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COMMUNICATION

Development of Diclofenac Sodium Controlled Release Solid Dispersion Tablet Using Optimization Strategy

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ABSTRACT

Directly compressed diclofenac sodium (DS) controlled release tablets were prepared from spray-dried DS controlled release solid dispersion of optimum dissolution profile. Optimization strategy using a central composite design and multiple regression was used to study the influences of four parameters; compression force, the amounts of spray-dried rice starch (Era-Tab^R), croscarmellose sodium (Ac-Di-Sol^R), and magnesium stearate, on tablet physical properties and dissolution. The optimum conditions of those parameters were searched and an optimum DS controlled release tablet formulation was formulated. The dissolution profile of the optimized DS controlled release tablet was similar to that of the DS controlled release solid dispersion. The mechanism of drug release from the optimized DS tablet was found to be diffusion controlled.

INTRODUCTION

In the previous work a spray-dried diclofenac sodium (DS) controlled release solid dispersion system of optimum dissolution profile was developed using ethylcellulose (EC) and chitosan as combined carriers (1). In this study the optimum DS controlled release solid dispersion was prepared and formulated into tablet dosage form by direct compression. In general, the dissolution of a drug from a directly compressed tablet depends on various parameters including compression force and tablet excipients (2-5). Therefore, to achieve the optimum DS controlled release tablet, the effects of the four parameters on tablet dissolution were investigated. These parameters were compression force, the amounts of compressible diluent, disintegrant, and lubricant employed in the tablet production. Spray-dried DS solid dispersion was bulky therefore spray-dried rice starch (Era-Tab^R), a compressible diluent of high bulk density, was used (6). The disintegrant and lubricant employed in this study were croscarmellose sodium (Ac-Di-Sol^R) and magnesium stearate, respectively.

Experimental Design

In order to study the effects of the four parameters on tablet dissolution, an orthogonal central composite design as listed in Table 1 was applied (7). By using a statistical computer program, the relationships between the four independent variables and the required properties of DS controlled release tablets could be established. Then, the optimized DS controlled release tablet could be developed.

MATERIALS

The following chemicals were supplied by commercial sources: diclofenac sodium (Batch No. DFSH 045, CFS PTE Ltd., Switzerland), chitosan (Unicord PCL, Thailand), ethylcellulose (Ethocel^R 10 cps, Dow Chemical Company, U.S.A.), spray-dried rice starch (Era-Tab^R, Lot No. T910118, Erawan Pharmaceutical Research and Laboratory Co. Ltd., Thailand), croscarmellose sodium (Ac-Di-Sol^R, Lot No. T934, AMC Co., U.S.A.), magnesium stearate, and colloidal silicon dioxide (Aerosil^R, Pharmaceutical Science Ltd., Part., Thailand).

METHODS

Preparation of DS Controlled Release Solid Dispersion

The optimized 10:(2.5 ± 0.02) DS:(EC + chitosan) controlled release solid dispersion was prepared by spray drying (Buchi 190 Mini Spray Dryer, Buchi Co., Switzerland) using inlet temperature of 110°C and spray feeding rate of 10 ml per minute (1).

Preparation of DS Controlled Release Tablets

Table 2 shows the detail of tablet formulations according to the half-fractional factorial central composite design. Each formulation (per tablet) consisted of 125.2 g DS solid dispersion (equivalent to 100 mg drug) and 1% Aerosil^R as a glidant. DS controlled release tablets were prepared by direct compression using a single stroke tableting machine equipped with a strain gauge.

Evaluation of Tablet Properties

The prepared DS tablets were evaluated for tablet weight variation (20 tablets), friability (20 tablets), hardness (5 tablets), disintegration time (6 tablets), and dis-

Table 1

Experimental Design by Orthogonal Central Composite Design

Experiment	X_1	X_2	X_3	X_4
1	-1	-1	-1	-1
2	1	-1	-1	1
3	-1	1	-1	1
4	1	1	-1	-1
5	-1	-1	1	1
6	1	-1	1	-1
7	-1	1	1	-1
8	1	1	1	1
9	1.414	0	0	0
10	-1.414	0	0	0
11	0	1.414	0	0
12	0	-1.414	0	0
13	0	0	1.414	0
14	0	0	-1.414	0
15	0	0	0	1.414
16	0	0	0	-1.414
17	0	0	0	0

Table 2

The Detail of DS Controlled Release Tablet Formulation

Formulation	Compression Force (psi)	Era-Tab^R (mg)	Ac-Di-Sol^R (%)	Magnesium Stearate (%)
I	560	174.8	1.5	0.25
II	840	174.8	1.5	0.75
III	560	214.8	1.5	0.75
IV	840	214.8	1.5	0.25
V	560	174.8	3.5	0.75
VI	840	174.8	3.5	0.25
VII	560	214.8	3.5	0.25
VIII	840	214.8	3.5	0.75
IX	900	194.8	2.5	0.50
X	500	194.8	2.5	0.50
XI	700	223.08	2.5	0.50
XII	700	166.52	2.5	0.50
XIII	700	194.8	3.914	0.50
XIV	700	194.8	1.086	0.50
XV	700	194.8	2.5	0.8535
XVI	700	194.8	2.5	0.1465
XVII	700	194.8	2.5	0.50

solution. Disintegration time of each tablet formulation was studied according to USP XXII and NF XVII (8). Dissolution studies of DS controlled release tablets were conducted according to Method A described under Drug Release in USP XXII & NF XVII using type II dissolution apparatus (8). The dissolution tests were run in 0.1N HCl for 2 hr and later in pH 6.8 phosphate buffer solution for 10 hr by using a stirring rate of 50 rpm. Sample solutions in acid and buffer media were assayed spectrophotometrically at 275 nm and 278 nm for DS content, respectively.

Validation of Optimized DS Controlled Release Tablet

The optimized DS controlled release tablet was prepared by direct compression using optimum conditions obtained from optimization of DS controlled release tablets, as in 2, and its dissolution profile was studied, as in 3.

RESULTS AND DISCUSSION

The ranges of tablet weight variation (Y_1), friability (Y_2), hardness (Y_3), and disintegration time (Y_4) of DS controlled release tablets prepared from 17 formulations were 1.29–4.27%, 0.05–0.45%, 2.86–5.90 kp, and 1.11–1.88 min, respectively. Their dissolution profiles are demonstrated in Figure 1. Since the ideal dissolution profile for a controlled release tablet should follow zero-order kinetics. Therefore, the zero-order dissolution rate constant (K^0) and the correlation coefficient of linearity of dissolution profile (R^2) were established as criteria in development of DS tablets having optimum controlled release profile. The K^0 and R^2 values of the designed DS controlled release tablet formulations, calculated from their dissolution profiles using linear regression, were 0.099279–0.200047 mg per min and 0.824239–0.951921, respectively. By multiple regression, the equations of Y_1, Y_2, Y_3, Y_4, K^0, and R^2 as functions of the levels of the four independent variables; the compression force level (X_1), the Era-Tab^R level (X_2), the Ac-Di-Sol^R level (X_3), and the magnesium stearate level (X_4), were derived as following.

$$Y_1 = 0.468702X_3 - 0.544521X_2^2 + 2.802536 \quad (r^2 = 0.646648) \quad (1.1)$$

$$Y_2 = -0.151517X_1 + 0.051686X_2 + 0.063388X_1X_2 - 0.072463X_1X_3 \quad (r^2 = 0.922900) \quad (1.2)$$

$$Y_3 = 1.231267X_1 - 0.209941X_1^2 - 0.399998X_3^2 - 0.259956X_4^2 + 5.306513 \quad (r^2 = 0.973461) \quad (1.3)$$

$$Y_4 = 0.130273X_1 - 0.173504X_3 + 0.186893X_1^2 + 0.144381X_4^2 + 1.060854 \quad (r^2 = 0.858690) \quad (1.4)$$

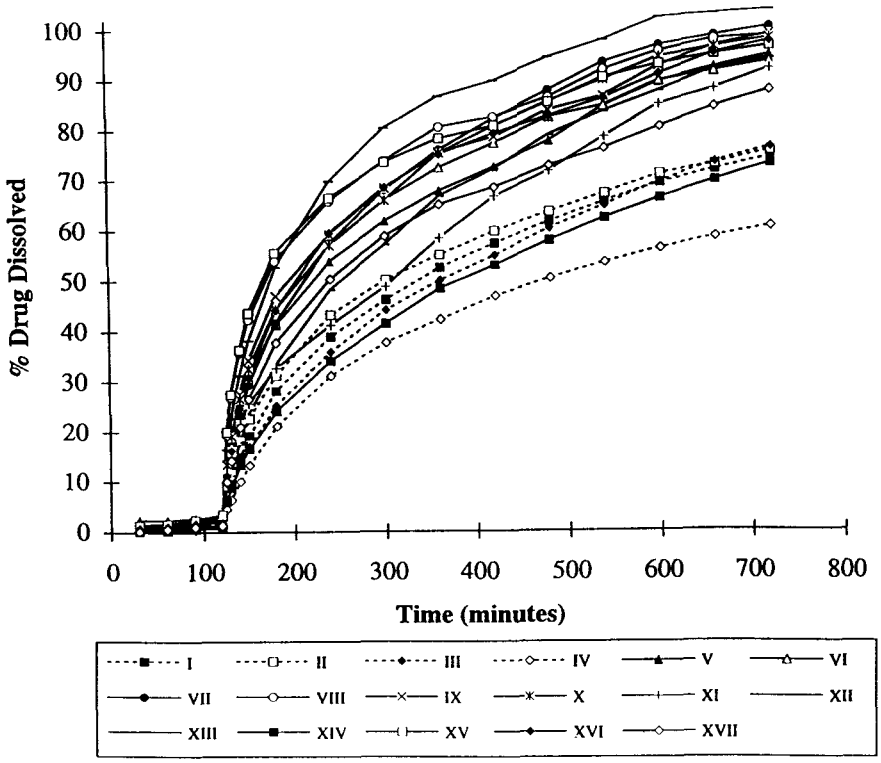

Figure 1. Dissolution profile of DS controlled release tablets prepared from formulation I–XVII.

$$K^0 = 0.025850X_3 + 0.009856X_2X_3 + 0.151641 \quad (r^2 = 0.913295) \quad (1.5)$$

$$R^2 = -0.011483X_1 - 0.020320X_3 - 0.008890X_2X_3 - 0.011330X_1^2 + 0.015385X_2^2 + 0.904841 \quad (r^2 = 0.927520) \quad (1.6)$$

The weight variation, friability, hardness, and disintegration time of the DS tablets prepared from the 17 formulations were within acceptable ranges, therefore the response of interest was focused on tablet dissolution. For diclofenac sodium the ideal K^0 was 0.139 mg per min or 8.33 mg per hr (1).

The influences of X_4 on the studied responses were negligible, therefore any level of magnesium stearate in the range between -1.414 to 1.414 could be chosen. Increasing X_1 caused a positive effect on tablet hardness and negative effects on R^2 value and friability. Hence, the level of compression force was set at the middle level in order to produce the tablets of adequate hardness and low friability while lessening the negative effect of the compression force on R^2 value. In this manner the predetermined levels of X_1 and X_4 both at 0 levels were set.

By setting X_1 and X_4 at the levels of 0 the contour plots of the equations representing the relationship between K^0 or R^2 and the remaining two independent variables could be drawn. Superimposition of the contour plots of K^0 and R^2, (Figure 2), yielded a restricted area which would result in K^0 between 0.137 and 0.141 mg per min and R^2 value of not less than 0.910. Thus an optimum tablet formulation (XVIII) consisting of X_1, X_2, X_3, and X_4, at the levels of 0 (700 psi), 0 (194.8 mg per tablet), -0.5 (6.4 mg per tablet), and 0 (1.6 mg per tablet), was firstly selected for development of DS controlled release tablets.

The optimized tablet formulation yielded the tablet having the weight variation, friability, hardness, disintegration time, K^0, and R^2 of 1.51%, 0.29%, 4.14 kp, 1.83 min, 0.125056 mg per min, and 0.928935, as compared to the predicted values of 2.61%, 0.18%, 5.16 kp, 1.08 min, 0.138735 mg per min, and 0.915020, respectively. However, the observed K^0 was still some different from the predicted K^0.

In order to improve the optimized K^0, the influence of the Ac-Di-Sol^R level (from -1.414 to 1.414 level) on the K^0 while fixing the levels of X_1, X_2, and X_4 at 0 (formulations XIII, XIV, XVII, XVIII) was investigated as expressed by a polynomial equation:

$$K^0 = 0.029456X_3 + 0.010363X_3^2 + 0.137739 \quad (r^2\ 0.999872). \quad (2)$$

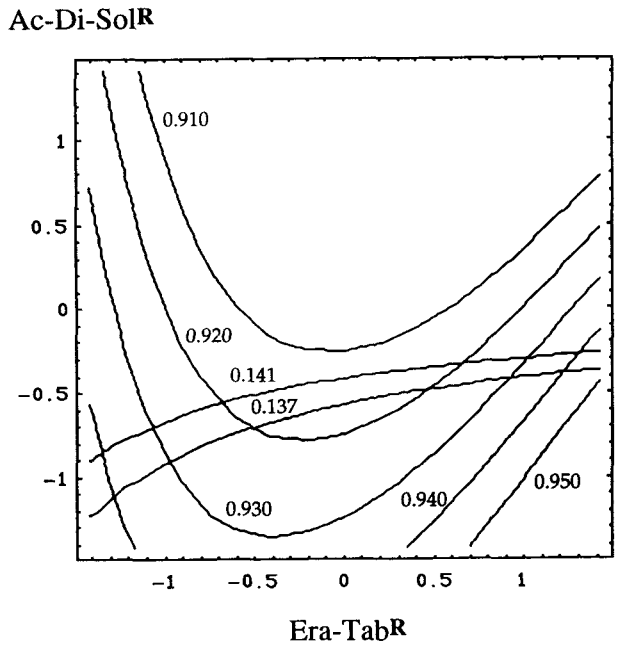

Figure 2. The superimposed contour plot of K^0 and R^2 as function of Era-Tab^R level (X_2) and Ac-Di-Sol^R level (X_3), when fixing compression force level (X_1) and magnesium stearate level (X_4) at 0.

From the polynomial equation, when X_3 was 0 then K^0 would be 0.137739 mg per min, which was very closed to the required K^0 of 0.139 mg per min. Therefore if X_1, X_2, X_3, and X_4 were fixed at 0 level the improved optimum DS controlled release tablets would be achieved. Formulation XVII consisting of X_1 (700 psi), X_2 (194.8 mg per tablet), X_3 (8 mg per tablet), and X_4 (1.6 mg per tablet), all at 0 levels, was selected as the improved optimum DS controlled release tablet formulation. The tablet weight variation, friability, hardness, and disintegration time of the improved optimum DS tablet were 2.50%, 0.26%, 5.26 kp, and 1.21 min, respectively. Figure 3 illustrates the dissolution profiles of the optimized and the improved optimum DS controlled release tablets as compared to that of optimized spray-dried DS controlled release powder. The observed K^0 and R^2 of the improved tablet profile were found to be 0.138213 mg per min and 0.896059 while those of the powder profile were 0.147128 mg per min and 0.928030, respectively. The mechanism of drug release from the improved optimum DS controlled release tablets in pH 6.8 phosphate buffer solution fitted well with Higuchi model rather to zero-order model. The plot between percentage of drug released and square root

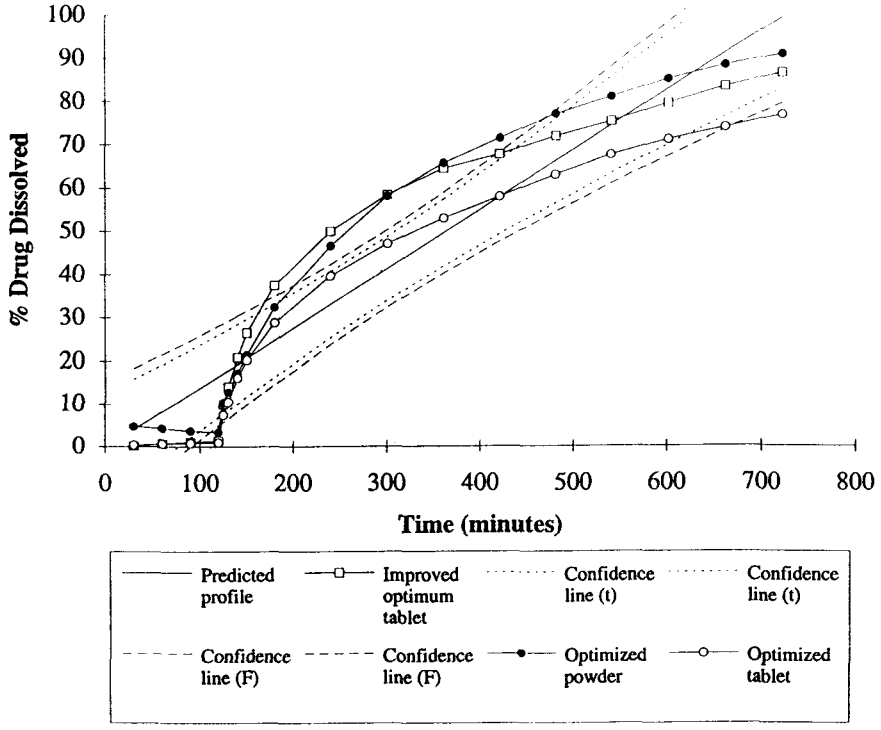

Figure 3. Dissolution profiles of improved optimum DS tablet, optimized DS tablet, and optimized DS solid dispersion powder as compared to predicted dissolution profile using 99% confidence level based on t-value and F-value.

time yielded r^2 of 0.968122 while the plot between percentage of drug released and time gave r^2 of 0.923884.

CONCLUSIONS

By optimization, using the orthogonal central composite design and statistical computer programs, the models representing the tablet physical properties and dissolution characteristics, as functions of compression force and tablet excipient levels, were established. From these models, the optimum conditions of tablet production, which would result in the required tablet properties, can then be located precisely using the superimposed contour plots. In this study the applied optimization strategy was proven to be useful in development of DS controlled release tablet from the DS controlled release solid dispersion powder exhibiting similar optimum dissolution profile.

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