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# Optimization of pH-independent release of nicardipine hydrochloride extended-release matrix tablets using response surface methodology

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**Abstract**

The purpose of this study was to optimize the pH-dependent release of nicardipine hydrochloride extended release formulations by using simultaneously combination two hydrophilic polymers: hydroxypropylmethylcellulose (HPMC) and sodium alginate as retardant and avicel as additive. The constrained mixture experimental design was used to prepare systematic model formulations which were composed of three formulation variables: the content of HPMC ($X_1$), avicel ($X_2$), and sodium alginate ($X_3$). The response surface methodology (RSM) and multiple response optimization utilizing the polynomial equation were used to search for the optimal formulation with specific release rate at different time intervals and to quantify the effect of each formulation variables. The drug release percent at 3, 6 and 12 h were the target responses and were restricted to 10–30% ($Y_{3\,h}$), 40–65% ($Y_{6\,h}$) and not less than 80% ($Y_{12\,h}$), respectively. The results showed that the effect of combination of HPMC and sodium alginate was the most influence factor on the drug release from extended-release matrix tablets. The observed results of $Y_{3\,h}$, $Y_{6\,h}$ and $Y_{12\,h}$ coincided well with the predictions in the RSM optimization technique, indicating it was quite useful for optimizing pharmaceutical formulation. The mechanism of drug release from extended-release matrix tablets was dependent on the added amount of alginate. The release kinetic of drug from HPMC matrix tablets with alginate was followed the zero-order release pattern.


*Keywords:* Extended-release dosage form; Mixture experimental design; Nicardipine response surface methodology; Dissolution

## 1. Introduction

Nicardipine, a dihydropyridine calcium channel antagonist, causes coronary and peripheral vasodilatation by blocking the influx of extracellular calcium across cell membranes. It has been reported that the action of nicardipine was arterioselective and effective for the

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treatment of hypertension, angina pectoris and cerebrovascular disease (Graham et al., 1985; Abernethy and Schwartz, 1988). The bioavailability is very limited about 15–45% and the elimination half-life is also very short about 1 h due to the hepatic biotransformation which often results in significant fluctuation in plasma concentration (Higuchi et al., 1980; Sorkin and Clissold, 1987; Fernandes et al., 2002). Therefore, it was chosen as a model drug for preparation of the extended-release dosage form.

The hydrophilic gel-forming matrix tablets are extensively used for oral extended-release dosage forms due to their simplicity, cost effectiveness and reduction of the risk of systemic toxicity due to dose dumping (Gao and Meury, 1996; Gohel and Amin, 1998). The hydroxypropylmethylcellulose (HPMC) is a pH-independent hydrophilic material, and it can form viscid gel in water, thereby retard the drug release. Therefore, it is widely used to prepare extended-release dosage forms of water-soluble or water-insoluble drugs such as promethazine and acetaminophen because of the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant (Ford et al., 1985; Lahdenpaa et al., 1997; Zuleger and Lippold, 2001; Sako et al., 2002). Hassegawa et al. (1986) reported that it is difficult to prepare a sustained-release dosage form of a drug when its solubility is pH-dependent. Nicardipine hydrochloride is a weak basic drug (p$K_a$ 7.2) which is easily soluble in acidic solution but poorly in alkaline solution. Therefore, the drug release rate should be affected largely by both gastric pH and transit time. In order to overcome the problem of pH-dependent solubility in the development of nicardipine hydrochloride extended-release matrix tablets, the sodium alginate which can swell in acidic solution but does not dissolve, and is soluble in alkali solution was chosen as a copolymer to modify the dissolution pattern in alkaline medium. In addition, some studies (Cressman and Summer, 1971; Uchida et al., 1986; Katori et al., 1991) report insufficient drug absorption from controlled release products in in vivo studies because of the suppression of drug release due to the environment of the colon (small volume of GI fluid and viscous colonic content) in the later stage. Incorporated water-soluble excipients such as polyethylene glycol, alginate and surfactants into the gel-forming matrix can improve the phenomenon of insufficient drug release and/or absorption because these excipients can stimulate the water penetration into the inner parts of the matrix, thus resulting in drug release from matrix (Feely and Davis, 1988; Eddington et al., 1998; Vlachou et al., 2000; Nokhodchi et al., 2002). Avicel is often regarded as one of the best excipients for direct compression (Lahdenpaa et al., 1997). Incorporated avicel into the formulation was shown to increase dissolution rates and compressibility of tablets made by high shear granulation (Li et al., 1996). Therefore, in this study, HPMC and sodium alginate were used as retardant, and the avicel was used to modify the drug release and ensure that most of drug is released in a period time comparable to the gastrointestinal residence time.

In the development of extended-release dosage form, an important issue was to design an optimized pharmaceutical formulation with appropriate dissolution rate in a short time period and minimum trails. For this purpose, a computer optimization technique, based on a response surface methodology (RSM) utilizing polynomial equation and artificial neural networks (ANN) has been widely used (Takayama and Nagai, 1989; Singh et al., 1995; Bouckaert et al., 1996; Karnachi and Khan, 1996; Wu et al., 2001; Huang et al., 2004a). The optimization procedure involved systematic formulations designs to minimize the number of trails, and analyze the response surfaces in order to realize the effect of causal factors and to obtain the appropriate formulations with target goals as well as the acceptable component region as process control conditions in practical preparation. Therefore, the purpose of this study was to prepare the pH-independent release of nicardipine extended-release matrix tablets with target release profiles using RSM and multiple responses optimization utilizing quadratic polynomial equation, and to evaluate the usability of RSM with multiple response optimization technology in development of the nicardipine hydrochloride extended-release dosage forms.

## 2. Materials and methods

### 2.1. Materials

The following reagents were used: nicardipine hydrochloride, *p*-hydroxybenzoate butyl ester, sodium

Table 1
Variables in the mixture design

| Formulation variables | Levels | |
|---|---|---|
| | Low | High |
| $X_1$ = fraction of HPMC in total excipients | 0.10 | 0.15 |
| $X_2$ = fraction of avicel in total excipients | 0.65 | 0.90 |
| $X_3$ = fraction of alginate in total excipients | 0.00 | 0.20 |
| Response variables | Constraints | |
| $Y_{3\,h}$ = percent dissolved in 3 h | $10\% \le Y_{3\,h} \le 30\%$ | |
| $Y_{6\,h}$ = percent dissolved in 6 h | $40\% \le Y_{6\,h} \le 65\%$ | |
| $Y_{12\,h}$ = percent dissolved in 12 h | $80\% \le Y_{12\,h}$ | |

The amount of nicardipine hydrochloride was fixed at 20 mg. The amount of total excipients was fixed at 80 mg. $X_1 + X_2 + X_3 = 1$.

alginate (TCI, Japan), hydroxypropylmethylcellulose (viscosity 4000 grade) (Shin Etsu, Japan), Magnesium stearate (Ajax, Australia), and Avicel PH-101 (Asahi, Japan). All other chemicals and solvents were of analytical reagent grade. The commercial nicardipine immediate release tablets (Yamanouchi) was purchased from local market.

### 2.2. Preparation of nicardipine hydrochloride HPMC matrix tablets

The composition of nicardipine extended release tablets are listed in Table 2. The drug and additives were weighed and mixed well. Water was added to make a wet mass. Then the wet component was granulated through a 40 mesh sieve. The granules were dried in an oven for 8 h at 40 °C, and then blended with 1% of magnesium stearate. Each tablet of 100 mg containing 20 mg nicardipine was compressed using 8 mm diameter flat-faced punches. The upper punch compaction pressure used was 140 kg/cm$^2$.

### 2.3. Determination of the release of nicardipine hydrochloride from HPMC matrix tablet

The U.S.P. paddle method was used for all the in vitro dissolution studies. The simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) with 0.1% Tween 80 were used as a dissolution medium. Tween was used to increase the wetability of water-insoluble drug in the medium. The rate of stirring was 50 rpm. The nicardipine tablets were placed in 900 ml of gastric fluid, intestinal fluid or pH change medium (pH 1.2 for first 2 h, and then change to pH 6.8 for another 10 h). At least six tablets of each formulation were determined. The mean and S.D. of dissolved percent were calculated. The samples were analyzed using a HPLC described in previous study (Huang et al., 2004b).

### 2.4. Data analysis

In the RSM analysis, the responses: the released drug percents at 3, 6, and 12 h of all model formulations were treated by Design-Expert® software. Suitable models for mixture designs consisting of three components include linear, quadratic and special cubic models. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient ($R^2$), adjusted multiple correlation coefficient (adjusted $R^2$), and the predicted residual sum of square (PRESS), proved by Design-Expert® software. Among them, PRESS indicates how well the model fits the data, and for the chosen model it should be small relative to the other models under consideration (Huang et al., submitted for publication).

Linear model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3$$

Quadratic model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3$$

Special cubic model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2\ X_3$$

In order to propose the possible release mechanism, the drug release from HPMC matrix tablets was fitted to the following power model (Ritger and Peppas, 1987).

$$\frac{M_t}{M_\infty} = kt^n$$

where $M_t/M_\infty$ is the fractional drug release percentage at time $t$. The $k$ is a constant related to the properties

of the drug delivery system and $n$ is the diffusional exponent, which characterizes the drug transport mechanism. A value of $n = 0.45$, indicates Case I (Fickian) diffusion, $0.45 < n < 0.89$ indicates anomalous (non-Fickian) diffusion and $n \geq 0.89$ indicates Case-II transport.

## 3. Results and discussion

The dissolution profiles of nicardipine commercial immediate release (IR) tablet and experimental extended release (ER) tablets in simulated gastric (pH 1.2) fluid and simulated intestinal (pH 6.8) fluid are presented in Fig. 1. As expected, the commercial IR tablet showed lower percentage of dissolved drug in intestinal fluid when compared with the gastric fluid. This result was attributed the pH-dependent of solubility of nicardipine hydrochloride (Hassegawa et al., 1986). The dissolution rate of nicardipine/HPMC/avicel (2/1/7) ER matrix tablets was slower than that of commercial IR tablets in pH 1.2 and pH 6.8 medium, showed that the nicardipine ER tablets could be obtained by using HPMC as retardant. But it can seen, the dissolution rate in pH 6.8 medium was too slow, only about 30% drug released at 8 h. In order to increase the drug dissolved percentage in intestinal fluid and prevent the burst effect in gastric fluid, the sodium alginate, which can swell in acidic solution but does not dissolve, and is soluble in alkali solution was chosen as a copolymer to modify the dissolution pattern. It was found that as the content of sodium alginate increased, the drug release rate decreased in pH 1.2 medium and increased in pH 6.8 medium.

In general, an optimal extended-release dosage form must have a minimal burst effect within most of the drug being released in a specific time period. In order to rapidly obtain the optimal nicardipine hydrochloride extended-release matrix tablets with specific release pattern, the RSM utilizing polynomial equation and systemic formulations design such as mixture experimental design were applied in this study. The content of HPMC ($X_1$), avicel ($X_2$), and alginate ($X_3$) were chosen as formulation variables and the drug release percent at 3, 6 and 12 h were selected as response variables to detect the burst effect and ensure complete drug release, shown in Table 1. According to the response requirement and the preliminary experimental result shown in Fig. 1, the levels of excipients was set at HPMC ($X_1$) from 0.1 to 0.15, avicel ($X_2$) from 0.65 to 0.9, and alginate ($X_3$) from 0 to 0.20. The compositions arranged according to mixture experimental design, the responses in pH change medium, and drug release mechanisms evaluated by power equation of all model formulations are summarized in Table 2. The wide variation of response ($Y_{3\,h}$, $Y_{6\,h}$ and $Y_{12\,h}$) indicated

Table 2
The composition, responses and drug release mechanism of model formulations of nicardipine extended release tablets

| Run | $X_1$ HPMC | $X_2$ avicel | $X_3$ alginate | $Y_{3\,h}$ | $Y_{6\,h}$ | $Y_{12\,h}$ | $r$ | $n$ | $k$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.150 | 0.850 | 0.000 | 21.39 | 25.64 | 38.12 | 0.9779 | 0.41 | 13.20 |
| 2 | 0.100 | 0.900 | 0.000 | 31.17 | 41.87 | 54.6 | 0.9856 | 0.40 | 21.39 |
| 3 | 0.125 | 0.775 | 0.100 | 15.83 | 56.42 | 79.29 | 0.9620 | 0.97 | 7.76 |
| 4 | 0.100 | 0.700 | 0.200 | 18.61 | 59.35 | 80.84 | 0.9662 | 0.89 | 9.93 |
| 5 | 0.138 | 0.712 | 0.150 | 18.45 | 56.46 | 81.27 | 0.9765 | 0.93 | 8.94 |
| 6 | 0.100 | 0.700 | 0.200 | 20.72 | 64.00 | 82.14 | 0.9611 | 0.87 | 10.64 |
| 7 | 0.113 | 0.838 | 0.050 | 21.45 | 46.75 | 73.45 | 0.9298 | 0.70 | 12.56 |
| 8 | 0.150 | 0.850 | 0.000 | 23.05 | 27.97 | 38.67 | 0.9749 | 0.35 | 15.59 |
| 9 | 0.133 | 0.800 | 0.067 | 18.71 | 52.98 | 81.35 | 0.9233 | 0.81 | 11.13 |
| 10 | 0.100 | 0.900 | 0.000 | 31.59 | 35.26 | 47.73 | 0.9587 | 0.28 | 22.41 |
| 11 | 0.125 | 0.675 | 0.200 | 20.89 | 60.66 | 92.10 | 0.9737 | 0.94 | 9.41 |
| 12 | 0.125 | 0.675 | 0.200 | 20.57 | 59.54 | 85.26 | 0.9771 | 0.92 | 9.84 |
| 13 | 0.117 | 0.750 | 0.133 | 18.95 | 56.78 | 80.99 | 0.9573 | 0.87 | 10.06 |
| 14 | 0.150 | 0.650 | 0.200 | 19.79 | 59.83 | 86.24 | 0.9798 | 0.97 | 8.83 |

The amount of nicardipine hydrochloride was fixed at 20 mg. The amount of total excipients was fixed at 80 mg. $Y_i$: responses, the drug release percent at 3 h ($Y_{3\,h}$), 6 h ($Y_{6\,h}$), and 12 h ($Y_{12\,h}$). The composition of each run was random and arranged according to the D-optimal model provided Design-Expert® software. Release mechanism fitted by power model: $M_t/M_\infty = kt^n$, $r$, $k$ and $n$ are correlation coefficient, release rate and diffusional exponent, respectively.

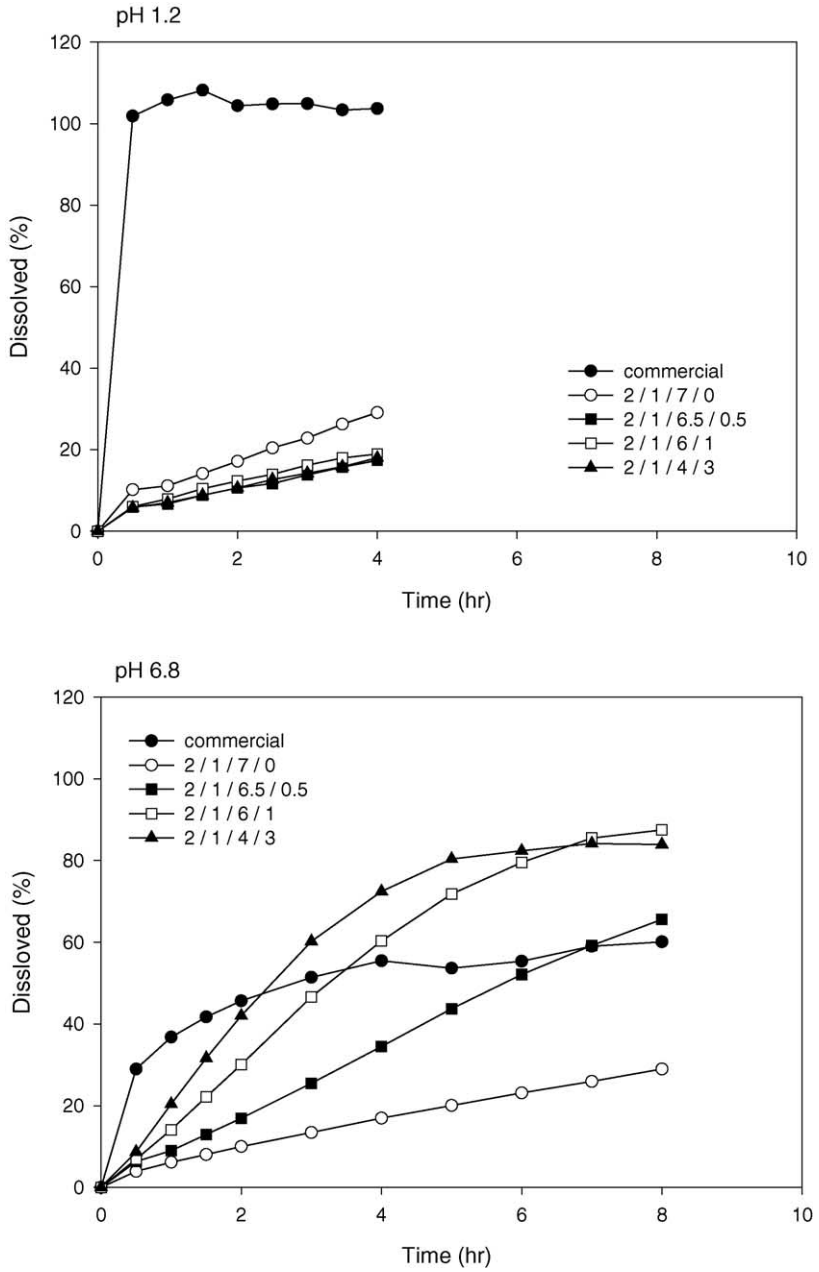


Fig. 1. Dissolution profiles of commercial nicardipine immediate release tablets and experimental 20 mg nicardipine hydrochloride extended-release matrix tablet (drug/HPMC/avicel/alginate) in gastric medium (pH 1.2) and intestinal medium (pH 6.8).

that the factor combinations resulted in different drug release rates. The causal factor and response variables were related using polynomial equation with statistical analysis through Design-Expert® software. As shown in Table 3, the approximations of response values ($Y_{3\,h}$, $Y_{6\,h}$, and $Y_{12\,h}$) based on the quadratic model was most suitable because its PRESS was smallest. The values of the coefficients $X_1$, $X_2$ and $X_3$ are related to the effect of these variables on the response. The contour plots illustrating the simultaneous effect of the causal

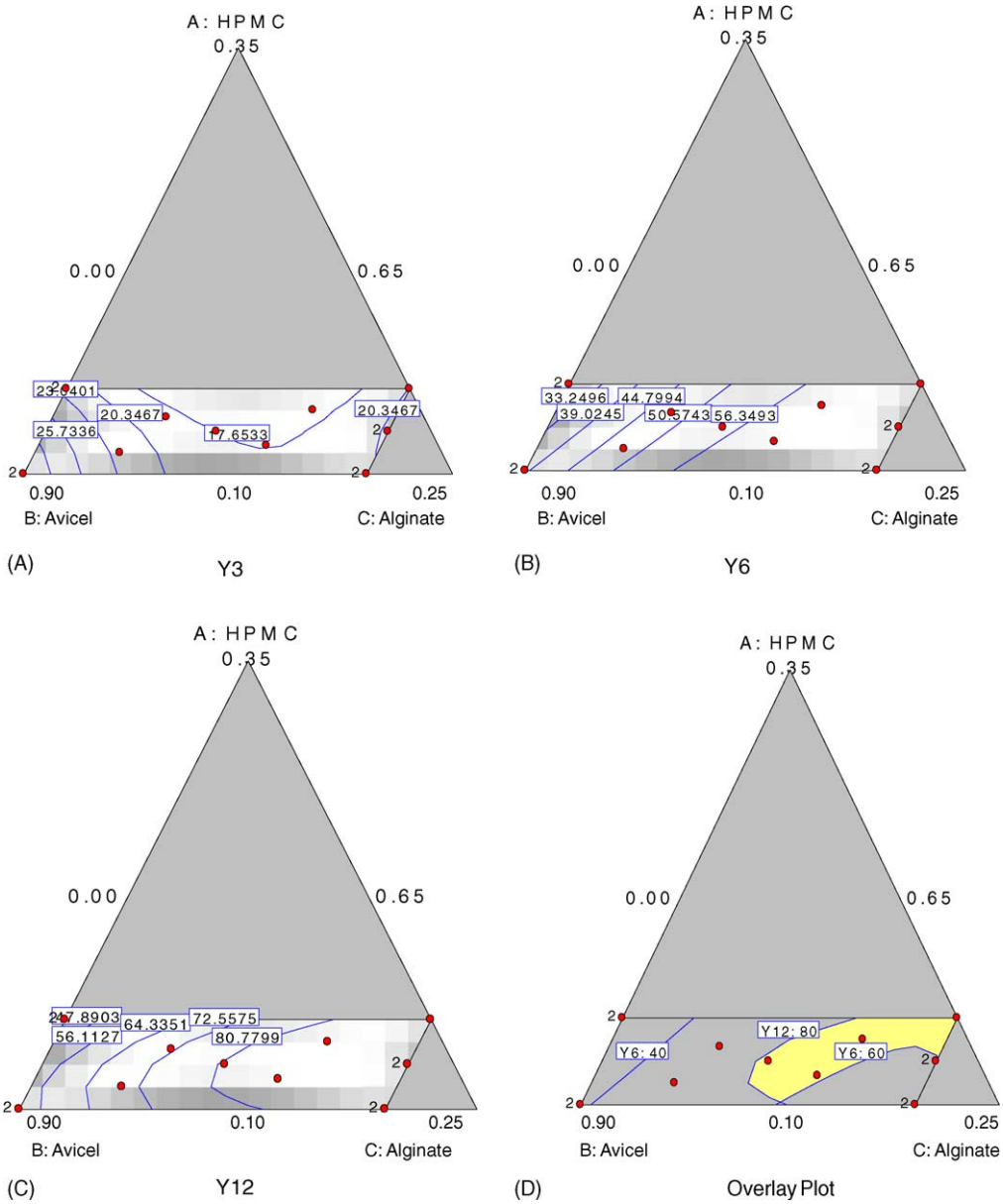


Fig. 2. The triangular-dimensional contour diagrams illustrating the effect of HPMC ($X_1$), avicel ($X_2$) and sodium alginate ($X_3$) on the release of nicardipine hydrochloride from matrix tablets. (A) 3 h drug release percent, (B) 6 h drug release percent, (C) 12 h drug release percent, (D) overlay plot.

Table 3
Optimal regression equation for each response variable

| Model | Coefficient | $Y_{3h}$ | $Y_{6h}$ | $Y_{12h}$ |
|---|---|---|---|---|
| | $b_1(X_1)$ | −62.52 | −12.96 | −526.96 |
| | $b_2(X_2)$ | 31.12 | 38.40 | 52.08 |
| | $b_3(X_3)$ | 24.89 | 55.97 | 73.69 |
| | $b_{12}(X_1X_2)$ | 61.17 | −4.10 | 646.24 |
| | $b_{13}(X_1X_3)$ | 81.46 | 106.18 | 815.22 |
| | $b_{23}(X_2X_3)$ | −39.63 | 54.07 | 69.17 |
| Linear | CV | 15.65 | 10.46 | 13.4 |
| | $R^2$ | 0.5351 | 0.8549 | 0.7629 |
| | Adjusted $R^2$ | 0.4506 | 0.8285 | 0.7189 |
| | PRESS | 204.59 | 489.93 | 1682.55 |
| Quadratic | CV | 5.78 | 6.16 | 7.07 |
| | $R^2$ | 0.9536 | 0.9634 | 0.9536 |
| | Adjusted $R^2$ | 0.9246 | 0.9405 | 0.9246 |
| | PRESS | 56.88 | 232.90 | 788.31 |
| Cubic | CV | 5.76 | 6.42 | 7.54 |
| | $R^2$ | 0.9597 | 0.9652 | 0.9539 |
| | Adjusted $R^2$ | 0.9251 | 0.9354 | 0.9143 |
| | PRESS | 77.34 | 1107.86 | 2783.82 |

factors on individual and combined response variable are represented in Fig. 2A–C. This expression gives an insight into the effect of the different independent variables (response). A positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response. The larger coefficient means the causal factor has more potent influence on the response. As shown in Table 3, the coefficient of $X_1X_3$ was largest, showed that the effect of combination of HPMC and alginate was the main influence factors on the drug release from ER matrix tablets in the whole stage dissolution. The value of coefficients of $X_2$ was less than that of $X_1$, $X_3$, $X_1X_2$ and $X_2X_3$, indicated that the influence of avicel ($X_2$) was less than that of HPMC ($X_1$), alginate ($X_3$), and the interaction effect of $X_1X_2$ and $X_2X_3$, but it was found that the influence extend of avicel ($X_2$) at later stage was higher than early stage. This result was similar to earlier studies (Vlachou et al., 2000; Nokhodchi et al., 2002) which reported that the hydrophilic material can stimulate the water penetration into the inner parts of the matrices, thus result the drug release from matrix in the later stage.

An optimal extended-release dosage form must have a minimal burst effect within most of the drug being released in a specific time period. Therefore, the range of responses of ER matrix tablets were restricted to $10\% < Y_{3h} < 30\%$; $40\% < Y_{6h} < 65\%$; $80\% \leq Y_{12h}$ (Table 1). Under these conditions, these three responses were then combined to determine an all over optimum region. Fig. 2D shows an acceptable region met the requirement of these responses. An optimum response was found with $Y_{3h}$, $Y_{6h}$, and $Y_{12h}$ of 17.53%, 56.97% and 83.72% at $X_1$, $X_2$ and $X_3$ values of 0.12, 0.77 and 0.11, respectively. To verify these values, the optimum formulation was prepared according the above values of the factors and subjected to the dissolution test. As shown in Table 4, the predicted and observed values of $Y_{3h}$, $Y_{6h}$, and $Y_{12h}$ of the optimum formulation showed no significant difference (*t*-test, $p > 0.05$) and the predicted error of $Y_{3h}$, $Y_{6h}$, and $Y_{12h}$ were below 6%, indicating that the RSM optimization technique was quite useful for optimizing nicardipine hydrochloride extended-release matrix tablets.

Table 4
The predicted and observed response variables of optimal nicardipine hydrochloride ER matrix tablets

| | $Y_{3h}$ | $Y_{6h}$ | $Y_{12h}$ |
|---|---|---|---|
| Predicted | 17.53 | 56.97 | 83.72 |
| Observed | $16.75 \pm 2.18$ | $55.96 \pm 4.63$ | $88.65 \pm 3.23$ |
| Predicted error (%) | −4.45 | −1.77 | 5.89 |

Predicted error (%) = (observed value − predicted value)/predicted value × 100%.

The release mechanisms of nicardipine from predicted HMPC matrix tablets were evaluated on the basis of a power model (Ritger and Peppas, 1987). As shown in Table 2, the correlation coefficients ($r$) of all HPMC tablets were above 0.9233 ($p < 0.01$). The values of exponent constants ($n$) were from 0.28 to 0.97 indicting that the mechanism of drug release from HMPC matrix tablets was affected by the content of alginate. The $n$ values of formulations without alginate were below 0.45, indicated that the release mechanism were followed the Fickian diffusion with a burst effect. On the contrary, the drug release formulations with high level of alginate showed a profile more close to a zero-order constant release profile up to above 80% drug release ($n$ value close to 1) (Fig. 3).

It was concluded that the response surface methodology and multiple response optimization utilizing polynomial equation could be applied to solve an optimization problem in design extended-release matrix tablets. The pH-independent releases of nicardipine

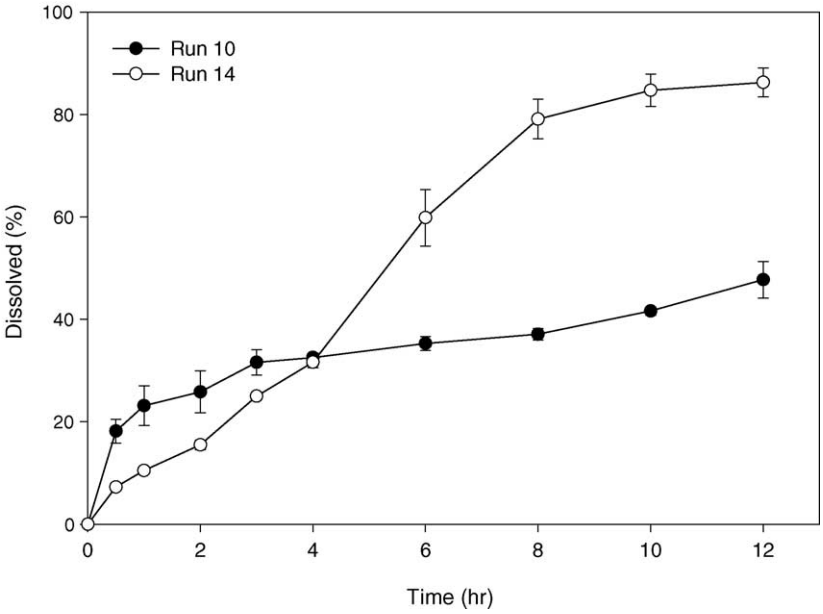


Fig. 3. Dissolution profiles of nicardipine hydrochloride extended-release matrix tablet with and without sodium alginate in pH change medium.

hydrochloride extended release matrix tablets with satisfactory release characteristics were successfully prepared with HPMC, sodium alginate and avicel.

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