Statistical Optimization of Tamsulosin Hydrochloride Controlled Release Pellets Coated with the Blend of HPMCP and HPMC

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The objective of the present study was to evaluate three coating parameters for the application of a blend of HPMCP and HPMC in ethylcellulose aqueous dispersions (Surelease®) in order to obtain controlled release of tamsulosin hydrochloride. The selected independent variables, HPMCP content (X_1), HPMC content (X_2) and coating level (X_3), were optimized with a three-factor, three-level Box–Behnken design. The selected dependent variables were the cumulative percentage values of tamsulosin hydrochloride that had dissolved after 2, 3 and 5 h. Various dissolution profiles of the drug from controlled release pellets were obtained. Optimization was performed for X_1, X_2 and X_3 using the following target ranges; $15\% \leq Y_1 \leq 30\%$; $50\% \leq Y_2 \leq 65\%$; $80\% \leq Y_3 \leq 95\%$. Results of the optimization procedure indicated that the optimized levels of HPMCP content (X_1), HPMC content (X_2) and coating level (X_3) were 30%, 15% and 25%, respectively. Controlled release pellets coated with the optimized formulation provided a release profile that was close to predicted values. In addition, the dissolution profiles of the controlled release pellets coated with the optimized formulation were similar to those of the commercial product Harunal® capsule ($f_1=4.6$, $f_2=78.7$).

Key words tamsulosin; controlled release; hydroxypropylmethylcellulose phthalate; HPMC

Tamsulosin hydrochloride is a highly selective α_{1A}-adrenoreceptor antagonist that was developed for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUPS/BPH). Since tamsulosin hydrochloride can have dose-related adverse effects, a controlled release dosage is necessary.[1] Moreover, following oral administration of 0.2—0.4 mg tamsulosin hydrochloride, the drug is absorbed from the intestine and is almost completely bioavailable. Therefore, the preferred formulation of tamsulosin hydrochloride provides controlled release that can modulate both the release rate of the drug and the absorption of drug in the intestinal tract.[2]

We previously described tamsulosin hydrochloride controlled release pellets prepared using ethylcellulose aqueous dispersion (Surelease®) alone or with additives such as sodium alginate, HPMCP.[3,4] Addition of HPMCP to Surelease® effectively provided pH-dependent drug release. Moreover, the addition of HPMC into film coats improves various film-forming properties such as toughness, elasticity and tensile strength.[4,5] In the present study, we applied the coating system containing Surelease®, HPMC and HPMCP to drug loaded spherical pellets prepared by conventional extrusion/spheronization techniques.

Statistical optimization designs have been previously documented for the formulation of many pharmaceutical solid dosage forms.[6—8] Additionally, it is a powerful, efficient and systematic tool that shortens the time required for the development of pharmaceutical dosage forms.[9]

The objective of the present study was to prepare tamsulosin hydrochloride controlled release pellets coated with a blend of HPMCP and HPMC in aqueous dispersions (Surelease®) and statistically determine the optimal levels of these factors using response surface methodology combined with Box-Behnken design. In addition, controlled release pellets coated with the optimized levels of the coating parameters were compared with commercially available controlled release pellets (Harunal® capsule) using difference (f_1) and similarity (f_2) factors.

Experimental

Materials The following materials were gifted: tamsulosin hydrochloride (Reyon Pharmaceutical Co., Korea), poloxamer 407 (Lutrol® F127, BASF, Germany), microcrystalline cellulose (Avicel™ PH102, FMC, U.S.A.), carbopol 974P NF (Noveon, U.S.A.) and ethylcellulose aqueous dispersion (Surelease® E-7-19010, Colorcon, U.S.A.). Sodium alginate (Duckalgin® NSPH) was purchased from Kibun Food Chemica (Japan). Hydroxypropyl methylcellulose (HPMC, Pharmacoat® 606) and hydroxypropyl methylcellulose phthalate (HPMCP, HP-55) were obtained from Shin-Etsu Chemical (Japan). All other chemicals were HPLC grade.

Experimental Design Response surface methodology combined with Box–Behnken design (BBD)[10] was used to ascribe the relationship between the independent variables and the responses as well as to determine the coating parameters for tamsulosin hydrochloride controlled release pellets. A three-factor, three-level BBD with three replicates at the center point was selected to build response surface models. Three factors, HPMCP content (X_1), HPMC content (X_2) and coating level (X_3), were used in the design and the responses were the cumulative percent of the drug dissolved after 2, 3 and 5 h. Table 1 summarizes the factors, the levels tested, and the responses. HPMCP content (w/w based on total solid content of coating compositions), HPMC content, and coating level were determined in the range of 10—30% (w/w), 5—15% (w/w) and 20—30% (w/w), respectively. From the data obtained, response surfaces were constructed using the software package Design Expert software (version 7.0, Stat-Ease Inc., Minneapolis, U.S.A.). A suitable polynomial model 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 square (PRESS), also provided by Design-Expert software.

Preparation of Coated Pellets with the Blend of HPMCP and HPMC The drug loaded pellets consisted of 0.17% (w/w) tamsulosin hydrochloride, 0.42% (w/w) poloxamer 407, 0.42% (w/w) carbopol 974P NF, 47.21% (w/w) microcrystalline cellulose, 5.20% (w/w) sodium alginate, 31.60% (w/w) magnesium trisilicate and 14.98% (w/w) Lactose. Briefly, tamsulosin hydrochloride (0.2 mg/capsule), poloxamer 407 and Carbopol® 974P NF were dissolved in 30% (w/v) ethanol. The drug solution was uniformly mixed with microcrystalline cellulose, sodium alginate, magnesium trisilicate and lactose. The wet mass was passed through a radial-basket extruder (Wooil Presicion Co. Ltd., Korea) with a 1 mm screen at 120 rpm. The extrudates were processed in a spheronizer (Sejeong Pharmatech Co. Ltd., Korea) fitted with a cross-hatched plate rotated at 800 rpm for 10 min. The spherical pellets were dried in a 60 °C drying oven for 24 h.

The drug-loaded pellets were coated with diluted Surelease® containing

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Table 1. Variables in Box–Behnken Design

Formulation variables	Levels used		
	−1	0	1
X_1=HPMCP content[a] (%)	10	20	30
X_2=HPMC content[a] (%)	5	10	15
X_3=coating weight gain (%)	20	25	30
Response variables	Constraints		
Y_1=cumulative % drug dissolved in 2 h	$15\% \leq Y_1 \leq 30\%$		
Y_2=cumulative % drug dissolved in 3 h	$50\% \leq Y_2 \leq 65\%$		
Y_3=cumulative % drug dissolved in 5 h	$80\% \leq Y_3 \leq 95\%$		

a) Base on total solid content of coating compositions.

HPMCP and HPMC. In each case, the calculated amount of HPMCP was dispersed in water and then added to Surelease®. 5% (w/w) HPMC solutions were prepared and stirred overnight and then added to the mixture of HPMCP and Surelease®. The final coating dispersions were adjusted to obtain *ca.* 15% (w/w) for the total solid content and stirred throughout the coating process. One kilogram of drug-loaded pellets from the 1000—1190 μm sieve fraction was used for coating. The drug-loaded pellets were coated using a Glatt (GPCG-3) bottom spray fluidized-bed coater and the following conditions: inlet temperature 47±3 °C, outlet temperature 40±3 °C, air flow 70 m^3/h, nozzle diameter 1.2 mm, and spray rate 6 ml/min. Following the application of the coating solution, the pellets were dried in a coater for an additional 30 min to prevent sticking. The coated pellets were spread onto paper trays and stored at 60 °C for 24 h.

***In Vitro* Dissolution Test** Release of tamsulosin hydrochloride from coated pellets was determined using a dissolution apparatus (Vankel VK7000, Cary, NC, U.S.A.) according to the USP XXV paddle method. Hard gelatin capsules (capsule No. 3, Su Heung Capsule Co. Ltd., Korea) were filled with coated pellets containing 0.2 mg drug. The capsules were added to 500 ml 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. A sinker was used to prevent capsule flotation. Five-milliliter samples were taken at defined time intervals, and the same volume of simulated gastric fluid was replaced. After 2 h, the solution was replaced with 500 ml simulated intestinal fluids without pancreatin (pH 7.2, phosphate buffer according to the USP without enzyme) and the dissolution testing was continued. Additional samples were taken at 3 and 5 h. Samples were analyzed by HPLC as described in the previous study.[3] Dissolution tests were repeated six times for all formulations and the % drug dissolved was calculated.

Results and Discussion

Experimental Design The experimental runs with independent variables and corresponding responses for the 15 formulations tested are presented in Table 2. The dependent variables were the cumulative percentages of drug dissolved within 2, 3 and 5 h. In this study, a three-factor, three-level Box–Behnken design was used and the design consists of replicated center points and a set of points lying at the midpoints of each edge of a multidimensional cube that defines the interesting area. Based on the Box–Behnken model, the factor combinations resulted in different drug release rates. Various models, such as Linear, 2FI, Quadratic and Cubic, were fitted to the data for three responses simultaneously using Design Expert software and adequacy, and good fit of the model was tested using analysis of variance (ANOVA). The multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS), provided by Design-Expert software, were used as factors for selection of adequate models. The lack of fit analysis (data not shown) shows that a quadratic model is appropriate for the description of all responses.

Table 2. Experimental Runs and Observed Responses for Box–Behnken Design

Run	Factor			Responses		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
1	20	10	25	20.5	47.45	67.5
2	20	15	20	42.8	80.7	98.5
3	30	10	20	36.8	71.4	98.9
4	20	10	25	21	48.25	69.8
5	10	15	25	23.5	43.7	63.2
6	20	5	20	33.5	67.4	93.2
7	10	10	20	35.7	60.3	92.6
8	20	10	25	19.2	45.8	65.9
9	20	15	30	21.5	46.1	71.8
10	10	10	30	11.5	26.8	48.7
11	20	5	30	9.4	35.6	60.4
12	10	5	25	15.5	34.5	56.3
13	30	5	25	16.1	47.9	76.2
14	30	10	30	10.9	41.2	71.2
15	30	15	25	23.1	55.8	88.1

From the results, the quadratic model was selected as a good fit for the model because its PRESS was the smallest. PRESS is a measure of the fit of the model to the points in design; the smaller PRESS the better the model fits to the data points.[11] The quadratic model generated by the design is of the form:

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

where A_0 is an intercept and A_1—A_9 are the coefficients of respective factors and their interaction terms. Mathematical relationships in the form of quadratic equations for all responses and their standardized main effects are shown in Tables 3 and 4, respectively. Positive or negative signs before a coefficient in quadratic models indicate a synergistic effect or an antagonistic effect for the factor.

As shown in Table 4, it can be noted that the statistically significant coefficients ($p<0.05$) were A_2, A_3, A_7 and A_9 for Y_1; A_1, A_2, A_3, A_7, A_8 and A_9 for Y_2; and A_1, A_2, A_3 and A_9 for Y_3, respectively. While the coefficients A_3 and A_7 demonstrated the antagonistic effects for both of Y_1 and Y_2, the coefficients A_3 showed the antagonistic effect in the case of Y_3. Other coefficients had synergistic effects. It is obvious that coating weight gain (X_3) had the highest antagonistic effects on the responses Y_1—Y_3. This effect of the coating weight gain on the responses Y_1—Y_3 might be due to the increased

Table 3. Quadratic Equations for the Quantitative Effect of Independent Variables (X_1, X_2, X_3) on the Responses (Y_1, Y_2, Y_3)

$$Y_1 = 20.23 + 0.087X_1 + 4.55X_2 - 11.94X_3 - 0.25X_1X_2 - 0.42X_1X_3 + 0.70X_2X_3 - 1.88X_1^2 + 1.20X_2^2 + 5.37X_3^2$$
$$Y_2 = 43.17 + 6.37X_1 + 5.11X_2 - 16.26X_3 - 0.33X_1X_2 + 0.82X_1X_3 - 0.70X_2X_3 - 4.61X_1^2 + 2.92X_2^2 + 7.37X_3^2$$
$$Y_3 = 67.73 + 9.20X_1 + 4.44X_2 - 16.39X_3 + 1.25X_1X_2 + 4.05X_1X_3 + 1.53X_2X_3 + 0.046X_1^2 + 3.17X_2^2 + 10.07X_3^2$$

Table 4. Standardized Main Effects of the Factors on the Responses

	Y_1			Y_2			Y_3		
	Estimated coefficient	Standard error	Standardized main effect (SME)[a)]	Estimated coefficient	Standard error	Standardized main effect (SME)[a)]	Estimated coefficient	Standard error	Standardized main effect (SME)[a)]
A_1	0.09	0.49	0.18	6.38	0.49	12.98**	9.20	1.21	7.60**
A_2	4.55	0.49	9.28**	5.11	0.49	10.41**	4.44	1.21	3.67*
A_3	−11.94	0.49	−24.34**	−16.26	0.49	−33.12**	−16.39	1.21	−13.55**
A_4	−0.25	0.69	−0.36	−0.33	0.69	−0.47	1.25	1.71	0.73
A_5	−0.43	0.69	−0.61	0.83	0.69	1.19	4.05	1.71	2.37
A_6	0.70	0.69	1.01	−0.70	0.69	−1.01	1.53	1.71	0.89
A_7	−1.88	0.72	−2.60*	−4.61	0.72	−6.38**	0.05	1.78	0.03
A_8	1.20	0.72	1.66	2.92	0.72	4.04*	3.17	1.78	1.78
A_9	5.37	0.72	7.44**	7.37	0.72	10.19**	10.07	1.78	5.66**

* Significant at 5% level. ** Significant at 1% level. *a*) Standardized main effects (SME) were calculated by dividing the estimated coefficient by the standard error of the estimated coefficient.

diffusional pathlength with increasing coating weight gain. Similar results were previously reported by many authors.[3,12,13)] Therefore, it can be suggested that drug release from the controlled release pellets coated with a blend of HPMCP (X_1) and HPMC (X_2) was dominated by diffusion through the coated film.

Based on the estimated quadratic equations, 2D contour and 3D response surface plots were obtained for the description of the relationship between the independent variables and the responses and presented in Fig. 1. The HPMCP content (X_1) showed significant synergistic effects ($p<0.05$) on Y_2 and Y_3, while it showed an insignificant effect on Y_1. In other words, factor X_1 demonstrated synergistic effects on drug release in dissolution medium at pH 7.2. HPMCP is insoluble in gastric fluid (pH *ca.* 1.5), but undergoes rapid dissolution above pH 5.5. Therefore, it can be expected that the leaching of HPMCP out of film coatings at pH 7.2 increases the permeability of the coated film, but the underlying mass transport phenomena might be more complex.[14)] In comparison with the HPMCP content (X_1), the HPMC content (X_2) showed significant synergistic effects on all responses, Y_1, Y_2 and Y_3. These effects may be attributed to the increased permeability of the coated film due to dissolution of HPMC, since HPMC has pH-independent solubility, in contrast to HPMCP. Accordingly, it has been suggested that HPMC increases the permeability of the coated film, irrespective of the pH of the dissolution medium.[13)]

These results indicate that drug release from the coated pellets is dominated by diffusion through the coated film. The permeability of the coated film can be controlled by the addition of additives. Moreover, the nature of the additives played an important role in changing the permeability of the coated film. Specifically, pH-dependent permeability could be achieved by using of enteric polymers, such as HPMCP.

Optimization In order to find the level of each independent variable that will lead to an optimized formula-

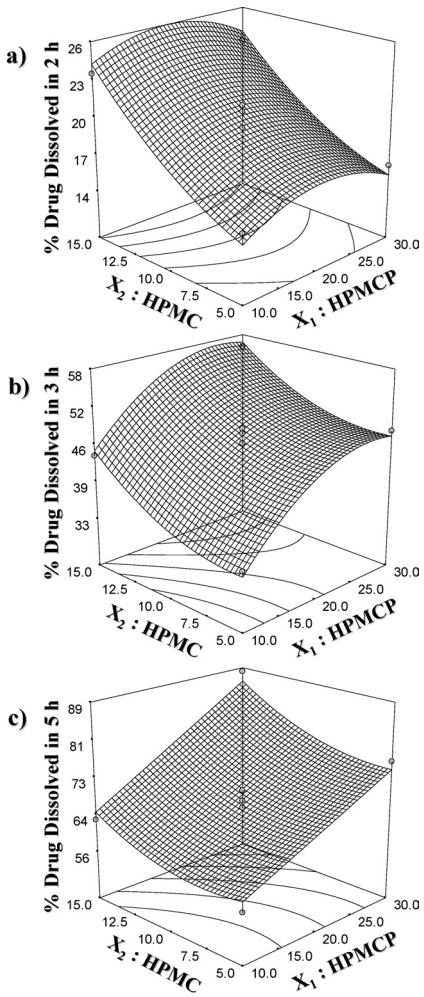

Fig. 1. Response Surface Plots Showing the Cumulative % Drug Dissolved after a) 2 h, b) 3 h and c) 5 h

Table 5. Predicted and Observed Responses of the Optimized Formulation

Responses	Predicted	Observed	Residuals[a)]
Y_1	23.9	23.5	−0.4
Y_2	56.6	55.5	−1.1
Y_3	85.8	88.7	2.9

a) Residual=observed value−predicted value.

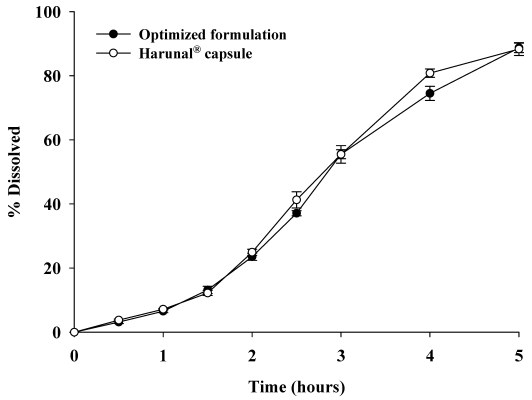

Fig. 2. Dissolution Profiles of Tamsulosin Hydrochloride for the Optimized Formulation and the Commercial Product (Harunal® Capsule)

tion, the optimization process was performed for X_1, X_2 and X_3 using the following target ranges; $15\% \leq Y_1 \leq 30\%$; $50\% \leq Y_2 \leq 65\%$; $80\% \leq Y_3 \leq 95\%$. The target ranges of these responses were determined based on the dissolution profiles of the Harunal® capsule, a commercial product. The optimization process was performed by graphical and numerical analysis using Design Expert software based on the methodology described by Myers and Montgomery.[15)] The optimized levels of each independent variable were based on the criterion of desirability. The optimized levels of HPMCP content (X_1), HPMC content (X_2) and coating level (X_3) were 30%, 15% and 25%, respectively, with a maximum value of desirability of 1.00. Table 5 shows the predicted and observed responses for the optimized formulations, indicating that the release profile of the tamsulosin hydrochloride pellet coated with the optimized formulation was close to the predicted values. The dissolution profiles of the optimized formulation and the commercial product (Harunal® capsule, Lot no. HRC801, Yamanouchi Pharmaceutical Co. Ltd., Korea) are presented in Fig. 2. These dissolution profiles were compared using two fit factors, difference factor (f_1) and similarity factor (f_2). The calculated values of f_1 and f_2 were 4.6 and 78.7, respectively, indicating that the dissolution profiles of the optimized formulation were comparable to those of the commercial Harunal® capsule.

Conclusions

In the present study, tamsulosin hydrochloride controlled release pellets were prepared using a blend of HPMCP and HPMC in aqueous dispersions (Surelease®). An optimization procedure using the Box–Behnken design gave values for HPMCP content (X_1), HPMC content (X_2) and coating level (X_3) of 30%, 15% and 25%, respectively, and the observed responses of the optimized formulation were very close to the predicted values. Furthermore, calculation of the difference and similarity factors indicated that the dissolution profiles of controlled release pellets coated with the optimized formulation were similar to those of the commercial Harunal® capsule.

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