Novel Computer Optimization Methodology for Pharmaceutical Formulations Investigated by Using Sustained-Release Granules of Indomethacin[1)]

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A modified optimization technique, based on the response surface methodology, was developed for selecting pharmaceutical formulations. In general optimization methods, it is difficult to insure that the optimum formulation is strictly obtainable. Thus, the combined use of random number techniques and Andrews' plots with general optimization methods was investigated for seeking the optimum formulation. The method developed in this study was applied to the optimization of a sustained-release formulation based on the interpolymer complex of polyvinylpyrrolidone with carboxyvinyl polymer. Indomethacin was selected as a model drug for which sustained-release formulations are desirable. Experimental results obtained for the optimum formulation agreed well with the predictions, indicating the usefulness of this approach.

Keywords optimization; response surface; random number; Andrews' plot; simplex method; experimental design; sustained release; polyvinylpyrrolidone; carboxyvinyl polymer; indomethacin

Introduction

A computer optimization technique, based on response surface methodology,[2)] has been proven to be a useful approach for selecting pharmaceutical formulations.[3-11)] Basically, the optimization methods include factorial experimental design, multiple regression analysis, and mathematical optimization algorithms for seeking the best formulation under a set of restrictions. Factorial experimental designs can be applicable to prepare systematic model formulations which are composed of several formulation factors and/or process factors. Response variables of these model formulations such as dissolution rate and stability are predicted quantitatively from the combination of these factors. In general, since theoretical relationships between response variables and factors are not clear, the multiple regression analysis can be applied to the prediction of response variables on the basis of a second-order polynomial equation. At the final step, optimization algorithms are applied for deciding the best formulation. As is typical in optimization problems, the best formulations for different response variables are not the same. Therefore, the optimum formulation has to be taken as an acceptable formulation which will sufficiently satisfy the primary objective under a set of various constraints.

Mathematically, the optimization of pharmaceutical formulations can be regarded as the minimization or maximization of the objective function under a set of constraints. In general, the constrained objective function is transformed to the unconstrained function by adding penalty functions in order to obtain the optimum solution.[12)] However, it is not easy to insure that a global optimum solution is strictly obtained, because the transformed objective function often has several local minima or maxima as a result of adding penalty functions. The purpose of the present study was to develop optimization methodology which can efficiently seek a global optimum solution of the transformed objective function. The method developed here was applied to the development of a sustained-release formulation based on the interpolymer complex formation between polyvinylpyrrolidone (PVP) and carboxyvinyl polymer (CP).[13)] Indomethacin (IMC) was selected as a model drug for which sustained-release formulations are desirable.

Theory

In general, pharmaceutical optimization problems are described mathematically so as to minimize the objective function, $F(\boldsymbol{X})$, under the following inequality and/or equality constraints:

$$G_i(\boldsymbol{X}) \geqq 0 \qquad i=1, 2, 3, \cdots, m \tag{1}$$

$$H_j(\boldsymbol{X}) = 0 \qquad j=1, 2, 3, \cdots, n \tag{2}$$

where $G_i(\boldsymbol{X})$ is the inequality constraint and $H_j(\boldsymbol{X})$ is the equality constraint. Usually, it is very difficult to solve the constrained optimization problem described above without any mathematical modifications. Thus, the constrained optimization problem is transformed to an unconstrained optimization problem by adding penalty functions as follows:

$$T(\boldsymbol{X}, r) = F(\boldsymbol{X}) + r^{-1} \sum_{i=1}^{m} \Phi_i [G_i(\boldsymbol{X})]^2 + r^{-1} \sum_{j=1}^{n} [H_j(\boldsymbol{X})]^2 \tag{3}$$

when $G_i(\boldsymbol{X}) < 0$, $\phi_i = 1$

when $G_i(\boldsymbol{X}) \geqq 0$, $\phi_i = 0$

where $T(\boldsymbol{X}, r)$ is the transformed unconstrained objective function which is obtained based on the external transformation, r is a perturbation parameter of $T(\boldsymbol{X}, r)$ and ϕ_i is a step function by which the objective function, $F(\boldsymbol{X})$, is penalized. Mathematical details of other transformations have been well described in the literature.[14)] The second and third terms in Eq. 3 act as penalty functions, because the values of the second or third terms will increase abruptly when the values of $G_i(\boldsymbol{X})$ are negative or the values of $H_j(\boldsymbol{X})$ deviate from zero. The meaning of perturbation parameter, r, can be explained using a simple optimization problem as follows:

$$F(\boldsymbol{X}) = X_1^2 + X_2^2 \tag{4}$$

$$G(\boldsymbol{X}) = -X_1 - X_2 - 1 \geqq 0 \tag{5}$$

Figure 1 shows the effects of r values on the three-dimensional diagrams for the transformed objective function, $T(\boldsymbol{X}, r)$, which is derived from Eqs. 4 and 5. The shape

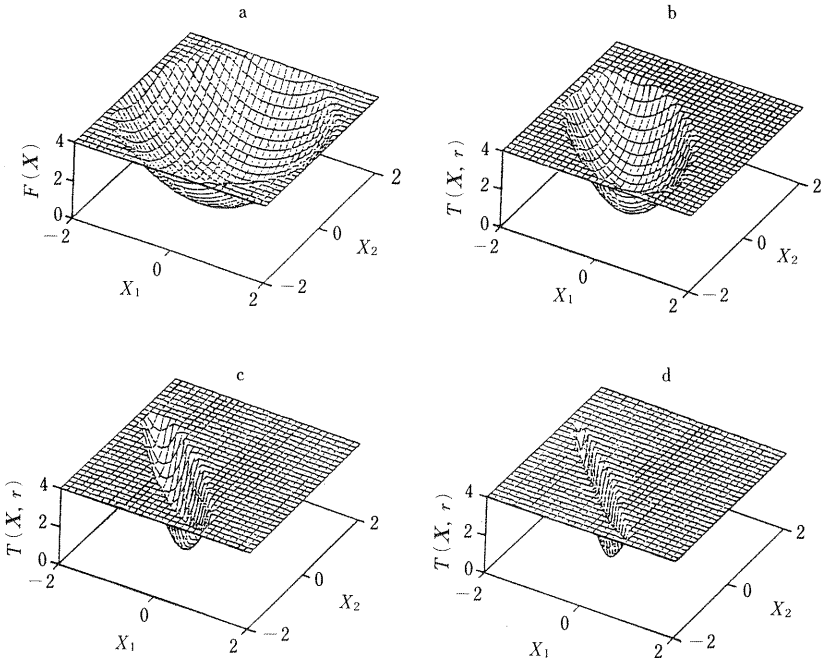

Fig. 1. Three-Dimensional Diagrams for the Objective Function, $F(\boldsymbol{X})$, and Transformed Objective Function, $T(\boldsymbol{X}, r)$, Derived from Eqs. 4 and 5 as a Function of X_1 and X_2

a, $F(\boldsymbol{X})$; b, $T(\boldsymbol{X}, r)$ at $r=1$; c, $T(\boldsymbol{X}, r)$ at $r=0.1$; d, $T(\boldsymbol{X}, r)$ at $r=0.01$.

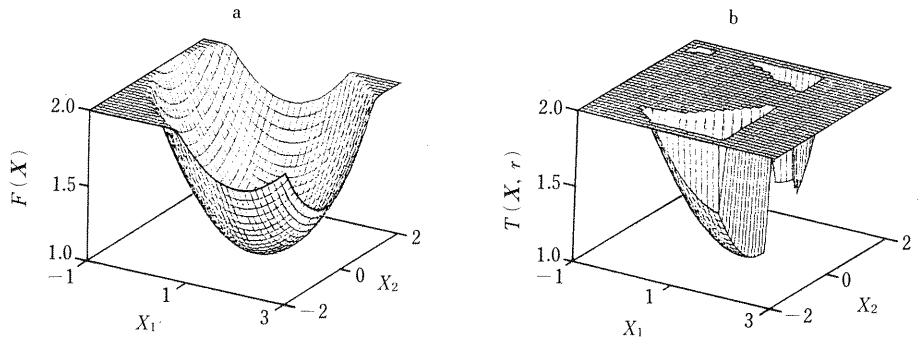

Fig. 2. Three-Dimensional Diagrams for the Objective Function, $F(\boldsymbol{X})$, and Transformed Objective Function, $T(\boldsymbol{X}, r)$, Derived from Eqs. 6, 7 and 8 as a Function of X_1 and X_2 at Constant Value of X_3 ($X_3=-1.35$)

a, $F(\boldsymbol{X})$; b, $T(\boldsymbol{X}, r)$ at $r=10^{-8}$.

of $T(\boldsymbol{X}, r)$ is gradually sharpened and the minimum points of $T(\boldsymbol{X}, r)$ sequentially approach the accurate solution of the optimization problem with decreasing r values. The optimum solution is obtained as the point, $\boldsymbol{X}(r)$, which gives the minimum value of $T(\boldsymbol{X}, r)$ when the value of r is sufficiently close to zero.

In a practical situation, however, it is rather difficult to insure that a global optimum is really obtained by the hasty application of general optimization techniques. In order to explain this, the optimization problem of IMC solid dispersions reported previously[8] is introduced here as an example:

$$F(\boldsymbol{X})=1.18-0.393X_1-0.172X_2-0.107X_3+0.199X_1^2+0.190X_2^2+0.0452X_3^2+0.126X_1X_2+0.121X_1X_3 \quad (6)$$

$$G_1(\boldsymbol{X})=-1.74-0.270X_2+0.158X_3+0.553X_1^2+0.543X_2^2+0.446X_3^2\geqq 0 \quad (7)$$

$$G_2(\boldsymbol{X})=-3.70-2.36X_1+1.87X_1^2+2.20X_2^2+1.34X_3^2-1.38X_1X_2\geqq 0 \quad (8)$$

where Eq. 6 is the objective function to minimize, and Eqs. 7 and 8 are inequality constraints. The physical meanings of these equations and factors X_1, X_2, and X_3 have been described previously.[8] Figure 2 shows three-dimensional diagrams for the objective function (Eq. 6) with and without constraints (Eqs. 7 and 8) as a function of X_1 and X_2 at a constant value of X_3 ($X_3=-1.35$). As is obvious from Fig. 2, some local minima exist within the search region for the optimum solution. This means that different starting points may lead to different optimum solutions, because a set of $\boldsymbol{X}$ vectors in the response surface is required as a starting point to apply the general optimization methods. Thus, it is difficult to insure that a global optimum is obtained, even though the optimization has been performed several times at different starting points in the response surface. In order to find a solution to this problem, we investigated an application of random number techniques, that is, a Monte Carlo approach.[15] First, a large number of search points (sets of $\boldsymbol{X}$ vectors) in the response surface is generated by means of an arithmetic random number.

Next, the values of $T(\boldsymbol{X}, r)$ obtained at these search points are compared with one another and 10 sets of $\boldsymbol{X}$ vectors are taken from the generated search points in the order of smaller $T(\boldsymbol{X}, r)$ values. When sufficient search points are generated in the response surface, several points taken in the order of smaller $T(\boldsymbol{X}, r)$ values may be located near the global minimum. This means that these points could be located very close to each other in a multi-dimensional space. The following equation reported by Andrews[16] can be applied to the geometrical mapping of the multi-dimensional distances among the search points into a two-dimensional graph:

$$A(\boldsymbol{X}, t) = X_1/\sqrt{2} + X_2\sin(t) + X_3\cos(t) + X_4\sin(2t) + X_5\cos(2t) + \cdots \quad (9)$$

According to Eq. 9, a set of $\boldsymbol{X}$ vectors in the multi-dimensional space is expressed as the Andrews' curve in the two-dimensional graph when the t values change from $-\pi$ to π. Figure 3 shows the Andrews' curves for 10 sets of search points taken in the order of smaller $T(\boldsymbol{X}, r)$ values in the optimization problem described by Eqs. 6—8. When the number of search points in the response surface is relatively small (the number of trials = 1000), the Andrews' curves are divided into several clusters, indicating that several local minima may exist in the transformed objective function. The Andrews' curves converge into a singular cluster when the number of search points increases sufficiently (the number of trials = 5000). The $\boldsymbol{X}$ vectors which belong to the singular cluster must be located near the global optimum solution in the response surface. By generating search points until the Andrews' curves converge into the singular cluster, we can rationally choose the starting point (a set of $\boldsymbol{X}$ vectors) in the response surface before the application of general optimization procedures. Thus, the global optimum solution in the pharmaceutical optimization problem can be obtained by means of the combined use of random number techniques, Andrews' plots, and general optimization procedures.

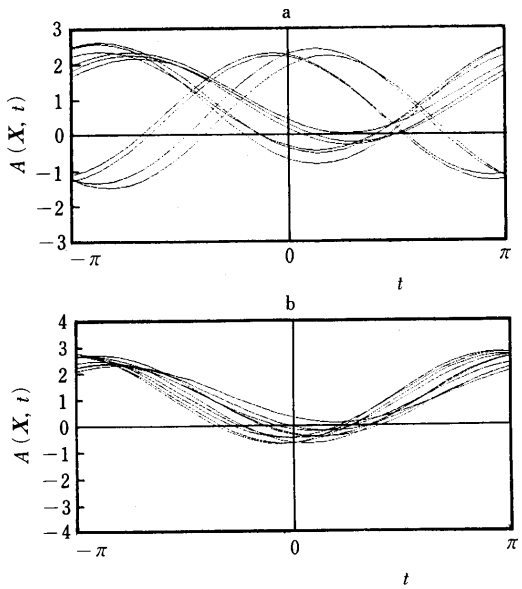

Fig. 3. Andrews' Plots for Ten Sets of Search Points Taken in the Order of Smaller Transformed Objective Function, $T(\boldsymbol{X}, r)$, Derived from Eqs. 6, 7 and 8

a, Number of trials = 1000; b, number of trials = 5000.

Experimental

Materials IMC was purchased from Sigma Chemical Co., Ltd. Polyvinylpyrrolidone K-90 (PVP) of extra pure reagent grade were purchased from Tokyo Kasei Industrial Co., Ltd. Carboxyvinylpolymer (CP) marketed as "HIVISWAKO 105" was supplied by Wako Pure Chemical Industries, Ltd. Other chemicals were of reagent grade.

Preparation of Sustained-Release Formulation The preparation method for sustained-release powders of IMC is shown in Chart 1. The amounts of PVP (X_1) and CP (X_2) were selected as formulation factors. The addition rate of PVP solution (X_3) into the IMC suspended CP solution was selected as a process factor. The composite spherical experimental design[17] for three factors was applied to prepare the model formulations. The experiments listed in Table I in coded form were transformed to the physical units as summarized in Table II. Sustained release granules were also prepared using the powder formulations described above. Flat-faced tablets of 150 mg weight and 13 mm diameter were made by compressing the given amount of powder formulations directly under 150 kg/cm^2 using a Shimadzu hydraulic press for KBr tablets for IR spectroscopy. Tablets were ground gently in a mortar and sieved. Crushed samples, passing through a No. 12 mesh (1410 μm) and remaining on a No. 18 mesh (850 μm), were taken as a sustained-release granule formulation of IMC.

IMC 200 mg
(1) disperse in CP solution (400 ml)
(2) add PVP solution (40 ml) to IMC suspended CP solution
(3) stir IMC suspended CP solution for 1 h
(4) filtrate the precipitate with a filter paper
(5) dry in vacuum at 50 °C for 24 h
(6) grind in a mortar
(7) sieve (100—200 mesh)
sample

Chart 1. Method for Sample Powder Preparation

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	−1	−1	1
6	1	−1	1
7	−1	1	1
8	1	1	1
9	$-\sqrt{3}$	0	0
10	$\sqrt{3}$	0	0
11	0	$-\sqrt{3}$	0
12	0	$\sqrt{3}$	0
13	0	0	$-\sqrt{3}$
14	0	0	$\sqrt{3}$
15	0	0	0

TABLE II. Levels of Factors in Physical Units

Factor	Factor level in coded form				
	$-\sqrt{3}$	−1	0	1	$\sqrt{3}$
X_1[a] (%)	1.13	1.50	2.00	2.50	2.87
X_2[b] (%)	0.0600	0.0875	0.125	0.163	0.190
X_3[c] (ml/min)	2.3	3.0	4.0	5.0	5.7

a) Concentration of PVP solution. *b*) Concentration of CP solution. *c*) Addition rate of PVP solution to IMC suspended CP solution.

Determination of Response Variables The response variables measured on the model formulations were: Y_1, 50% release time ($t_{50\%}$) of IMC from powders; Y_2, $t_{50\%}$ of IMC from granules; Y_3, moisture uptake of powders; Y_4, IMC content of powders; and Y_5, sample recovery. Each response variable was represented as the mean of three determinations. Dissolution profiles of IMC from samples were determined by employing a paddle method. The procedure and apparatus described in dissolution test No. 2 (paddle method) in JP XI were applied. A certain amount of sample powder or granules containing 25 mg of IMC was weighed accurately and dispersed in 500 ml of disintegration medium No. 2 (pH 6.8) in JP XI at 37°C at a paddle rotation speed of 50 rpm. At appropriate intervals, 5 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 an ultraviolet absorption method. The amount of moisture absorbed by the sample powders was determined as follows. The sample powders were first dried in vacuum at 50°C for 24 h. Each sample powder (200 mg) was weighed accurately, and placed in a small beaker (20 ml) and stored at 40°C under 75% relative humidity (R.H.). The amount of moisture uptake by the sample powders was determined gravimetrically as the difference between the initial weight of powders and the weight after storing them for 30 d at 40°C under 75% R. H. The content of IMC in the sample powders was determined by an ultraviolet absorption method. A mixture (1 : 1) of 1/15 M phosphate buffer (pH 7.2) and methanol was used as the solvent for extracting IMC from sample powders. The sample recovery was determined from the difference between the initial total weight of raw materials and the weight of final products.

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

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1^2 + b_5X_2^2 + b_6X_3^2 + b_7X_1X_2 + b_8X_1X_3 + b_9X_2X_3 \quad (10)$$

where Y is the response variable, b_i is the regression coefficient, and X_i is the factor level in coded form. The optimum regression equation was obtained by investigating the overall combination of factors at the point of statistical significance. 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, was used as an index for the selection of the optimum combination of factors.[18]

Computer Programs The following computer programs, all written by the authors, were used in this study on an NEC PC-9800 series personal computer. ALCORA was the program for multiple regression analysis involving selection of the best combination of factors. THREED was for the three-dimensional graph which allowed a visual understanding of the regression equations. NOPCON was the constrained nonlinear optimization program in which the simplex method[19] was incorporated, involving random number techniques and Andrews' plots. NOPCON, written in BASIC programming language, and its operating procedure are explained in the Appendix.

Results and Discussion

In the previous study,[13] interpolymer complex formation of PVP with CP was investigated with a view to its application to the control of drug release. The drug release from a tablet which consisted of a blend of PVP with CP was markedly affected by the complex formation following water penetration into the matrix. In the present study, the mathematical optimization methodology described in the theoretical section was applied to the optimization of a sustained-release formulation of IMC based on the interpolymer complex formation of PVP with CP. As a suitable index for the release properties of IMC from the powder samples, Wagner's dissolution model[20] was applied to the experimental data and 50% release times ($t_{50\%}$) were calculated. On the other hand, the release profiles of IMC from granule samples were found to be a linear function of time up to approximately 70% released. In this case, $t_{50\%}$ of granule formulations was calculated from the linear regression between the released amount of IMC and time.

Regression Analysis The release characteristics of each sample are listed in Table III with physical parameters such as moisture uptake, IMC content and sample recovery. A large deviation was observed among values of each response variable except moisture uptake, indicating that the change of factor levels significantly affected important characteristics of these formulations. The moisture uptake of sample powders was compared with those of PVP alone, CP alone and PVP/CP (1 : 1) physical mixture. The value of each sample powder was found to be very low (3.3—5.6%) when compared with those of PVP (28.9%), CP (17.7%) and the mixture (22.9%). Therefore, the application of PVP/CP complex to the sustained-release formulations seems to be effective for preventing quality deterioration following the moisture absorption of formulations.

Optimum regression equations obtained are summarized in Table IV. The response variables such as the $t_{50\%}$ of powders, the IMC content and sample recovery were predicted accurately by the second-order polynomial equation, because values of multiple correlation coefficients were satisfactory and the regression equations were sig-

Table III. Experimental Values of Response Variables

Formulation	Y_1[a] (min)	Y_2[b] (min)	Y_3[c] (%)	Y_4[d] (%)	Y_5[e] (%)
1	8.24	89.9	3.98	28.2	62.0
2	23.3	165.8	4.23	24.1	50.6
3	17.6	69.1	3.80	17.7	67.2
4	45.9	99.3	3.26	17.1	62.7
5	10.5	139.8	3.77	26.6	64.2
6	55.6	129.5	3.39	26.9	47.7
7	3.11	45.8	3.95	17.7	74.5
8	57.2	153.3	3.88	15.8	67.6
9	12.0	74.0	3.45	23.8	64.3
10	61.4	121.6	5.58	20.6	54.5
11	0.901	41.3	4.58	31.8	38.8
12	21.9	74.2	5.15	13.9	62.9
13	32.9	133.2	5.08	20.0	67.2
14	21.2	127.7	4.75	20.0	66.1
15	33.5	97.1	3.91	19.3	64.9

a) $t_{50\%}$ of powders. b) $t_{50\%}$ of granules. c) Moisture uptake. d) IMC content. e) Sample recovery.

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

Coefficient	Regression coefficient value				
	Y_1 (min)	Y_2 (min)	Y_3 (%)	Y_4 (%)	Y_5 (%)
b_0	36.8	104	4.18	19.8	67.4
b_1 (X_1)	16.3	20.4	0.211	−0.846	−4.02
b_2 (X_2)	4.47	—[a]	—	−4.89	6.37
b_3 (X_3)	—	—	—	—	—
b_4 (X_1^2)	—	—	—	0.822	−2.00
b_5 (X_2^2)	−7.88	−12.2	—	1.04	−4.85
b_6 (X_3^2)	−2.66	12.1	—	—	—
b_7 (X_1X_2)	2.78	—	—	—	2.06
b_8 (X_1X_3)	6.98	—	—	0.388	—
b_9 (X_2X_3)	−4.72	—	—	—	1.61
r[b]	0.973	0.736	0.303	0.991	0.964
s[c]	6.58	29.2	0.688	0.838	3.26
F_o[d]	17.5[e]	4.35[f]	1.31	103[e]	17.3[e]

a) This factor is not included in the optimum regression equation. b) Multiple correlation coefficient. c) Standard deviation. d) Observed F value. e) $p<0.01$. f) $p<0.05$.

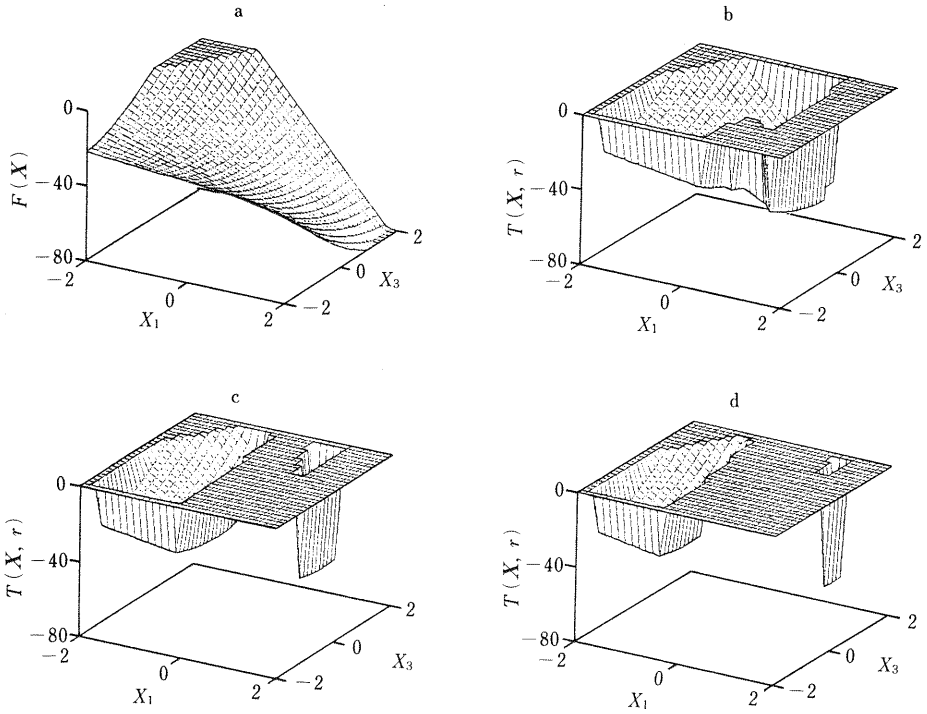

Fig. 4. Three-Dimensional Diagrams for the Objective Function, $F(\boldsymbol{X})$, and Transformed Objective Function, $T(\boldsymbol{X}, r)$, Derived from Eqs. 11, 12 and 13 as a Function of X_1 and X_3 at Various Values of X_2

a, $F(\boldsymbol{X})$ at $X_2=0$; b, $T(\boldsymbol{X}, r)$ at $X_2=-0.1$ and $r=10^{-8}$; c, $T(\boldsymbol{X}, r)$ at $X_2=0$ and $r=10^{-8}$; d, $T(\boldsymbol{X}, r)$ at $X_2=0.1$ and $r=10^{-8}$.

nificant, with high F_0 values. On the other hand, the predictability of $t_{50\%}$ of granules was rather poor and the moisture uptake was almost impossible to predict with the second-order polynomial equation. The process required for preparing granules might be the main reason for the poor predictability of $t_{50\%}$ of granules. In the case of moisture uptake, a small deviation among the observed values was considered to be the reason why this response variable was not predictable.

Mathematical Optimization The optimization of the sustained-release formulation of IMC was performed following the mathematical methodology stated in the theoretical section. The purpose of the optimization is to find a formulation giving sustained release of IMC and with acceptable values for the other characteristics. Thus, the regression equations of each response variable listed in Table IV were assembled as a constrained nonlinear optimization problem. However, the regression equations of $t_{50\%}$ of granules and moisture uptake were excluded because of their low predictabilities. Mathematically, this constrained nonlinear optimization problem can be described as follows:

$$F(\boldsymbol{X}) = -Y_1 \cdots \text{ to maximize } t_{50\%} \text{ of powders} \quad (11)$$

$$G_1(\boldsymbol{X}) = Y_4 - 20 \geqq 0 \cdots \text{ IMC content} \geqq 20\% \quad (12)$$

$$G_2(\boldsymbol{X}) = Y_5 - 60 \geqq 0 \cdots \text{ sample recovery} \geqq 60\% \quad (13)$$

where to minimize the objective function, $F(\boldsymbol{X})$, means to maximize $t_{50\%}$ of powders. The restricting values in equations 12 and 13 were selected according to the trade-off analysis in the same way as reported by Franz *et al.*[11] The set of constraints used in this study seems to be quite proper and significant, though these restricting values can be altered at the formulator's request. Constraints,

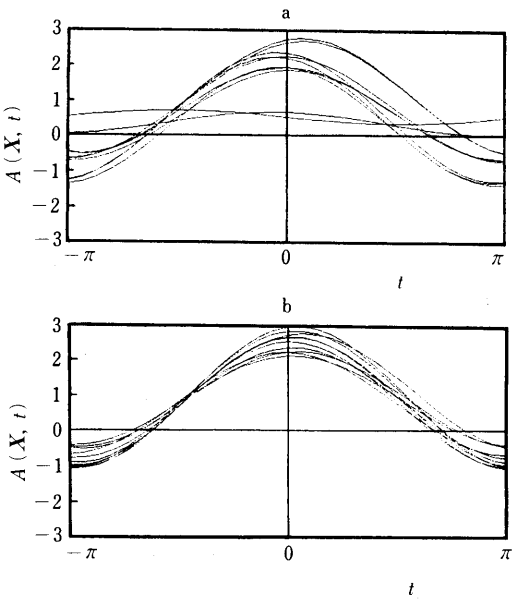

Fig. 5. Andrews' Plots for Ten Sets of Search Points Taken in the Order of Smaller Transformed Objective Function, $T(\boldsymbol{X}, r)$, Derived from Eqs. 11, 12 and 13

a, Number of trials = 1000; b, number of trials = 5000.

$-\sqrt{3} \leqq X_i \leqq \sqrt{3}$ $(i=1, 2, 3)$, were also employed to keep the values of X_1, X_2 and X_3 in the experimental region.

Figure 4 shows the three-dimensional diagrams for the objective function (Eq. 11) with and without constraints (Eqs. 12 and 13) as a function of X_1 and X_3 at various values of X_2. Although the three-dimensional diagram for the transformed objective function, $T(\boldsymbol{X}, r)$, was found to have a gently curved surface when the value of X_2 was -0.1, the surface abruptly changed to a complex shape when the

values of X_2 increased from -0.1 to 0.1. These results indicate that the three-dimensional graphical approach might not be helpful for selecting the starting point which is required to seek a global optimum by the application of general optimization procedures. Rational methods described in the theoretical section were applied to obtain proper and suitable starting points in this optimization problem. As shown in Fig. 5, the Andrews' curves were divided into several clusters when the number of search points was relatively small. However, these curves ultimately converged into a singular cluster when a sufficiently large number of search points was generated in the response surface. Thus, the optimization of the sustained release formulation of IMC was performed at the reasonable starting point obtained above, using the simplex method included in the NOPCON computer program. The time required for these calculations was approximately 20 min. As the optimum powder formulation, $X_1=1.55$, $X_2=0.337$, and $X_3=1.73$ were obtained in coded forms. These values were transformed to physical units and the following results were obtained: 2.77% as the concentration of PVP, 0.138% as the concentration of CP and 5.7 ml/min as the addition rate of PVP solution to IMC suspended CP solution. The predicted values of response variables coincided well with the experimental data as summarized in Table V. Figure 6 shows release profiles of IMC from granules prepared from the optimum formulation. The release rate of IMC was significantly affected by the granule size and the value of $t_{50\%}$ was found to be a linear function of the mean diameter of granules, as shown in Fig. 7.

Based on the above considerations, the optimization of the sustained-release formulation of IMC could reasonably be performed by application of the optimization method developed in this study. This sort of method, including random number techniques and Andrews' plots, should be applicable to solving this relatively complex problem, since it would be difficult to analyze the effects of many factors independently in pharmaceutical formulations.

TABLE V. Response Variables of the Optimum Formulation

Response	Predicted	Experimental[a]
Y_1: $t_{50\%}$ of powders (h)	1.20	1.04±0.08
Y_2: $t_{50\%}$ of granules (h)	—	2.58±0.19
Y_3: Moisture uptake (%)	—	5.11±0.15
Y_4: IMC content (%)	20.0	19.3 ±0.4
Y_5: Sample recovery (%)	60.0	59.0 ±0.5

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

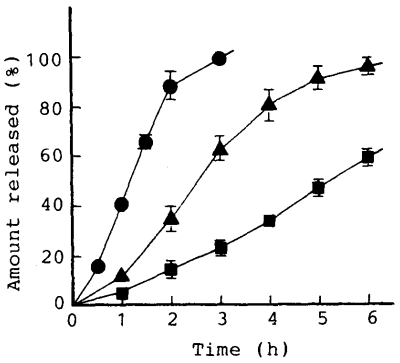

Fig. 6. Release Profiles of IMC from Granules Prepared by the Optimum Formulation

Granule diameters: ●, 0.81±0.26 mm; ▲, 1.59±0.31 mm; ■, 2.70±0.70 mm. Granule diameters are the mean±S.D. of two hundred measurements. Release data are the mean±S.D. of three determinations.

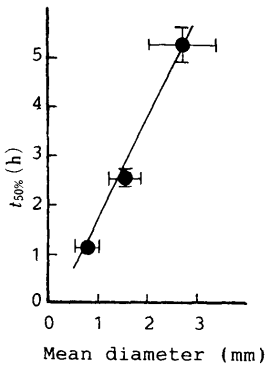

Fig. 7. Effect of Granule Diameter on the 50% Release Time, $t_{50\%}$, in the Optimum Formulation

Granule diameters are the mean±S.D. of two hundred measurements. $t_{50\%}$ values are the mean±S.D. of three determinations.

Appendix

The computer program NOPCON, which is written in BASIC programming language with the double precision mode, is listed in Table VI. The simplex method introduced by Nelder and Mead[19] was used as the optimization algorithm. A part of the Andrews' plot in NOPCON was written referring the statistical program package which was made by Wakiyama *et al.*[21] Before the execution of NOPCON, the objective

TABLE VI. Program List of NOPCON in BASIC Programming Language

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10 REM************************************************************
20 REM CONSTRAINED NONLINEAR OPTIMIZATION TECHNIQUE [NOPCON]
30 REM************************************************************
40 REM
50 REM F...OBJECTIVE FUNCTION
60 REM G,H...INEQUALITY AND EQUALITY CONSTRAINTS
70 REM T...TRANSFORMED FUNCTION
80 DEFDBL A-H,P-X
90 CONSOLE 0,25,0,1:CLS 3:SCREEN 0:BEEP:COLOR 7,0
100 TAU=.000001#:ESP=.000001#:A0=1:B0=.5:G0=2:STP=0:1C=0:1D=0
110 REM DATA INPUT
120 COLOR 6
130 PRINT"CONSTRAINED NONLINEAR OPTIMIZATION TECHNIQUE [NOPCON]"
140 COLOR 7:PRINT
150 PRINT"DEFINE OBJECTIVE FUNCTION (F) FOR MINIMIZATION ....10000"
160 PRINT"DEFINE INEQUALITY CONSTRAINTS (G(I)) >=  0      ....20000"
170 PRINT"DEFINE EQUALITY CONSTRAINTS   (H(I))  =  0      ....30000"
171 REM INPUT"OK (Y/N) ";A$
172 REM IF A$="N" OR A$="n" THEN CLS 3:LIST 10000-
180 PRINT
190 INPUT"TITLE FOR THE OPTIMIZATION PROBLEM  ";TL$
200 INPUT"HOW MANY INEQUALITY CONSTRAINTS     ";GN
210 INPUT"HOW MANY EQUALITY CONSTRAINTS       ";HN
220 INPUT"HOW MANY FACTORS FOR OPTIMIZATION   ";M
230 DIM XX(10,11),X(10),XS(10),FF(11),G(20),H(20)
240 DIM XA(10,10),FA(10),XL(10),XH(10),XLARGE(10),XSMALL(10)
250 BEEP:PRINT
260 INPUT"INITIAL SIZE OF SIMPLEX (0.1-1)     ";S0
270 INPUT"INITIAL SIZE OF R (0.001-0.1)       ";R0:PRINT
280 BEEP:PRINT"RANDOM SAMPLING FOR INITIAL X (Y/N) ";:INPUT A$
290 IF A$="Y" OR A$="y" THEN GOTO 1940
300 BEEP:PRINT:FOR I=1 TO M
310 PRINT"INITIAL VALUE OF X(";I;")= ";:INPUT X(I)
320 XX(I,1)=X(I):NEXT I
330 LPRINT TL$:LPRINT
340 LPRINT"INITIAL"
350 FOR I=1 TO M:IF I>4 AND ((I-1) MOD 4)=0 THEN LPRINT
360 LPRINT USING"X(###)=#########.########     ";I;X(I);
370 NEXT I:LPRINT
380 LPRINT USING"S0=    ########.########";S0
390 LPRINT USING"R0=    ########.########";R0
400 LPRINT
410 TIME$="00:00:00":CLS:COLOR 6:PRINT"INITIAL"
420 FOR I=1 TO M:PRINT USING"X(###)=#######.########";I;X(I)
430 NEXT I:COLOR 7
440 PM=S0*(SQR(M+1)-1+M)/M/SQR(2):QM=S0*(SQR(M+1)-1)/M/SQR(2)
450 FOR J=2 TO M+1:FOR I=1 TO M
460 IF I+1=J THEN XX(I,J)=XX(I,1)+PM:GOTO 480
470 XX(I,J)=XX(I,J)+QM
480 NEXT I
490 NEXT J
500 REM F(NH),FF(NS),FF(NL),FF(0)
510 FOR J=1 TO M+1
```

TABLE VI. (continued)

```
520 FOR I=1 TO M:X(I)=XX(I,J):NEXT I
530 GOSUB 1710
540 FF(J)=F
550 NEXT J
560 REM MAXIMUM & MINIMUM
570 FXH=FF(1):FXL=FF(1):NH=1:NL=1
580 FOR J=1 TO M+1
590 IF FF(J)>FXH THEN FXH=FF(J):NH=J
600 IF FF(J)<FXL THEN FXL=FF(J):NL=J
610 NEXT J
620 REM SECOND MAXIMUM
630 FXS=FF(1):NS=1
640 FOR J=1 TO M+1
650 IF J=NH THEN 670
660 IF FF(J)>FXS THEN FXS=FF(J):NS=J
670 NEXT J
680 REM CENTER
690 FOR I=1 TO M
700 XCT=0
710 FOR J=1 TO M+1
720 IF J=NH THEN 740
730 XCT=XCT+XX(I,J)
740 NEXT J
750 XX(I,0)=XCT/M:X(I)=XX(I,0)
760 NEXT I
770 GOSUB 1710
780 FF(0)=F
790 IF ID=24 THEN ID=0
800 LOCATE 30,ID
810 PRINT       "************************"
820 ID=ID+1:LOCATE 30,ID
830 PRINT USING"T(MAX)=########.########";FF(NH)
840 ID=ID+1:LOCATE 30,ID
850 PRINT USING"T(2ND)=########.########";FF(NS)
860 ID=ID+1:LOCATE 30,ID
870 PRINT USING"T(MIN)=########.########";FF(NL)
880 ID=ID+1:LOCATE 30,ID
890 PRINT USING"T(CNT)=########.########";FF(0)
900 REM CONVERGENCE OF SIMPLEX
910 SS=0
920 FOR I=1 TO M
930 SS=SS+(FF(I)-FF(0))^2
940 NEXT I
950 SS=SQR(SS/M)
960 ID=ID+1:LOCATE 30,ID
970 PRINT USING"SS(T) =########.########";SS:ID=ID+1
980 IF SS<=TAU THEN GOTO 1330
990 REM****************************************
1000 REM REFLECTION
1010 FOR I=1 TO M:X(I)=(1+A0)*XX(I,0)-A0*XX(I,NH):NEXT I
1020 GOSUB 1710
1030 FR=F
1040 IF FR<=FF(NS) THEN 1060
1050 GOTO 1190
1060 IF FR<FF(NL) THEN 1090
1070 FOR I=1 TO M:XX(I,NH)=X(I):NEXT I:FF(NH)=FR
1080 GOTO 560
1090 REM EXPANSION
1100 FOR I=1 TO M:XS(I)=X(I):NEXT I
1110 FOR I=1 TO M:X(I)=G0*XS(I)+(1-G0)*XX(I,0):NEXT I
1120 GOSUB 1710
1130 FE=F
1140 IF FE<FR THEN 1170
1150 FOR I=1 TO M:XX(I,NH)=XS(I):NEXT I:FF(NH)=FR
1160 GOTO 560
1170 FOR I=1 TO M:XX(I,NH)=X(I):NEXT I:FF(NH)=FE
1180 GOTO 560
1190 IF FR<FF(NH) THEN 1210
1200 GOTO 1220
1210 FOR I=1 TO M:XX(I,NH)=X(I):NEXT I
1220 REM CONTRACTION
1230 FOR I=1 TO M:X(I)=B0*XX(I,NH)+(1-B0)*XX(I,0):NEXT I
1240 GOSUB 1710
1250 FC=F
1260 IF FC<FF(NH) THEN 1310
1270 FOR J=1 TO M+1
1280 FOR I=1 TO M:XX(I,J)=(XX(I,J)+XX(I,NL))/2:NEXT I
1290 NEXT J
1300 GOTO 500
1310 FOR I=1 TO M:XX(I,NH)=X(I):NEXT I:FF(NH)=FC
1320 GOTO 560
1330 GOSUB 1710:FO=F:STP=STP+1
1340 COLOR 6:BEEP:CLS
1350 REM PRINT OUT TO DISPLAY
1360 PRINT USING"STEP###";STP
1370 FOR I=1 TO M
1380 PRINT USING"X(###)=#######.########";I;XX(I,NL)
1390 NEXT I
1400 PRINT USING"F(MIN)=#######.########";FO
1410 PRINT USING"T(X,R)=#######.########";FF(NL)
1420 REM CONVERGENCE OF T(X,R)
1430 CVT=ABS(FP-FF(NL))
1440 PRINT USING"DEF(T)=#######.########";CVT
1450 REM PRINT OUT TO PRINTER
1460 LPRINT USING"STEP###";STP
1470 FOR I=1 TO M
1480 IF I>4 AND ((I-1) MOD 4)=0 THEN LPRINT
1490 LPRINT USING"X(###)=########.########      ";I;XX(I,NL);
1500 NEXT I:LPRINT
1510 IF GN=0 THEN 1560
1520 FOR I=1 TO GN
1530 IF I>4 AND ((I-1) MOD 4)=0 THEN LPRINT
1540 LPRINT USING"G(###)=########.########      ";I;G(I);
1550 NEXT I:LPRINT
1560 IF HN=0 THEN 1610
1570 FOR I=1 TO HN
1580 IF I>4 AND ((I-1) MOD 4)=0 THEN LPRINT
1590 LPRINT USING"H(###)=########.########      ";I;H(I);
1600 NEXT I:LPRINT
1610 LPRINT USING"F(MIN)=########.########";FO
1620 LPRINT USING"T(X,R)=########.########";FF(NL)
1630 LPRINT
1640 IF CVT=<ESP AND STP>1 THEN LPRINT CHR$(&HC):COLOR 7:GOTO 1710
```

TABLE VI. (continued)

```
1650 COLOR 7
1660 FP=FF(NL)
1670 FOR I=1 TO M:X(I)=XX(I,NL):NEXT I
1680 R0=R0/10:S0=S0/10:ID=0
1690 GOTO 440
1700 REM COMPUTATION OF T(X,R)
1710 COLOR 4
1720 IC=IC+1:LOCATE 62,0:PRINT USING"CALL= ##########";IC
1730 LOCATE 62,1:PRINT"TIME=    ";TIME$
1740 IF CVT<=ESP AND STP>1 THEN COLOR 7:LOCATE 0,M+4:END
1750 COLOR 7
1760 GOSUB 10000:REM OBJECTIVE FUNCTION
1770 G=0:H=0
1780 IF SS<=TAU THEN RETURN
1790 IF GN=0 THEN G=0:GOTO 1860
1800 GOSUB 20000:REM INEQUALITY CONSTRAINTS
1810 FOR I=1 TO GN
1820 IF G(I)>=0 THEN 1840
1830 G=G+G(I)^2
1840 NEXT I
1850 G=G/R0
1860 IF HN=0 THEN H=0:GOTO 1920
1870 GOSUB 30000:REM EQUALITY CONSTRAINTS
1880 FOR I=1 TO HN
1890 H=H+H(I)^2
1900 NEXT I
1910 H=H/R0
1920 F=F+G+H
1930 RETURN
1940 REM INITIAL VALUE OF X (RANDOM SAMPLING METHOD)
1950 INPUT"RANDOM SAMPLING NUMBER (>=1000)     ";RN
1952 INPUT"RANDOM NUMBER SEED                  ";RS
1954 RANDOMIZE RS
1960 BEEP:PRINT:RN2=0
1970 FOR I=1 TO M
1980 PRINT"LOWER LIMIT OF X(";I;")= ";:INPUT XL(I)
1990 PRINT"UPPER LIMIT OF X(";I;")= ";:INPUT XH(I)
2000 NEXT I
2010 CLS 3:SCREEN 0:BEEP:TIME$="00:00:00"
2020 FOR J=1+RN2 TO RN+RN2
2030 COLOR 4
2040 LOCATE 40,0:PRINT USING"CALL= ########";J
2050 LOCATE 40,1:PRINT       "TIME= ";TIME$
2060 FOR I=1 TO M
2070 X(I)=XL(I)+(XH(I)-XL(I))*RND
2080 NEXT I
2090 GOSUB 10000:REM OBJECTIVE FUNCTION
2100 G=0:H=0
2110 IF GN=0 THEN G=0:GOTO 2180
2120 GOSUB 20000:REM INEQUALITY CONSTRAINTS
2130 FOR I=1 TO GN
2140 IF G(I)>=0 THEN 2160
2150 G=G+G(I)^2
2160 NEXT I
2170 G=G/R0
2180 IF HN=0 THEN H=0:GOTO 2240
2190 GOSUB 30000:REM EQUALITY CONSTRAINTS
2200 FOR I=1 TO HN
2210 H=H+H(I)^2
2220 NEXT I
2230 H=H/R0
2240 F=F+G+H
2250 IE=0:COLOR 6
2260 FOR I=1 TO M
2270 LOCATE 0,IE
2280 PRINT USING"X(###)=########.########";I,X(I):IE=IE+1
2290 NEXT I
2300 LOCATE 0,IE:PRINT USING"T(X,R)=########.########";F
2310 IF J>9 THEN 2330
2320 FA(J)=F:FOR I=1 TO M:XA(J,I)=X(I):NEXT I:GOTO 2360
2330 IF J=10 THEN 2350
2340 IF F>=FA(10) THEN 2360
2350 FA(10)=F:FOR I=1 TO M:XA(10,I)=X(I):NEXT I:GOSUB 2460
2360 NEXT J
2370 RN2=RN2+RN
2380 GOSUB 2550:REM ANDREWS' PLOT
2390 REM GOSUB 3240:REM PRINT OUT
2400 BEEP:COLOR 7:LOCATE 0,22
2410 INPUT"  RANDOM SAMPLING, AGAIN (Y/N) ";A$
2420 IF A$="N" OR A$="n" THEN 2430
2422 INPUT"  RANDOM SAMPLING SEED          ";RS
2424 RANDOMIZE RS:GOTO 2010
2430 FOR I=1 TO M:X(I)=XA(1,I):XX(I,1)=XA(1,I):NEXT I
2440 CLS 3:SCREEN 0:GOTO 330
2450 REM
2460 REM SORTING
2470 FOR K=1 TO 9:FOR L=K TO 9
2480 IF FA(K)<=FA(L+1) THEN 2530
2490 SWAP FA(K),FA(L+1)
2500 FOR I=1 TO M
2510 SWAP XA(K,I),XA(L+1,I)
2520 NEXT I
2530 NEXT L,K
2540 RETURN
2550 REM ANDREWS' PLOT
2560 BEEP:CLS 3:COLOR 7:PI=3.14159#:R2=SQR(2):ND=30
2570 DV=2*PI/ND
2580 FOR J=1 TO M
2590 XLARGE(J)=XA(1,J):XSMALL(J)=XA(1,J)
2600 FOR I=2 TO 10
2610 IF XA(I,J)>XLARGE(J) THEN XLARGE(J)=XA(I,J)
2620 IF XA(I,J)<XSMALL(J) THEN XSMALL(J)=XA(I,J)
2630 NEXT I,J
2640 REM
2650 YY=0
2660 FOR I=1 TO 10:YS=0
2670 FOR J=1 TO M:YS=YS+ABS(XA(I,J)):NEXT J
2680 IF YS>YY THEN YY=YS
2690 NEXT I
2700 YU=INT(YS+.9):YL=-YU
2710 REM
2720 K0=10:K1=629:L0=40:L1=339
2730 P0=-3.2:Q0=YL:P1=3.2:Q1=YU
```

TABLE VI. (continued)

```
2740 K2=K1-K0:L2=L1-L0:P1=P1-P0:Q1=Q1-Q0
2750 K3=K0:L3=L1:P2=P0:Q2=Q0
2760 REM
2770 SCREEN 3:LC=7
2780 WINDOW (K0,L0)-(K1,L1)
2790 VIEW (K0,L0)-(K1,L1)
2800 REM
2810 PX=-PI:PY=YU:GOSUB 3060:PX=PI:PY=YU:GOSUB 3100
2820 PX=-PI:PY=0:GOSUB 3060:PX=PI:PY=0:GOSUB 3100
2830 PX=-PI:PY=YL:GOSUB 3060:PX=PI:PY=YL:GOSUB 3100
2840 FOR IPY=YL TO YU:PY=IPY
2850 PX=-PI:GOSUB 3060:PX=-PI+.1:GOSUB 3100
2860 NEXT IPY
2870 PX=-PI:PY=YL:GOSUB 3060:PX=-PI:PY=YU:GOSUB 3100
2880 PX=0:PY=YL:GOSUB 3060:PX=0:PY=YU:GOSUB 3100
2890 PX=PI:PY=YL:GOSUB 3060:PX=PI:PY=YU:GOSUB 3100
2900 PRINT"  X-AXIS: (-3.14 , 3.14)";
2910 PRINT USING"              RANDOM SAMPLING NUMBER: ######";RN2
2920 PRINT USING"  Y-AXIS: ( #### , ####)";YL;YU;
2925 PRINT USING"              RANDOM NUMBER SEED:     ######";RS
2930 REM
2940 FOR I=1 TO 10
2950 IF I=1 THEN LC=2:GOTO 2960
2952 IF I=2 THEN LC=4:GOTO 2960
2954 IF I=3 THEN LC=1:GOTO 2960
2956 LC=6
2960 FOR L=0 TO ND
2970 PX=L*DV-PI:PY=XA(I,1)/R2
2980 FOR J=2 TO M
2990 K=INT(J/2):W=PX*K
3000 IF (J MOD 2)=1 THEN W=COS(W) ELSE W=SIN(W)
3010 PY=PY+XA(I,J)*W
3020 NEXT J
3030 IF L=0 THEN GOSUB 3060 ELSE GOSUB 3100
3040 NEXT L,I
3050 RETURN
3060 REM
3070 GOSUB 3150
3080 K3=K4:L3=L4
3090 RETURN
3100 REM
3110 GOSUB 3150
3120 LINE(K3,L3)-(K4,L4),LC
3130 K3=K4:L3=L4
3140 RETURN
3150 REM
3160 K4=INT((PX-P0)/P1*K2+.5)+K0
3170 L4=L1-INT((PY-Q0)/Q1*L2+.5)
3180 IF K4>K1 THEN K4=K1
3190 IF K4<K0 THEN K4=K0
3200 IF L4>L1 THEN L4=L1
3210 IF L4<L0 THEN L4=L0
3220 P2=PX:Q2=PY
3230 RETURN
3240 REM PRINT OUT OF INITIAL X (RANDOM SAMPLING METHOD)
3250 LPRINT TL$:LPRINT
3260 LPRINT"INITIAL X (RANDOM SAMPLING METHOD)":LPRINT
3262 LPRINT USING"RANDOM SAMPLING NUMBER=########";RN2
3264 LPRINT USING"RANDOM NUMBER SEED=     ########";RS:LPRINT
3270 FOR J=1 TO 10
3280 FOR I=1 TO M:IF I>4 AND ((I-1) MOD 4)=0 THEN LPRINT
3290 LPRINT USING"X(###)=########.########      ";I;XA(J,I);
3300 NEXT I:LPRINT
3310 LPRINT USING"T(X,R)=########.########";FA(J)
3320 LPRINT:NEXT J
3330 LPRINT CHR$(&HC)
3340 RETURN
10000 REM*** OBJECTIVE FUNCTION (TO MINIMIZE) ************
10010 F1=1.18-.393*X(1)-.172*X(2)-.107*X(3)+.199*X(1)^2+.19*X(2)^2
10020 F2=.0452*X(3)^2+.126*X(1)*X(2)+.121*X(1)*X(3)
10030 F=F1+F2
19990 RETURN
20000 REM*** INEQUALITY CONSTRAINTS (>=0) ****************
20010 G(1)=-1.74-.27*X(2)+.158*X(3)+.553*X(1)^2+.543*X(2)^2+.446*X(3)^2
20020 G(2)=-3.7-2.36*X(1)+1.87*X(1)^2+2.2*X(2)^2+1.34*X(3)^2-1.38*X(1)*X(2)
20030 G(3)=SQR(3)-X(1):G(4)=SQR(3)-X(2):G(5)=SQR(3)-X(3)
20040 G(6)=SQR(3)+X(1):G(7)=SQR(3)+X(2):G(8)=SQR(3)+X(3)
29990 RETURN
30000 REM*** EQUALITY CONSTRAINETS (=0) ******************
30010 H(1)=H1(X)
30020 H(2)=H2(X)
30030 H(3)=H3(X)
39990 RETURN
```

function, F, for minimization, the inequality constraints, $G(i)$, and/or the equality constraints, $H(j)$, must be defined at statement numbers 10000-, 20000-, and 30000-, respectively. For example, the definition methods of the Eqs. 6—8 in the theoretical section are described in Table VI. For the initial values of simplex at statement number 260 and perturbation parameter at 270, 0.1—1 and 0.001—0.1 are preferable, respectively. After the execution of NOPCON, the random searching process is started to find an initial set of X vectors and the Andrews' curves are drawn automatically. The random searching process should be repeated until the Andrews' curves converge into a singular cluster. After the convergence, the sequential optimization technique in which the simplex method is incorporated could be applied to find a global optimum. Finally, the optimum values of X vectors are printed out with the predicted values of objective function and constraints.

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