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DEVELOPMENT OF DICLOFENAC SODIUM CONTROLLED RELEASE SOLID DISPERSIONS BY SPRAY DRYING USING OPTIMIZATION STRATEGY I. POWDER FORMULATION

P. Dangprasirt* and G.C. Ritthidej**
*Faculty of Pharmacy, Rangsit University, Phatum Thani,
**Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

ABSTRACT

Diclofenac sodium (DS) controlled release solid dispersions were prepared by spray drying using ethylcellulose (EC), methacrylic acid copolymer (Eudragit), chitosan, hydroxypropyl methylcellulose (HPMC), and carbomer as single carriers and EC-chitosan as combined carriers. Among solid dispersions of 3:1 drug:single carrier, the system containing chitosan exhibited the slowest dissolution followed by the systems containing Eudragit, EC, HPMC, and carbomer, respectively. Combined carriers of EC-chitosan exhibited more dissolution retarding effect than single carrier of EC or chitosan. An Hadamard matrix H[8] was employed to estimate the main effects of four parameters: spray feeding volume and contents of absolute ethanol, EC, and chitosan. Optimization strategy using multiple linear regression and a feasibility computer program was utilized to obtain the optimum quantities of the four parameters that would result in a required DS controlled release solid dispersion. The validation of the optimum DS solid dispersion was confirmed by statistical analysis. The optimized 10:(2.5+0.02) DS:(EC+chitosan) controlled release solid dispersion exhibited a dissolution profile that was well fitted to Higuchi model.

INTRODUCTION

Solid dispersion technique has been employed frequently to improve dissolution rate of poorly soluble drugs (1). Recently, the applications of solid dispersion technique in the field of controlled release have been developed (2-5). By dispersing a given drug into an inert carrier the drug dissolution can either be accelerated or retarded depending on the nature of the carrier, whether hydrophilic or hydrophobic, respectively (6).

The use of hydrophobic carriers in controlled release solid dispersion included insoluble polymers such as methacrylic acid copolymer, ethycellulose, cellulose acetate phthalate, and waxes (1-3,5). Swellable polymers also have been employed in matrix system for controlling drug release such as HPMC, EC, and carbomer (7). Thus it is interesting to investigate the use of both insoluble polymer and swellable polymer together as combined carriers in order to achieve the better control of drug release from solid dispersion as compared to the use of either carrier alone. Therefore the release of drug from the resulting solid dispersion would be controlled by two mechanisms, diffusion of drug through insoluble polymer and through viscous environment of swellable polymer. In this investigation, insoluble polymers; methacrylic acid copolymer (Eudragit) and ethycellulose (EC), and swellable polymers; chitosan, hydroxypropyl methycellulose (HPMC), and carbomer, were used as carriers in DS controlled release solid dispersions. The first stage of this study was to select of a suitable insoluble polymer and a suitable swellable polymer which would then be used as combined carriers for the development of DS controlled release solid dispersion. The final stage of the investigation involved the optimization of the DS controlled release solid dispersion. Solid dispersions were prepared by spray drying technique for practical purpose.

Experimental Design

In the optimizing stage of the investigation, an Hadamard matrix H[8] was applied (8). This design is an optimum strategy leading to a good accuracy of the main effects from a minimal experiment number. The design will lead to eight experiments and four parameters can be studied about their main effects on each response. The experimental design requires an introduction of a reduced variable, X_i to each parameter, P_i (9).

$$X_i = \frac{2 . (P_i - P_{mean})}{P_{max} - P_{min}}$$

Where P_{mean} , P_{min} , and P_{max} are respectively the mean, minima and maxima values of P_i. The reduced variable, X_i will be in the range of -1 to 1 for any parameter. If the relationship between each response (Y_i) and reduced variables (X_i) is linear, the first order regression model will be achieved (10). Then,

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + \text{Residue } (\varepsilon_i) \quad \text{eq. (1).}$$

The residual (ε_i) is defined as the difference in the observed response and the predicted response.

The use of statistical t-value or F-value gives information on significant main effects. Data will be analyzed using a statistical computer program. This multiple linear equation can be used to select the optimum reduced variables which would yield a required response.

MATERIALS

Chemicals: The following chemicals were obtained from the commercial sources: diclofenac sodium (Batch No. DFSH 045, CFS PTE Ltd., Switzerland), chitosan (Unicord PCL, Thailand), carbomer (Carbopol 934, Batch No. A701031, S. Tong Chemicals Co. Ltd., Thailand), ethylcellulose and hydroxypropyl methylcellulose (Ethocel 10 cps and Methocel E4M, Dow Chemical Company, U.S.A.), methacrylic acid copolymer (Eudragit RS 100, Rohm Pharma, Germany).

Equipment: The equipment used in this study were analytical balance (Model A200S, Sartorius Co., Germany), spray dryer (Buchi 190 Mini Spray Dryer, Buchi Co., Switzerland), pH meter (Model CG 840, Schott Co., Germany), dissolution apparatus USP type II (Model TW II, Pharma Test Co., Germany), spectrophotometer (Spectronic 3000 Array, Milton Roy Company, U.S.A.).

METHODS

1. Preparation of DS Solid Dispersions

1.1 DS:Polymer Solid Dispersions

The ratio of 3:1 DS:polymer was initially chosen due to high dose of sustained release DS (11). The drug was dissolved in absolute ethanol while each

polymer was dissolved separately in ethanolic solution, except chitosan which was dissolved in 1% acetic acid. After adding the polymeric solution into the DS solution, the resulting solution or colloidal dispersion was spray-dried using a spray feeding rate of 10 ml per minute and inlet temperature between 110 to 130°C.

1.2 DS:(EC+chitosan) Solid Dispersions

EC as an insoluble polymer and chitosan as a swellable polymer were selected to be used as combined carriers. The ratio of 10:(0.95+0.05) DS:(EC+chitosan) was selected and compared to those of 10:1 DS:EC and 10:0.1 DS:chitosan. These three systems were prepared by the same procedure as in 1.1 except the inlet temperature in the spray drying process was fixed at 110°C.

In order to search for the optimum ratio of EC-chitosan and the optimum conditions of spray drying, an experimental design using Hadamard matrix H[8] as shown in Table 1 was generated. Since the influences of the amounts of carriers and solvent on dissolution of solid dispersion have been recognized. Also, the variation of solid content in spray feeding liquid can result in spray-dried powder of different properties. Therefore four parameters were studied for their main effects on dissolution profiles of the DS solid dispersions. Those parameters were the amount of EC, the amount of chitosan, the proportion of absolute ethanol employed, and the spray feeding volume. By varying these variables, eight DS:(EC+chitosan) solid dispersions were prepared as in 1.2.

2. Dissolution Studies of DS Solid Dispersions

Dissolution studies of DS solid dispersions, each equivalent to 100 mg drug, were conducted according to Method A described under Drug Release in USP XXII & NF XVII using type II dissolution apparatus (12). The dissolution tests were run by using a stirring rate of 50 rpm. Sample solutions in acid and buffer media were assayed spectrophotometrically at 275 nm and 278 nm for DS content, respectively.

3. Validation of Optimized Solid Dispersion

The optimized DS:(EC+chitosan) solid dispersion was prepared by spray drying using optimum ratio and conditions obtained from optimization of DS solid dispersions in 1.2 and its dissolution profile was studied by the same procedure as in 2.

TABLE 1

Experimental Design by Hadamard Matrix H[8] for Preparing DS:(EC+chitosan) Solid Dispersions

Formulation	Dclofenac Sodium (g)	Feeding Volume (ml)	Absolute Ethanol Proportion	EC Content (g)	Chitosan Content (g)
I	10.00	500	0.70	3.00	0.10
II	10.00	200	0.70	1.00	0.10
III	10.00	500	0.30	1.00	0.10
IV	10.00	200	0.30	3.00	0.10
V	10.00	500	0.70	3.00	0.02
VI	10.00	200	0.70	1.00	0.02
VII	10.00	500	0.30	1.00	0.02
VIII	10.00	200	0.30	3.00	0.02

RESULTS AND DISCUSSION

Solid Dispersions of 3:1 DS: Single Polymer

The dissolution profiles of DS and 3:1 DS:polymer solid dispersions are demonstrated in Figure 1. Since DS dissolved poorly in acid medium (13) therefore very low percentages of drug dissolved were observed in the first two hours. All solid dispersion systems showed slower dissolution than DS powder. Among these systems the dissolution of DS:chitosan solid dispersion system was the slowest followed by those of DS:Eudragit, DS:EC, DS:HPMC, and DS:carbomer, respectively. It obviously showed that carbomer and HPMC were not suitable to be used as dissolution retarding carriers since their dissolutions were too fast. Higher amount was to employ in order to yield slower dissolution since the dissolution retarding effect of any swellable polymer on a drug depends on the viscosity of polymer. Increasing the amount of the polymer in a matrix formulation increases the viscosity of gel layer and thus slows drug diffusion (7). However, increasing the amounts of HPMC and carbomer in DS controlled release formulation would result in too large dose size. For system of 3:1 DS:carbomer, it was also noticed that saturation of drug solution was achieved shortly after the acidic stage of dissolution. This might due to the competing for dissolution between the drug and polymer indicating that the amount of carbomer was too high.

In contrast, when chitosan or Eudragit was used, the dissolution was too slow that only 30% or 82% drug dissolved was reached after 12 hours. EC seemed to be a more suitable carrier since it gave continuous drug dissolved over 12 hours

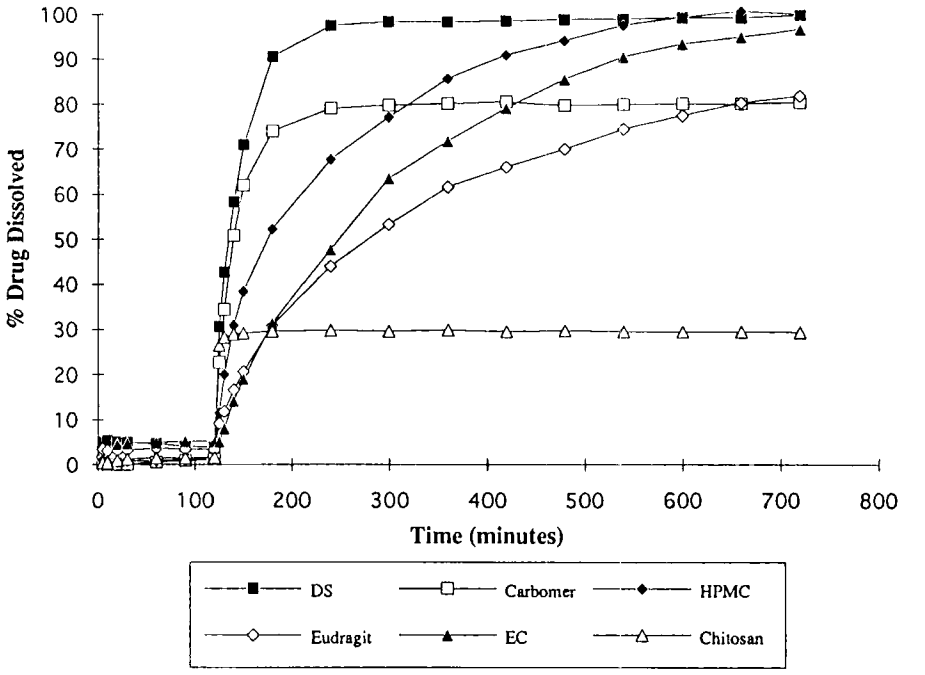

Figure 1
Dissolution profiles of 3:1 diclofenac sodium:polymer solid dispersions

period. However, the initial stage of this dissolution profile was still too rapid. Since the dissolution retarding effect of chitosan was obviously demonstrated therefore EC, an insoluble polymer, and chitosan, a swellable polymer, were used as combined carrier in an effort to improve the dissolution profile of DS solid dispersion.

Solid Dispersions of DS:(EC+chitosan)

Dissolution profile of 10:(0.95+0.05) DS:(EC+chitosan) solid dispersion compared with those of 10:1 DS:EC and 10:0.01 DS:chitosan is illustrated in Figure 2. The combined-carriers system showed slower dissolution than the single carrier system. However, the dissolution profile of the 10:(0.95+0.05) DS:(EC+chitosan) solid dispersion was too slow that only 83% drug dissolved was obtained after 12 hours. Since the ideal dissolution rate for the sustained release drug should follow zero-order kinetics therefore two criteria were established for

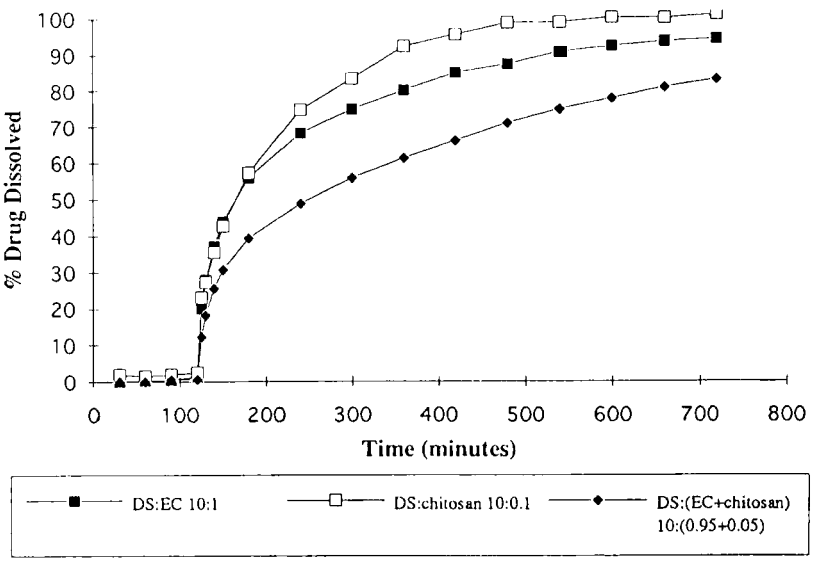

Figure 2
Dissolution profiles of 10:1 diclofenac sodium:EC, 10:0.01 diclofenac sodium:chitosan, and 10:(0.95+0.05) diclofenac sodium:(EC+chitosan) solid dispersions

the development of optimum dissolution profile. Those criteria were the zero-order dissolution rate constant (K^0) and the correlation coefficient of linear relationship (R^2) between drug release and time.

For diclofenac sodium the ideal K^0 was 0.139 mg per minute or 8.33 mg per hour. This value was calculated by assuming that the loading dose required to achieve the therapeutic drug level was 25 mg, the drug half-life was 2 hours and the required dosing interval was 12 hours (13,14). Therefore the amount of drug needed in the sustained release component was 103.9 mg which was adjusted to 100 mg in this study.

In order to search for optimum conditions to produce a required spray-dried DS controlled release solid dispersion; the influences of the amounts of EC and chitosan, the proportion of absolute ethanol employed, and the spray feeding volume on drug dissolution were studied as shown in Figure 3. Linear regression was applied to the dissolution data of the eight experiments. The K^0 and R^2 of each experiment were calculated as presented in Table 2. Then by using multiple linear

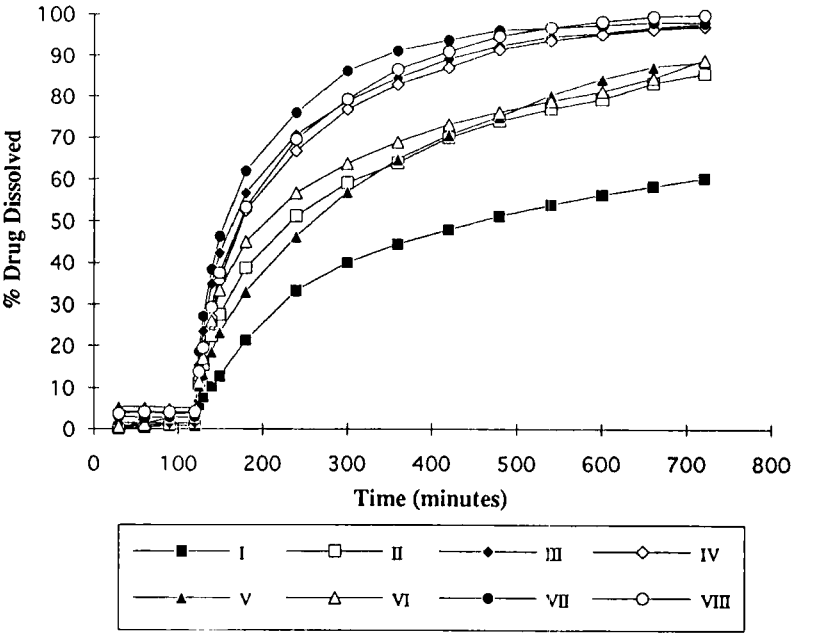

Figure 3
Dissolution profiles of diclofenac sodium:(EC+chitosan) solid dispersions prepared according to formulations I-VIII

TABLE 2
K^0 and R^2 Values of DS:(EC+chitosan) Solid Dispersions

Experiment	Experimental K^0 (mg/minute)	Experimental R^2	Predicted K^0 (mg/minute)	Predicted R^2
I	0.100740	0.913113	0.110952	0.922660
II	0.137521	0.887548	0.127189	0.874920
III	0.214311	0.854114	0.221342	0.854536
IV	0.212446	0.882822	0.205535	0.885481
V	0.142239	0.929054	0.132027	0.919507
VI	0.137932	0.859139	0.148264	0.871767
VII	0.249449	0.851806	0.242418	0.851384
VIII	0.219699	0.884987	0.226610	0.882328

regression the equations expressing the relationships between the response, K^0 or R^2, and the four variables were constructed.

$$K^0 = - 0.000001P_1 - 0.235921P_2 - 0.008011P_3 - 0.263441P_4 + 0.326832 \quad (1.1)$$

$$K^0 = - 0.000107X_1 - 0.047184X_2 - 0.008011X_3 - 0.010538X_4 + 0.176192 \quad (1.2)$$

$$R^2 = 0.000028P_1 + 0.071593P_2 + 0.019671P_3 + 0.039409P_4 + 0.795342 \quad (2.1)$$

$$R^2 = 0.004199X_1 + 0.014391X_2 + 0.019671X_3 + 0.001576X_4 + 0.882823 \quad (2.2)$$

The predicted responses calculated from the predicted response equations are also listed in Table 2. The fitness of linear models between each response and the four variables was confirmed by calculating the correlation coefficient of linear model (r^2) which were 0.968910 and 0.905006 for the response of K^0 and R^2, respectively. In order to evaluate the significant effect of each variable the statistical t-values and partial F-values were calculated using a statistical computer program. The results are presented in Table 3.

For any changing in the levels of reduced variables from -1 to 1, the following conclusions were established based on the t-values and partial F-values. The K^0 was influenced mainly by ethanol proportion ($\alpha = 0.01$) and was partially influenced by chitosan content ($\alpha = 0.10$) and EC content ($\alpha = 0.25$). While the R^2 was mainly influenced by EC content ($\alpha = 0.025$) and was partially influenced by ethanol proportion ($\alpha = 0.05$).

In order to achieve the optimum dissolution profile from the solid dispersion of DS:(EC+chitosan), the K^0 in the range of 0.138 to 0.140 mg per minute and R^2 of not less than 0.900 were set as the required responses.

The feasibility program named SIMOPT (15) was used to locate the value of each variable that would be used to prepare the required DS solid dispersion. The resulting optimum values consisted of the feeding volume of 200 ml, the ethanol proportion of 0.68, the EC content of 2.49 mg, and the chitosan content of 0.02 mg. To facilitate the further experiment the ethanol proportion and the EC content were adjusted to 0.70 and 2.50 mg respectively.

Validation of the Optimum Diclofenac:(EC+Chitosan) Solid Dispersion

The dissolution profile of the optimum DS solid dispersion is illustrated in Figure 4. The K^0 and R^2 were calculated and compared with the predicted K^0 and R^2. The experimental K^0 and R^2 were 0.147128 mg per minute and 0.928030 while the predicted K^0 and R^2 were 0.136248 mg per minute and 0.901275,

TABLE 3

The Statistical t-values and Partial F-values of Multiple Linear Regressions

Parameters	t-values		Partial F-values	
	K^0	R^2	K^0	R^2
Feeding Volume	-0.021186	0.905798	0.000449	0.820470
Ethanol Proportion	-9.309850	3.104402	86.673305	9.637312
EC Content	-1.580667	4.243532	2.498507	18.007566
Chitosan Content	-2.079168	0.340062	4.322938	0.115642

D.F. = 1, 3 : $F(\alpha = 0.01) = 34.12$, $F(\alpha = 0.025) = 17.44$, $F(\alpha = 0.05) = 10.13$, $F(\alpha = 0.10) = 5.54$, $F(\alpha = 0.25) = 2.02$

D.F. = 3 : $t(\alpha = 0.01) = 4.541$, $t(\alpha = 0.025) = 3.182$, $t(\alpha = 0.05) = 2.353$, $t(\alpha = 0.10) = 1.638$, $t(\alpha = 0.25) = 0.765$

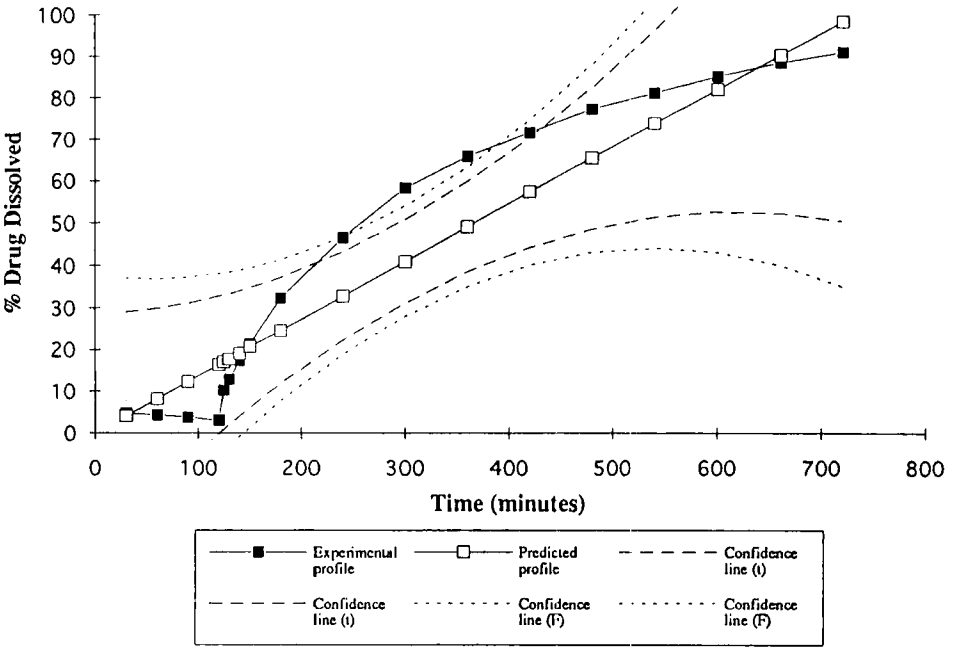

Figure 4

Dissolution profiles of optimized diclofenac sodium:(EC+chitosan) solid dispersion as compared to the predicted dissolution profile (K^0= 0.136248 mg per minute) using 90% confidence level based on t-value and F-value

respectively. The optimum conditions to prepare the required DS solid dispersion corresponded to the levels of the feeding volume, ethanol proportion, EC content, and chitosan content at -1, 1. 0.50, and -1, respectively.

To validate the accuracy of prediction, the obtained K^0 and R^2 from experiment IX were combined with those from experiment I-VIII and the multiple linear regression was performed. The result illustrated that for both responses, the K^0 and R^2, the data from all nine experiments showed the multiple linear relationship between each response and the four variables as confirmed by the values of correlation coefficent of linear model (r^2). The r^2 values obtained from experiments I-VIII and I-IX were 0.968910 and 0.966339 for the response K^0 and 0.905006 and 0.864298 for the response R^2, respectively. Therefore the equations 1.1 or 1.2 and 2.1 or 2.2 can be used to predict the K^0 and R^2 accurately.

From the equations 1.1 or 1.2 and 2.1 or 2.2, increasing the feeding volume from 200 ml to 500 ml did not impart any significant effect on K^0 or R^2. Economically, it would be benefit to fix the feeding volume to 200 ml. The response surface plots of equations 1.2 and 2.2 were demonstrated in Figure 5. Figures 5a and 5b show that when fixing the feeding volume and ethanol proportion at -1 and 1 levels and at -1 and -1 levels, the variation in EC and chitosan contents in the range of -1 to 1 levels would result in the K^0 of 0.110 to 0.150 mg per minute and 0.205 to 0.240 mg per minute, respectively. Therefore the required K^0 of 0.139 mg per minute could be obtained by selecting the optimum levels of EC and chitosan contents while fixing the levels of feeding volume and ethanol proportion at -1 and 1 respectively. Similarly from Figures 5c and 5d, when fixing the levels of feeding volume and ethanol proportion at -1 and 1, the variation in EC and chitosan contents would result in R^2 of 0.870 to 0.910, respectively.

By fixing the levels of feeding volume and ethanol proportion at -1 and 1, the two contour plots of K^0 and R^2 as function of EC and chitosan contents were superimposed as shown in Figure 6. From this plot a restricted area which would give a required K^0 between 0.136 to 0.142 mg per minute with the acceptable R^2 value of more than 0.880 was identified. Subsequently, the optimum levels of EC and chitosan contents yielding the required K^0 and R^2 could be chosen.

The mechanism of drug release from the optimized 10:(2.5+0.02) DS:(EC+chitosan) solid dispersion in pH 6.8 phosphate buffer solution appeared to fit well with Higuchi model rather to zero-order model. The plot between

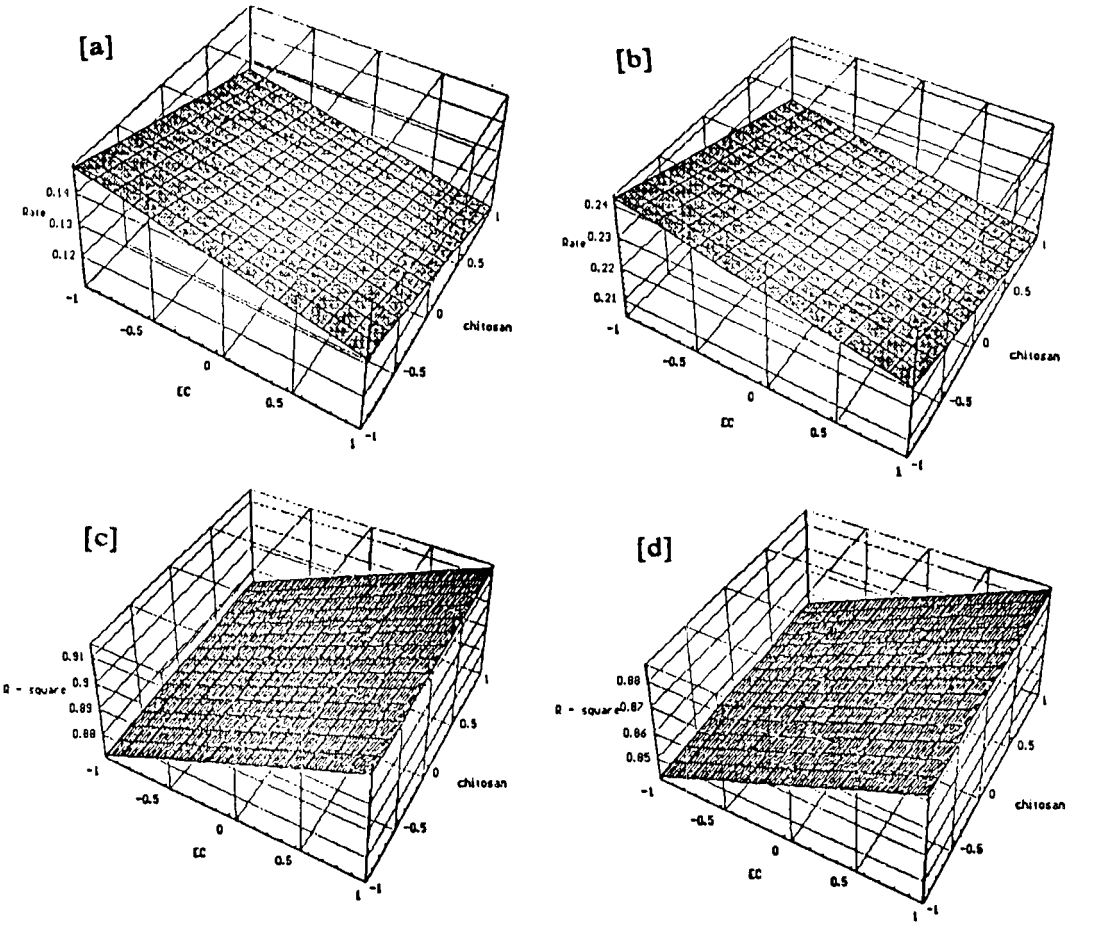

Figure 5
The response surface plots of K^0 and R^2 equations,
[a] K^0 when fixing $X_1 = -1$ and $X_2 = 1$, [b] K^0 when fixing $X_1 = -1$ and $X_2 = -1$,
[c] R^2 when fixing $X_1 = -1$ and $X_2 = 1$, [b] R^2 when fixing $X_1 = -1$ and $X_2 = -1$

percentage of drug released and square root time yielded r^2 of 0.963302 while the plot between percentage of drug released and time gave r^2 of 0.913806. Hence, by using optimization strategy the optimized DS controlled release solid dispersion of the best possible required zero-order kinetics drug release could be achieved.

CONCLUSIONS

This investigation revealed the usefulness of optimization strategy in controlled release product development. By using suitable statistical experimental

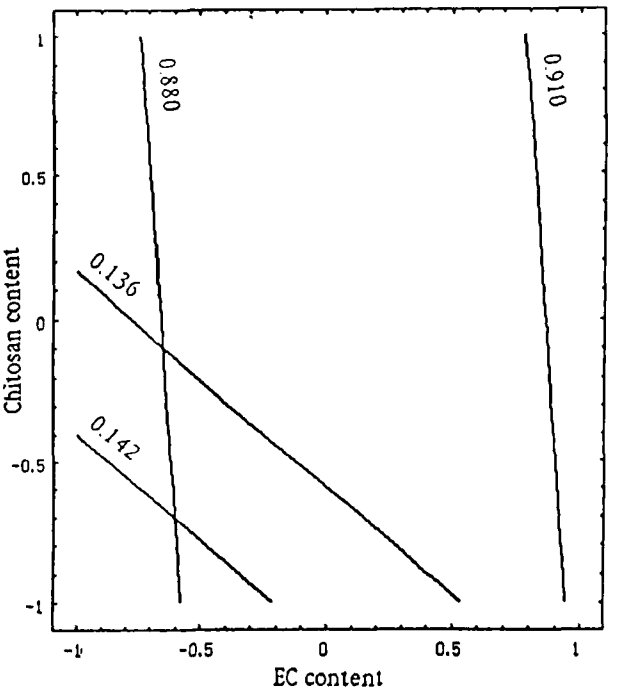

Figure 6
The superimposed contour plot of K^0 and R^2 equations when $X_1 = -1$ and $X_2 = 1$

design and computer programs the development of optimum DS controlled release solid dispersion was achieved with small experimental number. The roles of EC and chitosan as combined carriers in preparing spray-dried DS controlled release solid dispersion were also demonstrated. Their use resulted in reducing the amount of carriers utilized in controlled release solid dispersion. In this investigation the optimum DS controlled release solid disperion was developed. The resulting powder can be developed further into optimum DS controlled release tablets.

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