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Computer Optimization of the Formulation of Acrylic Plaster

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A computer optimization technique was applied to obtain the optimum formula of acrylic plaster vehicle containing ketoprofen (KPF). The dissolution rate of KPF, *in vivo* percutaneous absorption of KPF, stability of the dissolution behavior of KPF and adhesiveness of the plaster were determined as characteristics for deciding the formula of an optimum plaster vehicle. The amounts of 2-ethylhexyl acrylate (X_1), vinyl acetate (X_2) and 2-hydroxyethyl acrylate (X_3) were selected as factors (independent variables). The plaster characteristics were predicted by the second-order polynominal regression equation involving these factors. The physical meaning of the regression equation for each characteristic was defined by the application of contour graphs. A mixture of 65 g of X_1, 60 g of X_2 and 1.38 g of X_3 was predicted to be the optimum for the plaster vehicle.

Keywords——acrylic plaster; ketoprofen; 2-ethylhexyl acrylate; vinyl acetate; 2-hydroxyethyl acrylate; computer optimization; regression equation; experimental design; contour graph

Plasters for transdermal drug absorption are considered to afford a useful therapeutic dosage form. In general, vehicles of plasters for external use are classified into two categories, *i.e.*, elastic base and resin polymer base.[1,2] Acrylic adhesive polymer as a kind of resin polymer base is prepared by copolymerization of various monomers, such as vinyl acetate, 2-ethylhexyl acrylate and 2-hydroxyethyl acrylate. The adhesiveness of the acrylic polymer, which should be taken into consideration from the practical pharmaceutical viewpoint, depends strongly on the mixing ratio of the monomers. In this paper, following a previous paper,[3] the optimization technique was applied to obtain the optimum mixing ratio of these monomers for the synthesis of acrylic adhesive polymer as a plaster vehicle.

Experimental

Materials——Ketoprofen (KPF) was generously supplied by Rhone-Poulenc Yakuhin Co., Ltd. 2-Ethylhexyl acrylate and 2-hydroxyethyl acrylate were purchased from Tokyo Kasei Co., Ltd. Vinyl acetate and poly-vinyl acetate as a reference for gel-filtration were purchased from Wako Junyaku Co., Ltd.

Experimental Design and Method of Preparation for Acrylic Adhesive Polymer——The method of preparation for acrylic adhesive polymer is shown in Chart 1. The characteristics of these synthetic polymers on gel-filtration are shown in Table I. Based on the previously reported method,[3] the amounts of 2-ethylhexyl acrylate (X_1), vinyl acetate (X_2) and 2-hydroxyethyl acrylate (X_3) were selected as the factors for the three-dimensional composite experimental design, as shown in Table II. The levels of factors in coded form were translated to physical units in an empirical way as summarized in Table III. Other factors in sample preparations were kept constant through out the experiment.

Dissolution Test and Stability of Dissolution Behavior——Dissolution of KPF from a plaster sample (total area = 8 cm^2) was determined as follows; two pieces of plaster sample (area of each piece = 4 cm^2) were fixed on a rubber board and placed vertically in a 200 ml beaker containing 120 ml of saline at 37 °C. The solution was stirred with a magnetic stirrer at a rotation speed of 100 rpm. At appropriate intervals, 4 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 KPF was determined by the ultraviolet absorption method at 260 nm using a Hitachi 124 spectrophotometer. In order to investigate the stability of dissolution behavior, the dissolution test was also done on

TABLE I. The Results of Gel-Filtration of Synthetic Polymers

Sample No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Ref.
	(% for added sample weight)															
Fraction No.																
1																
⋮																
8				0.8												
9			1.0	0.6				0.6		2.3	0.8					
10	0.5		3.6	2.2		1.1		2.4	0.6	2.6	2.3					
11	3.6	3.3	7.1	1.7	1.7	2.7	1.1	5.7	3.4	2.8	3.0	2.6	1.3	1.7	0.9	
12	5.7	4.8	10.7	7.7	4.9	4.7	1.5	6.2	6.3	3.6	4.8	6.1	3.6	4.9	4.0	
13	7.0	5.7	11.8	9.7	6.3	5.6	2.6	7.7	7.6	4.0	4.9	9.4	5.5	6.4	5.4	
14	8.0	6.7	11.7	11.3	6.8	6.7	2.6	8.8	8.4	4.5	5.7	9.2	7.6	7.6	6.8	
15	9.1	7.6	10.5	11.6	7.5	7.9	3.8	10.2	9.0	4.8	6.1	10.0	9.6	8.7	7.3	
16	9.2	9.8	7.3	6.6	8.3	8.5	5.7	11.2	10.2	6.4	7.1	4.5	10.5	9.5	8.9	
17	11.3	8.9	8.8	8.6	9.7	9.8	7.4	11.0	11.5	8.2	8.1	10.0	11.2	10.0	11.3	
18	12.1	9.4	7.5	8.4	9.8	10.3	9.1	10.2	10.9	9.8	9.1	9.7	11.1	10.3	12.2	
19	11.1	9.2	7.4	7.7	9.6	9.3	10.4	8.4	9.9	15.4	8.3	9.4	10.5	10.7	13.4	
20	8.4	8.4	5.8	5.4	9.1	9.0	10.7	6.4	8.6	10.2	8.2	7.8	8.9	10.6	11.4	
21	5.9	7.2	3.3	4.0	8.4	8.0	10.0	4.3	6.3	9.2	8.5	6.1	7.6	8.4	8.7	
22	3.3	6.3	0.5	6.3	7.1	6.4	9.6	2.2	4.4	5.9	7.2	5.1	5.0	5.9	4.8	
23	1.8	5.6	1.1	3.2	3.9	4.4	7.7	1.9	1.5	3.5	6.1	4.1	3.3	3.6	2.1	
24	1.7	3.4	1.1	1.3	1.8	2.9	5.7	1.6	1.2	2.4	4.8	1.3	1.9	1.3	1.1	2.4
25	0.7	2.5	0.6	0.9	1.6	1.2	5.0	1.1	0.6	2.4	2.8	3.8	1.2	0.5	0.8	3.4
26	0.5	0.7		0.7	1.4	1.0	3.1			2.1	1.5	0.9	1.2		0.9	3.5
27		0.3		0.7	1.1	0.6	1.9				0.6					4.9
28				0.5	0.9		1.2									6.7
29							0.9									8.8
30																10.5
31																10.1
32																8.4
33																9.1
34																5.7
35																5.4
36																4.1
37																4.4
38																3.8
39																4.4
40																3.0
41																1.4
⋮																
50																

Conditions: fraction collector, Toyo SF-160K; carrier, Sephacryl S-200 (Pharmacia Co., Ltd.), 35 × 2 cm i.d.; mobile phase, ethyl acetate; fraction size, 4 g; reference polymer, poly-vinyl acetate (n = 1400—1600); weight of sample added, 200 mg.

X_1: 2-ethylhexyl acrylate
X_2: vinyl acetate
X_3: 2-hydroxyethyl acrylate
↓
—add α,α'-azobis (isobutyronitrile) (2% of total monomer, w/w)
—add toluene (twice total monomer, v/w)
↓
stir mechanically, 70°C, 4 h
↓
evaporation
↓
evaporation after washing with benzene
↓
evaporation after washing with chloroform
↓
acrylic polymer
—add ketoprofen (KPF) (2% of polymer, w/w)
—add chloroform
↓
original sample (0.1 g/ml)
↓
prepared sample on backing sheet (polyethylene film) (2×2 cm, weight of plaster = 5 mg/cm^2)

Chart 1. Method for Preparation of Samples

TABLE II. Experimental Design for Three Factors

Formulation number	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	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

TABLE III. Translation of Experimental Conditions to Physical Units

Factor	Factor level in coded form				
	−2	−1	0	1	2
X_1: 2-ethylhexyl acrylate (g)	5.0	20.0	35.0	50.0	65.0
X_2: vinyl acetate (g)	0	15.0	30.0	45.0	60.0
X_3: 2-hydroxyethyl acrylate (g)	0	0.5	1.0	1.5	2.0

samples which had been kept for a month at 40 °C and 75% relative humidity (R.H.). The difference between the amount dissolved at 1 and 4 h in the freshly prepared sample and that after the acceleration procedure was used as an index of the stability of dissolution behavior.

Adhesiveness Test——The adhesiveness test was done in the same way as reported by Yamagami *et al.*,[4] with a Fudo Kogyo NRM-2001 rheometer. The plunger used was a stainless steel disk of 10 mm diameter carrying lyophilized porcine skin (ALLOASK®, Kotaikasei Kogyo Co., Ltd.). The adhesiveness (F) was represented by $F = A/B \times 100$ (g), where B was the force applied to the sample, and A was the force required to pull apart the sample and the plunger.

Percutaneous Absorption from Rat Back Skin——Male Wistar rats weighing 180—200 g were used. The rats were fixed and the hair of the back was shaved with electric hair clippers and an electric shaver. The sample (total area =

blood 0.5 ml
|
|——methanol solution 1.0 ml
| (internal standard: diclofenac sodium, 50 ng/ml)
centrifuge (3000 rpm, 5 min)
|
filtration (0.45 m)
|
HPLC (254 nm)
Shimadzu LC-1A, μ-BONDAPAC C-18 (30 cm × 3.9 mm)
mobile phase: 0.2 M phosphate buffer (pH=4): acetonitrile=2: 1.8

Chart 2. Procedure for Measurement of the Concentration of KPF in Rat Serum

16 cm^2) was attached to the shaved skin. Water intake was permitted freely during the experiment. At 4 and 8 h after application, 0.5 ml of blood was taken from the jugular vein. The concentration of KPF was determined with a Shimadzu LC-1A high-performance liquid chromatograph (HPLC). The flow chart of the analysis is shown in Chart 2.

Results and Discussion

Characteristics of the Synthesized Acrylic Polymer

The results in Table I indicate that the molecular weights of the polymers synthesized were larger than that of the vinyl acetate polymer ($n=1400$—1600) which was used as a reference. The difference of degree of polymerization among these synthetic polymers was slight.

Dissolution Behavior of KPF and Other Characteristics of the Sample

Figure 1 shows the dissolution profiles of KPF from No. 8 and 15 formulations in Table II. The dissolution profiles of these samples after storing them at 40 °C under 75% R.H. for a month were also determined, and are shown in Fig. 1. In the early stage of dissolution, the amount of KPF released increased rapidly and reached about a half of the amount released at 4 h. It was considered that KPF molecules in the vicinity of the sample surface were released rapidly and then slow release occurred of KPF in the polymer matrix of the plaster. A significant difference in the dissolution of KPF from samples was observed among the 15 formulations in Table II. The pattern of dissolution curves after the accelerated test was similar to that immediately after preparation, but the amount of KPF released was lowered by

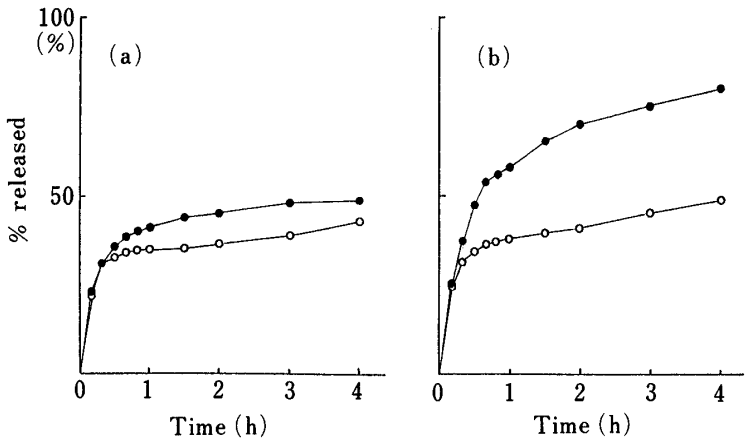

Fig. 1. Dissolution Profiles of Ketoprofen (KPF) from Formulations No. 8(a) and No. 15(b)

—●—: immediately after preparation. —○—: after storing for a month at 40 °C and 75%R.H.

TABLE IV. Raw Data

Formulation number	Dissolution[a]			Stability of dissolution[a]		Adhesiveness[b]	Percutaneous absorption[c]	
	$C_{0.5h}$	C_{1h} (%)	C_{4h}	Ds_{1h}	Ds_{4h}	F (g)	C_{4h} (μg/ml)	C_{8h} (μg/ml)
1	42.2	50.3	64.3	−15.4	−20.6	65.3	2.20	3.64
2	46.5	51.3	60.3	−19.0	−18.9	54.2	1.40	3.41
3	45.3	55.6	66.5	−11.7	−13.2	76.7	0.87	4.40
4	38.2	42.1	50.4	−7.2	−4.3	52.1	2.22	1.70
5	33.5	39.6	49.8	−1.9	−5.8	82.0	1.78	2.23
6	42.1	54.3	65.2	−26.2	−29.2	62.0	0.87	2.68
7	41.8	51.1	56.6	−4.9	−5.1	95.0	1.14	1.45
8	35.9	40.6	48.4	−6.1	−5.6	59.4	0.98	1.87
9	35.0	44.6	64.1	−4.8	−14.5	68.4	1.26	4.52
10	27.1	37.2	55.3	−4.0	−4.8	41.4	1.19	2.69
11	28.1	34.2	53.8	5.3	−5.8	63.7	3.16	4.16
12	42.9	44.2	48.8	3.4	8.7	83.4	3.42	2.22
13	32.7	37.2	46.1	10.4	9.7	93.8	1.29	1.62
14	39.6	43.0	50.6	−0.8	−1.6	51.0	1.65	1.84
15	47.8	57.6	79.3	−20.8	−32.6	63.4	1.73	2.35

a) Each datum is the mean of three determinations. *b*) Each datum is the mean of seven or eight determinations. *c*) Each datum is the mean of three or four determinations.

the acceleration. These results may be due to a change of steric configuration of the sample polymer in the accelerated test. The raw data obtained in these experiments are listed in Table IV.

From the adhesiveness test data, significant differences in adhesiveness were observed among the samples, though the adhesive force of all samples was almost enough for actual application. However, in the cases of samples with large F values, the adhesive force between the sample and the plunger tended to exceed the adhesive force between the polymer and the backing. In the case of the *in vivo* percutaneous absorption test, significant differences were also observed; in paticular, the value of absorption observed with sample No. 9 at 8 h was about 3 times larger than the value with sample No. 7.

Regression Equation for the Prediction of the Plaster Characteristics

In order to predict each characteristic of the model plaster formulation, the amounts of 2-ethylhexyl acrylate (X_1), vinyl acetate (X_2) and 2-hydroxyethyl acrylate (X_3) were selected as the independent variables. The following equation was used for the prediction of each characteristic.

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

where Y is the level of the characteristic, b_i is the regression coefficient, and X_i is the level of the independent variable. Optimum regression equations obtained are summarized in Table V. The correlation coefficient which was doubly adjusted with degrees of freedom was used as the index for selection for the optimum combination of factors.[5] High correlation coefficients with statistical significance were observed in all cases.

Contour Curves and Relationships among the Experimental Parameters

The physical significance of the regression equation was explored by means of contour graphs. Figures 2 and 3 show the contour curves for each dissolution characteristics as a function of X_1, X_2 and X_3 and for the stability of the dissolution behaviors, respectively. The

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

Y	$Y=b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_1^2+b_5X_2^2+b_6X_3^2+b_7X_1X_2+b_8X_1X_3+b_9X_2X_3$											
	b_0	b_1	b_2	b_3	b_4	b_5	b_6	b_7	b_8	b_9	r[a]	F[b]
Dissolution												
$C_{0.5\,h}$ (%)	50.52	2.17	—	—	−4.53	−3.42	−3.52	—	—	−3.42	0.954	3.90[c]
$C_{1\,h}$ (%)	60.48	1.79	—	—	−4.59	−5.01	−4.75	—	—	−4.96	0.875	5.94[c]
$C_{4\,h}$ (%)	62.75	2.43	—	—	—	−2.63	−3.37	—	3.39	−4.49	0.827	8.18[d]
Stability of dissolution												
$Ds_{1\,h}$	−27.23	—	—	2.94	4.84	7.06	7.17	—	—	3.90	0.815	3.55[c]
$Ds_{4\,h}$	−35.93	—	−4.17	—	6.17	8.94	9.60	—	−4.31	—	0.980	8.45[d]
Adhesiveness												
F (g)	71.82	—	−3.71	11.04	−4.07	—	—	—	—	—	0.855	9.93[d]
Percutaneous absorption												
$C_{4\,h}$ (g/ml)	1.17	0.13	—	—	—	0.48	—	—	−0.20	0.37	0.899	10.24[d]
$C_{8\,h}$ (g/ml)	1.94	0.54	0.40	—	0.42	0.31	—	—	0.48	—	0.912	8.89[d]

a) Multiple correlation coefficient. *b*) Level of significance. *c*) $p<0.05$. *d*) $p<0.01$.

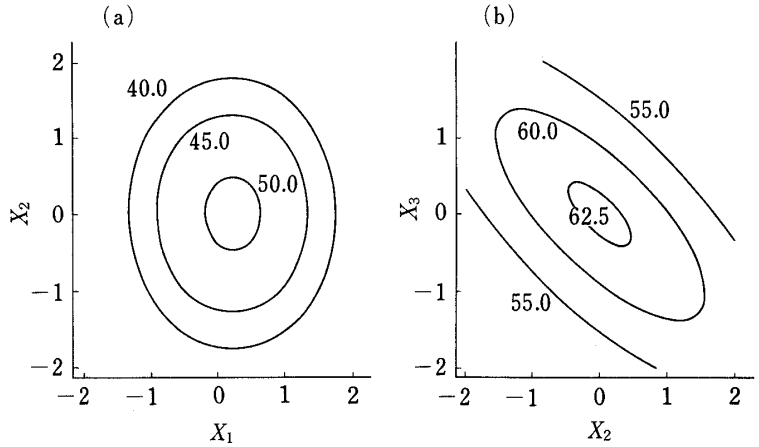

Fig. 2. Contour Curves for Amount of KPF Dissolved (C) as a Function of X_1, X_2 and X_3

(a) $C_{t=0.5\,h}$ (%), $X_3=0$. (b) $C_{t=4.0\,h}$ (%), $X_1=0$.

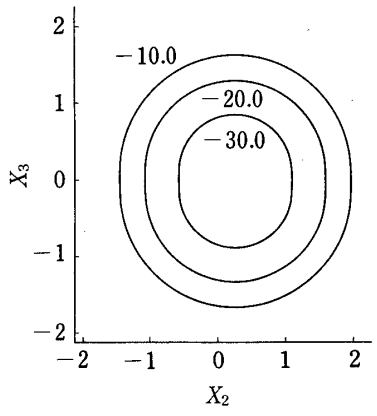

Fig. 3. Contour Curves for Stability of Dissolution Profile (Ds) as a Function of X_1, X_2 and X_3

$Ds_{t=4.0\,h}$ (%), $X_1=0$.

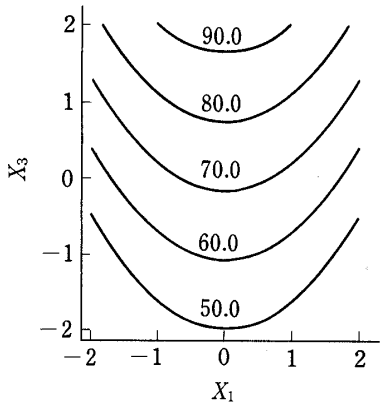

Fig. 4. Contour Curves for Adhesiveness (F) as a Function of X_1, X_2 and X_3

F (g), $X_2=0$.

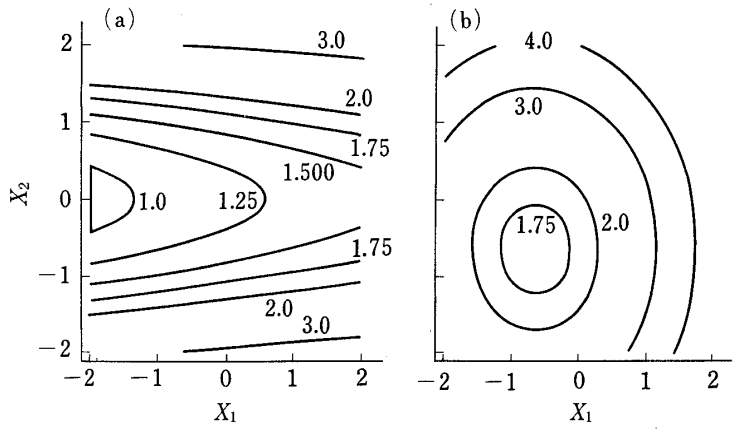

Fig. 5. Contour Curves for Percutaneous Absorption as a Function of X_1, X_2 and X_3
(a) $C_{t=4\,h}$ (μg/ml), $X_3=0$. (b) $C_{t=8\,h}$ (μg/ml), $X_3=0$.

TABLE VI. Conditions for the Synthesis of Acrylic Plaster Polymer

X_1:	65.0 g
X_2:	60.0 g
X_3:	1.375 g

TABLE VII. Predicted and Experimental Values of Each Characteristic of the Optimum Acrylic Plaster

Characteristic	Predicted	Experimental
$C_{8\,h}$ (μg/ml)	7.5	3.9
$Ds_{4\,h}$ (%)	14.0	−3.7
F (g)	57.7	52.9

optimum point was observed at the center of the contour graph, as shown in Fig. 2. In the early dissolution stage ($C_{0.5\,h}$), the factors X_1 and X_2 strongly affected the dissolution of KPF. On the other hand, contribution of the factors X_2 and X_3 was mainly observed in the final dissolution stage ($C_{4\,h}$). The worst point of stability of dissolution behavior was observed at the center of the graph. Therefore, it is clear that a plaster which gives a high dissolution value of KPF is not stable to heat and moisture. Figure 4 shows the contour curves for adhesiveness of the plaster as a function of X_1, X_2 and X_3. The increase of X_3 resulted in an increase of adhesiveness when X_1 was fixed, and this seemed to be the effect of the increase of functional groups such as the hydroxyl group of X_3 in the polymer vehicle with increase of the amount of X_3. Figure 5 shows the contour curves for percutaneous absorption as a function of X_1 and X_2. The absorption of KPF was decreased near the center of the graphs, indicating that the dissolution behavior of KPF in this *in vitro* system was not correlated to the percutaneous absorption under these experimental conditions.

Optimization of the Conditions for the Synthesis of Acrylic Plaster Polymer

The optimization process used in this study was almost the same as described in the previous paper.[6] Four kinds of regression equations shown in Table V were structured as a constrained non-linear optimization problem for determining the best conditions for the synthesis of acrylic plaster polymer. The equation for $C_{8\,h}$ was treated as the object function because increase of the percutaneous absorption was considered to be the primary objective. The adhesiveness (F) and the stability of the dissolution behavior ($Ds_{4\,h}$) were used as constraints: those were $F \leqq 60$ and $Ds_{4\,h} \geqq -10$. Under these constraints, the optimum solution which gives the maximum value of $C_{8\,h}$ was calculated, and the results are summarized in Table VI. Predicted and experimental values of characteristics which were obtained with the optimum solution are listed in Table VII. The experimental value of $C_{8\,h}$ of

the optimum formulation was higher than those of the 15 model formulations, though the experimental and predicted values of $C_{8\,h}$ did not agree well. The reason for this might be that the optimum solution was located close to the boundary of the area covered by this research.

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References and Notes

1) K. Fukuzawa, "Nenchakugijutsu," Kobunshikankokai, Kyoto, 1978.
2) I. Koyama, 7th Conference on Pharmaceutical Technology, Shirakabako, July 1982.
3) K. Takayama, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **31**, 4496 (1983).
4) I. Yamagami, Y. Akitoshi and T. Nagai, *Yakuzaigaku*, **44**, 109 (1984).
5) T. Haga, H. Takeuchi and T. Okuno, *Quality, J.S.Q.C.*, **6**, 35 (1976).
6) K. Takayama, H. Imaizumi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **33**, 292 (1985).