[Chem. Pharm. Bull. 31(12)4496—4507(1983)]

Computer Optimization of Formulation of Flufenamic Acid/Polyvinylpolypyrrolidone/Methyl Cellulose Solid Dispersions[1,2]

KOZO TAKAYAMA,* NAOKI NAMBU, and TSUNEJI NAGAI

Faculty of Pharmaceutical Sciences, Hoshi University,[3]
Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

(Received April 8, 1983)

A computer optimization technique was applied to obtain flufenamic acid (FFA)/polyvinylpolypyrrolidone (PVPP)/methyl cellulose (MC) solid dispersions which provide a high dissolution rate and high stability of FFA. The amounts of PVPP, MC and ethanol were selected as independent variables. Both PVPP and MC are formulation variables, and ethanol, which was used for the preparation of solid dispersions, is a process variable. Twelve dissolution parameters were selected as dependent variables for deciding the optimum formulation. These dissolution parameters were predicted quantitatively by the best combination of independent variables. The physical significance of the regression equation for each dissolution parameter was defined with the application of contour graphs. The optimum formulation of FFA/PVPP/MC solid dispersions was obtained by placing a set of restrictions on the regression equations. Experimental results for the optimum formulation agreed well with the predictions.

Keywords——computer optimization; regression equation; experimental design; contour graph; solid dispersion; polyvinylpolypyrrolidone; methyl cellulose; flufenamic acid; dissolution profile

Many studies have been done with a view to enhancement of the solubility and dissolution rate of slightly soluble drugs by the use of crystalline modifications.[4] The authors reported the effectiveness of polyvinylpolypyrrolidone (PVPP) as a carrier compound of solid dispersions.[5] The dissolution properties of flufenamic acid (FFA), a model compound of slightly soluble drugs, from solid dispersions with PVPP were determined by the dispersed amount method, showing a typical supersaturated phenomenon providing high bioavailability. However, the supersaturated state of FFA was not stable and was quickly translated to a stable form with the appearance of crystallization. In an attempt to stabilize the supersaturation, the effect of addition of water-soluble polymers to FFA/PVPP solid dispersions was investigated, and an adequate stabilization was obtained by adding methyl cellulose (MC). An analysis of factors affecting the dissolution profiles of FFA was carried out by multiple regression analysis, and the effect of MC added as the third component could be explained theoretically in detail.

In this paper, in order to obtain an optimum formulation of FFA/PVPP/MC solid dispersions which provide a high dissolution rate and high stability, a computer optimization technique was applied for selecting the best ratio of each component and also the best preparative conditions.

The optimization techniques used in the pharmaceutical field may be classified into two categories. The first is the simplex method[6] and the second is the method based on the statistically designed experiment as reported by Schwartz *et al.*[7] The former demands a single index throughout the experiment which will express the overall response for a given formulation to allow comparison with other formulations in the simplex. On the other hand, in the latter case, the selection of the combination of responses such as the dissolution rate and stability, which will decide the pharmaceutical formulation, may be more flexible even if the

experiments have been completely finished. In this study, the optimization technique reported by Schwartz *et al.*,[7] was applied with some modifications to FFA/PVPP/MC solid dispersions.

Experimental

Materials——FFA, generously supplied by Taisho Pharmaceutical Co., Ltd., was used after recrystallization from ethanol–water. 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.

Experimental Design and Preparative Method for Solid Dispersions——The preparative method for FFA/PVPP/MC sample powders is shown in Chart 1. The amounts of PVPP (X_1), MC (X_2), and ethanol (X_3) were selected as

FFA 500 mg

(1) dissolve in ethanol (50—250 ml)
(2) add PVPP (1—5 g)
(3) add MC (0.1—0.5 g)
(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. Preparative Method for Sample Powder

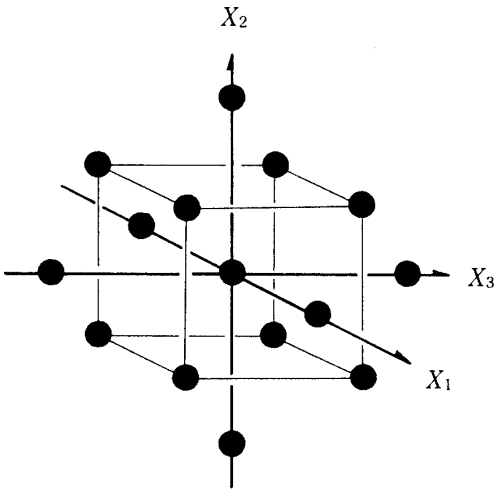

Fig. 1. Geometrical Illustration of the Experimental Design for Three Factors

independent variables, where 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 in the preparation of solid dispersions. The experimental design used in this study is represented geometrically in Fig. 1, and 15 experiments corresponding to each point in Fig. 1 were required, as summarized in Table I. The experimental units were translated to physical units in an empirical way as summarized in Table II. Other factors in sample preparation were kept constant throughout the experiment.

Procedure for Determination of Response Resulting from Sample Powders——A paddle method and dispersed amount method were applied to the sample powders. In order to determine the stability of samples, these dissolution tests were also applied to samples which had been kept for 5 d at 40 °C under relative humidity (R.H.) 75%.

a) Paddle Method: The procedure and apparatus described in dissolution test No. 2 (paddle method) in JP X were applied. With a paddle rotation speed of 50 rpm, a certain amount of sample powder which contained 66 mg of FFA was weighed accurately and dispersed in 900 ml of 1/15 M phosphate buffer solution (pH 6.4) at 37 °C. 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 FFA was determined by the ultraviolet (UV) absorption method.

b) Dispersed Amount Method: Using a dissolution cell similar to that described by Sekiguchi *et al.*,[8] a certain

Table I. Experimental Design for Three Factors

Formulation number	Factor level (e.u.)[a]		
	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	2	0	0
10	−2	0	0
11	0	2	0
12	0	−2	0
13	0	0	2
14	0	0	−2
15	0	0	0

a) Experimental units.

Table II. Translation of Experimental Conditions to Physical Units

Factor	Factor level (e.u.)[a]				
	−2	−1	0	1	2
X_1: PVPP (g)	1	2	3	4	5
X_2: MC (g)	0.1	0.2	0.3	0.4	0.5
X_3: Ethanol (ml)	50	100	150	200	250

a) Experimental units.

excess of sample powder (equivalent to five times the saturated concentration of FFA) was weighed accurately and put in the dissolution cell, which was kept at 37 °C by circulating constant temperature water in the outer vessel. Next, 1/15 M phosphate buffer solution (pH 6.4) which had been brought to 37 °C was added. Immediately after the addition, stirring (500 rpm) was begun with a magnetic stirrer. The solution was sampled at appropriate intervals and filtered through a Toyo TM-2 membrane filter (0.45 μm). The concentration of FFA in the filtrate was determined by the UV absorption method.

Results and Discussion

Determination of Dissolution Parameters

Figure 2 shows the dissolution profile of FFA from formulation No. 1 in Table I as determined by the paddle method. The solid curve was drawn by applying Wagner's dissolution model[9,10] to the experimental data. The dissolution model based on the Weibull distribution function[10,11] was also applied, but the fit to the experimental data was not as good as in the former case. Wagner's dissolution model is based on the log-normal density function, and the 16% dissolution time ($t_{16\%}$), 50% dissolution time ($t_{50\%}$), and 84% dissolution time ($t_{84\%}$) are quite proper and convenient dissolution parameters for a given formulation to allow quantitative comparison with other formulations, because these parameters are closely related to the mean and standard deviation ($\pm\sigma$) of the log-normal density function.

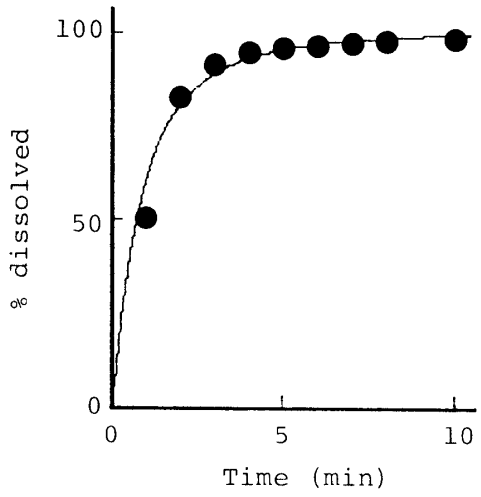

Fig. 2. Dissolution Profile of FFA from Formulation No. 1 by the Paddle Method in 900 ml of 1/15 M Phosphate Buffer (37 °C, 50 rpm)

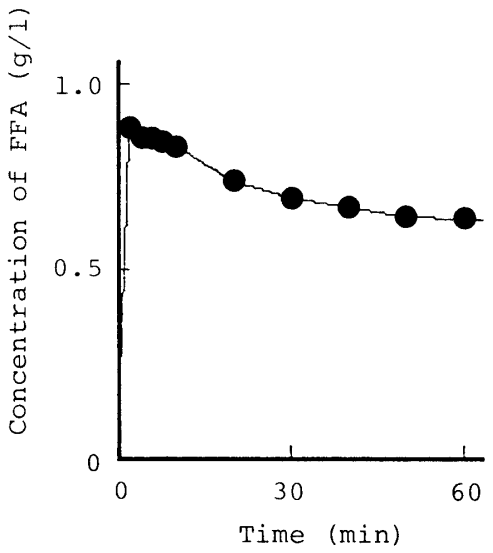

Fig. 3. Dissolution Profile of FFA from Formulation No. 1 by the Dispersed Amount Method in 50 ml of 1/15 M Phosphate Buffer (37 °C, 500 rpm)

Figure 3 shows the dissolution profile of FFA from formulation No. 1 as determined by the dispersed amount method. The concentration of FFA rose very quickly and then decreased gradually, showing a typical supersaturation phenomenon. Therefore, it might be considered that the results from the dispersed amount method reflect the stability of the supersaturated state of FFA of each formulation. The area under the dissolution curve (*AUDC*) and the maximum concentration (C_{max}) and the minimum concentration (C_{min}) of FFA were determined as quantitative dissolution parameters. C_{min} corresponds to the concentration at 60 min in all cases. The dissolution parameters obtained are summarized in Table III.

Regression Equations for Dissolution Parameters[12]

In order to predict each dissolution parameter, the amount of PVPP (X_1), MC (X_2), and ethanol (X_3) were selected as independent variables. X_1 and X_2 are the formulation variables and X_3 is the process variable. These variables are considered to be directly controllable factors. The evaporating temperature and the mixing time of the sample preparation should be taken into consideration as process variables, but the contribution of these variables to the dissolution of FFA was not very great as determined in the preliminary experiment, so these factors were fixed at constant values throughout the experiment.

The following equation was used for the prediction of each dissolution parameter:

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

where Y is the level of the dissolution parameter, b_i is the regression coefficient, and X_i is the level of the independent variable. In order to obtain the optimum regression equation, the overall combination of independent variables was investigated at the point of statistical significance, that is, the best combination of independent variables for the prediction of each dissolution parameter was selected from among 511 ($2^9 - 1$) kinds of regression equations. Correlation coefficients with doubly adjusted degrees of freedom[13] were used as an index for the selection of the optimum combination of factors. Optimum regression equations obtained are summarized in Table IV. The data on $t_{16\%}$, $t_{50\%}$, and $t_{84\%}$ were translated to logarithmic

TABLE III. Dissolution Parameters Determined by Paddle Method and Dispersed Amount Method

Formulation	Immediately after preparation						After 5d at 40 °C under R.H. 75%					
	$t_{16\%}$ (min)	$t_{50\%}$ (min)	$t_{84\%}$ (min)	*AUDC* (g·min/l)	C_{max} (g/l)	C_{min} (g/l)	$t_{16\%}$ (min)	$t_{50\%}$ (min)	$t_{84\%}$ (min)	*AUDC* (g·min/l)	C_{max} (g/l)	C_{min} (g/l)
1	0.243	0.767	2.42	43.4	0.881	0.638	0.185	1.15	7.10	42.9	0.893	0.633
2	0.466	1.03	2.29	43.8	0.913	0.648	0.171	1.16	7.93	42.5	0.903	0.633
3	0.0626	0.288	1.32	42.5	0.907	0.604	0.0940	0.783	6.53	37.9	0.925	0.537
4	0.142	0.592	2.47	42.9	0.893	0.616	0.102	0.868	7.42	38.2	0.901	0.553
5	0.110	0.797	5.78	45.6	0.929	0.680	0.134	1.02	7.69	43.0	0.965	0.649
6	0.0510	0.497	4.86	45.2	0.967	0.671	0.407	1.87	8.60	43.3	0.967	0.646
7	0.145	1.82	22.8	43.6	0.866	0.670	0.103	1.97	37.5	42.5	0.864	0.618
8	0.0284	0.702	17.4	44.3	0.896	0.683	0.101	1.54	23.5	43.4	0.859	0.668
9	0.0945	0.402	1.71	43.8	0.864	0.644	0.0626	0.656	6.88	39.3	0.846	0.575
10	2.15	12.8	76.7	42.8	0.732	0.684	0.320	5.60	98.0	30.4	0.529	0.529
11	0.153	0.562	2.06	39.7	0.943	0.545	0.314	2.09	14.0	43.0	0.946	0.624
12	0.0995	0.662	4.40	44.0	0.898	0.654	0.215	1.60	12.0	37.8	0.944	0.551
13	0.0777	0.403	2.09	44.0	0.953	0.651	0.115	1.12	10.9	41.9	0.949	0.615
14	0.217	0.620	1.78	44.9	0.946	0.672	0.0930	0.917	9.04	42.3	0.965	0.632
15	0.117	0.508	2.21	45.5	0.922	0.684	0.0595	0.913	14.0	42.6	0.934	0.620

TABLE IV. Optimum Regression Equation for Each Dissolution Parameter Determined by Multiple Regression Analysis

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

Y	b_0	b_1	b_2	b_3	b_4	b_5	b_6	b_7	b_8	b_9	r[b]	s[c]	F[d]
Immediately after preparation													
$\log t_{16\%}$[a]	0.716	—	—	—	0.144	—	—	—	−0.211	—	0.555	0.395	2.66
$\log t_{50\%}$[a]	1.49	−0.224	—	—	0.157	—	—	0.146	−0.134	—	0.891	0.209	9.64**
$\log t_{84\%}$[a]	2.28	−0.381	−0.0994	—	0.152	—	−0.0405	0.174	−0.0563	—	0.985	0.113	44.4**
$AUDC$ (g·min/l)	44.9	—	—	—	−0.384	−0.746	—	—	—	—	0.603	1.26	3.44
C_{max} (g/l)	0.937	0.0125	0.0136	—	−0.0338	—	—	−0.0175	—	—	0.881	0.0313	8.68**
C_{min} (g/l)	0.668	−0.0174	−0.00962	—	—	−0.0169	—	—	—	—	0.800	0.0257	6.50**
After 5d at 40 °C under R.H. 75%													
$\log t_{16\%}$[a]	0.742	−0.105	0.0989	—	0.0518	0.119	—	—	—	—	0.816	0.175	4.97*
$\log t_{50\%}$[a]	1.74	−0.166	—	—	0.0754	0.0692	—	0.0625	—	—	0.907	0.116	11.6**
$\log t_{84\%}$[a]	2.77	−0.226	−0.0588	—	0.0898	—	—	0.150	—	—	0.909	0.161	11.9**
$AUDC$ (g·min/l)	42.6	—	1.26	—	−1.71	—	—	—	—	—	0.728	2.61	6.78**
C_{max} (g/l)	0.963	0.0375	—	—	−0.0657	—	—	−0.0300	—	—	0.885	0.0567	13.3**
C_{min} (g/l)	0.635	—	0.0207	—	−0.0184	−0.00952	—	0.0209	—	—	0.784	0.0327	3.99*

a) Data were translated to logarithmic form after changing the dimension from minute to second.
b) Multiple correlation coefficient.
c) Standard deviation.
d) Level of significance. *, $p<0.05$; **, $p<0.01$.

form for the purpose of enhancement of the statistical significance of the regression equations. Other dissolution parameters were treated as intact data. While a contribution of X_3 to the dissolution parameters of log $t_{16\%}$, log $t_{50\%}$ and log $t_{84\%}$, which were determined immediately after the preparation, was observed, the other dissolution parameters were represented as a function of X_1 and X_2 without X_3. Therefore, it might be considered that the contribution of the amount of ethanol to the dissolution and stability was relatively small in comparison with those of the amounts of PVPP and MC. The physical significance of the regression equation was explored by means of contour graphs.

Graphical Approach with Contour Curves[12]

The contour graph is quite useful to elucidate the significance of a regression equation. Figures 4 and 5 show the contour curves as a function of X_1 and X_2 for each dissolution parameter, determined immediately after the sample preparation. In the cases of $t_{50\%}$ and $t_{84\%}$, the optimum point was observed at a larger value of X_1 and smaller value of X_2, while the minimum points of these dissolution parameters are located out of the range of the graphs. The maximum position of *AUDC* was defined at the center of the graph. C_{max} was mainly a function of X_1, because the value of C_{max} scarcely changed with the change of X_2. An optimum value of X_2 was observed in the case of C_{min}, though the effect of X_1 was relatively weak.

The contour curves of the dissolution parameters determined after the accelerated test

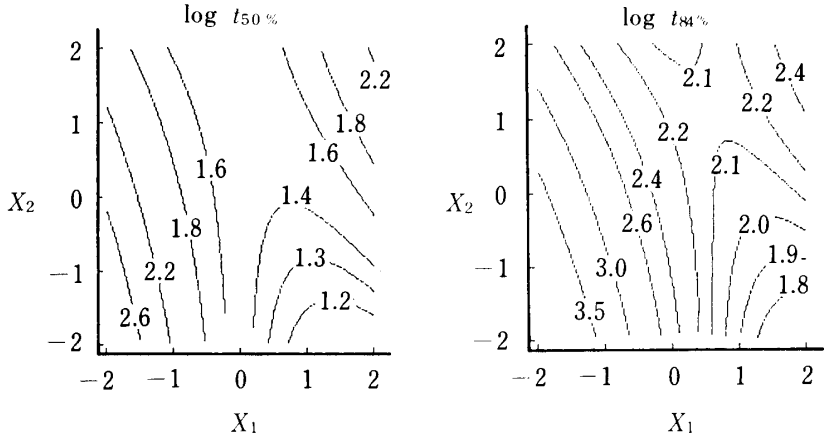

Fig. 4. Contour Curves of log $t_{50\%}$ and log $t_{84\%}$ as a Function of X_1 and X_2 Determined Immediately after Sample Preparation ($X_3=0$)

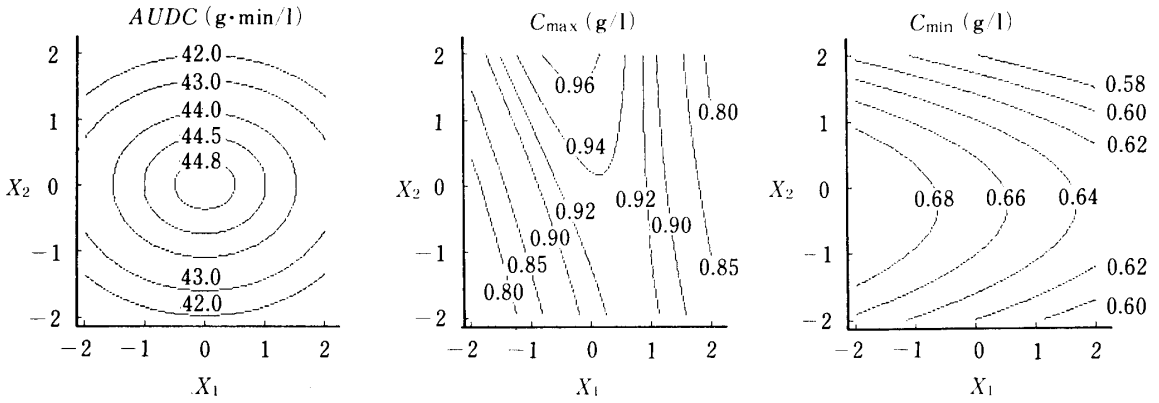

Fig. 5. Contour Curves of *AUDC*, C_{max} and C_{min} as a Function of X_1 and X_2 Determined Immediately after Sample Preparation

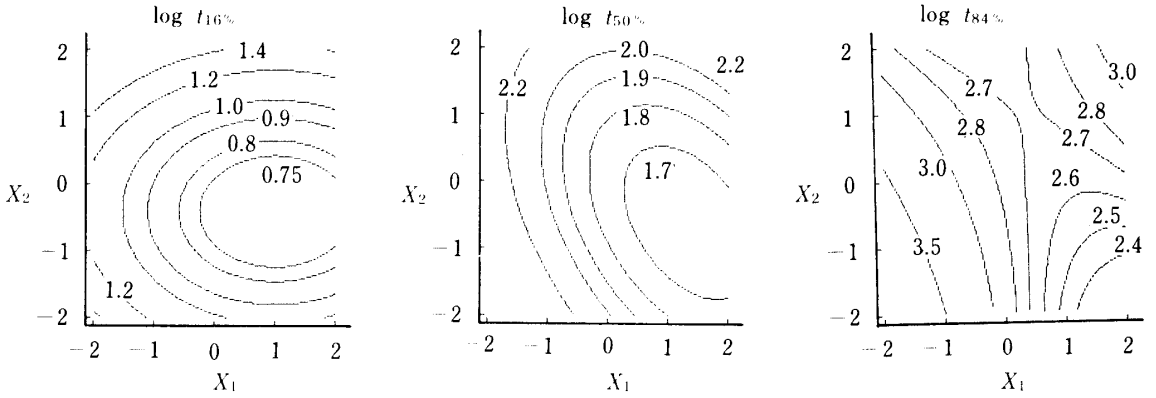

Fig. 6. Contour Curves of $\log t_{16\%}$, $\log t_{50\%}$ and $\log t_{84\%}$ as a Function of X_1 and X_2 Determined after Accelerated Test (for 5 d at 40 °C under R.H. 75%)

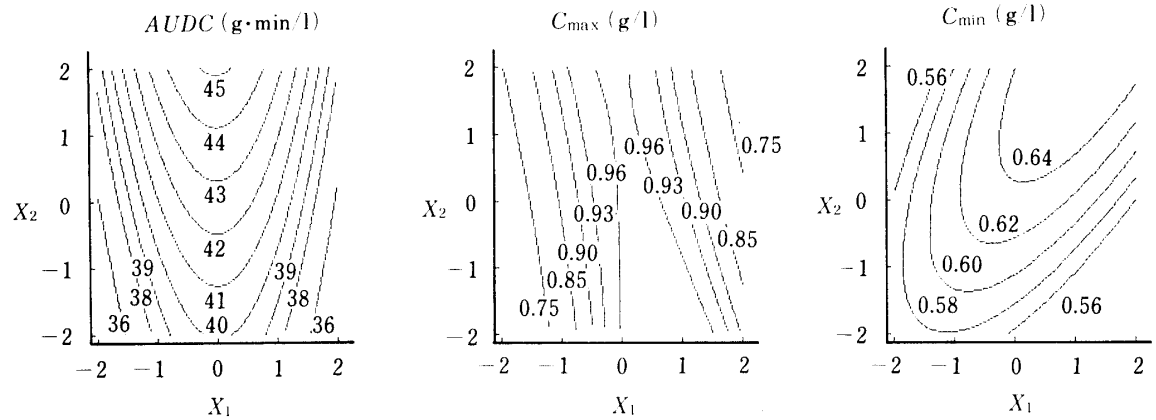

Fig. 7. Contour Curves of $AUDC$, C_{max} and C_{min} as a Function of X_1 and X_2 Determined after Accelerated Test (for 5 d at 40 °C under R.H. 75%)

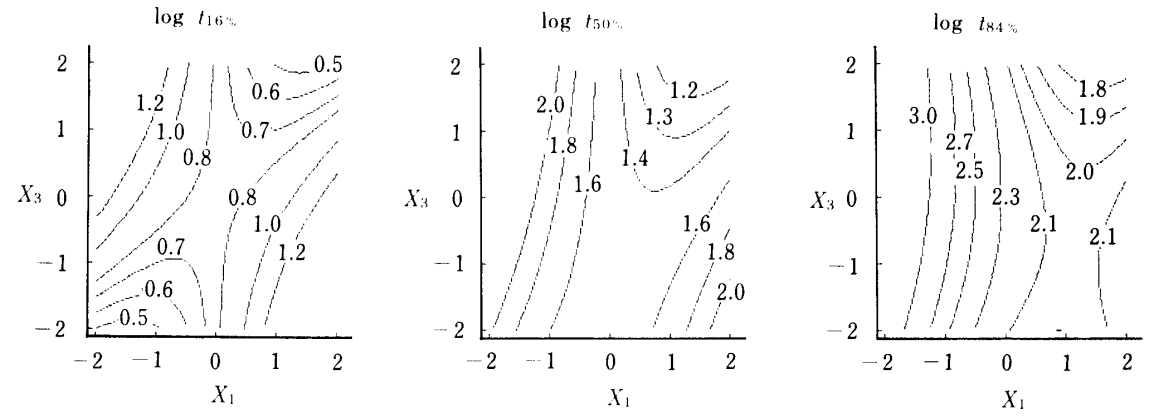

Fig. 8. Contour Curves of $\log t_{16\%}$, $\log t_{50\%}$ and $\log t_{84\%}$ as a Function of X_1 and X_3 Determined Immediately after Sample Preparation ($X_2=0$)

are represented in Figs. 6 and 7. The application of the accelerated test to the samples moved the optimum positions of dissolution parameters to the upper region (to the region of larger MC amounts) on the contour graphs. This indicated that MC was important as a stabilizing agent of solid dispersions.

Figure 8 shows the contour curves of $t_{16\%}$, $t_{50\%}$ and $t_{84\%}$, which were determined immediately after the preparation, as functions of X_1 and X_3. It appears that desirable results

Table V. Maximum and Minimum Dissolution Parameters

Dissolution parameter	Predicted value	
	Maximum	Minimum
Immediately after preparation		
$\log t_{16\%}$	2.19	0.459
$\log t_{50\%}$	3.69	0.550
$\log t_{84\%}$	4.62	1.24
$AUDC$ (g·min/l)	44.9	40.4
C_{max} (g/l)	0.967	0.680
C_{min} (g/l)	0.703	0.546
After 5d at 40 °C under R.H. 75%		
$\log t_{16\%}$	1.83	0.669
$\log t_{50\%}$	2.90	1.63
$\log t_{84\%}$	4.30	2.19
$AUDC$ (g·min/l)	45.1	33.2
C_{max} (g/l)	0.995	0.505
C_{min} (g/l)	0.662	0.398

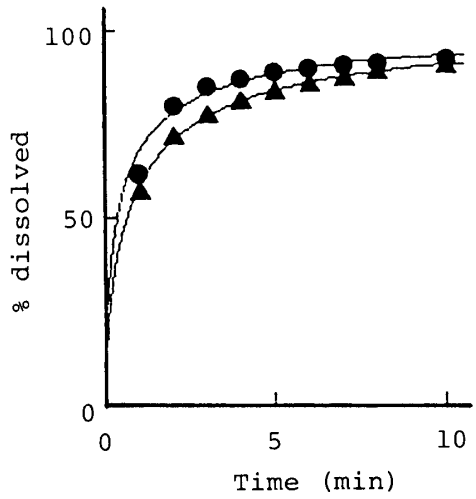

Fig. 9. Dissolution Profile of FFA from the Optimum Formulation (No. 5 in Table VII) by the Paddle Method in 900 ml of 1/15 M Phosphate Buffer (at 37 °C, 50 rpm)

—●—, immediately after preparation; —▲—, after 5d at 40 °C under R.H. 75%.

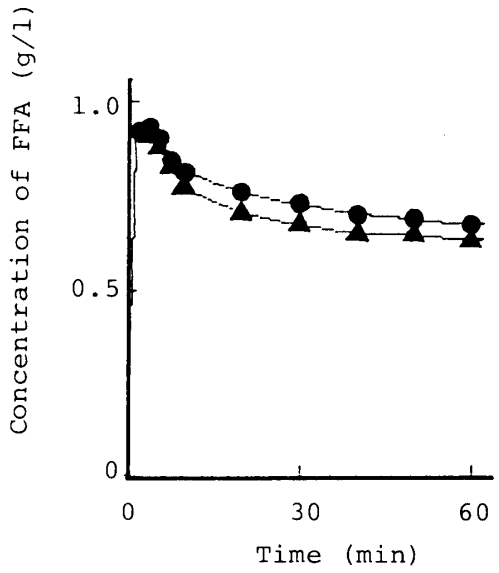

Fig. 10. Dissolution Profile of FFA from the Optimum Formulation (No. 5 in Table VII) by the Dispersed Amount Method in 50 ml of 1/15 M Phosphate Buffer (at 37 °C, 500 rpm)

—●—, immediately after preparation; —▲—, after 5d at 40 °C under R.H. 75%.

were obtained with a larger value of X_3, that is, a larger amount of ethanol is better for good dissolution and stability.

Optimization of FFA/PVPP/MC Solid Dispersions[12]

The formulation which gives the optimum value of each response might be easily obtained within the constant limits of values of X_i. Usually, the maximum or the minimum points might be predicted as the optimum values of each response. However, if we select the formulation of $X_1 = 2$ and $X_2 = -2$ as the optimum one to minimize the value of $t_{50\%}$ according to the contour graph, it leads to the worst result in $AUDC$. Therefore, the

TABLE VI. Change of Constraints for Optimum Formulation

Step of searching	Immediately after preparation						After 5 d at 40 °C under R.H. 75%						Number of solutions
	$\log t_{16\%}$	$\log t_{50\%}$	$\log t_{84\%}$	$AUDC$ (g·min/l)	C_{max} (g/l)	C_{min} (g/l)	$\log t_{16\%}$	$\log t_{50\%}$	$\log t_{84\%}$	$AUDC$ (g·min/l)	C_{max} (g/l)	C_{min} (g/l)	
1	0.459	0.550	1.24	44.9	0.967	0.703	0.669	1.63	2.19	45.1	0.995	0.662	0
2[a]	0.632	0.864	1.58	44.4	0.938	0.688	0.785	1.76	2.41	43.9	0.946	0.635	0
3[a]	0.805	1.18	1.92	44.0	0.910	0.672	0.902	1.88	2.62	42.7	0.897	0.609	0
4[a]	0.978	1.49	2.26	43.5	0.881	0.656	1.02	2.01	2.83	41.6	0.848	0.583	26
5[b]	0.956	1.45	2.21	43.6	0.884	0.658	1.00	2.00	2.80	41.7	0.854	0.586	6
6[b]	0.945	1.43	2.19	43.6	0.886	0.659	0.996	1.99	2.79	41.8	0.857	0.588	5

a) The process of relaxation. *b*) The process of tightening.

TABLE VII. Optimum Formulation of FFA/PVPP/MC Solid Dispersions Predicted by Computer Searching Technique

Formulation number	Factor level (e.u.)[a]			Immediately after preparation						After 5 d at 40 °C under R.H. 75%					
	X_1	X_2	X_3	$\log t_{16\%}$	$\log t_{50\%}$	$\log t_{84\%}$	$AUDC$ (g·min/l)	C_{max} (g/l)	C_{min} (g/l)	$\log t_{16\%}$	$\log t_{50\%}$	$\log t_{84\%}$	$AUDC$ (g·min/l)	C_{max} (g/l)	C_{min} (g/l)
1	0.5	0.0	0.0	0.804	1.42	2.13	44.8	0.935	0.659	0.702	1.68	2.68	42.2	0.965	0.630
2	0.5	0.0	0.5	0.751	1.38	2.10	44.8	0.935	0.659	0.702	1.68	2.68	42.2	0.965	0.630
3	0.5	0.0	1.0	0.699	1.35	2.06	44.8	0.935	0.659	0.702	1.68	2.68	42.2	0.965	0.630
4	0.5	0.0	1.5	0.646	1.32	1.99	44.8	0.935	0.659	0.702	1.68	2.68	42.2	0.965	0.630
5	0.5	0.0	2.0	0.593	1.28	1.91	44.8	0.935	0.659	0.702	1.68	2.68	42.2	0.965	0.630

a) Experimental units.

Table VIII. Experimental and Predicted Values of Dissolution Parameters for the Optimum Formulation (No. 5 in Table VII)

Dissolution parameter	Experimental	Predicted
Immediately after preparation		
$\log t_{16}$	0.420	0.593
$\log t_{50\%}$	1.37	1.28
$\log t_{84\%}$	2.32	1.91
$AUDC$ (g·min/l)	45.1	44.8
C_{max} (g/l)	0.921	0.935
C_{min} (g/l)	0.671	0.659
After 5 d at 40 °C under R.H. 75%		
$\log t_{16\%}$	0.708	0.702
$\log t_{50\%}$	1.62	1.68
$\log t_{84\%}$	2.52	2.68
$AUDC$ (g·min/l)	42.7	42.2
C_{max} (g/l)	0.917	0.965
C_{min} (g/l)	0.629	0.630

optimum formulation has to be taken as a systematically acceptable formulation which will sufficiently satisfy the overall responses. In this study, the following method was applied to obtain the optimum formulation of FFA/PVPP/MC solid dispersions. First, the maximum and minimum values of each response were calculated within the limits of $-2 \leqq X_i \leqq 2$, where the value of X_i increased from -2 to 2 in steps of 0.5. Then, prediction was carried out for 729 (9^3) kinds of formulations. These values were listed in Table V. The search for the optimum formulation was started under the set of these values as the first constraints. The constraints were systematically relaxed until solutions were found. The relaxation method of constraints used in this study was as follows. In the first searching step, 1/10 of the difference between the maximum and minimum values of each response was used as the width of the relaxation. This relaxation step continued until several kinds of solutions were found. After that, the width of relaxation was reduced to half its initial size, and the searching was returned back to the previous step. That is, after the gradual relaxation, the constraints were tightened. The searching was started again. This process was continued until only a few solutions were found. The change of constraints in this study is summarized in Table VI. The flow of searching was as follows: no solution was obtained under the first constraints (step 1). The constraints were relaxed until solutions were found, and 26 solutions were obtained as acceptable formulations (steps 2—4). The constraints were tightened and the number of solutions decreased from 26 to 6 (step 5). The searching was started again and repeated. Finally, only 5 solutions were obtained as optimum formulations (step 6). These are summarized in Table VII. The optimum formulation (No. 5 in Table VII) can easily be decided from among the 5 formulations. It was observed that the dissolution rates of the optimum formulation of FFA/PVPP/MC solid dispersions were not only high but also stable, as shown in Figs. 9 and 10. Moreover, the dissolution parameters which were determined in the same manner coincided well with the predicted values, as summarized in Table VIII.

Based on the above considerations, prediction of the characteristics of FFA/PVPP/MC solid dispersions could reasonably be done by application of the computer optimization technique. Some of the methods described in this paper should be applicable to other optimization problems in the practical pharmaceutical field.

Acknowledgement A part of this study was supported by a Grant-in-Aid for Scientific Research from the

Ministry of Education, Science, and Culture, Japan. The authors are very grateful to Taisho Pharmaceutical Co., Ltd. and BASF Japan Ltd. for supplying materials. Thanks are also due to Dr. Naoya Ohgusa and Mr. Suehiro Kikkawa of Daiichi Pharmaceutical Co., Ltd. and Mr. Shigeru Itai of Taisho Pharmaceutical Co., Ltd. for their suggestions relating to this work and to Miss Atsuko Tashiro for her assistance in the experimental work.

References and Notes

1) This paper forms Part XLI of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XL: H. Imaizumi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **31**, 2510 (1983).
2) A part of this work was presented at the 7th Conference on Pharmaceutical Technology, Shirakabako, July 1982.
3) Formerly, Hoshi Institute of Pharmaceutical Sciences.
4) *e.g.*, J. Haleblian, *J. Pharm. Sci.*, **64**, 1269 (1975).
5) K. Takayama, H. Imaizumi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **30**, 3701 (1982).
6) E. Shek, M. Ghani, and R. E. Jones, *J. Pharm. Sci.*, **69**, 1135 (1980).
7) J. B. Schwartz, *J. Soc. Cosmet. Chem.*, **32**, 287 (1981); J. B. Schwartz, J. R. Flamhortz, and R. H. Press, *J. Pharm. Sci.*, **62**, 1165 (1973).
8) K. Sekiguchi, E. Owada, and K. Ito, *Chem. Pharm. Bull.*, **15**, 873 (1967).
9) J. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969).
10) This calculation was carried out on a Toshiba PA-7010 personal computer with a program written by Shigeru Itai of Taisho pharmaceutical Co., Ltd.
11) F. Langenbucher, *J. Pharm. Pharmacol.*, **24**, 979 (1972).
12) This calculation was carried out on a Toshiba PA-7010 personal computer with a program written by the authors.
13) T. Haga, H. Takeuchi, and T. Okuno, *Quality, J.S.Q.C.*, **6**, 35 (1976).