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A pharma-robust design method to investigate the effect of PEG and PEO on matrix tablets

Jun Sang Park[a,c], Ji Yeon Shim[a], Nguyen Khoa Viet Truong[b], Jung Soo Park[a], Sangmun Shin[b], Young Wook Choi[c], Jaehwi Lee[c], Jeong-Hyun Yoon[d], Seong Hoon Jeong[d,*]

[a] GL PharmTech Corp., Seongnam, Gyeonggi, 462-807, South Korea
[b] Department of System Management & Engineering, Inje University, Gimhae, 621-749, South Korea
[c] College of Pharmacy, Chung-Ang University, Seoul, 156-756, South Korea
[d] Collegel of Pharmacy, Pusan National University, Busan, 609-735, South Korea

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ABSTRACT

Even though polyethyleneoxide (PEO)–polyethyleneglycol (PEG) blends have been used widely for sustained release matrix tablets, evaluations of the effects of PEG or PEO on the matrix properties have been limited. In order to evaluate gelling behavior and drug release profiles of PEG, various contents of the polymers were investigated through a robust experimental design method. When exposed to an aqueous environment, the PEO–PEG matrix hydrated slowly and swelled, causing a thick gel layer to form on the surface, the thickness of which increased significantly depending on the PEG contents. Since polyacrylate plates were used for the study, the matrix was not completely hydrated and gelled even after 5 h. However, the results could be applied to the time-oriented responses RD (robust design) models to obtain optimal settings and responses for the observed times. The optimal settings of PEO and PEG were 94.26 and 140.04 mg, respectively (PEG rate of 148.57%). Moreover, as the amount of PEG increased, the release rate also increased. When the formulation contained more than 150% of PEG, most of the drug loaded in the tablet was released in about 12 h. When the amount of PEG was less than 100%, the drug release rate was sustained significantly. Based on the RD optimization model for drug release, the optimal settings were PEG and PEO of 124.3 and 110 mg, respectively (PEG rate of 88.50%). Therefore, PEG rate of about 90–150% is suggested for matrix tablet formulations, and the exact ratio could be formulated according to the resulting tablet's properties.

1. Introduction

Hydrophilic swellable polymers have been used widely in matrix tablet formulations to control the release rate of a drug (Alderman, 1984; Ford et al., 1991; Juarez et al., 2001; Rao et al., 1990; Dhawan et al., 2005). The main goal of the matrix system is to extend drug release with zero-order release kinetics to maintain a constant *in vivo* plasma drug concentration and a consistent pharmacological effect. To achieve a constant release rate, a number of matrix devices have been developed with various types of polymeric excipients, either alone or in a mixture, to modify tablet hydration and to change the release rate and mechanism (Ebube and Jones, 2004; Madhusudan et al., 2001; Neau et al., 1999; Nerurkar et al., 2005).

The matrix tablets are usually composed of active pharmaceutical ingredients and hydrophilic swellable polymers that form gels when exposed to an aqueous environment. Among the various types of polymers, hydroxypropyl methylcellulose (HPMC) is one of the most common because of its safety, application, and compatibility with many drugs (Conti et al., 2007a; Khurahashi et al., 1996; Reynolds et al., 1998). Moreover, blends of pharmaceutically approved polymeric materials have been used extensively, including systems of Na CMC (carboxymethylcellulose)–HPMC (Conti et al., 2007a,b), PEO (polyethylene oxide)–carbopol (carboxyvinyl polymer) (Hong and Oh, 2008), and PEO–PEG (polyethylene glycol) (Kojima et al., 2008; Sako et al., 1996).

When administered, the surface of the matrix tablets is hydrated upon exposure to the gastrointestinal (GI) fluid, forming a viscous-gel layer that may hinder water penetration. Therefore, water penetration may be the rate-controlling step during gel formation. It is both the formation of the gel layer and its physicochemical properties that can modify the drug release kinetics from the matrix system. Water penetration may be dependent on the polymers' chemical structure, concentration, and viscosity. If the gelling rate or swelling is too slow, *i.e.*, more than 5–6 h after administration (incomplete gelation while passing through stomach and small

* 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).

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intestine), part of the tablet may not be fully wetted or hydrated, resulting in a 'dry core' and incomplete drug release. Moreover, the mechanical strength of the viscous-gel layer should be strong enough to maintain its integrity and release rate and mechanism. If too weak, most of the gel will disintegrate quickly without any significant sustained release effect.

Depending on the mechanical properties of the gel layer, drug release is controlled by different mechanisms with different kinetics (Conti et al., 2007a). In the case of low viscosity gelling agents, erosion of the swollen polymer is the major release factor that generally leads to zero-order release kinetics. If high viscosity polymers are used, a mechanically stable gel can be formed and polymer dissolution/disintegration will be minimal (Conti et al., 2007a). Therefore, the diffusion-controlled mechanism will be the major mechanism for drug release from the swollen matrix. Both mechanisms can be modulated by formulating different types of polymers.

Among the polymeric blends for the matrix tablet, combination of PEO and PEG showed significant sustained release of a drug throughout the GI tract, including the colon, where the amount of aqueous media is limited (Sako et al., 1996). In the blend, PEO was incorporated as a gel-forming polymer and PEG was used as a hydrophilic agent to facilitate water uptake into the tablet matrix. The tablet showed stable drug release in the GI tract without any significant burst effect (Kojima et al., 2008).

Even though the PEO–PEG blend can be used for matrix tablets, most previous studies investigated a fixed ratio between both excipients and the effects of different ratios of PEO and PEG on the matrix tablets have not been quantitatively evaluated. The present study investigates the properties of matrix systems containing various ratios of the two polymers to find a correlation and optimum ratio for a specific purpose. Among the tablet properties, gelling behavior and drug dissolution profiles are evaluated together with a robust experimental design method.

Robust design (RD) is an enhanced process/product design methodology to determine the best factor settings while minimizing process variability and bias (*i.e.*, the deviation from the target value of a product). The primary procedure in RD includes experimental design, estimation of model parameters, and optimization to obtain the optimal factor settings. By exploiting the information about the relationships between input factors and output responses from an experimental design, RD methods reveal robust solutions that are less sensitive to input variations. Given this fact, one of the main challenges is the optimal design of pharmaceutical formulations to identify better approaches to various unmet clinical needs. Traditional design methods have often been applied to situations in which the primary characteristics of interest are time-insensitive. However, in pharmaceutical processes, time-oriented characteristics, such as drug release and gelation kinetics, are often of interest. In this study, a new 'pharma-RD method' is proposed and this method aims to apply RD techniques to those time-oriented characteristics. In each experimental run, mean and variance values of drug release and gelation kinetics are measured over time. In this situation, both responses are functions of control factors and observed time since the tentative relationship can be analyzed according to both vertical and horizontal directions. The response surface methodology (RSM) is utilized for both analysis directions.

2. Materials and methods

2.1. Materials

The model drug, Terazosin HCl dihydrate (molecular weight 459.93, free base 387.43, log P 1.4), was purchased from Hanseo Chemical (Seoul, Korea), which is freely soluble in water. PEO (Polyox WSR-303) of average molecular weight 7.0×10^6 and viscosity 7,500–10,000 mPa (1% solution) was purchased from Dow Chemical (Midland, MI, USA). Polyethylene glycol 6000 (PEG 6000) was purchased from Sanyo Chemical Industries (Ibaraki, Japan). Magnesium stearate was purchased from Faci Asia (Jurong Island, Singapore). All other reagents used were of analytical grade.

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) before mixing to remove any aggregates. The model drug (Terazosin HCl dihydrate) was mixed manually with PEO and PEG in a mortar and then blended with magnesium stearate. The resultant mixture was compressed on a single-punch hydraulic laboratory press using plane-face punches with a diameter of 9.0 mm. The compression force was kept constant at 8.0 MPa and the total weight of each tablet was around 241 mg. The thickness of the tablets was about 4.0 mm.

2.3. Evaluation of tablet gelation

Gelation index might be a useful tool to represent the portion of a tablet that has undergone gelation on time. Each tablet was inserted between two transparent polyacrylate plates (5 cm × 5 cm) and held tight with a rubber band. The polyacrylate plates and tablet were immersed in 900 mL of dissolution medium (pH 6.8) and stirred with a magnetic bar (180 rpm/min). Due to the size of the plates, gelation study was performed in a different condition compared to drug release test. Test tablets were removed from the medium at predetermined time intervals (30, 60, 90, 120, 180, 240, and 300 min) and the diameters of 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).

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

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

Table 1
Formulation compositions of the matrix tablets.

Components (mg)	PEG 10%	PEG 50%	PEG 100%	PEG 150%	PEG 300%	PEG 500%
Terazosin HCl, $2H_2O$	5.935	←	←	←	←	←
Polyox WSR 303 (PEO)	213.00	156.20	117.15	93.71	58.58	39.05
PEG 6000	21.30	78.10	117.15	140.57	175.73	195.23
Magnesium stearate	0.96	←	←	←	←	←
Total weight	241.2	←	←	←	←	←
Percentage of PEG to PEO	10%	50%	100%	150%	300%	500%

2.4. Drug release test

Drug release tests were conducted according to USP 27 Apparatus 2 guidelines (paddle method) (Vankel® VK 7000, Vankel, Edison, NJ) with 900 mL of dissolution medium maintained at 37 ± 0.5 °C and mixed at 100 rpm. Due to the high solubility of the model drug, simulated intestinal fluid (SIF) (pH = 6.8, 50 mM phosphate buffer) without any enzymes was selected as a dissolution medium in this study. Samples were withdrawn at predetermined time intervals and analyzed for drug content using an HPLC system (Agilent 1100 Series, Agilent Technologies, Waldbronn, Germany) at a wavelength of 254 nm. Samples were filtered with 30-μm PE filters, and then 20 μL of each sample was injected. A μ-Bondapak® C_{18} 10 μm (3.9 mm × 300 mm) (Waters, Milford, US) column was used. The mobile phase was a mixture of aqueous buffer (0.75% (w/w) sodium citrate and 0.54% (w/w) citric acid), methanol, and acetonitrile in a volume ratio of 80:5:15, respectively.

2.5. Analysis of drug release kinetics

The drug release data can be fitted to the well-known exponential equation, which has been used extensively to describe the drug release behavior from polymeric systems (Korsmeyer et al., 1983)

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

where M_t/M_∞ is the fraction of drug released at time t. k is the proportionality constant, which shows the structural and geometrical properties of the matrix. A higher k value may suggest burst drug release from the matrix. The exponent, n, is the diffusional exponent, which can indicate the mechanism of drug release and depends on the polymer swelling characteristics and the relaxation rate at the swelling front. The equation is valid only for the early stages (≤70%) of drug release. According to the criteria for release kinetics from swellable systems of cylindrical geometry, a release exponent value, $n = 0.45$, $0.45 < n < 0.89$, and $0.89 < n < 1.0$ indicates Fickian (case I) diffusion, non-Fickian (anomalous) diffusion, and zero-order (case II) transport, respectively (Peppas, 1983; Ritger and Peppas, 1987).

3. Robust design model development

3.1. Experimental framework and response surface methodology (RSM)

Robust design (RD) techniques are based on exploiting the mean and variance information of responses. The concept building robustness into a design is increasingly popular in the pharmaceutical field because of its practicality. There have been many attempts to integrate Taguchi's RD principles with well-established statistical techniques in order to directly model responses as functions of input factors (Vining and Myers, 1990; Shin and Cho, 2005). In practice, it is necessary to handle the responses (*i.e.*, drug release rate and gelation rates) as time series data, which are called "time-oriented responses" in this study. The associated experimental format is shown in Table 2. x, $\bar{y}_i$, s_i^2, and t_i represent the vector of input control factors, mean, variance, and time of data sampling, respectively. At each time t_i, mean response y_i and variance response s_i^2 based on the number of replications are shown in Table 3.

Response surface methodology (RSM) is a collection of mathematical and statistical techniques useful for modelling and analyzing problems when the response of interest is influenced by several factors, and the objective is to optimize (either minimize or maximize) this response. RSM is typically used to optimize the response by estimating an input-response functional form when the exact functional relationship is not known or is very complicated (Box and Draper, 1987; Khuri and Cornell, 1987; Myers and Montgomery, 2002; Shin and Cho, 2009). To a comprehensive presentation of RSM, Shin and Cho (2005) provided insightful comments on the current status and future direction of RSM. Using the output responses (*i.e.*, mean responses $\bar{y}_i$ and variance responses s_i^2), the estimated response functions of the process mean and variance are given as

$$\hat{\mu}_i(\boldsymbol{x}) = \hat{\alpha}_0 + \boldsymbol{x}^T\boldsymbol{a} + \boldsymbol{x}^T\boldsymbol{A}\boldsymbol{x} \quad (1)$$

$$\hat{\sigma}_i^2(\boldsymbol{x}) = \hat{\beta}_0 + \boldsymbol{x}^T\boldsymbol{b} + \boldsymbol{x}^T\boldsymbol{B}\boldsymbol{x} \quad (2)$$

where

$$\boldsymbol{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_k \end{bmatrix}, \quad \boldsymbol{a} = \begin{bmatrix} \hat{\alpha}_1 \\ \hat{\alpha}_2 \\ \vdots \\ \hat{\alpha}_k \end{bmatrix}, \quad \boldsymbol{A} = \begin{bmatrix} \hat{\alpha}_{11} & \hat{\alpha}_{12}/2 & \cdots & \hat{\alpha}_{1k}/2 \\ \hat{\alpha}_{12}/2 & \hat{\alpha}_{22} & \cdots & \hat{\alpha}_{2k}/2 \\ \vdots & \vdots & \ddots & \vdots \\ \hat{\alpha}_{1k}/2 & \hat{\alpha}_{2k}/2 & \cdots & \hat{\alpha}_{kk} \end{bmatrix},$$

$$\boldsymbol{b} = \begin{bmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \\ \vdots \\ \hat{\beta}_k \end{bmatrix}, \quad \boldsymbol{B} = \begin{bmatrix} \hat{\beta}_{11} & \hat{\beta}_{12}/2 & \cdots & \hat{\beta}_{1k}/2 \\ \hat{\beta}_{12}/2 & \hat{\beta}_{22} & \cdots & \hat{\beta}_{2k}/2 \\ \vdots & \vdots & \ddots & \vdots \\ \hat{\beta}_{1k}/2 & \hat{\beta}_{2k}/2 & \cdots & \hat{\beta}_{kk} \end{bmatrix}$$

and where vector **a** and matrix **A** are the estimated regression coefficients for the process mean, and vector **b** and matrix **B** are the estimated regression coefficients for the process variance. The eventual objective of RSM is to determine optimal operating conditions (*i.e.*, optimal control factor levels) for a system.

Table 2
Experimental format for time-oriented responses.

Runs	Input factors, x	t_1		t_2		...		t_i		...		t_m	
		$\bar{y}_1$	s_1^2	$\bar{y}_2$	s_2^2	...	...	$\bar{y}_i$	s_i^2	...	...	$\bar{y}_m$	s_m^2
1	Control factors	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
...		...	...	...	...	...	...	...	...	...	...	...	...
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	$\mathbf{T}_{t1}$		$\mathbf{T}_{t2}$				$\mathbf{T}_{ti}$				$\mathbf{T}_{tn}$	

3.2. Proposed RD models based on RSM and time-oriented responses

The proposed RD procedure consists of three stages: model building, robust design model selection, and optimization. With static responses, RSM is utilized in the model building stage as discussed in the previous section. In this study, the time-oriented responses need to be handled and the empirical models need to

Table 3
Experimental format for each time t_i.

Runs	Input factors, x	y_i (replications)						$\bar{y}_i$	s_i^2
1	Control factors	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		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

be developed in the model building stage. Because of the feature of time series data, an empirical relationship between the time-oriented responses and control factors must be established.

The proposed analysis combines two directional approaches, such as vertical and horizontal approaches, because the response **Y** is a function of control factors and time, and the tentative relationship can be analyzed by both directions. In the vertical directional approach, letting $\mathbf{Y} = [\mathbf{Y}_{c1}, \mathbf{Y}_{c2}, \ldots \mathbf{Y}_{cm}]$, which is the matrix of mean responses where $\mathbf{Y}_{c1}$, $\mathbf{Y}_{c2}$, …, and $\mathbf{Y}_{cm}$ 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 2, each column of **Y** can be a function of design matrix **X**. In the horizontal directional approach, each row of **Y** becomes a function of time *t*.

In the vertical directional approach, the general vertical form of the relationship between **Y** and **X** can be expressed as

$$\boldsymbol{Y} = \begin{bmatrix} 1 & x_1 & x_2 & \cdots \end{bmatrix} \times \boldsymbol{M}_c \tag{3}$$

where $\mathbf{M}_c$ denotes a matrix of parameters vertical analysis given as follows:

$$\boldsymbol{M}_c = \begin{bmatrix} \boldsymbol{m}_{c1} & \boldsymbol{m}_{c2} & \cdots & \boldsymbol{m}_{cm} \end{bmatrix} = (\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T\boldsymbol{Y} \tag{4}$$

While vertical analysis can express the relationship between responses **Y** and input control factors *x* represented by design matrix **X**, horizontal analysis is also proposed to build the relationship between responses **Y** and time *t*. In the horizontal directional approach, if $\mathbf{Y} = [\mathbf{Y}_{r1}, \mathbf{Y}_{r2}, \ldots \mathbf{Y}_{rn}]$ is the matrix of mean responses where $\mathbf{Y}_{r1}, \mathbf{Y}_{r2}, \ldots$ and $\mathbf{Y}_{rn}$ represent row vectors of mean responses or row vectors of variance responses in Table 2, $\mathbf{Y}_r$ indicates a function of *t* as following:

$$\boldsymbol{Y}_r = \boldsymbol{m}_r \times \begin{bmatrix} 1 & t & \cdots \end{bmatrix}^T \tag{5}$$

where the mean vector $\mathbf{m}_r$, represented by rows, can be estimated as

$$\boldsymbol{m}_r = (\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T\boldsymbol{Y}_r. \tag{6}$$

As a result, the general horizontal form of the relationship can be derived as follows:

$$\boldsymbol{Y} = \boldsymbol{M}_{r\_mean} \times \begin{bmatrix} 1 & t & \cdots \end{bmatrix}^T \tag{7}$$

where $\boldsymbol{M}_{r\_mean} = [\boldsymbol{m}_{r1}, \boldsymbol{m}_{r2}, \cdots, \boldsymbol{m}_{rn}]^T$ is the transposed matrix of parameters for horizontal analysis. Using Eqs. (3), (4) and (7), the two directional approaches can be combined into the following general relationship of **Y** as a function of *x* and *t* given that

$$\boldsymbol{Y}(\boldsymbol{x}, t) = \begin{bmatrix} 1 & x_1 & x_2 & \cdots \end{bmatrix} \times (\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T\boldsymbol{M}_{r\_mean}\begin{bmatrix} 1 & t & \cdots \end{bmatrix}^T. \tag{8}$$

Similarly, the empirical relationships between variance and input control factors are then developed. The functional form of variance model can be obtained as

$$\boldsymbol{S}(\boldsymbol{x}, t) = \begin{bmatrix} 1 & x_1 & x_2 & \cdots \end{bmatrix} \times (\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T\boldsymbol{M}_{r\_var}\begin{bmatrix} 1 & t & \cdots \end{bmatrix}^T. \tag{9}$$

Based on the general functional relationships of mean and variance, the next stage of the RD procedure focuses on RD model development in order to find the robust optimal solutions (*i.e.*, the optimal factor settings, **x**). The proposed RD optimization model based on *p*-norm and MSE concepts can be formulated as follows:

$$\begin{aligned} &\text{minimize} \sum_{i=1}^{m} \left(\left| \boldsymbol{Y}(\boldsymbol{x}, t_i) - \boldsymbol{T}_{ti} \right| \right)^p + \sum_{i=1}^{m} \left(\left| \boldsymbol{S}(\boldsymbol{x}, t_i) \right| \right)^p \\ &\text{S.t. } \boldsymbol{x} \in \Omega \end{aligned} \tag{10}$$

where $\mathbf{T}_{ti}$ denotes the target value of responses (*i.e.*, drug release rate and gelation) and norm $p = 2$ in this study.

4. Results and discussion

4.1. Effects of PEG on the gelation of PEO matrix tablets

Generally, water-soluble excipients such as PEG in the tablet dissolve quickly before a tight gel layer can form on the surface, allowing water to penetrate into the inner matrix of the tablet and thus causing most of the inner matrix to gel. In order to investigate the effects of PEG on the gelation of PEO matrix tablets, the diameters of the gelated and non-gelated parts of tablets with varying ratios of PEG in the formulations were measured; the gelation index was then calculated together with a target value (Table 4). The target was selected after a lot of 'in-house' investigations. The gelation index is the percentage of the tablet that has undergone gelation after immersion. When a matrix tablet is exposed to the dissolution medium, swelling, macromolecular changes in gel networks, takes place and expands the tablet surface. However, the effective swelling was limited only to the horizontal side of the tablet by the application of polyacrylate plates in this study.

Upon contact with the medium, the matrix tablet hydrated slowly and swelled, causing a thick gel layer to form. Fig. 1 shows pictures of the gelation using the polyacrylate plates from time 0 to 4 h. The gel thickness increased significantly moving inward as the hydration progressed. Therefore, the dimensions of the solid core decreased as shown in Fig. 2 and Table 4. However, due to the limited area of actual swelling, the matrix was not completely hydrated or gelled, even after 5 h, in all the formulations (Figs. 1 and 2). 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., 2007a,b). However, it might be useful to understand and also differentiate various formulations.

The swelling process took place rapidly after the first 30 min of contact with the dissolution medium (Fig. 2). However, after the fast initial swelling, the 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 solid polymer. However, once a viscous-gel layer had formed on the tablet surface, it could serve as a barrier to media penetration, reducing disintegra-

Table 4
Experimental results for the gelation study (gelation index, *y*, with standard deviation, *s*) depending on the amount of incorporated PEG in the matrix tablet formulations.

Runs	PEG (%)	PEO	PEG	0.5 h		1 h		1.5 h		2 h		3 h		4 h		5 h	
		x_1	x_2	$\bar{y}_1$	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
1	10	213.00	21.30	41.91	3.32	56.93	4.69	69.54	1.26	73.77	2.30	79.14	4.15	84.65	0.78	91.4	1.41
2	50	156.20	78.10	39.23	2.27	43.93	2.65	55.51	1.15	63.13	2.86	75.00	2.41	81.40	1.25	88.9	0.28
3	100	117.15	117.15	37.79	1.40	49.06	0.99	59.02	0.44	65.9	0.98	77.39	1.78	86.33	0.69	90.6	0.57
4	150	93.71	140.57	37.61	1.77	49.21	1.47	60.28	1.27	67.06	0.99	80.05	0.92	86.78	2.17	90.1	0.74
5	300	58.50	175.80	40.78	1.71	48.64	0.81	60.29	1.05	68.7	0.88	79.25	0.65	87.66	1.05	91.8	0.68
6	500	39.00	195.00	41.13	1.34	55.32	0.86	62.8	1.10	70.07	0.65	85.44	2.47	91.07	0.77	94.3	0.80
Targets	37.75	1.10	47.61	1.99	56.71	3.7	65.54	0.56	77.55	2.52	88.42	0.45	88.80	2.77			

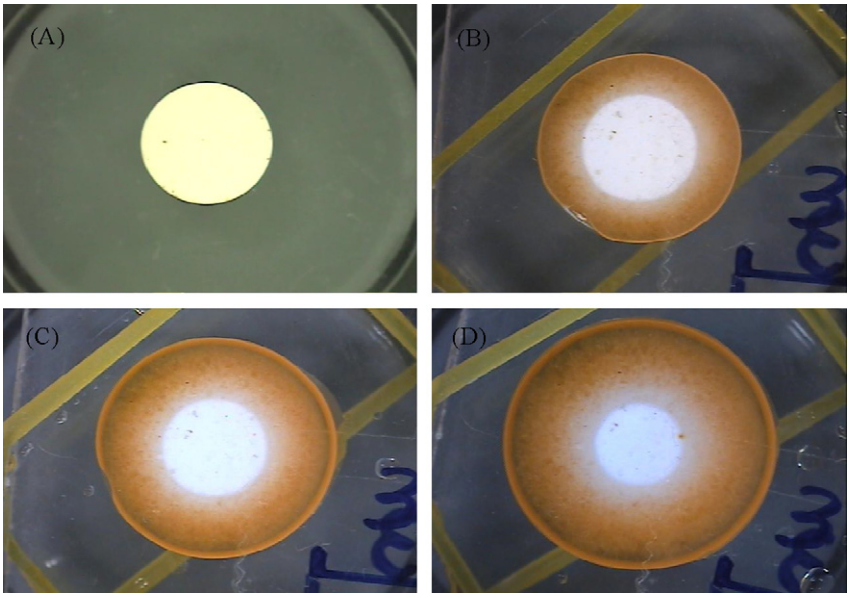

Fig. 1. Pictures of the intact matrix tablet (A) in the polyacrylate plates and gelled tablets depending on time: (B) 1 h, (C) 2 h, and (D) 4 h.

tion of the tablet and decreasing the rate of diffusion of the fluid into the matrix. Throughout the gelation study, the tablets, except PEG 300% and 500%, maintained their original form with an increase of their overall dimensions. When the PEG content was higher than 300%, the gelled part disintegrated inconsistently resulting in various thicknesses of the gelled parts. Especially, gelation of PEG 500% showed significant inconsistency in the thickness as shown in Fig. 2, which might be related to the low mechanical strength of the gelled tablets.

By implementing the mean and variance models of RSM as shown in Eqs. (8) and (9), Table 5 shows the results of vertical and horizontal analysis for the gelation study using six experimental runs based on the PEG ratio and seven observed times from 0.5 to 5.0 h. Since the solid dosage form can stay in the upper digestive tract for about 5 h after administration, in which the amount of fluid is sufficient to make it gel, the 5-h time point might be sufficient for swelling (Davis et al., 1986). The above results were then applied to the proposed time-oriented responses RD models as shown in Eq. (10). As an optimization result, the optimal settings and solutions were obtained for the observed times (Table 6). Table 6 also provided biases and their associated percentages between the optimal solutions and the target values. The optimal settings for PEO

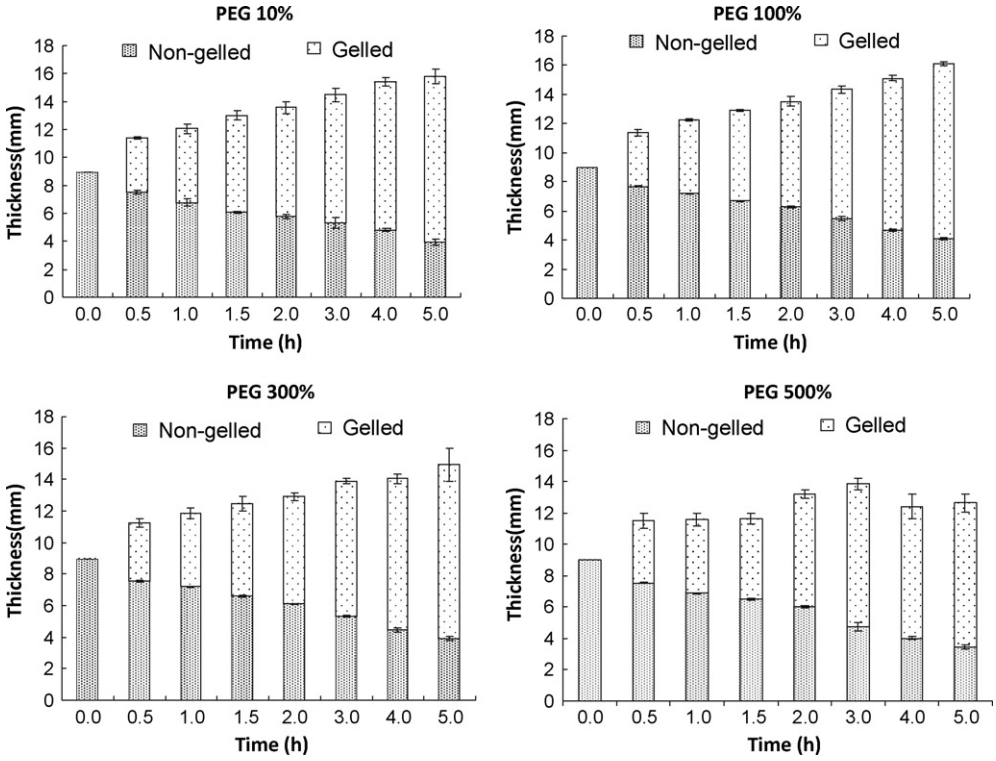

Fig. 2. Changes in the thickness of non-gelated and gelated parts of the matrix tablets.

Table 5
Results of vertical and horizontal analysis for the gelation study.

Observed times (h)	Vertical analysis		PEG/PEO (%)	Horizontal analysis	
	R^2 for mean model	R^2 for variance model		R^2 for mean model	R^2 for variance model
0.5	0.908($\bar{y}_1$)	0.945(s_1^2)	10(R_1)	0.954	0.287
1.0	0.735($\bar{y}_2$)	0.965(s_2^2)	50(R_2)	0.993	0.627
1.5	0.777($\bar{y}_3$)	0.226(s_3^2)	100(R_3)	0.999	0.127
2.0	0.831($\bar{y}_4$)	0.710(s_4^2)	150(R_4)	0.999	0.073
3.0	0.874($\bar{y}_5$)	0.980(s_5^2)	300(R_5)	0.997	0.499
4.0	0.821($\bar{y}_6$)	0.238(s_6^2)	500(R_6)	0.996	0.107
5.0	0.919($\bar{y}_7$)	0.722(s_7^2)			

Table 6
Optimal solutions for the gelation study.

RD model	Optimal settings			Optimal gelation rates (%) at observed times (h)						
	PEG/PEO (%)	PEO (mg)	PEG (mg)	0.5 h	1.0 h	1.5 h	2.0 h	3.0 h	4.0 h	5.0 h
MSE Model	148.57	94.26	140.04	38.06	48.25	57.34	65.32	77.99	86.25	90.10
Target values (%)				37.75	47.61	56.71	65.54	77.55	88.42	88.81
Bias				0.32	0.64	0.63	−0.21	0.44	−2.17	1.29
Bias (%)				0.84	1.34	1.11	−0.33	0.57	−2.46	1.45

and PEG were 94.26 and 140.04 mg, respectively, corresponding to a PEG rate of 148.57%. At these optimal settings, the optimal gelation rates can be estimated by utilizing the proposed model from 0.5 to 5.0 h, in comparison to the target values. Fig. 3 clearly illustrates that the optimal solutions had similar values compared to the target values, which were internally selected after many investigations over the observed times in this particular gelation study. In addition, Fig. 4 illustrates a three-dimensional relationship among gelation rates, PEG percentages, and observed times by using a contour plot. Based on the contour lines representing three-dimensional surfaces of the gelation rates over time, dark diamond dots denote the optimal gelation rates.

4.2. In vitro drug release from matrix tablets

Fig. 5 shows the drug release profiles of the matrix tablets with varying ratios of PEG to PEO. As the amount of PEG increased, the release rate also increased. Both PEG and PEO can significantly influence the dissolution rate of the system. When the formulation contained more than 150% PEG, most of the drug loaded in the tablet was released in about 12 h. Moreover, drug release profiles reached a plateau earlier as the amount of PEG increased. When the amount of PEG was less than 100%, the drug release rate was significantly sustained near that of PEO. Since non-ionic PEO and PEG are independent of pH, the effect of pH in the release medium was insignificant (data not shown).

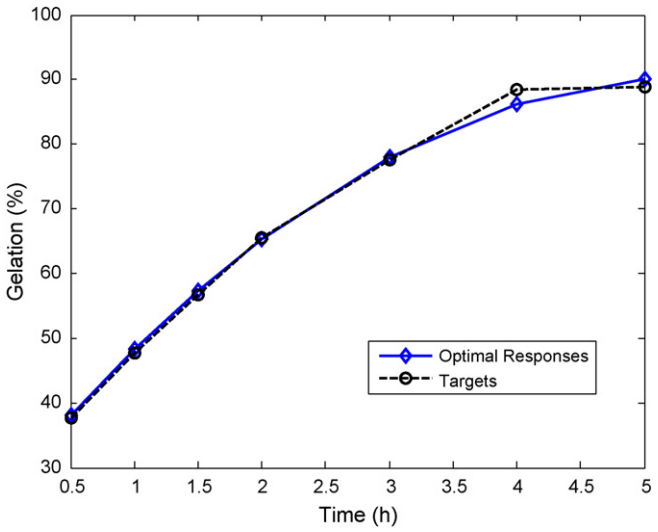

Fig. 3. The optimal solutions vs. internal target values for the gelation study.

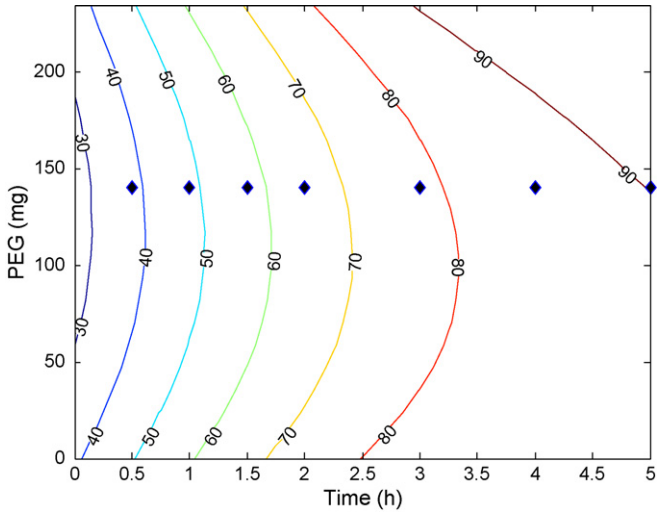

Fig. 4. Contour plot of gelation vs. PEG and time.

The mixture of the two polymers, used as a mechanical support and a release modulator, enables easy modification of the system depending on the target release profiles. Interactions between PEO and PEG 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 the two excipients can deliver the active ingredient at a nearly constant rate. The total amount of drug loaded in the matrices was released in about 24 h depending on the ratio between the two polymer excipients. The drug release rate was nearly constant until 90% of the loaded drug was released and the kinetics of the release process were dependent on the amount of PEG added.

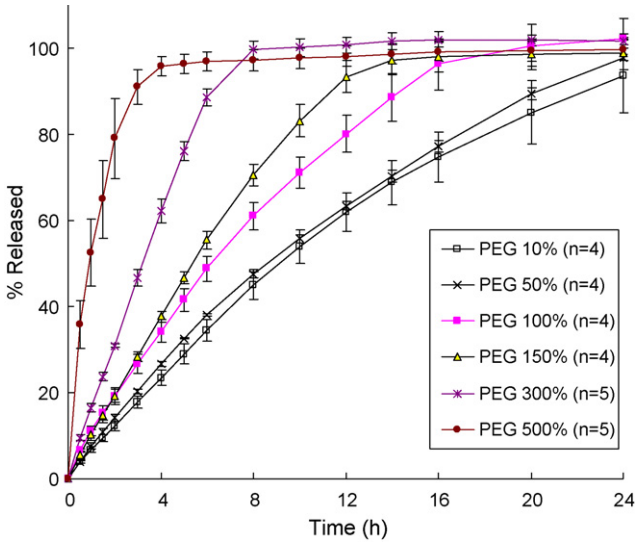

Fig. 5. Drug release profiles of the model drug in buffer at pH 6.8.

Both PEG and PEO can influence the dissolution rate of the system. In order to further investigate the dissolution profiles of the formulations, $t20$ and $t80$ were obtained and their values were $t20$ (0.28, 1.25, 2.09, 2.10, 2.96, and 3.40 h) and $t80$ (2.08, 5.30, 9.50, 11.98, 16.90, and 18.00 h) as the ratio of PEG increased from 10% to 500%. $t20$ and $t80$ were defined as the time needed by the systems for the delivery of 20% and 80% of the total amount of drug incorporated into the tablet. As the amount of PEG increased, the $t20$ and $t80$ also increased. Unlike the PEG 300% and 500% formulations, tablets with PEG 10% and 50% showed similar release kinetics and the overall release rates of both were comparable. Moreover, formulations of PEG 100% and 150% showed comparable properties.

Similarity factor (f_2 values) can be calculated to compare the dissolution profiles (Shah et al., 1998). The value ranges from 0 to 100 and the higher values indicate more similarity between the two profiles. For example, when the two profiles are identical, f_2 value will be 100. Taking PEG 10% as a reference batch, the f_2 values of PEG 50%, 100%, 150%, 300%, and 500% are 78.2, 41.7, 33.8, 22.0, and 14.0, respectively. Compared to the data from the gelation study, differences among release profiles with changing ratios of PEG were more significant. This might be related to the different effective diffusion coefficients with different PEG and PEO contents, together with disintegration of the gelled area. Further experiments on the diffusion properties are ongoing.

The mechanisms of drug release from the matrix system are complicated and might exhibit a combination of diffusion and/or matrix erosion. Drug release from the system containing different ratio of PEG and PEO showed a good fit into the Korsmeyer relationship (Table 7). For the tested formulations containing up

Table 7
Evaluation of drug release kinetics.

	PEG 10%	PEG 50%	PEG 100%	PEG 300%	PEG 500%
n	0.810	0.876	0.812	0.906	0.542
k	0.605	7.650	11.170	17.013	52.268
R^2	0.998	0.999	0.999	0.997	1.000

Table 8
Experimental results of drug release study.

Hours	1		2		3		4		5		6		Internal targets
	PEG 10%(100)		PEG 50%(100)		PEG 100%(100)		PEG 150%(100)		PEG 300%(100)		PEG 500%(100)		
	$\bar{y}$	s	$\bar{y}$	s	$\bar{y}$	s	$\bar{y}$	s	$\bar{y}$	s	$\bar{y}$	s	
0.5	4.0	0.3	4.0	0.5	6.6	0.4	5.6	0.8	9.5	0.7	35.9	5.5	6.0
1.0	6.8	0.6	7.6	0.6	11.1	1.1	10.1	1.2	16.4	1.0	52.5	7.7	11.0
1.5	9.5	0.9	10.9	0.7	15.3	1.6	14.7	1.5	23.7	0.9	64.9	9.1	12.8
2.0	12.3	1.1	14.2	0.8	19.2	2.0	19.2	1.5	30.9	0.3	79.1	9.3	16.1
3.0	17.7	1.5	20.2	0.6	26.7	2.3	28.3	1.0	46.6	2.0	91.0	4.0	22.6
4.0	23.4	1.8	26.6	0.5	34.3	2.6	37.6	1.2	62.2	2.8	95.9	2.2	29.8
6.0	34.5	2.6	38.1	0.3	48.8	2.8	55.5	2.1	88.6	1.8	97.1	2.2	43.5
8.0	44.9	3.2	47.5	1.0	61.1	3.2	70.6	2.5	99.6	2.1	97.3	2.5	51.4
10.0	54.0	3.9	55.7	0.9	71.1	3.7	83.1	3.7	100.2	2.1	97.7	2.4	60.3
12.0	62.0	4.5	63.5	0.9	80.1	4.4	93.5	3.7	100.8	1.8	98.2	2.4	68.5
14.0	68.8	5.2	70.2	1.4	88.7	5.6	97.3	3.6	101.7	2.0	98.7	2.4	74.1
16.0	74.8	5.9	77.2	1.3	96.3	5.9	98.1	3.6	102.0	1.8	99.2	2.3	76.3

Table 9
Results of vertical and horizontal analysis of the drug release study.

Observed times (h)	Vertical analysis		PEG/PEO (%)	Horizontal analysis	
	R^2 for mean model	R^2 for variance model		R^2 for mean model	R^2 for variance model
0.5	$0.989(\bar{y}_1)$	$0.999(s_1^2)$	$10(R_1)$	0.999	0.999
1.0	$0.989(\bar{y}_2)$	$0.997(s_2^2)$	$50(R_2)$	0.999	0.714
1.5	$0.989(\bar{y}_3)$	$0.992(s_3^2)$	$100(R_3)$	0.999	0.955
2.0	$0.990(\bar{y}_4)$	$0.983(s_4^2)$	$150(R_4)$	0.998	0.898
3.0	$0.989(\bar{y}_5)$	$0.765(s_5^2)$	$300(R_5)$	0.987	0.532
4.0	$0.988(\bar{y}_6)$	$0.448(s_6^2)$	$500(R_6)$	0.793	0.662
6.0	$0.990(\bar{y}_7)$	$0.096(s_7^2)$			
8.0	$0.999(\bar{y}_8)$	$0.098(s_8^2)$			
10.0	$0.990(\bar{y}_9)$	$0.063(s_9^2)$			
12.0	$0.946(\bar{y}_{10})$	$0.119(s_{10}^2)$			
14.0	$0.918(\bar{y}_{11})$	$0.199(s_{11}^2)$			
16.0	$0.892(\bar{y}_{12})$	$0.262(s_{12}^2)$			

Table 10
Optimal solutions for drug release study.

RD model	Optimal settings			Optimal drug release rates (%) for observed times (h)											
	PEO (mg)	PEG (mg)	PEG/PEO (%)	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	14.0 h	16.0 h
MSE model	124.30	110.00	88.50	3.93	8.12	12.21	16.21	23.94	31.29	44.88	56.99	67.62	76.76	84.42	90.60
Targets values (%)				6.00	11.00	12.80	16.10	22.60	29.80	43.50	51.40	60.30	68.50	74.10	76.30
Bias				3.93	8.12	12.21	16.21	23.93	31.29	44.88	56.99	67.62	76.76	84.42	90.60
Bias (%)				−34.45	−26.20	−4.60	0.70	5.91	4.99	3.17	10.87	12.13	12.06	13.93	18.74

to 300% PEG, the n exponent values ranged from 0.810 to 0.906, indicating that more than one release mechanism of the model drug from the matrices might be involved including matrix erosion and drug diffusion in the swollen area (Table 7). In these cases, the gel thicknesses were maintained constantly and the dissolution trend was close to zero-order transport. However, release profiles of PEG 500% showed an n-value of 0.542, indicating anomalous non-Fickian mechanism, suggesting that both diffusion of the drug in the gel layer and a macromolecular relaxation process affect the drug release profiles. Regarding the tablet structure, as the tablets swell, the drug diffusional path length increased and thus the drug release rate decreased with time.

The experimental results of the drug release study are tabulated in Table 8 with mean and standard deviation values of six different PEG ratios and 12 observed time points. According to the observed time points, the desired target values are also provided in this table. Similar to Table 5 for the gelation study implementing the mean and variance models of RSM, Table 9 shows the results of both vertical and horizontal analyses, including R^2 values of mean and variance models for drug release. By using the RD optimization model for the drug release study as shown in Eq. (10), the optimal PEO and PEG settings and the optimal drug release rates based on the specific times can be obtained (Table 10). Similar to Table 6, Table 10 provides that the optimal settings of PEG and PEO are 124.3 and 110 mg, respectively, which represent a PEG rate of 88.50%. Based on these optimal settings, the optimal drug release rates and their associated target values from the observed times from 0.5 to 16 h are given in Table 10, which also provides biases and their associated percentages between the optimal drug release rates and the target values. Fig. 6 shows the optimal responses and the target values over the observed time points for the drug release study. To illustrate the three-dimensional relationship among drug release rate, PEG percentage, and observed time, the associated contour plot is given in Fig. 7. Contour lines and dark diamond dots in Fig. 7 represent the surfaces of drug release rates and their associated optimal solutions over time. Contrary to the optimum content of PEG (88.5%) based on the drug release study, the swelling study recommended an optimum content of 148% PEG. Therefore, a PEG rate of 90–150% can safely be suggested for matrix tablet formulations, and the formulation scientists would then be responsible for 'fine-tuning' the tablet formulations. Swelling kinetics and drug release profiles need to be considered simultaneously, together with the tablet's mechanical behavior *in vivo*.

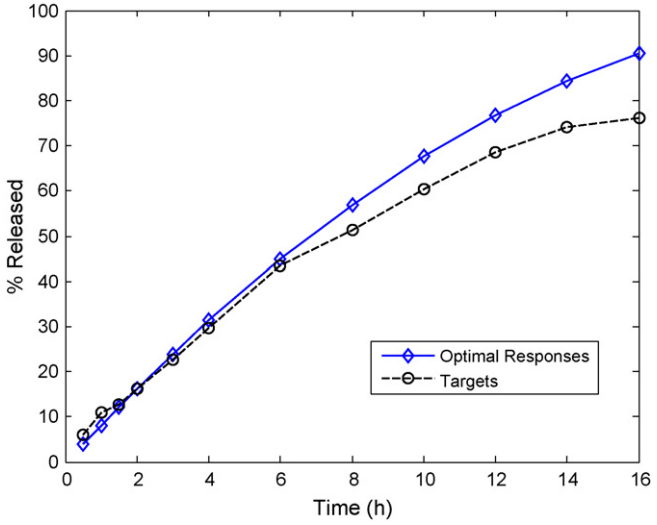

Fig. 6. The optimal solutions vs. target values for the drug release study.

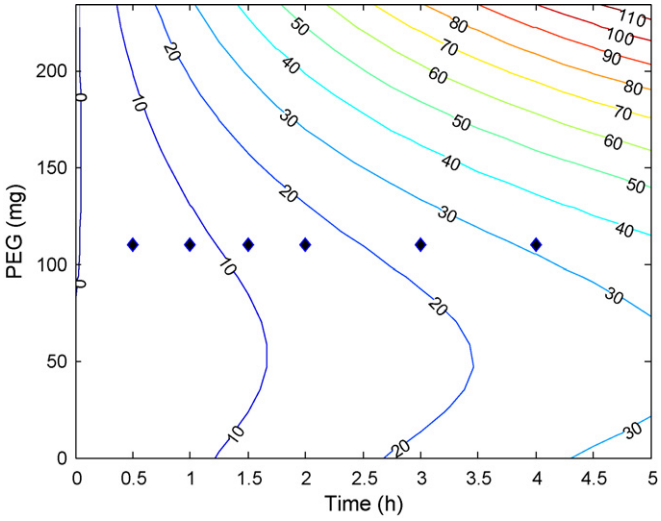

Fig. 7. Contour plot of drug release rates vs. PEG and time.

5. Conclusions

When exposed to an aqueous environment, PEO–PEG matrix tablets hydrated slowly and swelled, causing a thick gel layer to form on the surface. After swelling, the test tablets kept their overall integrity with an increase of their dimensions. As the content of soluble PEG increased, the swollen gel front disintegrated inconsistently due to the low mechanical strength of the gelled tablets. Since polyacrylate plates were applied for the gelation study, the matrix was not completely hydrated and gelled even after 5 h. However, the gelation results were applied to the proposed time-oriented responses RD models, and the optimal input control settings and responses for observed times were obtained. The optimal settings of PEO and PEG were 94.26 and 140.04 mg, respectively, corresponding to a PEG rate of 148.57%.

Moreover, as the amount of PEG increased, the release rate also increased. When the formulation contained more than 150% PEG, most of the drug loaded in the tablet was released in about 12 h. When the amount of PEG was less than 100%, the drug release rate

was significantly sustained near that of PEO. By using the RD optimization model for the drug release study, the optimal PEO and PEG settings and responses for the observed times were obtained and the optimal settings of PEG and PEO were 124.3 and 110 mg, respectively, representing a PEG rate of 88.50%. Therefore, a PEG rate of 90–150% is suggested for matrix tablet formulations and the exact ratio is dependent on the formulation's properties.

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