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Development and optimization of a novel oral controlled delivery system for tamsulosin hydrochloride using response surface methodology

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Abstract

The purpose of this study was to develop and optimize oral controlled-release formulations for tamsulosin hydrochloride using a combination of two cellulose ester derivatives, hydroxypropyl methylcellulose (HPMC) and hydroxypropyl methylcellulose phthalate (HPMCP), with Surelease® as a coating material. A three-factor, three-level Box-Behnken design was used to prepare systematic model formulations, which were composed of three formulation variables, the content of HPMC (X_1) and HPMCP (X_2) and the coating level (X_3), as independent variables. The response surface methodology (RSM) and multiple response optimization utilizing the polynomial equation were used to search for the optimal coating formulation with a specific release rate at different time intervals. The drug release percentages at 2, 3 and 5 h were the target responses and were restricted to 15–30% (Y_1), 50–65% (Y_2) and 80–95% (Y_3), respectively. The optimal coating formulation was achieved with 10% HPMC and 20% HPMCP at a coating level of 25%, and the observed responses coincided well with the predicted values from the RSM optimization technique. The drug release from pellets coated with the optimized formulation showed a controlled-release pattern (zero-order), in comparison with a commercial product (Harunal® capsule). In conclusion, a novel, oral, controlled-release delivery system for tamsulosin hydrochloride was successfully developed by incorporating HPMC and HPMCP as coating additives into Surelease® aqueous ethylcellulose dispersion.

Keywords: Tamsulosin hydrochloride; HPMC; HPMCP; Surelease®; Box-Behnken design

1. Introduction

Tamsulosin hydrochloride is a highly selective alpha 1A-adrenoreceptor antagonist that has been used for treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) (O'Leary, 2001). Moreover, following oral administration of 0.4 mg tamsulosin hydrochloride, the drug is absorbed from the intestine and is almost completely bioavailable (Van Hoogdalem et al., 1996). However, many LUTS/BPH patients are elderly subjects with impaired cardiovascular regulation. They are particularly at risk for cardiovascular adverse events, which are not only unpleasant, but can also lead to serious morbidity, such as falls and fractures, potentially resulting in hospitalization, nursing home placement and/or death (Chapple and Andersson, 2002). Therefore, the preferred formulation of tamsulosin hydrochloride provides a controlled-release that can modulate both the release rate of the drug and the absorption of the drug in the intestinal tract (Wilde and McTavish, 1996; Matsushima et al., 1998).

Pellets are frequently used in controlled-release systems because they are freely dispersed in the gastrointestinal tract and they offer flexibility for further modifications, such as coating. Ethylcellulose is the most widely used water-insoluble polymer in film coatings (Iyer et al., 1993). The application of aqueous polymeric dispersions of ethylcellulose, such as Aquacoat® and Surelease®, is commonplace in the pharmaceutical industry and is the method of choice for film coating (Bodmeier and Paeratakul, 1994; Sadeghi et al., 2000, 2003). In addition, drug release from a controlled-release dosage form coated with aqueous ethylcellulose dispersion may be modified by additives (Yuen et al., 1993; Semdé et al., 2000; Sadeghi et al., 2001; Rohera and Parikh, 2002; Chan et al., 2005). In preliminary

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studies (Kim et al., 2006, submitted for publication), we reported that the blends of Surelease® and neutralized HPMCP based on aqueous coating formulations for oral controlled-release delivery systems were effective tools to provide the pH-dependent tamsulosin hydrochloride release profile. This can produce a controlled-release drug delivery system where drug release is controlled in the upper gastrointestinal tract, while drug release is accelerated in the colonic region by enhanced permeability of the ethylcellulose membrane via the leaching of HPMCP, which dissolves at pH levels greater than 5.5. The further inclusion of HPMC into film coatings provides the flexibility of systems for control dissolution profiles and improves the film-forming properties, such as toughness, elasticity and tensile strength (Ofori-Kwakye and Fell, 2003; Kim et al., submitted for publication). Therefore, it can be expected that tamsulosin hydrochloride release from coated pellets is controlled by the inclusion of HPMC at the initial dissolution phase.

Designing controlled-release formulations with the minimum number of trials is very crucial for pharmaceutical scientists (Hamed and Sakr, 2001). The response surface method has been commonly used for the optimization of formulations with various kinds of drugs in the development of controlled-release formulation design (Gupta et al., 2001; Ko et al., 2004; Nutan et al., 2005). The objective of this study was to develop a novel oral controlled delivery system for tamsulosin hydrochloride using HPMC, HPMCP and Surelease® as coating materials. The present study was carried out to evaluate the effect of three factors (amount of HPMC, HPMCP and coating level) on tamsulosin hydrochloride release from pellets and to optimize the level of these factors using response surface methodology combined with Box-Behnken design in order to obtain the targeted dissolution profiles for tamsulosin hydrochloride.

2. Materials and methods

2.1. Materials

Tamsulosin hydrochloride was purchased from Youn Sung Fine Chemicals Co. Ltd. (99.6% purity, Korea). Poloxamer 407 (Lutrol® F127, BASF, Germany), microcrystalline cellulose (Avicel™ PH102, FMC, USA), sodium alginate (Duckalgin® NSPH, Kibun Food Chemica, Japan), Surelease® (E-7-19010, Colorcon, USA), hydroxypropyl methylcellulose (HPMC, Pharmacoat® 606, Shin-Etsu Chemical Co., Japan) and hydroxypropyl methylcellulose phthalate (HPMCP, HP-55, Shin-Etsu Chemical Co., Japan) were used. For comparison, Harunal® capsule (Lot no. HRC801, Yamanouchi Pharmaceutical Co. Ltd., Korea) containing 0.2 mg of tamsulosin hydrochloride was purchased from market. All organic solvents were of high performance liquid chromatography (HPLC) grade. All other chemicals were of reagent grade.

2.2. Experimental design

A three-factor, three-level Box-Behnken design was used for the optimization procedure with HPMC content (X_1), HPMCP content (X_2) and coating level (X_3) as the independent variables (Table 1). The levels for these three parameters were determined from the preliminary trials. The percentages of the drug released at 2, 3 and 5 h were used as dependent variables for desirable drug release, as described in literature (Lee et al., 2004; Kim et al., 2006; Seo et al., 2006). Design-Expert software (V. 7.0, Stat-Ease Inc., Minneapolis, USA) was used for the generation and evaluation of the statistical experimental design.

Table 1
Variables in Box-Behnken design

Formulation variables	Level used		
	−1	0	1
X_1 = HPMC content[a] (%)	0	5	10
X_2 = HPMCP content[a] (%)	10	20	30
X_3 = coating level (%)	20	25	30

Response variables	Constraints
Y_1 = cumulative % drug released in 2 h	$15\% \leq Y_1 \leq 30\%$
Y_2 = cumulative % drug released in 3 h	$50\% \leq Y_2 \leq 65\%$
Y_3 = cumulative % drug released in 5 h	$80\% \leq Y_3 \leq 95\%$

[a] Based on total solid content of coating compositions.

2.3. Preparation of drug-loaded pellets

The composition of pellets consisted of tamsulosin hydrochloride (0.17%, w/w), poloxamer 407 (0.41%, w/w), microcrystalline cellulose (29%, w/w), sodium alginate (20.71%, w/w), magnesium trisilicate (29%, w/w) and Surelease® (20.71%, w/w, by solid) (Kim et al., 2005a). Briefly, tamsulosin hydrochloride (0.2 mg/capsule) and poloxamer 407 were dissolved in distilled water. The drug/surfactant solution was uniformly mixed with microcrystalline cellulose, sodium alginate and magnesium trisilicate. The mixture was then kneaded with Surelease® diluted in distilled water in a mixer (Kitchen Aid Inc., MI, USA). The pellets were prepared using a novel designed pelletizer-equipped piston extruder and double-arm counter-rotating rollers using a process previously reported in detail (Jee et al., 2004; Kim et al., 2005a; Lee et al., 2005). The pellets were dried in a 60 °C drying oven for 24 h. The physical properties of the prepared pellets were as follows: diameter 1269 ± 1.10 μm, as geometric mean diameter ± geometric standard deviation, aspect ratio 1.06 ± 0.04, friability 0.5%, bulk density 1.24 g/mL and porosity 18.3 ± 0.3%.

2.4. Coating procedure

The calculated amount of HPMCP was dispersed in water and then added to Surelease®. Solutions of HPMC (5%, w/w) were prepared and held overnight. Then, HPMC solution was added to the diluted Surelease® containing HPMCP to produce the required HPMC contents and was stirred throughout the coating processes. HPMCP was completely dissolved in water-diluted Surelease® by ammonia-neutralization and confirmed by measurement of the particle size using an electrophoretic light scattering spectrophotometer (ELS-8000, Otsuka Electronics, Japan) and observation using optical microscopy (Olympus, BX-51, Japan). The coating formulations were adjusted to obtain

approximately 15% (w/w) total solids content. For coating, 500-g quantities of drug-loaded pellets from the 1000 to 1190 μm sieve fraction were used. The drug-loaded pellets were coated using a coating pan (HS Spray System, Han Sung Engineering, Korea). The temperature and rotating speed of the coating pan were maintained at 55–60 °C and 50–60 rpm during the coating process. Meanwhile, the coating solution was applied at a rate of 2–5 mL min^{-1}. Following coating solution application, the pellets were dried in a coating pan for an additional 30 min to keep the pellets from sticking. The coated pellets were spread onto paper trays and stored at 60 °C for 24 h. Drug content in the pellets was between 98.2 and 102.3% of the expected values, which was determined by the method described in a previous study (Kim et al., 2005a).

2.5. Dissolution studies

The release of the drug from the coated pellets was performed according to the USP XXV paddle method using a dissolution apparatus (Vankel VK7000, Cary, NC). The coated pellets containing 0.2 mg of tamsulosin hydrochloride were filled into hard gelatin capsules (capsule no. 3, Su-Heung Capsule Co. Ltd., Korea). The capsules were added into 500 mL of simulated gastric fluid without pepsin (adjusted to pH 1.2 with HCl) containing polysorbate 80 (0.003%, w/w) at 37 ± 0.1 °C and with a paddle speed of 100 rpm. To avoid capsule flotation, a sinker was used. Each sample (5 mL) was withdrawn at defined time intervals, and the same volume of simulated gastric fluid was compensated. Two hours after incubation in simulated gastric fluid, 500 mL of simulated intestinal fluids without pancreatin (pH 7.2, phosphate buffer according to the USP without enzyme) were added into the vessel to adjust the pH of the medium from 1.2 to 7.2. The samples were analyzed using HPLC as described in a previous study (Kim et al., 2005a,b). Dissolution tests were repeated six times for all formulations and the drug percentage released over time was calculated.

3. Results and discussion

For the response surface methodology involving Box-Behnken design, a total of 15 experiments were performed for three factors at three levels each. This number is equal to the mid-point of each edge and the three replicated center points of the cube. The experiment runs with independent variables and the observed responses for the 15 formulations are shown in Fig. 1 and Table 2. A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters, such as the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of squares (PRESS), provided by the Design-Expert software. As presented in Table 3, the quadratic model was selected as a suitable statistical model for optimized coating formulations because it had the smallest value of PRESS. Predicted residual sum of squares (PRESS) is a measure of the fit of the model to the points in the design. The smaller the PRESS statistic is, the better the model fits to the data points (Segurola et al., 1999). The

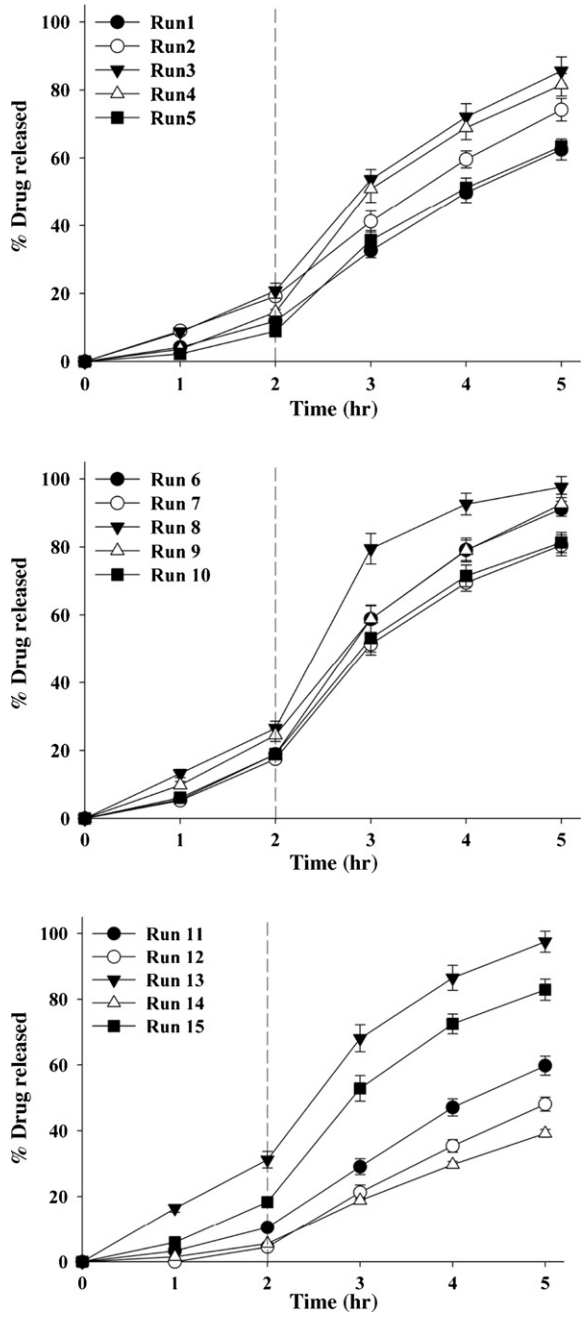

Fig. 1. Dissolution profiles of all formulations (dashed line shows the change of medium pH from 1.2 to 7.2, $n = 6$).

model showed a statistically insignificant lack of fit, as shown in Table 3. The adequacy of the model was also confirmed with residual plot tests of regression models. Analysis of variance (ANOVA) was applied to estimate the significance of the model at the 5% significance level. The quadratic model generated by the design is given in Eq. (1):

$$Y_k = b_0 + \sum_{i=1}^{n} b_i X_i + \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} b_{ij} X_i X_j + \sum_{i=1}^{n} b_{ii} X_i^2 \quad (1)$$

where b_i was the estimated coefficient for the factor X_i, while Y_k was the measured response. The coefficients corresponding

Table 2
The composition and observed responses from randomized runs in Box-Behnken design

Run	Factors			Responses		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
1	0	10	25	11.9	32.6	62.5
2	10	10	25	19.2	41.2	74.2
3	5	10	20	20.8	53.7	85.6
4	0	30	25	14.5	50.9	81.5
5	5	30	30	8.9	35.7	63.4
6	0	20	20	18.9	58.8	91.2
7	5	20	25	17.5	51.4	80.5
8	5	30	20	26.5	79.5	97.6
9	10	30	25	24.5	58.8	92.6
10	5	20	25	18.9	53.2	81.3
11	10	20	30	10.5	29.1	59.8
12	0	20	30	4.5	21.3	48.1
13	10	20	20	31.2	68.1	97.5
14	5	10	30	5.5	18.8	39.2
15	5	20	25	18.3	52.9	82.9

to linear effects (b_i), interaction (b_{ji}) and quadratic effects (b_{ii}) were determined from the results of the experiment.

The coefficient estimate and standardized main effects (SME) values in the form of a polynomial equation for the responses are listed in Table 4. SME values were calculated by dividing the main effects by the standard error of the main effects. In addition, the contour plots and three-dimensional response surface plots were presented to estimate the effects of the independent variables on each response (Fig. 2). The largest SME of coating level (X_3) indicated that the effect of coating level was found to be the main influential factor on the drug release from coated pellets in the whole stage dissolution. The decrease in drug release with increasing coating level may be attributed to the increased diffusional path length with an increase in the thickness of the coating membrane, as previously reported by many authors (Sadeghi et al., 2000, 2003; Kim et al., 2005a).

It was obvious that the drug release was increased with increasing content of HPMC (X_1) and HPMCP (X_2). The content of HPMC (X_1) was found to be most effective on Y_1 (%drug released in 2 h) while the content of HPMCP (X_2) was found to be most effective on the Y_2 (%drug released in 3 h) and Y_3 (%drug released in 5 h). As shown in Fig. 2D–F, Y_1 increased from 11.9 to 19.2% and from 14.5 to 24.5% when the content of HPMC (X_1) was increased from 0 to 10% at the low and high levels, respectively, of HPMCP (X_2). Y_2 and Y_3 also increased with increased content of HPMCP (X_2), due to its pH-dependent nature; it dissolves at a pH above 5.5. In addition, the SME of HPMCP (X_2) was less than that of HPMC (X_1) at Y_1, indicating that the influence of HPMCP (X_2) was less than that of HPMC (X_1), but it was found that the influence of HPMCP (X_2) at later stages (Y_2 and Y_3) was higher than in the early stage. In fact, drug release from coated pellets at pH 7.2 was increased with increasing content of HPMCP due to mechanically weak ethylcellulose coating membranes, as previously reported (Lecomte et al., 2005; Kim et al., 2006, submitted for publication). However, the underlying mass transport phenomena might be more complicated.

Table 3
Summary of results of: (a) model analysis, (b) lack of fit and (c) *R*-square analysis for measured responses

Source	Y_1		Y_2		Y_3	
	Sum of squares	$P > F$	Sum of squares	$P > F$	Sum of squares	$P > F$
(a) Model analysis						
Mean vs. total	4220.17		33229.07		86321.09	
Linear vs. mean	772.54	<0.0001	3924.24	<0.0001	4141.44	<0.0001
2FI[a] vs. linear	13.07	0.2160	20.49	0.7491	44.59	0.6473
Quadratic vs. 2FI	16.92	0.0063**	124.39	0.0019**	200.73	0.0003**
Cubic vs. quadratic	0.91	0.6677	6.43	0.3169	3.06	0.6396
Residual	0.99		1.86		2.99	
Total	5024.60		37306.48		90713.91	
(b) Lack of fit						
Linear	30.90	0.1319	151.31	0.0535	248.38	0.0524
2FI	17.83	0.1492	130.82	0.0415*	203.79	0.0427*
Quadratic	0.91	0.6677	6.43	0.3169	3.06	0.6396
Cubic	0.000		0.000		0.000	
Pure error	0.99		1.86		2.99	

	Adjusted *R*-square	PRESS	Adjusted *R*-square	PRESS	Adjusted *R*-square	PRESS
(c) *R*-square analysis						
Linear	0.9496	60.95	0.9522	238.18	0.9272	438.29
2FI	0.9591	69.37	0.9431	328.84	0.9176	680.59
Quadratic	0.9934	16.78	0.9943	107.06	0.9961	55.76
Cubic	0.9914	ND[b]	0.9968	ND	0.9952	ND

[a] Two-factor interaction.
[b] PRESS statistic not defined.
* Significant at 5% level.
** Significant at 1% level.

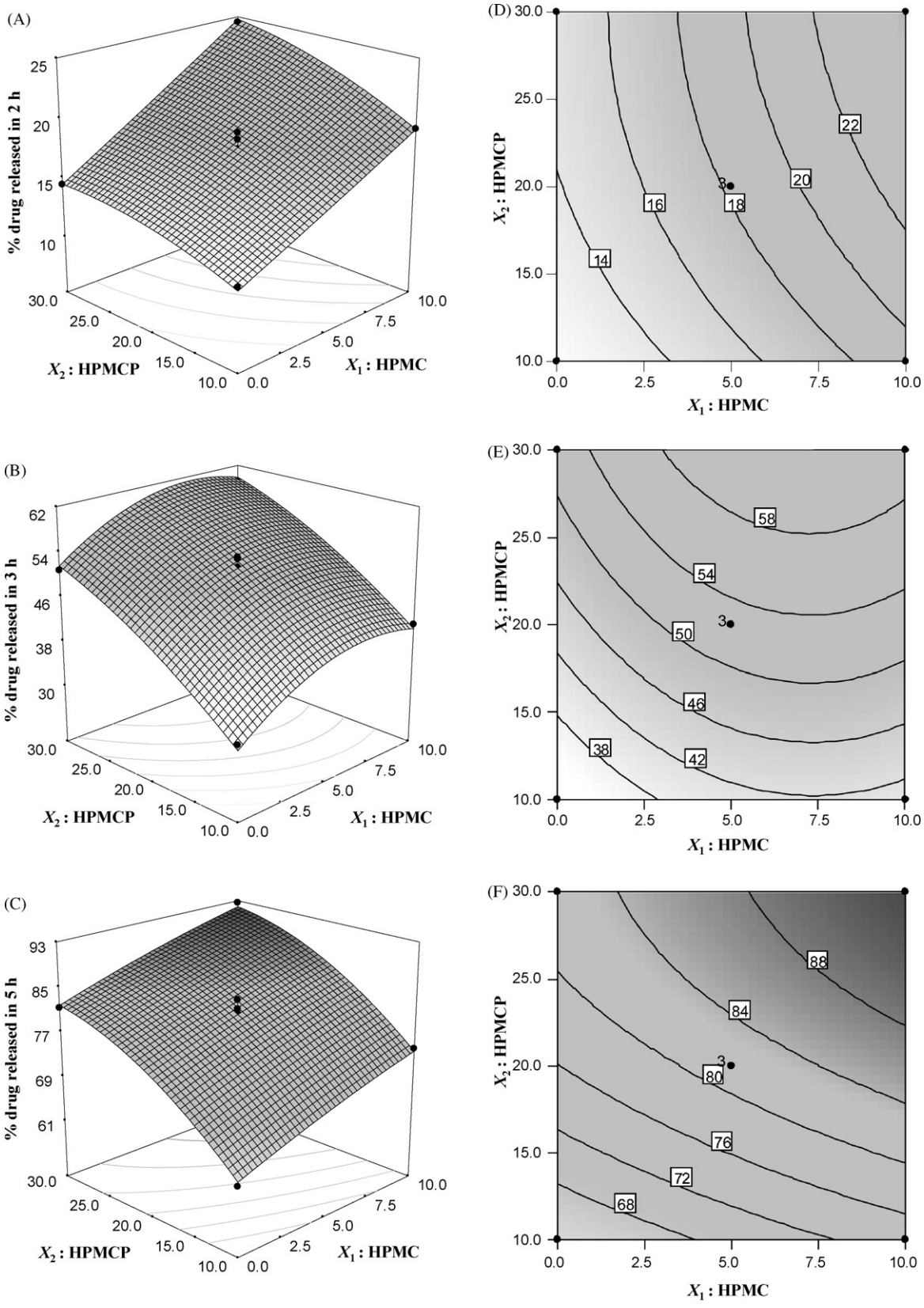

Fig. 2. Effect of the contents of HPMC (X_1) and HPMCP (X_2) on response using response surface plot (A–C) and its contour plot (D–F) at 25% (w/w) coating level.

Table 4
Standardized main effects of the factors on the responses

	Y_1			Y_2			Y_3		
	Coefficient estimate	*P*-value	SME[a]	Coefficient estimate	*P*-value	SME	Coefficient estimate	*P*-value	SME
b_0	18.23	<0.0001	51.28	52.50	<0.0001	70.62	81.57	<0.0001	128.42
b_1	4.45	<0.0001	20.44	4.20	0.0003	9.23	5.10	<0.0001	13.11
b_2	2.13	0.0002	9.76	9.83	<0.0001	21.58	9.20	<0.0001	23.65
b_3	−8.50	<0.0001	−39.03	−19.40	<0.0001	−42.61	−20.18	<0.0001	−51.87
b_{12}	0.68	0.0799	2.19	−0.18	0.7966	−0.27	−0.15	0.7960	−0.27
b_{13}	−1.58	0.0037	−5.11	−0.38	0.5855	−0.58	1.35	0.0576	2.45
b_{23}	−0.58	0.1208	−1.87	−2.23	0.0181	−3.46	3.05	0.0026	5.54
b_{11}	0.07	0.8338	0.22	−4.61	0.0010	−6.88	−0.58	0.3550	−1.02
b_{22}	−0.78	0.0593	−2.43	−2.01	0.0300	−3.00	−3.28	0.0023	−5.73
b_{33}	−2.03	0.0015	−6.33	−3.56	0.0031	−5.32	−6.83	<0.0001	−11.94

[a] Standardized main effects (SME) were calculated by dividing the main effect by the standard error of the main effect.

Table 5
Comparative levels of predicted and observed responses for optimized coating formulations

Responses (predicted, %)	Observed (%)	Predicted error[a] (%)
Y_1 (22.8)	23.5 ± 2.5	3.07
Y_2 (52.1)	54.8 ± 3.2	5.18
Y_3 (86.1)	89.5 ± 4.1	3.95

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

After generating the polynomial equations relating the dependent and independent variables, the coating formulation was optimized for the responses Y_1, Y_2 and Y_3. The desirable range of these responses were restricted to $12\% \leq Y_1 \leq 39\%$, $44\% \leq Y_2 \leq 70\%$ and $70\% \leq Y_3 \leq 100\%$, respectively, as described in literature (Lee et al., 2004; Kim et al., 2006; Seo et al., 2006). In this study, the target range of these responses were restricted to the more strict range shown in Table 1, considering the dissolution profiles of a commercial product (Harunal® capsule) (Kim et al., 2005b). The optimum values of the variables were obtained by graphical and numerical analyses using the Design-Expert software and based on the criterion of desirability (Myers and Montgomery, 2002). The optimized formulation was achieved with 10% HPMC and 20% HPMCP at a coating level of 25%. Therefore, a new batch of pellets coated with the predicted levels of formulation factors was prepared to confirm the validity of the optimization procedure. Table 5 and Fig. 3 demonstrate that the observed values of a new batch were mostly similar with predicted values within 5% of predicted error.

The difference factor (f_1) and similarity factor (f_2) were also calculated to compare the dissolution profiles between pellets coated with the optimized formulation and the commercial product (Harunal® capsule). The calculated f_1 and f_2 values obtained in this study were 4.6 and 78.2, respectively, indicating that the dissolution profiles coated with the optimized formulation and the commercial product (Harunal® capsule) were similar (Moore and Flanner, 1996). In addition, the dissolution tests were performed at pH 6.8 in order to determine the drug release mechanisms from the pellet prepared with optimized formulation and the commercial product (Harunal® capsule). The dissolution profiles are presented in Fig. 4, and four models (zero-order, Hixon-Crowell, Higuchi and Korsmeyer-Peppas) are applied in Table 6. The optimum values for the parameters

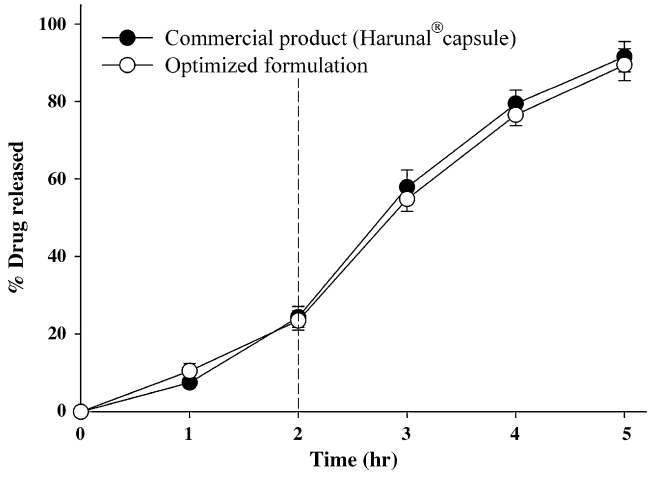

Fig. 3. Dissolution profiles of tamsulosin hydrochloride for pellets coated with optimized formulation and for a commercial product (Harunal® capsule) (dashed line shows the change of medium pH from 1.2 to 7.2, $n = 12$).

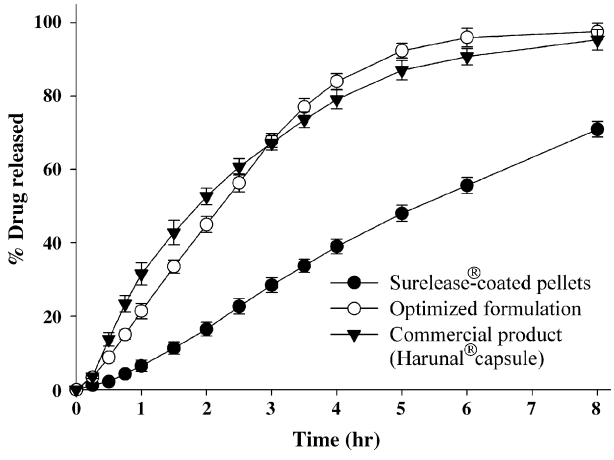

Fig. 4. Dissolution profiles of tamsulosin hydrochloride for pellets coated with Surelease®, the optimized formulation and for a commercial product (Harunal® capsule) in a dissolution medium at pH 6.8 ($n = 12$).

Table 6
The various mathematical models and statistics obtained from dissolution profiles

Model[a]	Statistics[b]	Surelease®	Optimized formulation	Commercial product
Zero-order	R^2	0.9949	0.9967	0.9431
	k	9.51×10^{-2}	0.22	0.17
	S.E.	2.35×10^{-3}	4.87×10^{-3}	1.51×10^{-2}
Hixon-Crowell	R^2	0.9772	0.9736	0.9935
	k	3.75×10^{-2}	9.81×10^{-2}	0.11
	S.E.	1.46×10^{-3}	4.99×10^{-3}	2.34×10^{-3}
Higuchi	R^2	0.9686	0.9857	0.9953
	k	0.31	0.56	0.49
	S.E.	1.77×10^{-2}	2.55×10^{-2}	1.20×10^{-2}
Korsmeyer-Peppas	R^2	0.9966	0.9998	0.9992
	k	0.11	0.25	0.60
	S.E.	1.18×10^{-2}	9.04×10^{-3}	6.06×10^{-2}
	n	0.97	0.97	0.44
	S.E.	5.69×10^{-2}	2.90×10^{-2}	4.42×10^{-2}

[a] Zero-order: $M_t/M_\infty = kt + C$; Hixon-Crowell: $M_t/M_\infty = 1 - (1 - kt)^3$; Higuchi: $M_t/M_\infty = k\sqrt{t} + C$; Korsmeyer-Peppas: $M_t/M_\infty = kt^n + C$. M_t/M_∞: the fraction of drug released up to time t, k: the kinetic constant and C: constant. For comparison, only the points within the interval $M_t/M_\infty \leq 0.9$ were used (Korsmeyer-Peppas model: $M_t/M_\infty \leq 0.6$).
[b] R^2, determination coefficient: S.E., standard error of parameters, k and n.

presented in each equation were determined by nonlinear regression using SPSS 11.0 software (SPSS, Chicago, IL, USA). As shown in Table 6, the dissolution data of the commercial product was well fitted according to the Hixon-Crowell model and Higuchi model, while that of the optimized formulation was well fitted according to the zero-order model. This indicates that drug release from the commercial product was dominated by the surface erosion relative to the drug diffusion inside the pellets. In addition, the n value (0.44) obtained from the Korsmeyer-Peppas model indicates that drug release was dominated by the diffusion process up to the initial 60% of the drug released (Korsmeyer et al., 1983; Costa and Sousa Lobo, 2001). However, the n value for the optimized formulation was 0.97, indicating zero-order transport. Interestingly, the drug release from Surelease®-coated pellets without HPMC and HPMCP as additives also showed a zero-order release profile. Despite the difference in drug release from Surelease®-coated pellets with and without additives, their dissolution profiles showed a membrane-controlled (zero-order) release mechanism, as previously reported (Rohera and Parikh, 2002).

In addition, the optimized formulation in this study is found to be stable for 2 years under ambient conditions.

4. Conclusions

The optimized formulation for tamsulosin hydrochloride was obtained with HPMC, HPMCP and Surelease® using response surface methodology based on a Box-Behnken design. It was found that the optimized formulation was achieved with 10% HPMC (X_1), 20% HPMCP (X_2) and 25% coating level (X_3) and the observed responses were close to the predicted values for the optimized formulation. The drug release from pellets coated with the optimized formulation showed a controlled-release pattern (zero-order), in comparison with a commercial product (Harunal® capsule). In conclusion, a novel, oral controlled-release delivery system for tamsulosin hydrochloride was successfully developed by incorporating HPMC and HPMCP as coating additives into Surelease® aqueous ethylcellulose dispersion.

Acknowledgments

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