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Studies on Controlled Release of Indomethacin from PVA Hydrogel

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The polyvinyl alcohol (PVA) hydrogel containing 1-methyl-2-pyrrolidinone (MP) and sorbitol was preapred by the freeze and thaw method. The release rate of indomethacin from PVA hydrogel was used as a criterion for deciding the optimum formula of hydrogel using the computer optimization technique. The hydrogel of optimum formula was composed of PVA (10 w/v%), MP (0 w/v%), and sorbitol (40 w/v%) and the release rate of indomethacin was 1.981 $\mu g/ml \cdot min^{1/2}$.

Key words: PVA hydrogel, Indomethacin, Release rate, Computer optimization, Optimum formula

INTRODUCTION

Recent progress in the area of polymer gel is one of the great current research interests. Hydrogels, especially, have been receiving a lot of attention as devices for drug delivery systems (Geng and Ikada, 1986; Takamura *et al.*, 1987; Moromoto *et al.*, 1990; *Kwon et al.*, 1991; Watanabe *et al.*, 1991). The rheological properties and characteristics of PVA hydrogel have been reported through a number of experiments (Watase, 1983; Watase *et al.*, 1983; Urushizaki *et al.*, 1990).

In the present study, the release rates of indomethacin through hydrogel containing sorbitol and MP were examined to develop a controlled-release hydrogel which would provide a constant skin permeation rates of drug. Sorbitol and MP were chosen to control drug release from hydrogel effectively, and their interactions with other ingredients of hydrogel were investigated by means of computer optimization technique (Fonner *et al.*, 1970; Shek *et al.*, 1980; Akitoshi *et al.*, 1985; Takamura *et al.*, 1985; Montgomery, 1976).

EXPERIMENT

Materials

Polyvinylalcohol (PVA, MW. 70,000-100,000), indomethacin (IMD), 1-methyl-2-pyrrolidinone (MP), potassium phosphate monobasic anhydrous, and disodium hydrogen phosphate anhydrous were purchased from Sigma Chemical Co. (St. Louis, M.O., U.S.A.) and D-sorbitol from Shinyo Pure Chemical Co. (Japan). All the other chemicals used were of reagent grade and used without further purification.

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Instruments

UV spectrophotometer (LKB, Model 4050, U.K.), autoclave (Eyela, Japan), incubator (Napco, Model 330, U.S.A.) and dissolution tester (Model 82, GCA U.S.A.) fitted with driving control motor and thermostatic bath were used.

Preparation of indomethacin hydrogels

The entire process of the preparation of IDM hydrogels are shown in Chart I. 15 formulations, according to the experimental design as described in the previous report (Lee and Shin, 1988), were listed in Table I and the code levels of independent variables were translated into their physical unit in Table II. After dissolving appropriate amount of sorbitol from each formulations in Table I in pH 7.4 phosphate buffer solution, PVA was added and dissolved in autoclave (121℃, 30 min). Then MP and IDM were added and dissolved into PVA hydrogel solution and the concentration of IDM was set up to 10 mg/disk. The PVA hydrogel solutions were poured to each disks (diameter 10 mm, height 2 mm), and were frozen and thawed

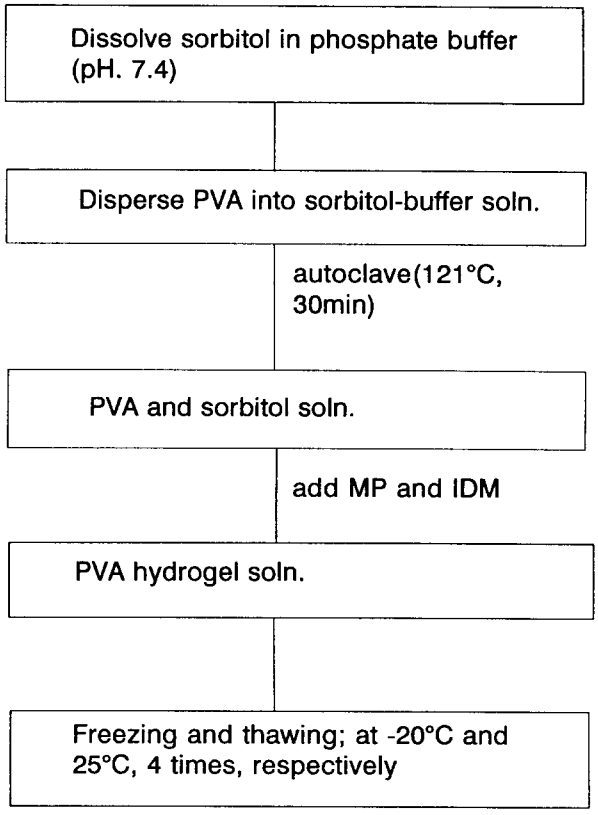

Chart I. Preparation scheme of PVA hydrogel.

for two hours, respectively. Such freezing and thawing operations were repeated four times.

The release tests

The release test of IDM from PVA hydrogel was performed at 37± 0.5℃ by the paddle method with a sinker and a rotation speed of 100 rpm as described in the USP XXI (USP, 1985). 500 ml of pH 7.4 phosphate buffer solution as a release solution was placed in a 1000 ml beaker. At appropriate intervals, 5 ml of sample was withdrawn from the dissolution medium and an eqivalent volume of fresh dissolution medium was added to keep the volume of the dissolution medium constant. The released IDM was determined at 267 nm by UV spectrophotometer. The results were plotted as the released amount of IDM versus the square root of time and the release rates were obtained by the linear regression method from each experiments with the aid of computer. The mean value of experiments repeated three times was taken as the release rate.

RESULTS AND DISCUSSION

Drug release rate

The release tests of IDM were carried out with PVA hydrogels prepared according to the formulations in Table I. The amount of IDM released from PVA hydrogel was a linear as a function of the square root of time and the results agreed well with the mathematical model postulated by Higuchi (Highuchi, 1961) for the release of drug from ointment bases.

Some release profiles of IDM from hydrogels of for-

Table I. Experimental Design for the three Factors

Fromulation No.	Factor level in coded from		
	X_1(PVA)	X_2(MP)	X_3(sorbitol)
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	0	0	0
10	2	0	0
11	−2	0	0
12	0	2	0
13	0	−2	0
14	0	0	0
15	0	0	−2

Table II. Physical amount of statistical code for experimetns

Factor (w/v%)	Factor level in coded from				
	−2	−1	0	1	2
X_1 (PVA)	10	15	20	25	30
X_2 (MP)	0	1	2	3	4
X_3 (Sorbitol)	0	10	20	30	40

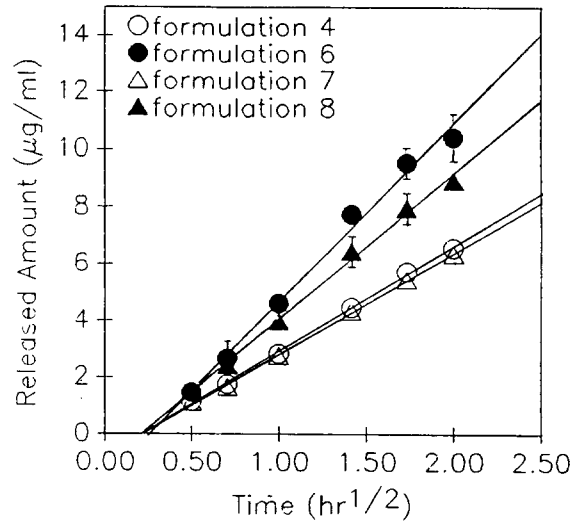

Fig. 1. Release profile of indomethacin obtained from some of the hydrogels prepared according to each formulations.

Table III. Comparison of the release rates obtained form both of the experiments and the second-order regression equation

Formulation No.	Release rate ($\mu g/ml \cdot min^{1/2}$)		
	Predicted values	Experimental values	R^{2*}
1	3.817	3.789	0.999
2	3.705	3.900	0.998
3	3.740	3.550	0.999
4	3.494	3.726	0.999
5	4.132	4.063	0.991
6	5.444	5.797	0.977
7	3.624	3.592	0.999
8	4.801	4.991	0.995
9	4.028	4.045	0.994
10	3.505	3.262	0.999
11	5.188	5.228	0.984
12	4.272	4.129	0.999
13	3.553	3.707	0.999
14	3.348	3.534	0.996
15	4.413	4.009	0.999

*R^2 is the determination coefficient.

mulations with varying ratios of X_1, X_2, and X_3 as listed in Table I were shown in Fig. 1. The release rates, which could be obtained from the slopes of these straight lines, were calculated by the least-square method. The prediction values of release rates of IDM from each of hydrogels prepared by 15 formulations were obtained from second-order regression equation (Lee and Shin, 1988) with the aid of computer and the results were listed in Table III. Form Fig. 1 and Table III, the release patterns of IDM from various formulas were different. Slower release of IDM were shown in higher concentrations of both PVA and sorbitol in hydrogel preparations. On the other hand, MP enhanced IDM release. Therefore, it was considered that the concentrations of PVA, sorbitol, and MP were important factors in optimizing drug release from hydrogels.

Polynomial regression equation for drug releases

The second-order polynomial regression equation was used in order to predict the properties of hydrogel formulation in Table I. The amounts of PVA (X_1), MP (X_2), and sorbitol (X_3), which were considered to be controllable directly, were selected as independent variables, and the released amount of drug from hydrogel was selected as a dependent variable (Y). The number of cycles and the temperatures used in freezing and thawing might be variables to be taken into consideration, but were neglected since hydrogels were prepared under the constant conditions of freezing at −20℃ and thawing at 25℃ repeatedly for four-times. Regression analysis of dependent variables was made with

Table IV. Parameters of second-order polynomial regression equation for the release rates determined by multiple regression analysis

Coefficient	Coefficient values
b_0	4.208
$b_1(X_1)$	−0.451
$b_2(X_2)$	0.180
$b_3(X_3)$	−0.266
$b_{11}(X_1)^2$	0.042
$b_{12}(X_1X_2)$	−0.108
$b_{13}(X_1X_3)$	0.356
$b_{22}(X_2)^2$	−0.074
$b_{23}(X_2X_3)$	−0.034
$b_{33}(X_3)^2$	−0.082
R^2	0.917
F	6.126

R^2 and F are the determination coefficient and the level of significance, respectively.

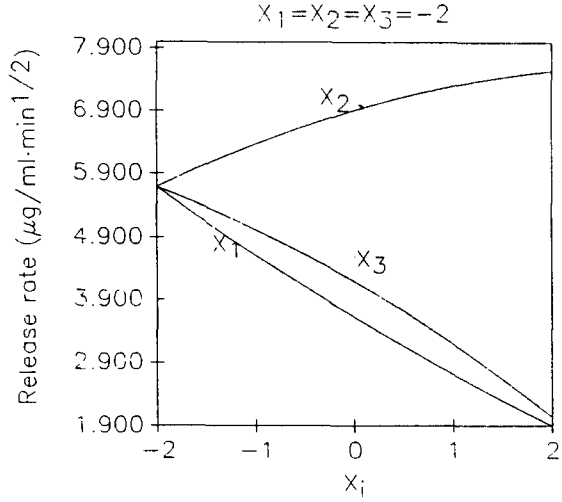

Fig. 2. Composite partial derivative plots for the release rate of indomethacin as a function of each independent variables of X_i (i=1, 2, 3). The solid lines are drawn by the computer.

the aid of personal computer using SAS (statistical analysis system) and the optimum regression equation of the dependent variable was selected on the basis of statistical significance from 511 (2^9-1) equations, the overall combination of three factors and five levels. The results of regression analysis were summarized in Tablve IV. The determination coefficient reflected that the optimum combination of independent variables was 0.917. The physical meaning of the regression equation was described by means of graphical approach.

Graphical approach

In the optimization process, two graphical techniques have been used to explain the interactions between each of the independent variables and the response

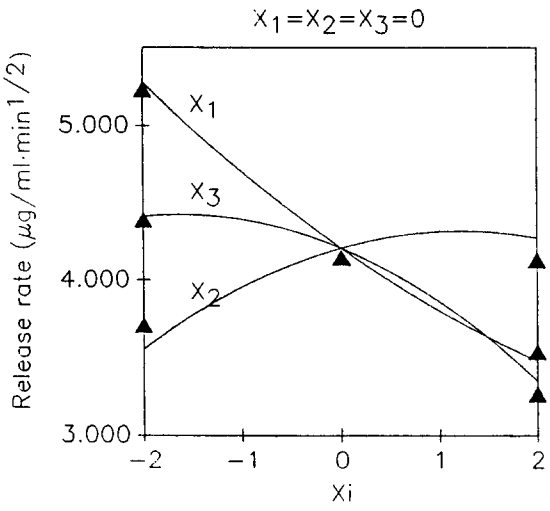

Fig. 3. Composite partial derivative plots for the release rate of indomethacin as a function of each independent variables of X_i (i=1, 2, 3). Each point represents experimental values and the solid lines are drawn by the computer.

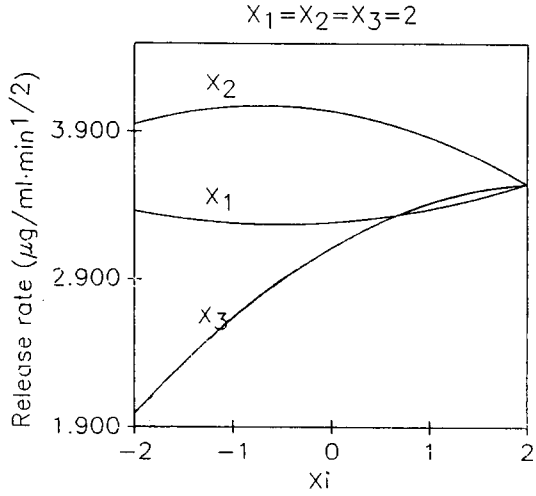

Fig. 4. Composite partial derivative plots for the release rate of indomethacin as a function of each independent variables of X_i (i=1, 2, 3). The solid lines are drawn by the computer.

variable (Fonner *et al.*, 1970; Lee and Shin, 1988). One is composite partial derivative plot which draw a given response variable as a function of one of the independent variables, changing the level of one of the independent factors continuously, while holding the others constant. Fig. 2, 3, and 4 show the composite partial derivative plots for the release rates of IDM as a function of each of the independent variables, X_i (i=1, 2, 3). In composite partial derivative plots, solid lines superimposed by computer represent changes in release rates according to the changes of the independent variable. The values noted at the top of Fig. 2, 3, and 4 mean the level at which any other variables are being held constant during the partial derivative

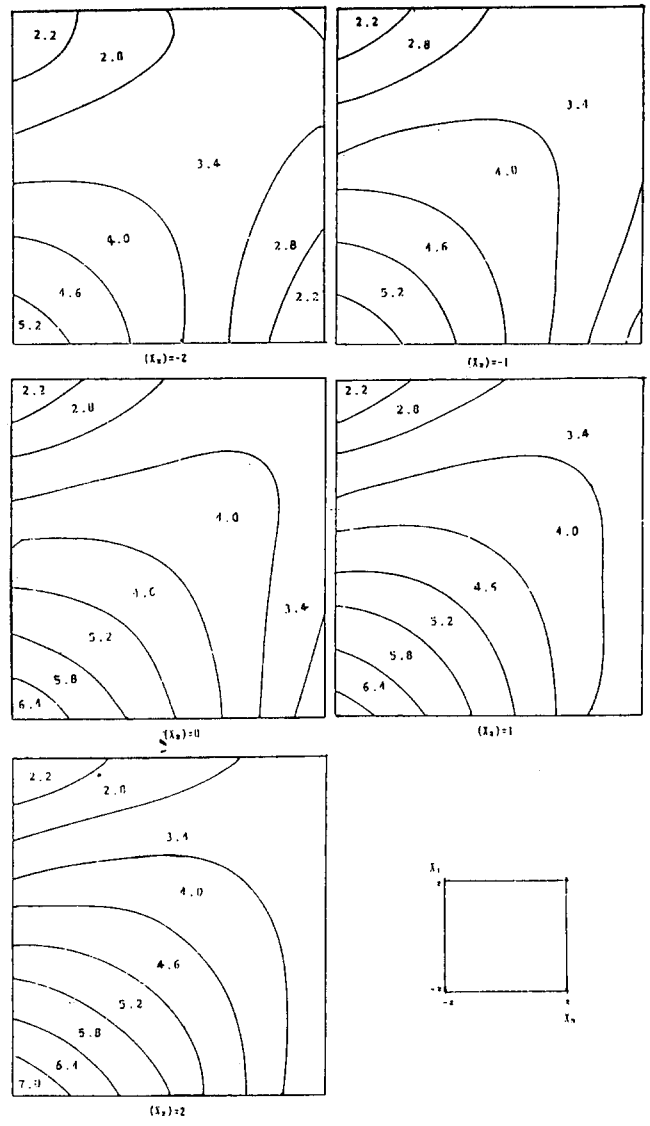

Fig. 5. Contour plots of the release rate of indomethacin as a function of PVA (X_1) and sorbitol (X_3) at various, constant amount of MP (X_2).

operation. One can generate an infinitive number of such plots because the constant value noted at the top of composite plots can cover the entire experimental range for each of the independent variables. Therefore, some consideration must be given to the selection of constant levels. Here, −2, 0, and 2 levels were selected, respectively. Generally, composite partial derivative plots would permit to know overall effect of any single response. In Fig. 3, two inflection points could be seen in the curve of X_3 ($X_3 \cong -1.4$) and X_2 ($X_2=1.2$), and three inflection points appeared in the curves of X_1 ($X_1=-0.5$), X_2 ($X_2=-0.7$) and X_3 ($X_3=2$) in Fig. 4. From these results, it could be predicted that there was an optimum formula providing the controlled-release of IDM from hydrogels.

The other graphical approach is the contour graph-known as response surface contour (RSC) (Lee and

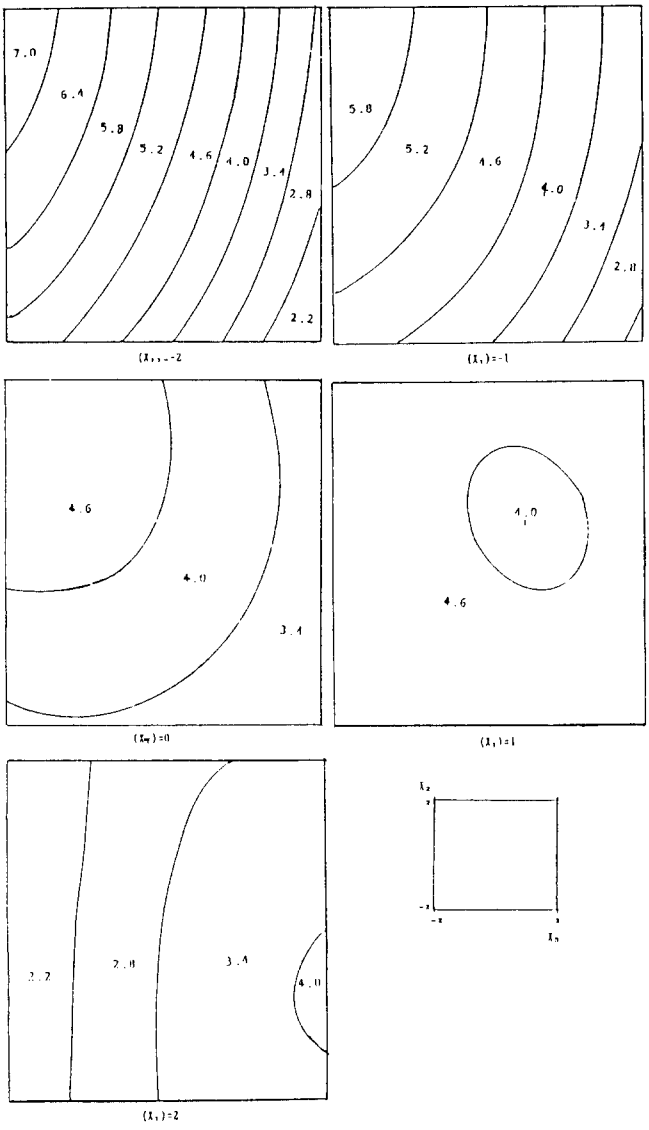

Fig. 6. Contour plots of the release rate of indomethacin as a function of MP (X_2) and sorbitol (X_3) at various, constant amount of PVA (X_1).

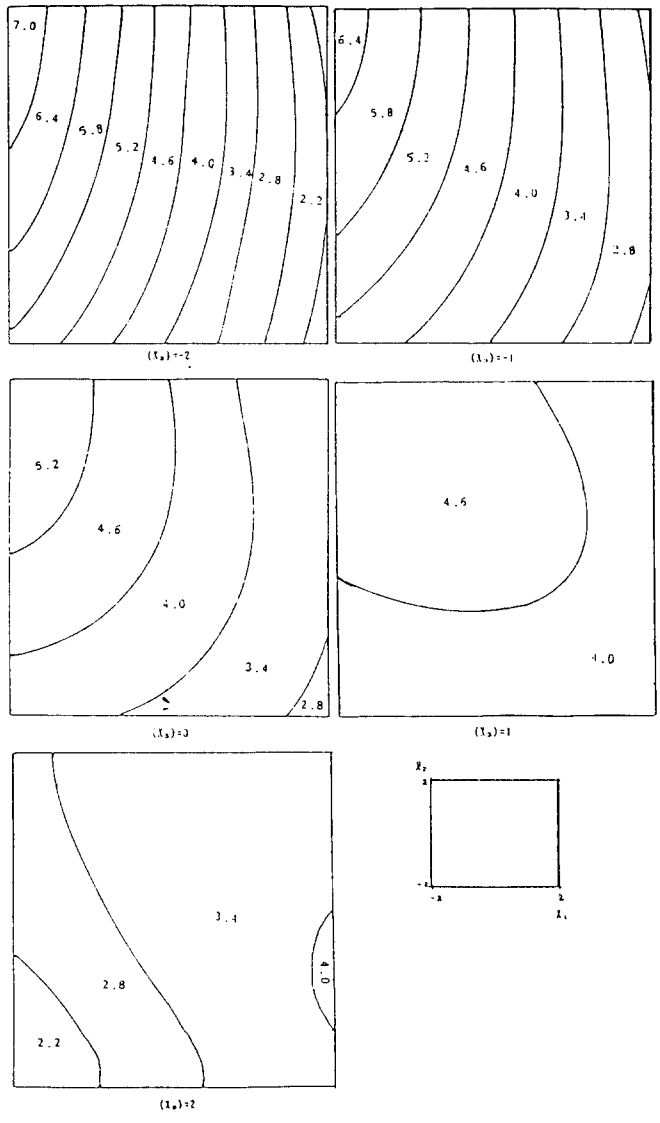

Fig. 7. Contour plots of the release rate of indomethacin as a function of PVA (X_1) and MP (X_2) at various, constant amount of sorbitol (X_3).

Shin, 1988), which is generated by the changes in responses produced by continuous variation in values of two interacting factors with another factor fixed at constant level. Fig. 5, shows the contour graphs observed when the amount of MP (X_2) was fixed at various constant values (-2, -1, 0, 1, and 2). The minimum release rate of IDM were represented at $2<X_1<1.5$ and $1.5<X_3<2$, and $-1.5<X_1<-2$ and $-2<X_3<-1.5$, respectively, and the values of release rate increased with moving from this area along with X_1 or X_3 axis. The plots of X_3 versus X_2 at the various constant levels of X_1 were in Fig. 6. From Fig. 6, it was known that MP (X_2) did not interact with X_1 or X_3. That is, the release rate of IDM from hydrogel increased only with the increase of MP, but there was a significant interaction between PVA (X_1) and sorbitol (X_3). Thus, when the amount of PVA was low ($X_1=-2$), the release rate of IDM decreased with increasing the amount of sorbitol, and the minimum release rate appeared at the area of the high value of sorbitol. On the other hand, when the amount of PVA was high ($X_1=2$), the release rate of IDM increased with an increase of sorbitol (X_3) and the minimal release rate appeared at the low levels of sorbitol. In Fig. 7, the level of X_3 was also fixed and the response values of X_1 to X_2 were plotted. There were some resemblance between Fig. 6 and Fig. 7. At the low levels of PVA and sorbitol, both PVA and sorbitol were noncompetitive factors controlling the release of IDM from hydrogel. But they were not compatible for controlling the release of drug at their high levels. In this study, it was found that there were two areas indicating the controlled release rate. In fact, it was so hard to manipulate PVA solution of high concentration because its viscosity increased

Table V. The optimum formula of indomethacin hydrogel

Variable	Code level	Physical amount (w/v%)
X_1 (PVA)	−2	10
X_2 (MP)	−2	0
X_3(sorbitol)	2	40

Table VI. Comparison of the experimental value and the predicted value obtained from the optimum formula

Response variable	Experimental value	Calculated value
release rate ($\mu g/ml \cdot min^{1/2}$)	1.981	2.044

with the increase of PVA concentration. Therefore, the controlled release rate of IDM resulted from low PVA concentration and high sorbitol concentration offered very interesting information for the preparation of PVA hydrogel.

Optimization procedure

The second-order regression equation was constructed to determine the optimal controlled release rate of IDM from PVA hydrogel. The optimum formula was obtained from computer minimization method with the increment of 0.1 within the constant limits of X_i ($-2 \leq X_i \leq 2$). The result was listed in Table V.

IDM hydrogel was prepared again according to the optimum formula in Table V, and the release rate was measured in the same manner as the previous. The values calculated by the computer and obtained from the experiment were summarized in Table VI. As shown in Table VI, the experimental value ageed very well with the calculated value.

CONCLUSION

A computer optimization technique was applied to obtain the optimum formula for controlling the release of IDM from PVA hydrogel. The release rate of IDM was chosen as the response variable for a criterion of optimum formula and the amounts of PVA, MP, and sorbitol were selected as the independent variables, respectively. The following results were obtained.

1) PVA hydrogels prepared by the method of freezing and thawing repeatedly were a good vehicle for controlling the release of IDM from PVA hydrogel and it was proportional to the square root of time and the amount of PVA.

2) The values of independent variables for optimum formula of IDM hydrogel were X_1(PVA)$=-2$, X_2(MP)$=-2$, and X_3(sorbitol)$=2$, respectively.

3) Sorbitol had the sustained release effect of IDM from hydrogel containing a low concentration of PVA, but didn't have its effect at the high concentration of PVA.

4) Since the release of indomethacin from PVA hydrogel was increased with the increase of MP, it was known that MP was an excellent vehicle for controlling the release of drug from PVA hydrogel as it is intended.

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