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D-Optimal Mixture Design: Optimization of Ternary Matrix Blends for Controlled Zero-Order Drug Release From Oral Dosage Forms

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ABSTRACT The objective of the present study was to develop a tablet formulation with a zero-order drug release profile based on a balanced blend of three matrix ingredients. To accomplish this goal, a 17-run, three-factor, two-level D-Optimal mixture design was employed to evaluate the effect of Polyox™ (X_1), Carbopol® (X_2), and lactose (X_3) concentrations on the release rate of theophylline from the matrices. Tablets were prepared by direct compression and were subjected to an in vitro dissolution study in phosphate buffer at pH 7.2. Polynomial models were generated for the responses Y_4 (percent released in 8 h) and Y_6 (similarity factor or f_2). Fitted models were used to predict the composition of a formulation that would have a similar dissolution profile to an ideal zero-order release at a rate of 8.33% per hour. When tested, dissolution profile of the optimized formulation was comparable to the reference profile (f_2 was 74.2, and n [release exponent] was 0.9). This study demonstrated that a balanced blend of matrix ingredients could be used to attain a zero-order release profile. Optimization was feasible by the application of response surface methodology, which proved efficient in designing controlled-release dosage forms.

KEYWORDS Hydrophilic matrices, Controlled release, Response surface methodology, D-optimal design, Optimization; Dissolution

INTRODUCTION

Most of the experimentation in drug product development is performed by changing the levels of each variable (factor) separately at a time while keeping the remaining variables constant; this leads to a large number of experiments and often relies on the experience of the analyst (Kincl et al., 2004). The traditional method of experimental design (one-factor-at-a-time) may be inefficient and cost prohibitive. It does not provide any information about the position of the optima and can, at its best, lead only to a local optimum in the system. The one-at-a-time optimization also ignores interaction between factors and may call for an

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unnecessarily large number of runs. With the rapid increase in the cost of experiments, it is becoming increasingly important that the development and optimization of any dosage form is performed with few experiments and with minimal cost as possible (Bolton, 1990; Bloomfield & Butler, 2000; Parojcic et al., 2001; Kincl et al., 2004).

The application of statistical experimental design in pharmaceutical product development has been demonstrated to be an efficient and satisfactory method to acquire the necessary information that correlate the independent variables, or factors, with the dependent variables, or responses relevant to formulation composition, and/or manufacturing processing parameters (Sastry & Khan, 1998; Jumaa et al., 1999; Nazzal et al., 2002; Gao et al., 2004). One of the most popular experimental design methods is response surface methodology (RSM). RSM, such as the D-optimal design, is commonly used to reveal main effects and interaction effects between the independent variables of the experiment. When the responses of interest are expressed in a model as a continuous function of the composition of the mixture, the model could reveal, graphically or mathematically, regions of desirable formulation compositions that satisfy the criteria imposed by the experimenter.

Among the most attractive pharmaceutical products that require methodical optimization are the extended-release dosage forms. They provide greater selectivity of pharmacological activity by allowing therapeutically beneficial reduction in dosing frequency. One aspect of research about controlled-release dosage forms that is gaining considerable interest involves the design of systems with zero-order drug release for a specific biopharmaceutical requirement of an active moiety, that is, producing steady-state plasma drug level. To meet this objective numerous design variations have been reported. Proposed mechanisms to obtain zero-order controlled drug release include chemical reaction, osmosis, and balanced erosion and swelling (Yang & Fassihi, 1996; Kim & Fassihi, 1997; Sastry & Khan, 1998). A balanced movement of the erosion and swelling fronts could be accomplished by combining different polymers each with unique physical properties. Polymeric matrices, where the drug is dispersed or dissolved uniformly throughout the polymer blend, are commonly used for controlled drug release because of their ease of manufacture and their ability to extend drug release over a prolonged period of time (Lee, 1992; Peppas, 1998).

In the present study, the authors hypothesize that controlled drug diffusion through a polymeric matrix could be achieved by optimal levels of ternary blends of low molecular weight hydrophilic polymer, such as Polyox, cross-linked swellable polymer, such as Carbopol, and water soluble filler, such as lactose. Lactose, a channeling agent, is expected to modify the internal geometry of the tablet during dissolution and balance the swelling and erosion of the polymer blend.

The objectives of the present study were therefore (1) to evaluate the effect of three matrix ingredients–X_1 (Polyox), X_2 (Carbopol), and X_3 (lactose)–on theophylline release rates using a three-factor, two-level D-optimal design; and (2) to develop an optimized matrix formulation with a 12-h, zero-order drug release profile.

Theophylline, a prescription drug with a long history as an asthma medication (Mannino et al., 1998; Busse & Lemanske, 2001), was selected as the model drug in this study. In recent years, theophylline had fallen out of favor with some physicians because of toxicity concerns from having too much of the drug in 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).

MATERIALS AND METHOD

Materials

Theophylline was provided by BASF Corp. (Mount Olive, NJ). Poly(ethylene oxide) (Polyox™ WSR-205, approximate molecular weight: 600,000 g/mol) was supplied by Dow Chemical Company (Midland, MI). Carbopol® 71 G NF was provided by Noveon Inc. (Cleveland, OH). Spray dried, directly compressible lactose (Pharmatose® DCL 14) was obtained from DMV International (Verghel, Netherlands). Potassium phosphate, sodium hydroxide, and sodium chloride were purchased from Spectrum Quality Products, Inc. (New Brunswick, NJ, USA). Chemicals and raw materials were used as received without further processing.

Experimental Design

A 17-run, three-factor, two-level D-optimal mixture design was employed in this study to construct polynomial models for the optimization process. This design provides an empirical mathematical model to describe

the effect of formulation ingredients on the dissolution of matrix formulations. The model is of the form:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_2X_3 + A_6X_1X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 + E$$

where $A_1 - A_0$ are the coefficients of the respective variables and their interaction terms, and E is an error term. Factors evaluated in this study were Polyox (X_1), Carbopol (X_2), and lactose (X_3) concentrations. Table 1 summarizes the dependent and independent variables evaluated and the constraints that were placed on the responses. The range of each factor was chosen based on preliminary studies. The amount of theophylline (100 mg), magnesium stearate (0.2%), and talc powder (0.3%) was kept constant in each of the 17 formulations.

The experimental design was generated using the Design-Expert software (v. 5.07; State-Ease, Inc., Minneapolis, MN). The software selected a set of candidate points as a base design. These included factorial points (high and low level from the constraints on each factor), centers of edges (points midway between adjacent factorial points), constraints plane centroids, axial check points, and an overall center point. A schematic representation of the design is given in Fig. 1.

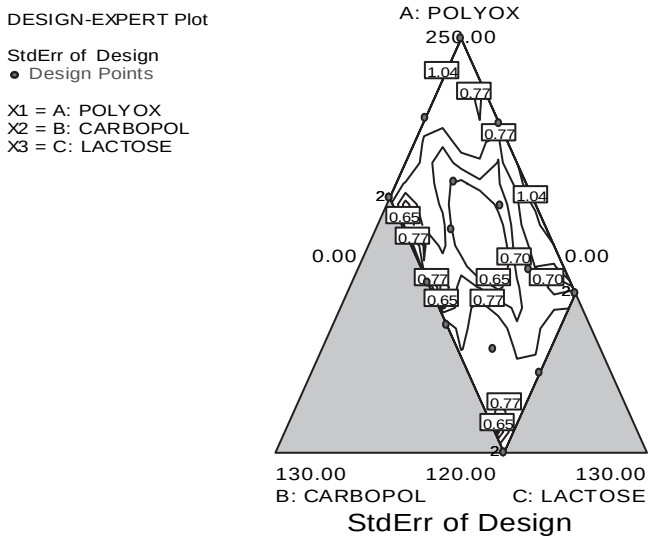


FIGURE 1 **Schematic Representation of the of Three-Component D-Optimal Mixture Design.**

Tablet Preparation

Theophylline tablets were prepared according to the predefined composition (Table 2) provided by the statistical design. Initially, ingredients–Polyox, Carbopol, and lactose–in the amount required to prepare each formulation were passed through a standard USP sieve No. 22 and mixed in a Turbula blender (T2A No. 690994, Basel, Switzerland) for 10 min. Then, magnesium stearate (0.2%) and talc powder (0.3%) were added to the blend and mixed for an additional 5 min. Powder blends were accurately weighed and manually fed into a single punch tablet press (Enerpac, model MTCM-1 Enerpac; New Brunswick, NJ). Tablets were prepared under a compression force of 2268 kg-force (5000 lb) using 10.3-mm concave-faced punches. Each tablet weighed 351.75 mg and contained 100 mg of theophylline.

TABLE 1 **Independent and Dependent Variables of the D-Optimal Mixture Design**

Independent variables	Low level		High level
X1=Polyox amount (mg)	120		250
X2=Carbopol amount (mg)	0		50
X3=Lactose amount (mg)	0		80
	Constraints		
Dependent variables	Low limit	Upper limit	Goal
Y1=Percent theophylline released in 2 h	13	21	In range
Y2=Percent theophylline released in 4 h	30	36	In range
Y3=Percent amount released in 6 h	28.3	53	In range
Y4=Percent amount released in 8 h	63	73	In range
Y5=Percent amount released in 12 h	95	100	In range
Y6=Similarity factor (f2)	30.2	79.8	Maximize

TABLE 2 Observed Responses for the Three-Component D-Optimal Mixture Design

Random order	Polyox (mg)	Carbopol (mg)	Lactose (mg)	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6
1	173.3	50.0	26.7	15.8	21.6	32.3	42.1	64.4	33.3
2	250.0	0.0	0.0	20.4	32.2	50	69	91.5	66.9
3	120.0	50.0	80.0	14.9	19.3	28.7	39.7	60.7	35
4	225.0	25.0	0.0	15	21.1	31.8	44.6	69.9	35.6
5	145.0	25.0	80.0	19.2	30.2	43.6	62.8	91.6	62.8
6	170.0	0.0	80.0	21.7	40.5	60.2	79.4	103.6	54.8
7	205.0	25.0	20.0	17.7	26.9	40.9	54.7	82.3	48.1
8	197.5	12.5	40.0	18.9	31.5	47.8	65.6	96.9	79.8
9	190.0	33.3	26.7	15.1	22.3	35.7	50.3	79.5	42.2
10	152.5	37.5	60.0	16.2	21.3	31.9	47.3	72.7	37.4
11	223.3	0.0	26.7	22.9	38.3	52.3	70.8	91.6	61.1
12	170.0	0.0	80.0	24.2	41.8	61.7	82.9	91.5	48.8
13	120.0	50.0	80.0	16	20.6	30.5	44.6	70	35.6
14	160.0	50.0	40.0	16.1	22.5	32.2	41.7	64.7	33.4
15	200.0	50.0	0.0	16.2	20.8	30.6	41.1	61.1	31.7
16	177.5	12.5	60.0	19.1	32.2	53.6	75.2	91.5	61.4
17	200.0	50.0	0.0	14	18.7	28.3	38.7	59.8	30.2

Dissolution Studies

Dissolution experiments were performed using a type II dissolution apparatus (VK 7000; Varian Inc., Cary, NC) at 50 rpm in 900 mL of USP phosphate buffer of pH 7.2. Temperature of the dissolution medium was kept constant at 37 ± 0.5°C. Samples (3 mL) were withdrawn at predetermined time intervals; then they were filtered and analyzed spectrophotometrically at 270 nm (Cary 50 probe-UV spectrophotometer; Varian Inc.). Samples were replaced with fresh dissolution medium. Experiments were performed in triplicates, unless otherwise specified. Derivation of the spectral data was not necessary. In controlled-dissolution experiments, excipients did not show interferences with the UV absorption of theophylline.

Swelling Studies

Swelling behavior of the optimized formulation was evaluated using a 0.9 mm penetration probe adapted to a texture analyzer instrument (TA.XTPlus Texture Analyzer; Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK). In each experiment, a theophylline tablet was placed in the center of a platform and immersed in 700 mL of phosphate buffer (pH 7.2). The modified dissolution vessel was designed to enable medium flow using a rotating bar. A custom designed macro was used whereby the probe was forced against the swelling tablet at a rate of 10 mm/sec and a maximum penetration force of 150 *g*. This was sufficient to differentiate between the thicknesses of the swelling layer and the glassy core. Once the probe reaches its maximum penetration force it retracts to its original position. This test was automatically repeated once every hour for up to 12 h, which was the duration of the dissolution study. All experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Experimental Design

A 17-run, three-factor, two-level D-optimal design was utilized in this study to correlate the effect of formulation ingredients with the observed responses. The independent and dependent design variables are listed in Table 1. Experimental runs and the observed responses are given in Table 2. A schematic representation of the experimental design is shown in Fig. 1. The dots on the diagram represent the 17 design points. Dots with a "2" indicate that the point was replicated. The two primary responses that were investigated in this study were (1) percent theophylline released in 8 h, denoted as Y_4, and (2) similarity factor (f_2), denoted as Y_6. Similarity factor (f_2) was measured for each of the 17 dissolution profiles against an ideal 12-h zero-order

release profile. The ideal profile was based on a theoretical release of 8.3% of the drug per hour. Dissolution profiles of the 17 formulations and the ideal release profile, given as the reference profile, are shown in Figs. 2 and 3. The percent theophylline released in 8 h ranged from 41.1% (formulation 15) to 82.9% (formulation 12). A good reproducibility in tablet preparation and dissolution analysis was exemplified by the good agreement between the four test replicates (formulations 6, 12, 15, and 17).

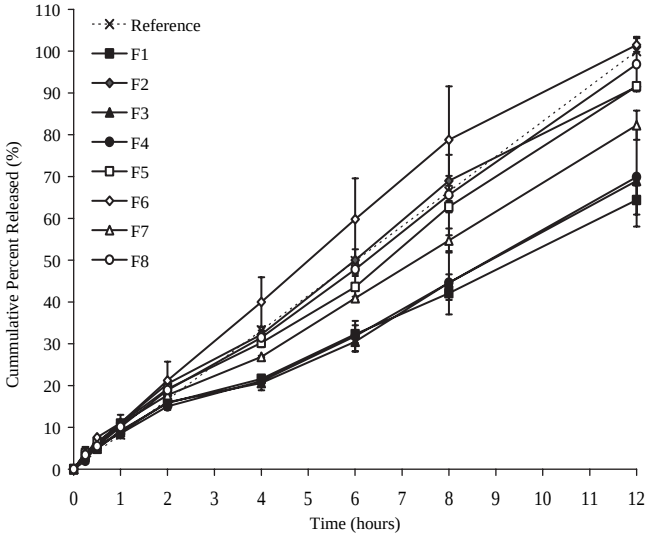


FIGURE 2 **Reference and Dissolution Profiles of the Matrices for Formulations 1–8.**

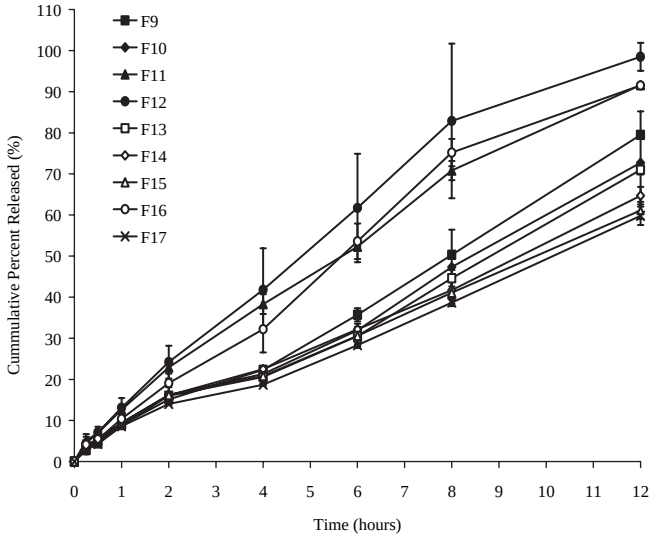


FIGURE 3 **Dissolution Profiles of the Matrices for Formulations 9–17.**

The primary responses–percent theophylline released in 8 h (Y_4) and similarity factor (Y_6)–were analyzed using the Design-Expert software. The probability value (α) for determination of statistical significance was set at 0.05, which indicates that a "hypothesis" theory would be rejected if the calculated p-value was less than 0.05 in favor of an alternative theory. The first step toward an optimal statistical analysis was to select the model that best (1) describes and (2) fits the data. Therefore, results were analyzed by the sequential model comparison and lack-of-fit tests. Results of the sequential model comparison, which indicate whether a model could describe a response, are given in Table 3. As seen from the table, the linear model was statistically significant ($p < 0.0001$), which indicates that the model adequately describes the response (Y_4). Statistical significance, however, was not improved by adding either quadratic or cubic terms. For the response Y_6, both the linear and the cubic models were statistically significant (p: 0.0008 and 0.0157, respectively), that is, both models adequately describe the response. The lack of fit test was subsequently performed to further demonstrate the suitability of a given model. Lack-of-fit test, which was calculated based on the residual sum of squares, diagnoses whether a model adequately fits the data. As seen in Table 3, a large p-value of the linear model (p=0.0931) for Y_4 indicates that the linear model adequately fits the data. Similarly, for Y_6 the cubic model was the only model to have a $p > 0.05$, and thereby it was the only model that could fit the data. While the linear model was shown to adequately describe the response Y_6, it failed the lack-of-fit test and was therefore rejected from further consideration. Table 4 lists other statistical data that

TABLE 3 **Sequential Model Comparison and the Corresponding Lack-of-Fit Tests for Y_4 and Y_6**

	Sequential comparison		Lack of fit	
	p Value		*p* Value	
Type of model	Y_4	Y_6	Y_4	Y_6
Linear	<0.0001	0.0008	0.0931	0.0181
Quadratic	0.1352	0.3713	0.1208	0.0174
Special cubic	0.7055	0.9113	0.1044	0.0145
Cubic	0.1961	0.0157	0.1269	0.0532

TABLE 4 **Model Comparison: Summary Statistics for the Percent Theophylline Released in 8 h (A) and the Similarity Factor (B)**

(A) Summary statistics for Y_4

Source	Standard deviation	R^2	Adjusted R^2	Predicted R^2	PRESS
Linear	3.7	0.95	0.94	0.92	275.88
Quadratic	3.27	0.97	0.95	0.91	318.99
Special cubic	3.41	0.97	0.95	0.79	738.99
Cubic	2.97	0.98	0.96	0.71	1026.39

(B) Summary statistics for Y_6

Source	Standard deviation	R^2	Adjusted R^2	Predicted R^2	PRESS
Linear	9.62	0.64	0.59	0.49	1845.25
Quadratic	9.47	0.73	0.6	0.35	2336.51
Special cubic	9.92	0.73	0.56	0.22	4404.93
Cubic	5.9	0.93	0.85	0.36	2292.15

PRESS=Small predicted residual sum of squares.

were used to compare the four models–linear, quadratic, special cubic, and cubic. As seen from the table, the linear and cubic models that were deemed suitable to describe Y_4 and Y_6, respectively, had small standard deviations, large predicted R^2 values, and small predicted residual sum of squares (PRESS), which further exemplifies their suitability to fit the data. Detailed analysis of variance (ANOVA) for the responses Y_4 and Y_6 is summarized in Table 5.

Based on the preceding arguments, the following linear and cubic polynomial equations were constructed and used in subsequent discussion to demonstrate the relationship between the formulation ingredients–Polyox (X_1), Carbopol (X_2), and lactose (X_3)–and the responses Y_4 and Y_6.

$$Y_4 = 0.27632X_1 - 0.38455X_2 + 0.40804X_3 \quad (1)$$

$$\begin{aligned} Y_6 = {} & 0.26X_1 + 5.32X_3 - 0.55X_1X_2 \\ & - 0.62X_2X_3 + 2.22X_1X_2X_3 \\ & + 8.89X_1X_2(X_1 - X_2) - 1.12 \times 10^{-3} \\ & X_2X_3(X_2 - X_3) \end{aligned} \quad (2)$$

TABLE 5 **Analysis of Variance (ANOVA) for the Linear Model of the Response Y_4 (A) and the Cubic Model for the Response Y_6 (B)**

(A) ANOVA for Y_4

Source	Sum of squares	Degrees of freedom	Mean square	Calculated *F* value	*p* Value
Model	3393.14	2	1696.57	124.24	<0.0001
Residual	191.18	14	13.66		
Lack of fit	182.17	11	16.56	5.52	0.0931
Pure error	9.01	3	3		
Corrected total	3584.32	16			

(B) ANOVA for Y_6

Source	Sum of squares	Degrees of freedom	Mean square	Calculated *F* value	*p* Value
Model	3357.64	9	373.07	10.73	0.0025
Residual	243.36	7	34.77		
Lack of fit	224.06	4	56.01	8.7	0.0532
Pure error	19.31	3	6.44		
Corrected total	3601	16			

Effect of Formulation Ingredients on the Response Y_4

Polyox, Carbopol, and lactose had a significant effect on Y_4 (cumulative percent of theophylline released in 8 h). Polyox and lactose amounts had a positive impact on Y_4, whereas Carbopol had a negative effect on the response. There were no interactions or higher level or quadratic effects. Each factor had a linear and independent effect on the response; this is exemplified by the linear model, which is represented by Eq. (1). Polyox, a non-ionic water soluble polymer, had a positive effect on theophylline release. Increase in drug release with an increase in Polyox concentration could be attributed to the free movement of polymer chains when exposed to the dissolution medium. Water imbibition into the matrix during tablet dissolution forces the polymer to swell and results in decreased polymer concentration and increased macromolecule mobility (Siepmann et al., 2002). On a molecular level, movement of polyox chains, which is facilitated by water imbibition, permanently changes the structure of the polymer network. Within this network, entangled polymer chains can either disentangle or modify their entanglement configuration, while disentangled polymer chains can entangle (Siepmann et al., 2002). Once disentangled, polymer chains diffuse through the unstirred and swollen layer surrounding tablet core. Because a low molecular weight Polyox was used in this study, the critical water concentration above which disentanglement occurs is decreased (Ju et al., 1995, 1997) and the diffusion coefficient of the disentangled polymer chains is increased when compared to a higher molecular weight polyox (Fan & Singh, 1989; Ju et al., 1995, 1997). Therefore, the mobility of the polymer chains on water imbibition is increased according to the free volume theory of diffusion (Fan & Singh, 1989). Consequently, increasing the concentration (percentage) of the low molecular weight Polyox is expected to increase the mobility of the polymer matrix during dissolution, leading to an increase in theophylline release. In contrast, Carbopols are swellable high molecular-weight and cross-linked acrylic polymers. They contain 56% to 68% of carboxylic acid(–COOH) groups (Reilly, 2005). In 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 the polymer and results in gel formation. Carbopol gel, which consists of closely packed swollen particles, forms a barrier against drug release and explains the negative effect of Carbopol concentration on the release of theophylline from the matrices. Lactose, on the other hand, is a water soluble disaccharide, which facilitates formation of channels within the polymeric matrix. Channel formation enhances water penetration and drug release, which explains the positive effect of lactose on Y_4. Increase in the concentration of lactose led to an increase in the percent theophylline released with time (Y_4). While it does not behave as a polymer, lactose could be regarded as filler that can modify the internal geometry of polymeric matrices during dissolution.

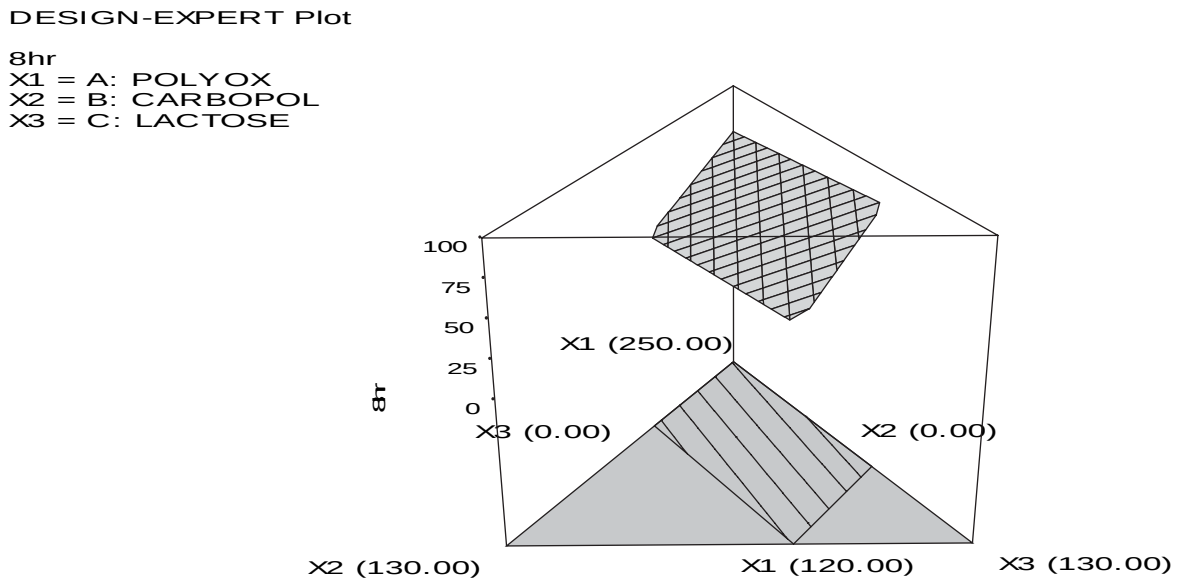
The effect of formulation ingredients on the response Y_4 is schematically represented in Fig. 4 as a two-dimensional (2D) contour plot and a 3D response surface plot. These plots could be used to extrapolate data about drug release at any given concentration of the ingredients within the limits of the experimental design. For example, when the amount of Carbopol increased from 0 to 50 mg per tablet, and no lactose was added, the percent theophylline released in 8 h decreased from 69.0% to 38.7%. Similarly, when 80 mg of lactose was added to each tablet blend and the amount of Carbopol increased from 0 to 50 mg, the percent theophylline released decreased from 79.4% to 44.6%.

Effect of Formulation Ingredients on the Response Y_6

The primary objective of this study was to use statistical modeling to develop a hydrophilic matrix with a 12-h zero-order theophylline release. An ideal matrix is expected to release theophylline at a constant rate of approximately 8.33% per hour. In this study, the ideal profile was treated as the reference curve and was used to calculate its similarity (f_2) to the dissolution profiles of the 17 test formulations. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the test and reference curves (Moore & Flanner, 1996). The similarity factor was calculated using the following equation:

$$f_2 = 50 \ \log 10 \ \left\{ 1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^{-0.5} x 100 \right\}$$

A



B

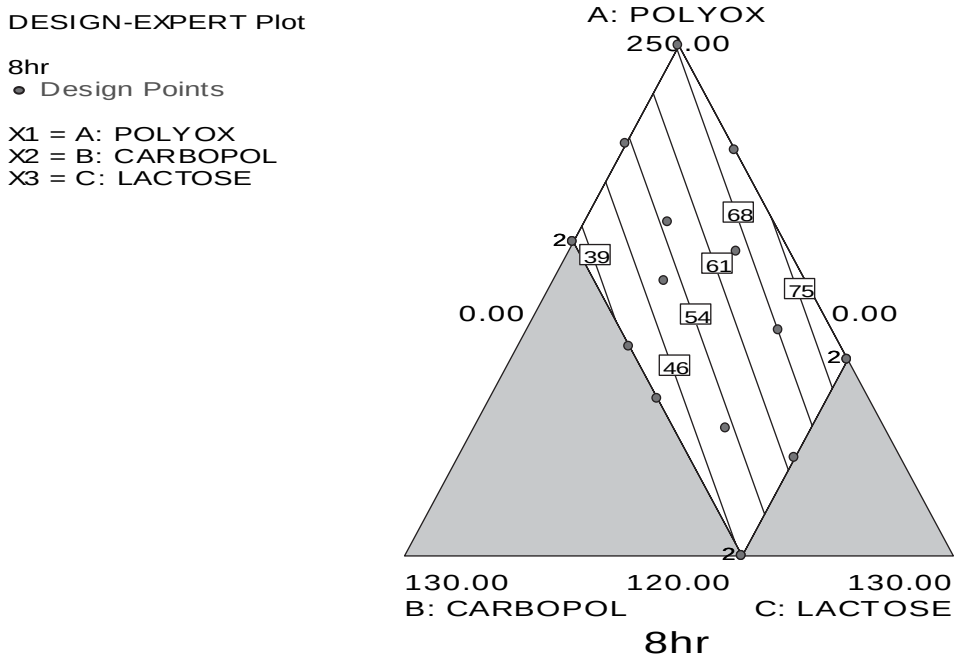


FIGURE 4 **Response Surface Plot (A) and Contour Plot (B) Showing the Effect of the Amount of Polyox (X_1), Carbopol (X_2), and Lactose (X_3) on the Response Y_4.**

W_t (an optional weight factor) is applied to the value or values that are deemed more important than others. It was taken as one, since all the dissolution time points were treated equally. To be considered similar, dissolution profiles should have f_2 values close to 100. Generally, f_2 values greater than 50 (50–100) ensure similarity or equivalence of the two curves (CDER, 1997). The f_2 fit factors, denoted as Y_6, are given in Table 3 for each of the 17 formulations. Test formulations had an f_2 value that ranged between 30.2 and

79.8. Polynomial Eq. (2), given above, illustrates the impact of formulation ingredients on the response (Y_6). Test factors had mixed effects on Y_6 due to main effects as well as interaction and quadratic effects. These effects are exemplified by the response surface and contour plots given in Fig. 5A and B, respectively.

Optimization of the Matrix Formulation

After generating the polynomial equations relating the dependent and independent variables, the process was optimized for the response (Y_6). Optimization was performed to obtain the levels of $X_1 - X_3$, which maximize Y_6 at the constrained conditions listed in Table 1 for Y_1 through Y_5. Constraints were made in an effort to obtain an optimized matrix formulation that releases theophylline over 12 h in a pattern that follows zero-order release kinetics. To accomplish this goal, constraints were placed on the responses ($Y_1 - Y_5$) so that approximately 8.33% of the formulation is released from the tablet per hour. The optimized level of formulation ingredients and the predicted responses ($Y_1 - Y_5$) are given in Table 6. To verify these values, a new formulation was prepared according to the predicted levels of X_1, X_2, and X_3. The dissolution profile of the optimized formulation is given in Fig. 6, which shows both the ideal and experimental release profiles. Experimentally derived Y_6 value was in a close agreement with the predicted value. Predicted similarity between the optimized formulation and the ideal profile was 70.7; the experimentally derived f_2 value was 74.2. Statistically, when the similarity factor (f_2 value) is greater than 65, there is a 95% confidence that the test and reference profiles are comparable (Shah et al., 1998). Therefore, it could be concluded that the release profile of the optimized formulation is identical to the ideal zero-order release profile.

To further illustrate the mechanism of drug release from the optimized formulation, the [n] coefficient, an exponent indicative of the release mechanism, was estimated from the following model (Korsmeyer et al., 1983; Peppas & Sinclair, 1983):

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

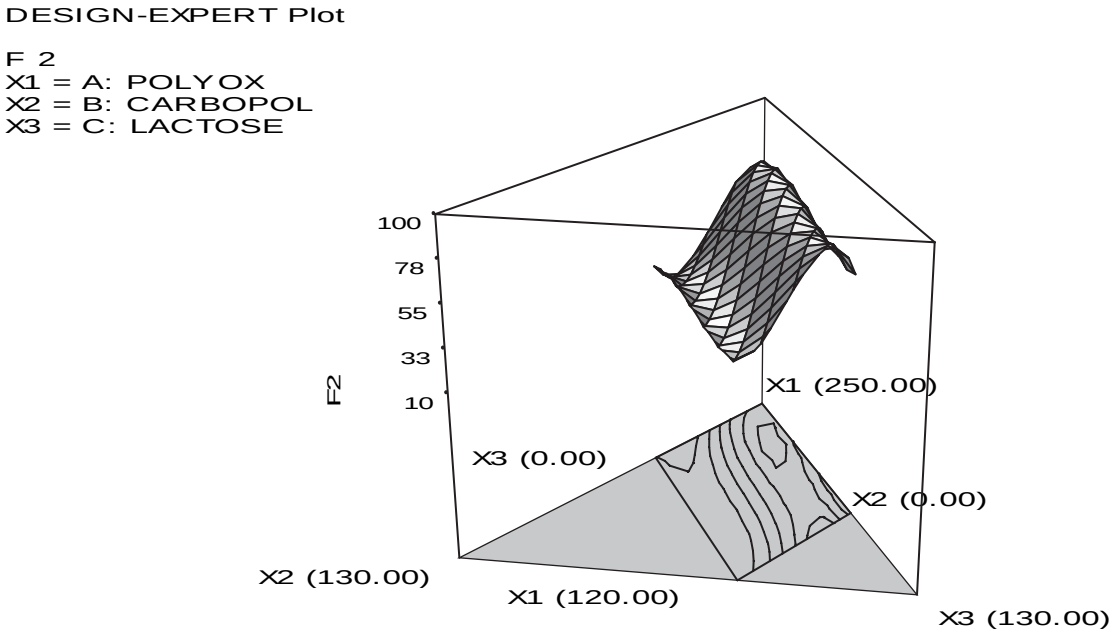
M_t/M_∞ is the fraction of the drug released at time t, and K represents a constant. When [n] approximates 0.5, drug release is governed by square root of time kinetics where drug diffuses via fluid-filled channels (Jantzen & Robinson, 2002). When [n] approximates 1, the mechanism of drug transport is governed by diffusion via the polymer layer itself, which is characterized by constant drug release rate (zero-order release). The third case, when $0.5 < [n] < 1$, indicates anomalous drug release mechanism. In the present study the estimated [n] value of the optimized formulation was found to be 0.90, which indicates a zero-order release profile and corroborates the measured f_2 values.

Swelling Properties

The swelling study was performed to visualize morphological changes that accompanied the dissolution of the optimized theophylline formulation. When the matrix is brought into contact with the dissolution medium it starts to swell, during which a front is observed within the polymer matrix that separates the swollen rubbery region and the glassy core. Glassy core is the region of the tablet that remains unpenetrated by the dissolution fluid. The movement of the glassy/rubbery front of the optimized theophylline formulation was observed by texture analysis. Figure 7 shows the change in thickness and, subsequently, the movement of the swollen rubbery region and the glassy core with time. Increase in the thickness of the swelling layer lasted for approximately 4 h before it started to erode with time. A similar dissolution phenomenon for extended-release dosage forms was observed in tablets made with low molecular weight Polyox without any additives (Kim, 1994). The rate of drug diffusion through the swollen matrices is determined by the structural characteristics of the swollen layer. Two mechanisms for drug transport in the swollen layer were suggested: pore-mechanism, in which the drug permeates by diffusion through the solvent-filled pores, and the partition mechanism, in which drug diffuses through the polymer (Lyman & Kim, 1973).

In the present study, no apparent synchronization was observed in the swelling rate, which was estimated from the change in thickness with time, between the internal glassy core and the external swelling rubbery region. Instead, gradual change in diffusion coefficient with time is the probable factor contributing to the Fickian ($n \sim 1$) pattern of drug release. By its very

A



B

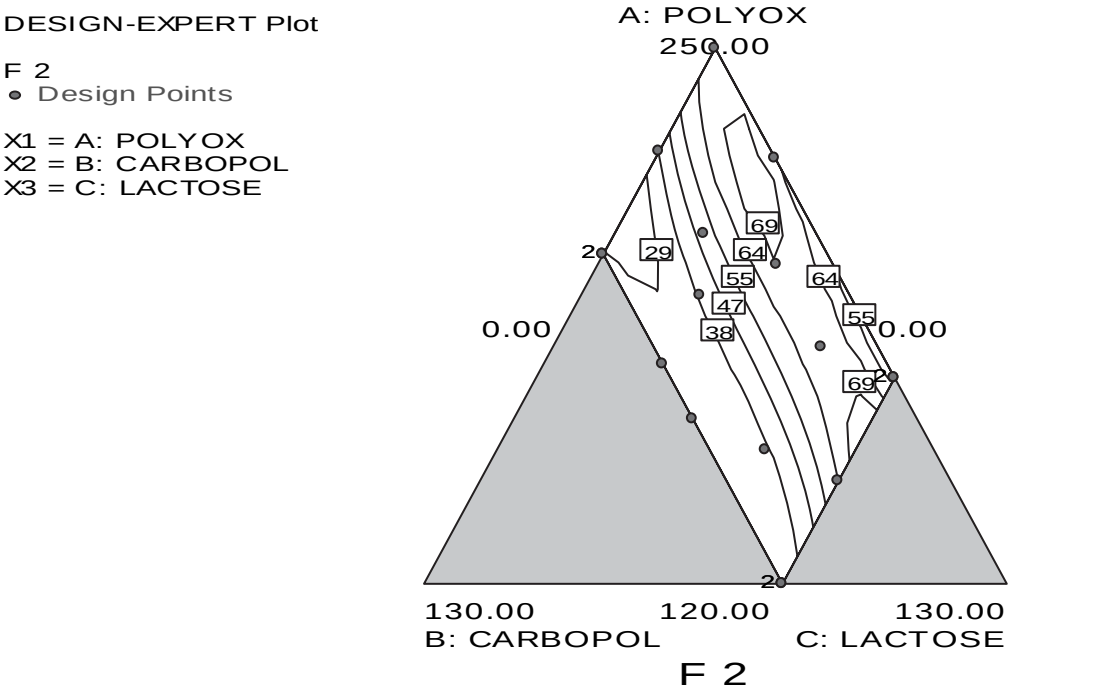


FIGURE 5 **Response Surface Plot (A) and Contour Plot (B) Showing the Effect of the Amount of Polyox (X_1), Carbopol (X_2), and Lactose (X_3) on the Response Y_6.**

TABLE 6 Optimized Formulation Obtained by the Constraints Applied on $Y_1 - Y_5$

Variable	Amount (mg)	Response	Observed values	Predicted values	Residual values
Polyox	162.99	Y_1	13.9	20.4	–6.5
Carbopol	10.53	Y_2	31.9	36	–4.1
Lactose	76.47	Y_3	53.4	52.4	1
		Y_4	71.6	72.2	–0.6
		Y_5	100	95.1	4.9

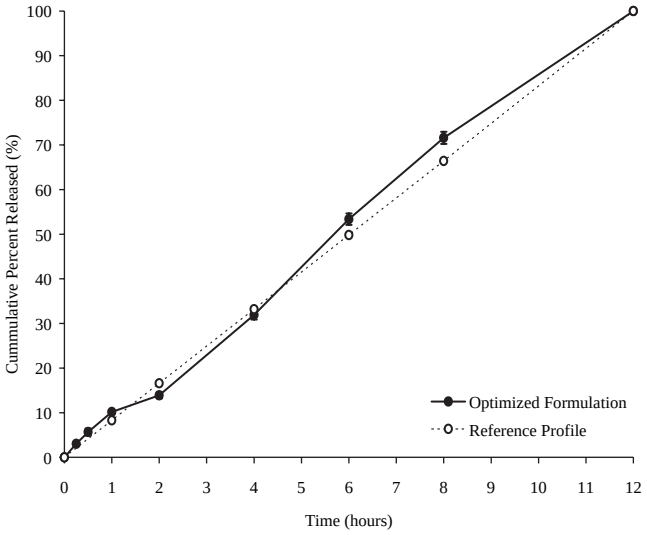


FIGURE 6 Reference and Experimental Dissolution Profiles of the Optimized Formulation in pH 7.2 Phosphate Buffer.

nature, diffusion coefficient is a measure of the ability of the system to dissipate a concentration gradient of the drug within the swollen matrix. While diffusion coefficient could not be measured by textural analysis, it is probable that the presence of lactose facilitated drug release at the beginning of the dissolution process when the moving rubbery/glassy interface was most prominent. On the other hand, Carbopol might have played a greater role in modulating drug release at later stages of the dissolution process when the erosion of the swollen layer was most dominant.

CONCLUSION

In this study a practical approach, based on statistical analysis, was used to develop a matrix formulations with a zero-order drug release profile. A ternary blend of Polyox, Carbopol, and lactose, each with unique

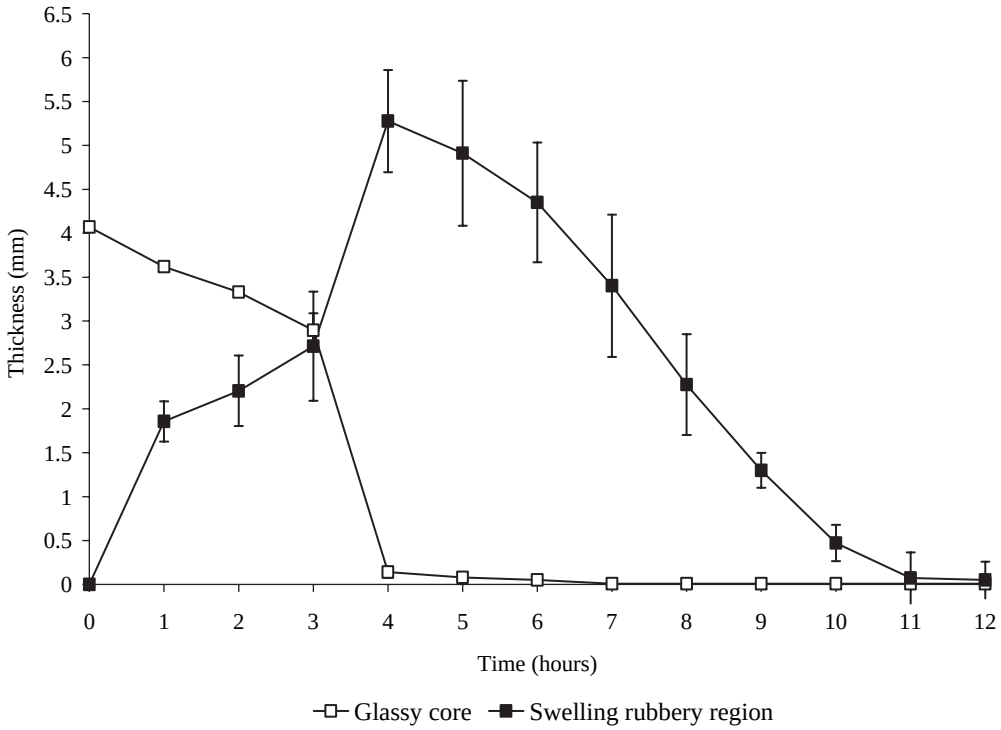


FIGURE 7 Textural Analysis of the Optimized Formulation Showing the Change in Thickness of the Glassy Core and the Swelling Rubbery Region With Time.

physical properties, was evaluated by a D-optimal mixture design. Each ingredient had a critical role in controlling drug release. Both Polyox and lactose increased theophylline release whereas Carbopol suppressed the release of the drug. This ternary blend contributed to a controlled drug diffusion and release from the matrix. Even though a pseudo-zero-order release is commonly used to describe these systems, the dissolution profile of the optimized formulation reported in this study demonstrated an almost identical release to an ideal zero-order profile. Optimized formulation was predicted according to the polynomial models generated by the design. RSM, and the D-optimal design, was shown to be an efficient approach for the optimization of controlled-release matrices. By applying a one-factor-at-a-time approach, it would have been difficult, and at times challenging, to achieve the objective of optimization for such a controlled system.

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