International Journal of Pharmaceutics 407 (2011) 53–62

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Time-oriented experimental design method to optimize hydrophilic matrix formulations with gelation kinetics and drug release profiles

Sangmun Shin[a], Du Hyung Choi[b], Nguyen Khoa Viet Truong[a], Nam Ah Kim[b], Kyung Rok Chu[b], Seong Hoon Jeong[b,*]

[a] Department of System Management & Engineering, Inje University, Gimhae 621-749, South Korea
[b] College of Pharmacy, Pusan National University, 30 Geumjeong-gu, Busan 609-735, South Korea

ARTICLE INFO

Article history:
Received 13 September 2010
Received in revised form 6 January 2011
Accepted 11 January 2011
Available online 18 January 2011

Keywords:
Matrix tablet
Robust design
Response surface methodology
Drug releases
swelling

ABSTRACT

A new experimental design methodology was developed by integrating the response surface methodology and the time series modeling. The major purposes were to identify significant factors in determining swelling and release rate from matrix tablets and their relative factor levels for optimizing the experimental responses. Properties of tablet swelling and drug release were assessed with ten factors and two default factors, a hydrophilic model drug (terazosin) and magnesium stearate, and compared with target values. The selected input control factors were arranged in a mixture simplex lattice design with 21 experimental runs. The obtained optimal settings for gelation were PEO, LH-11, Syloid, and Pharmacoat with weight ratios of 215.33 (88.50%), 5.68 (2.33%), 19.27 (7.92%), and 3.04 (1.25%), respectively. The optimal settings for drug release were PEO and citric acid with weight ratios of 191.99 (78.91%) and 51.32 (21.09%), respectively. Based on the results of matrix swelling and drug release, the optimal solutions, target values, and validation experiment results over time were similar and showed consistent patterns with very small biases. The experimental design methodology could be a very promising experimental design method to obtain maximum information with limited time and resources. It could also be very useful in formulation studies by providing a systematic and reliable screening method to characterize significant factors in the sustained release matrix tablet.

1. Introduction

Formulation development for a drug delivery system may seem simple and straightforward, because a large number of experimental designs are routinely assessed by changing the levels of one component or a factor at a time while keeping other components constant. However, this strategy usually ignores interactions among the factors and results in many unnecessary runs, making this strategy inefficient. Moreover, it does not define the optimum condition. It can give marginal effects of specific factors on the selected response and lead to a local optimum for the system (Kincl et al., 2005); however, this often depends on the experience and knowledge of the investigators. In reality, modern pharma-experimentation requires many disciplines and systematic ways to identify formulation variables, to characterize the drug release process, and to optimize the procedure. Reducing the number of experiments and the cost is beneficial and important for the development and optimization of pharmaceutical formulations (Bloomfield and Butler, 2000; Kincl et al., 2005).

Drug products are composed of many ingredients that may induce mixture issues by their nature. These issues need to be taken into account when selecting specific ingredients and their amounts as well as their proportions within the mixture. The ingredients in the formulations are inherently dependent on each other, which may exclude implementing design of experiment methodologies commonly used in optimization studies. Instead, a special type of experimental design is needed to conduct what is referred to as the 'mixture experiment'. In such an experiment, the factors in question can be the ingredients of a mixture and the quality characteristic or response is based on the proportionality of each ingredient. Mixture experiments are of great interest to pharmaceutical industries that want to optimize and accelerate the product development process.

Matrix tablets are the most popular method of oral drug administration, and polymeric swellable materials have been used broadly in matrix formulations to modify and modulate drug release rate (Alderman, 1984; Ford et al., 1991; Juarez et al., 2001; Rao et al., 1990). The main goal of the system is to extend drug release profiles to maintain a constant *in vivo* plasma drug concentration and a consistent pharmacological effect (Ebube and Jones,

* Corresponding author. Tel.: +82 51 510 2812; fax: +82 51 513 6754.
E-mail addresses: shjeong@pusan.ac.kr, ricjeong@hotmail.com (S.H. Jeong).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.01.013

2004; Madhusudan Rao et al., 2001; Neau et al., 1999; Nerurkar et al., 2005). A large number of formulation factors, including the physicochemical properties of the materials, their composition and ratio in the formulations, and manufacturing process parameters, can influence the drug release behavior from the final drug product (Mitchell et al., 1993; Gao et al., 1996; Campos-Aldrete and Villafuerte-Robles, 1997). Therefore, high resource-consuming formulation studies may be inevitable in order to develop a final product with the required quality properties. However, the conventional 'one-at-a-time' approximation may not yield the optimal formulation, because it cannot characterize possible interactions among the variables.

In order to conduct an efficient experimental design and its associated result analysis, robust design (RD) is an alternative methodology for determining the optimal matrix formulations. The RD methodology can be specified by three main procedures: experimental design, parameter estimation, and optimization to obtain the optimal factor settings (Shin and Cho, 2009). By exploiting the information about the relationships between input control factors and output responses from an experimental design, RD methods can reveal robust solutions that are less sensitive to input variations. Given this, one of the main challenges is the optimal design of pharmaceutical formulations to identify better approaches for various unmet pharmaceutical development needs. Traditional design methods have often been applied to situations in which the primary characteristics of interest are time-insensitive. However, in pharmaceutical processes, the main characteristics are often represented by time–response patterns, such as drug release and gelation kinetics. To this end, a new RD optimization model was developed in this study by integrating the well-established response surface methodology (RSM) and the time series modeling. RSM is often considered a superior alternative for modeling process relationships as it separately estimates the response functions of the mean and variance associated with drug release and gelation kinetics measured over time (Park et al., 2010; Shin and Cho, 2005; Vining and Myers, 1990). In this situation, both parameters (i.e., mean and variance) of the two responses (i.e., drug release and gelation kinetics) are collected over time as a matrix. The tentative relationships between these responses and control factors over time can be analyzed in both vertical and horizontal directions. The specific relationships between those responses and control factors can be identified in analyses of the vertical direction. Meanwhile, the relationships between those responses and time can be investigated in analyses of the horizontal direction.

2. Materials and methods

2.1. Materials

The model drug, terazosin HCl dihydrate, was purchased from Hanseo Chemical (Seoul, Korea). Magnesium stearate was purchased from Faci Asia (Jurong Island, Singapore). Polyox WSR (water soluble resin) N-10 (average molecular weight 1×10^5) and Polyox WSR-303 (PEO, average molecular weight 7×10^6, mean particle size 150 μm) were obtained from Dow Chemical (Midland, MI, USA). Pharmacoat 603 (hypromellose USP, mean particle size 60 μm) and LH-11 (Low-substituted hydroxypropyl cellulose, NF, mean particle size 55 μm) were obtained from Shin-Etsu (Tokyo, Japan). Ac-Di-Sol (croscarmellose sodium, NF, mean particle size 65 μm) was obtained from FMC BioPolymer (Philadelphia, PA, USA). Syloid (Syloid® Silica C 1007, mean particle size 7 μm) and HEC 250L (hydroxyethyl cellulose, mean particle size 175 μm) were purchased from GRACE (Baltimore, MD, USA) and Ashland Inc. (Wilmington, DE, USA), respectively. Sodium CMC (carboxymethylcellulose sodium, mean particle size 58 μm) was purchased from Akzo Nobel (Amersfoort, Netherlands). Sodium phosphate, monobasic ($NaH_2PO_4 \cdot 2H_2O$) and citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$) were purchased from Sigma–Aldrich (St. Louis, MO, USA). They were milled with a mortar and pestle and sieved with US standard sieve #200. All other reagents were of analytical or HPLC grade and used as received.

2.2. Preparation of matrix tablets

The formulations of each tablet are shown in Table 1. All materials were passed through a sieve (#40 mesh) to remove any aggregates before mixing. The model drug (terazosin HCl dihydrate) was mixed manually with excipients of each formulation in a mortar and then blended with magnesium stearate for 5 min. The resultant mixture was compressed on a single punch Carver Laboratory Press (Carver Inc., Wabash, IN, USA) at 30 MPa using plane-face punches with a diameter of 9.0 mm. The total weight of each tablet was around 243 mg. The dimensions were measured with a digital slide caliper (Mitutoyo Corp., Kawasaki, Japan).

2.3. Evaluation of tablet gelation

The gelation index is a useful tool to represent the portion of a tablet that has undergone gelation in time. Each tablet was inserted between two transparent polyacrylate plates (5 cm × 5 cm) and held tight with a rubber band. The tablet and polyacrylate plates were immersed in 900 mL of dissolution medium (pH 6.8, 37 °C) and stirred with a magnetic bar (300 rpm/min). Test tablets were removed from the medium at predetermined time intervals (30, 60, 90, 120, 150, 180, 240, and 300 min) and the diameters of the gelated tablets were measured with a caliper. After the gel layer was carefully peeled off, the diameter of the non-gelated core was also measured (D_{obs}). The gelation index was calculated using the following equation (Sako et al., 1996).

$$\text{Gelation Index } (G, \%) = \left\{ 1 - \frac{(D_{obs})^3}{(D_{ini})^3} \right\} \times 100$$

where D_{obs}: diameter of the portion not gelled after the test; D_{ini}: diameter of the tablet before the test.

2.4. Drug release test

Drug release tests were conducted according to USP 27 Apparatus 2 guidelines (paddle method) (Varian 705 DS, Varian, Cary, NC, USA) with 900 mL of dissolution medium maintained at 37 ± 0.5 °C and mixed at 100 rpm. Each tablet was enclosed in a dissolution sinker (20 mm long × 12 mm in diameter) to prevent the tablet from floating on the surface of the buffer solution or sticking to the inner surface of dissolution vessels ($n = 4$). The dissolution medium used in this study was simulated intestinal fluid (SIF) (pH = 6.8, 50 mM phosphate buffer) without any enzymes. Samples were withdrawn at predetermined time intervals and analyzed for drug content using an HPLC system (Agilent 1100 Series, Agilent Technologies, Santa Clara, CA, USA) at a wavelength of 254 nm. Samples were collected in Eppendorf tubes and centrifuged for 1 min; 10 μL of each sample's supernatant was then injected onto the HPLC. An Agilent Eclipse® XDB-C18 3.5 μm (4.6 mm × 50 mm) (Agilent Technologies, Waldbronn, Germany) column was used and maintained at about 30 °C. The mobile phase was a mixture of aqueous buffer (pH 3.2 20 mM citrate buffer) and acetonitrile in a volume ratio of 85:15, respectively. The flow rate was 1.0 mL/min. The cumulative % drug released was calculated for the formulations and the results are presented as the mean value of at least four tablets.

Table 1
Experimental format for gelation and drug release tests.

Std order	Run order	API		Input factors									
		Terazosin	Mg.St	x_1 PEO	x_2 LH-11	x_3 Syloid	x_4 Ac-Di-Sol	x_5 Na-CMC	x_6 HEC	x_7 NaH_2 PO_4	x_8 Citric acid	x_9 Pharma coat 603	x_{10} Polyox N10
8	1	5.93	2.76	93.71	0	0	0	0	0	0	140.6	0	0
19	2	5.93	2.76	100.74	7.03	7.03	7.03	7.03	7.03	7.03	77.33	7.03	7.03
3	3	5.93	2.76	93.71	0	140.6	0	0	0	0	0	0	0
15	4	5.93	2.76	100.74	7.03	7.03	77.33	7.03	7.03	7.03	7.03	7.03	7.03
6	5	5.93	2.76	93.71	0	0	0	0	140.6	0	0	0	0
10	6	5.93	2.76	93.71	0	0	0	0	0	0	0	0	140.6
17	7	5.93	2.76	100.74	7.03	7.03	7.03	7.03	77.33	7.03	7.03	7.03	7.03
14	8	5.93	2.76	100.74	7.03	77.33	7.03	7.03	7.03	7.03	7.03	7.03	7.03
11	9	5.93	2.76	107.77	14.06	14.06	14.06	14.06	14.06	14.06	14.06	14.06	14.06
16	10	5.93	2.76	100.74	7.03	7.03	7.03	77.33	7.03	7.03	7.03	7.03	7.03
18	11	5.93	2.76	100.74	7.03	7.03	7.03	7.03	7.03	77.33	7.03	7.03	7.03
4	12	5.93	2.76	93.71	0	0	140.6	0	0	0	0	0	0
20	13	5.93	2.76	100.74	7.03	7.03	7.03	7.03	7.03	7.03	7.03	77.33	7.03
9	14	5.93	2.76	93.71	0	0	0	0	0	0	0	140.6	0
12	15	5.93	2.76	171.04	7.03	7.03	7.03	7.03	7.03	7.03	7.03	7.03	7.03
2	16	5.93	2.76	93.71	140.6	0	0	0	0	0	0	0	0
13	17	5.93	2.76	100.74	77.33	7.03	7.03	7.03	7.03	7.03	7.03	7.03	7.03
1	18	5.93	2.76	234.31	0	0	0	0	0	0	0	0	0
7	19	5.93	2.76	93.71	0	0	0	0	0	140.6	0	0	0
21	20	5.93	2.76	100.74	7.03	7.03	7.03	7.03	7.03	7.03	7.03	7.03	77.33
5	21	5.93	2.76	93.71	0	0	0	140.6	0	0	0	0	0

3. Robust design model development

3.1. Experimental framework and response surface methodology (RSM)

In the pharmaceutical industry as well as in many other science and engineering fields, the sampled responses must be handled as time series data, which is called "time-oriented response" in this study. The standard experimental format for time-oriented responses is given in Table 2. To each time-oriented response t_i, a specified standard experimental format is identified in Table 3. In this table, x, y, s^2, and t represent the vector of control factors, mean, variance, and time of data sampling, respectively. At each time t_i, mean responses y_i, and variance responses s_i^2 can be determined according to Table 3.

In pharmaceutical studies, mixture experiments are often required. In such an experiment, the factors in question are the ingredients of a mixture and the quality characteristic or response is based on the proportionality of each of those ingredients; hence, the quality of the pharmaceutical product is influenced by such designs in the early stages of drug development. As such, mixture experiments are of great interest to pharmaceutical companies that want to optimize and accelerate the movement of a drug from the R&D stages towards its introduction into the marketplace.

Scheffé first introduced his theory on the prediction of the responses of mixtures based on their proportion (Scheffé, 1958). The theory defines x_i as the proportion of ingredient i in the mixture. Furthermore, the proportionality idea of this theory provides the experiment with a property in which the proportions of the k ingredients within the mixture must equal 100%, as illustrated by the equation $\sum_{i=1}^{k} x_i = x_1 + x_2 + \cdots + x_k = 1$, where $x_i \geq 0 \ \forall\, i = 1, 2, \ldots, k$. He employed a simplex lattice design to represent the design points of the feasible experimental region of the ingredients. The simplex lattice design is defined by the notation $\{k, m\}$, where $m+1$ defines the number of equally spaced proportion values from 0 to 1 for each experiment and those proportions are determined by the equation $x_i = 0, 1/m, 2/m, \ldots, 1$. All possible combinations of the proportions are used to determine the design points within the simplex lattice design. In general, the number of design points in a $\{k, m\}$ simplex lattice design is defined as follows:

$$n = \frac{(k+m-1)!}{m!(k-1)!}$$

In drug development studies, the relationships between interested output responses and a number of candidate input control factors have been surveyed. When prior information is not available or is unreliable, the screening experiment is a suitable choice. To screen for significant factors among a large number of control factors, stepwise regression is regarded as an effective method. The stepwise regression method based on a correlation model can select step by step the significant control factors affecting to the output responses. To be more specific, this method adds and removes factors from the regression model for the purpose of identifying a useful subset of predictors. The criterion for this selection procedure is identified by the p-value in the model compared to the significant level alpha. Based on the stepwise regression results, RSM is conducted to establish the estimated response functions of the time-oriented responses.

3.2. The proposed time-oriented RD methodology based on RSM

The proposed RD procedure consists of three stages: model building, robust design model selection, and optimization. When responses are available at only a given time, also considered as static responses, RSM is utilized in the model building step to estimate the relationship between responses and control factors (Vining and Myers, 1990). In this study, the time-oriented responses available in multi-factors mixture designed experiment need to be handled and the empirical models need to be developed. Because of the nature of pharmaceutical formulation problems, time series data at all treatments are collected. In the model building step, an empirical relationship between the time-oriented responses and the control factors must be established.

In pharmaceutical experiments, the responses (i.e., the mean and variance of drug release and gelation kinetics) represent experimental results associated with a number of designed combinations of mixture input ingredients based on observed times. Hence, it

Table 2
Experimental format with time-oriented responses.

Runs	Input factors **x**	t_1		t_2		...		t_i		...		t_m	
		$\mathbf{y}_1$	$\mathbf{s}_1^2$	$\mathbf{y}_2$	$\mathbf{s}_2^2$	...	...	$\mathbf{y}_i$	$\mathbf{s}_i^2$	...	...	$\mathbf{y}_m$	$\mathbf{s}_m^2$
1		y_{11}	s_{11}^2	y_{21}	s_{21}^2	...	...	y_{i1}	s_{i1}^2	...	...	y_{m1}	s_{m1}^2
2		y_{12}	s_{12}^2	y_{22}	s_{22}^2	...	...	y_{i2}	s_{i2}^2	...	...	y_{m2}	s_{m2}^2
...	Control factor settings (**X**)	...	...	...	...	...	...	...	...	...	...	...	...
u		y_{1u}	s_{1u}^2	y_{2u}	s_{2u}^2	...	...	y_{iu}	s_{iu}^2	...	...	y_{mu}	s_{mu}^2
...		...	...	...	...	...	...	...	...	...	...	...	...
n		y_{1n}	s_{1n}^2	y_{2n}	s_{2n}^2	...	...	y_{in}	s_{in}^2	...	...	y_{mn}	s_{mn}^2
	Targets	T_{t1}		T_{t2}				T_{ti}				T_{tn}	

is reasonable to assume that the response is a function of input control factors and time. Based on this idea, the proposed analysis combines two directional approaches: vertical approaches for control factors and horizontal approaches for time, and the tentative relationship can be analyzed by both directions. In the vertical direction approach, letting $\mathbf{D} = [\mathbf{D}_{1v}\, \mathbf{D}_{2v} \ldots \mathbf{D}_{mv}]$ as the matrix of the responses, in which $\mathbf{D}_{1v}, \mathbf{D}_{2v}, \ldots,$ and $\mathbf{D}_{mv}$ denote mean column vectors of $\bar{y}_1, \bar{y}_2, \ldots, \bar{y}_m$ or variance column vectors of $s_1^2, s_2^2, \ldots, s_m^2$ in Table 3, the estimated response matrix $\hat{\mathbf{D}}$ can be a function of design matrix **X** as follows:

$$\hat{\mathbf{D}} = [\,1 \quad x_1 \quad x_2 \quad \cdots\,] \times (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{D} \tag{1}$$

While vertical analysis can express the relationship between responses **D** and input control factors **x** represented by design matrix **X**, horizontal analysis is proposed to build the relationship between responses **D** and time t. In the horizontal direction approach, the response matrix can be analyzed horizontally $\mathbf{D} = [\mathbf{D}_{1h}; \mathbf{D}_{2h}; \ldots; \mathbf{D}_{nh}]$ where $\mathbf{D}_{1h}, \mathbf{D}_{2h}, \ldots$ and $\mathbf{D}_{nh}$ represent row vectors of mean responses or row vectors of variance responses in Table 3. For the response matrix **D** representing entire rows, the general horizontal form of the relationship can be expressed by a function of t as follows:

$$\hat{\mathbf{D}} = \mathbf{P}_h \times [\,1 \quad t \quad \cdots\,]^{\mathrm{T}} \tag{2}$$

where $\mathbf{P}_h = [\mathbf{P}_{1h}, \mathbf{P}_{2h}, \ldots, \mathbf{P}_{nh}]^{\mathrm{T}}$ is the transposed matrix of parameters for horizontal analysis. The vector of model parameters $\mathbf{p}_{uh}$ for column i response can be estimated as

$$\mathbf{p}_{uh} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{D}_{uh} \tag{3}$$

Using Eqs. (1) and (2), the two directional approaches can be combined into the following general relationship of response **D** as a function of **x** and t given that

$$\hat{\mathbf{D}}(x,t) = [\,1 \quad x_1 \quad x_2 \quad \cdots\,] \times (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{P}_h \times [\,1 \quad t \quad \cdots\,]^{\mathrm{T}} \tag{4}$$

From Eq. (4), the empirical relationships between mean, variance and input control factors over time then can be developed in similar ways. The functional form of mean model can be obtained as

$$\hat{\mathbf{M}}(x,t) = [\,1 \quad x_1 \quad x_2 \quad \cdots\,] \times (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{P}_{h\_\mathrm{mean}}[\,1 \quad t \quad \cdots\,]^T \tag{5}$$

For the variance responses, the functional form of the empirical relationship between the variance and the control factors can be identified as

$$\hat{\mathbf{V}}(x,t) = [\,1 \quad x_1 \quad x_2 \quad \cdots\,] \times (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{P}_{h\_\mathrm{var}}[\,1 \quad t \quad \cdots\,]^{\mathrm{T}} \tag{6}$$

Based on the general functional relationships of mean and variance, the next step of the RD procedure focuses on RD model development in order to find the robust optimal solutions (i.e., the optimal factor settings, $\mathbf{x}^*$). The proposed RD optimization model based on mean squares error (MSE) concepts can be formulated as follows:

$$\begin{aligned} &\text{Minimize} \quad \sum_{i=1}^{m}\{\hat{\mathbf{M}}(x,t_i) - T_{ti}\}^2 + \sum_{i=1}^{m}\hat{\mathbf{V}}(x,t_i) \\ &\text{Subject to} \quad x \in \Omega \end{aligned} \tag{7}$$

where T_{ti} and Ω denotes the target value of responses (i.e., drug release rate and gelation) and the feasible region of control factors, respectively.

4. Results and discussion

When administered, the surface of the matrix tablets is hydrated as exposed to the GI fluid, forming a viscous-gel layer that may hinder water penetration. PEO is a gel-forming agent and the other excipients tested in this study are gel-enhancing agents that may or may not facilitate water absorption into the tablets. If the amount of PEO is too high, the swelling rate might be slow and part of the tablet might not be fully wetted or hydrated, resulting in a 'dry core' and incomplete drug release. If the amount of PEO is too low, the mechanical strength of the viscous-gel layer might not be strong enough to maintain its integrity and release rate. If too weak, most of the gel would disintegrate quickly without any significant sustained release effect. Therefore, maximum and minimum concentrations of the PEO were chosen and the extremes were ruled out to achieve better results as shown in Table 1.

Evaluations of tablet gelation and drug release tests are conducted with ten factors from x_1 to x_{10} and two other default factors, terazosin and magnesium stearate. The selected control factors are arranged in a mixture simplex lattice design with 21 experimental runs as displayed in Table 1. Experimental design methodology is used to evaluate the effect of various excipients and their ratios

Table 3
Experimental frame for each time t_i.

Runs	Input factors **x**	y (Replications)					$\mathbf{y}_i$	$\mathbf{s}_i^2$
1		y_{11}	y_{12}	...	y_{1v}	... y_{1r}	y_{i1}	s_{i1}^2
2		y_{21}	y_{22}	...	y_{2v}	... y_{2r}	y_{i2}	s_{i2}^2
⋮		⋮	⋮	⋱	⋮	⋮ ⋮	⋮	⋮
u	Control factor settings (X)	y_{u1}	y_{u2}	...	y_{uv}	... y_{ur}	y_{iu}	s_{iu}^2
⋮		⋮	⋮	...	⋮	⋱ ⋮	⋮	⋮
n		y_{n1}	y_{n2}	...	y_{nv}	... y_{nr}	y_{in}	s_{in}^2

Table 4
Experimental results for the gelation study based on the experimental design format with target values.

Runs	0.5 h		1 h		1.5 h		2 h		2.5 h		3 h		4 h		5 h	
	$\bar{y}_1$	s_1^2	$\bar{y}_2$	s_2^2	$\bar{y}_3$	s_3^2	$\bar{y}_4$	s_4^2	$\bar{y}_5$	s_5^2	$\bar{y}_6$	s_6^2	$\bar{y}_7$	s_7^2	$\bar{y}_8$	s_8^2
1	49.61	2.67	62.06	1.14	77.19	1.19	84.62	1.14	87.72	1.13	91.64	1.28	94.73	0.53	96.09	0.11
2	48.46	1.86	66.35	0.62	77.24	1.67	82.12	0.57	86.14	1.64	87.40	1.45	93.57	0.63	94.97	1.09
3	14.56	1.17	22.00	4.24	27.63	4.57	31.32	4.78	36.50	1.81	37.25	0.83	54.48	1.86	64.74	1.36
4	33.41	3.53	19.33	2.59	49.04	4.13	62.12	4.26	65.84	2.93	60.27	2.02	59.69	1.75	59.85	2.44
5	33.50	2.38	53.13	1.80	61.85	0.67	70.57	1.45	74.24	1.62	83.18	0.67	89.47	1.18	95.40	0.48
6	41.13	1.34	56.48	1.23	66.64	2.08	77.61	0.41	81.04	0.82	85.02	1.04	91.67	0.83	95.67	0.68
7	40.83	1.98	56.56	2.04	69.34	1.51	78.12	1.84	81.09	0.90	87.71	1.01	94.87	0.81	97.94	1.03
8	10.04	2.91	8.90	4.89	41.43	0.97	40.94	4.52	46.97	5.86	56.43	3.01	59.99	3.47	68.16	3.98
9	37.11	2.22	55.18	0.64	63.17	7.66	77.97	1.86	82.88	1.35	90.11	1.76	96.48	0.40	98.61	0.25
10	37.45	3.48	54.34	3.20	68.03	2.83	74.78	2.86	83.35	1.53	86.90	0.40	94.80	0.58	96.24	0.88
11	34.05	3.16	47.94	3.24	58.73	1.52	64.07	1.15	73.24	0.11	77.73	0.47	85.64	1.31	92.99	0.96
12	22.82	2.18	35.46	1.46	50.78	1.92	61.46	2.38	70.03	1.01	79.11	2.75	86.35	1.29	97.16	0.25
13	34.74	3.18	45.80	1.81	58.03	1.82	66.09	1.49	75.26	1.69	83.93	0.78	90.95	0.86	96.43	0.74
14	22.82	2.01	37.16	2.77	48.81	2.86	53.43	1.95	65.32	3.58	75.69	1.50	82.78	2.60	91.85	1.59
15	41.84	0.6	58.87	0.9	66.38	0.6	76.01	0.8	81.03	0.7	84.58	1.1	92.78	0.4	96.90	0.3
16	14.99	2.47	25.57	3.12	40.31	1.58	47.40	0.72	55.51	1.15	63.77	1.65	67.70	0.61	80.32	2.07
17	35.96	0.82	48.02	2.68	55.70	3.33	70.98	2.55	78.17	1.94	83.29	1.19	93.38	1.18	94.85	0.44
18	37.42	1.79	52.18	0.90	59.83	1.31	68.09	0.64	75.22	0.57	81.01	0.67	87.58	1.11	93.10	0.46
19	43.33	1.40	58.05	2.75	65.47	2.99	71.65	1.92	81.72	2.39	88.40	1.24	91.15	1.77	92.73	2.48
20	42.28	2.09	56.91	0.73	64.41	1.26	72.38	1.51	81.62	1.22	84.53	1.02	91.53	0.36	97.11	0.79
21	37.13	1.00	56.06	2.80	64.24	4.56	76.47	2.17	81.72	0.50	87.04	1.04	95.17	0.96	98.55	0.47
Targets	37.75		47.61		56.71		65.54		69.32		77.55		88.42		88.81	

on both swelling and drug release from matrix tablets. The main purposes are to identify the most significant factors in determining swelling and release rate and their relative levels to optimize the experimental responses. One of the basic principles of experimental design is randomization that involves randomly allocating the experimental runs across the treatments. By performing randomization, the bias can be reduced because of factors equalization that has not been accounted for in the experimental design. The randomized experiments provide great reliability and validity of statistical estimations of treatment effects (Montgomery, 2001). The amount of model drug and magnesium stearate was fixed as shown in the table since the amount of the drug would not be changed due to its pharmacological effect. Moreover, hydrophobic magnesium stearate is one of the most commonly used excipients for tablet manufacturing and was therefore not considered as a control factor in this study.

In pharmaceutical experiments, RD can be an alternative technique for improving the output quality, especially with the trend of global competition. The concept of building quality into a design is increasingly popular in the pharmaceutical industry because of its practicality. The first basic step of the RD technique is experimental design to decide how to exploit the mean and variance information of responses. There have been many attempts to integrate Taguchi's excellent RD techniques with well-established statistical techniques in order to model the response directly as a function of control factors (Vining and Myers, 1990); this is known as response surface methodology (RSM).

Due to the nature of drug products, pharmaceutical formulations are related to experimental mixtures and their issues. These problems take into account not only the amounts of the ingredients, but the proportions within the mixture; thus, the ingredients in such formulations are inherently dependent upon one another, excluding the implementation of experimental methodologies commonly used in optimization studies (Cho et al., 2009). Instead, for mixture problems, a special kind of experimental design is used to conduct what is referred to as a mixture experiment.

4.1. Effects of various excipients on the gelation of matrix tablets

To evaluate the effects of various excipients on the gelation of PEO matrix tablets, the diameters of the gelated and non-gelated parts of tablets were measured with various excipients while changing their ratios in the formulations. The gelation index was then calculated using the equation and compared with a target value (Table 4). The target profiles were selected as suggested in the previous study (Park et al., 2010). However, target profiles can be modified, if necessary, depending on the intended use and kinetics. The gelation index is the percentage of the tablet that has undergone gelation after immersion. Upon contact with the dissolution medium, the matrix tablet hydrated and swelled, causing a thick gel layer to form and expanding the tablet's surface. However, the effective swelling was limited only to the horizontal side of the tablet due to the application of polyacrylate plates in this study.

The gelation study was conducted for 5 h, and 4 replications were performed for all the experimental runs. Solid dosage forms usually stay in the upper GI tract for about 5 h after administration, where the amount of GI fluid is sufficient to cause gelation (Davis et al., 1986). Therefore, the 5-h time point should be sufficient to differentiate the formulations. Table 4 shows the mean and variance data for the gelation study and shows various types of gelation kinetics; the gelation at the end of 5 h ranged from 59.85% (Run order 4) to 98.61% (Run order 9). The gelling process was rapid after the first 30 min of contact with the dissolution medium (Fig. 1). However, after the fast initial swelling of 1–2 h, subsequent gelling kinetics was not fast enough for the tablets to gel completely. One plausible reason for this was that the media penetration rate was faster at the beginning since the fluid was in direct contact with the hydrophilic solid polymer. However, once a viscous gel layer had formed on the tablet surface, it could serve as a barrier to media penetration, decreasing the rate of diffusion of fluid into the matrix.

Run order 18 was composed of PEO only with the drug and magnesium stearate, and it was used as a reference to compare the gelation kinetics. Gelation properties can be divided into three categories: fast, medium, and slow. Large amounts of water-soluble ingredients, such as citric acid and NaH_2PO_4, caused fast swelling as shown in the Run order of 1, 2, and 19. When incorporated into a tablet, water-soluble salts might dissolve out quick, facilitating penetration of the medium into the inner matrix and causing most of the tablet to become a gel. Water-soluble and less viscous Polyox WSR N-10 also showed fast swelling (Run order 6). However, LH-11 and hydrophobic Syloid showed slow swelling kinetics (Run order 3 and 16) and large amounts of Ac-Di-Sol and Pharmacoat 603

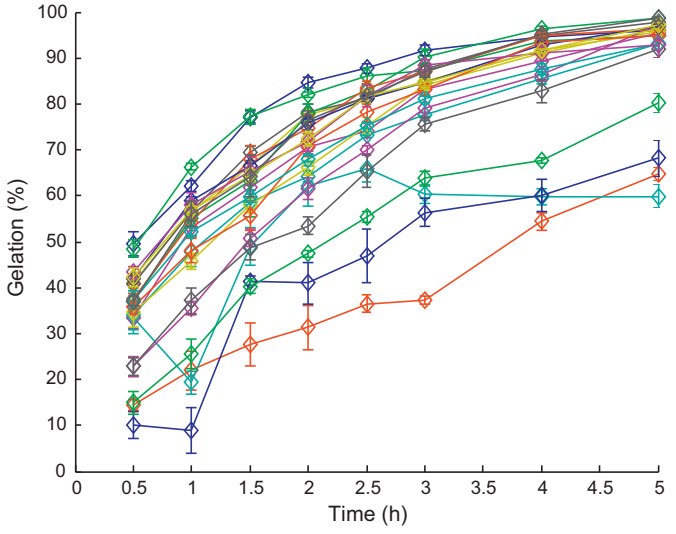

Fig. 1. Graphical representation of gelation/swelling profiles showing the gelation indices (%) against time for the various matrix tablet formulations ($n = 4$). Experimental runs were selected from the simplex lattice design as shown in Table 1. Due to the large number of runs, the key was not included in the figure.

caused slow swelling (Run order 12, 14). Na-CMC and HEC showed moderate swelling kinetics (Run order 5, 21).

Although it is not easy to generalize the properties, hydrophilic excipients in the tablet may absorb medium or dissolve quickly before a tight gel layer can form on the surface, allowing medium to penetrate into the inner matrix of the tablet and thus causing most of the matrix to become a gel. Moreover, the viscosity of the gel might be important to consider due to its barrier properties for media penetration (El-Malah and Nazzal, 2006; Siepmann et al., 2002). The drug release rate might be also dependent on the swelling properties because of increased diffusion resistance with longer distance.

Gel thickness increased significantly moving inward as the hydration progressed, so the dimensions of the solid core decreased. However, due to the limited area of actual swelling, a couple of the tablets were not completely hydrated or gelled (less than 80%), even after 5 h. Due to the limited unidirectional contact of the dissolution medium, the gelation kinetics seemed to be very slow compared to those in previous studies (Sako et al., 1996; Conti et al., 2007). However, this method might be useful to differentiate various formulations and design better ones.

From the obtained data of the gelation study with 21 experimental runs based on ten control factors over seven observed times from 0.5 to 5.0 h, vertical and horizontal analyses were applied. In order to conduct the factor screening procedure, stepwise regression was utilized for ten control factors from x_1 to x_{10} and for each point of time t_i corresponding to y_i. By integrating both forward selections and backward eliminations using Minitab software package based on significant level alpha ($\alpha = 0.15$), six significant factors for both mean and variance functions were selected, such as PEO (x_1), LH-11 (x_2), Syloid (x_3), Ac-Di-sol (x_4), citric acid (x_8), and Pharmacoat 603 (x_9). The first-order model for all factors was selected in the vertical analysis and the second-order for time t was selected in the horizontal analysis. By implementing Eqs. (5) and (6), the mean and variance models of RSM with six selected control factors over time were obtained. Finally, as demonstrated in Table 5, the optimal solutions of four control factors were obtained by using the proposed RD optimization methodology as identified in Eq. (7). Table 5 also provides target values and validation experiment results for the gelation study. The graphical representation of gelation profiles and gelation results (i.e., the optimal solutions, the

Table 5
Optimal solutions, target values and validation experiment results for the gelation study with % biases.

RD model	Optimal settings				Gelation rates (%) at observed times (hours)							
	PEO (mg)	LH-11 (mg)	Syloid (mg)	Pharma coat (mg)	0.5 h	1.0 h	1.5 h	2.0 h	2.5 h	3.0 h	4.0 h	5.0 h
MSE model	215.33	5.68	19.27	3.04	37.21	47.65	56.92	65.04	71.99	77.77	85.86	89.31
Target values (%)					37.75	47.61	56.71	65.54	69.32	77.55	88.42	88.81
Absolute biases O – T[a] (% biases)					0.54 (1.43)	0.04 (0.08)	0.21 (0.37)	0.50 (0.76)	2.67 (3.85)	0.22 (0.28)	2.56 (2.90)	0.50 (0.56)
Validation experiment results					37.68	48.26	57.10	66.71	70.91	77.81	88.82	89.36
Absolute biases V – T[b] (% biases)					0.07 (0.19)	0.65 (1.37)	0.39 (0.69)	1.17 (1.79)	1.59 (2.29)	0.26 (0.34)	0.40 (0.45)	0.55 (0.62)
Absolute biases V – O[c] (% biases)					0.47 (1.26)	0.61 (1.28)	0.18 (0.32)	1.67 (2.57)	1.08 (1.50)	0.04 (0.05)	2.96 (3.45)	0.05 (0.06)

[a] Absolute biases O – T = Abs (optimal values – Targets).
[b] Absolute biases V – T = Abs (validated values – targets).
[c] Absolute biases V – O = Abs (validated values – optimal values).

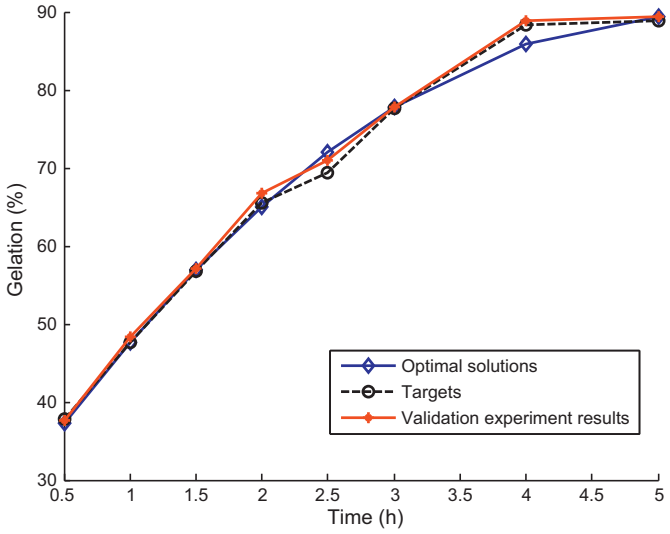

Fig. 2. Swelling profiles showing the gelation indices (%) against time for the matrix tablets with optimal solutions, target values, and validation experiment results ($n = 4$). The three profiles are similar and have consistent patterns with small deviation.

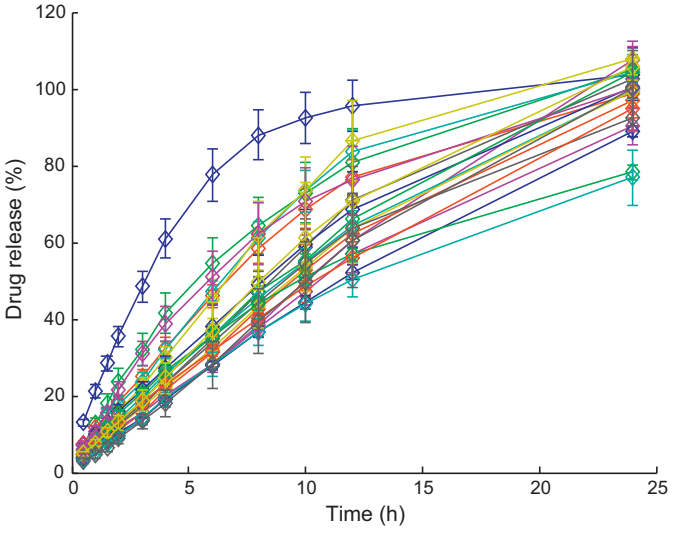

Fig. 3. Graphical representation of drug release profiles against time for the various matrix tablet formulations ($n = 4$). Experimental runs were selected from the simplex lattice design as shown in Table 1. Due to the large number of runs, the key was not included in the figure.

target values, and the validation experiment results) are illustrated in Figs. 1 and 2, respectively.

The optimal settings of the excipients were PEO, LH-11, Syloid, and Pharmacoat with weight ratios of 215.33 (88.50%), 5.68 (2.33%), 19.27 (7.92%), and 3.04 (1.25%), respectively. At these optimal settings, optimal gelation rates can be estimated by utilizing the proposed model from 0.5 h to 5.0 h compared with the target values. Fig. 2 clearly illustrates that the optimal solutions had similar values compared to the target values. Table 5 also provides biases and their associated percentages between the optimal solutions and the target values. For validation of the optimal setting, matrix tablets of the setting were prepared and the gelation was evaluated as shown in the Table 5. Absolute (validated values – optimal values) and percent biases were less than 3%, supporting the validity of the optimal settings. Based on these results, three results (i.e., optimal solutions, target values, validation experiment results) over time were similar and had consistent patterns with small biases.

4.2. *In vitro drug release from matrix tablets*

Fig. 3 shows the drug release profiles of the matrix tablets with different excipients at various ratios in the formulations. The percent released at the end of 24 h ranged from 78% (Run order 16) to 100%. The excipients can significantly influence the dissolution rate of the system. The mixture of the excipients, used as a mechanical support and release modulator, enables easy modification of the system depending on the target release profiles. Interactions among the excipients result in gel formation on the surface of the tablet, which can reduce the burst effect seen with typical matrix tablets. In this strategy, a combination of excipients can deliver the active ingredient at a nearly constant rate.

In the drug release tests, the output responses were measured from 0.5 h to 24 h and four replications were performed at all experimental runs so that mean and variance data could be calculated. Tables 6 and 7 provide the results of drug release kinetics for mean and variance, respectively. Run order 18 is composed of PEO only with API and magnesium stearate and showed slow drug release. Upon contact with the medium, the matrix tablet hydrated slowly and swelled, causing a thick viscous gel layer. The gel thickness increased moving inward as the hydration progressed. The viscous gel layer could be a diffusion barrier for the medium and the drug inside the matrix, causing slower drug release.

Similar to the gelation study, large amounts of water-soluble salts, such as citric acid and NaH_2PO_4, caused faster drug release as shown in the Run order of 1, 2, and 19. These salts can be used to modulate the micro-environmental pH with positive expectation on polymer swelling and drug release. The salts might dissolve easily due to their high water-solubility and thus have the ability to form channels within the polymer matrix and facilitate the penetration of release medium into the tablet inducing faster drug release (El-Malah and Nazzal, 2006). Large amounts of water-soluble and less viscous Polyox WSR N-10 resulted in faster drug release (Run order 6). It facilitated formation of channels through polymer matrix, enhancing water penetration and drug release (Khan and Jiabi, 1998). LH-11 and hydrophobic excipient, Syloid, showed slower drug release kinetics (Run order 3 and 16). These

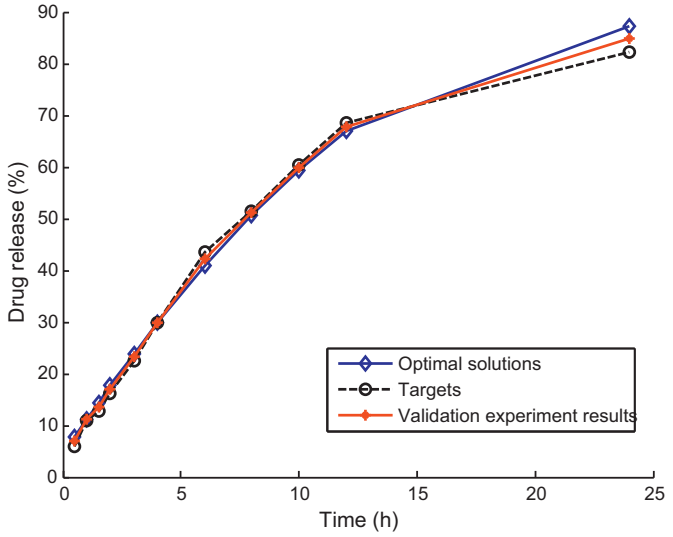

Fig. 4. Drug release profiles of the matrix tablets with optimal solutions, target values, and validation experiment results ($n = 4$). The three profiles are similar and have consistent patterns with small deviation.

Table 6
Experimental results for the drug release kinetics (mean) based on the experimental design format with target values.

Runs	0.5 h $\bar{y}_1$	1 h $\bar{y}_2$	1.5 h $\bar{y}_3$	2 h $\bar{y}_4$	3 h $\bar{y}_5$	4 h $\bar{y}_6$	6 h $\bar{y}_7$	8 h $\bar{y}_8$	10 h $\bar{y}_9$	12 h $\bar{y}_{10}$	24 h $\bar{y}_{11}$
1	13.03	21.21	28.48	35.44	48.45	60.99	77.59	88.05	92.53	95.64	103.83
2	7.17	12.64	18.03	23.71	32.00	41.55	54.44	64.51	72.90	80.77	105.02
3	7.46	11.61	15.05	18.31	25.25	32.53	45.99	58.31	68.67	76.88	98.76
4	5.91	9.40	14.88	17.88	23.79	32.02	47.36	61.09	73.40	83.80	104.44
5	3.94	8.12	8.12	9.66	13.70	19.31	28.23	38.34	49.98	60.68	107.48
6	5.60	9.22	12.72	16.10	22.52	30.04	45.16	61.78	73.55	86.49	107.75
7	4.64	7.94	9.99	12.91	17.98	23.37	34.94	46.90	58.87	71.02	102.57
8	7.21	10.08	13.10	16.08	21.60	27.13	38.24	48.99	59.60	68.66	100.60
9	4.79	7.58	10.11	13.00	18.73	25.17	35.68	47.34	55.17	66.19	104.56
10	3.66	6.40	8.60	10.98	15.73	21.54	31.44	42.56	52.67	62.40	96.91
11	4.91	8.31	11.68	13.88	19.99	25.84	35.66	45.60	54.79	64.26	99.63
12	7.29	9.26	10.55	11.84	15.75	20.11	28.22	37.55	47.21	56.98	90.32
13	4.29	7.06	9.35	12.00	16.86	22.20	32.49	43.19	53.64	63.61	99.34
14	4.05	6.98	9.52	12.29	17.48	23.49	33.83	44.33	54.69	63.62	92.62
15	3.63	6.54	8.16	10.28	14.36	19.25	27.91	36.59	44.49	52.24	88.97
16	5.09	8.48	12.13	15.30	20.99	26.65	35.58	44.03	51.03	56.94	78.26
17	4.87	7.55	10.83	13.40	18.31	22.87	31.70	40.24	48.50	55.85	95.00
18	3.29	5.32	7.62	9.58	14.16	19.39	28.15	36.70	44.10	50.38	76.89
19	6.04	10.73	15.66	21.49	31.09	38.66	50.89	62.28	70.66	76.23	100.14
20	4.92	7.71	10.55	13.06	18.74	24.57	37.11	49.48	61.34	70.60	105.72
21	2.92	4.82	6.34	8.81	13.35	18.06	28.15	39.49	49.59	60.48	100.15
Targets	6.00	11.00	12.80	16.10	22.60	29.80	43.50	51.40	60.30	68.50	82.30

may reduce the matrix erosion process and hinder drug diffusion (Furlanetto et al., 2006).

Similar to the gelation study, the stepwise regression approach was also applied to drug release study. Based on the stepwise regression results, five significant factors, PEO (x_1), Syloid (x_3), NaH_2PO_4 (x_7), citric acid (x_8), and Polyox WSR N-10 (x_{10}), for both mean and variance functions were selected. Moreover, the first-order model for all factors was selected in the vertical analysis and second-order for time t was selected in horizontal analysis. After utilizing the MSE-based RD optimization model, two control factors x_1 and x_8 were chosen as the optimal settings. The optimal settings of the excipients were PEO and citric acid with weight ratios of 191.99 (78.91%), and 51.32 (21.09%), respectively. At these optimal settings, the optimal drug release rates were estimated by utilizing the proposed model compared to the target values. Fig. 4 clearly illustrates that the optimal solutions had similar values compared to the target values, as well as the validation experiment results. Table 8 also provides biases and their associated percentages between the optimal solutions and the target values. For validation of the optimal setting, matrix tablets were prepared and the drug release profiles were evaluated. As shown in Table 8 and Fig. 4, the optimal solutions, target values, and validation experiment results for the drug release study are similar and have consistent patterns with small biases. The low biases prove the high prognostic ability of the method.

With the hydrophilic matrix, the absorption of dissolution medium occurs in the matrix and initiates dissolution of the drug from the inner layer. The dissolution rate is counter-balanced by gel formation in the matrix, which takes place simultaneously. The balance between the swelling and the gelling characteristics of the matrix system is critical in maintaining the desired drug release rate (Chopra et al., 2007; Pham and Lee, 1994). As dissolution proceeds, the gradual swelling of the outer layer provides new diffusion areas. Moreover, water-soluble drugs are released mainly by diffusion of dissolved drug molecules across the swollen gel layer. However, poorly soluble drugs are usually released by erosion (Skpoug et al.,

Table 7
Experimental results for the drug release kinetics (variance) based on the experimental design format.

Runs	0.5 h s_1^2	1 h s_2^2	1.5 h s_3^2	2 h s_4^2	3 h s_5^2	4 h s_6^2	6 h s_7^2	8 h s_8^2	10 h s_9^2	12 h s_{10}^2	24 h s_{11}^2
1	0.90	1.69	1.90	2.53	4.06	5.18	6.95	6.43	6.67	6.65	6.85
2	0.79	1.74	2.57	3.49	4.17	5.14	6.79	7.40	7.88	8.83	3.95
3	0.80	0.65	1.62	1.35	1.57	2.69	2.95	3.83	5.12	4.87	3.40
4	1.01	1.35	1.83	1.90	2.21	2.26	2.77	4.49	5.44	5.49	0.72
5	0.41	1.00	1.00	1.18	1.15	1.80	2.09	2.69	4.03	4.45	4.99
6	0.93	1.02	1.42	1.38	2.37	2.85	5.08	9.07	8.80	10.41	0.57
7	0.27	0.64	0.83	0.50	1.48	1.85	2.99	5.63	7.17	8.72	3.98
8	0.50	0.89	1.21	1.54	2.04	3.11	5.34	7.55	8.90	9.81	3.04
9	0.33	0.54	0.52	0.18	1.12	1.03	2.30	3.82	2.01	4.55	0.99
10	0.47	0.25	1.08	0.79	1.35	2.46	4.05	5.57	6.78	8.05	4.61
11	0.32	0.76	0.14	0.14	1.22	1.48	2.05	3.13	3.67	4.13	1.88
12	0.56	0.39	0.27	0.34	0.68	0.54	1.22	2.15	3.40	4.92	4.73
13	0.39	0.79	0.55	0.74	0.96	1.96	2.92	4.42	6.09	7.20	3.03
14	0.48	0.55	0.67	1.10	2.12	3.07	5.04	6.88	8.61	8.84	5.06
15	0.10	0.30	0.40	0.30	0.30	0.80	1.20	1.50	1.70	1.80	1.40
16	0.83	0.77	0.56	0.99	0.90	1.63	1.44	1.85	1.85	1.63	1.81
17	0.21	0.36	0.70	0.53	1.08	1.22	1.98	2.59	3.94	4.35	5.89
18	0.45	0.42	0.70	1.02	1.22	2.29	3.18	3.38	4.80	4.57	7.31
19	0.74	1.29	1.51	2.31	3.12	4.58	6.80	8.22	8.77	8.97	10.82
20	0.36	0.97	1.08	1.99	2.93	4.10	7.38	11.76	14.20	15.90	2.01
21	0.63	1.12	1.04	1.16	1.90	3.50	6.15	8.38	10.61	12.34	9.91

Table 8
Optimal solutions, target values, and validation experiment results for the drug release study with % biases.

RD model	Optimal settings		Optimal drug release rates (%) for observed times (hours)									
	PEO (mg)	Citric acid (mg)	0.5 h	1.0 h	1.5 h	2.0 h	3.0 h	4.0 h	6.0 h	8.0 h	10.0 h	12.0 h	24.0 h
MSE model	191.99	51.32	7.77	11.15	14.45	17.67	23.91	29.85	40.86	50.70	59.36	66.85	87.21
Target values (%)			6.00	11.00	12.80	16.10	22.60	29.80	43.50	51.40	60.30	68.50	82.30
Absolute biases O – T[a] (% biases)			1.77 (29.50)	0.15 (1.36)	1.65 (12.89)	1.57 (9.75)	1.31 (5.80)	0.05 (0.17)	2.64 (6.07)	0.70 (1.36)	0.94 (1.56)	1.65 (2.41)	4.91 (5.97)
Validation experiment results			6.90	11.10	13.60	16.90	23.30	29.80	42.20	51.10	59.80	67.70	84.80
Absolute biases V – T[b] (% biases)			0.90 (15.00)	0.10 (0.91)	0.80 (6.25)	0.80 (4.97)	0.70 (3.10)	0.00 (0.00)	1.30 (2.99)	0.30 (0.58)	0.50 (0.83)	0.80 (1.17)	2.50 (3.04)
Absolute biases V – O[c] (% biases)			0.87 (1120)	0.05 (0.45)	0.85 (5.88)	0.77 (4.36)	0.61 (2.55)	0.05 (0.17)	1.34 (3.28)	0.4 (0.79)	0.44 (0.74)	0.85 (1.27)	2.41 (2.76)

[a] Absolute biases O – T = Abs (optimal values – targets).
[b] Absolute biases V – T = Abs (validated values – targets).
[c] Absolute biases V – O = Abs (validated values – optimal values).

1991). Therefore, the hydrophilic property of an API needs to be considered when evaluating the drug release profiles.

Further work is planned to find a specific formulation satisfying both gelling properties and drug release profiles compared to specific targets. Moreover, conventional prioritization and weighting methods will be integrated and customized based on *in vivo* results in order to optimize the gelation and drug release at the same time.

5. Conclusions

A new experimental design strategy was developed by integrating the well-established response surface methodology (RSM) and the time series modeling. It proved very useful in formulation studies aimed at the development of SR matrix tablet allowing a systematic and reliable screening method to characterize significant factors influencing drug release. Some formulation variables are expected to have significant effects on the amount and kinetics of swelling and drug release. By exploiting the relationships between control factors and output responses from an experimental design, RD methods could reveal robust solutions that are less sensitive to input variations. Based on the results of matrix gelation and drug release, optimal solutions, target values, and validation experiment results over time were similar and showed consistent patterns with small biases. The experimental design methodology could be a very economic way to obtain maximum information, which can save a significant amount of time. Moreover, it can reduce the materials used for analyses and the personal costs as well.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (20100002579).

Appendix A.

In this study, the gelation experiment was conducted for 5 h compared to 24 h of the drug release profiles. In most cases the gelation index was greater than 90% within 5 h. However, there were a few cases that the index was less than 90% even about 60% after 5 h. In such a low gelation situation, especially for the samples (Runs) of 3, 8, and 16, prolonged gelation study might be necessary and was conducted to investigate if there are any internal relationships between the gelation vs. release kinetics. The sampling points were 6 h, 12 h, and 24 h ($n = 4$).

The gelation index showed that the samples did not gel completely even after 24 h (Table A.1). After 5 h the index did not increase significantly. One reason was that the samples contained relatively hydrophobic excipients, especially Syloid and LH-11 and they may not wet easily causing the data collection difficult. The indices could be obtained by measuring the diameters of the portions that gelled after immersion in the medium. As already shown previously (Park et al., 2010), tablets with hydrophilic excipients could give clear swelling front and also consistent data.

Table A.1
Additional experimental results of the prolonged gelation study for the samples of low gelation index ($n = 4$).

Runs	6 h		12 h		24 h	
	Gelation (%)	S.D.	Gelation (%)	S.D.	Gelation (%)	S.D.
3	67.46	0.50	75.10	5.67	80.51	1.69
8	72.19	6.18	75.34	4.18	76.68	3.77
16	80.71	1.57	80.78	1.05	81.09	0.55

For the hydrophobic excipients, initial measurements were pretty reasonable showing relatively clear swelling front. However, as the immersion time increased, the swelling front was not clear and not circular either, which made the measurement and the calculation of the index difficult. Even after 24 h of gelation, there were dry spots in the center, which were considered to be not swollen due to the hydrophobic excipients. Aqueous medium might bypass the hydrophobic area and wet hydrophilic portion inside the tablet matrix. It is believed that the spots may not affect significantly on the drug release because tablets are swollen mostly and the model drug is hydrophilic. Hydrophobic drugs may behave differently.

The gelation study applied in here was designed to differentiate the formulations focusing on the initial gelation to mimic *in vivo* environment. If the gelation study can represent *in vivo* and also be integrated with drug release, it would be the optimum. More work is ongoing how to integrate the release profiles and the gelation study. Moreover, one more reason why not comparing the 12 h or even 24 h gelation was that for the experimental design method, all the data need to be arranged horizontally and also vertically in a table. If there are any data missing or erroneous in the table, the developed design method may not be applicable in that time causing the interpretation inconsistent. Since many formulations swelled mostly in less than 5 h, the design model was applied in that time scale.

References

Alderman, D.A., 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms. Int. J. Pharm. 5, 1–9.

Bloomfield, M.S., Butler, W.C., 2000. Robustness testing, using experimental design, of a flow-through dissolution method for a product where the actives have markedly differing solubility properties. Int. J. Pharm. 206, 55–61.

Campos-Aldrete, M.E., Villafuerte-Robles, L., 1997. Influence of the viscosity degree and the particle size of HPMC on metronidazole release from matrix tablets. Eur. J. Pharm. Biopharm. 43, 173–178.

Cho, B.R., Shin, S.M., Choi, Y., Kovach, J., 2009. Development of a multidisciplinary optimization process for designing optimal pharmaceutical formulations with constrained experimental regions. Int. J. Adv. Manuf. Tech. 44, 841–853.

Chopra, S., Patil, G.V., Motwani, S.K., 2007. Release modulating hydrophilic matrix systems of losartan potassium: optimization of formulation using statistical experimental design. Eur. J. Pharm. Biopharm. 66, 73–82.

Conti, S., Maggi, L., Segale, L., Ochoa Machiste, E., Conte, U., Grenier, P., Vergnault, G., 2007. Matrices containing NaCMC and HPMC 2 Swelling and release mechanism studies. Int. J. Pharm. 333, 143–151.

Davis, S.S., Hardy, J.G., Fera, J.W., 1986. Alimentary tract and pancreas: transit of pharmaceutical dosage forms through the small intestine. Gut 27, 886–892.

Ebube, N.K., Jones, A.B., 2004. Sustained release of acetaminophen from heterogeneous mixture of two hydrophilic non-ionic cellulose ether polymers. Int. J. Pharm. 272, 19–27.

El-Malah, Y., Nazzal, S., 2006. Hydrophilic matrices: application of Placket-Burman screening design to model the effect of POLTOX-carbopol blends on drug release. Int. J. Pharm. 309, 163–170.

Ford, J.L., Mitchell, K., Rowe, P., Armstrong, D.J., Elliott, P.N.C., Rostron, C., Hogan, J.E., 1991. Mathematical modeling of drug release from hydroxypropylmethylcellulose matrices: effect of temperature. Int. J. Pharm. 71, 95–104.

Furlanetto, S., Cirri, M., Maestrelli, F., Corti, G., Mura, P., 2006. Study of formulation variables influencing the drug release rate from matrix tablets by experimental design. Eur. J. Pharm. Biopharm. 62, 77–84.

Gao, P., Skoug, J.W., Nixon, P.R., Ju, T.R., Stemm, N.L., Sung, K.C., 1996. Swelling of hydroxypropylmethylcellulose matrix tablets Mechanistic study of the influence of formulation variables on matrix performance and drug release. J. Pharm. Sci. 85, 732–740.

Juarez, H., Rico, G., Villafuerte, L., 2001. Influence of admixed carboxymethylcellulose on release of 4-aminopyridine from hydroxypropyl methylcellulose matrix tablets. Int. J. Pharm. 216, 115–125.

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 n release rate of the drug. J. Control. Release 54, 185–190.

Kincl, M., Turk, S., Vrečer, F., 2005. Application of experimental design methodology in development and optimization of drug release method. Int. J. Pharm. 291, 39–49.

Madhusudan Rao, Y., Krishna Veni, J., Jayasagar, G., 2001. Formulation and evaluation of dichlorofenac sodium using hydrophilic matrices. Drug. Dev. Ind. Pharm. 27, 759–766.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C., Hogan, J.E., 1993. The influence of concentration on the release of drugs from gel and matrices containing Methocel. Int. J. Pharm. 100, 155–163.

Montgomery, D.C., 2001. Design and Analysis of Experiments. John Wiley & Sons Inc.

Neau, S.H., Howard, M.A., Claudius, J.S., Howard, D.R., 1999. The effect of aqueous solubility of xanthine derivates on the release mechanism from ethylcellulose matrix tablets. Int. J. Pharm. 179, 97–105.

Nerurkar, J., Jun, H.W., Price, J.C., Park, M.O., 2005. Controlled release matrix tablet of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rate. Eur. J. Pharm. Biopharm. 61, 56–68.

Park, J.S., Shim, J.Y., Truong, N.K.V., Park, J.S., Shin, S., Choi, Y.W., Lee, J., Yoon, J.H., Jeong, S.H., 2010. A pharma-robust design method to investigate the effect of PEG and PEO on matrix tablets. Int. J. Pharm. 393, 79–87.

Pham, A.T., Lee, P.I., 1994. Probing the mechanism of drug release from hydroxypropylmethyl cellulose matrices. Pharm. Res. 11, 1379–1385.

Rao, K.V.R., Devi, K.P., Buri, P., 1990. Influence of molecular size and water solubility of the solute on its release from swelling and erosion controlled polymeric matrices. J. Control. Release 12, 133–141.

Sako, K., Nakashima, H., Sawada, T., Fukui, M., 1996. Relationship between gelation rate of controlled-release acetaminophen tablets containing polyethylene oxide and colonic drug release in dogs. Pharm. Res. 13, 594–598.

Scheffé, H., 1958. Experiments with mixtures. J. R. Statist. Soc. B 20, 334–360.

Shin, S.M., Cho, B.R., 2009. Studies on a Bi-objective robust design optimization problem. IIE Trans. 41, 957–968.

Shin, S.M., Cho, B.R., 2005. Bias-specified robust design optimization and an analytical solutions. Comput. Ind. Eng. 48, 129–148.

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.

Skpoug, J.W., Borin, M.T., Fleishaker, J.C., Cooper, A.M., 1991. In vitro and in vivo evaluation of whole and half tablets of sustained release adinazolam mesylate. Pharm. Res. 8, 1482–1488.

Vining, G.G., Myers, R.H., 1990. Combining taguchi and response surface philosophies: a dual response approach. J. Qual. Technol. 22, 38–45.