CHAPTER IV

RESULTS AND DISCUSSION

PART I - SOLID DISPERSION POWDERS

3:1 Diclofenac Sodium:Polymer Solid Dispersions

The dissolution profiles of diclofenac sodium powder and 3:1 diclofenac sodium : polymer solid dispersions are demonstrated in Figure 7. Since diclofenac sodium dissolved poorly in acid medium (Adeyeye and Li, 1990) therefore the very low percentages of drug release were observed in the first two hours. All solid dispersion systems showed slower dissolution profiles than diclofenac sodium powder. Among these systems the dissolution profile of the drug:chitosan solid dispersion system was the slowest following by those of drug:Eudragit, drug:EC, drug:HPMC, and drug:carbomer, respectively. By comparing dissolution profiles of these systems, it obviously showed that carbomer and hydroxypropyl methylcellulose were not suitable to be used as carriers in preparing diclofenac sodium controlled release solid dispersions since their dissolution profiles were too fast. Higher amounts of these two polymers were to employ in order to yield slower dissolution since the dissolution retarding effect of any swellable polymer on a drug depends on the polymer viscosity. Increasing viscosity of the polymer in a matrix formulation increases the gel layer viscosity and thus slows drug diffusion (Alderman, 1984). However, increasing the amounts of HPMC

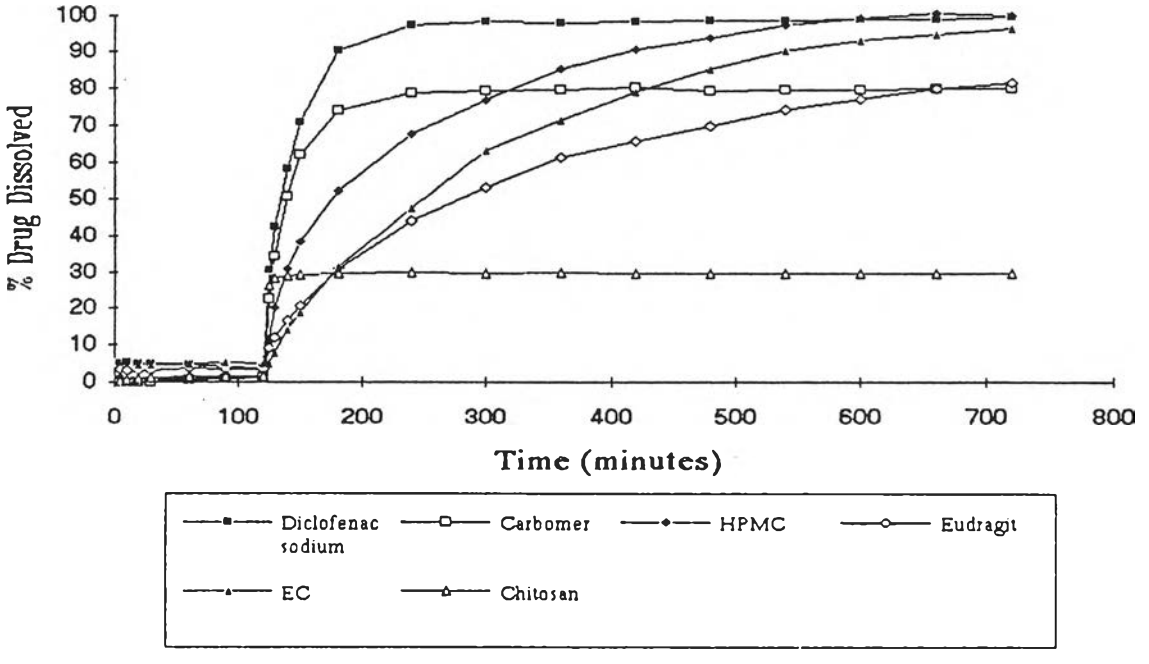

Figure 7. Dissolution profiles of 3:1 diclofenac sodium:polymer solid dispersions.

and carbomer in diclofenac sodium controlled release formulation would result in too large dose size. For 3:1 diclofenac sodium:carbomer solid dispersion system, it was also noticed that saturation of drug solution was achieved shortly after the initial stage of dissolution profile. This might be due to competing in dissolution between the drug and carbomer indicating that the amount of carbomer was too high.

In contrast when chitosan or Eudragit was used the dissolution profile was too slow that only 30% or 82% drug dissolved was reached after 12 hours. Ethylcellulose seemed to be a more suitable carrier since it gave continuous drug dissolved over 12 hours period. However, the initial stage of this dissolution profile was still too rapid. Since the dissolution retarding effect of chitosan was obviously demonstrated therefore ethylcellulose, an insoluble polymer, and chitosan, a swellable polymer, were used as combined carrier in an effort to improve the dissolution profile of diclofenac sodium solid dispersion.

Diclofenac Sodium:(EC+chitosan) Solid Dispersion

Dissolution profile of 10:(0.95+0.05) diclofenac sodium :(EC+chitosan) solid dispersion as compared with those of 10:1 diclofenac sodium:EC and 10:0.01 diclofenac sodium:chitosan is illustrated in Figure 8. The combined-carriers solid dispersion system showed slower dissolution than the single carrier solid dispersion 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 controlled release drug should follow zero-order kinetics therefore two criteria were

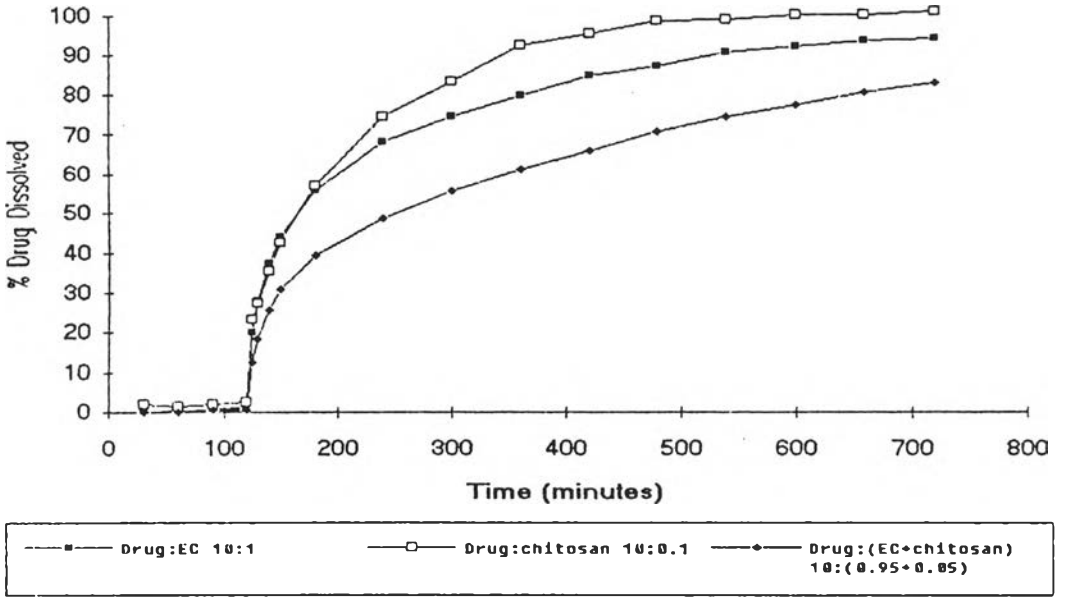

Figure 8. Dissolution profiles of 10:1 diclofenac sodium:EC , 10:0.01 diclofenac sodium:chitosan, and 10:(0.95+0.05) diclofenac sodium:(EC+chitosan) solid dispersions.

established for 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 is 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 is 25 mg, the drug half-life is 2 hours (Adeyeye and Li, 1990) and the required dosing interval is 12 hours. Calculation of the amount of the drug needed in the sustained component can be accomplished according to the following relationship (Abdou, 1989)

Rate of drug input = Rate of drug output. (a)

If it is considered that elimination is generally a first-order process, then

Rate of drug output = DK_e (b)

where D is the loading dose required to achieve the therapeutic blood level, and Ke is the first-order rate constant of elimination. The value of K_e can be obtained if the biological half-life of the drug ($t_{1/2}$) is known

$$K_e = \frac{0.693}{t_{1/2}} . \qquad (c)$$

Therefore, the rate of drug output after administering a single dose, D, can be calculated from the equation

$$\text{Rate of drug output} = \frac{0.693\,(D)}{t_{1/2}}. \qquad \text{(d)}$$

Substituting for equation (d) in equation (a),

$$\text{Rate of drug input} = \frac{0.693\,(D)}{t_{1/2}}. \qquad \text{(e)}$$

Thus, in order to calculate the amount of drug needed in the sustained component to represent the dose required for administration at every T hr of dosing intervals, equation (e) can be multiplied by T.

Amount of drug needed in the sustained released component

$$= \frac{0.693(D)T}{t_{1/2}}.$$

In the case of sustained release diclofenac sodium; the values of D, $t_{1/2}$, and T are 25 mg, 2 hours, and 12 hours, respectively. Therefore the amount of drug needed in the sustained released component was:

$$\frac{0.693 \times 25 \times 12}{2} = 103.9 \text{ mg},$$

which was adjusted to 100 mg in this study. Thus the required K^0 became 8.33 mg per hour or 0.139 mg per minute.

In order to achieve the optimum dissolution profile for development of diclofenac sodlium controlled release drug delivery system it was necessary to search for the optimum ratio of ethylcellulose and chitosan to be used. Since variation of solid content in spray feeding liquid can result in spray-dried powder of different properties

(Broadhead, Rouan, and Rhodes, 1992). Therefore the influence of the solid content or in another word the spray feeding volume on the drug release profile was also studied. In order to prepare the diclofenac:(EC+chitosan) solid dispersions, ethanolic solution was utilized as a common solvent of the drug and carriers. The alcohol fraction of the spray feeding liquid was examined for its influence on the dissolution of the resulting spray-dried solid dispersions. The influences of the amounts of ethylcellulose and chitosan, the fraction of absolute ethanol employed, and the spray feeding volume on drug dissolution are shown in Figure 9.

Linear regression was applied to the dissolution data of the eight experiments designed by Hadamard matrix H[8]. The K^0 and R^2 of each experiment are calculated and presented in Table 17. Then by using multiple linear regression the equations expressing the relationships between the response, K^0 or R^2, and the four variables were constructed. The multiple linear regression was performed using a statistical computer program. The resulting printouts consisting of the values of regression model coefficients (b_i) and the correlation coefficients of linear model (r^2) were demonstrated in Figures 10-14. The statistical t-values and partial F-values were also calculated by the computer program as presented in Table 18. The constructed equations are shown in Table 19. Equations 1.1 and 2.1 represented the equations obtained when the studied variables were calculated in the term of their real values while equations 1.2 and 2.2 represented the equations obtained when the studied variables were calculated in the term of their reduced variables (-1 to 1). The fitness of linear models between each response and the four variables were confirmed by the calculated r^2 which were 0.968910 and 0.905006 for

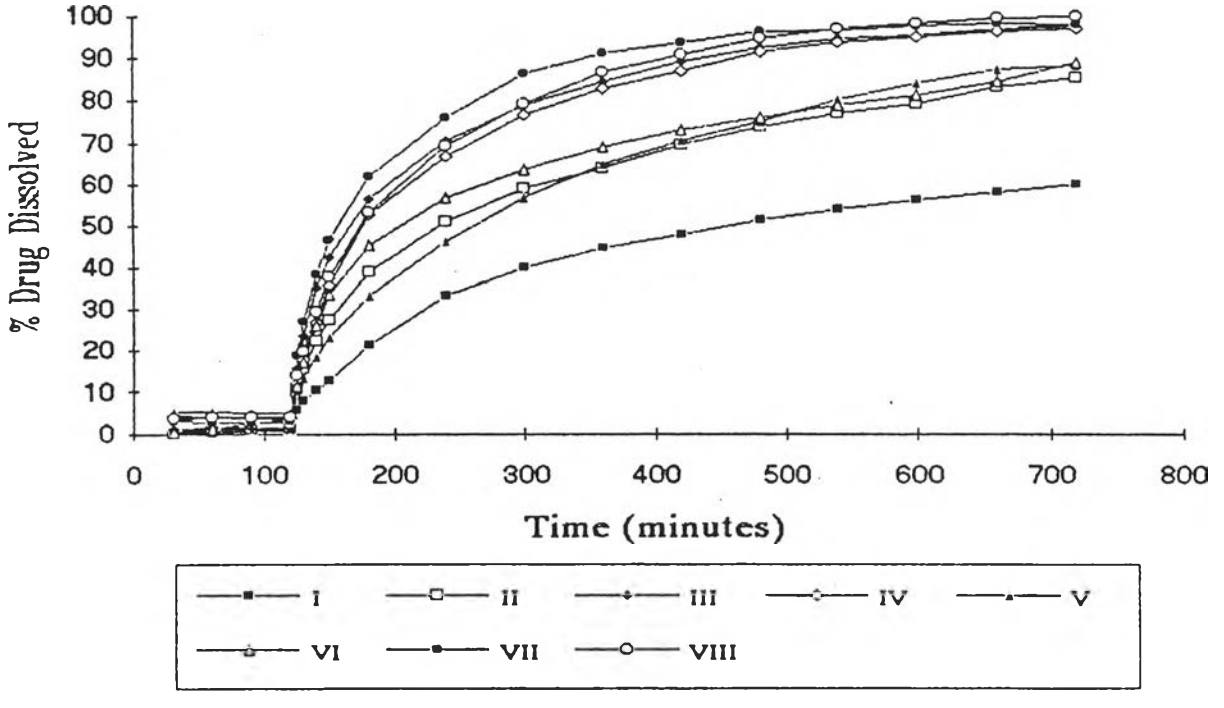

Figure 9. Dissolution profiles of diclofenac sodium:(EC+chitosan) solid dispersions.

TABLE 17. 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

TABLE 18. 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 fraction	-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 : $t(\alpha = 0.01) = 4.541$, $t(\alpha = 0.025) = 3.182$, $t(\alpha = 0.05) = 2.353$, $t(\alpha = 0.10) = 1.638$, $t(\alpha = 0.25) = 0.765$

[a]

	Volume	Alc.	E.C.	Chitosan	R-square	Rate	Predicted R-square	Predicted Rate
	X	X	X	X	Y	Y		
1	500	.70	3.00	.10	.913113	.100740	.922660	.110952
2	200	.70	1.00	.10	.887548	.137521	.874920	.127189
3	500	.30	1.00	.10	.854114	.214311	.854536	.221342
4	200	.30	3.00	.10	.882822	.212446	.885481	.205535
5	500	.70	3.00	.02	.929054	.142239	.919507	.132027
6	200	.70	1.00	.02	.859139	.137932	.871767	.148264
7	500	.30	1.00	.02	.851806	.249449	.851384	.242418
8	200	.30	3.00	.02	.884987	.219699	.882328	.226610

[b]

	Volume	Alc.	E.C.	Chitosan	R-square	Rate	Predicted R-square	Predicted Rate
	X	X	X	X	Y	Y		
1	1.00	1.00	1.00	1.00	.913113	.100740	.922660	.110952
2	-1.00	1.00	-1.00	1.00	.887548	.137521	.874920	.127189
3	1.00	-1.00	-1.00	1.00	.854114	.214311	.854536	.221342
4	-1.00	-1.00	1.00	1.00	.882822	.212446	.885481	.205535
5	1.00	1.00	1.00	-1.00	.929054	.142239	.919507	.132027
6	-1.00	1.00	-1.00	-1.00	.859139	.137932	.871767	.148264
7	1.00	-1.00	-1.00	-1.00	.851806	.249449	.851384	.242418
8	-1.00	-1.00	1.00	-1.00	.884987	.219699	.882328	.226610

Figure 10. The printout of multiple regression program utilizing data from experiments I - VIII showing predicted zero-order dissolution rate constant and R^2 value: [a] data were calculated in term of real values of parameters, [b] data were calculated in term of reduced variables.

Multiple - Y : Rate Four X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
7	.96891	.014335	8.108403

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	.019213	.004803	23.3738
RESIDUAL	3	.000616	.000205	.01 < p < .025
TOTAL	7	.019829		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.326832	.022059	14.815966	
Volume	-.000001	.000034	-.021186	.000449
Alc.	-.235921	.025341	-9.30985	86.673305
E.C.	-.008011	.005068	-1.580667	2.498507
Chitosan	-.263441	.126705	-2.079168	4.322938

2

Figure 11. The printout of multiple regression program for zero-order dissolution rate constant utilizing data from experiments I - VIII in term of real values of parameters.

Multiple - Y : R-square Four X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
7	.905006	.013111	1.48516

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	.004913	.001228	7.145248
RESIDUAL	3	.000516	.000172	.05 < p < .10
TOTAL	7	.005429		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.795342	.020176	39.419523	
Volume	.000028	.000031	.905798	.82047
Alc.	.071953	.023178	3.104402	9.637312
E.C.	.019671	.004636	4.243532	18.007566
Chitosan	.039409	.115889	.340062	.115642

2

Figure 12. The printout of multiple regression program for R^2 vlaue utilizing data from experiments I - VIII in term of real values of parameters.

Multiple - Y : Rate Four X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
7	.96891	.014335	8.108403

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	.019213	.004803	23.3738
RESIDUAL	3	.000616	.000205	.01 < p < .025
TOTAL	7	.019829		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.176792	.005068	34.882667	
Volume	-.000107	.005068	-.021186	.000449
Alc.	-.047184	.005068	-9.30985	86.673305
E.C.	-.008011	.005068	-1.580667	2.498507
Chitosan	-.010538	.005068	-2.079168	4.322938

2

Figure 13. The printout of multiple regression program for zero-order dissolution rate constant utilizing data from experiments I - VIII in term of reduced variables.

Multiple - Y : R-square Four X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
7	.905006	013111	1.48516

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	.004913	.001228	7.145248
RESIDUAL	3	.000516	.000172	.05 < p < .10
TOTAL	7	.005429		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.882823	.004636	190.446016	
Volume	.004199	.004636	.905798	.82047
Alc.	.014391	.004636	3.104402	9.637312
E.C.	.019671	.004636	4.243532	18.007566
Chitosan	.001576	.004636	.340062	.115642

2

Figure 14. The printout of multiple regression program for R^2 value utilizing data from experiments I - VIII in term of reduced variables.

Table 19. The Multiple Linear Equations Expressing the Relationships between the Responses and the Independent Variables.

Responses	Pedicted Response Equations in Term of Parameters and Reduced Variables*	r^2
Zero -order Dissolution Rate Constant (K^0)	$K^0 = -0.000001x_1 - 0.235921x_2 - 0.008011x_3 - 0.263441x_4 + 0.326832$ [Equation 1.1]	0.968920
	$K^0 = -0.000107X_1 - 0.047184X_2 - 0.008011X_3 - 0.010538X_4 + 0.176792$ [Equation 1.2]	
Correlation Coefficient of Dissolution Profile (R^2)	$R^2 = 0.000028x_1 + 0.071953x_2 + 0.019671x_3 + 0.039409x_4 + 0.795342$ [Equation 2.1]	0.905006
	$R^2 = 0.004199X_1 + 0.014391X_2 + 0.019671X_3 + 0.001576X_4 + 0.882823$ [Equation 2.2]	
% Drug Released at 12 th Hour (C_{12})	$C_{12} = -0.02262x_1 - 43.1437x_2 - 3.07375x_3 - 108.281x_4 + 131.3712$ [Equation 3.1]	0.782123
	$C_{12} = -3.39375X_1 - 8.62875X_2 - 3.07375X_3 - 4.33125X_4 + 89.23625$ [Equation 3.2]	

- x_1 , x_2 , x_3 , x_4 are the quantities of the feeding volume, ethanol fraction, EC content, and chitosan content, respectively.
- X_1 , X_2 , X_3 , X_4 are the quantities of the feeding volume, ethanol fraction, EC content, and chitosan content in term of the reduced variables.

* These equations are valid only in the range of -1 to +1 for the values of each reduced variable.

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 calculated from the statistical computer program were analyzed. The predicted responses being calculated from the predicted response eqution are also listed in Table 17.

Effects of Independent Variables on Zero-order Dissoluton Rate Constant of Diclofenac Sodium:(EC+chitosan) Solid Dispersions

From the predicted K^0 equation (equation 1.2) of the diclofenac sodium:(EC+chitosan) solid dispersions of

$$K^0 = - 0.000107X_1 - 0.047184X_2 - 0.008011X_3 - 0.010538X_4 + 0.176792,$$

the following conclusions could be established basing on the t-values and partial F-values. For any changing in the levels of reduced variables from -1 to 1, K^0 was influenced mainly by alcohol fraction ($\alpha = 0.01$) and was partially influenced by chitosan content ($\alpha = 0.10$) and ethylcellulose content ($\alpha = 0.25$). While the volume of feeding solution didn't impart any significant effect on K^0. Therefore the change in the level of the feeding volume from -1 to 1 level didn't alter the K^0 of the prepared diclofenac sodium : (EC+chitosan) solid dispersions.

Effects of Independent Variables on the Correlation Coefficient of Linearity of Dissolution Profile of Diclofenac Sodium: (EC+chitosan) Solid Dispersions

From the predicted R^2 equation (equation 2.2) of the diclofenac sodium:(EC+chitosan) solid dispersions of

$$R^2 = 0.004199X_1 + 0.014391X_2 + 0.019671X_3 + 0.001576X_4 + 0.882823,$$

the following conclusions could be finalized basing on the statistical t-values and partial F-values. For any changing in the levels of reduced variables from -1 to 1, R^2 was mainly influenced by ethylcellulose content ($\alpha = 0.025$) and was partially influenced by alcohol fraction ($\alpha = 0.05$). While the spray feeding volume and chitosan content didn't impart significant effects on R^2. Therefore the change in the feeding volume from -1 level (200 ml) to 1 level (500 ml) didn't alter the R^2 value of the investigated diclofenac sodium:(EC+chitosan) solid dispersions.

Optimization of Diclofenac Sodium:(EC+Chitosan) Solid Dispersions

In order to achieve the optimum dissolution profile from diclofenac sodium:(EC+chitosan) controlled release solid dispersion, 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. Additional criteria of maximum drug release at twelfth hour (C_{12}) was also established, therefore another multiple linear equation representing the relationship between C_{12} and the four variables was constructed and listed in Table 19. A feasibility computer program named SIMOPT (Kalvelgen and Tijms, 1990) was

used to locate the value of each variable that would be used to prepare diclofenac sodium solid dispersion yielding the dissolution profile that would meet all the criteria being set above. The goal of this program was to maximize an objective function by specifying given constraints. In order to run this program the objective function and the constrainted functions must be set. Since this program could not performed on the input of negative values therefore only the equations of the real parameter values (x_1, x_2, x_3, x_4), equations 1.1, 2.1, and 3.1, would be used as input of the program.

In the present study the objective function was the function of C_{12} which depended on the four independent parameters, the feeding volume (x_1), the alcohol fraction (x_2), the ethylcellulose content (x_3) and the chitosan content (x_4). The constraints were the K^0 of between 0.138 to 0.140 mg per minute and the R^2 of not less than 0.900. Therefore the aim of the study was to maximize C_{12} subjecting to K^0 of 0.138 to 0.140 mg per minute and R^2 of not less than 0.900, the range of the parameter values being studied also were feeded into the program. Hence, the input of the program became:

Maximize

$$-0.02262x_1 - 43.1437x_2 - 3.07375x_3 - 108.381x_4 + 131.3712$$

(Equation of C_{12})

Subject to

$$-0.000001x_1 - 0.235921x_2 - 0.008011x_3 - 0.263441x_4 + 0.326862 >= 0.138$$

(Equation of K^0)

$-0.000001x_1 - 0.235921x_2 - 0.008011x_3 - 0.263441x_4$

$+ 0.326862 <= 0.140$

(Equation of K^0)

$0.000028x_1 + 0.071953x_2 + 0.019671x_3 + 0.039409x_4$

$+ 0.795342 >= 0.90$

(Equation of R^2)

$x_1 >= 200$

$x_1 <= 500$

$x_2 >= 0.30$

$x_2 <= 0.70$

$x_3 >= 1$

$x_3 <= 3$

$x_4 >= 0.02$

$x_4 <= 0.10$

The printout of the program is demonstrated in Figure 15. The resulting optimum values consisted of the feeding volume of 200 ml, the alcohol fraction of 0.68, the ethylcellulose content of 2.49 mg, and the chitosan content of 0.02 mg. To facilitate the further experiment the alcohol proportion and the ethylcellulose content were adjusted to 0.70 and 2.50 mg, respectively. Therefore the feeding volume of 200 ml (-1 level), the alcohol fraction of 0.70 (1 level), the ethylcellulose content of 2.50 mg (0.5 level) and the chitosan content of 0.02 mg (-1 level) were chosen to combine with 10.00 g of diclofenac sodium in order to prepare the required optimum diclofenac sodium controlled release solid dispersion. However, this set of optimum conditions was not the only one that fulfilling the required criteria. In fact it was the first one that was

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The following model was read:

Objective Function :
   MAX -0.0228 X1 -43.1437 X2 -3.0737 X3 -108.2810 X4 +131.3712 X5
Subject to :
   1.  1.0000 X5 =   1.0000
   2. -0.0000 X1 -0.2359 X2 -0.0080 X3 -0.2634 X4 +0.3268 X5 >=  0.1380
   3. -0.0000 X1 -0.2359 X2 -0.0080 X3 -0.2634 X4 +0.3268 X5 <=  0.1400
   4.  0.0000 X1 +0.0720 X2 +0.0197 X3 +0.0384 X4 +0.7853 X5 >=  0.9000
   5.  1.0000 X1 >= 200.0000
   6.  1.0000 X1 <= 500.0000
   7.  1.0000 X2 >=  0.3000
   8.  1.0000 X2 <=  0.7000
   9.  1.0000 X3 >=  1.0000
  10.  1.0000 X3 <=  3.0000
  11.  1.0000 X4 >=  0.0200
  12.  1.0000 X4 <=  0.1000


Summary of Results

Value Objective Function :         87.5037

Variable        Activity Level    Reduced Cost
--------        --------------    ------------
X1          :         200.0000        0.0000
X2          :           0.6841        0.0000
X3          :           2.4934        0.0000
X4          :           0.0200        0.0000
X5          :           1.0000        0.0000
```

Figure 15. The printout of SIMOPT program searching for the optimized solid dispersion.

calculated by the computer program and one should acknowledge the existence of the other sets of optimum conditions.

To search for the optimum range of spray drying conditions for preparing the optimized diclofenac sodium:(EC+chitosan) controlled release solid dispersions, the application of response surface plot and contour plot were employed. The surface plots and contour plots of K^0 and R^2 were obtained by fixing two variables at constant levels and varying the levels of the two remaining variables in the range that being studied. Those plots are illustrated in Figures 16-19 .

From the equations 1.1 or 1.2 and 2.1 or 2.2, the increase in the volume of feeding solution from 200 ml to 500 ml didn't impart any significant effect on K^0 or R^2. Economically it would be benefit to fix the volume of feeding solution to 200 ml (-1 level). The response surface plot of equation 1.2 is demonstrated in Figure 16. Figure 16a showed that when fixing the feeding volume at -1 level and alcohol proportion at 1 level, the variation in ethylcellulose or chitosan content or both would result in the K^0 of diclofenac sodium solid dispersions in the range of 0.110 to 0.150 mg per minute. While Figure 16b demonstrated that when the feeding volume and alcohol fraction were fixed at -1 and -1 respectively, the variation in ethylcellulose or chitosan content or both would yield the K^0 in the range of 0.205 to 0.240 mg per minute. These results could be used as a guideline to select the levels of variables that will give the required optimum K^0. Therefore the K^0 of 0.139 mg per minute could be obtained by fixing the levels of feeding volume and alcohol fraction at -1 and 1 respectively, and then the optimum levels of ethylcellulose and chitosan contents could be selected properly. To

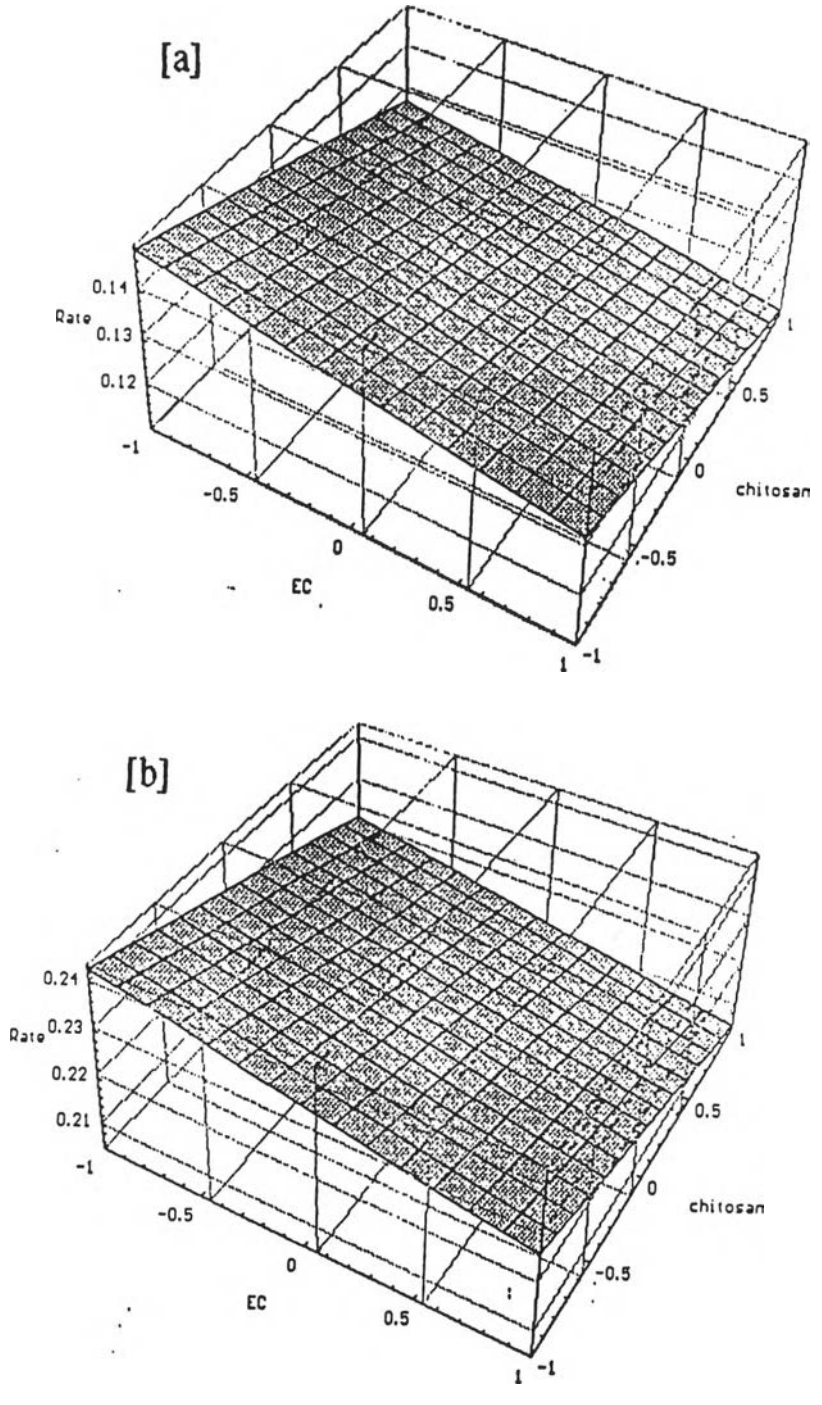


Figure 16. The response surface plots for zero-order dissolution rate constant (mg/minute) as functions of ethylcellulose and chitosan contents : [a] fixing $X_1 = -1$ and $X_2 = 1$, [b] fixing $X_1 = -1$ and $X_2 = -1$.

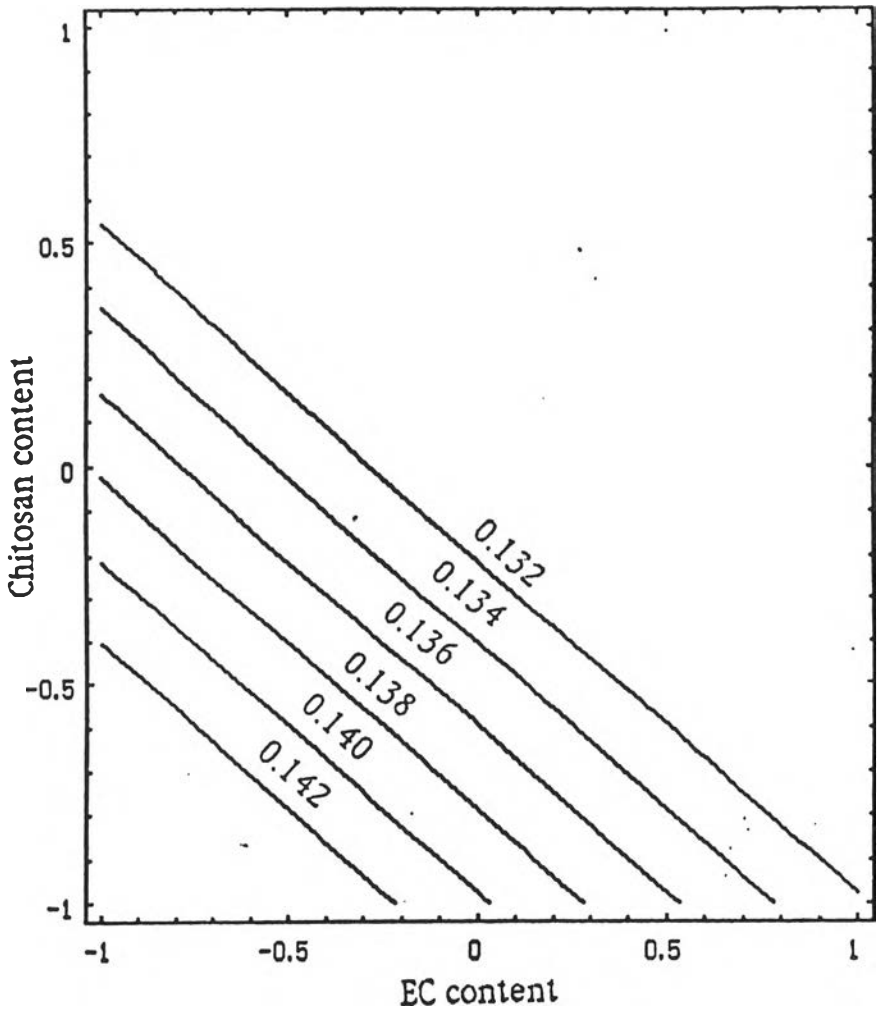


Figure 17. The contour plot for zero-order dissolution rate constant (mg/minute) as a function of ethylcellulose and chitosan contents when $X_1 = -1$ and $X_2 = 1$.

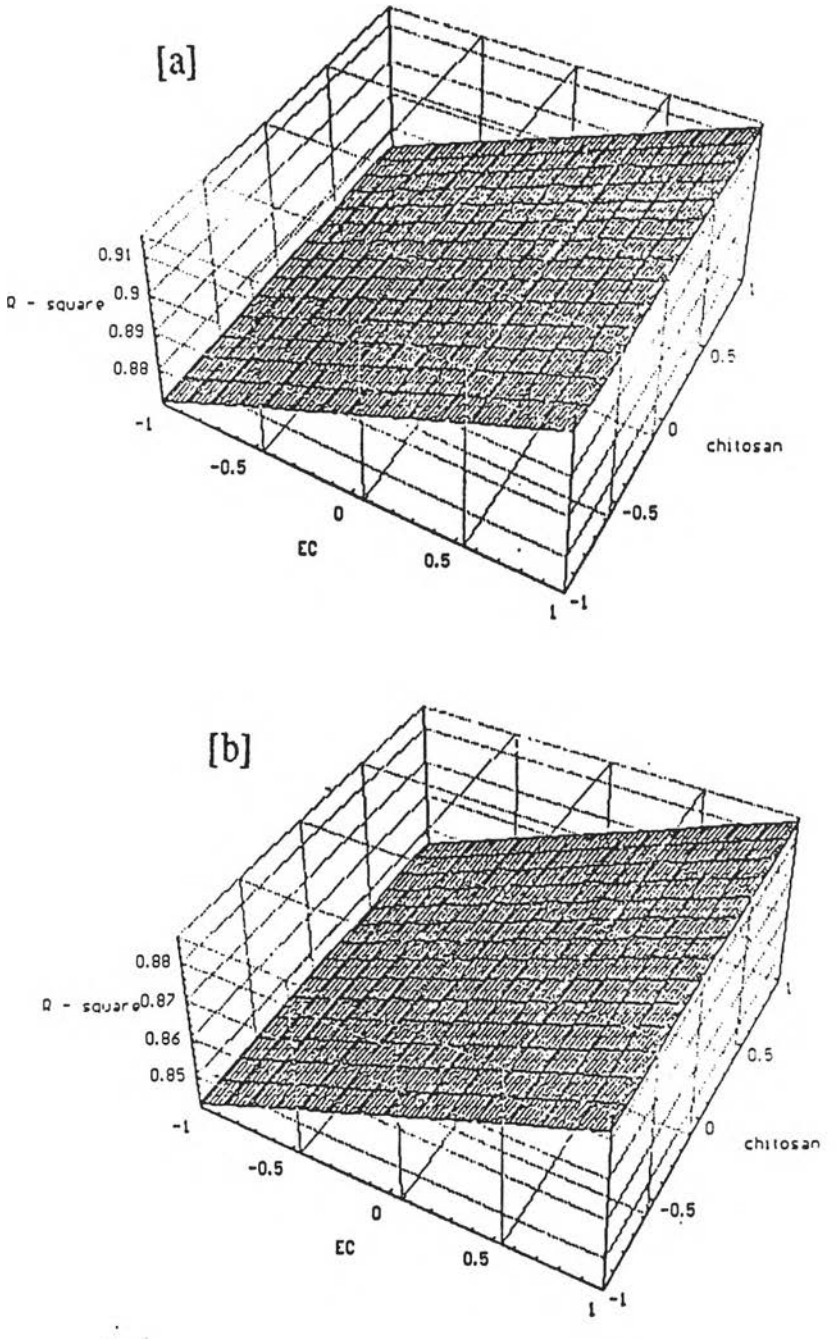


Figure 18. The response surface plots for R^2 value as a function of ethylcellulose and chitosan contents : [a] fixing $X_1 = -1$ and $X_2 = 1$, [b] fixing $X_1 = -1$ and $X_2 = -1$.

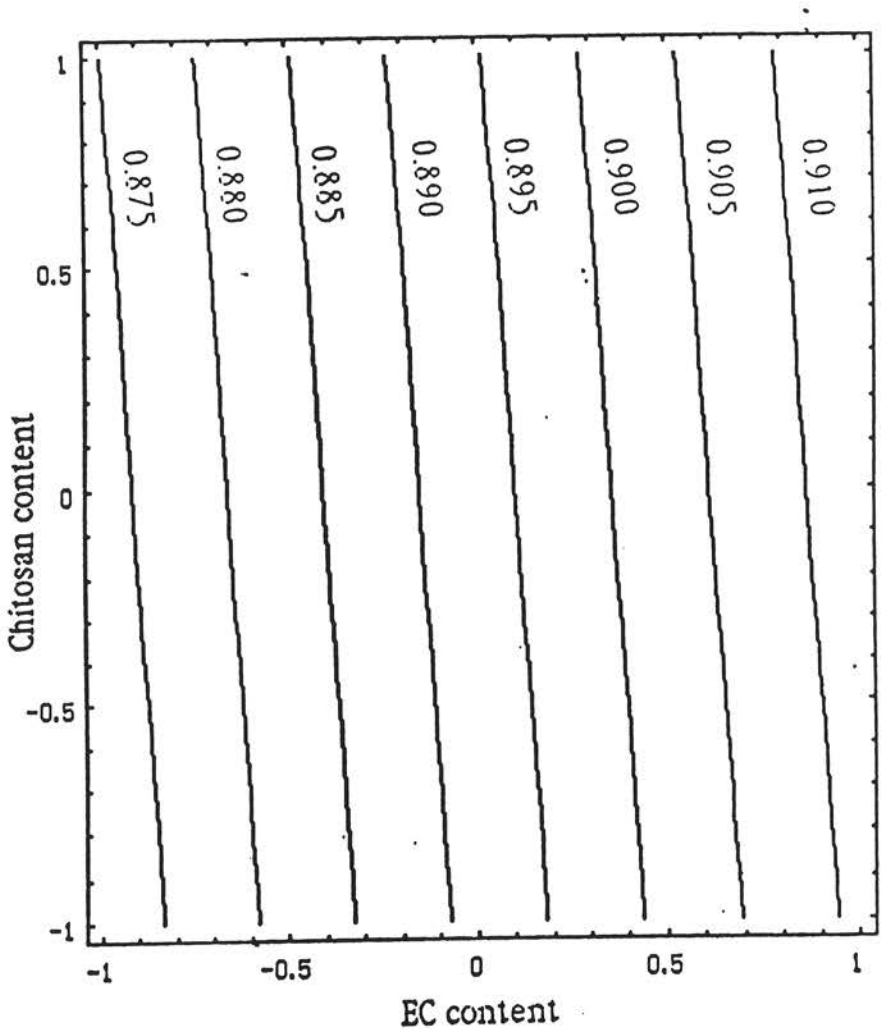


Figure 19. The contour plot for R^2 value as a function of ethylcellulose and chitosan contents when $X_1 = -1$ and $X_2 = 1$.

facilitate the selection of the optimum levels of ethylcellulose and chitosan contents the contour plot of fixing the levels of feeding volume and alcohol proportion at -1 and 1 was constructed as shown in Figure 17.

The surface plots and contour plot of the response R^2 are also illustrated in Figures 18 and 19, respectively. These graphs were also plotted by fixing the levels of feeding volume and alcohol fraction at -1 and 1 or -1 and -1, respectively. The surface plot showed that R^2 of 0.870 to 0.910 could be achieved by fixing the levels of the feeding volume and alcohol fraction at -1 and 1 respectively while varying the levels of EC and chitosan contents freely from -1 to 1.

In order to search for the optimum levels of ethylcellulose and chitosan contents that would give the most possible required K^0 with the acceptable R^2 value, the two contour plots of K^0 and R^2 were superimposed as shown in Figure 20. From this superimposed contour plot a restricted area which would give the K^0 between 0.136 to 0.142 mg per minute and the R^2 value of more than 0.880 was identified. Within this area the optimum levels of ethylcellulose and chitosan contents which would give the most possible required K^0 of 0.136 to 0.142 mg per minute with the aceeptable R^2 value of more than 0.880 could be chosen.

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

The dissolution profile of the optimum diclofenac sodium solid dispersion (experiment IX), the 10:(2.5+0.02) diclofenac sodium:(EC+ chitosan), is illustrated in Figure 21. The K^0 and R^2 were calculated and

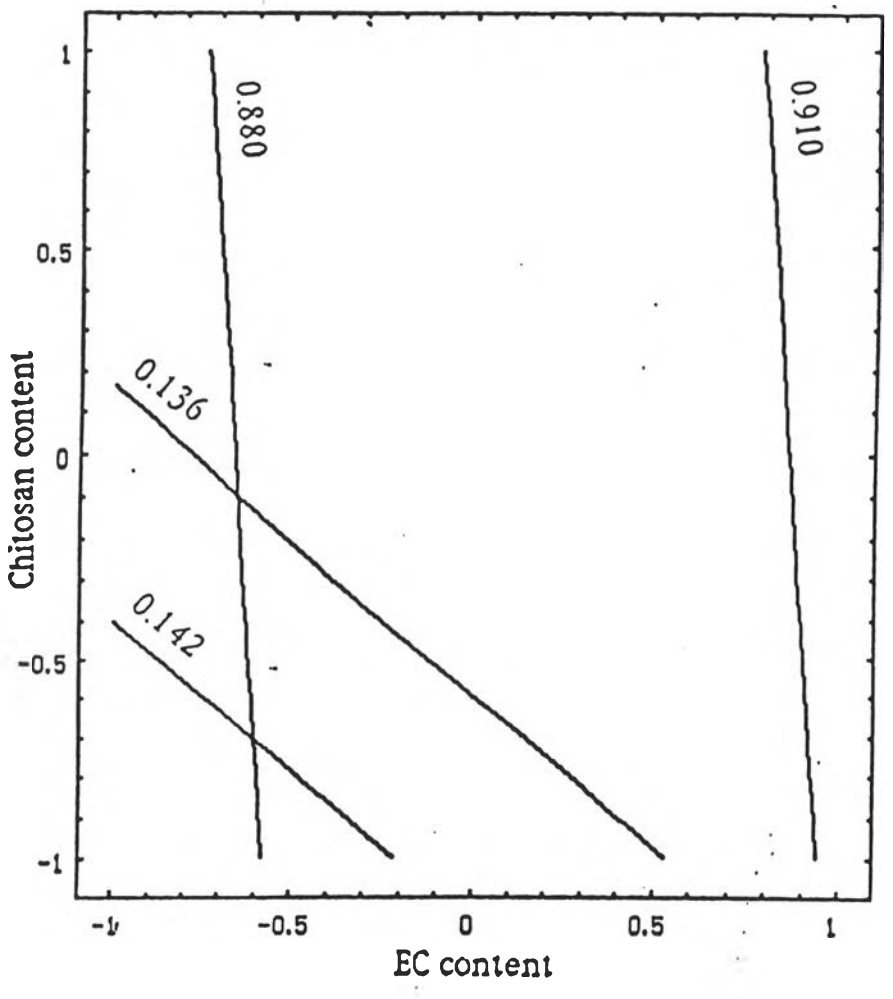


Figure 20. The superimposed contour plots for zero-order dissolution rate constant (0.136-0.142 mg/minute) and R^2 value (0.880-0.910) when $X_1 = -1$ and $X_2 = 1$.

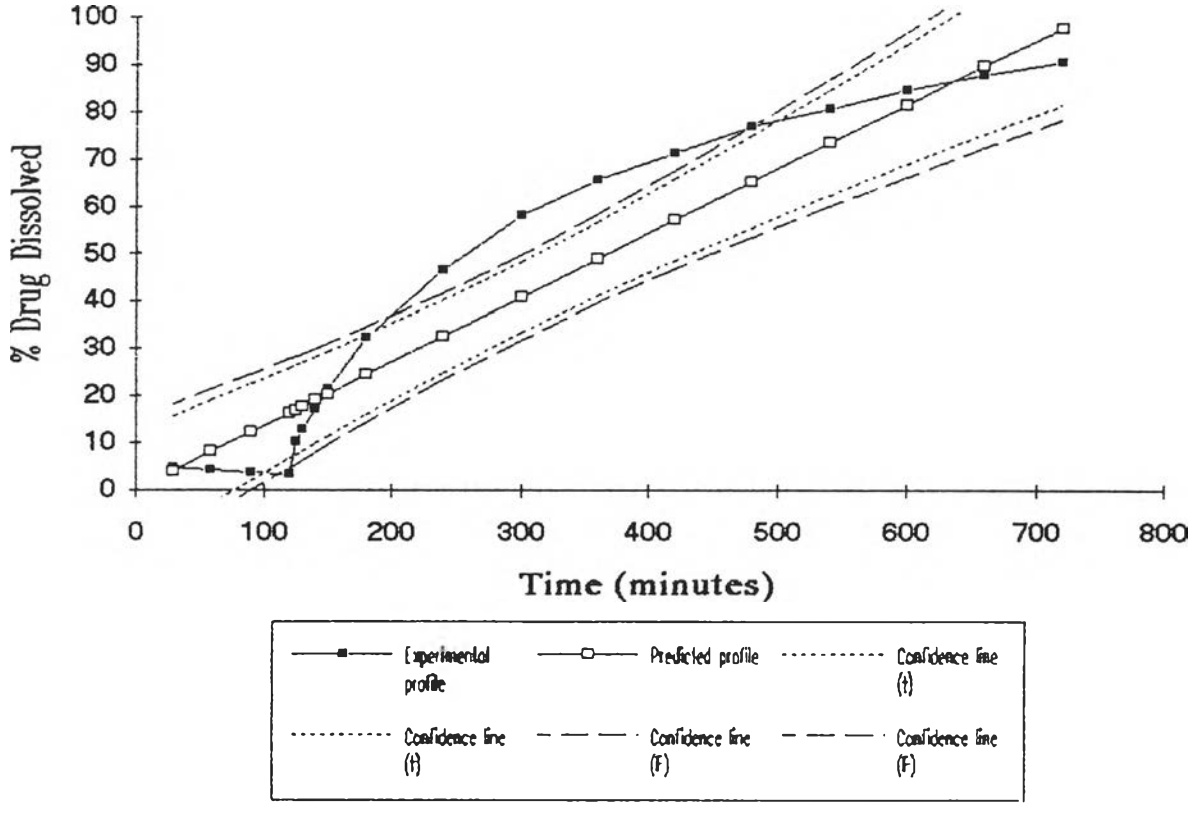


Figure 21. Dissolution profile of the optimized 10:(2.5+0.02) diclofenac sodium:(EC+chitosan) solid dispersion as compared to the predicted dissolution profile with 99% confidence level.

compared with the predicted K^0 and R^2 being calculated from the multiple linear equations. Those informations are shown in Table 20. The experimental K^0 and R^2 were 0.147128 mg per minute and 0.928030 while the the predicted K^0 and R^2 were 0.136248 mg per minute and 0.901275, respectively. From the predicted K^0, the predicted dissolution profile having R^2 of 1.0000 could be drawn as shown in Figure 21. The 99% confidence lines of the predicted dissolution profile were constructed according to t-value ($t_{1/2}$ = 2.921) and F-value ($F_{0.1,2,16}$ = 6.23). The experimental profile of the optimized diclofenac sodium solid dispersion lied almost completely within the 99% confidence band indicating the validity of the prediction by the K^0 equation. To confirm 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. Figures 22-24 show the printouts of the multiple linear regression model. The model regression coefficients, the statistical t-values and partial F-values, and the correlation of linearity of the model (r^2) were all expressed in the printouts. 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. Table 21 shows the r^2 values obtained from experiments I-VIII and I-IX which were 0.968910 and 0.966339 for the response K^0 and 0.905006 and 0.864298 for the response R^2, respectively. Similarity between those values confirmed the validity of the predicted equations for the two responses. Therefore the equations 1.1 or 1.2 and 2.1 or 2.2 could be used to predict K^0 and R^2 accurately.

Table 20. Experimental Design of the Optimized Diclofenac Sodium: (EC+chitosan) Solid Dispersions (Experiment IX) and the Observed and Predicted Responses.

Drug	Reduced Variables				Observed		Predicted	
	X_1	X_2	X_3	X_4	K^0	R^2	K^0	R^2
10 (g)	-1	1	0.5	-1	0.147128	0.928030	0.136248	0.901275

Drug	Parameters				Observed		Predicted	
	x_1	x_2	x_3	x_4	K^0	R^2	K^0	R^2
10 (g)	200 (ml)	0.70	2.50 (g)	0.02 (g)	0.147128	0.928030	0.136248	0.901275

Table 21. Comparison of the r^2 Values Calculated from Experiments I-VIII and I-IX.

Responses	Experiments I-VIII r^2	Experiments I-IX r^2
K^0	0.968910	0.966339
R^2	0.905006	0.864298

	Volume	Alc.	E.C.	Chitosan	R-square	Rate	Predicted R-square	Predicted Rate
	X	X	X	X	Y	Y		
1	1.00	1.00	1.00	1.00	.913113	.100740	.923752	.111396
2	-1.00	1.00	-1.00	1.00	.887548	.137521	.878196	.128521
3	1.00	-1.00	-1.00	1.00	.854114	.214311	.849076	.219122
4	-1.00	-1.00	1.00	1.00	.882822	.212446	.886573	.205979
5	1.00	1.00	1.00	-1.00	.929054	.142239	.924968	.134248
6	-1.00	1.00	-1.00	-1.00	.859139	.137932	.879412	.151373
7	1.00	-1.00	-1.00	-1.00	.851806	.249449	.850292	.241974
8	-1.00	-1.00	1.00	-1.00	.884987	.219699	.887789	.228831
9	-1.00	1.00	.50	-1.00	.928030	.147128	.910557	.140022

Figure 22. The printout of multiple regression program, utilizing data from experiments I - IX in term of reduced variables, showing predicted zero-order dissolution rate constant and R^2 value.

Multiple - Y : Rate Four X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
8	.966339	.01317	7.590928

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	.019917	.004979	28.708113
RESIDUAL	4	.000694	.000173	.005 < p < .01
TOTAL	8	.020611		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.17768	.004462	39.819108	
Volume	-.000996	.004462	-.223116	.049781
Alc.	-.046296	.004462	-10.375161	107.643965
E.C.	-.007567	.004609	-1.641961	2.696034
Chitosan	-.011426	.004462	-2.56059	6.556622

2

Figure 23. The printout of multiple regression program for zero-order dissolution rate constant utilizing data from experiments I - IX in term of reduced variables.

Multiple - Y : R-square Four X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
8	.864298	.015678	1.765887

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	4	.006262	.001566	6.369082
RESIDUAL	4	.000983	.000246	.05 < p < .10
TOTAL	8	.007246		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.885007	.005312	166.60309	
Volume	.002015	.005312	.379268	.143844
Alc.	.016575	.005312	3.120216	9.73575
E.C.	.020763	.005486	3.78457	14.32297
Chitosan	-.000608	.005312	-.114419	.013092

2

Figure 24. The printout of multiple regression program for R^2 value utilizing data from experiments I - IX in term of reduced variables.

PART II - SOLID DISPERSION TABLETS

Evaluation of Diclofenac Sodium Controlled Release Tablets

In order to formulate the optimized 10:(2.5÷0.02) diclofenac sodium:(EC+chitosan) solid dispersion into optimum controlled release tablet dosage form by direct compression, the parameters having influences on tablet dissolution must be controlled at the optimum levels. Four parameters considered having these influences were compression force, compressible excipient, disintegrant, and lubricant utilized in diclofenac sodium tablet production. Lin and Lin (1993) studied the effects of different types of direct compressible excipients on direct-compressed theophylline tablets containing Eudragit RSPM/RLPM. They demonstrated that the tablets made by dicalcium phosphate anhydrous (DCPA) or microcrystalline cellulose (Avicel PH 101) exhibited the most controlled release behavior. However, the release rate of theophylline from the tablets produced by dicalcium phosphate changed significantly when pH of the dissolution medium was altered from 1.2 to 6.5, while the pH change showed much less effect on the drug release rate from the tablets of microcrystalline cellulose. Therefore, it appeared that Avicel PH 101 should be the direct compressible excipient of choice for fabricating diclofenac sodium controlled release tablets. However, the prepared spray-dried diclofenac sodium solid dispersion was bulky and thus a compressible diluent having high bulk density was required. Bulk density of Avicel PH 101 is quite low of 0.28 g/cc (American Pharmaceutical Association, 1986) therefore it was not appropriate to be used in fabricating the diclofenac sodium controlled release tablets by direct compression.

Era-Tab, a direct compressible excipient, is spray-dried rice starch having high bulk density of 0.53 g/cc (Varavinit and Mitrevej, 1989). It was demonstrated that the release rate of tablets made by starch was pH-independent (Lin and Lin, 1993). Therefore the decision was made to employ Era-Tab as compressible excipient in the diclofenac sodium controlled release tablet formulation. Fassihi, Parker, and PourKavoos (1985) studied the influence of compression force on the release rate of theophylline from solid dispersed system tablets. The release rate of drug dispersed in a polymeric mixture of polyethylene glycol and acrylic/methacrylic esters was found to depend on the compression force. In order to counter the effect of compression on tablet dissolution, a disintegrant is required in the tablet formulation. In this study croscarmellose sodium (Ac-Di-Sol) was selected due to its high disintegrating effect on the tablets (Shangraw, Wallace, and Bowers, 1981). The retarding effect of hydrophobic lubricants on tablet disintegration was commonly known. Hence, the optimum level of the hydrophobic lubricant, magnesium stearate, utilized in the diclofenac sodium controlled release tablet formulation must be searched.

The weight variation, friability, hardness and disintegration time of diclofenac sodium:(EC+chitosan) solid dispersion tablets prepared from all 17 formulations are shown in Table 22. Dissolution profiles of the investigated tablet formulations are also demonstrated in Figure 25. The K^0 and R^2 of the designed diclofenac sodium controlled release tablet formulations calculated from their dissolution profiles using linear regression are presented in Table 22. The second-order multiple regression was employed to construct the relationships between a response (Y_i) and the four variables, the compression force (X_1), the

Table 22. Tablet Properties of Diclofenac Sodium Controlled Release Tablets From Various Formulations.

Formulation	Weight Variation (%)	Friability (%)	Hardness (kp)	Disintegration Time (minutes)
I	2.12	0.20	2.86	1.66
II	1.88	0.10	5.12	1.88
III	2.20	0.38	3.36	1.52
IV	1.29	0.15	5.80	1.73
V	4.07	0.35	3.24	1.13
VI	1.74	0.08	5.90	1.46
VII	2.05	0.71	2.96	1.11
VIII	2.44	0.06	6.16	1.80
IX	2.94	0.05	6.40	1.40
X	2.49	0.45	3.42	1.32
XI	2.18	0.15	5.80	1.61
XII	1.55	0.11	4.46	1.14
XIII	4.27	0.20	4.52	1.11
XIV	2.28	0.19	4.54	1.48
XV	1.86	0.22	4.58	1.23
XVI	3.03	0.23	5.04	1.32
XVII	2.50	0.26	5.26	1.21

Formulation	K^0 (mg per minute)	R^2
I	0.119907	0.922725
II	0.119997	0.903966
III	0.122161	0.945490
IV	0.099279	0.925693
V	0.147456	0.908940
VI	0.149350	0.882547
VII	0.177620	0.911575
VIII	0.179568	0.838984
IX	0.154044	0.881433
X	0.156840	0.891720
XI	0.143407	0.951921
XII	0.154080	0.928060
XIII	0.200047	0.873209
XIV	0.116939	0.945551
XV	0.145629	0.824239
XVI	0.154524	0.880134
XVII	0.138216	0.896059

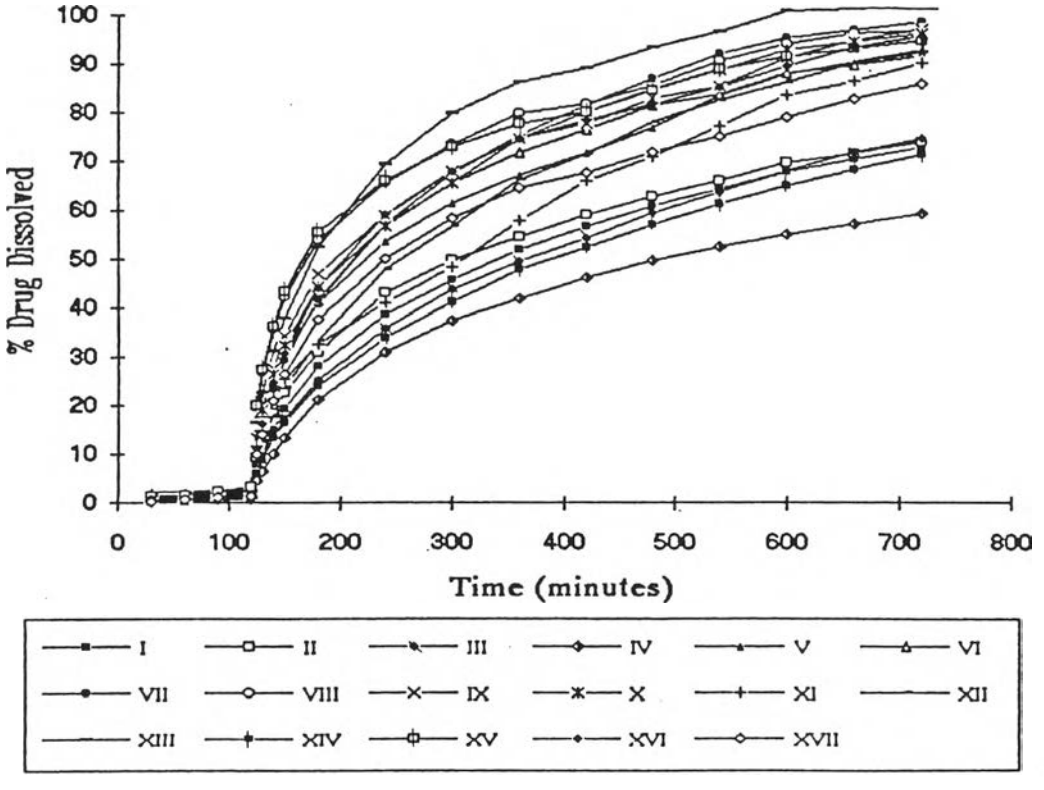


Figure 25. Dissolution profiles of diclofenac sodium controlled release tablets prepared from the designed tablet formulations.

amount of Era-Tab (X_2) , the amount of Ac-Di-Sol (X_3) and the amount of magnesium stearate (X_4). The equations expressed the second-order relationships between the four variables and tablet weight variation (Y_1), friability (Y_2), hardness (Y_3), disintegration time (Y_4), K^0 (Y_5), and R^2 (Y_6) therefore were derived. The printouts obtained from the multiple regression program are shown in Figures 26-32.

In order to determine the fitness of the investigated relationships to the second-order model, the correlation coefficient (r^2) for each investigated relationship was calculated. The r^2 value of more than 0.800 was justified as an indication of acceptable fitness of the second-order model. It is of benefit to assume a second-order model to any relationship since it is also applicable if the relationship is a first-order model. In such case the regression coefficients (b_i) of the interactions ($x_{k-1}X_k$) and the squared term (X_k^2) will be insignificant and the model can be reduced to first-order model automatically. The significance of the main effects, the interactions, or the squared-term effects can be determined utilizing the statistical t-values or the partial F-values.

Determination of the Predicted Response Equations

Since the central composite design of four variables being utilized in this study based on half fractional factorial therefore every two-factor interaction was aliased with another two-factor interaction (Montgomery, 1991). These alias relationships were: $X_1X_2 = X_3X_4$, $X_1X_3 = X_2X_4$, and $X_2X_3 = X_1X_4$, respectively. In order to distinguish these two-factor interactions, the central composite design must base on the full factorial design and hence the total of 27 experiments should be employed (Franz

	Pressure	EraTab	Ac-Di-Sol	Mg. St.	X1X2=X3X4	X1X3=X2X4	X1X4=X2X3	X1X1	X2X2
	X	X	X	X	X	X	X	X	X
1	-1.000	-1.000	-1.000	-1.000	1.000	1.000	1.000	1.000	1.000
2	1.000	-1.000	-1.000	1.000	-1.000	-1.000	1.000	1.000	1.000
3	-1.000	1.000	-1.000	1.000	-1.000	1.000	-1.000	1.000	1.000
4	1.000	1.000	-1.000	-1.000	1.000	-1.000	-1.000	1.000	1.000
5	-1.000	-1.000	1.000	1.000	1.000	-1.000	-1.000	1.000	1.000
6	1.000	-1.000	1.000	-1.000	-1.000	1.000	-1.000	1.000	1.000
7	-1.000	1.000	1.000	-1.000	-1.000	-1.000	1.000	1.000	1.000
8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
9	1.414	0	0	0	0	0	0	1.999	0
10	-1.414	0	0	0	0	0	0	1.999	0
11	0	1.414	0	0	0	0	0	0	1.999
12	0	-1.414	0	0	0	0	0	0	1.999
13	0	0	1.414	0	0	0	0	0	0
14	0	0	-1.414	0	0	0	0	0	0
15	0	0	0	1.414	0	0	0	0	0
16	0	0	0	-1.414	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0

	X3X3	X4X4	Hardness	Rate	R-square	Friability	Wt. Var.	Disint. time
	X	X	Y	Y	Y	Y	Y	Y
1	1.000	1.000	2.86	.119907	.922725	.2009	2.12	1.66
2	1.000	1.000	5.12	.119997	.903966	.0977	1.88	1.88
3	1.000	1.000	3.36	.122161	.945490	.3825	2.20	1.52
4	1.000	1.000	5.80	.099279	.925693	.1492	1.29	1.73
5	1.000	1.000	3.24	.147456	.908940	.3534	4.07	1.13
6	1.000	1.000	5.90	.149350	.882547	.0838	1.74	1.46
7	1.000	1.000	2.96	.177620	.911575	.7068	2.05	1.11
8	1.000	1.000	6.16	.179568	.853287	.0602	2.44	1.80
9	0	0	6.40	.154044	.881433	.0511	2.94	1.40
10	0	0	3.42	.156840	.891720	.4509	2.49	1.32
11	0	0	5.80	.143407	.951921	.1499	2.18	1.61
12	0	0	4.46	.154080	.928060	.1094	1.55	1.14
13	1.999	0	4.52	.200047	.873209	.1984	4.27	1.11
14	1.999	0	4.54	.116939	.945551	.1892	2.28	1.48
15	0	1.999	4.58	.145629	.824239	.2176	1.86	1.23
16	0	1.999	5.04	.154524	.880134	.2261	3.03	1.32
17	0	0	5.26	.136216	.896059	.2615	2.50	1.21

Figure 26. The printout of multiple regression program utilizing data from experiment I - XVII in term of reduced variables. (Compression pressure = X_1, Era-Tab content = X_2, Ac-Di-Sol content = X_3, magnesium stearate content = X_4)

Multiple - Y : Wt. Var. Eleven X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
16	.643948	.854321	35.518366

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	6.6001	.600009	.822083
RESIDUAL	5	3.649323	.729865	p > .25
TOTAL	16	10.249424		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	2.76225	.529709	5.214653	
Pressure	-.204496	.246634	-.829147	.687485
EraTab	-.078273	.246634	-.317365	.10072
Ac-Di-Sol	.468702	.246634	1.900398	3.611513
Mg. St.	.14465	.246634	.586496	.343977
X1X2	.25625	.302048	.848375	.71974
X1X3	-.09875	.302048	-.326935	.106886

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4	-.10125	.302048	-.335211	.112367
X1X1	-.056414	.313501	-.179947	.032381
X2X2	-.481542	.313501	-1.536016	2.359344
X3X3	.223671	.313501	.713463	.509029
X4X4	-.191454	.313501	-.610698	.372952

3

Figure 27. The printout of multiple regression program for tablet weight variation (%) utilizing data from experiments I-XVII in term of reduced variables.

Multiple - Y : Friability Eleven X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
16	.94486	.070168	30.675933

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	.421849	.03835	7.788972
RESIDUAL	5	.024618	.004924	.01 < p < .025
TOTAL	16	.446467		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.189093	.043507	4.346264	
Pressure	-.151517	.020257	-7.47975	55.946664
EraTab	.051686	.020257	2.551513	6.510218
Ac-Di-Sol	.032246	.020257	1.591834	2.533935
Mg. St.	-.021579	.020257	-1.065254	1.134765
X1X2	-.063388	.024808	-2.555092	6.528494
X1X3	-.072463	.024808	-2.920897	8.531637

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4	.012087	.024808	.487236	.237399
X1X1	.040014	.025749	1.554003	2.414926
X2X2	-.020679	.025749	-.803116	.644995
X3X3	.011405	.025749	.442942	.196198
X4X4	.025435	.025749	.98779	.975728

3

Figure 28. The printout of multiple regression program for tablet friability (%) utilizing data from experiments I-XVII in term of reduced variables.

Multiple - Y : Hardness Eleven X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
16	.969885	.36054	7.717431

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	20.932501	1.902955	14.639323
RESIDUAL	5	.649946	.129989	.005 < p < .01
TOTAL	16	21.582447		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	5.262922	.223548	23.542724	
Pressure	1.231267	.104084	11.829527	139.937707
EraTab	.254589	.104084	2.44599	5.982865
Ac-Di-Sol	.090986	.104084	.874156	.764148
Mg. St.	-.024206	.104084	-.232559	.054084
X1X2	.09	.12747	.706047	.498503
X1X3	.145	.12747	1.137521	1.293953

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4	-.15	.12747	-1.176745	1.38473
X1X1	-.176879	.132303	-1.336922	1.787361
X2X2	-.066846	.132303	-.505249	.255276
X3X3	-.366937	.132303	-2.773449	7.69202
X4X4	-.226894	.132303	-1.714956	2.941073

3

Figure 29. The printout of multiple regression program for tablet hardness (kp) utilizing data from experiments I-XVII in term of reduced variables.

Multiple - Y : Disint. time Eleven X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
16	.858785	.181575	12.904609

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	1.002505	.091137	2.764264
RESIDUAL	5	.164848	.03297	.10 < p < .25
TOTAL	16	1.167353		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	1.12314	.112583	9.976085	
Pressure	.130273	.052419	2.485229	6.176364
EraTab	.057887	.052419	1.104324	1.219531
Ac-Di-Sol	-.173504	.052419	-3.30995	10.955771
Mg. St.	.02023	.052419	.385936	.148947
X1X2	.04375	.064197	.6815	.464442
X1X3	.07375	.064197	1.148815	1.319775

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4	.07625	.064197	1.187757	1.410768
X1X1	.129324	.066631	1.9409	3.767093
X2X2	.136826	.066631	2.053495	4.216841
X3X3	.049299	.066631	.73989	.547437
X4X4	.086811	.066631	1.302863	1.697453

3

Figure 30. The printout of multiple regression program for tablet disintegration time (minutes) utilizing data from experiments I-XVII in term of reduced variables.

Multiple - Y : Rate Eleven X variables

DF: -	R-squared:	Std. Err.:	Coef. Var.:
16	.913295	.01343	9.209406

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	.009499	.000864	4.787916
RESIDUAL	5	.000902	.00018	.025 < p < .05
TOTAL	16	.010401		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.155905	.008327	18.722851	
Pressure	-.001909	.003877	-.492338	.242397
EraTab	.002236	.003877	.576664	.332541
Ac-Di-Sol	.02585	.003877	6.667349	44.453546
Mg. St.	.000871	.003877	.224602	.050446
X1X2	-.002865	.004748	-.603339	.364018
X1X3	.003329	.004748	.701166	.491634

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4	.009856	.004748	2.075698	4.308524
X1X1	-.002442	.004928	-.495604	.245623
X2X2	-.005793	.004928	-1.17542	1.381611
X3X3	-.000916	.004928	-.185965	.034583
X4X4	-.005126	.004928	-1.040137	1.081884

3

Figure 31. The printout of multiple regression program for tablet zero-order dissolution rate constant (mg per minute) utilizing data from experiments I-XVII in term of reduced variables.

Multiple - Y : R-square Eleven X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
16	.92752	.016491	1.829126

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	.0174	.001582	5.816749
RESIDUAL	5	.00136	.000272	.025 < p < .05
TOTAL	16	.01876		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.890664	.010225	87.108066	
Pressure	-.011483	.004761	-2.412055	5.818009
EraTab	.004301	.004761	.903433	.816192
Ac-Di-Sol	-.02032	.004761	-4.268304	18.218422
Mg. St.	-.009159	.004761	-1.923802	3.701013
X1X2	-.004117	.00583	-.706069	.498534
X1X3	-.005766	.00583	-.9889	.977923

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4	-.00889	.00583	-1.524717	2.324763
X1X1	-.00137	.006051	-.226405	.051259
X2X2	.025345	.006051	4.188282	17.541708
X3X3	.010035	.006051	1.658313	2.750002
X4X4	-.01857	.006051	-3.068751	9.41723

3

Figure 32. The printout of multiple regression program for tablet R^2 value utilizing data from experiments I-XVII in term of reduced variables.

et al., 1990). However, in the present study the central composite design based on half fractional factorial was chosen since this design would yield only 17 experiments while the main effect of each independent variable could be completely analyzed. If any one of these main effects was proven to be insignificant then this half fractional factorial-based central composite design would be sufficient to use for evaluation of a required relationship. Since it was possible to project this half fractional factorial-based central composite design into a full factorial-based central composite design of the remaining three significant variables. In contrast if all the four independent variables were proven to have significant main effects on an investigated dependent variable then the design could be expanded later to base on full factorial of four variables. Therefore by multiple regression using a statistical computer program, the relationships between an investigated response (Y_i) and the remaining three independent variables could be established. These relationships are expressed by equations in Table 23. The values of r^2 of these equations were also shown. The statistical t-values and the partial F-values of the equations are calculated and listed in Table 24.

1. Weight Variation

The relationships between the tablet weight variation and the four investigated variables as shown in equations 4.1 or 4.2 were obtained from the half fractional-factorial based central composite design. The printout of multiple regression program for weight variation obtained from the 17 experiments is shown in Figure 27. The regression coefficient of each variable and the r^2 value of the multiple regression also were calculated.

Table 23. The Values of Correlation Coefficient (r^2) Calculated According to the Number of Independent Variables Being Included.

Variable Included	Correlation Coefficient (r^2)					
	Weight Variation	Friability	Hardness	Disintegration time	K^0	R^2
X_1, X_2, X_3, X_4	0.643948	0.944860	0.969855	0.858785	0.913295	0.92752
X_1, X_2, X_3	0.646648	0.922900	0.971002	0.827682	0.897598	0.915356
X_1, X_2, X_4	0.359951	0.914577	0.956758	0.582090	0.176894	0.752110
X_1, X_3, X_4	0.558026	0.879773	0.973461	0.858690	0.890414	0.834168
X_2, X_3, X_4	0.589813	0.374740	0.151079	0.641715	0.904438	0.842658

Equations Derived From Full Factorial Central Composite Designs of Three Variables.

$$Y_1 = -0.204496X_1 - 0.078273X_2 + 0.468702X_3 + 0.256250X_1X_2 - 0.098750X_1X_3 - 0.101250X_2X_3 - 0.119392X_1^2 - 0.544521X_2^2 + 0.160692X_3^2 + 2.802536 \quad (4.3) \quad (r^2=0.646648)$$

$$Y_2 = -0.151517X_1 + 0.051686X_2 + 0.032246X_3 - 0.063388X_1X_2 - 0.072463X_1X_3 + 0.012087X_2X_3 + 0.043688X_1^2 - 0.017005X_2^2 + 0.015079X_3^2 + 0.196254 \quad (5.3) \quad (r^2=0.922900)$$

$$Y_3 = 1.231267X_1 + 0.090986X_3 - 0.024206X_4 + 0.145000X_1X_3 - 0.150000X_1X_4 + 0.090000X_3X_4 - 0.209941X_1^2 - 0.399998X_3^2 - 0.259956X_4^2 + 5.306513 \quad (6.3) \quad (r^2=0.973461)$$

$$Y_4 = 0.130273X_1 - 0.173504X_3 + 0.020230X_4 + 0.073750X_1X_3 + 0.076250X_1X_4 + 0.043750X_3X_4 + 0.186893X_1^2 + 0.106869X_3^2 + 0.144381X_4^2 + 1.060854 \quad (7.3) \quad (r^2=0.858690)$$

$$Y_5 = 0.002236X_2 + 0.025850X_3 + 0.000871X_4 + 0.009856X_2X_3 + 0.003329X_2X_4 - 0.002865X_3X_4 - 0.004805X_2^2 + 0.000072X_3^2 - 0.004138X_4^2 + 0.151641 \quad (8.3) \quad (r^2=0.904438)$$

$$Y_6 = -0.011483X_1 + 0.004301X_2 - 0.020320X_3 - 0.004117X_1X_2 - 0.005766X_1X_3 - 0.008890X_2X_3 - 0.011330X_1^2 + 0.015385X_2^2 + 0.000075X_3^2 + 0.904841 \quad (9.3) \quad (r^2=0.915356)$$

Table 24. The Statistical t-values and Partial F-values Obtained from Multiple Regression Equations Derived from the Full Factorial Central Composite Design of Three Variables.

Parameters	t-value				
	Friability	Hardness	Disintegration Time	K^0	R^2
X_1	-6.326483	13.022432	2.613865	-	-2.829727
X_2	2.158107	-	-	0.555015	1.059872
X_3	1.346397	0.962307	-3.481274	6.417042	-5.007405
X_4	-	-0.256011	0.405912	0.21617	-
X_1X_2	-2.161134	-	-	-	-0.828332
X_1X_3	-2.470538	1.25223	1.208278	-	-1.160138
X_1X_4	-	-1.29541	1.249236	-	-
X_2X_3	0.412111	-	-	1.997772	-1.788738
X_2X_4	-	-	-	0.674843	-
X_3X_4	-	0.777246	0.716775	-0.580688	-
X_1^2	1.216108	-1.480285	2.499949	-	-1.861342
X_2^2	-0.473366	-	-	-0.795131	2.527521
X_3^2	0.419751	-2.820373	1.429519	0.111867	0.012351
X_4^2	-	-1.83294	1.931283	-0.684794	-

Parameters	Partial F-value				
	Friability	Hardness	Disintegration Time	K^0	R^2
X_1	40.024392	169.583734	6.832293	-	8.007354
X_2	4.657427	-	-	0.308041	1.123329
X_3	1.812784	0.926034	12.119272	41.178427	25.074104
X_4	-	0.065542	0.164765	0.046729	-
X_1X_2	4.670502	-	-5	-	0.686134
X_1X_3	6.103556	1.568079	1.459935	-	1.34592
X_1X_4	-	1.678087	1.560591	-	-
X_2X_3	0.169836	-	-	3.991093	3.199583
X_2X_4	-	-	-	0.455413	-
X_3X_4	-	0.604111	0.513766	0.337199	-
X_1^2	1.478919	2.191244	6.249745	-	3.464594
X_2^2	0.224075	-	-	0.632233	6.388361
X_3^2	0.176191	7.954503	2.043524	0.000141	0.000153
X_4^2	-	3.359668	3.729845	0.468943	-

D.F. = 1,5: F (α=.01) = 16.26, F (α=.025) = 10.01, F (α=.05) = 6.61, F (α=.10) = 4.06, F (α=.25) = 1.69

D.F. = 5: t (α=.0005) = 6.869, t (α=.001) = 5.893, t (α=.0025) = 4.773, t (α=.005) = 4.002, t (α=.01) = 3.365, t (α= .025) = 2.571, t (α=.05) = 2.015, t (α=.10) = 1.476, t (α=.25) = 0.727

Weight variation equation ($r^2 = 0.643948$)

$$Y_1 = -0.204496X_1 - 0.078273X_2 + 0.468702X_3 + 0.14465X_4 + 0.25625X_1X_2 - 0.09875X1X_3 - 0.101250X_1X_4 - 0.056414X_1^2 - 0.481542X_2^2 + 0.223671X_3^2 - 0.191454X_4^2 + 2.76225 \quad (4.1)$$

or

$$Y_1 = -0.204496X_1 - 0.078273X_2 + 0.468702X_3 + 0.14465X_4 + 0.25625X_3X_4 - 0.09875X_2X_4 - 0.101250X_2X_3 - 0.056414X_1^2 - 0.481542X_2^2 + 0.223671X_3^2 - 0.191454X_4^2 + 2.76225 \quad (4.2)$$

The r^2 value obtained from the multiple regression of the equation 4.1 or 4.2 was 0.643948 which was quite low. Therefore the assumption could be concluded that the equation 4.1 or 4.2 was not valid. Thus the influences of independent variables on tablet weight variation couldn't be accurately predicted by the equation. However, the tablet weight variations obtained from all 17 tablet formulations were within acceptable range of $\pm$7.5% (The United State Pharmacopeil Convention, 1980) therefore any change in the levels of independent variables from -1.414 to 1.414 yielded the diclofenac sodium tablets of acceptable weight variation. Figures 33-36 are the printouts of the multiple regression program calculated in terms of only three variables.

2. Tablet Friability

Equation 5.1 or 5.2 described the relationship between the friability of diclofenac sodium tablets (Y_2) and the independent variables. These equations were derived by multiple regression using tablet friability

Multiple - Y : Wt. Var. Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.646648	.822014	34.25059

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	6.182864	.686985	1.01669
RESIDUAL	5	3.378536	.675707	p > .25
TOTAL	14	9.5614		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	2.802536	.67102	4.176533	
Pressure	-.204496	.237307	-.861734	.742586
EraTab	-.078273	.237307	-.329838	.108793
Ac-Di-Sol	.468702	.237307	1.975088	3.900972
X1X2	.25625	.290626	.881718	.777426
X1X3	-.09875	.290626	-.339784	.115453
X2X3	-.10125	.290626	-.348386	.121373

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.119392	.355961	-.335408	.112499
X2X2	-.544521	.355961	-1.529722	2.340049
X3X3	.160692	.355961	.451433	.203792

3

Figure 33. The printout of multiple regression program for tablet weight variation (%) utilizing data of 3 independent variables (X_1 , X_2 , X_3) from 15 experiments in term of reduced variables.

Multiple - Y : Wt. Var. Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.589813	.902604	38.18123

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	5.857288	.65081	.798839
RESIDUAL	5	4.073472	.814694	p > .25
TOTAL	14	9.93076		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	2.712508	.736806	3.68144	
EraTab	-.078273	.260573	-.300388	.090233
Ac-Di-Sol	.468702	.260573	1.79874	3.235465
Mg. St.	.14465	.260573	.555122	.308161
X2X3	-.10125	.319119	-.31728	.100667
X2X4	-.09875	.319119	-.309446	.095757
X3X4	.25625	.319119	.802992	.644797

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X2X2	-.476993	.390859	-1.220373	1.489309
X3X3	.22822	.390859	.583893	.340931
X4X4	-.186906	.390859	-.478192	.228668

3

Figure 34. The printout of multiple regression program for tablet weight variation (%) utilizing data of 3 independent variables (X_2 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Wt. Var. Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.558026	.911024	36.774369

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	5.239472	.582164	.701432
RESIDUAL	5	4.149821	.829964	p > .25
TOTAL	14	9.389293		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	2.995927	.743679	4.028521	
Pressure	-.204496	.263003	-.777541	.604569
Ac-Di-Sol	.468702	.263003	1.782116	3.175939
Mg. St.	.14465	.263003	.549992	.302491
X1X3	-.09875	.322096	-.306586	.093995
X1X4	-.10125	.322096	-.314348	.098815
X3X4	.25625	.322096	.795571	.632934

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.264451	.394505	-.670336	.44935
X3X3	.015634	.394505	.03963	.001571
X4X4	-.399491	.394505	-1.01264	1.02544

3

Figure 35. The printout of multiple regression program for tablet weight variation (%) utilizing data of 3 independent variables (X_1 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple – Y : Wt. Var. Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.359951	.916019	40.012473

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	2.35944	.26216	.312434
RESIDUAL	5	4.195453	.839091	p > .25
TOTAL	14	6.554893		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	2.525785	.747757	3.377816	
Pressure	-.204496	.264445	-.7733	.597994
EraTab	-.078273	.264445	-.295989	08761
Mg. St.	.14465	.264445	.546993	.299201
X1X2	.25625	.323862	.791233	.62605
X1X4	-.10125	.323862	-.312634	.09774
X2X4	-.09875	.323862	-.304914	.092973

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.088191	.396668	.222331	.049431
X2X2	-.336937	.396668	-.849419	.721512
X4X4	-.046849	.396668	-.118107	.013949

3

Figure 36. The printout of multiple regression program for tablet weight variation (%) utilizing data of 3 independent variables (X_1 , X_2 , X_4) from 15 experiments in term of reduced variables.

data obtained from the 17 tablet formulations. Figure 28 shows the printout of the multiple regression program.

Friability equation ($r^2 = 0.944860$)

$$Y_2 = -0.151517X_1 + 0.051686X_2 + 0.032246X_3 - 0.021579X_4 - 0.063388X_1X_2 - 0.072463X_1X_3 + 0.012087X_1X_4 + 0.040014X_1^2 - 0.020679X_2^2 + 0.011405X_3^2 + 0.025435X_4^2 + 0.189093 \quad (5.1)$$

or

$$Y_2 = -0.151517X_1 + 0.051686X_2 + 0.032246X_3 - 0.021579X_4 - 0.063388X_3X_4 - 0.072463X_2X_4 + 0.012087X_2X_3 + 0.040014X_1^2 - 0.020679X_2^2 + 0.011405X_3^2 + 0.025435X_4^2 + 0.189093 \quad (5.2)$$

The r^2 of the relationship was 0.944860 indicating the validity of the equation. One could notice that this value was obtained from the half fractional factorial-based central composite design of four variables. In order to differentiate the two-factor interaction alias, the experimental data were submitted to the full factorial-based central composite design of three variables. This could be done by omitting one variable at a time therefore the four equations represented the relationships between the tablet weight variation and the remaining three variables could be established by running the multiple regression program. The printouts of the multiple regression are presented in Figures 37-40 the r^2 of those relationships were also calculated as shown in Table 23. From these r^2 value one could recognize the significance of compression force (X_1) on the diclofenac sodium tablet friability since when X_1 was omitted the r^2 of the relationship became 0.374740 while when either X_2, X_3, or X_4 was obmitted the r^2 were 0.879773, 0.914577,

Multiple - Y : Friability Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.9229	.08296	36.122807

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.411912	.045768	6.650099
RESIDUAL	5	.034412	.006882	.025 < p < .05
TOTAL	14	.446323		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.196254	.067721	2.89798	
Pressure	-.151517	.02395	-6.326483	40.024392
EraTab	.051686	.02395	2.158107	4.657427
Ac-Di-Sol	.032246	.02395	1.346397	1.812784
X1X2	-.063388	.029331	-2.161134	4.670502
X1X3	-.072463	.029331	-2.470538	6.103556
X2X3	.012087	.029331	.412111	.169836

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.043688	.035924	1.216108	1.478919
X2X2	-.017005	.035924	-.473366	.224075
X3X3	.015079	.035924	.419751	.176191

3

Figure 37. The printout of multiple regression program for tablet friability (%) utilizing data of 3 independent variables (X_1 , X_2 , X_3) from 15 experiments in term of reduced variables.

Multiple - Y : Friability Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.37474	.213769	94.682847

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.136939	.015215	.332964
RESIDUAL	5	.228485	.045697	p > .25
TOTAL	14	.365424		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.186534	.174502	1.068953	
EraTab	.051686	.061713	.837521	.701442
Ac-Di-Sol	.032246	.061713	.522512	.273018
Mg. St.	-.021579	.061713	-.349664	.122265
X2X3	.012087	.075579	.159933	.025578
X2X4	-.072463	.075579	-.95877	.91924
X3X4	-.063388	.075579	-.838696	.703411

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X2X2	-.009715	.092569	-.104948	.011014
X3X3	.02237	.092569	.241654	.058397
X4X4	.036399	.092569	.393208	.154613

3

Figure 38. The printout of multiple regression program for tablet friability (%) utilizing data of 3 independent variables (X_2 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Friability Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.879773	.100899	41.701749

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.372488	.041388	4.065347
RESIDUAL	5	.050903	.010181	.05 < p < .10
TOTAL	14	.42339		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.226996	.082365	2.755988	
Pressure	-.151517	.029128	-5.201677	27.057439
Ac-Di-Sol	.032246	.029128	1.107016	1.225485
Mg. St.	-.021579	.029128	-.740814	.548806
X1X3	-.072463	.035673	-2.031292	4.126148
X1X4	.012087	.035673	.338841	.114813
X3X4	-.063388	.035673	-1.776899	3.15737

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.020629	.043693	.472131	.222908
X3X3	-.00798	.043693	-.182639	.033357
X4X4	.006049	.043693	.13845	.019168

3

Figure 39. The printout of multiple regression program for tablet friability (%) utilizing data of 3 independent variables (X_1 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Friability Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.914577	.087061	37.301342

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.405759	.045084	5.948057
RESIDUAL	5	.037898	.00758	.025 < p < .05
TOTAL	14	.443657		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.205607	.071069	2.89305	
Pressure	-.151517	.025134	-6.028426	36.341917
EraTab	.051686	.025134	2.056433	4.228917
Mg. St.	-.021579	.025134	-.858558	.737123
X1X2	-.063388	.030781	-2.059317	4.240789
X1X4	.012087	.030781	.392696	.15421
X2X4	-.072463	.030781	-2.354144	5.541993

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.036673	.037701	.972734	.946212
X2X2	-.024021	.037701	-.637145	.405953
X4X4	.022093	.037701	.586018	.343417

3

Figure 40. The printout of multiple regression program for tablet friability (%) utilizing data of 3 independent variables (X_1 , X_2 , X_4) from 15 experiments in term of reduced variables.

or 0.922900, respectively. Thus when one independent variable was obmitted the equation 5.3 having the best r^2 value of 0.922900 was chosen to describe the relationship between tablet friability and the studied independent variables. By examining the statistical t-values or the partial F-values of the main effects, the interactions, and the squared-term effects it was confirmed that tablet friability was mainly influenced by compression force, X_1, (α = 0.001) and was partially influenced by Era-Tab content, X_2, (α = 0.05) interaction between compression force and Era-Tab content, X_1X_2, (α = 0.05), and interaction between compression force and Ac-Di-Sol content, X_1X_3, (α = 0.05), respectively. Therefore the friability equation could be reduced to the first order relationship.

$$Y_2 = - 0.151517X_1 + 0.051686X_2 + 0.063388X_1X_2 - 0.072463X_1X_3 + 0.196254 \quad (5.3)$$

(α = 0.10)

From equation 5.3, increasing in compression force caused decreasing in tablet friability while increasing in Era-Tab content resulted in increasing in tablet friability. The positive effect of compression force on tablet friabiliy was well-known elsewhere. It was noticed that when the levels of the indepenent variables varied from -1.414 to 1.414, the obtained values of tablet friability were between 0.05 to 0.71% which were within acceptable range of tablet production. (Banker and Anderson, 1986). Hence, any change in the levels of the investigated independent variables didn't cause any deviation of tablet friability from the aceeptable limit.

3. Tablet Hardness

Equation 6.1 or 6.2, obtained from the multiple regression program as shown in Figure 29, expressed the relationship between tablet hardness (Y_3) and the independent variables.

Hardness equation ($r^2 = 0.969885$)

$$Y_3 = 1.231267X_1 + 0.254589X_2 + 0.090986X_3 - 0.024206X_4 + 0.900000X_1X_2 + 0.145000X_1X_3 - 0.150000X_1X_4 - 0.176879X_1^2 - 0.066846X_2^2 - 0.366937X_3^2 - 0.226894X_4^2 + 5.262922 \quad (6.1)$$

or

$$Y_3 = 1.231267X_1 + 0.254589X_2 + 0.090986X_3 - 0.024206X_4 + 0.900000X_3X_4 + 0.145000X_2X_4 - 0.150000X_2X_3 - 0.176879X_1^2 - 0.066846X_2^2 - 0.366937X_3^2 - 0.226894X_4^2 + 5.262922 \quad (6.2)$$

This relationship was valid since the r^2 value of the equation was 0.965885. In order to establish the accurate relationship between tablet hardness and the independent variables the equations obtained by omitting one independent variable as described in Table 23 were derived by multiple regression and the equation having the highest r^2 value of 0.973461 which was comparable to the r^2 value of eqution 6.1 or 6.2 was selected. The printouts of the program are demonstrated in Figures 41-44. From the calculated t-values or the partial F-values it was demonstrated that the tablet hardness of diclofenac sodium tablets was influenced mainly by compression force, X_1, ($\alpha = 0.0005$) and was partially influenced by squared-term effects of Ac-Di-Sol, X_3^2, ($\alpha = 0.025$), compression force, X_1^2, ($\alpha = 0.10$), and magnesium stearate, X_4^2, ($\alpha =$

Multiple - Y : Hardness Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.971002	.352568	7.576672

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	20.811813	2.312424	18.602964
RESIDUAL	5	.62152	.124304	.0001 < p < .005
TOTAL	14	21.433333		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	5.413211	.287805	18.808596	
Pressure	1.231267	.101783	12.097022	146.337943
EraTab	.254589	.101783	2.5013	6.256499
Ac-Di-Sol	.090986	.101783	.893923	.799097
X1X2	.09	.124652	.722013	.521302
X1X3	.145	.124652	1.163243	1.353134
X2X3	-.15	.124652	-1.203355	1.448062

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.289973	.152674	-1.899295	3.607322
X2X2	-.17994	.152674	-1.178588	1.38907
X3X3	-.48003	.152674	-3.144153	9.885696

3

Figure 41. The printout of multiple regression program for tablet hardness (kp) utilizing data of 3 independent variables (X_1 , X_2 , X_3) from 15 experiments in term of reduced variables.

Multiple - Y : Hardness Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.151079	1.6996	36.629305

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	2.570404	.2856	.09887
RESIDUAL	5	14.443196	2.888639	p > .25
TOTAL	14	17.0136		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	5.379868	1.387403	3.877653	
EraTab	.254589	.490657	.518874	.26923
Ac-Di-Sol	.090986	.490657	.185437	.034387
Mg. St.	-.024206	.490657	-.049333	.002434
X2X3	-.15	.600899	-.249626	.062313
X2X4	.145	.600899	.241305	.058228
X3X4	.09	.600899	.149776	.022433

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X2X2	-.15493	.735985	-.210507	.044313
X3X3	-.45502	.735985	-.618246	.382229
X4X4	-.314978	.735985	-.427968	.183156

3

Figure 42. The printout of multiple regression program for tablet hardness (kp) utilizing data of 3 independent variables (X_2 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Hardness Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.973461	.327513	7.103384

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	19.672368	2.185819	20.377745
RESIDUAL	5	.536325	.107265	.0001 < p < .005
TOTAL	14	20.208693		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	5.306513	.267353	19.848341	
Pressure	1.231267	.09455	13.022432	169.583734
Ac-Di-Sol	.090986	.09455	.962307	.926034
Mg. St.	-.024206	.09455	-.256011	.065542
X1X3	.145	.115793	1.25223	1.568079
X1X4	-.15	.115793	-1.29541	1.678087
X3X4	.09	.115793	.777246	.604111

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.209941	.141825	-1.480285	2.191244
X3X3	-.399998	.141825	-2.820373	7.954503
X4X4	-.259956	.141825	-1.83294	3.359668

3

Figure 43. The printout of multiple regression program for tablet hardness (kp) utilizing data of 3 independent variables (X_1 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Hardness Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.956758	.431577	9.200758

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	20.6054	2.289489	12.29199
RESIDUAL	5	.931293	.186259	.005 < p < .01
TOTAL	14	21.536693		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	5.506573	.352301	15.630297	
Pressure	1.231267	.124592	9.882412	97.662057
EraTab	.254589	.124592	2.043385	4.175422
Mg. St.	-.024206	.124592	-.194281	.037745
X1X2	.09	.152585	.589833	.347903
X1X4	-.15	.152585	-.983056	.966398
X2X4	.145	.152585	.950287	.903046

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.360001	.186888	-1.926297	3.710621
X2X2	-.249968	.186888	-1.337531	1.788988
X4X4	-.410016	.186888	-2.193918	4.813278

3

Figure 44. The printout of multiple regression program for tablet hardness (kp) utilizing data of 3 independent variables (X_1 , X_2 , X_4) from 15 experiments in term of reduced variables.

0.10), respectively. Therefore the hardness equation could be simplified into the following second-order multiple relationship.

$$Y_3 = 1.231267X_1 - 0.209941X_1^2 - 0.399998X_3^2 - 0.259956X_4^2 + 5.306513 \quad (6.3)$$

$$(\alpha = 0.10)$$

All 17 diclofenac sodium tablet formulations yielded the tablets having the hardness in the range of about 2 - 7 kp, however the tablet friabilities of all formulations were acceptable. Increasing in compression force caused increasing in tablet hardness while variations in the other variables imparted little change in tablet hardness.

4. Tablet Disintegration

The r^2 value of equation 7.1 or 7.2 indicated the validity of the relationship between tablet disintegration time and the independent variables. Figure 30 shows the printout of multiple regression program and was utilized to describe the relationship between the tablet disintegration time and the independent variables as expressed by the following eqution.

Disintegration time equation ($r^2 = 0.858785$)

$$Y_4 = 0.130273X_1 + 0.057887X_2 - 0.173504X_3 + 0.020230X_4 + 0.043750X_1X_2 + 0.073750X_1X_3 + 0.076250X_1X_4 + 0.129324X_1^2 + 0.136826X_2^2 + 0.049299X_3^2 + 0.086811X_4^2 + 1.123140 \quad (7.1)$$

or

$$Y_4 = 0.130273X_1 + 0.057887X_2 - 0.173504X_3 + 0.020230X_4 + 0.043750X_3X_4 + 0.073750X_2X_4 + 0.076250X_2X_3 + 0.129324X_1^2 + 0.136826X_2^2 + 0.049299X_3^2 + 0.086811X_4^2 + 1.123140 \quad (7.2)$$

However, the accurate relationship could be expressed precisely by choosing the appropriate equation of highest r^2 value from the equations obtaining by omitting one independent variable at a time. The printouts of the computer program utilized in defining these equations are illustrared in Figures 45-48. The selected equation demonstrated that the tablet disintegration time was mainly affected by compression force, X_1 , ($\alpha = 0.01$) and the amount of Ac-Di-Sol, X_3, ($\alpha = 0.01$), and was partially affected by the squared-term effect of compression force, X_1^2, ($\alpha = 0.05$) and the squared-term effect of magnesium stearate, X_4^2, ($\alpha = 0.10$). Therefore the following predicted disintegration time equation ($r^2 = 0.858690$) was obtained.

$$Y_4 = 0.130273X_1 - 0.173504X_3 + 0.186893X_1^2 + 0.144381X_4^2 + 1.060854 \quad (7.3)$$

($\alpha = 0.10$)

The disintegration times of diclofenac sodium controlled release tablets obtained from all formulations were within few minutes which were considered to be very fast. However, the obtained tablet disintegration times were based on the test utilizing distilled water as medium and hence no swelling action of chitosan, an swellable polymer, was observed since this swelling action was found to occur in acidic

Multiple - Y : Disint. time Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.827682	.196798	13.813588

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.930127	.103347	2.668457
RESIDUAL	5	.193646	.038729	.10 < p < .25
TOTAL	14	1.123773		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	1.094197	.160648	6.811142	
Pressure	.130273	.056813	2.292999	5.257843
Era.ab	.057887	.056813	1.018905	1.038168
Ac-Di-Sol	-.173504	.056813	-3.053928	9.326477
X1X2	.04375	.069578	.628787	.395373
X1X3	.07375	.069578	1.059955	1.123504
X2X3	.07625	.069578	1.095885	1.200964

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.161883	.08522	1.89959	3.608443
X2X2	.169386	.08522	1.987624	3.950649
X3X3	.081859	.08522	.960561	.922678

3

Figure 45. The printout of multiple regression program for tablet disintegration time (minutes) utilizing data of 3 independent variables (X_1 , X_2 , X_3) from 15 experiments in term of reduced variables.

Multiple - Y : Disint. time Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.641715	.288201	20.391613

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.743833	.082648	.99504
RESIDUAL	5	.4153	.08306	p > .25
TOTAL	14	1.159133		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	1.065856	.235262	4.530501	
EraTab	.057887	.083201	.695757	.484077
Ac-Di-Sol	-.173504	.083201	-2.085367	4.348754
Mg. St.	.02023	.083201	.243151	.059123
X2X3	.07625	.101895	.748322	.559986
X2X4	.07375	.101895	.723787	.523868
X3X4	.04375	.101895	.429365	.184355

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X2X2	.190644	.124801	1.527583	2.33351
X3X3	.103118	.124801	.826256	.682699
X4X4	.140629	.124801	1.126825	1.269734

3

Figure 46. The printout of multiple regression program for tablet disintegration time (minutes) utilizing data of 3 independent variables (X_2 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Disint. time Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var..
14	.85869	.17264	12.232373

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.905551	.100617	3.375902
RESIDUAL	5	.149022	.029804	.05 < p < .10
TOTAL	14	1.054573		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	1.060854	.140928	7.527648	
Pressure	.130273	.049839	2.613865	6.832293
Ac-Di-Sol	-.173504	.049839	-3.481274	12.119272
Mg. St.	.02023	.049839	.405912	.164765
X1X3	.07375	.061037	1.208278	1.459935
X1X4	.07625	.061037	1.249236	1.560591
X3X4	.04375	.061037	.716775	.513766

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.186893	.074759	2.499949	6.249745
X3X3	.106869	.074759	1.429519	2.043524
X4X4	.144381	.074759	1.931283	3.729854

3

Figure 47. The printout of multiple regression program for tablet disintegration time (minutes) utilizing data of 3 independent variables (X_1 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Disint. time Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.58209	.2763	19.25882

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.531665	.059074	.77381
RESIDUAL	5	.381708	.076342	p > .25
TOTAL	14	.913373		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	1.119205	.225547	4.962185	
Pressure	.130273	.079765	1.633213	2.667385
EraTab	.057887	.079765	.725726	.526679
Mg. St.	.02023	.079765	.253625	.064326
X1X2	.04375	.097687	.44786	.200579
X1X4	.07625	.097687	.780556	.609268
X2X4	.07375	.097687	.754964	.569971

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.143126	.119647	1.19623	1.430966
X2X2	.150628	.119647	1.258933	1.584913
X4X4	.100613	.119647	.840912	.707134

3

Figure 48. The printout of multiple regression program for tablet disintegration time (minutes) utilizing data of 3 independent variables (X_1 , X_2 , X_4) from 15 experiments in term of reduced variables.

environment (Standford, 1989). But in the real situation the diclofenac sodium controlled release tablets were ingested into the acidic environment of stomach. In that situation the swelling action of chitosan would occur imparting high viscosity environment to the tablets and hence resulting in retardation of tablet disintegration. This situation was beleived to be a mechanism in control the release of diclofenac sodium from the diclofenac sodium:(chitosan+EC) controlled release solid dispersion tablets. Therefore the disintegration time of diclofenac sodium solid dispersion tablets was not a factor to be considered in development of diclofenac sodium controlled release solid dispersion tablets.

5. Tablet Dissolution

The relationship between the K^0 (Y_5) or R^2 (Y_6) and the four independent variables were expressed by equation 8.1 or 8.2 and 9.1 or 9.2, respectively. The printouts of the employed multiple regression computer program are demonstrated in Figures 31 and 32.

K^0 equation ($r^2 = 0.913295$)

$$Y_5 = - 0.001909X_1 + 0.002236X_2 + 0.025850X_3 + 0.000871X_4 - 0.002865X_1X_2 + 0.003329X_1X_3 + 0.0098596X_1X_4 - 0.002442X_1^2 - 0.005793X_2^2 - 0.000916X_3^2 - 0.005126X_4^2 + 0.155905 \quad (8.1)$$

or

$$Y_5 = - 0.001909X_1 + 0.002236X_2 + 0.025850X_3 + 0.000871X_4 - 0.002865X_3X_4 + 0.003329X_2X_4 + 0.0098596X_2X_3 - 0.002442X_1^2 - 0.005793X_2^2 - 0.000916X_3^2 - 0.005126X_4^2 + 0.155905 \quad (8.2)$$

R^2 equation ($r^2 = 0.927520$)

$$Y_6 = - 0.011483X_1 + 0.004301X_2 - 0.020320X_3 - 0.009159X_4 - 0.004117X_1X_2 - 0.005766X_1X_3 - 0.008890X_1X_4 - 0.001370X_1^2 + 0.025345X_2^2 + 0.010035X_3^2 - 0.018570X_4^2 + 0.890664 \quad (9.1)$$

or

$$Y_6 = - 0.011483X_1 + 0.004301X^2 - 0.020320X_3 - 0.009159X_4 - 0.004117X_3X_4 - 0.005766X_2X_4 - 0.008890X_2X_3 - 0.001370X_1^2 + 0.025345X_2^2 + 0.010035X_3^2 - 0.018570X_4^2 + 0.890664 \quad (9.2)$$

The validiy of the K^0 and R^2 equations was confirmed by the calculated r^2 value of 0.913295 and 0.927520, respectively. The appropriate K^0 and R^2 equations were obtained from the equations in Table 23 which were derived by assuming that the effect of one independent variable was negligable. The printouts of the multiple regression program showing the relationships between K^0 or R^2 and the remaining three independent variables are presented in Figures 49-56. The selected predicted K^0 equation and the selected R^2 equation exhibited the r^2 values of 0.904438 and 0.915356, respectively. The K^0 and R^2 of diclofenac sodium controlled release tablets were found to depend mainly on the amount Ac-Di-Sol, X_3, being employed ($\alpha = 0.001$ and $\alpha = 0.0025$). The other effects on K^0 came from interaction between Era-Tab content and Ac-Di-Sol content, X_2X_3, ($\alpha = 0.10$). The R^2 was also partially influenced by compression force, X_1, ($\alpha = 0.025$), the interaction between Era-Tab and Ac-Di-Sol contents, X_2X_3, ($\alpha = 0.10$), the squared-term effects of Era-Tab, X_2^2, ($\alpha = 0.05$) and compression force, X_1^2, ($\alpha = 0.10$). Therefore the two second-order relationships could be written into the following equations.

Multiple - Y : Rate Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.897598	.014538	10.008485

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.009264	.001029	4.869688
RESIDUAL	5	.001057	.000211	.025 < p < .05
TOTAL	14	.01032		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.15343	.011868	12.928204	
Pressure	-.001909	.004197	-.454797	.20684
EraTab	.002236	.004197	.532693	.283761
Ac-Di-Sol	.02585	.004197	6.158955	37.932728
X1X2	-.002865	.00514	-.557333	.310621
X1X3	.003329	.00514	.647701	.419517
X2X3	.009856	.00514	1.917424	3.676514

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.002796	.006296	-.444145	.197265
X2X2	-.006146	.006296	-.976302	.953165
X3X3	-.00127	.006296	-.201761	.040707

3

Figure 49. The printout of multiple regression program for tablet zero-order dissolution rate constant (mg per minute) utilizing data of 3 independent variables (X_1 , X_2 , X_3) from 15 experiments in term of reduced variables.

Multiple - Y : Rate Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.904438	.013954	9.653497

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.009214	.001024	5.258023
RESIDUAL	5	.000974	.000195	.025 < p < .05
TOTAL	14	.010187		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.151641	.011391	13.312888	
Eratab	.002236	.004028	.555015	.308041
Ac-Di-Sol	.02585	.004028	6.417042	41.178427
Mg. St.	.000871	.004028	.21617	.046729
X2X3	.009856	.004933	1.997772	3.991093
X2X4	.003329	.004933	.674843	.455413
X3X4	-.002865	.004933	-.580688	.337199

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X2X2	-.004805	.006042	-.795131	.632233
X3X3	.000072	.006042	.011867	.000141
X4X4	-.004138	.006042	-.684794	.468943

3

Figure 50. The printout of multiple regression program for tablet zero-order dissolution rate constant (mg per minute) utilizing data of 3 independent variables (X_2 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Rate Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.890414	.015043	10.343103

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.009193	.001021	4.514015
RESIDUAL	5	.001131	.000226	.05 < p < .10
TOTAL	14	.010325		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.153875	.01228	12.530861	
Pressure	-.001909	.004343	-.439545	.1932
Ac-Di-Sol	.02585	.004343	5.952419	35.431293
Mg. St.	.000871	.004343	.200518	.040208
X1X3	.003329	.005318	.625981	.391852
X1X4	.009856	.005318	1.853124	3.43407
X3X4	-.002865	.005318	-.538644	.290137

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.00313	.006514	-.48043	.230813
X3X3	-.001604	.006514	-.246174	.060602
X4X4	-.005813	.006514	-.892394	.796366

3

Figure 51. The printout of multiple regression program for tablet zero-order dissolution rate constant (mg per minute) utilizing data of 3 independent variables (X_1 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : Rate Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.176894	.032922	22.840189

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.001165	.000129	.119395
RESIDUAL	5	.005419	.001084	p > .25
TOTAL	14	.006584		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.150624	.026874	5.604771	
Pressure	-.001909	.009504	-.200842	.040337
EraTab	.002236	.009504	.235241	.055338
Mg. St.	.000871	.009504	.091623	.008395
X1X2	-.002865	.01164	-.246123	.060576
X1X4	.009856	.01164	.846749	.716984
X2X4	.003329	.01164	.28603	.081813

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.000691	.014256	-.048484	.002351
X2X2	-.004041	.014256	-.283489	.080366
X4X4	-.003375	.014256	-.236723	.056038

3

Figure 52. The printout of multiple regression program for tablet zero-order dissolution rate constant (mg per minute) utilizing data of 3 independent variables (X_1 , X_2 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : R-square Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.915356	.014057	1.547842

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.010684	.001187	6.007853
RESIDUAL	5	.000988	.000198	.025 < p < .05
TOTAL	14	.011672		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.904841	.011475	78.855978	
Pressure	-.011483	.004058	-2.829727	8.007354
EraTab	.004301	.004058	1.059872	1.123329
Ac-Di-Sol	-.02032	.004058	-5.007405	25.074104
X1X2	-.004117	.00497	-.828332	.686134
X1X3	-.005766	.00497	-1.160138	1.34592
X2X3	-.00889	.00497	-1.788738	3.199583

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	-.01133	.006087	-1.861342	3.464594
X2X2	.015385	.006087	2.527521	6.388361
X3X3	.000075	.006087	.012351	.000153

3

Figure 53. The printout of multiple regression program for tablet R^2 value utilizing data of 3 independent variables (X_1 , X_2 , X_3) from 15 experiments in term of reduced variables.

Multiple - Y : R-square Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.842658	.02393	2.648445

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.015335	.001704	2.975324
RESIDUAL	5	.002863	.000573	.10 < p < .25
TOTAL	14	.018198		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.893374	.019535	45.733003	
EraTab	.004301	.006908	.622569	.387592
Ac-Di-Sol	-.02032	.006908	-2.94135	8.651538
Mg. St.	-.009159	.006908	-1.325719	1.757532
X2X3	-.00889	.008461	-1.050705	1.10398
X2X4	-.005766	.008461	-.681465	.464395
X3X4	-.004117	.008461	-.486562	.236743

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X2X2	.023986	.010363	2.314663	5.357665
X3X3	.008676	.010363	.837252	.700991
X4X4	-.019929	.010363	-1.923183	3.698632

3

Figure 54. The printout of multiple regression program for tablet R^2 value utilizing data of 3 independent variables (X_2 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : R-square Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.834168	.022399	2.498711

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.012619	.001402	2.79456
RESIDUAL	5	.002509	.000502	.10 < p < .25
TOTAL	14	.015128		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.875564	.018285	47.884594	
Pressure	-.011483	.006466	-1.775783	3.153407
Ac-Di-Sol	-.02032	.006466	-3.142376	9.874529
Mg. St.	-.009159	.006466	-1.416326	2.005978
X1X3	-.005766	.007919	-.72804	.530042
X1X4	-.00889	.007919	-1.122515	1.26004
X3X4	-.004117	.007919	-.519816	.270209

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.01063	.0097	1.095891	1.200976
X3X3	.022035	.0097	2.271719	5.160707
X4X4	-.00657	.0097	-.677378	.458841

3

Figure 55. The printout of multiple regression program for tablet R^2 value utilizing data of 3 independent variables (X_1 , X_3 , X_4) from 15 experiments in term of reduced variables.

Multiple - Y : R-square Nine X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
14	.75211	.028169	3.128048

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	9	.012037	.001337	1.685582
RESIDUAL	5	.003967	.000793	p > .25
TOTAL	14	.016005		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.885771	.022994	38.521134	
Pressure	-.011483	.008132	-1.412082	1.993975
EraTab	.004301	.008132	.528894	.279729
Mg. St.	-.009159	.008132	-1.126245	1.268429
X1X2	-.004117	.009959	-.413352	.17086
X1X4	-.00889	.009959	-.892611	.796754
X2X4	-.005766	.009959	-.578929	.335158

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X1	.002974	.012198	.24382	.059448
X2X2	.029689	.012198	2.433937	5.92405
X4X4	-.014226	.012198	-1.166262	1.360168

3

Figure 56. The printout of multiple regression program for tablet R^2 value utilizing data of 3 independent variables (X_1 , X_2 , X_4) from 15 experiments in term of reduced variables.

$$Y_5 = 0.025850X_3 + 0.009856X_2X_3 + 0.151641 \quad (8.3)$$

$$Y_6 = -0.011483X_1 - 0.020320X_3 - 0.008890X_2X_3 - 0.011330X_1^2 + 0.015385X_2^2 + 0.904841 \quad (9.3)$$

$$(\alpha = 0.10)$$

From the above equations one could conclude that only the content of the disintegrant, Ac-Di-Sol, exhibited significant effect on the K^0 of the drug. Increasing in Ac-Di-Sol level in the rage of -1.414 to 1.414 caused faster drug release. Swelling action of Ac-Di-Sol was thought to cause widening in the pores of the matrix and hence resulting in faster diffusion of drug molecule from the more loosen matrix.

Searching for the Optimum Conditions

Since the weight variation and friability of the diclofenac sodium tablets prepared from the 17 formulations were within acceptable ranges. While the tablet disintegration time of each tablet formulation was found to be very fast. Although the hardness of diclofenac sodium controlled release tablets was affected mainly by compression force however their friabilities were acceptable for all tablet formulations. Therefore, the main consideration in developing the optimum diclofenac sodium controlled release tablet was aimed at their dissolutions regardless of the other responses.

In order to achieve the optimum dissolution profile for the diclofenac sodium controlled release tablets, the K^0 in the range of 0.137 to 0.141 mg per minute and R^2 of not less than 0.910 were considered as the required responses. By examining the equation which described the

relationship between the tablet K^0 and the independent variables, it was noticable that the main effect of Ac-Di-Sol (X_3) and the interactions between Era-Tab and Ac-Di-Sol (X_2X_3) played important roles in determining the K^0 of diclofenac sodium controlled release tablets. While the relationship between R^2 and the independent variables implied that the important factors having influences on R^2 value came from the main effect of Ac-Di-Sol (X_3), compression force (X_1), and the squared-term effect of Era-tab (X_2^2). Since the influences of magnesium stearate level (X_4), on K^0 and R^2 were negligible therefore any magnesium stearate level in the range of -1.414 to 1.414 could be chosen. Furthermore, the level of compression force (X_1) was selected at middle level of 0 in order to produce the tablets of adequate hardness and low friability. In this manner X_1 and X_4 were set at the predetermined level of 0.

By setting X_1 and X_4 at 0 level, the response surface plots and the contour plots of the equations representing the relationships between K^0 or R^2 and the remaining two independent variables, the level of Era-Tab (X_2), and the level of Ac-Di-Sol (X_3), were drawn and presented in the Figures 57-60. The response surface plot of K^0 equation showed that when fixing X_1 and X_4 at 0 level, then variation in the levels of Era-Tab and Ac-Di-Sol contents freely from -1.414 to 1.414 would result in the K^0 of diclofenac sodium controlled release tablets in the range of 0.100 to 0.210 mg per minute. Similary, the response surface plot of R^2 demonstrated that when fixing X_1 and X_4 at 0 level, then variation in the levels of Era-Tab and Ac-Di-Sol contents from -1.414 to 1.414 would result in R^2 value in the range of 0.880 to 0.990.

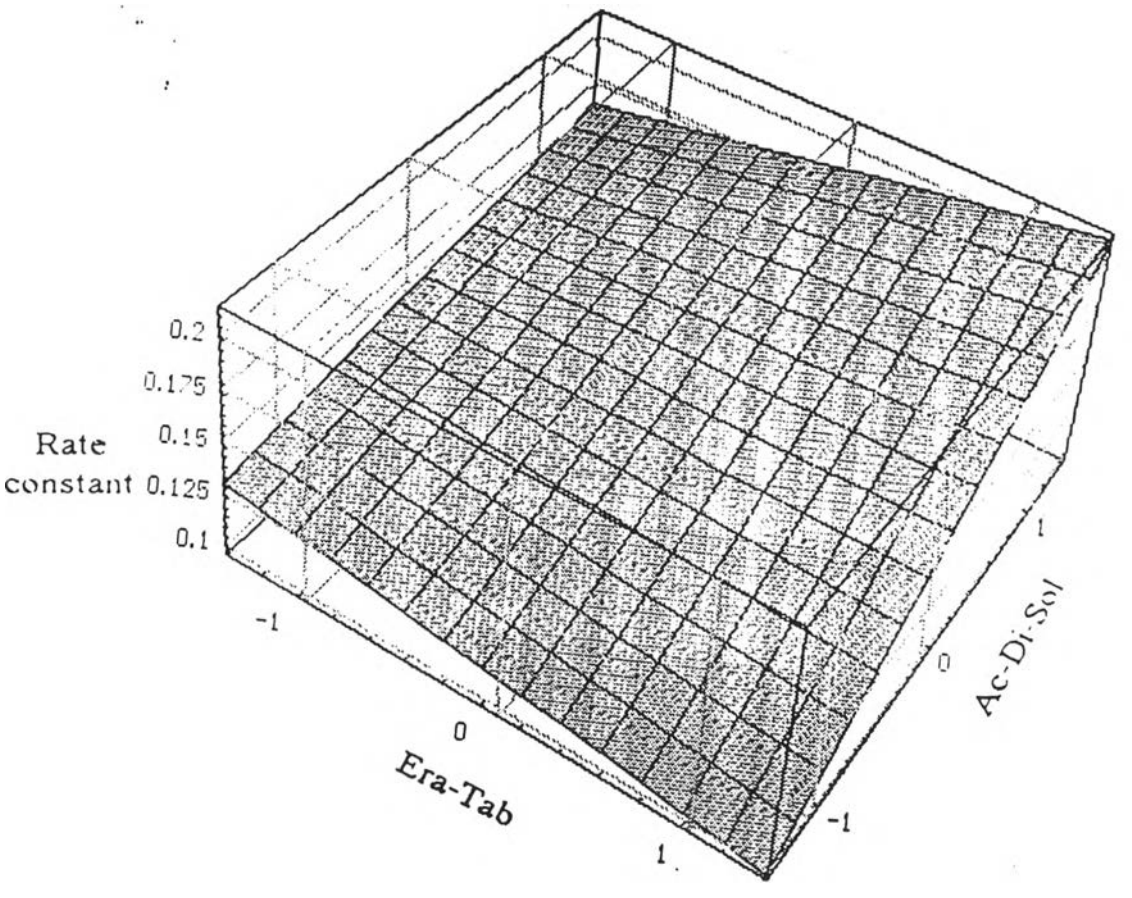


Figure 57. The response surface plot for zero-order dissolution rate constant (mg/minute) as a function of Era-Tab and Ac-Di-Sol contents when $X_1 = 0$ and $X_4 = 0$.

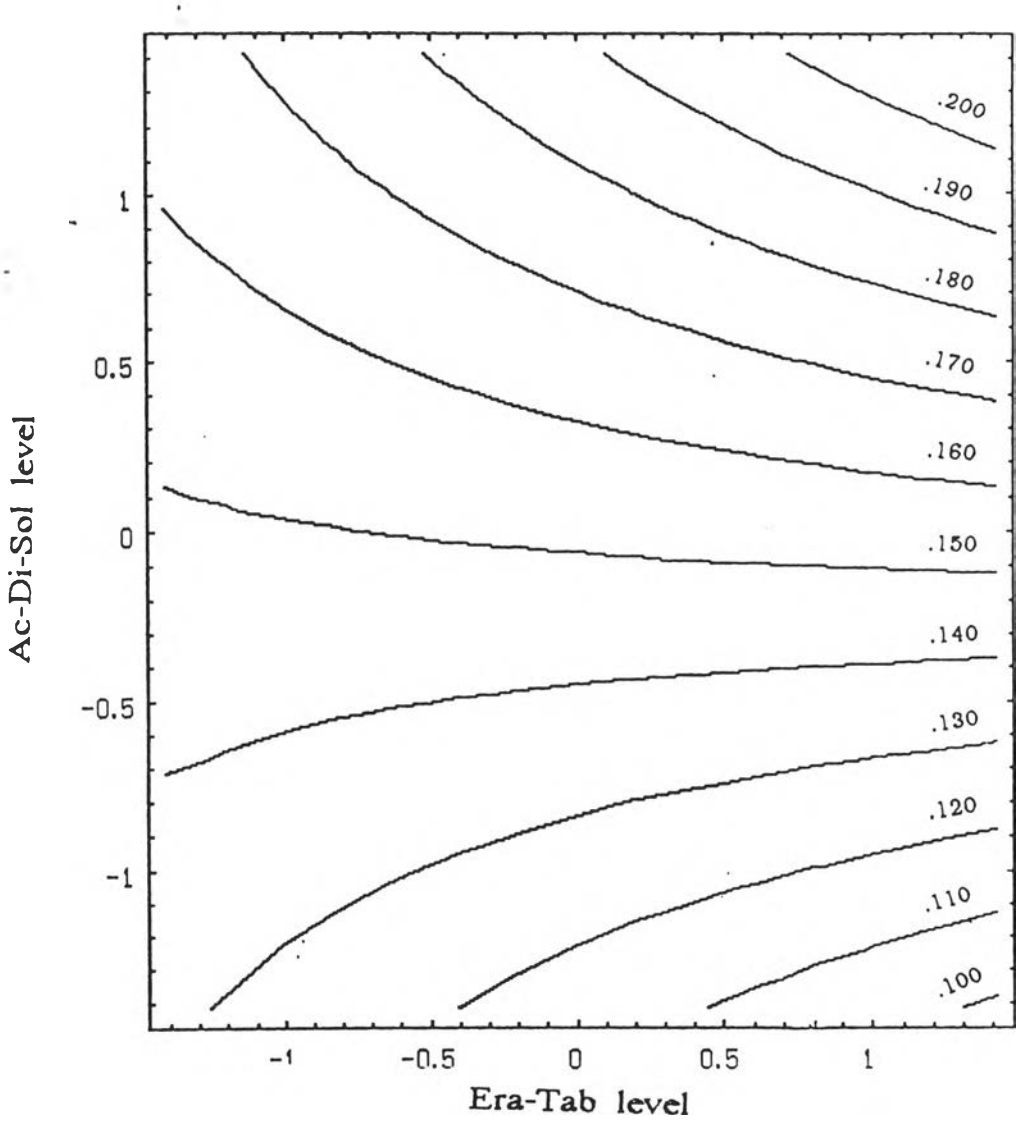


Figure 58. The contour plot for zero-order dissolution rate constant (mg/minute) as a function of Era-Tab and Ac-Di-Sol contents when $X_1 = 0$ and $X_4 = 0$.

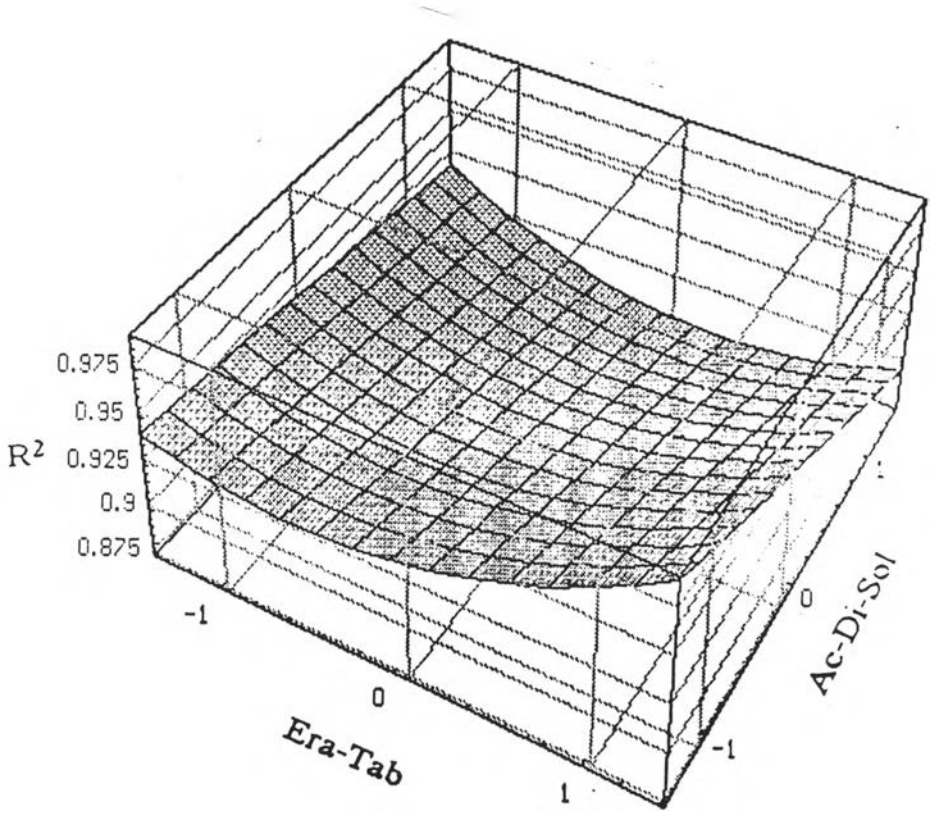


Figure 59. The response surface plot for R^2 value as a function of Era-Tab and Ac-Di-Sol contents when $X_1 = 0$ and $X_4 = 0$.

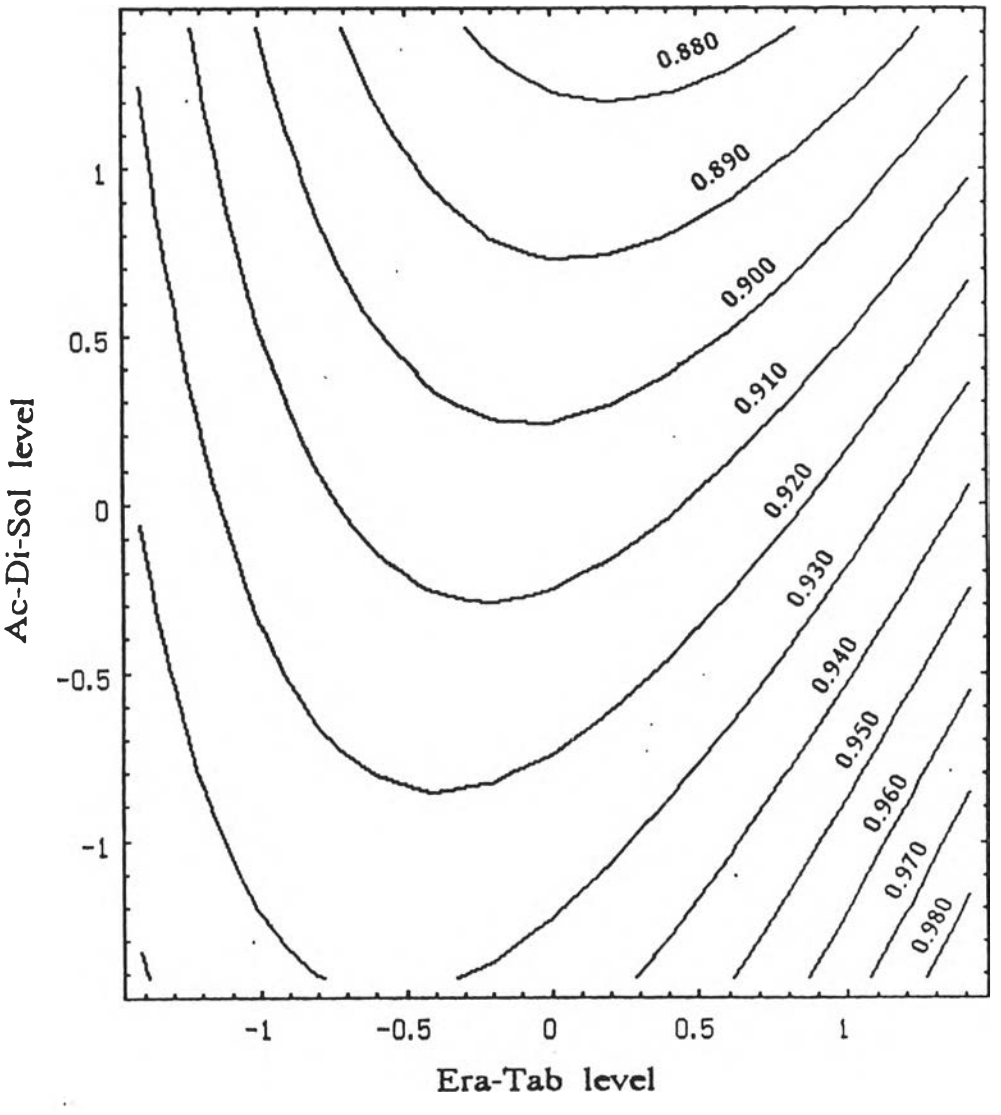


Figure 60. The contour plot for R^2 value as a function of Era-Tab and Ac-Di-Sol contents when $X_1 = 0$ and $X_4 = 0$.

In order to search for the optimum levels of Era-Tab and Ac-Di-Sol contents which would yield the most possible required K^0 with the acceptable R^2 value, the two contour plots of K^0 and R^2 were superimposed as shown in Figure 61. From this superimposed contour plot a restricted area which would give the K^0 beween 0.137 to 0.141 mg per minute and the R^2 value of not less than 0.910 was identified. Within this area the optimum levels of Era-Tab and Ac-Di-Sol contents which would yield the most possible required K^0 between 0.137 to 0.141 mg per minute with the acceptable R^2 value of not less than 0.910 could be chosen. Figure 62 demonstrates the superimposed contour plot of the same two responses but in this case the more specific in the required K^0 of 0.139 mg per minute was defined rather than the range of acceptable K^0. From the superimposed contour plots the optimum tablet formulation consisting of X_1, X_2, X_3, and X_4 at the levels of 0, 0, -0.5, and 0 was selected for development of diclofenac sodium controlled release tablet. These optimum conditions were corresponded with the compression force of 700 psi, the Era-Tab content of 194.8 mg per tablet, the Ac-Di-Sol content of 6.4 mg per tablet, and the magnesium stearate content of 1.6 mg per tablet, respectively. The optimized tablet formulation is shown in Table 25.

Validation of the Optimized Diclofenac Sodium Controlled Release Tablet

The dissolution profile of the optimized diclofenac sodium controlled release tablet is illustrated in Figure 63. The K^0 and R^2 were computed and compared with the predicted K^0 and R^2 calculated from the predicted response equations. Those informations are shown in Table 26. The optimized tablet formulation gave the tablets having K^0 of 0.125056

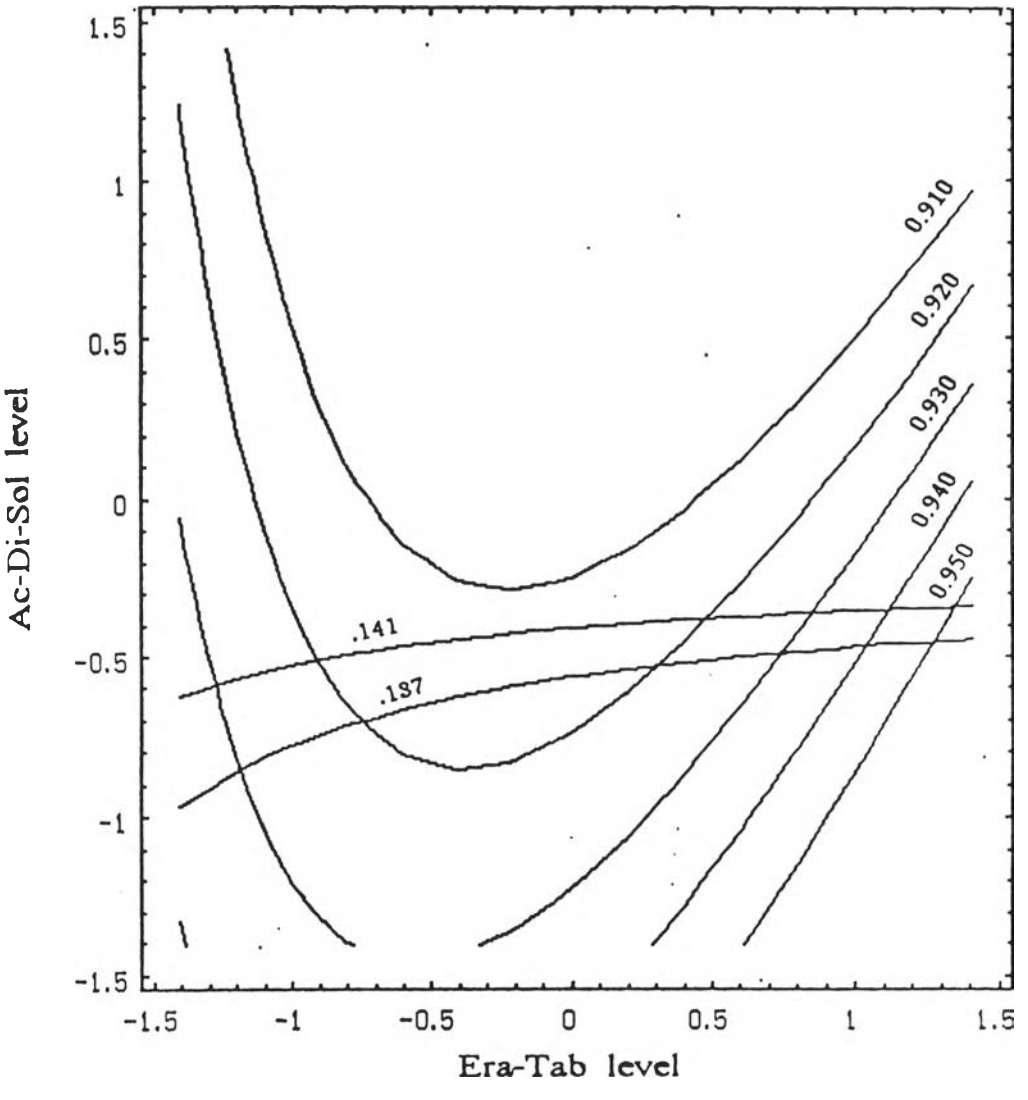


Figure 61. The superimposed contour plot for zero-order dissolution rate constant (0.137-0.141 mg/minute) and R^2 value (0.910-0.950) when $X_1 = 0$ and $X_4 = 0$.

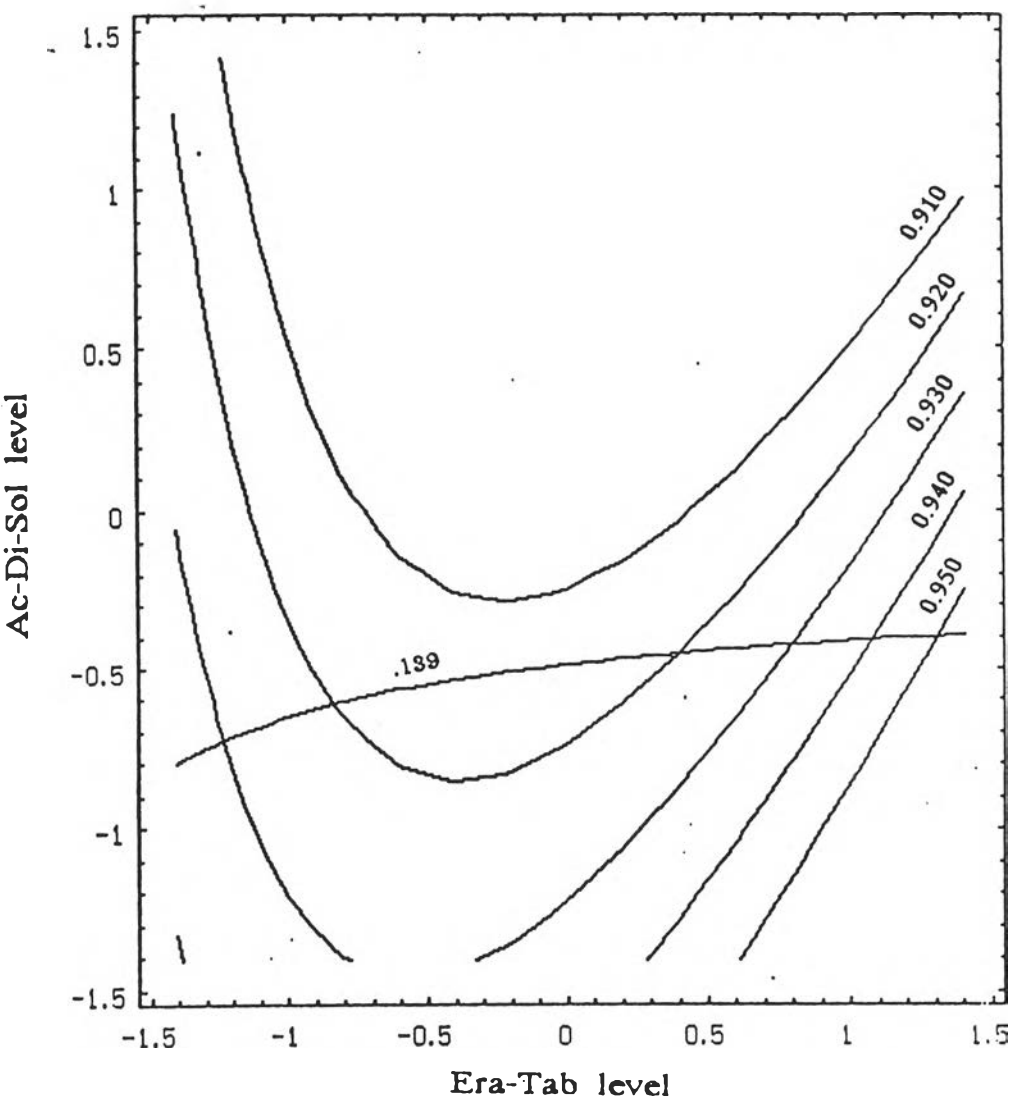


Figure 62. The superimposed contour plot for zero-order dissolution rate constant (0.139 mg/minute) and R^2 value (0.910-0.950) when $X_1 = 0$ and $X_4 = 0$.

Table 25. Formulation of Optimized Diclofenac Sodium Controlled Release Solid Dispersion Tablet.

Ingredient	Amount Per Tablet (mg)	Level of Reduced Variable
Diclofenac Sodium Solid Dispersion	125.2	-
Era-Tab	194.8	0
Ac-Di-S0l	6.4	-0.5
Magnesium Stearate	1.6	0
Aerosil	0.32	-
Compression Force	700 psi	0

Table 26. The Observed and Predicted Responses of the Optimized Diclofenac Sodium Controlled Release Solid Dispersion Tablet.

Responses	Observed	Predicted
Weight variation (%)	1.51	2.61
Friability (%)	0.29	0.18
Hardness (kp)	4.14	5.16
Disintegration Time (minute)	1.83	1.08
K^0 (mg / minute)	0.125056	0.138735
R^2	0.928935	0.915020

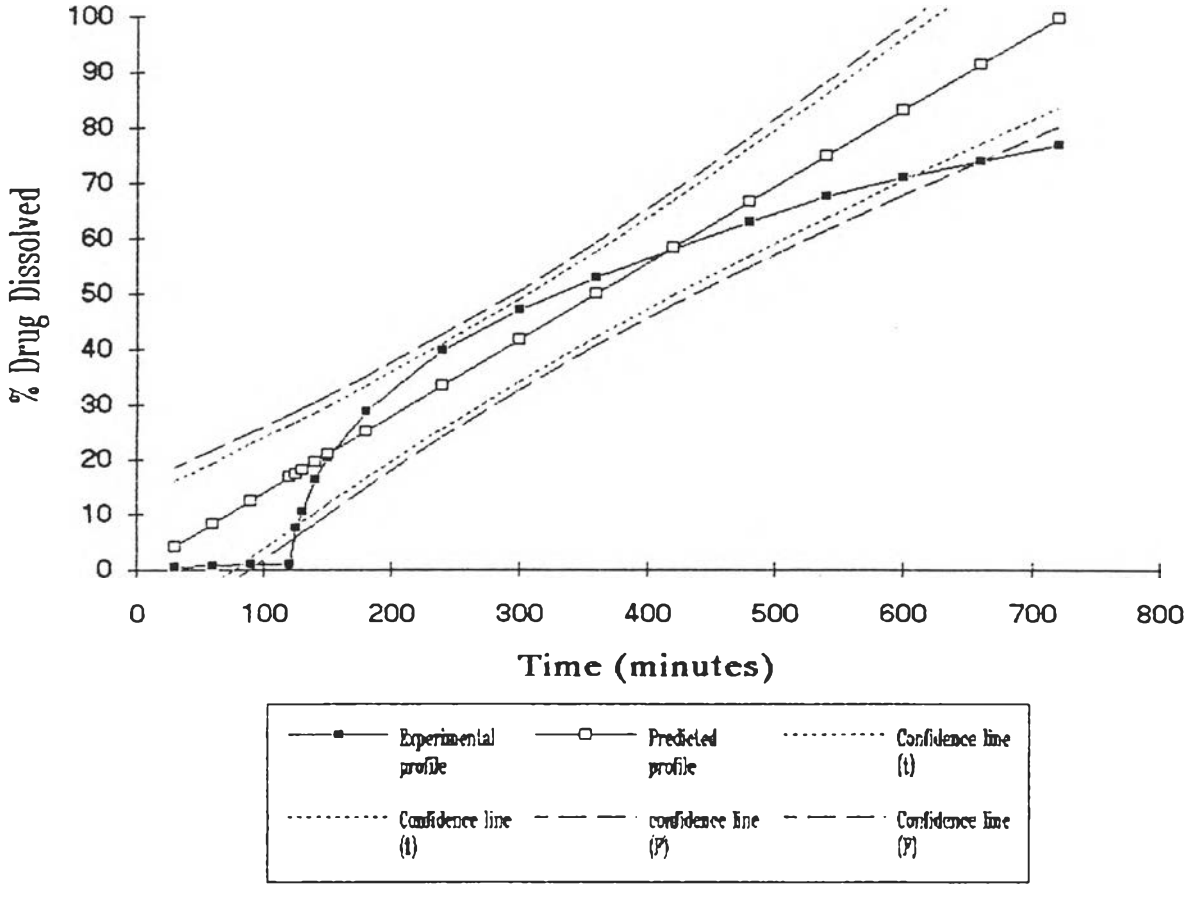


Figure 63. Dissolution profile of the optimized diclofenac sodium controlled release tablet ($X_1 = 0$, $X_2 = 0$, $X_3 = -0.5$, $X_4 = 0$) as compared to the predicted dissolution profile with 99% confidence level.

mg per minute and R^2 of 0.928935, while the predicted K^0 and R^2 were 0.138735 mg per minute and 0.915020, respectively. From the predicted K^0, the predicted dissolution profile having R^2 of 1.0000 could be drawn as shown in Figure 63. The 99% confidence lines of the predicted dissolution profile were constructed according to t-value ($t_{0.1/2,16} = 2.921$) and F-value ($F_{0.1,2,16} = 6.23$). The experimental dissolution profile of the optimized diclofenac sodium tablet lied almost completely within the 99% confidence band indicating the validity of the predicted K^0 equation.

To validate the accuracy of prediction, the obtained K^0 and R^2 from the optimized formulation (formulation XVIII) were combined with those from formulation I-XVII and the second-order multiple regression was performed. The printouts of the multiple regression program are presented in Figures 64-66. The result indicated that for both responses, K^0 and R^2, the data from all 18 formualtions showed the nonlinear relationship between each response and the four independent variables as confirmed by the values of correlation coefficient (r^2) of the model which were 0.895202 and 0.905325 as listed in Table 27.

However, the observed K^0 of 0.125056 mg per minute which was obtained from the optimized diclofenac sodium controlled release tablet was still some different from the predicted K^0 of 0.138735 mg per minute calculated from the predicted response equation. While the different between the observed R^2 and the predicted R^2 of the optimized diclofenac sodium controlled release tablet was relatively small as shown in Table 26. This result comformed with the r^2 values of the second order relationships obtained from the central composite design of 17 experiments. Since the r^2 of 0.904438 indicated that the relationship

	Pressure	Eratab	Ac-Di-Sol	Mg. St.	X1X2=X3X4	X1X3=X2X4	X1X4=X2X3	X1X1	X2X2
	X	X	X	X	X	X	X	X	X
1	-1.000	-1.000	-1.000	-1.000	1.000	1.000	1.000	1.000	1.000
2	1.000	-1.000	-1.000	1.000	-1.000	-1.000	1.000	1.000	1.000
3	-1.000	1.000	-1.000	1.000	-1.000	1.000	-1.000	1.000	1.000
4	1.000	1.000	-1.000	-1.000	1.000	-1.000	-1.000	1.000	1.000
5	-1.000	-1.000	1.000	1.000	1.000	-1.000	-1.000	1.000	1.000
6	1.000	-1.000	1.000	-1.000	-1.000	1.000	-1.000	1.000	1.000
7	-1.000	1.000	1.000	-1.000	-1.000	-1.000	1.000	1.000	1.000
8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
9	1.414	0	0	0	0	0	0	1.999	0
10	-1.414	0	0	0	0	0	0	1.999	0
11	0	1.414	0	0	0	0	0	0	1.999
12	0	-1.414	0	0	0	0	0	0	1.999
13	0	0	1.414	0	0	0	0	0	0
14	0	0	-1.414	0	0	0	0	0	0
15	0	0	0	1.414	0	0	0	0	0
16	0	0	0	-1.414	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0
18	0	0	-.500	0	0	0	0	0	0

	X3X3	X4X4	Rate	R-square
	X	X	Y	Y
1	1.000	1.000	.119907	.922725
2	1.000	1.000	.119997	.903966
3	1.000	1.000	.122161	.945490
4	1.000	1.000	.099279	.925693
5	1.000	1.000	.147456	.908940
6	1.000	1.000	.149350	.882547
7	1.000	1.000	.177620	.911575
8	1.000	1.000	.179568	.853287
9	0	0	.154044	.881433
10	0	0	.156840	.891720
11	0	0	.143407	.951921
12	0	0	.154080	.928060
13	1.999	0	.200047	.873209
14	1.999	0	.116939	.945551
15	0	1.999	.145629	.824239
16	0	1.999	.154524	.880134
17	0	0	.138216	.896059
18	.250	0	.125056	.928935

Figure 64. The printout of multiple regression program utilizing data from experiment I - XVIII in term of reduced variables. (Compression pressure = X_1, Era-Tab content = X_2, Ac-Di-Sol content = X_3, magnesium stearate content = X_4)

Multiple - Y : Rate Eleven X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
17	.895202	.01374	9.497135

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	.009676	.00088	4.65934
RESIDUAL	6	.001133	.000189	.025 < p < .05
TOTAL	17	.010808		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.151264	.007414	20.401825	
Pressure	-.001909	.003967	-.48123	.231582
EraTab	.002236	.003967	.563653	.317705
Ac-Di-Sol	.026393	.003936	6.705724	44.966738
Mg. St.	.000871	.003967	.219535	.048195
X1X2=X3X4	-.002865	.004858	-.589726	.347777
X1X3=X2X4	.003329	.004858	.685347	.4697

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4=X2X3	.009856	.004858	2.028867	4.116301
X1X1	-.000969	.004863	-.199211	.039685
X2X2	-.004319	.004863	-.888188	.788879
X3X3	.000149	.004949	.030155	.000909
X4X4	-.003652	.004863	-.751082	.564124

3

Figure 65. The printout of multiple regression program for tablet zero-order dissolution rate constant (mg/minute) utilizing data from experiments I-XVIII in term of reduced variables.

Multiple - Y : R-square Eleven X variables

DF:	R-squared:	Std. Err.:	Coef. Var.:
17	.905325	.017527	1.940752

Analysis of Variance Table

Source	DF:	Sum Squares:	Mean Square:	F-test:
REGRESSION	11	.017624	.001602	5.215865
RESIDUAL	6	.001843	.000307	.025 < p < .05
TOTAL	17	.019467		

1

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
INTERCEPT	.897378	.009458	94.883759	
Pressure	-.011483	.00506	-2.269494	5.150601
EraTab	.004301	.00506	.850037	.722563
Ac-Di-Sol	-.021107	.005021	-4.203946	17.673165
Mg. St.	-.009159	.00506	-1.810098	3.276454
X1X2=X3X4	-.004117	.006197	-.664338	.441345
X1X3=X2X4	-.005766	.006197	-.930452	.865741

2

Beta Coefficient Table

Parameter:	Value:	Std. Err.:	T-Value:	Partial F:
X1X4=X2X3	-.00889	.006197	-1.434601	2.05808
X1X1	-.003502	.006203	-.564643	.318822
X2X2	.023213	.006203	3.742269	14.00458
X3X3	.008493	.006313	1.345351	1.80997
X4X4	-.020703	.006203	-3.3376	11.139573

3

Figure 66. The printout of multiple regression program for tablet R^2 value utilizing data from experiments I-XVIII in term of reduced variables.

Table 27. Comparison of the Values of r^2 Calculated from Experiments I-XVII and XVIII.

Responses	Experiments	
	I-XVII	I-XVIII
Weight Variation (%)	0.643948	0.591179
Friability (%)	0.944860	0.940259
Hardness (%)	0.969885	0.937461
Disintegration Time (minute)	0.858785	0.656516
K^0 (mg/minute)	0.913295	0.895202
R^2	0.927520	0.905325

between K^0 and the four variables although seemed to follow the established relationship but some deviation was still existed ($\alpha = 0.05$).

In order to improve this optimized K^0, the influence of the amount of Ac-Di-Sol (X_3), on K^0 while fixing the levels of X_1, X_2, and X_4 at 0 level was investigated as shown in Table 28 and Figure 67. In the range of X_3 from -1.414 to 1.414, a polynomial equation ($r^2 = 0.999872$) was found to be more suitable to the relationship between K^0 and the amount of Ac-Di-Sol than the linear equation ($r^2 = 0.911532$). The polynomial equation and its r^2 are listed in Table 29. This table also showed the linear relationship between R^2 and the amount of Ac-Di-Sol ($r^2 = 0.934241$) when the levels of X_1, X_2, and X_4 were fixed at 0.

The polynomial equation of K^0 and the linear equation of R^2 were

$$Y_5 = 0.029456X_3 + 0.010363X_3^2 + 0.137739 \qquad (10.1)$$

$$(r^2 = 0.999872)$$

and

$$Y_6 = -0.026586X_3 + 0.907615 \qquad (11.2)$$

$$(r^2 = 0.934241).$$

From the polynomial equation it was evident that when X_3 was at 0 level, then K^0 would be 0.137739 mg per minute which was very close to the required K^0 of 0.139 mg per minute. While the linear equation of the response R^2 indicated that when X_3 was at 0 level the R^2 value would be 0.907615 which was within aceeptable limit. Therefore if X_1, X_2, X_3, and X_4 were fixed at 0 level the improved optimum diclofenac sodium controlled release tablet would be achieved. Formulation XVII consisted

Table 28. The K^0 and R^2 of Diclofenac Sodium Controlled Release Tablets as Function of Ac-Di-Sol Content (X_3), When fixing $X_1 = 0$, $X_2 = 0$, and $X_4 = 0$.

K^0	R^2	Ac-Di-Sol (X_3)	Experiment
0.116939	0.945551	-1.414	XIV
0.125056	0.928935	-0.5	XVIII
0.138216	0.896095	0	XVII
0.200047	0.873209	1.414	XIII

Table 29. The Equations Representing the Relationships between K^0 (Y_5) and X_3 When $X_1 = X_2 = X_4 = 0$.

Polynomial Equation (r^2 = 0.999872)	
$Y_5 = 0.029456X_3 + 0.010363X_3^2 + 0.137739$	(10.1)
Linear Equation (r^2 = 0.911532)	
$Y_5 = 0.030461X_3 + 0.148872$	(10.2)

The Equations Representing the Relationships between R^2 (Y_6) and X_3 When $X_1 = X_2 = X_4 = 0$.

Polynomial Equation (r^2 = 0.941640)	
$Y_6 = -0.026840X_3 + 0.002586X_3^2 + 0.904838$	(11.1)
Linear Equation (r^2 = 0.934241)	
$Y_6 = -0.026586X_3 + 0.907615$	(11.2)

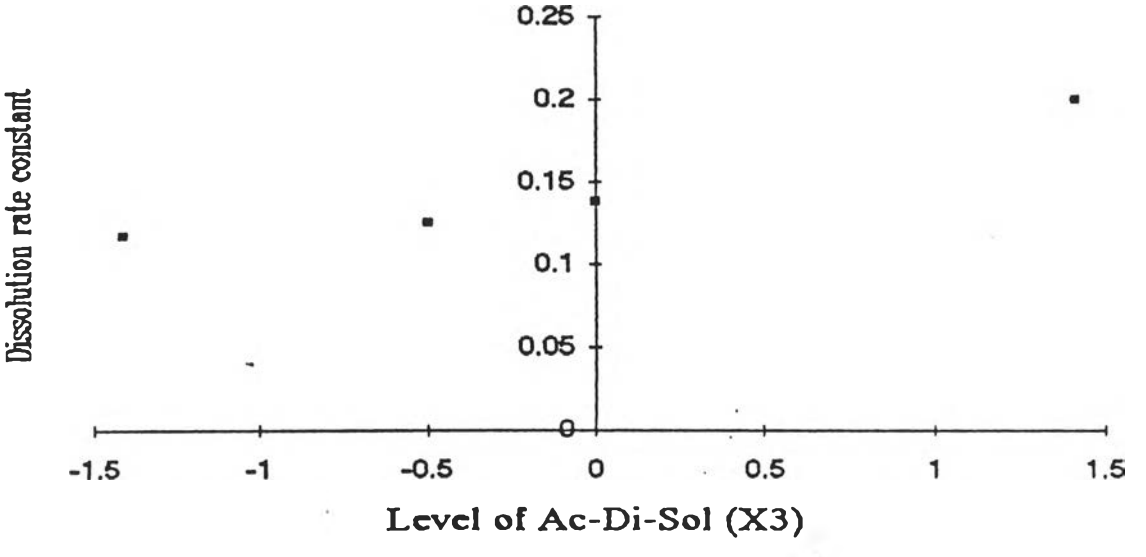


Figure 67. The relationship between zero-order dissolution rate constant and the level of Ac-Di-Sol (-1.414 to 1.414) when $X_1 = X_2 = X_4 = 0$.

of X_1, X_2, X_3, and X_4 at 0 level, hence this formulation was chosen as the improved optimum diclofenac sodium controlled release tablet formulation. The selected formulation thus consisted of compression force of 700 psi, Era-Tab content of 194.8 mg per tablet, Ac-Di-Sol content of 8 mg per tablet, and magnesium stearate content of 1.6 mg per tablet. Figure 68 illustrates the dissolution profile of this improved diclofenac sodium controlled release tablet and the predicted dissolution profile according to the predicted K^0. The 99% confidence bands of the predicted dissolution profile were constructed according to t-value ($t_{0.1/2,16} = 2.921$) and F-value ($F_{0.1,2,16} = 6.23$). The experimental dissolution profile of the improved optimum diclofenac sodium controlled release tablet lied almost completely within the 99% confidence bands. The K^0 and R^2 of this profile were found to be 0.138213 mg per minute and 0.896059 which were comparable to the predicted K^0 and R^2 of 0.137739 mg per minute and 0.907615, respectively. The tablet weight variation, friability, hardness, and disintegration time of the improved optimum diclofenac sodium tablet were 2.50%, 0.26%, 5.26 kp, and 1.21 minute, respectively. Table 30 demonstrates the information of the improved optimum diclofenac sodium controlled release tablet formulation. The various tablet characteristics of the diclofenac sodium controlled release tablet manufactured from this formulation is shown in Table 31.

Comparison between Optimized Powder and Tablet

In this study the optimized diclofenac sodium controlled release solid dispersion powder was formulated into tablets. This investigation demonstrated that the optimized diclofenac sodium controlled release

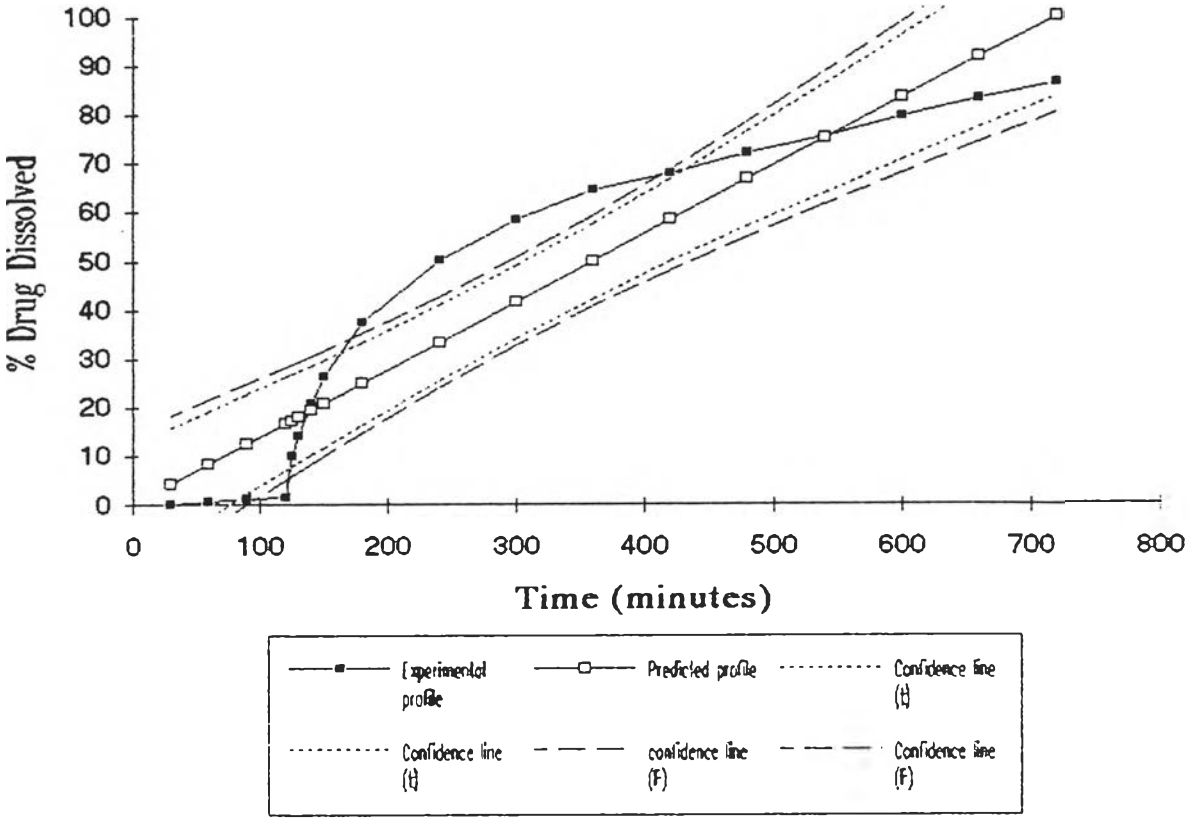


Figure 68. Dissolution profile of the improved optimum diclofenac sodium controlled release tablets ($X_1 = 0$, $X_2 = 0$, $X_3 = 0$, $X_4 = 0$) as compared to the predicted dissolution profile with 99% confidence level.

Table 30. Formulation of Improved Optimum Diclofenac Sodium Controlled Release Tablet.

Ingredient	Amount Per Tablet (mg)
Diclofenac Sodium Solid Dispersion	125.2
Era-Tab	194.8
Ac-Di-Sol	8.0 (2.5%)
Magnesium Stearate	1.6 (0.5%)
Aerosil	3.2 (1%)
Compression Force	700 psi

Table 31. Various Properties of the Improved Optimized Diclofenac Sodium Controlled Release Tablet.

Responses	Experimental	Predicted
Weight Variation (%)	2.50	2.80[a]
Friability (%)	0.26	0.20[b]
Hardness (kp)	5.26	5.3[c]
Disintegration Time (minute)	1.21	1.06[d]
K^0 (mg / minute)	0.138216	0.137739[e]
R^2	0.896059	0.907615[f]

[a]computed from equation 4.3

[b]computed from equation 5.3

[c]computed from equation 6.3

[d]computed from equation 7.3

[e]computed from equation 10.1

[f]computed from equation 11.2

solid dispersion having experimental K^0 of 0.147128 mg per minute and R^2 of 0.910577 could be developed into diclofenac sodium controlled release tablets having experimental K^0 between 0.099279 to 0.200047 mg per minute and R^2 between 0.824239 to 0.951921. Higher K^0 obtained from some tablet formulations when compared to the optimized solid dispersion powder might due to wetting effect. The diclofenac sodium controlled release solid dispersion powder was poorly wetted when dissolution study was performed since it floated over the dissolution medium in the initial period of the test. In contrast the diclofenac sodium controlled release tablets sank in the dissolution midium and hence more wetting of the drug was achieved resulting in faster dissolution in some tablet formulations.

Table 32 compares the K^0 and R^2 obtained from the prepared optimized diclofenac sodium controlled release solid dispersion powder and tablets in term of both experimental and predicted values. One could acknowledge that the values of the experimental and predicted K^0 and R^2 of the improved optimum diclofenac sodium controlled release tablet were very close to those of the optimized diclofenac sodium controlled release solid dispersion powder. Therefore the applied optimization strategy was proven to be useful in development of the diclofenac sodium controlled release tablet from the diclofenac sodium controlled release solid dispersion powder yielding almost the same optimum dissolution profile for controlled release. Dissolution profiles of the optimum diclofenac sodium controlled release solid dispersion powder and tablet were compared as shown in Figure 69.

Table 32. Comparison Between the Experimental and Predicted K^0 and R^2 between Optimized Diclofenac Sodium Solid Dispersion Powder and Improved Optimum Diclofenac Sodium Solid Dispersion Tablet.

	Experimental		Predicteded	
	K^0 (mg/minute)	R^2	K^0 (mg/minute)	R^2
Optimized Powder	0.147128	0.928030	0.136248	0.901275
Optimum Tablet	0.138216	0.896059	0.137739	0.907615

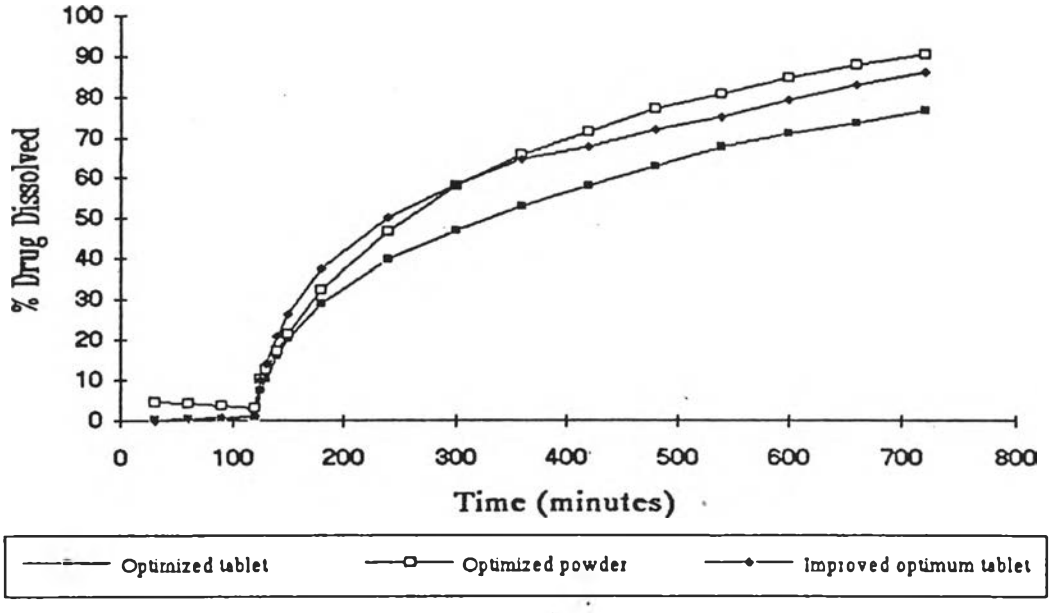


Figure 69. Dissolution profiles of the optimum diclofenac sodium controlled release powder and tablets.

The dissolution profile of a commercially available sustained release diclofenac sodium, Valtaren SR (Ciba-Geigy Limited), was also studied as illustrated in Figure 70. Drug release from the commercial tablet reached only about 78% at twelfth hour interval while the improved optimum tablet yield the C_{12} of about 86%. The initial stage of dissolution profile of the improved optimum tablet was faster than the one of the commercial tablet. The K^0 and R^2 of the commercial tablet were 0.132203 mg per minute and 0.983305, respectively. Therefore the commercial tablet was still apart from the required K^0 although its R^2 was quite high. The fast intial stage of dissolution profile of the improved optimum diclofenac sodium tablet might be benefit in the case of achieving rapid therapeutic blood level without using an additional loading dose. Whereas the drug release pattern of the following stage of the improved optimum tablet was similar to the commercial tablet in term of the slope of the dissolution profile. More complete in drug release was also observed in the improved optimum tablet comparing to the commercial tablet.

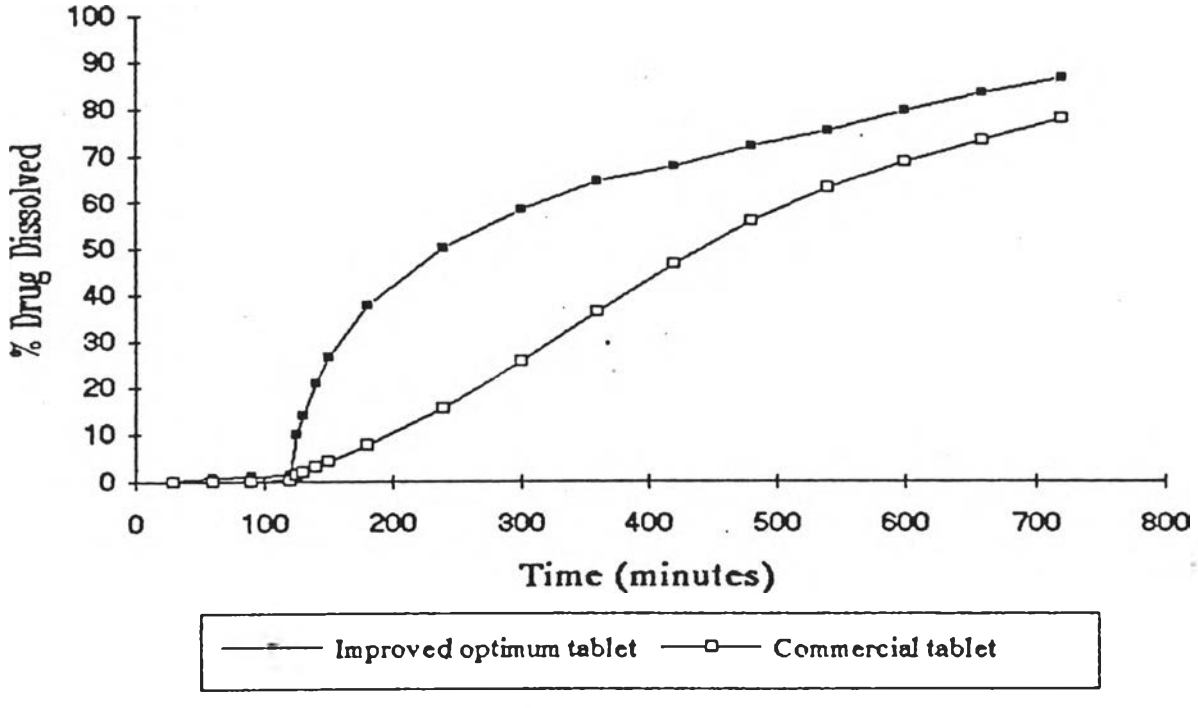


Figure 70. Dissolution profiles of the improved diclofenac sodium controlled release tablet and the commercial sustained release diclofenac sodium tablet.

PART III - CONTROLLED RELEASE MECHANISM

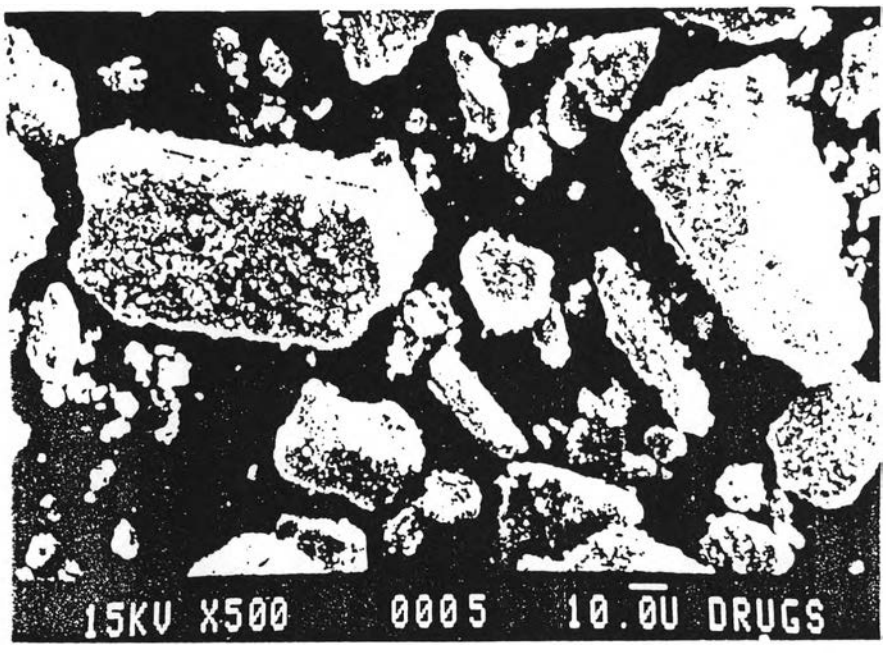
Scanning Electron Microscope Study

The photomicrographs of diclofenac sodium and the optimized 10:(2.5+0.02) diclofenac sodium:(EC+chitosan) solid dispersion obtained from the scanning electron microscope are displayed in Figures 71 and 72, respectively. The 10:(3+0.02) diclofenac sodium:(EC+chitosan) solid dispersion prepared by utilizing 200 ml of spray feeding liquid having low absolute ethanol fraction of 0.3 was also photographed by the scanning electron microscope and its photomicrograph is shown in Figure 73.

By comparing the photomicrographs of diclofenac sodium and the diclofenac sodium solid dispersions it was clearly demonstrated that the particle size of the drug was enormously reduced in the solid dispersions. Almost complete solid dispersion formation was observed in the photomicrograph of the optimized diclofenac sodium solid dispersion. In the solid dispersion obtained from the spray feeding liquid of low alcoholic proportion the photomicrograph indicated incomplete solid dispersion formation as shown by the presence of the separated particles of drug, ethylcellulose, chitosan, and the solid dispersion. The optimized diclofenac sodium solid dispersion was prepared from 200 ml of spray feeding liquid consisting of high ethanol fraction of 0.7 and hence increasing ethanol fraction in the feeding liquid resulted in more complete formation of solid dispersion.

The photomicrographs of chitosan (Ritthidej, et al., 1994) and ethylcellulose (Ethocel) are presented in Figure 74 (American

[a]



[b]

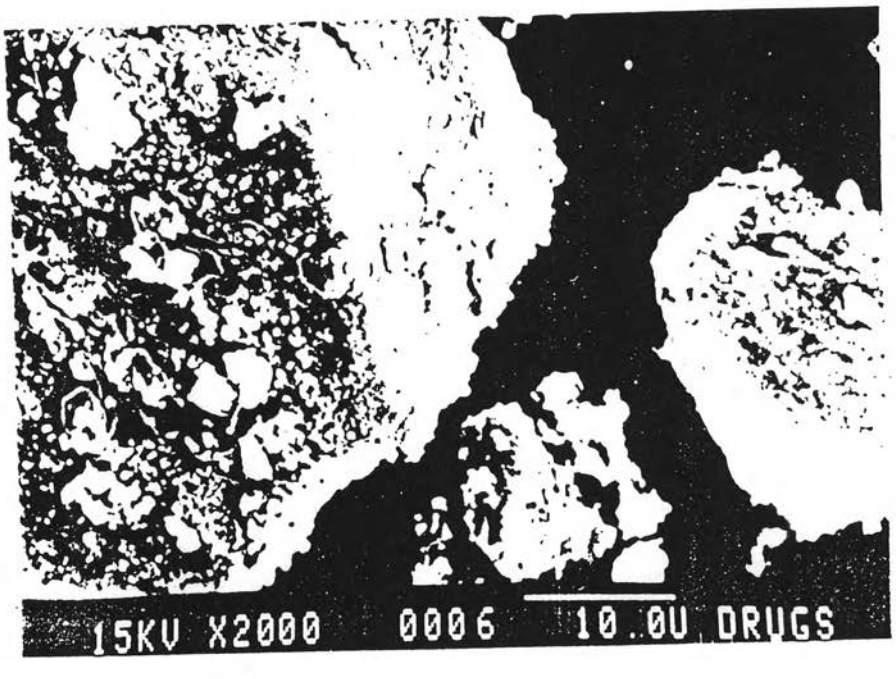


Figure 71. The photomicrographs of diclofenac sodium powder: [a] x500, [b] x2000

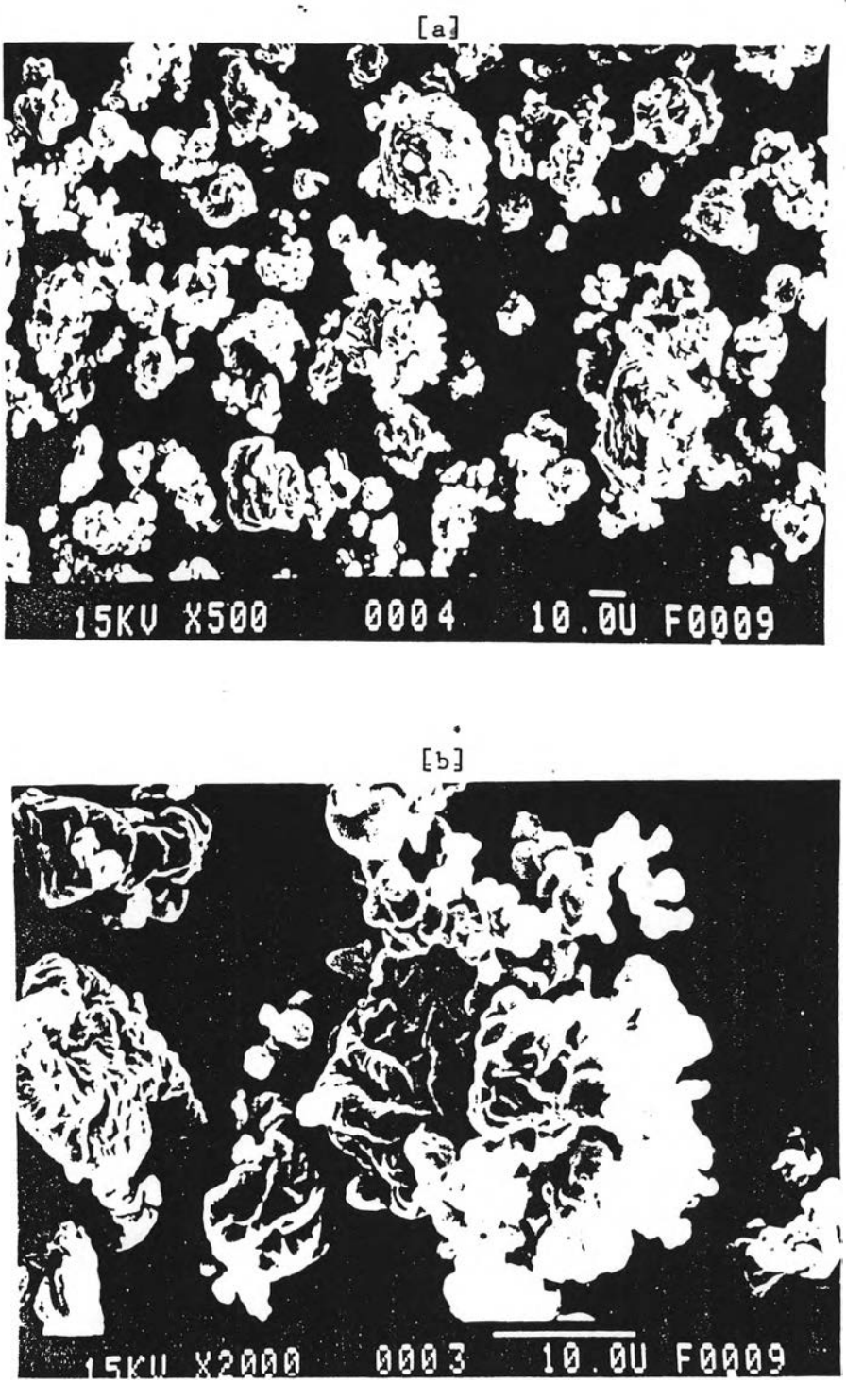
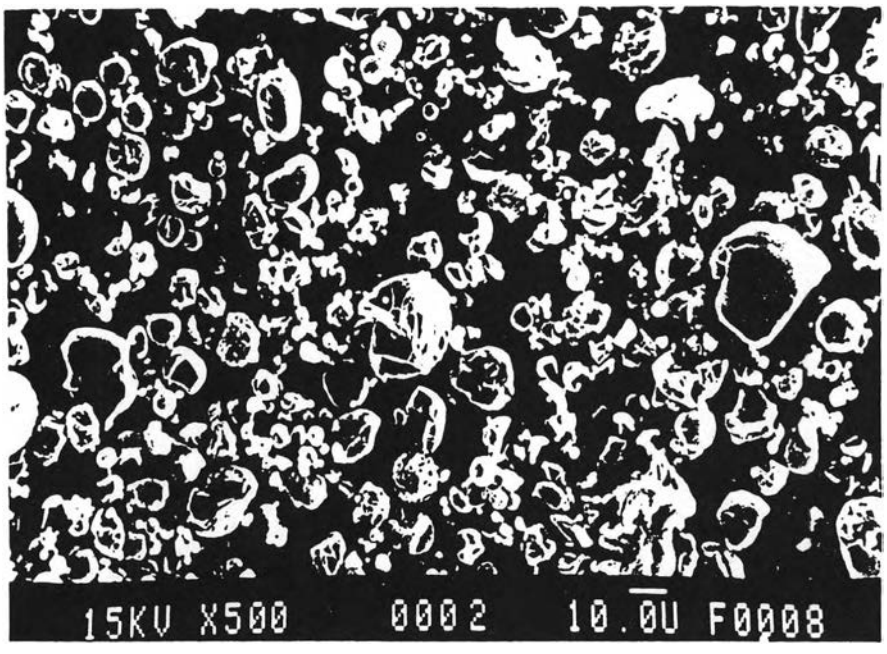


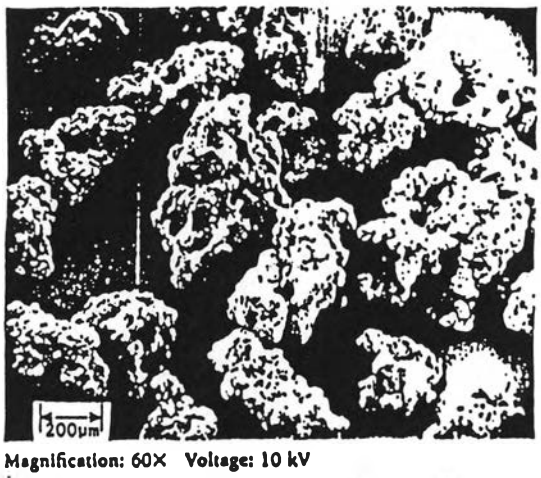
Figure 72. The photomicrographs of the optimized 10::(2.5 + 0.02) diclofenac sodium:(EC + chitosan) solid dispersion: [a] x500, [b] x2000.

[a]



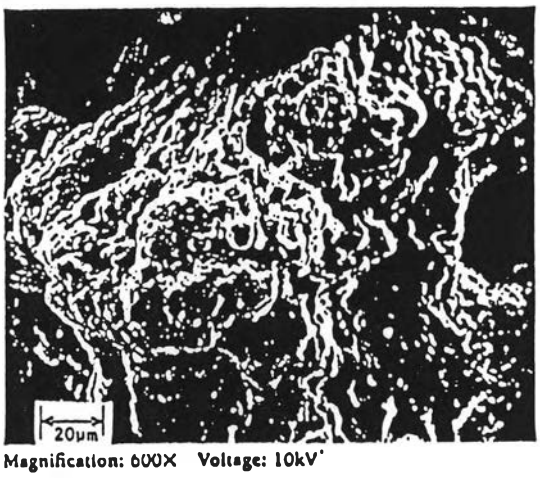
[b]

Figure 73. The photomicrographs of 10:(3 + 0.02) diclofenac sodium :(EC + chitosan) solid dispersion prepared from 200 ml spray feeding liquid having alcohol proportion of 0.3: [a] x500, [b] x2000.



Magnification: 60× Voltage: 10 kV

[a]



Magnification: 600× Voltage: 10kV

[b]

[c]

Figure 74. The photomicrographs of ethylcellulose (Ethocel): [a] x60, [b] x600 (American Pharmaceutical Association, 1984), and chitosan: [c] x50 (Ritthidej et al., 1994)

Pharmaceutical Association, 1986). The similarity between the appearances of ethylcellulose and the optimized 10:(2.5+0.02) diclofenac sodium:(EC+chitosan) solid dispersion was observed indicating the formaion of solid dispersion of the drug in ethylcellulose matrix.

Differential Thermal Analysis Study

The major use of thermal analysis in evaluation spray-dried products is in the identification of the polymorphic or crystalline form of the drug in the product since spray drying may result in a polymorphic change (Ford and Timmins, 1989). Corrigan and Holohan (1984) incorporated polyvinylpyrrolidone (PVP) into the spray-dried ethanolic solution of hydroflumethiazide. Differential scanning calorimetry (DSC) scan of the spray-dried products displayed an exotherm corresponding to recrystallization of the amorphous sample. Corrigan, Holohan, and Reilly (1985) similarly examined spray-dried indomethacin and naproxen with and without PVP and found that the samples containing 40% PVP were amorphous. Yakou et al. (1984) prepared phenytoin-polyethylene glycol 6000 solid dispersion by metlting method. The melt containing 10% phenytoin displayed only an endotherm equivalent to the melting of the polyethylene glycol and as the characteristic peaks of the drug were inapparent in X-ray diffraction spectra then finally the conclusion was assumed that the drug was dispered in the molecular or amorphous state.

Figures 75 and 76 demonstrate the DTA thermograms of diclofenac sodium and the optimized diclofenac sodium solid dispersion, respectively. The sharp melting peak of diclofenac sodium thermogram was observed at about 290°C indicating the drug melting point. The solid

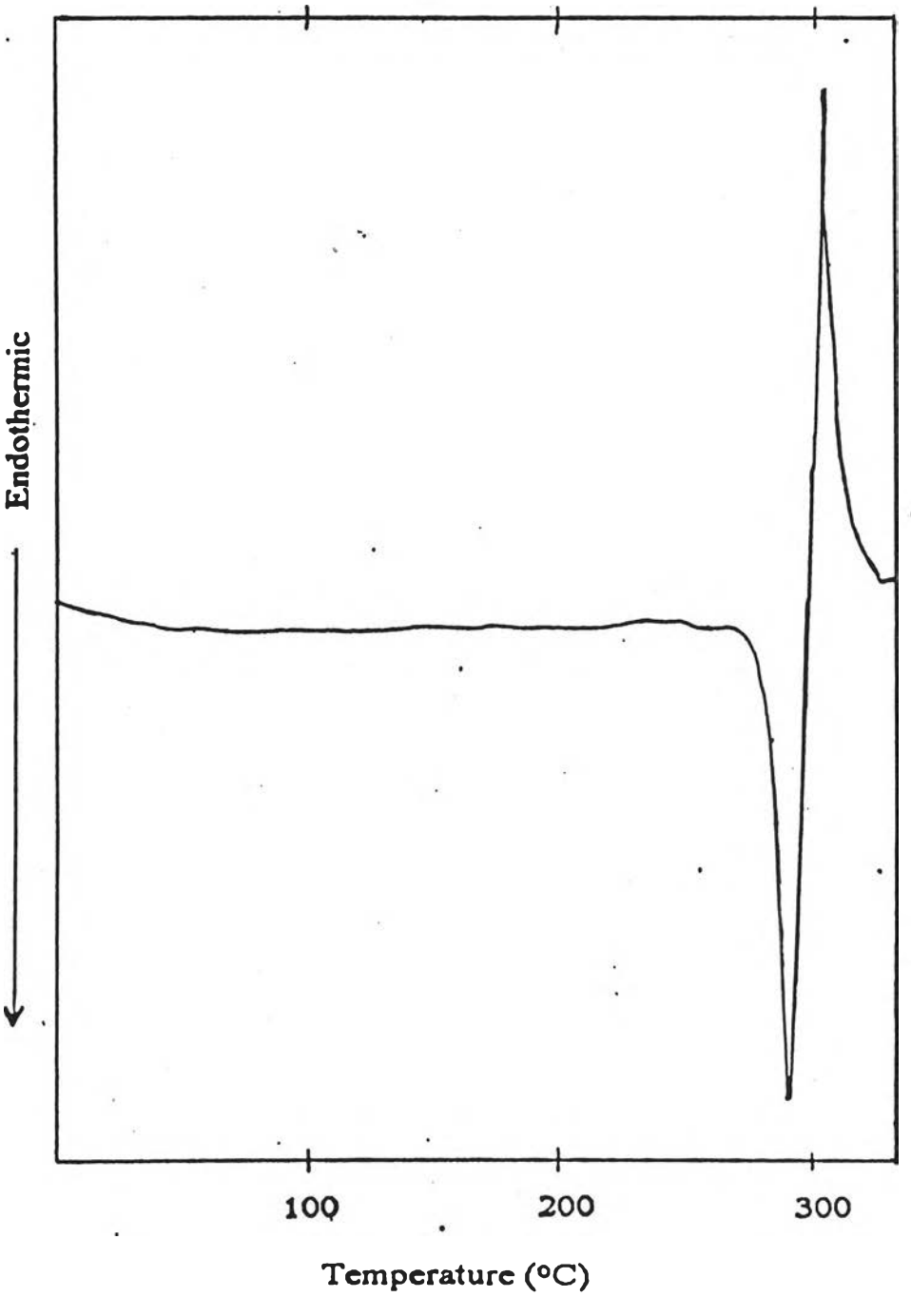


Figure 75. The thermogram of diclofenac sodium.

(Heating rate 10 °C / minute, sensitivity ± 50 μV)

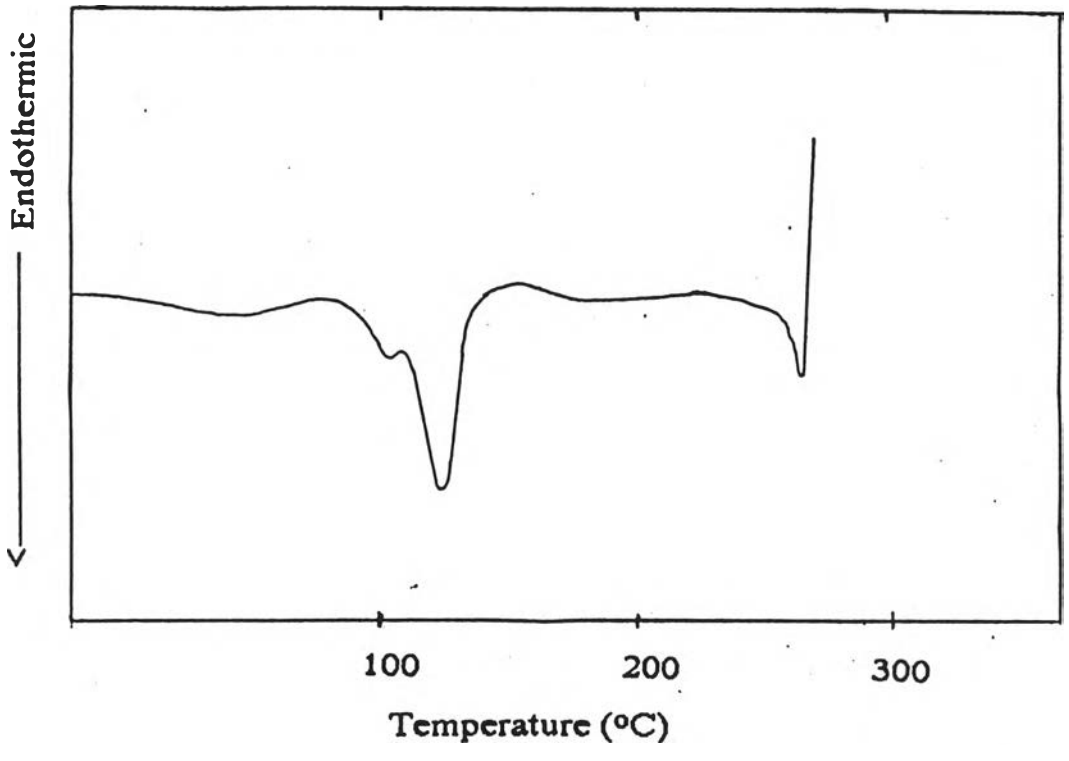


Figure 76. The thermogram of the optimized diclofenac sodium solid dispersion.
(Heating rate 10 °C / minute, sensitivity ± 50 μV)

dispersion thermogram showed a broad melting point peak at about 100 to 140°C and a sharp melting point peak at about 265°C, respectively. The thermograms of ethylcellulose and chitosan are shown in Figures 77 and 78 indicating melting peaks at 210°C and 165°C, respectively. Since ethylcellulose (Ethocel 10 cps) was reported to have softening point range between 135 to 155°C and melting point range between 165 to 185°C depending on ethoxy content (The Dow Chemical Company, 1978), and chitosan was shown to have melting peak at about 165°C. Therefore the broad melting peak range between 100 to 140°C of the optimized solid dispersion was considered to represent the softening and melting point range of the mixture of ethylcellulose and chitosan. The remaining sharp melting peak of 265°C shown in the thermogram was determined as the melting point of diclofenac sodium.

The observed melting point of pure diclofenac sodium was higher than the one obtained from the optimized diclofenac sodium solid dispersion thermogram. The lowering in melting point of diclofenac sodium in the solid dispersion indicated the presence of a metastable form or polymorh of diclofenac sodium in the solid dispersion. The photomicrographs of the optimized diclofenac sodium:(EC+chitosan) solid dispersion revealed the system of almost complete solid dispersion formation. Some traces of other particles rather than the solid dispersion particles were observed in the picture. Those particles were beleived to be the microparticle of diclofenac sodium in polymorphic state.

The thermogram of the 10:(3+0.02) diclofenac sodium: (EC+chitosan) solid dispersion prepared from 200 ml of spray feeding liquid having low alcoholic fraction of 0.3 is illustrated in Figure 79.

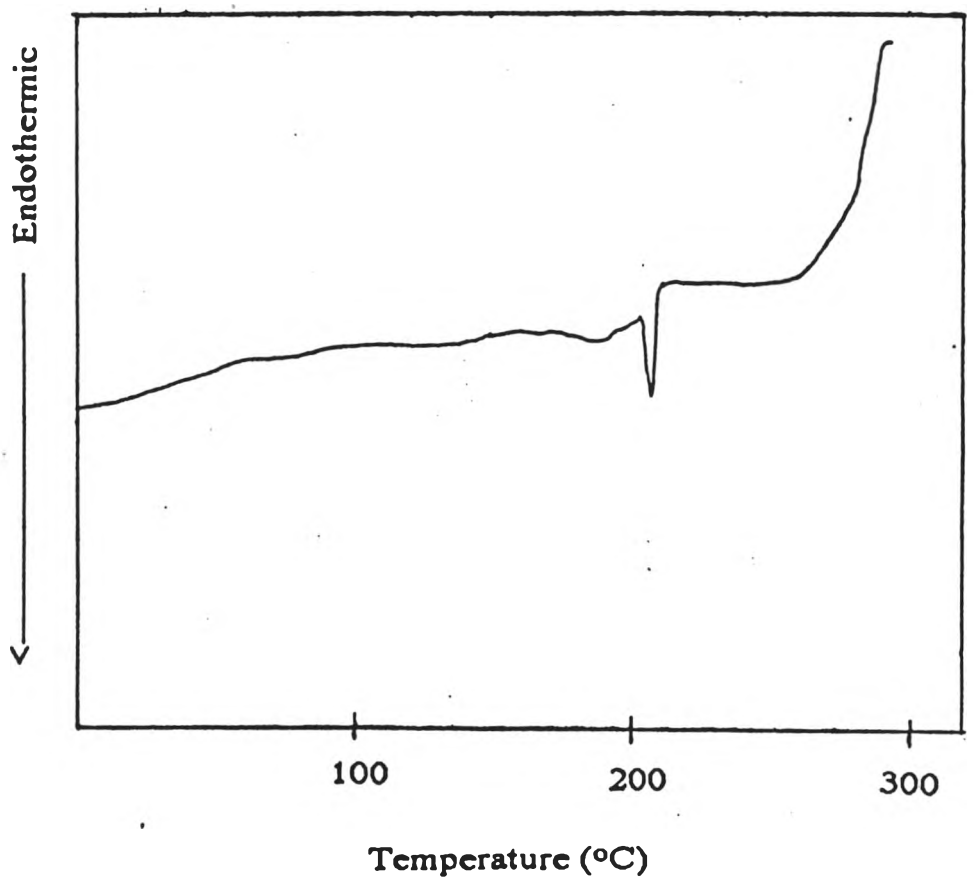


Figure 77. The thermogram of ethylcellulose.
(Heating rate 10 °C / minute, sensitivity ± 25 μV)

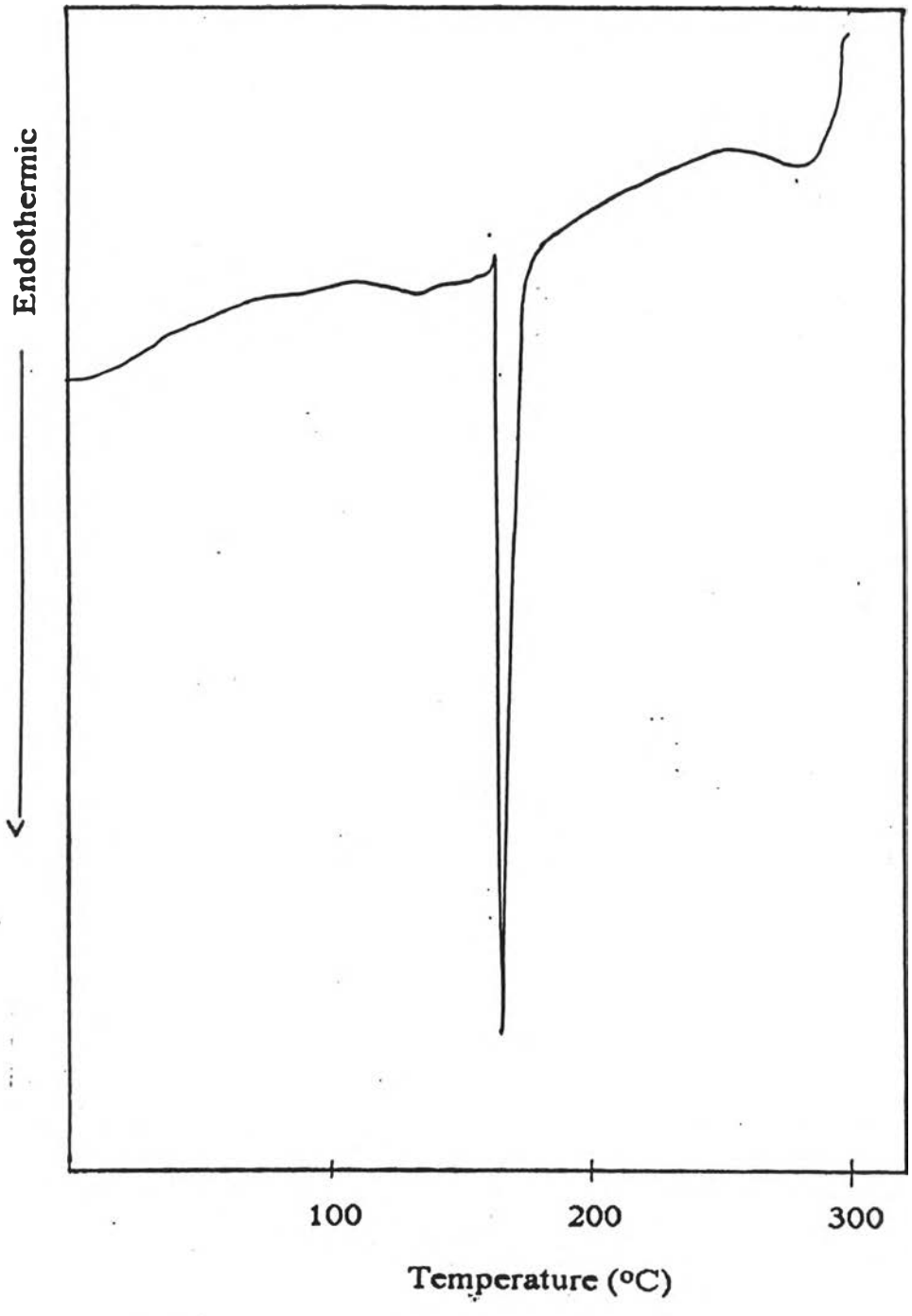


Figure 78. The thermogram of chitosan.

(Heating rate 10 °C / minute, sensitivity ± 25 μV)

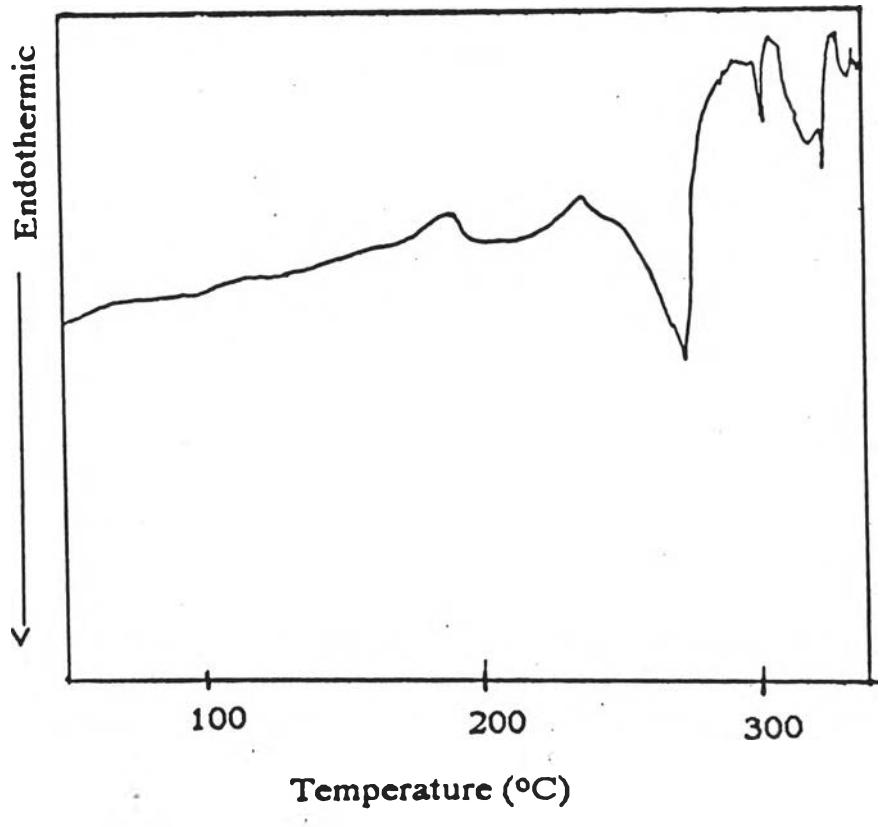


Figure 79. The thermogram of 10:(3+0.02) diclofenac sodium :(EC+chitosan) solid dispersion prepared from 200 ml spray-dried liquid having alcohol fraction of 0.3. (Heating rate 10 °C / minute, sensitivity ± 25 μV)

The thermogram showed a broad melting peak at about 250 to 290°C, with a sharp melting point at 280°C, and a broad melting range between 190 to 230°C. The broad melting peak as compared to the melting point of diclofenac sodium of 290°C indicated that some polymorphic formation was occurred. The high melting temperature of about 290°C indicated the presence of some diclofenac sodium in the crystalline form. The drug melting point at 280°C, as compared to the drug melting point at 265°C of the optimized solid dispersion thermogram, indicated the presence of the drug as a more stable polymorphic form in the 10:(3+0.02) diclofenac sodium:(EC+chitosan) solid dispersion. The remaining broad melting range between 190 to 230°C was beleived to represent softening and melting ranges of ethycellulose and chitosan. Therefore the thermogram of the 10:(3+0.02) diclofenac sodium:(EC+chitosan) indicated the presence of diclofenac sodium as both polymorphic form and the more stable crystalline form.

X-Ray Diffraction Study

The X-ray diffractograms of diclofenac sodium and the optimized 10:(2.5+0.02) diclofenac sodium:(EC+chitosan) solid dispersion are demonstrated in Figure 80. Figure 80 also demonstates the X-ray diffractogram of spray-dried diclofenac sodium prepared from feeding liquid containing 10 g drug dissolved in 200 ml of ethanolic solution having ethanol fraction of 0.7. This diffractogram was similar to the diffractogram of the drug indicating the presence of of diclofenac sodium as crystalline form in the spray-dried drug. The diffractogram of the 10:(3+0.02) diclofenac sodium:(EC+chitosan) solid dispersion prepared by utilizing 200 ml of spray feeding liquid having low absolute ethanol

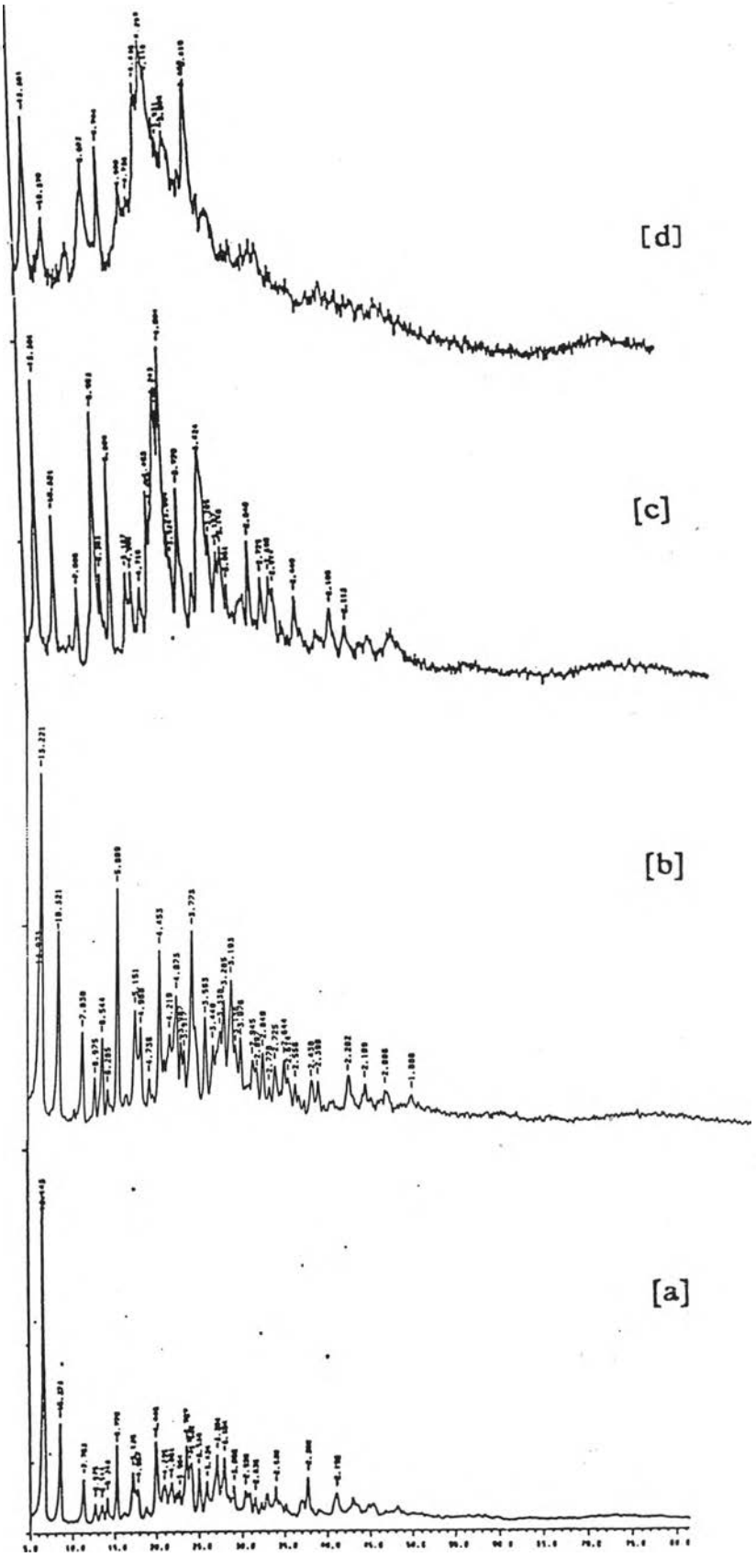


Figure 80. X-ray diffractograms of [a] diclofenac sodium [b] spray-dried diclofenac sodium, [c] 10:(3+0.02) diclofenac sodium: (EC+chitosan) solid dispersion prepared from 200 ml feeding liquid having absolute ethanol fraction of 0.3, [d] optimized 10:(2.5+0.02) diclofenac sodium:(EC+chitosan) solid dispersion.

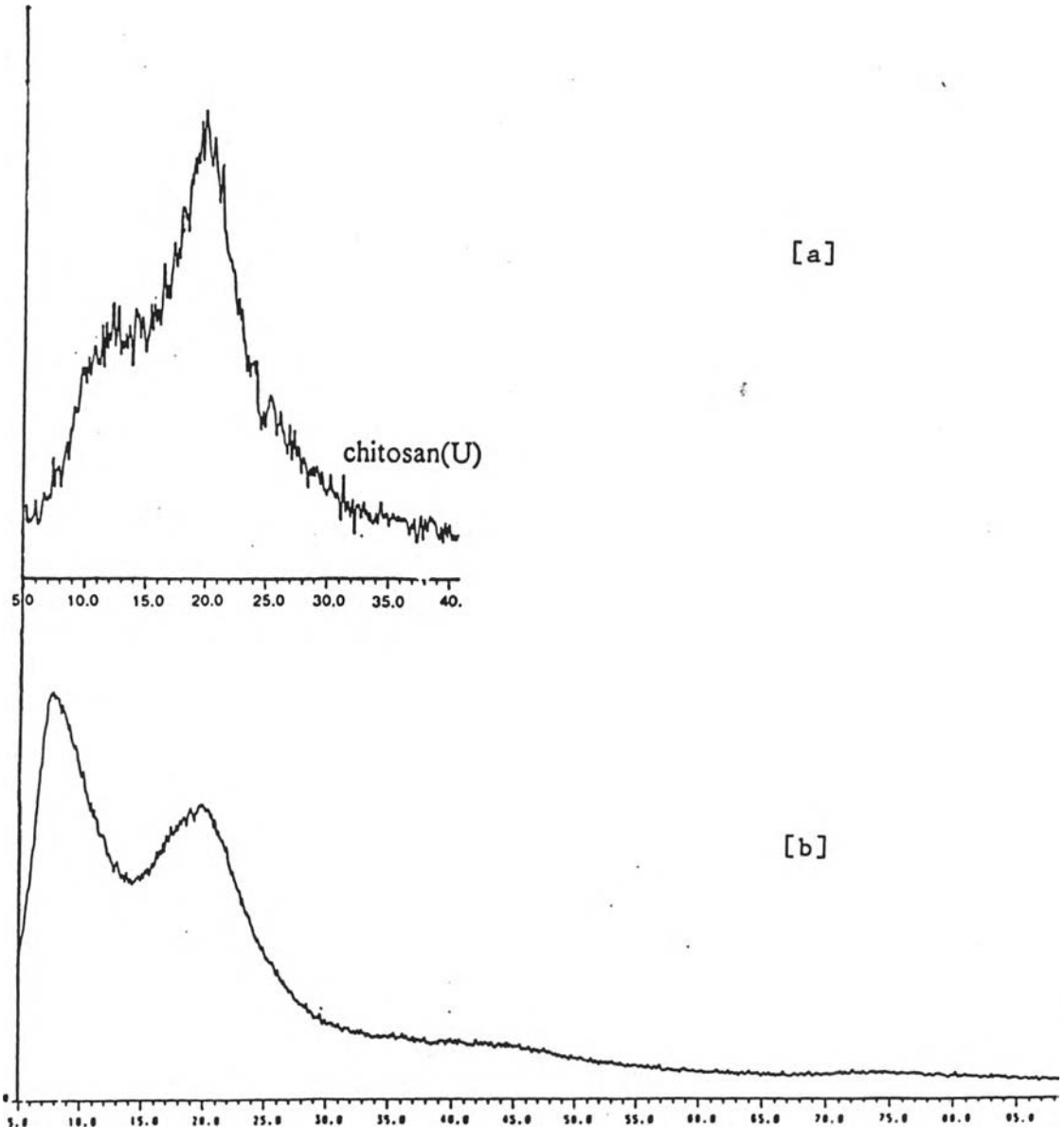


Figure 81. X-ray diffractograms of [a] chitosan (Ritthidej, et al., 1994), [b] ethylcellulose.

fraction of 0.3 is also shown. Figure 81 demonstrates X-ray diffractograms of chitosan (Ritthidej, et al., 1994) and ethylcellulose, both diffractograms did not exhibit any prominent peak indicating the presence of both polymers in amorphous state.

By comparing the diffractogram of the optimized diclofenac sodium solid dispersion with the one of diclofenac sodium, the change in the pattern of the diffractogram was observed by raising in the base line and absence in some peaks of diclofenac sodium. The optimized diclofenac sodium solid dispersion still displayed well-defined peaks corresponding to the peaks of diclofenac sodium indicated the presence of diclofenac sodium in polymorphic form. The result obtained from differential thermal analysis confirmed the presence of diclofenac sodium as polymorphic form in the optimized diclofenac sodium solid dispersion.

The presence of the drug as molecular or colloidal dispersion in the optimized solid dispersion was demonstrated by raising in the base line of the diffractogram. In general the diffractogram of the drug presented as amorphous or molecular dispersion would exhit absence in diffractogram peaks (Biswas et al., 1993; Chiou, 1971; Chiou, 1977; Flego, Levrecich, and Rubessa, 1988; Imai et al., 1989; Ravis and Chen, 1981) while the polymorphic drug would show the well-defined peaks indicating the presence of crystal lattice. Therefore X-ray diffractogram of the solid dispersion consisting of both molecular dispersion and polymorphic form of the drug would also exhibit both diffractogram patterns. The diffractogram of the optimized diclofenac sodium solid dispersion illustrated this phenomenon.

The diffractogram of the diclofenac sodium solid dispersion prepared from 200 ml of spray feeding liquid having low alcoholic content was similar to the diffractogram of the drug. The similarity between the two diffractograms indicated the presence of the crystalline drug in the solid dispersion. This result was supported by the photomicrograph of the solid dispersion which illustrated the presence of the drug and the two carriers separately from the solid dispersion of drug in the carriers. The solid dispersion diffractogram also showed some raising of the base line but in less extent than the one of the optimized solid dispersion. Therefore more amorphous formation was achieved from the optimized diclofenac sodium solid dispersion. This phenomenon might be attributed from the formation of solid dispersion in larger extent in the optimized diclofenac sodium solid dispersion. Since the photomicrograph of the solid dispersion prepared from spray feeding liquid having low alcoholic content exhibited the formation of solid dispersion in small extent. Therefore the results obtained from X-ray diffractogram and photomicrograph confirmed that the solid dispersion formation was achieved more completely from the spray feeding liquid using higher alcoholic content.

Mechanism of Drug Release from the Optimized Controlled Release Solid Dispersion

The mechanism of drug release from the optimized 10:(2.5+0.02) diclofenac sodium:(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 percentage of drug released and square root time is shown in Figure 82. This plot yielded r^2 of 0.963302 while

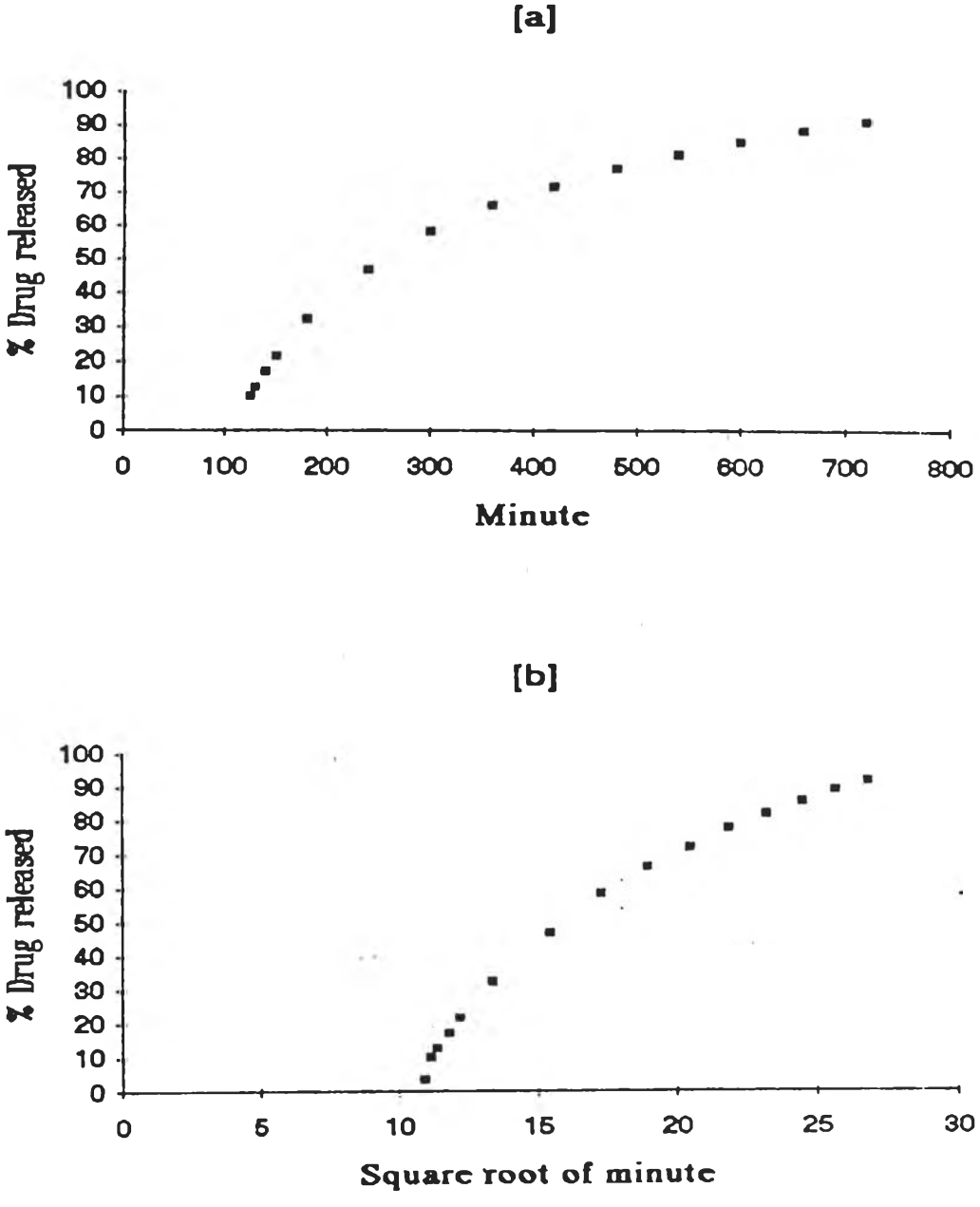


Figure 82. Linearization of the release profiles of the optimized diclofenac sodium solid dispersion according to :
[a] zero-order model, [b] Higuchi model.

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

From the K^0 equation as a function of feeding volume (X_1), absolute ethanol fraction (X_2), ethylcellulose content (X_3), and chitoan content (X_4) of

$$K^0 = -0.000107X_1 - 0.047184X_2 - 0.008011X_3 - 0.010538X_4 + 0.176192.$$

The change in ethanol fraction in spray feeding liquid from 0.30 (-1 level) to 0.70 (1 level) caused decreasing in K^0. In another word, increasing alcohol fraction resulted in more retardation of drug release from the diclofenac sodium:(EC+chitosan) solid dispersions. Since the drug and ethylcellulose dissolve well in absolute ethanol but are poorly soluble in water. Therefore decreasing alcohol fraction of spray feeding liquid would result in less drug and ethycellulose being dissolved in the feeding liquid. This could be evident by the appearance of the spray feeding liquids in the form of white colloidal dispersions when the alcohol proportion was 0.3 while the light yellowish solutions were obtained when the ethanol fraction was 0.7.

When the feeding liquid of low ethanol fraction was spray dried the resulting powder was beleived to consist of drug, ethylcellulose, chitosan, and drug-carriers solid dispersion separately since the feeding liquid was colloidal dispersion rather than homogeneous solution as in the case of high alcohol fraction. During spray drying the drug,

ethylcellulose, and chitosan dispersed particles precipitated out first while the remaining drug-carriers solution would undergo to be spray-dried solid dispersion later on. The photomicrograph of the 10:(3+0.02) diclofenac sodium:(EC+chitosan) solid dispersion obtained by using low fraction of absolute ethanol confirmed this conclusion since the photomicrograph showed the appearance of separated particles of drug, carriers, and the solid dispersion.

For the spray feeding liquid having high ethanol fraction of 0.7, the drug and carriers were in homogeneous solution resulting in more complete in formation of solid dispersion. After spray drying most of the spray-dried powder thus consisted of molecular or colloidal dispersion of diclofenac sodium in the carriers while some portion of the powder represented the drug in polymorphic form.

Since more complete in solid dispersion formation was found in the optimized diclofenac sodium solid dispersion as compared to the solid dispersion prepared from the feeding liquid of low alcoholic content, therefore more dissolution retarding effect was found in the optimized solid dispersion.

Increasing evaporation rate due to higher fraction of alcohol also resulted in shorter period of time being utilized for crystallization of drug molecules. Thus the polymorphic form of the drug was expected in solid dispersions obtained from spray feeding liquid having higher fraction of absolute ethanol since the short interval of solidification is critical in formation of metastable solid dispersions (Chiou and Riegelman, 1969). The data from the thermogram and X-ray diffractogram of the optimized

diclofenac sodium solid dispersion revealed the appearance of diclofenac sodium in polymorhic form. In contrast slower evaporation occured in spray drying of the feeding liquid which consisted of low ethanol fraction. As the result more time was available for crystallization of drug molecules and thus more stable polymorphic form of diclofenac sodium was formed in this case as evident by its thermogram and X-ray diffractogram.

One could notice from the predicted equation that the higher the amount of ethylcellulose or chitosan was utilized, the more dissolution retarding effect was obtained. In preparing solid dispersion the influence of the amount of carrier on dissolution modifying effect was recognized elsewhere. In general the higher the amount of the carrier being employed, the more dissolution modifying effect was achieved (Ford, 1986). The effects of ethylcellulose and chitosan on dissolution retardation were additive as clearly demonstrated by the minus sign of their regression model coefficients in the predicted equation. The combined mechanisms of drug diffusion through insoluble matrix and through viscous environment were beleived to be responsible for the additive effects. Increasing chitosan content imparted more viscous environment around the solid dispersions and thus delayed the diffusion of the drug from the solid dispersions. Higher amount of an insoluble carrier, ethylcellulose, presented in the solid dispersions also resulted in less pathway available for dissolution medium penetration and drug diffusion, therefore more retardation in drug dissolution was achieved.

Molecular or colloidal dispersion of drugs in some linear polymer were proposed to occur in solid dispersions (Chiou and Riegelman, 1969; Chiou and Reigelman, 1971; McGinity, Maness, and Yakatan, 1974-

1975). Molecular or colloidal dispersion can be achieved by coprecipitation in the form of interstitial solid solution. Crystalline polymers of high molecular weight appear to be logical choices for interstitial solid solutions since they are capable of entrapping low molecular weight compounds in their interstitial space. High viscosity of polymers is another factor which may contribute to the formation of metastable solid solutions (Chiou and Riegelman,1971). The effect of viscosity of carriers being utilized in preparation of coprecipitates has been mentioned previously (Chiou and Riegelman, 1969; Chiou and Riegelman, 1971). In the viscous medium the crystallization of drug is retarded due to the difficulty in nucleation of the drug. Thus in this study as the more viscous feeding solution was employed in spray drying, the more reduction in particle size of the drug being dispersed in the solid dispersions would be the result. The optimized 10:(2.5+0.02) diclofenac sodium:(EC+chitosan) solid dispersion was prepared from the feeding liquid containing high amount of ethylcellulose and absolute ethanol. In the optimized feeding liquid thus the complete dissolution of ethylcellulose was achieved resulting in the feeding liquid of high viscosity and consequently the formation of molecular or colloidal dispersion of drug in the carriers was obtained as supported by its thermogram and X-ray diffractogram. While incomplete dissolution of ethylcellulose was observed in the 10:(3+0.02) diclofenac sodium: (EC+chitosan) feeding liquid of low alcoholic content as evident by the appearance of the feeding liquid as white colloidal dispersion rather than solution. Therefore the low alcoholic feeding liquid was less viscous and hence molecular or colloidal dispersion was less accomplished.

From the R^2 equation as a function of feeding volume (X_1), absolute ethanol fraction (X_2), ethylcellulose content (X_3), and chitoan content (X_4) of

$$R^2 = 0.004199X_1 + 0.014391X_2 + 0.019671X_3 + 0.001576X_4 + 0.882823.$$

Increasing ethanol fraction from 0.30 (-1 level) to 0.70 (1 level) resulted in higer R^2. Thus, when ethanol fraction was increased the drug release profile became closer to the zero-order kinetics model of release. Since the spray-dried powder obtained from the low alcoholic feeding liquid consisted of diclofenac sodium as both solid dispersion and separated drug particles while the spray-dried powder obtained from the high alcoholic feeding liquid consisted of diclofenac sodium largely as solid dispersion. Therefore the more consistency in drug release was obtained in the solid dispersion prepared from the feeding liquid of higher alcohol fraction.

In conclusion, the mechanism of drug release from the optimized diclofenac sodium controlled release solid dispersion derived from molecular or colloidal dispersion of drug in the matrix of ethylcellulose and chitosan causing:

1. Slow diffusion of drug through the insoluble carrier, ethylcellulose, and

2. Slow diffusion of drug through viscous environment produced by swelling action of the swellable carrier, chitosan, in acidic medium.

Mechanism of Drug Release from the Optimized Diclofenac Sodium Controlled Release Solid Dispersion Tablets

The mechanism of drug release from the improved optimum diclofenac sodium controlled release tablet in pH 6.8 phosphate buffer solution fit well with Higuchi model rather to zero-order model. The plot between percentage of drug released and square root time is shown in Figure 83. This plot gave r^2 of 0.968122 while the r^2 of the plot between percentage of drug released and time was 0.923884. Therefore the diclofenac sodium controlled release tablet of optimum zero-order kinetics drug release could be developed with small number of experiments by using optimization strategy.

Referring to the equation of K^0 as a function of four variables; compression force (X_1), Era-Tab level (X_2), Ac-Di-Sol level (X_3), and magnesium stearate level (X_4), in the form of

$$K^0 = 0.025850X_3 + 0.009856X_2X_3 + 0.151641.$$

Only Ac-Di-Sol level and interaction between Era-Tab level and Ac-Di-Sol level imparted significant effect on K^0. Ac-Di-Sol level was the most prominent factor imparting effect on K^0 or drug release rate. Increasing Ac-Di-Sol level in the range of -1.414 to 1.414 caused faster drug release. As the amount of Ac-Di-Sol in the diclofenac sodium controlled release tablets increased, the tablets should disintegrate more rapidly into the diclofenac sodium solid dispersions and subsequently faster drug release was obtained. Since chitosan swelled in acidic medium imparting binding effect to the tablets due to high viscosity therefore high

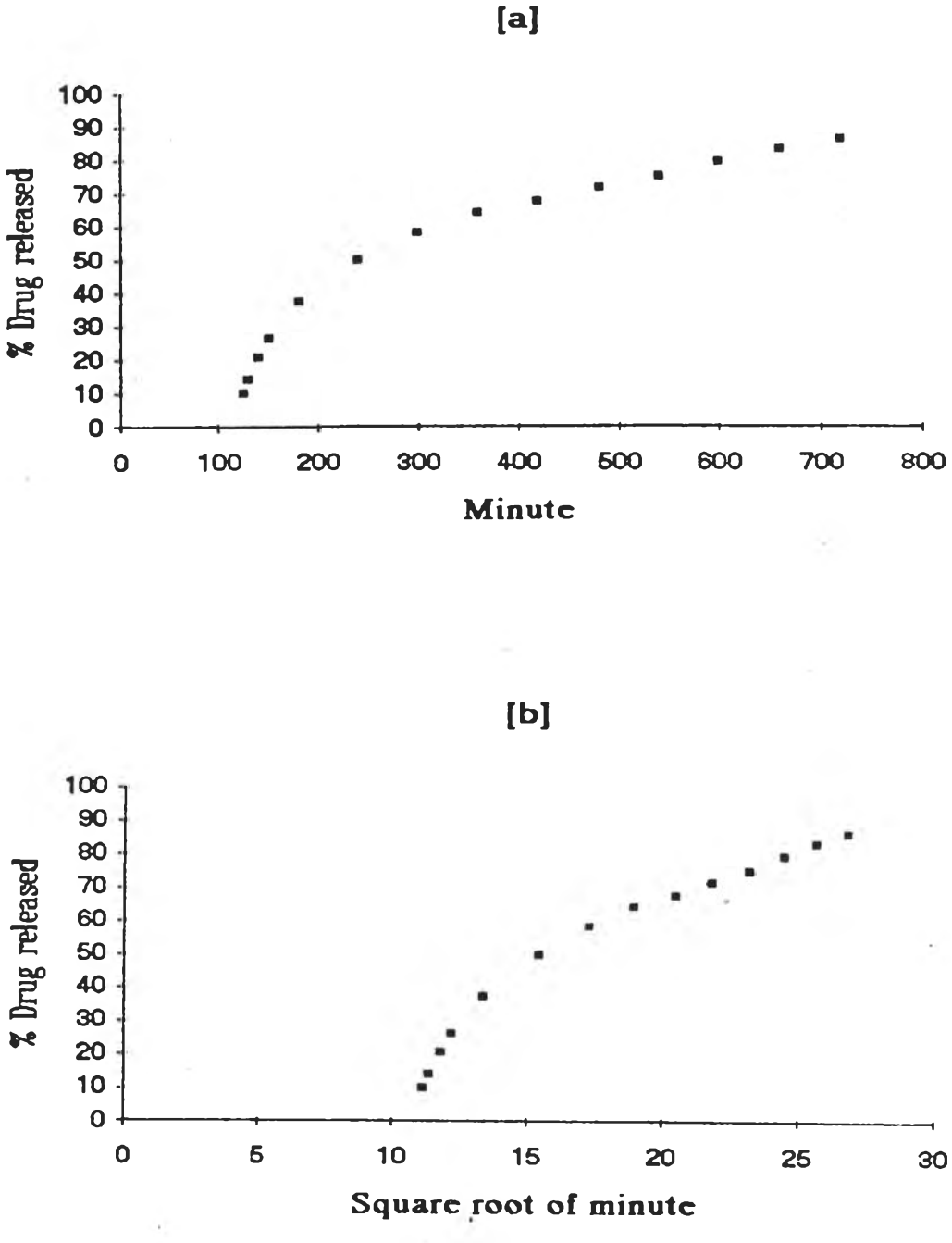


Figure 83. Linearization of the release profiles of the improved optimum diclofenac sodium controlled release tablet according to : [a] zero-order model, [b] Higuchi model.

amount of Ac-Di-Sol was needed in order to counter this effect otherwise too slow in drug release would be the result. However, if too high in the amount of Ac-Di-Sol was used the tablets would disintegrate too fast resulting in too high in the value of K^0. Hence, the optimum level of Ac-Di-Sol was required.

The K^0 was also function of interaction between Ac-Di-Sol level and Era-Tab level. At too low level of Ac-Di-Sol level, the tablets would not disintegrate due to disintegration retarding effect of chitosan. Increasing Era-Tab level in this case would cause more dissolution retarding effect since Era-Tab was spray-dried rice starch which was insoluble and hence was trapped in the tablets. As the content of Era-Tab increased, higher amount of Era-Tab would be trapped and thus creating less diffusion pathway available for the passage of dissolution medium and drug through the tablets. As the result, drug release by diffusion was retarded. But at high level of Ac-Di-Sol, the disintegrating effect of Ac-Di-Sol overcame the disintegration retarding effect of chitosan and the tablets were able to disintegrate into solid dispersion powders. In this situation increasing the amount of Era-Tab would result in higher K^0 due to swelling action of Era-Tab which contributed to disintegrating effect of Ac-Di-Sol.

When comparing the effects of Ac-Di-Sol at low and at high level of Era-Tab, it was recognized that more enhancement in K^0 was observed in the latter case. At high level of Era-Tab, the contributing effect of Era-Tab on tablet disintegration would be higher and consequently faster drug release or higher K^0 would be achieved.

Compression force (X_1) was found to have insignificant effect on K^0 of the diclofenac sodium controlled release tablets. Although the influence of compression force on solid dispersion tablets prepared from theophylline dispersed in a polymeric mixture of polyethylene glycol and acrylic/methacrylic esters was reported (Fassihi, Parker, and PourKavoos, 1985). However, compression force has usually been thought to have little influence on drug release from matrix tablets. Since the porosity of the hydrated matrix, which does affect release as in Higuchi's model, is independent of the initial porosity. There seems to be a basis for this statement, at least in the case of matrices of hydrosoluble active principles. Most of the available data point along these lines (Mitchell et al., 1990; Nakano et al., 1983). Nevertheless, as indicated by Korsmeyer et al. (1983), the initial porosity might be more important than it may at first seem. In the diclofenac sodium controlled release solid dispersion tablets the mechanism of Ac-Di-Sol as tablet disintegrant was swelling action. High swelling capacity of Ac-Di-Sol was thought to eliminate the effect of initial porosity on drug release from tablets. Therefore the changing of compression force, while affecting the initial porosity of the directly compressed diclofenac sodium controlled release tablets, did not impart any significant effect on K^0.

The effect of magnesium stearate, an insoluble lubricant, on tablet dissolution retardation has been recognized. Hydrophobic lubricants such as magnesium stearate, aluminum stearate, stearic acid and talc, decrease the effective drug-solvent interfacial area by changing the surface characteristics of the tablets which results in reducing its wettability, prolonging its disintegration time and decreasing the area of the interface between the active ingredient and solvent (Levy and Gumtow, 1963). In

this study, the variation in the level of magnesium stearate used in diclofenac sodium tablet formulations did not impart significant effect on K^0. Since the concentration of magnesium stearate imparting dissolution retarding effect on tablets was found to depend on the nature of active ingredient. Iranloye and Parrott (1978) compared the effect of several hydrophobic lubricants on the dissolution rate of aspirin and salicylic acid tablets. With magnesium stearate, they found that a concentration of 0.5% decreased the dissoluton rate of salicylic acid and aspirin by 33 and 27%, respectively. Jaminet, DeLatta, and Delporte (1969) investigated the effect of different lubricants on the dissolution rate of phenobarbital tablets and found that the optimum concentration of magnesium was about 1% or less. Increasing its quantity to 1.5% resulted in tablets with decreased disolution rate. In this investigation the concentration of magnesium stearate used in the diclofenac sodium tablet formulations were between 0.15 to 0.85%, which were sufficient to yield tablets of acceptable tablet properties. Therefore the absence of dissolution retarding effect of magnesium stearate on the diclofenac sodium controlled release tablets was resulted from not high enough in the amount of magnesium stearate was utilized.

From the R^2 equation as a function of compression force (X_1), Era-Tab level (X_2), Ac-Di-Sol level (X_3), and magnesium stearate level (X_4) of

$$R^2 = -0.011483X_1 - 0.020320X_3 - 0.008890X_2X_3 - 0.011330X_1^2 + 0.015385X_2^2 + 0.904841.$$

Ac-Di-Sol was the most important factor in determining R^2 value of the diclofenac sodium controlled release tablets. Increasing level of Ac-Di-Sol in the range of -1.414 to 1.414 caused more deviation of dissolution profile from the zero-order kinetics model. However, the effect of Ac-Di-Sol on R^2 value also depended on the level on Era-Tab as demonstrated by the interaction between Ac-Di-Sol and Era-Tab. At low Era-Tab level, the negative effect of Ac-Di-Sol on R^2 value was less prominent than at high Era-Tab level. Similarly, the effect of Era-Tab on R^2 value depended on Ac-Di-Sol level. Moreover, the Era-Tab effect itself was found to have squared-term effect on R^2 value. Compression force also imparted significant effect on R^2 value. Its influence was complicated as demonstrated by both its main effect and squared-term effect.