Computer Optimization for the Formulation of Controlled-Release Theophylline Tablet Made of Micronized Low-Substituted Hydroxypropylcellulose and Methylcellulose[1)]

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A computer optimization technique based on response surface methodology was applied to the formulation optimization of a controlled-release tablet made of micronized low-substituted hydroxypropylcellulose (L-HPC) and methylcellulose (MC) as matrix carriers. Theophylline was selected as the model drug, and was directly compressed with these carriers. Since the tablet showed slow disintegration from the outer layer, release was estimated to involve a coupling of diffusion and erosion release mechanisms. The percentage of drug released at time i (D_i) and percent disintegration of the matrix not including the drug at 5 h (Dis_5) were examined. D_i and Dis_5 decreased with an increase in the amount of micronized L-HPC (X_1) and with a decrease in the amount of MC (X_2) in the tablet. In contrast, they were little affected by compression pressure (X_3). These response variables—D_i and Dis_5—were predicted well by a multiple regression equation involving the combination of X_1, X_2 and X_3. In the optimization study, formulation of the controlled-release tablet was examined to obtain zero-order release over 10 h. The predicted release rate obtained from the optimum formula agreed well with experimental values. The result suggests that the technique is useful for the formulation optimization of this matrix system, and that this system has the potential to control the release rate, including zero-order release profile.

Keywords controlled release; matrix tablet; response surface methodology; micronized low-substituted hydroxypropylcellulose; methylcellulose; theophylline

Cellulose derivatives are in broad use as ingredients of pharmaceutical excipients, such as disintegrants, binder and coating agents *etc.* In recent years, much work has been done to investigate and develop novel functions for these compounds in order to improve conventional dosage forms.[2,3)] Water-soluble and swellable cellulose derivatives have been used as the matrix carrier of controlled-release tablets.[4)] Derivatives like hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (CMC-Na) and hydroxypropylcellulose (HPC) form a gel on contact with water which controls the release of drug from the matrix.

We earlier reported that water-insoluble and swellable celluloses of fine particle size have potential use as a matrix carrier in controlled-release tablets.[5–7)] For example, while intact low-substituted hydroxypropylcellulose (L-HPC) has been used as disintegrant, micronized L-HPC with a particle size less than 5 μm gives a non-disintegrating, controlled-release tablet. This is presumed due to the rapid hydration of the micronized L-HPC on contact with water, resulting in the formation of a diffusion-limiting gel layer at the surface of the tablet. This layer in turn slows drug release and water penetration into the tablet. Kawashima *et al.*[8)] also reported that micronized L-HPC works as a controlled-drug release matrix.

We recently found that the addition of methylcellulose (MC) as a swellable polymer, the hydration rate of which is not fast enough to form a gel layer, to the micronized L-HPC matrix tablet provides a controlled-release tablet with slow disintegration.[9)] Even though the release of low-solubility drugs from non-disintegrating controlled-release tablets generally tends to be incomplete, sustained and complete release of drug can be obtained by slow disintegration from the outer layer of the tablet.

The optimization technique based on the response surface method has proven its usefulness in a number of pharmaceutical studies.[10–13)] These have not been limited to formulation studies; the technique has found wide application in the optimization of manufacturing processes[14–16)] and analytical methods.[17)] The technique has become important in formulation studies of controlled-release systems, since the quantitative prediction of release rate is required to precisely control bioavailability.

The aim of the present study was to optimize the formulation and process conditions of a theophylline controlled-release tablet made of micronized L-HPC and MC as matrix carriers by means of a computer optimization technique based on the response surface method.[18–20)] The effect of three independent formulation and process variables, namely the amount of micronized L-HPC, that of MC, and compression pressure, on the release rate and tablet disintegration was examined. The optimum combination of independent variables was determined by analysis of data using the set of computer programs developed by Takayama and Nagai.[18)]

Experimental

Materials Micronized L-HPC (type LH-41, Shin-Etsu Chemical Co., Ltd., Japan) was generously donated by the manufacturer. Theophylline (Shiratori Pharmaceutical Co., Ltd., Japan), MC (type SM-15, Shin-Etsu Chemical Co., Ltd., Japan) and magnesium stearate (Nittou Kasei Kogyo Co., Ltd., Japan) were of JP XI grade.

Experimental Design The experimental design employed was a central

TABLE I. Formulation and Compression Pressure of Controlled-Release Theophylline Tablet for Central Composite Spherical Experimental Design

Experiment number	Factor level in coded form			Formula (mg/tablet)					Compression pressure (t)
	X_1	X_2	X_3	THEO[a]	L-HPC[b]	MC[c]	Mg-St[d]	Total weight	
1	−1	−1	−1	100	92.2	92.2	3	287.4	0.71
2	1	−1	−1	100	207.8	92.2	3	403.0	0.71
3	−1	1	−1	100	92.2	207.8	3	403.0	0.71
4	1	1	−1	100	207.8	207.8	3	518.6	0.71
5	−1	−1	1	100	92.2	92.2	3	287.4	1.29
6	1	−1	1	100	207.8	92.2	3	403.0	1.29
7	−1	1	1	100	92.2	207.8	3	403.0	1.29
8	1	1	1	100	207.8	207.8	3	518.6	1.29
9	$-\sqrt{3}$	0	0	100	50.0	150.0	3	303.0	1.00
10	$\sqrt{3}$	0	0	100	250.0	150.0	3	503.0	1.00
11	0	$-\sqrt{3}$	0	100	150.0	50.0	3	303.0	1.00
12	0	$\sqrt{3}$	0	100	150.0	250.0	3	503.0	1.00
13	0	0	$\sqrt{3}$	100	150.0	150.0	3	403.0	0.50
14	0	0	$-\sqrt{3}$	100	150.0	150.0	3	403.0	1.50
15	0	0	0	100	150.0	150.0	3	403.0	1.00
16	0	0	0	100	150.0	150.0	3	403.0	1.00
17	0	0	0	100	150.0	150.0	3	403.0	1.00

a) Theophylline. *b*) Micronized low-substituted hydroxypropylcellulose: LH-41. *c*) Methylcellulose: SM-15. *d*) Magnesium stearate.

composite spherical design for three factors. The amounts of micronized L-HPC (X_1) and MC (X_2) were selected as independent formulation variables, and the compression pressure of tabletting (X_3) was selected as an independent process variable. Experimental units were translated to physical units as summarized in Table I. Regarding formulation variables, the weight amount instead of percentage amount was used as physical unit, and thus the total weight of tablet varied among the experiments; however, X_1 and X_2 can vary independently. For the physical unit using percentage amount, the total weight of tablet can be identical, but X_1 and X_2 are no longer independent of each other. Seventeen experiments were performed according to the design matrix, including three replications of the center point.

Preparation of Controlled-Release Tablet Theophylline, micronized L-HPC, MC and magnesium stearate as a lubricant were mixed in a polyethylene bag for 5 min. The mixture was then passed through an 80 mesh sieve, and directly compressed into tablets by a universal testing machine (Autograph, type AG-5000B, Shimadzu Co., Ltd., Japan) at a compression speed of 5 mm/minutes. A flat-face punch 10 mm in diameter was used for tabletting. Each sample tablet contained 100 mg of theophylline; preparation was performed in 50 tablet batches.

Determination of Response Variables The response variables measured on the resulting tablets were: D_i, % released at i h (i=1—10); and Dis_5, % of matrix carrier disintegration at 5 h. Both variables were represented as the mean of three determinations.

a) Dissolution Studies: Dissolution testing was performed by the JP XII paddle method at 50, 100 and 200 rpm in 900 ml of water at 37 °C. Theophylline was assayed by an automated flow-through UV spectrophotometric procedure at 272 nm with a cell length of 1 mm (Automated Dissolution Apparatus, Toyama Sangyo Co., and Shimadzu Co., Ltd., Japan).

b) Determination of % Disintegration: % Disintegration of the matrix carrier of the tablet at 5 h in the dissolution test (Dis_5) was determined as follows. The sample tablet was first weighed, and dissolution testing was carried out as described above for 5 h. The test fluid was carefully screened with a 12 mesh sieve to remove the remaining core of the tablet, which was then dried at 50 °C for 24 h. The dried core was weighed as the remaining core of the tablet, and Dis_5 was calculated according to the following equation:

$$Dis_5\ (\%) = \frac{W_i(\mathrm{mg}) - W_d\ (\mathrm{mg}) - 100\ (\mathrm{mg}) \times D_5\ (\%)/100}{W_i\ (\mathrm{mg}) - 100\ (\mathrm{mg})} \times 100 \quad (1)$$

where W_d is the weight of the remaining tablet core, W_i is the initial weight of the sample tablet, D_5 is the percentage of theophylline released from the tablet at 5 h, and 100 (mg) is the content of theophylline in the tablet.

Prediction of Response Variables The response variables were predicted using the second-order polynomial equation shown in Eq. 2:

$$Y = b_0 + b_1 \times X_1 + b_2 \times X_2 + b_3 \times X_3 + b_4 \times X_1^2 + b_5 \times X_2^2 + b_6 \times X_3^2 + b_7 \times X_1 \times X_2 + b_8 \times X_1 \times X_3 + b_9 \times X_2 \times X_3 \quad (2)$$

where Y is the response variable, b_i (i=0—9) is the regression coefficient for a second-order polynomial, and X_i (i=1, 2 and 3) is the independent variable in coded form. The optimum regression equation was obtained using the computer programs.

Computer Programs A set of computer programs developed by Takayama *et al.*[18] was used in this study. Written in BASIC, the programs consisted of a multiple regression analysis, a three-dimension graph and a constrained nonlinear optimization program.

Results and Discussion

Regression Analysis and Response Surface The release profiles and % disintegration at 5 h (Dis_5) of the matrix tablets are shown in Fig. 1 and Table II, respectively. A wide variation in these variables among experiments was observed, indicating that they were greatly affected by changes in the level of factors. The fastest sample released almost 100% of the drug within 3 h (experiment No. 9), and the slowest only approximately 85% at 15 h (experiment No. 13). For Dis_5, the highest samples gave 100% (experiment Nos. 3 and 9), but the lowest less than 5% (experiment Nos. 2, 6 and 11). In addition, only a small difference in release profile was observed among the triplicate data of the center point (experiment Nos. 15, 16 and 17), indicating that the release profile of the tablet showed good reproducibility across batches. The relative standard deviation (RSD) of % released at 5 h (D_5) and RSD of Dis_5 at the center point were 2.9% and 8.0%, respectively.

The response variables of D_i (i=1—10) and Dis_5 of the matrix (Table I) were predicted by regression analysis according to Eq. 1. To obtain the optimum regression equation, the overall combination of factors was investigated; the best combination was subsequently selected by using the correlation coefficient which was doubly adjusted with degrees of freedom as an index. The optimum regression equations are summarized in Table

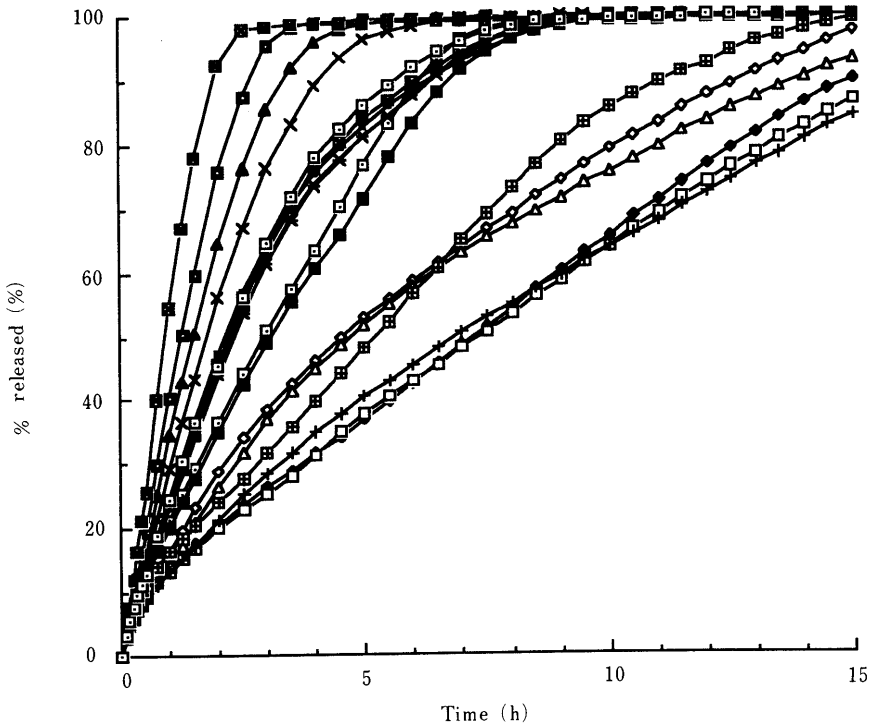

Fig. 1. Release Profiles of Controlled-Release Theophylline Tablets Obtained by Central Composite Spherical Experimental Design for Three Factors

—⊡—, ex. No. 1; —◆—, ex. No. 2; —■—, ex. No. 3; —◇—, ex, No. 4; —■—, ex, No. 5; —□—, ex. No. 6; —▲—, ex. No. 7; —△—, ex. No. 8; —⊠—, ex. No. 9; —+—, ex. No. 10; —⊞—, ex. No. 11; —×—, ex. No. 12; —✳—, ex. No. 13; —⧅—, ex. No. 14; —■—, ex. No. 15; ———, ex. No. 16; —⊡—, ex. No. 17.

TABLE II. % Released at 5 h (D_5) and % Disintegration at 5 h (Dis_5) of Matrix Obtained by Central Composite Spherical Experimental Design for Three Factors

Experiment number	% released at 5 h (D_5)	% disintegration at 5 h (Dis_5)
1	76.9	66.3
2	36.8	4.7
3	99.5	100.2
4	52.8	30.8
5	71.5	58.1
6	37.7	4.2
7	98.7	98.6
8	51.7	26.9
9	98.9	100.5
10	40.5	12.0
11	48.2	3.4
12	96.4	91.5
13	81.0	75.2
14	83.8	65.7
15	82.8	72.3
16	81.3	62.0
17	86.0	70.4

III. All response variables are predicted accurately, since the values of the multiple correlation coefficient were satisfactory and the regression equations were significant, with high F_0 values.

Both D_i (or release rate) and Dis_5 decreased with increasing amounts of micronized L-HPC (X_1) and with decreasing amounts of methylcellulose (X_2). However, they were only slightly affected by compression pressure (X_3).

Table III shows that the level of compression pressure (X_3), its second-order term (X_3) and interaction with other factors ($X_1 \times X_3$ and $X_2 \times X_3$) had no significance on regression coefficients in any response variable, in contrast to regression coefficients of the other factors (X_1 and X_2), which were significant. Figures 2a, 2b and 2c show the response surfaces for D_5, D_{10} and Dis_5, respectively, as a function of X_1 and X_2. As the amount of micronized L-HPC (X_1) increased or the amount of MC (X_2) decreased, the depression of D_5, D_{10} and Dis_5 as a function of X_1 and X_2 steepened. The slope of response surface of D_{10} was more gentle than that of D_5.

Release Mechanism Alderman[4] reported that a hydrophilic matrix tablet made of water-soluble polymer forms a gel layer on contact with dissolution medium, and that the gel layer controls the release of the drug in two ways. One is by the diffusion of drug through the gel layer, and the other is the erosion of the gel layer so that the drug is strictly exposed to the dissolution medium regardless of its solubility. Additionally, the release rate of drugs decreases as polymer concentration in the matrix increases; this is due to the enhancement of strength of the gel layer, which results in the reduction of drug diffusion and water uptake through the gel layer.

In the present study, the release rate decreased as the amount of micronized L-HPC (X_1) increased. This may suggest that the strength of the gel layer is affected by the concentration of polymer, as is the case with water-soluble polymer matrix described above. Additionally, an increase in polymer concentration in the matrix leads to a decrease in the release rate, as can be understood through Higuchi's

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

Coefficient	Regression coefficient value										
	D_1 (%)	D_2 (%)	D_3 (%)	D_4 (%)	D_5 (%)	D_6 (%)	D_7 (%)	D_8 (%)	D_9 (%)	D_{10} (%)	Dis_5 (%)
b_0	21.7[a]	48.5[a]	59.7[a]	75.8[a]	80.6[a]	86.9[a]	92.1[a]	95.6[a]	97.5[a]	98.2[a]	66.8[a]
b_1 (X_1)	−9.27[a]	−17.1[a]	−19.6[a]	−19.7[a]	−19.2[a]	−18.7[a]	−17.7[a]	−16.2[a]	−14.4[a]	−12.6[a]	−29.3[a]
b_2 (X_2)	4.25[a]	9.93[a]	12.9[a]	13.2[a]	11.7[a]	9.33[a]	7.22[a]	5.68[a]	4.48[a]	3.58[a]	19.7[a]
b_3 (X_3)	—[b]	—	—	—	—	—	—	—	—	—	—
b_4 ($X_1 \times X_1$)	2.89[a]	—	—	−4.7[a]	−5.63[a]	−6.57[a]	−7.35[a]	−7.68[a]	−7.51[a]	−6.79[a]	−5.44
b_5 ($X_2 \times X_2$)	—	−4.20[a]	−3.96[a]	−5.54[a]	−4.76[a]	−4.84[a]	−4.90[a]	−4.64[a]	−3.93[a]	−3.16[a]	−8.37
b_6 ($X_3 \times X_3$)	—	−2.60	—	−2.16	—	—	—	—	—	—	—
b_7 ($X_1 \times X_2$)	−3.71[a]	−6.70[a]	−7.09[a]	−5.39[a]	—	—	—	3.09	3.16	3.08	—
b_8 ($X_1 \times X_3$)	—	—	—	—	—	—	—	—	—	—	—
b_9 ($X_2 \times X_3$)	—			—	—	—	—	—		—	—
r[c]	0.942	0.961	0.976	0.980	0.967	0.967	0.961	0.965	0.966	0.969	0.973
s[d]	4.24	6.80	5.83	5.97	6.62	6.26	6.45	5.83	5.15	4.34	9.27
F_o[e]	23.5[f]	26.3[f]	61.5[f]	40.3[f]	43.7[f]	43.6[f]	36.0[f]	30.0[f]	30.7[f]	33.3[f]	53.9[f]

a) *t*-statistic, significant at the 5% level. *b*) This factor is not included in the optimum regression equation. *c*) Multiple correlation coefficient. *d*) Standard deviation. *e*) Observed *F* value (mean square regression/mean square residual). *f*) Significant at the 1% level.

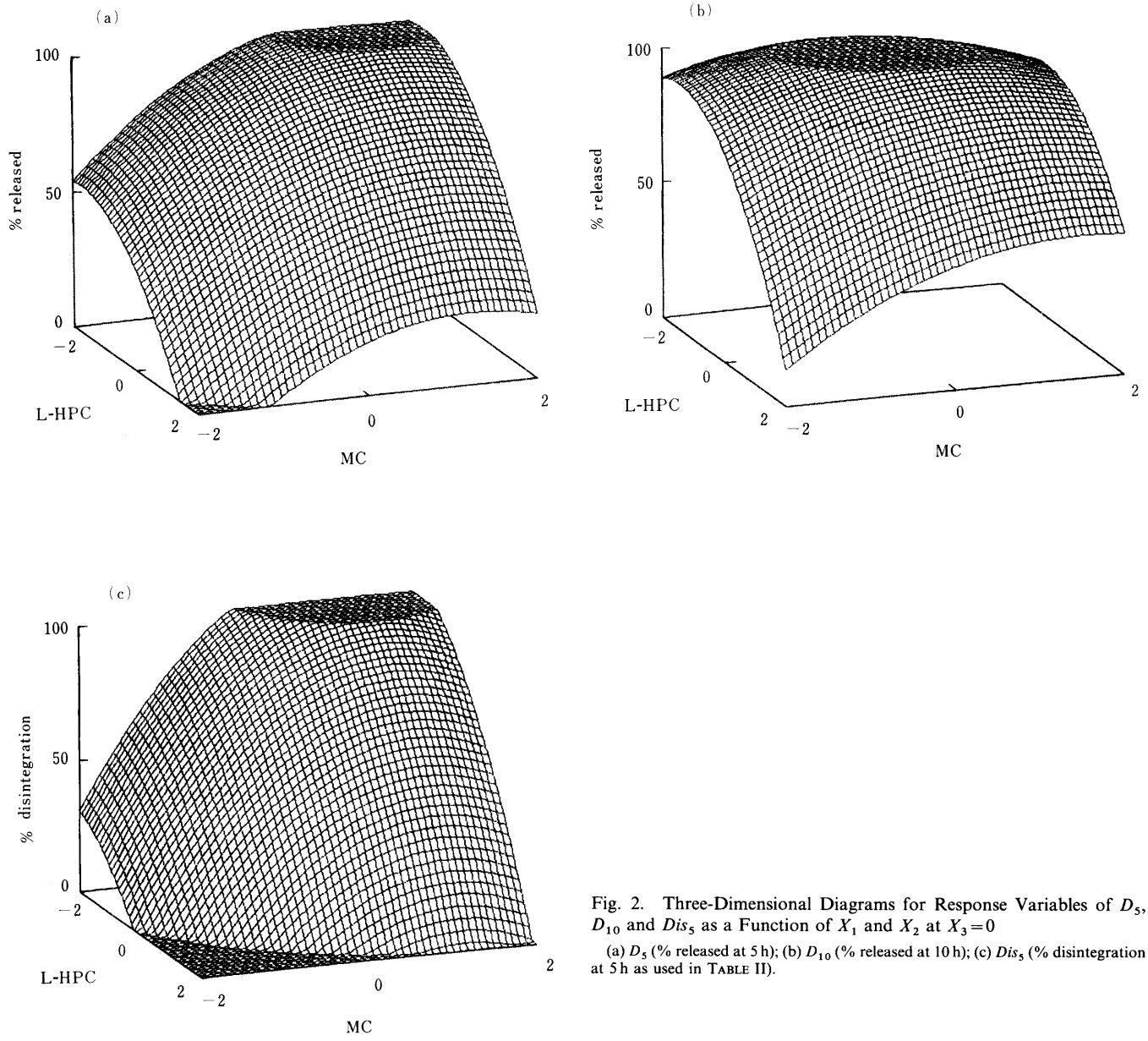

Fig. 2. Three-Dimensional Diagrams for Response Variables of D_5, D_{10} and Dis_5 as a Function of X_1 and X_2 at $X_3=0$

(a) D_5 (% released at 5 h); (b) D_{10} (% released at 10 h); (c) Dis_5 (% disintegration at 5 h as used in TABLE II).

equation.[21] The amount of drug released per unit area of tablet at time t is proportional to the square root of the term $2A-\varepsilon C$, where A is the concentration of drug in the matrix, ε is porosity of the matrix and C is the solubility of drug in the dissolution medium.

In contrast, the release rate increased with an increase in the amount of MC (X_2). MC hydrates and swells similarly to micronized L-HPC, although the hydration rate is presumed to be different. While the MC matrix tablet does not hydrate fast enough to protect the tablet from fast disintegration and dissolution,[4] the micronized L-HPC tablet does hydrate fast enough to form a diffusion-limiting gel layer and shows sustained release action. Thus, the swelling action of MC may weaken the structure of the gel layer. As the amount of MC (X_2) increased, the strength of the gel layer decreased and the layer was unable to maintain its form over the entire range of drug release. Disintegration of swollen particles of micronized L-HPC from the outer layer of the tablet was observed during the dissolution test. This slow disintegration of the gel layer consequently leads to an increase in the release rate; the drug could diffuse out and/or be exposed to the dissolution medium more easily.

Generally, a decrease in compression pressure increases rate of water uptake due to increase in tablet porosity, resulting in the acceleration of tablet disintegration and drug release. In our matrix system, the water uptake, however, might be little affected by the porosity but, rather, be limited by the fast formation of the gel layer; hence the effect of compression pressure (X_3) on the drug release was not observed.

As shown in Table II, D_5 was larger than Dis_5 in all samples. This indicates that the drug was released not only from disintegration of the outer layer but also from the matrix through the outer gel layer. In other words, drug release from the matrix was probably controlled by diffusion through the gel layer and by tablet disintegration.

Ranga Rao *et al.*[22] and Devi *et al.*[23] reported that a zero-order release tablet can be obtained by mixing and directly compressing a drug with an optimum amount of nonionic polymer such as HPC or MC and the ionic polymer CMC-Na. The rate of erosion of the matrix is faster than that of a matrix containing only drug and HPC, and surface area of the matrix decreases with time due to erosion. The coupling of diffusion and erosion is therefore well balanced with the size reduction of the matrix due to erosion, and thus at optimum formulation a nearly zero-order release can be obtained. Since our matrix system gradually disintegrates from the outer layer and releases at nearly zero-order in the optimum formulation as described later, we assumed that a similar drug release mechanism is involved. However, the difference in the mechanism of tablet erosion should be noted: water-soluble polymer matrix erodes as the swollen polymer slowly dissolves, while the disintegration of the micronized L-HPC/MC matrix system proceeds as swollen MC slowly disintegrates from the swollen micronized L-HPC gel layer.

Mathematical Optimization As a model of optimized controlled release, we develop a controlled-release tablet with zero-order release over 10 h.

Generally, the optimization problem can be attributed to the minimization of the objective function under a set of constraints. In order to optimize the release profile, a set of objective values of release amounts at ten definite periods of a dissolution test was used. Therefore, ten objectives are included so that a multi-objective optimization can be adapted. Since all the objectives are optimized simultaneously, all response variables should be incorporated into a single objective function. Although there are many mathematical approaches for the integration of a multi-objective into a single objective function, we employed the simple square summation of the difference between the simultaneous optimal value and the ideal value of each response variable as given in Eq. 3:

$$F(X)=\sum_{i=1}^{10}(D_i-Q_i)^2 \tag{3}$$

where $F(X)$ is the single objective function for simultaneous optimization, D_i is % released at i h and is predicted by regression analysis, and Q_i is the ideal value for each D_i.

In the case of zero-order release over 10 h, the ideal objective value as Q_i (%) at i h ($i=1$—10) of the dissolution test would be equal to ten times i (10% at 1 h—100% at 10 h). We first investigated whether each ideal objective value (Q_i) was located within the experimental region ($X_1^2+X_2^2+X_3^2\leq 3$). Only Q_1 (10% at 1 h) was found to be outside this region; the closest to the ideal value was 13.1% at $X_1=1.56$ and $X_2=0.76$.

We therefore tried to solve two cases of the optimization problem: Case 1 is the optimization with constraint for search limit of optimum formula over the experimental region; case 2 is the optimization without constraint for search limit. Since it is rather difficult to solve a constrained optimization problem (case 1) without any mathematical modifications, the function, $F(X)$, was converted to the transformed function, $T(X, r)$, by adding a penalty function as shown below.[18]

Case 1: with constraint over the experimental region

$$\begin{aligned}F(X)=&(D_1-13.1)^2+(D_2-20)^2+(D_3-30)^2+(D_4-40)^2\\&+(D_5-50)^2+(D_6-60)^2+(D_7-70)^2+(D_8-80)^2\\&+(D_9-90)^2+(D_{10}-100)^2\end{aligned} \tag{4}$$

$$T(X, r)=F(X)+(1/r)\phi G(X)^2 \tag{5}$$

$$G(X)=3-(X_1^2+X_2^2+X_3^2) \tag{6}$$

where $G(X)<0$, $\phi=1$; where $G(X)\geq 0$, $\phi=0$

where $G(X)$ is the inequality function restricted by the experimental region, ϕ is a step function, and r is a perturbation parameter ($r>0$). With decreasing r values, the minimum point of $T(X, r)$ sequentially approaches the accurate solution of the optimization problem.

Case 2: without constraint

$$\begin{aligned}F(X)=&(D_1-10)^2+(D_2-20)^2+(D_3-30)^2+(D_4-40)^2+(D_5-50)^2\\&+(D_6-60)^2+(D_7-70)^2+(D_8-80)^2+(D_9-90)^2\\&+(D_{10}-100)^2\end{aligned} \tag{7}$$

The results estimated for these two cases are shown in Table IV. The optimum formula with constraint was located on the boundary of the experimental region, while

that without constraint was out of the experimental region. Figure 3 shows the three-dimensional diagrams for the objective function with and without constraint (Eqs. 5 and 7) as a function of X_1 and X_2 at $X_3=0$. In these diagrams, a large negative peak was observed, and the minimum points of both functions agreed with the respective optimum formula. Additionally, it was confirmed that the optimum formula in case 1 was well restricted by the constraint over the experimental region, since the outer side of the negative peak was sharper than the case without constraint.

TABLE IV. Optimum Formulation of Controlled-Release Theophylline Tablet

Factor	With constraint		Without constraint	
	Coded form	Physical unit	Coded form	Physical unit
X_1	−0.409	126.4 mg	−0.634	113.4 mg
X_2	−1.694	52.2 mg	−1.802	45.9 mg
X_3	0.000	1.00 ton	0.002	1.00 ton

Figure 4 shows the predicted and the experimental release profiles of the respective optimum formulae. Both optimum formulae gave a satisfactory release profile in prediction, since both predictions coincided with the ideal release profile and gave nearly zero-order release. Regarding the experimental release profile, the optimum formula with constraint showed good agreement with the predicted release profile and released at nearly zero-order. In contrast, the optimum formula without constraint deviated somewhat from the predicted release profile. This suggests a limitation in predicting the response variable located at the outer region of the experimental design.

Considering the variation in gastrointestinal motility, the effect of agitation rate of dissolution testing on release rate of the optimum formula with constraint was examined. The release profile at 50 rpm agreed well with that at 100 rpm over the range of the test period. The release profile at 200 rpm agreed well with that at 100 rpm until 5 h, then at 200 rpm gradually deviated from the profile at 100 rpm upward. But the deviation is slight, that is, while % released at 10 h at 100 rpm was approximately

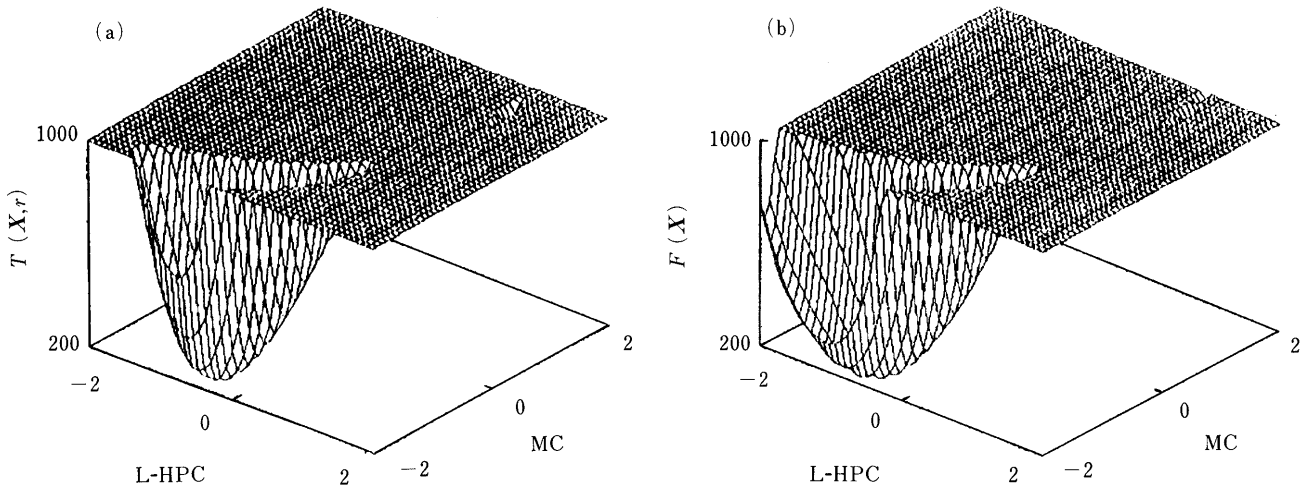

Fig. 3. Three-Dimensional Diagrams for the Transformed Objective Function, $T(X, r)$, Defined as Eq. 5, and Unconstrained Objective Function, $F(X)$, Defined as Eq. 7, as a Function of X_1 and X_2 at $X_3=0$

(a) With constraint ($r=0.01$); (b) without constraint.

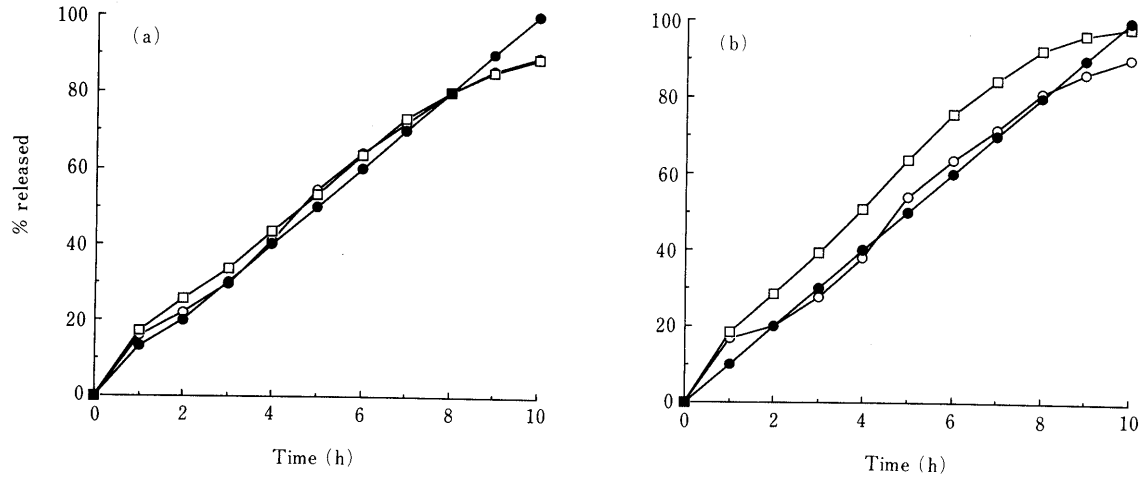

Fig. 4. Release Profiles of Controlled-Release Theophylline Tablets of Optimum Formulation

(a) Optimum formula determined with constraint; (b) optimum formula determined without constraint. —●— ideal, —○— predicted, —□— experimental.

90%, complete release was observed at 10 h at 200 rpm. Thus, it is concluded that the release rate of the optimum formula with constraint is not appreciably affected by mechanical forces.

In conclusion, these findings demonstrate that a computer optimization technique based on response surface methodology is useful in optimization of the formulation of controlled-release tablets made of micronized L-HPC and MC as matrix carrier. In particular, this technique is invaluable in the prediction and control of release rate. This study indicates that this matrix system has the potential to control the release rate, including zero-order release profile, by the mixing of the drug with an optimum amount of micronized L-HPC and MC.

References and Notes

1) This paper was presented in part at the 113th Meeting of the Pharmaceutical Society of Japan, Osaka, March 1993.
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