Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 309 (2006) 163–170
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Hydrophilic matrices: Application of Placket–Burman screening design to model the effect of POLYOX–carbopol blends on drug release

Yasser El-Malah, Sami Nazzal *

Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of Louisiana at Monroe, Monroe, LA 71209-0497, United States

Received 28 September 2005; received in revised form 23 November 2005; accepted 25 November 2005
Available online 4 January 2006

Abstract

The aim of the present study was to screen the effect of seven factors – POLYOX molecular weight (X_1) and amount (X_2); carbopol (X_3), lactose (X_4), sodium chloride (X_5), citric acid (X_6); compression pressure (X_7) – on (1) the release of theophylline from hydrophilic matrices, demonstrated by changes in dissolution rate, and (2) their impact on the release exponent [n] indicative of the drug transport mechanism through the diffusion matrix. This objective was accomplished utilizing the Placket–Burman screening design. Theophylline tablets were prepared according to a 7-factor–12-run statistical model and subjected to a 24-h dissolution study in phosphate buffer at pH 7.2. The primary response variable, Y_4, was the cumulative percent of theophylline dissolved in 12 h. The regression equation for the response was $Y_4 = 66.2167 - 17.5833X_1 - 3.3833X_2 - 9.366X_3 - 1.1166X_4 - 0.6166X_5 + 2.6X_6 - 2.783X_7$. This polynomial model was validated by the ANOVA and residual analysis. The results showed that only two factors (X_2 and X_3) had significant effect (p-value < 0.10) on theophylline release from the hydrophilic polymer matrix. Factors (X_2 and X_7) had significant effect (p-value < 0.10) on [n], the exponent.

Keywords: Theophylline; Hydrophilic polymer matrix; Placket–Burman; Screening; Controlled release; Dissolution

1. Introduction

Asthma, a chronic inflammatory disease of the central and peripheral lung airways, afflicts more than 15 million people in the United States (Mannino et al., 1998; Busse and Lemanske, 2001). Theophylline is a prescription drug with a long history as an asthma medication. As one of the first long-term bronchodilators, it has been used to treat respiratory disorders such as bronchitis and chronic obstructive pulmonary disease (COPD). In recent years, theophylline had fallen out of favor with some physicians because of concerns about the danger of toxicity from having too much of the drug in the bloodstream. However, new discoveries about the medication's effects on inflammation and immune function related to asthma have renewed interest in theophylline (Hansel et al., 2004).

Theophylline is available in a variety of dosage forms. While extended-release forms of the medication have made it somewhat easier to ensure a constant drug plasma level, a treatment based on theophylline controlled-release dosage form would not be optimal (Bussemer et al., 2001). Several diseases and body functions, such as bronchial asthma show distinct daily fluctuation. Many investigations demonstrated the effect of circadian rhythms on the incidence and occurrence of bronchial asthma (Robertson et al., 1990; Fitzpatrick et al., 1991; Weersink et al., 1997; Bender and Annett, 1999; Diette et al., 2000). Dethlefsen and Repges (1985), for example, reported a sharp increase in the incidence of asthmatic attacks during the early morning hours, with a maximum occurring at 4 a.m.

As a result of these investigations, there was a growing interest among clinicians in drug delivery systems that tailor drug release to the circadian pattern of the disease. A therapeutic scheme that gives consideration to diurnal variation in the prevalence of asthmatic symptoms should be more effective. In order to achieve this goal, it is necessary to modify current extended-release dosage forms into chrono-relevant drug delivery platforms. A first step in this process is to illustrate how formulation and process variables could alter drug release patterns.

* Corresponding author. Tel.: +1 318 342 1726; fax: +1 318 342 1737.
E-mail address: nazzal@ulm.edu (S. Nazzal).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.11.032

Numerous design variations have been proposed to prepare extended-release dosage forms. Polymer-based hydrophilic matrices are considered one of the more attractive approaches to achieve controlled drug delivery. Several studies reported the impact of polymer concentration, blend consistency, diluents, osmotic agents, and processing variables such as compression force on the physicochemical properties of hydrophilic matrices (Kim, 1994; Khan and Jiabi, 1998; Zaghloul et al., 2001; Varma et al., 2004). Nevertheless, the ability to utilize formulation and process variables to modulate drug release from the matrices was not adequately addressed.

Drug release from hydrophilic matrices rely on balanced swelling and erosion of the polymer, thereby providing both Fickian [$n \sim 0.5$] or non-Fickian release kinetics [$0.5 < n < 1$] (Conte et al., 1993; Kim, 1994; Yang and Fassihi, 1996). [n] is defined as the release exponent indicative of the transport mechanism and could be estimated from the following model (Korsmeyer et al., 1983; Peppas and Sinclair, 1983):

$$\log \frac{M_t}{M_\infty} = \log K + n \log t$$

where M_t/M_∞ is the fractional drug released, t the release time, K the constant, and n is the release exponent indicative of the release mechanism.

Data reported in this study address the argument whether modification in formulation or process parameters during the preparation of hydrophilic matrices have an impact on the rate and profile of drug release. Therefore, the objective of this study was to screen the effect of seven factors – POLYOX concentration and molecular weight; carbopol, lactose, sodium chloride, citric acid concentrations; compression pressure – on (1) the release of theophylline from hydrophilic matrices demonstrated by changes in the dissolution rate, and (2) their impact on the release exponent [n] indicative of the drug transport mechanism through the diffusion matrix.

2. Materials and method

2.1. Materials

Theophylline was a gift from the BASF Corp. (Mount Olive, NJ). Polyethylene oxide (POLYOX) WSR 205 and 303—NF grades were supplied by DOW chemical company (Midland, MI). Carbopol 71 NF was provided by Noveon Inc. (Cleveland, OH). Pharmatose, DCL 14 was obtained from DMV International (Netherlands). Chemicals and raw materials were used as received without further processing.

2.2. Experimental design

Screening designs are commonly used when little is known about a system or process. These designs, in general, are a fractional factorial of a 2^n design that estimates main effects. They can identify main factors from a large number of suspected contributor factors for the desired response variables. Therefore, these designs are extremely useful in preliminary studies where the aim is to identify formulation variables that can be fixed or eliminated in further investigation. The Placket–Burman factorial design was employed in this study to correlate dependent and independent variables using the following polynomial model:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_4 + \cdots + A_nX_n$$

where Y is the response, A_0 the constant, and A_1–A_n are the coefficients of the response values. The Placket–Burman design analyzes the input data and presents a rank ordering of the variables with magnitude of effect, and designates signs to the effects to indicate whether an increase in factor value is advantageous or not (Murray, 1994).

2.3. Release exponent estimation

Release exponent (n) values were estimated by fitting dissolution data to the following Peppas model (Korsmeyer et al., 1983; Peppas and Sinclair, 1983) using JMP IN statistical software, Version 5 (SAS Institute Inc., NC):

$$\log \frac{M_t}{M_\infty} = \log K + n \log t$$

These values provide a numerical estimation of the drug transport mechanism. When [n] approximates 0.5, drug release is governed by the square root of time kinetics where drug diffusion is accomplished via fluid-filled channels (Jantzen and Robinson, 2002). When [n] equals to 1, the mechanism of drug transport is governed by diffusion via the polymer layer itself, which is characterized by a constant drug release rate (zero-order release). The third case, when $0.5 < [n] < 1$, indicates an anomalous drug release mechanism.

2.4. Tablet preparation

Tablet ingredients, as defined by the statistical design, along with theophylline were passed through a standard US sieve number 22 and mixed in a Turbula blender (T2A No. 690994, Switzerland) for 10 min. Blends were accurately weighed and manually fed into a single-station tablet press (Enerpac press model MTCM-1, New Brunswick, NJ). Tablets were compressed at the specified compression force using 10.3-mm concave-faced punches. Each tablet contained 100 mg of theophylline.

2.5. Dissolution studies

Tablet batches were subjected to a dissolution study at $37 \pm 0.5\,^\circ$C. Dissolution experiments were performed using dissolution apparatus II (paddle method) at 50 rpm in 900 mL of pH 7.2 phosphate buffer (VK 7000, Varian Inc., Cary, NC). Samples (3 mL) were withdrawn at predetermined time intervals, filtered and analyzed spectrophotometrically at 270 nm (Cary 50 probe UV spectrophotometer, Varian Inc.). Controlled-dissolution experiments showed no interferences in the UV absorption due to excipients. Samples were replaced with fresh dissolution medium (3 mL). Experiments were performed in triplicates, unless otherwise specified.

Table 1
Factors in the Placket–Burman screening design

	Low level	High level
Independent factors		
X_1: POLYOX molecular weight	6×10^5	7×10^6
X_2: POLYOX amount (mg)	100	300
X_3: carbopol amount (mg)	0	50
X_4: lactose amount (mg)	0	100
X_5: sodium chloride amount (mg)	0	20
X_6: citric acid amount (mg)	0	5
X_7: compression force (lb)	1000	5000
Dependent factors		
Y_1: time to 50% release		
Y_2: n value		
Y_3: percent amount released in 6 h		
Y_4: percent amount released in 12 h		

Table 3
Placket–Burman screening design randomized runs and responses

Formula	Y_1	Y_2	Y_3	Y_4
1	10.5	0.67	34.2	54.1
2	12.8	0.72	27.8	41.6
3	4.2	0.66	79.3	100.5
4	10.4	0.8	31.4	67
5	12	0.69	26.9	46.5
6	8.9	0.77	32.9	67.4
7	10.5	0.72	28.7	52.4
8	7.5	0.79	46.2	94.3
9	11.4	0.68	27.7	49.4
10	8.4	0.73	36	70.8
11	11.4	0.67	32.5	47.8
12	1.3	0.49	102.8	102.8

3. Results and discussion

3.1. Statistical design and analysis

The Placket–Burman screening design was used in the present study to evaluate the main effects of seven independent variables. The levels of dependent and independent variables evaluated in this study are listed in Table 1. The level of independent variables was identified in preliminary experiments. While the Placket–Burman design does not evaluate the interaction terms, it considerably reduces the number of experiments that are required to evaluate the main effects. A 7-factor–12-run Placket–Burman screening design at two levels was generated using STATGRAPHICS statistical experiment design software (Table 2). Responses estimated in the present work were Y_1 [time to 50% release], Y_2 [n value], Y_3 [percent amount released in 6 h], and Y_4 [percent amount released in 12 h]. Responses and their magnitude for each of the 12 experiments are given in Table 3.

Polynomial equations were generated for each response [Y_1–Y_4]. This was critical to understand the mathematical relationship between independent and dependent variables. Polynomial equations for responses Y_1–Y_4 are listed in Table 4.

The relationship between study variables and the response Y_4 (percent of drug released in 12 h) is given by the following polynomial equation:

$$Y_4 = 66.22 - 17.58X_1 - 3.38X_2 - 9.37X_3 - 1.12X_4 - 0.62X_5 + 2.60X_6 - 2.78X_7$$

The regression coefficient obtained for Y_4 was 0.98, which indicates that the model as fitted explains 98% of the variability around the mean. The magnitude and direction of the factor coefficient in the above equation explains the nature of the effect of factors (X_1–X_7) on the response Y_4 [percent drug released in 12 h]. Factors with coefficients of greater magnitude show a high effect on the response. The concentration of citric acid (X_6) was the only factor with a positive effect on the response, whereas the remaining factors (X_1–X_5 and X_7) had a negative effect on the response. The effect of factors on the response is further elucidated in subsequent sections.

Using analysis of variance (ANOVA), the significance (p-value < 0.10) of the ratio of mean square variation due to regression coefficient and residual error was tested. The calculated F-value for factors [POLYOX molecular weight] and [carbopol amount] are greater than the critical value (3.98), which indicates a significant effect of the two factors on the response Y_4 [percent of drug released in 12 h]. The analysis of variance of the model parameters for response Y_4 are shown in Table 5.

Table 2
Placket–Burman screening design with seven variables (randomized runs)

Formula	POLYOX molecular weight	POLYOX (mg)	Carbopol (mg)	Lactose (mg)	Sodium chloride (mg)	Citric acid (mg)	Compression force (mg)
1	7×10^6	100	0	0	20	5	5000
2	7×10^6	100	50	0	0	0	5000
3	6×10^5	100	0	0	0	0	1000
4	6×10^5	300	50	0	20	0	1000
5	7×10^6	300	50	0	20	5	1000
6	6×10^5	300	50	100	0	5	5000
7	7×10^6	300	0	100	20	0	5000
8	6×10^5	300	0	0	0	5	5000
9	7×10^6	300	0	100	0	0	1000
10	6×10^5	100	50	100	20	0	5000
11	7×10^6	100	50	100	0	5	1000
12	6×10^5	100	0	100	20	5	1000

Table 4
Regression equations of the fitted models

$Y_1 = 9.10833 + 2.325X_1 + 1.00833X_2 + 1.54167X_3 - 0.45833X_4 - 0.25833X_5 - 0.508333X_6 + 0.65833X_7$
$Y_2 = 0.699167 - 0.0075X_1 - 0.0425X_2 - 0.030833X_3 - 0.0225X_4 - 0.01583X_5 + 0.0191667X_6 - 0.0341667X_7$
$Y_3 = 42.2 - 12.5667X_1 - 9.9X_2 - 10.95X_3 + 1.2333X_4 + 1.1333X_5 + 3.71667X_6 - 7.9X_7$
$Y_4 = 66.2167 - 17.5833X_1 - 3.3833X_2 - 9.366X_3 - 1.1166X_4 - 0.6166X_5 + 2.6X_6 - 2.783X_7$

Table 5
Analysis of variance for Y_4

Source	Sum of squares	d.f.	Mean square	*F*-ratio	*p*-Value
X_1	3710.08	1	3710.08	79.82	0.0009
X_2	137.36	1	137.36	2.96	0.1607
X_3	1052.81	1	1052.81	22.65	0.0089
X_4	14.963	1	14.963	0.32	0.6008
X_5	4.563	1	4.563	0.1	0.7697
X_6	81.12	1	81.12	1.75	0.257
X_7	92.963	1	92.963	2	0.2302
Residual	185.927	4	46.4817		
Total (corrected)	5279.8	11			

Standard deviation of the residuals = 6.8. Explained variation about the mean = 96.4. Mean absolute error = 3.36. Confidence that the regression equation predict the observed values better than the mean = 98.2.

Table 6
Analysis of variance for Y_2

Source	Sum of squares	d.f.	Mean square	*F*-ratio	*p*-Value
X_1	0.000675	1	0.000675	0.24	0.6524
X_2	0.021675	1	0.021675	7.58	0.0512
X_3	0.0114083	1	0.0114083	3.99	0.1164
X_4	0.006075	1	0.006075	2.13	0.2186
X_5	0.0030083	1	0.0030083	1.05	0.3629
X_6	0.0044083	1	0.0044083	1.54	0.2821
X_7	0.0140083	1	0.0140083	4.90	0.0912
Residual	0.011433	4	0.00285833		
Total (corrected)	0.0726917	11			

Standard deviation of the residuals = 0.053463. Explained variation about the mean = 84.2715. Mean absolute error = 0.0252778. Confidence that the regression equation predict the observed values better than the mean = 91.7.

The regression coefficient obtained for Y_2 [n value] was 0.91. The analysis of variance of the model parameters is given in Table 6. The test indicates significant (p-value < 0.10) effect of POLYOX amount (X_2) and compression force (X_7) on the response Y_2. The correlation between study factors and the response Y_2 is given by the following polynomial equation:

$$Y_2 = 0.70 - 0.01X_1 - 0.04X_2 - 0.03X_3 - 0.02X_4 - 0.02X_5 + 0.02X_6 - 0.03X_7$$

Predicted values of Y_2 [n value] and Y_4 [percent of drug released in 12 h] could be obtained for each of the 12 experiments by substituting the values of X_1–X_7 in the polynomial equations. Observed and predicted values, given in Table 7, were found to be in close agreement, which further validates the suitability of the model.

3.2. Effect of study factors on theophylline dissolution and release exponent [n]

Dissolution profiles of formulations 1–6 and 7–12 are shown in Figs. 1 and 2, respectively. The percent of theophylline released at the end of 12 h ranged between 41.6% (formulation 2) and 100% (formulation 12). Release exponent [n] values varied from 0.49 to 0.80. The effect of formulation and process variables is further outlined in the following sections.

3.2.1. Effect of POLYOX molecular weight (X_1)

The effect of POLYOX concentration and molecular weight, at mid-level of the remaining factors, on Y_4 [percent amount released in 12 h] is shown in Fig. 3. At low loading level, increasing POLYOX molecular weight from 6×10^5 to 7×10^6 resulted in decreasing the percent amount of theophylline released from about 87 to 53%. At high levels of POLYOX, the percent of theo-

Table 7
Observed and predicted values of the responses (Y_4 and Y_2)

Formula	Y_4			Y_2		
	Observed value	Predicted value	Residual	Observed value	Predicted value	Residual
1	54.1	61.7	7.6	0.67	0.64	−0.03
2	41.6	39	−2.6	0.72	0.771	0.051
3	100.5	98.4	−2.1	0.66	0.656	−0.004
4	67	71.7	4.7	0.8	0.771	−0.029
5	46.5	41.7	−4.8	0.69	0.718	0.028
6	67.4	70.3	2.9	0.77	0.788	0.018
7	52.4	47.5	−4.9	0.72	0.718	−0.002
8	94.3	91.3	−3	0.79	0.771	−0.019
9	49.4	54.3	4.9	0.68	0.681	0.001
10	70.8	70.7	−0.1	0.73	0.71	−0.02
11	47.8	47.5	−0.3	0.67	0.62	−0.05
12	102.8	100.2	−2.6	0.49	0.541	0.051

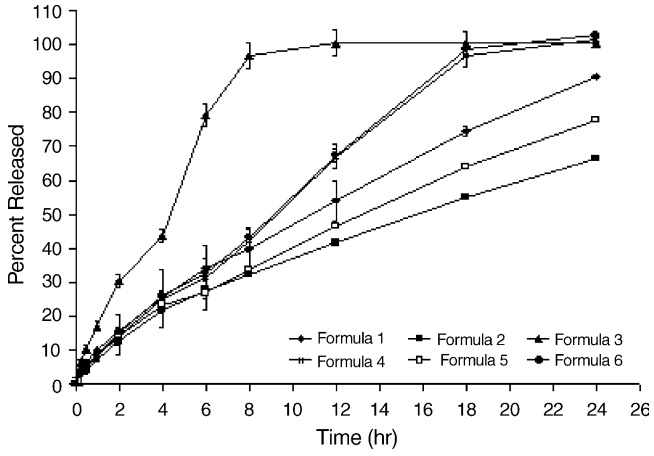

Fig. 1. Dissolution profile of theophylline tablet formulations (1–6) in pH 7.2 phosphate buffer media.

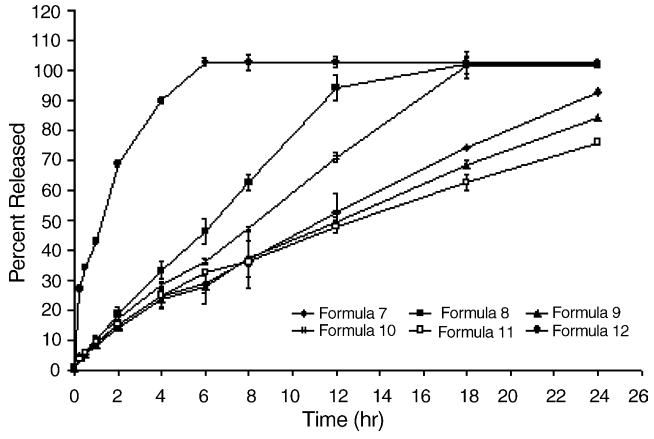

Fig. 2. Dissolution profile of theophylline tablet formulations (7–12) in pH 7.2 phosphate buffer media.

phylline released decreased from approximately 80 to 45% with increasing POLYOX molecular weight from 6×10^5 to 7×10^6, respectively. The effect of molecular weight on theophylline release could be explained as follows. Water imbibition causes the polymer to swell and results in decreased polymer concentration and increased macromolecule mobility (Siepmann et al., 2002). On a molecular level, the snake-like motion of the polymer chains, which is caused by water imbibition, permanently changes the structure of the network. Within the network, entangled polymer chains can either disentangle or modify their entanglement configuration, while disentangled polymer chains can entangle (Siepmann et al., 2002).

Water diffusion into the matrix results in a destruction of the polymer network. Once the macromolecules are disentangled, the polymer chains diffuse through the unstirred layer surrounding the tablet, which is characterized by a distinct polymer concentration gradient. With increasing polymer molecular weight, the degree of entanglement of the macromolecules increases. Thus, the critical water concentration above which disentanglement occurs increases (Ju et al., 1995, 1997). In addition, the diffusion coefficient of the disentangled polymer chains through the unstirred layer surrounding the tablet decreases with increasing molecular weight (Fan and Singh, 1989; Ju et al., 1995, 1997). With decreasing polymer molecular weight, the degree of entanglement of the macromolecules decreases. Thus, the mobility of the polymer chains on water imbibition increases according to the free volume theory of diffusion. The probability for a diffusing molecule to jump from one cavity into another consequently increases (Fan and Singh, 1989).

Increase in chain mobility at lower molecular weights correlates well with the data observed in this study and explains the increase in drug release. While POLYOX molecular weigh has an apparent effect on the cumulative amount of theophylline released per unit time, it had insignificant effect on the mechanism of drug release. The effect of POLYOX molecular weight on the release exponent indicative of the transport mechanism [n] is given in Table 5. All [n] values were calculated using the following model (Korsmeyer et al., 1983; Peppas and Sinclair, 1983):

$$\log \frac{M_t}{M_\infty} = \log K + n \log t$$

As shown in Fig. 4, [n] values ranged from 0.73 to 0.75 at low and high POLYOX molecular weights, respectively, which indicates that drug release from the hydrophilic matrices follows an anomalous drug release pattern.

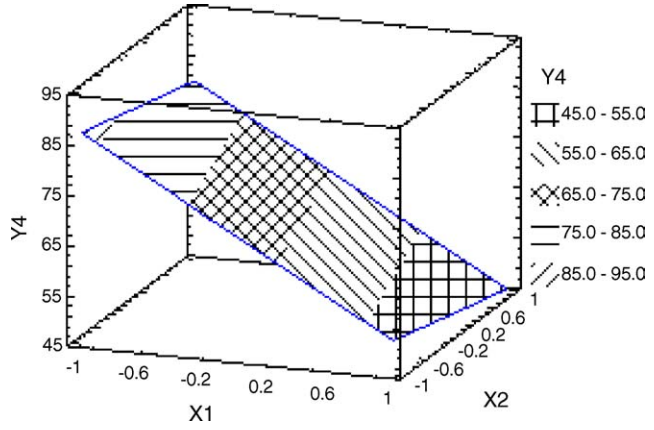

Fig. 3. Response surface plot showing the effect of independent variables, POLYOX molecular weight (X_1) and POLYOX amount (X_2) on response Y_4.

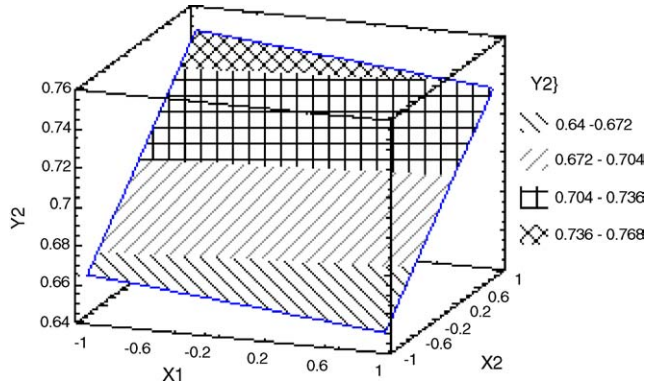

Fig. 4. Response surface plot showing the effect of independent variables, POLYOX molecular weight (X_1) and POLYOX amount (X_2) on response Y_2.

3.2.2. Effect of POLYOX amount (X_2)

At low level of POLYOX molecular weight and mid-levels of the remaining factors, increasing POLYOX content per tablet from 100 to 300 mg decreased the percent of theophylline released from 53 to 45% (Fig. 3). Apparently, as the amount of POLYOX increased, the number of entangling polymer chains and consequently entrapment of the drug inside the polymer network increased, which should cause a delay in drug diffusion from the matrix. This effect, however, was statistically insignificant. On the other hand, the amount of POLYOX per tablet had a significant effect on the release exponent [n], p-value < 0.10. Increasing the amount of POLYOX from 100 to 300 mg per tablet increased the [n] values from 0.65 to 0.74. Increasing the amount of POLYOX, and thereby matrix-to-drug ratio, resulted in decreasing the fluid-filled channels through which the drug may diffuse and increasing the transpolymer-diffusional pathway out the matrix. Fluid-filled channels are characteristic of the Fickian square root of time release pattern whereas transpolymer diffusion is pertinent to the anomalous drug release where $n > 0.5$.

3.2.3. Effect of carbopol amount (X_3)

Carbopols are high molecular weight, cross-linked, acrylic acid-based polymers. They contain 56–68% of carboxylic acid (–COOH) groups (Kibbe, 2000). In a phosphate buffer at pH 7.2, the carboxylic groups of the polymer are highly dissociated. The repulsion between the negatively charged carboxyl groups causes uncoiling and expansion of molecules and results in gel formation. The formed gel consists of closely packed swollen particles, which delay drug release from the matrices. This explains the significant effect of carbopol amount on the release rate of theophylline. By increasing the concentration of carbopol from 0 to 50 mg per tablet, the gel layer at the tablet core–water interface increased in thickness, resulting in decreased drug released after 12 h from about 79 to 54% (Fig. 5). These findings are in agreement with previously reported studies on the effect of carbopol on drug release (Khan and Jiabi, 1998). Carbopol, however, had an insignificant effect on the mechanism of drug release. At low level of POLYOX amount and mid-level

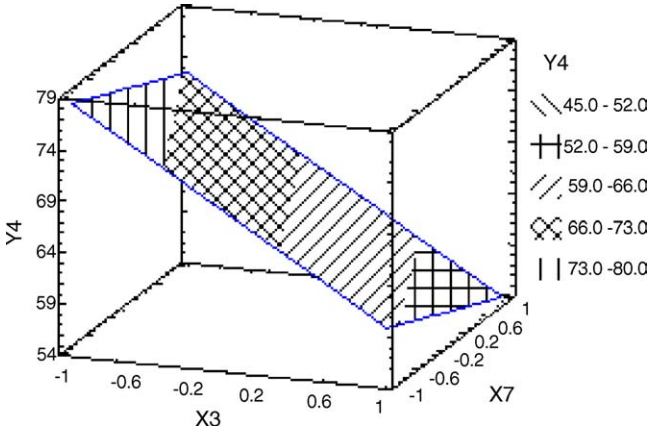

Fig. 5. Response surface plot showing the effect of independent variables, carbopol amount (X_3) and compression force (X_7) on response Y_4.

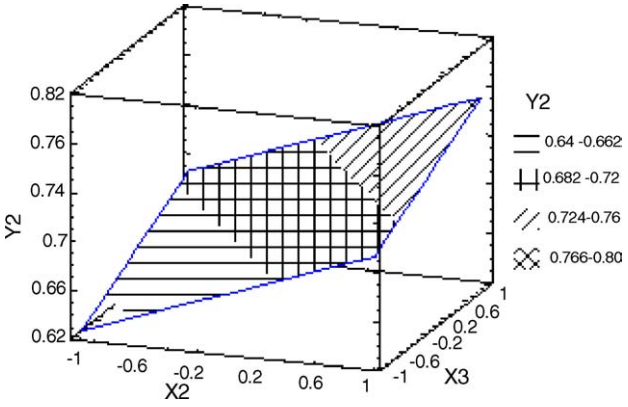

Fig. 6. Response surface plot showing the effect of independent variables, carbopol amount (X_3) and POLYOX amount (X_2) on response Y_2.

of other factors, [n] varied from 0.62 to 0.66 at low and high carbopol concentrations, respectively (Fig. 6).

3.2.4. Effect of lactose (X_4)

Lactose had an insignificant effect on both responses (p-value > 0.10, [0.22 for Y_2 and 0.60 for Y_4]). The presence of water-soluble lactose, however, had a marginal positive effect on Y_4 [percent drug released in 12 h] as it facilitated formation of channels through the polymer matrix, which enhanced water penetration and drug release. Similar observations on the effect of water-soluble excipients on drug release from hydrophilic matrices were reported in the literature (Khan and Jiabi, 1998).

3.2.5. Effect of electrolyte concentration (X_5)

Electrolyte concentration showed a negative effect on drug release. This effect, however, was insignificant on both responses Y_2 [n value] and Y_4 [percent drug released in 12 h]. At the concentration levels used in this study, an electrolyte present within the polymer matrix competes for water molecules, which dehydrates the polymer and decreases the solubility of the incorporated drug. Consequently, this results in decreased drug release (Pillay and Fassihi, 2001). On the other hand, at relatively higher concentrations beyond those evaluated in this study, a monovalent salt like sodium reduces the swelling of polyacrylic acids (Khan and Jiabi, 1998).

3.2.6. Effect of citric acid (X_6)

Citric acid was added to the formulations in an attempt to modulate the micro-environmental pH, which can affect carbopol swelling capacity and consequently drug release. Data show that increasing the citric acid amount from zero to 5 mg per tablet resulted in an insignificant increase in the percent of theophylline released after 12 h. In addition to modulating micro-environmental pH, increased drug release could be due to the water solubility of citric acid and its ability to form channels within the polymer matrix. Citric acid had an insignificant effect on the release exponent [n] (Table 5).

3.2.7. Effect of compression force (X_7)

Compression force had an insignificant effect on Y_4 [percent drug released in 12 h] but a significant effect on Y_2 [n value]. For-

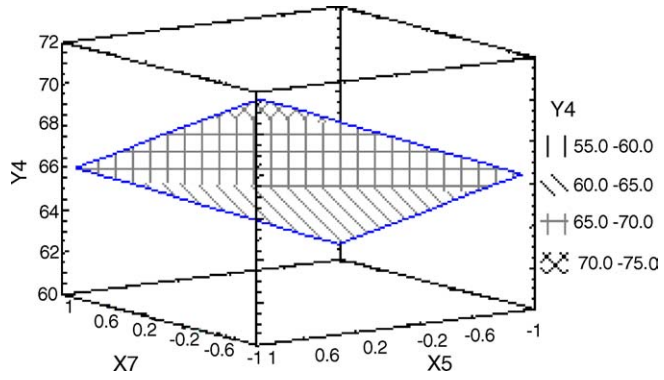

Fig. 7. Response surface plot showing the effect of independent variables, citric acid amount (X_6) and compression force (X_7) on response Y_4.

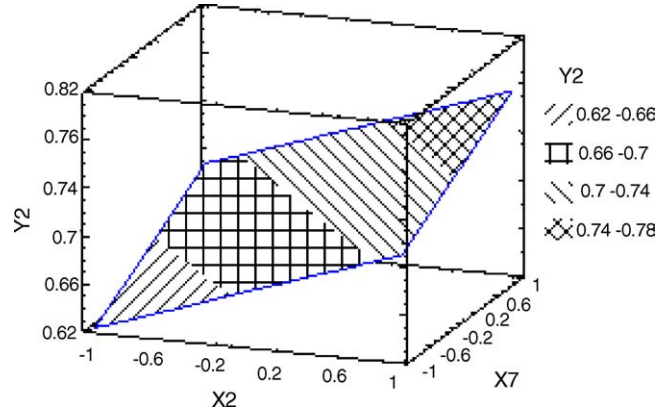

Fig. 8. Response surface plot showing the effect of independent variables, POLYOX amount (X_2) and compression force (X_7) on response Y_2.

mation of compacts at higher compression forces was reported to delay or even hinder the release of drugs (Kim and Fassihi, 1997a,b; Zaghloul et al., 2001). As expected, compression force had a negative effect on drug release (Fig. 7). While compression force delays drug release by decreasing the porosity of the tablet, it also decreases the probability of channel formations. As discussed earlier, channel formations are critical for a Fickian square root of time release, and subsequently [n] exponent (Fig. 8). As shown in the figure, at a low level of POLYOX amount, increasing compression pressure from 1000 to 5000 lb, increased [n] from 0.62 to 0.73.

4. Conclusion

Within the limits commonly used to prepare hydrophilic controlled-release matrices, some formulation and process variables are expected to have significant effect on the amount and pattern of drug release. Of the 12 formulations investigated in this study, 11 had a drug release pattern that follows the anomalous (non-Fickian) release. Only two factors, carbopol concentration and POLYOX molecular weight, had a significant and negative effect on the cumulative percent of drug released with time, whereas POLYOX amount and compression force had a significant and positive effect on [n] value. It could be concluded from this study that in hydrophilic matrices, intended for a 12-h sustained drug release, blends of POLYOX and carbopol could be used synergistically to modulate both the amount and rate of drug release. It is evident that when both polymers are combined, only carbopol is responsible for modulating the cumulative percent of drug released in 12 h. POLYOX content per tablet is expected to have an impact on the pattern by which the drug is released from the matrix, i.e., from square root of time kinetics to a linear zero-order release pattern, without a significant effect on the cumulative amount of drug released. This observation should be valuable in a clinical setting when adjustment in the pattern of drug release is desired without a change in the cumulative amount released. Diluents, electrolytes, and buffers, on the other hand, are expected to have an insignificant or marginal effect on both responses, assuming they were within the limits used in this study.

References

Bender, B.G., Annett, R.D., 1999. Neurophysiological outcomes of nocturnal asthma. Chronobiol. Int. 16, 695–710.

Busse, W.W., Lemanske, R.F., 2001. Asthma. N. Engl. J. Med. 344, 350–362.

Bussemer, T., Otto, I., Bodmeier, R., 2001. Pulsatile drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 18, 433–458.

Conte, U., Maggi, L., Colombo, P., La Manna, A., 1993. Multi-layered hydrophilic matrixes as constant release devices (Geomatrix systems). J. Control. Release 26, 39–47.

Dethlefsen, U., Repges, R., 1985. Eines neues Therapieprincip bei nächtlichen Asthma. Med. Klinik 80, 44–47.

Diette, G.B., Markson, L., Skinner, E.A., 2000. Nocturnal asthma in children affects school attendance, school performance, and parents' work attendance. Arch. Pediatr. Adolesc. Med. 154, 923–928.

Fan, L.T., Singh, S.K., 1989. Controlled Release. Springer-Verlag, Berlin.

Fitzpatrick, M.F., Engleman, H., Whyte, K.F., 1991. Morbidity in nocturnal asthma: sleep quality and daytime cognitive performance of normal subjects. Thorax 46, 569–573.

Hansel, T.T., Tennant, R.C., Tan, A.J., Higgins, L.A., Neighbour, H., Erin, E.M., Barnes, P.J., 2004. Theophylline: mechanism of action and use in asthma and chronic obstructive pulmonary disease. Drugs Today 40, 55–69.

Jantzen, G.M., Robinson, J.R., 2002. Sustained and controlled-release drug-delivery system. In: Banker, G.S., Rhodes, C.T. (Eds.), Modern Pharmaceutics, vol. 121. Dekker, New York, pp. 501–528.

Ju, R.T.C., Nixon, P.R., Patel, M.V., Tong, D.M., 1995. Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer. J. Pharm. Sci. 84, 1464–1477.

Ju, R.T.C., Nixon, P.R., Patel, M.V., 1997. Diffusion coefficient of polymer chains in the diffusion layer adjacent to a swollen hydrophilic matrix. J. Pharm. Sci. 86, 1293–1298.

Khan, G.M., Jiabi, Z., 1998. Formulation and in vitro evaluation of ibuprofen-carbopol 974P-NF controlled release matrix tablets III: influence of co-excipients on release rate of the drug. J. Control. Release 54, 185–190.

Kibbe, A.H., 2000. Carbomer. In: Handbook of pharmaceutical excipient. In American Pharmaceutical Association, third ed. Pharmaceutical Press, Washington, DC, pp. 79–82.

Kim, C.J., 1994. Drug release from compressed hydrophilic POLYOX-WSR tablets. J. Pharm. Sci. 84, 303–306.

Kim, H., Fassihi, A.R., 1997a. Application of a binary polymer system in drug release rate modulation. 2. Influence of formulation variables and hydrodynamic conditions on release kinetics. J. Pharm. Sci. 86, 323–328.

Kim, H., Fassihi, A.R., 1997b. Application of a binary system in drug release rate modulation. 1. Characterization of release mechanism. J. Pharm. Sci. 86, 316–322.

Korsmeyer, R.W., Gurney, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Mannino, D.M., Homa, D.M., Pertwski, C.A., 1998. Surveillance for asthma—United States, 1960–1995. MMWR CDC Surveil Summ 47, 1–27.

Murray, J., 1994. X-Stat, Version 2.02: Statistical Experimentation Design, Data Analysis and Nonlinear Optimisation. John Wiley and Sons, New York.

Peppas, N.A., Sinclair, J.L., 1983. Anomalous transport of penetrants in glassy polymers. Colloid Polym. Sci. 261, 404–408.

Pillay, V., Fassihi, A.R., 2001. Probing of matrix hydration in the presence of electrolytes. Drug Deliv. 8, 87–92.

Robertson, C.F., Rubinfeld, A.R., Bowes, G., 1990. Death from asthma in Victoria: a 12-month survey. Med. J. Aust. 152, 511–517.

Siepmann, J., Streubel, A., Peppas, N.A., 2002. Understanding and prediction drug delivery from hydrophilic matrix tablets using the sequential layer model. Pharm. Res. 19, 306–313.

Varma, M., Singla, A.K., Dhawan, S., 2004. Release of deltiazem hydrochloride from hydrophilic matrices of polyethylene oxide and carbopol. Drug Dev. Ind. Pharm. 30, 545–553.

Weersink, E.J., Van Zomeren, E.H., Koeter, G.H., 1997. Treatment of nocturnal airway obstruction improves daytime cognitive performance in asthmatics. Am. J. Respir. Crit. Care Med. 156, 1144–1150.

Yang, L., Fassihi, R., 1996. Zero-order release kinetics from a self-correcting floatable asymmetric configuration drug delivery system. J. Pharm. Sci. 85, 170–173.

Zaghloul, A.A., Faltinek, J., Vaithiyalingam, S.R., Reddy, I.K., Khan, M.A., 2001. Naproxen-Eudragit microspheres: screening of process and formulation variables of extended release tablets. Pharmazie 56, 321–324.