certain amount of sample powder which contained 10 mg of IMC was weighed accurately, and agitated well in 50 ml of ethanol containing 0.012% ketoprofen as an internal standard. One ml of the filtrate of this solution was diluted with 4 ml of acetonitrile. The concentration of IMC was determined by the high performance liquid chromatography (HPLC) method.[14]

Results and Discussion

In order to obtain a suitable index for the dissolution of IMC from the samples, Wagner's dissolution model[15] was applied to the experimental data and the 16% dissolution time ($t_{16\%}$), 50% dissolution time ($t_{50\%}$) and 84% dissolution time ($t_{84\%}$) were calculated. Wagner's dissolution model is based on the log normal density function,[15] and these dissolution parameters are quite proper and convenient for quantitative comparison of a given formulation with other formulations, because they are closely related to the mean and standard deviation ($\pm\sigma$) of the log normal density function. In general, $t_{50\%}$ is widely used as a dissolution index for pharmaceutical formulations. Therefore, $t_{50\%}$ was selected as the most important response variable for the comparison of dissolution behavior. The stability of the dissolution profile (D_s) was calculated by use of the following equation:

$$D_s=[(t_{16\%}-t_{16\%}{}^*)/t_{16\%}]^2+[(t_{50\%}-t_{50}{}^*)/t_{50\%}]^2 +[(t_{84\%}-t_{84\%}{}^*)/t_{84\%}]^2$$

where $t_{16\%}{}^*$, $t_{50\%}{}^*$ and $t_{84\%}{}^*$ represent the dissolution parameters determined after storing samples for 30 d at 40 °C under 75% R.H. The value of D_s is represented as the sum of the squares of the normalized differences of each dissolution parameter. It was considered that the dissolution profile was stable when the value of D_s was sufficiently small. Chemical stability of IMC in solid dispersions (C_s) was expressed as the residual amount of IMC after storing samples for 30 d at 60 °C under 75% R.H. These response variables are listed in Table III.

TABLE III. Experimental Values of Response Variables

Formulation	$t_{50\%}$ (min)	D_s	C_s (%)
1	2.00	0.680	95.1
2	1.23	0.954	87.9
3	1.86	1.25	94.9
4	1.16	0.973	90.4
5	2.52	1.12	96.1
6	1.10	1.35	90.7
7	2.08	0.657	92.5
8	1.49	1.88	93.9
9	1.54	1.86	87.5
10	1.17	1.26	88.5
11	1.18	2.74	86.3

Each datum is the mean of three determinations.

TABLE IV. Optimum Regression Equation for Each Response Variable Determined by Multiple Regression Analysis

Coefficient	Regression coefficient value		
	$t_{50\%}$ (min)	D_s	C_s (%)
b_0	1.18	2.74	86.3
b_1 (X_1)	−0.393	—[a]	−2.36
b_2 (X_2)	−0.172	0.270	—
b_3 (X_3)	−0.107	−0.158	—
b_4 (X_1^2)	0.199	−0.553	1.87
b_5 (X_2^2)	0.190	−0.543	2.20
b_6 (X_3^2)	0.0452	−0.446	1.34
b_7 (X_1X_2)	0.126	—	−1.38
b_8 (X_1X_3)	0.121	—	—
b_9 (X_2X_3)	—	—	—
r[b]	0.995	0.931	0.905
s[c]	0.105	0.316	2.08
F_0[d]	25.6[e]	6.54[e]	4.50[f]

a) This factor is not included in the optimum regression equation.
b) Multiple correlation coefficient. c) Standard deviation.
d) Observed F value. e) $p<0.05$. f) $p<0.1$.

Regression Analysis

The following second-order polynomial equation was used for the prediction of each response variable:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1^2 + b_5X_2^2 + b_6X_3^2 + b_7X_1X_2 + b_8X_1X_3 + b_9X_2X_3$$

where X_1, X_2 and X_3 are the amounts of PVPP, MC and ethanol, respectively. These factors are considered to be directly controllable. Y is the response variable and b_i is the regression coefficient. The optimum regression equation was obtained by investigating the overall combination of factors at the point of statistical significance, that is, the best combination of factors for the prediction of each response was selected from among 511 (2^9-1) kinds of regression equations. The correlation coefficient, which was doubly adjusted with degrees of freedom,[16] was used as an index for the selection of the optimum combination of factors. Optimum regression equations obtained are summarized in Table IV. Each response variable was predicted accurately by the second-order polynomial equation, because values of r were satisfactory and the regression equations were significant with high F_0 values. The physical significance of the regression equation was expressed by means of contour graphs.

Contour Graphs

The significance of each regression equation was elucidated by the application of contour graphs. Figure 2 shows the contour graphs for $t_{50\%}$. As the value of $t_{50\%}$ was predicted as a function of all factors, the contour graphs were drawn by using the combination of the cross section of the X_3 axis against the response surface for $t_{50\%}$ which was expressed by X_1 and X_2. The contour graphs of D_s and C_s were also drawn in the same way, as shown in Figs. 3 and 4. The optimum position of $t_{50\%}$ was defined as being at about the center of the graphs ($X_1 = 1$,

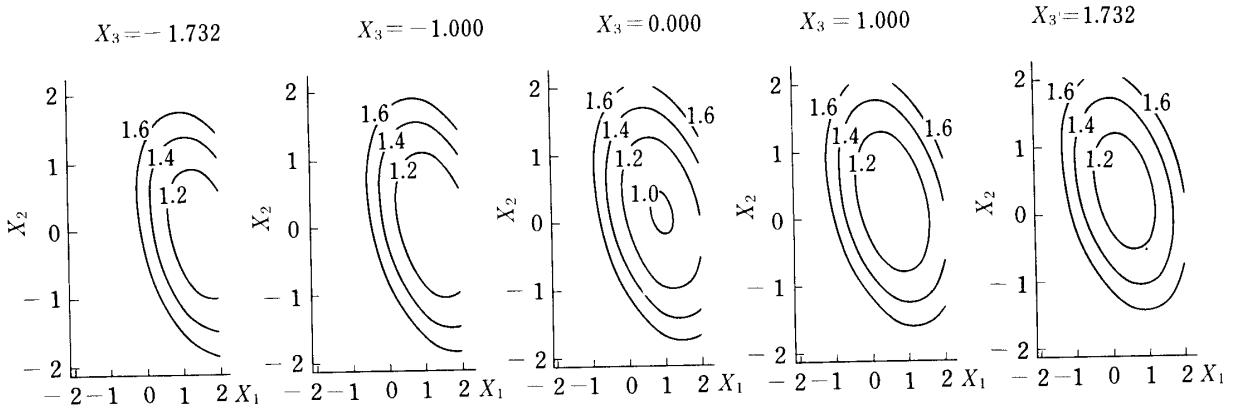

Fig. 2. Contour Curves of $t_{50\%}$ (min) as a Function of X_1, X_2 and X_3

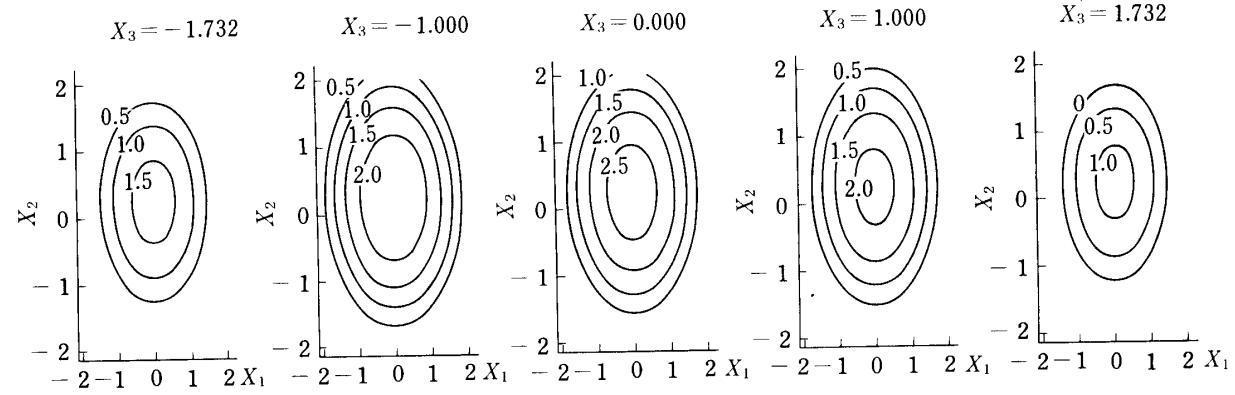

Fig. 3. Contour Curves of D_s as a Function of X_1, X_2 and X_3

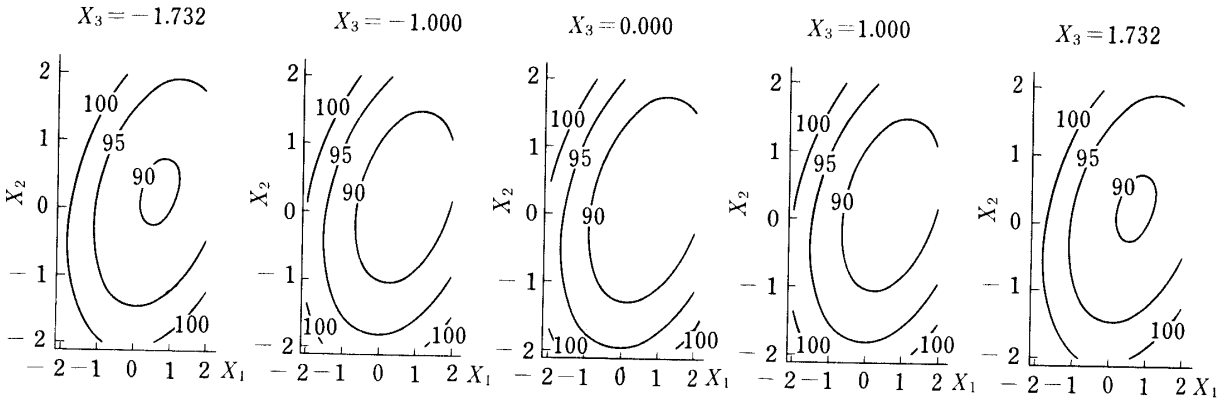

Fig. 4. Contour Curves of C_s (%) as a Function of X_1, X_2 and X_3

$X_2=0$ and $X_3=0$ in coded form), but this position leads to the worst results for D_s and C_s as shown in Figs. 3 and 4. Therefore, it is obvious that a formulation with a high dissolution rate of IMC is not stable to heat and moisture. Though the primary objective in solid dispersions is to enhance the dissolution rate, at the same time, we should also consider the stability of the dissolution profile and chemical stability. A constrained mathematical optimization method was applied to solve this problem as follows.

Mathematical Optimization

The optimization of the formulation of IMC/PVPP/MC solid dispersions was done by an application of the SUMT method.[12,17] In general, the constrained nonlinear optimization problem is to minimize the object function, $f(x)$, under the following inequality and equality constraints:

$$g_i(x)\geqq 0 \quad i=1,\ 2,\ 3,\ \ldots,\ m \tag{1}$$

$$h_j(x)=0 \quad j=1,\ 2,\ 3,\ \ldots,\ p \tag{2}$$

where $g_i(x)$ is the inequality constraints and $h_j(x)$is the equality constraints. The constrained optimization problem described above was transformed to the unconstrained optimization problem by adding penalty functions as follows:

$$P(x,r)=f(x)-r\sum_{i=1}^{m}\ln[g_i(x)]+(1/r)\sum_{j=1}^{p}[h_j(x)]^2 \tag{3}$$

where $P(x, r)$ is the transformed object function and r is a parameter of $P(x, r)$. The second and third terms in equation 3 correspond to inequality constraints, $g_i(x)$, and equality constraints, $h_j(x)$, respectively. These terms act as the penalty functions, because the values of the second or third terms will increase abruptly when the values of $g_i(x)$ are close to zero or the values of $h_j(x)$ deviate from zero. The minimization of the function $P(x, r)$ was carried out by means of general unconstrained nonlinear optimization methods under constant value of r ($r>0$). The optimum solution is obtained as the point, $x(r)$, which gives the minimum value of $P(x, r)$ when the value of r is sufficiently close to zero.

Fonner *et al.* reported the application of the Lagrangian method to solve a similar problem,[5] and the optimization of tablet formulation was demonstrated in the case of two factors. However, the approach to the optimization problem with the Lagrange multipliers, though applicable to many responses, is generally limited to two factors.[6,18] On the other hand, the SUMT method is applicable to more complex and realistic optimization problems.

The purpose of the optimization of IMC/PVPP/MC solid dispersions is to find a formulation with a high dissolution rate as well as acceptable stability of the dissolution profile and acceptable chemical stability. Thus, the regression equations of each response

Table V. Optimum Formulation

IMC (g)	1
PVPP (g)	4.55
MC (mg)	185
Ethanol (ml)	46

Table VI. Response Variables of the Optimum Formulation

Response	Predicted	Experimental[a]
$t_{50\%}$ (min)	1.02	0.994 ± 0.031
D_s	0.751	0.973 ± 0.058
C_s (%)	90.0	89.3 ± 0.5

a) Represented as the mean ± S.D. of 6 determinations.

variable listed in Table IV were structured as a constrained nonlinear optimization problem. Based on the contour graphs of D_s and C_s, two kinds of constraints ($D_s \leqq 1$ and $C_s \geqq 90\%$) were selected as proper and acceptable critical conditions for stability of the dissolution profile and chemical stability.

Mathematically, this constrained nonlinear optimization problem can be described as follows: Minimization of $t_{50\%}$ under the following constraints,

$$1 - D_s \geqq 0 \tag{4}$$

$$C_s - 90 \geqq 0 \tag{5}$$

$$3 - X_1^2 \geqq 0 \tag{6}$$

$$3 - X_2^2 \geqq 0 \tag{7}$$

$$3 - X_3^2 \geqq 0 \tag{8}$$

Equations 6, 7 and 8 are constraints to keep the values of X_1, X_2 and X_3 in the experimental region. In this study, Powell's conjugate gradient method[19] was used to solve this unconstrained nonlinear optimization problem, which was transformed by the SUMT method. Thus, $X_1 = 1.55$, $X_2 = -0.149$ and $X_3 = -1.35$ were obtained in coded forms as the optimum formulation of IMC/PVPP/MC solid dispersions. These values were transformed to physical units and the results are listed in Table V. While the experimental value of D_s was a little larger than predicted, the predicted values of other responses coincided well with the experimental data as summarized in Table VI. Chemical stability of IMC in the optimum formulation was also investigated after storing it for 30 d at 40 °C under 75% R.H., and $98.2 \pm 0.3\%$ (mean ± S.D.) of IMC remained (residual amount; 6 determinations). Thus, it was considered that IMC in the optimum formulation was very stable under the usual storage conditions.

The optimum formulation is defined on the contour graphs shown in Fig. 5. It was found that the optimum point corresponds to the intersection of the contour line for $t_{50\%} = 1.02$ min (optimum value) and the constrained curve for $C_s = 90\%$. On the other hand, the optimum point was placed in the outer region defined by the constrained curve for $D_s = 1$. Therefore, the optimum formulation was not directly affected by the constraint of $D_s \leqq 1$. This result shows that the optimum formulation may be varied by minor changes of the restricting values assigned to the constraints. Changes of the predicted values of $t_{50\%}$ resulting from modifications of the restricting values are shown in Figs. 6 and 7.

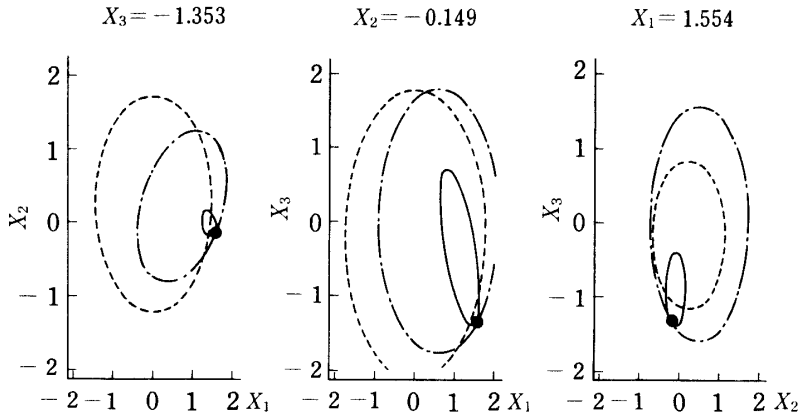

Fig. 5. Optimum Point (●) on Contour Graphs of $t_{50\%} = 1.02$ min, $D_s = 1$ and $C_s = 90\%$ as a Function of X_1, X_2 and X_3
——, $t_{50\%}$; – – –, D_s; — · —, C_s.

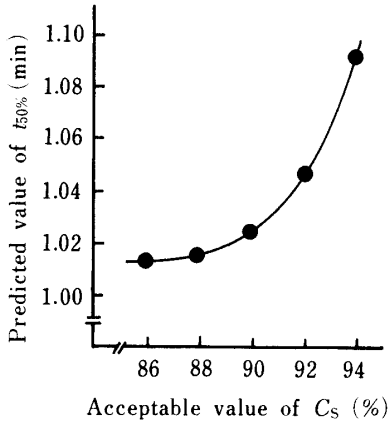

Fig. 6. Optimum Value of $t_{50\%}$ as a Function of Restrictions on C_s (Restriction of $D_s \leqq 1.0$)

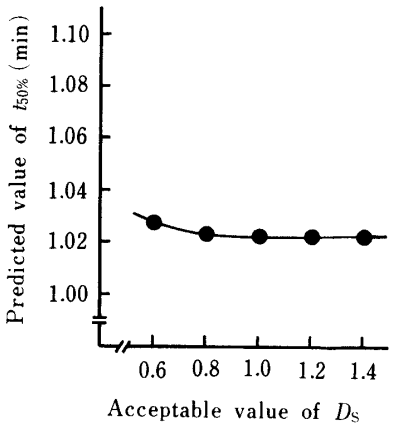

Fig. 7. Optimum Value of $t_{50\%}$ as a Function of Restrictions on D_s (Restriction of $C_s \geqq 90\%$)

The value of $t_{50\%}$ increased abruptly when the restricting values of C_s were increased to more than 90%, as shown in Fig. 6. Though the change of $t_{50\%}$ was relatively small upon modification of the restricting values of D_s as shown in Fig. 7, the value of $t_{50\%}$ increased when the restricting values of D_s were decreased to less than 1. Determination of the sensitivity of the primary objective to the tightening or relaxation of restrictions made it possible to decide suitable restricting values for the multiple constraints. It appears that the restricting values of D_s and C_s selected in this study were quite proper and significant.

Based on the above considerations, the optimization of formulation of IMC/PVPP/MC solid dispersions could reasonably be done by application of the SUMT method. The methods described in previous papers[6,10] have various disadvantages, *e.g.*, they frequently give plural solutions for the suitable formulations, while the SUMT method gives a singular solution strictly obtainable as the best formulation. Furthermore, the SUMT method is applicable to more complex and realistic optimization problems in comparison with the Lagrangian method.[5] This sort of approach, including a spherical experimental design based on the simplex method, should be applicable to other practical optimization problems in the pharmaceutical field.

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