Optimization of Sustained-Release Propranolol Dosage form Using Factorial Design and Response Surface Methodology

Yaw-Bin HUANG, Yi-Hung TSAI, Wan-Chiech YANG, Jui-Sheng CHANG, and Pao-Chu WU*

School of Pharmacy, Kaohsiung Medical University; Kaohsiung City 80708, Taiwan.
Received January 19, 2004; accepted June 7, 2004

The purpose of this study was to develop propranolol extended release formulations containing hydroxypropylmethylcellulose (HPMC). The results indicate that the drug release from the tablet form containing a high amount of HPMC was incomplete, and avicel addition could increase the release percent at a later stage. In order to readily obtain an optimal formulation, response surface methodology and multiple response optimization utilizing a quadratic polynomial equation was used. The model formulations were prepared according to a factorial design. The effects of causal factors including the HPMC/drug ratio (X_1) and avicel level (X_2), on drug release were also measured. The drug release percentage at 1.5, 4, 8, 14 and 24 h were the target response and were restricted to not more than 25%, 35—50%, 55—70%, 75—90%, and 95—110%, respectively. The results showed that the optimized formulation provided a dissolution pattern equivalent to the predicted curve, which indicated that the optimal formulation could be obtained using response surface methodology. The mechanism of drug release from HMPC matrices tablets followed quasi-Fickian diffusion.

Key words propranolol; hydroxypropylmethylcellulose (HPMC); dissolution test; response surface methodology

Hydrophilic gel-forming matrix tablets are extensively used for oral extended release dosage forms due to their simplicity, cost effectiveness, and reduction of the risk of systemic toxicity due to dose dumping.[1,2] Furthermore, pH-independent drug release is preferable for oral extended release formulations, so drug release in the GI tracts is not affected by intra- and inter-subject variations in both gastric pH and GI transit time. Hydroxypropylmethylcellulose (HPMC) is a pH-independent material and the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant.[3] Therefore, HPMC is widely used to prepare the extended release dosage forms of water-insoluble drugs such as promethazine and water-soluble drugs such as acetaminophen.[3—5]

Propranolol, a non-selective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. It is highly lipophilic and is almost completely absorbed after oral administration. However, much of the drug is metabolized by the liver during its first passage through the portal circulation; on average, only about 30% reaches the systemic circulation. Its elimination half-life is also relatively short (about 2—6 h).[6—8] Therefore, it was chosen as a model drug for preparation of the once-daily extended-release dosage form.

In the development of an extended release dosage form, an important issue was to design an optimized pharmaceutical formulation with an appropriate dissolution rate in a short time period and minimum trials. For this purpose, a computer optimization technique, based on a response surface methodology (RSM) utilizing a polynomial equation and artificial neural networks (ANN) has been widely used.[9—12] The optimization procedure involved systematic formulation designs to minimize the number of trials and analyze the response surfaces in order to realize the effect of causal factors and to obtain the appropriate formulations with target goals and the acceptable component region as process control conditions in practical preparation. Therefore, the primary purpose of this study was to develop and optimize the propranolol extended release formulations with target release profiles using RSM and multiple response optimization utilizing a quadratic polynomial equation. The second aim of the study was to evaluate and demonstrate the usefulness of RSM with multiple response optimization technology in the development of extended-release dosage forms containing water-soluble drug.

MATERIALS AND METHODS

Materials Propranolol hydrochloride and *p*-hydroxybenzoate-butyl ester were purchased from TCI Co. (Japan). Hydroxypropylmethylcellulose (HPMC, viscosity 4000 grade) was obtained from Shin Etsu (Japan). Microcrystalline cellulose (Avicel) was purchased from Asahi Co. (Japan). All other chemicals and solvents were of analytical reagent grade.

Preparation of Propranolol HPMC Matrix Tablets The drug and additives were weighed and mixed well. Water was added to make a wet mass. The wet component was then granulated through a 40 mesh sieve. The granules were dried in an oven for 3 h at 40 °C, and then blended with 1% magnesium stearate. Tablets containing 100 mg of propranolol were compressed using 5 mm diameter flat-faced punches. The upper punch compaction pressure used was 135 kg/cm^2.

Determination of Propranolol Release from HPMC Matrix Tablets The United States Pharmacopoeia (USP)[13] basket method was used for all of the *in vitro* dissolution studies. Simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) without enzymes were used as dissolution mediums. The rate of stirring was 100 rpm. The propranolol tablets were placed in 900 ml of gastric fluid and maintained at 37 °C. Five milliliters of samples were taken at appropriate intervals. After 1.5 h the dissolution medium pH was changed from 1.2 to 6.8 by adding 80 ml of concentrated phosphate buffer to simulate intestinal fluid and was then run

* To whom correspondence should be addressed. e-mail: pachwu@kmu.edu.tw

for the time specified. The samples were analyzed using an ultraviolet/visible spectrophotometer at 290 nm.

Data Analysis Response surface methodology (RSM) utilizing polynomial regression analysis and the evaluation of the quality of fit of the model were performed with an Alcora program written by Takayama and co-workers (Japan). Briefly, the release data were fitted to the quadratic polynomial equation to obtain an individual optimum regression equation for each response. The multi-objective simultaneous optimization was performed according to the generalized distance function method[14] to obtain the simultaneous optimum value.

The similarity factor f_2 is defined by the following equation and was used to measure the similarity between two curves.[15]

$$f_2 = 50 \times \log\left\{\left[1+(1/n)\sum_{t=1}^{n}(Rt-Tt)^2\right]^{-0.5} \times 100\right\}$$

where n is the number of dissolution sample times, and Rt and Tt are the individual percentages dissolved at each time point, t, for the reference and test dissolution profiles, respectively. The f_2 values greater than 50 (50—100) represent sameness or equivalence of the two curves.

In order to propose a possible release mechanism, drug release from HPMC matrix tablets was fitted to the following simple exponential model.[16]

$$M_t/M_\infty = kt^n$$

where M_t/M_∞ is the fractional drug release percentage at time t, k is a constant related to the properties of the drug delivery system, and n is the diffusional exponent, which characterizes the drug transport mechanism. When $n=0.5$, the drug diffuses through and is released from the polymeric matrix with a quasi-Fickian diffusion mechanism. For $n>0.5$, an anomalous, non-Fickian drug diffusion occurs. When $n=1$, a non-Fickian, case II or zero-order release kinetics can be observed.

RESULTS AND DISCUSSION

In order to rapidly design and obtain optimal propranolol extended-release formulations with specific release patterns, the RSM utilizing polynomial equations and systemic formulations design such as factorial design must be applied.[9—12] In the build-up to the approach, significant factors and the range of each process variable must be predetermined. According to previous studies,[3—5] the polymer type, polymer/drug ratio, and incorporated water-soluble excipients are the most potent factors that influence drug release from sustained-release dosage forms. Therefore, the effects of HPMC type including HPMC 4000, HPMC 15000, and HPMC 30000, and the HPMC/drug ratio on the dissolution rate were evaluated (Fig. 1)[17] to be established the causal factor variables. As shown in Fig. 1,[17] the HPMC 400 showed the least burst effect on the dissolution patterns compared to HPMC 15000 and HPMC 30000 at a polymer/drug ratio of 1/5, so the low viscosity polymer (HPMC 4000) was selected as the retardant thereinafter. Varying the polymer/drug ratio decreased, as expected, the drug release rate with

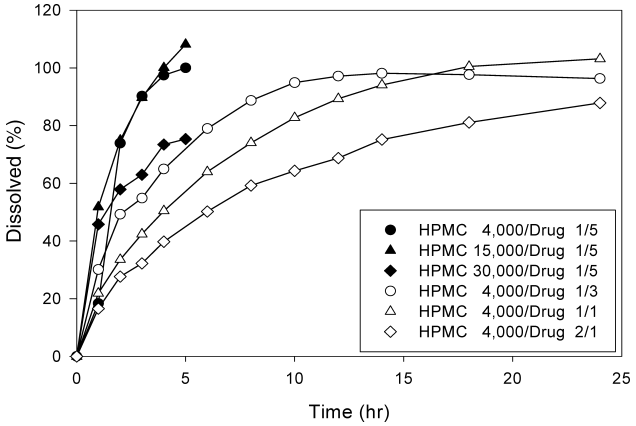

Fig. 1. The Effect of Polymer Type and Polymer/Drug Ratio on the Drug Dissolution Profiles

an increase in the tablet content of HPMC. These results could be attributed to an increase in thickness of the gel layer resulting in a reduction of drug release. However, the drug release from tablets containing a high amount of HPMC was incomplete, the percent release at 24 h was only about 85%. Some studies[18—20] have reported insufficient drug absorption from controlled release products *in vivo* because of the suppression of drug release due to the environment of the colon (small volume of GI fluid and viscous colonic content) in the later stage. Incorporated water-soluble excipients into the gel-forming matrices can improve the phenomenon *in vitro* and/or *in vivo* because these excipients can stimulate water penetration into the inner parts of the matrices, resulting in drug release from the matrix.[21—24] Avicel is widely used in pharmaceuticals. It can improve the manufacturing process and adjust the drug release. Therefore, various amounts of avicel were incorporated into the HPMC tablets to modify the drug release in this study.

According to the results above and preliminary experiments,[17] a two-factor, three-level full factorial design and RSM utilizing a polynomial equation were used in this study to obtain an optimal formulation with an adequate release rate and quantify the influence of factors including individual and interaction effects on the dissolution rate. As shown in Table 2, 11 types of model formulation including 3^2 factorial runs and two center runs were prepared and subjected to the release test. The center runs were added to augment the statistical design and provide extra degrees of freedom needed to test for pure error. According to the USP23[13] monograph for propranolol extended release dosage form, the drug release percentages at 1.5, 4, 8, 14 and 24 h were selected as responses. These time points were selected to detect the burst effect at an earlier stage and ensure that most of the drug is released in a period of time comparative to the gastrointestinal residence time. The drug release percentages from these model formulations at different time points are listed in Table 1. The drug release percentage at 24 h was 87—109%, indicating that avicel could increase drug release at the later stage. The causal factor and response variable were related using a quadratic polynomial equation with statistical analysis. As shown in Table 2, the approximations of the response values (Y_1, Y_2, Y_3, Y_4, Y_5) based on the polynomial regression equation were substantial ($p<0.01$). The three-dimensional

Table 1. The Causal Factor and Responses of Model Formulations of Propranolol Extended Release Tablets Utilizing 3^2 Factorial Design

Trial	X_1	X_2	Y_1	Y_2	Y_3	Y_4	Y_5
1	1	1	26±1	40±3	59±3	77±3	92±5
2	0	0	26±1	48±2	71±2	90±3	103±3
3	1	−1	21±1	43±2	66±3	89±5	104±4
4	0	0	25±2	45±5	66±7	85±7	101±5
5	−1	0	27±2	48±2	71±3	89±2	98±2
6	0	0	25±2	46±3	67±3	86±3	100±5
7	0	−1	20±1	44±2	66±3	87±4	101±2
8	−1	1	31±1	54±1	79±1	95±1	102±1
9	−1	−1	30±3	52±1	71±3	86±5	100±5
10	0	1	22±4	42±2	62±2	82±2	96±2
11	1	0	19±1	35±2	55±3	74±4	91±3

The amount of propranolol was fixed at 100 mg. X_1: causal factor, polymer/drug ratio, the level from 1 to 2. X_2: causal factor, the tablet content of avicel, the level from 8% to 20%. Y: responses, the release percent at 1.5 h (Y_1), 4 h (Y_2), 8 h (Y_3), 14 h (Y_4) and 24 h (Y_5).

Table 2. Optimal Regression Equation for Each Response Variable Determined by Multiple Regression Analysis

Regression coefficient	Y_1	Y_2	Y_3	Y_4	Y_5
b_0 (constant)	23.463	44.306	66.583	85.413	100.363
$b_1(X_1)$	−4.458	−6.116	−6.833	−5.094	−2.075
$b_2(X_2)$	—[a]	—[a]	—[a]	−1.458	−2.491
$b_{11}(X_1X_1)$	1.506	—[a]	—[a]	—[a]	−2.488
$b_{22}(X_2X_2)$	—[a]	1.435	—[a]	—[a]	—[a]
$b_{12}(X_1X_2)$	—[a]	−1.395	−3.666	−5.354	−3.504
r[b]	0.7893	0.8073	0.7930	0.7392	0.6545
S[c]	2.688	3.506	4.332	4.768	4.116
Fo[d]	52.060[e]	38.700[e]	53.377[e]	24.901[e]	11.428[e]

a) Not included in the optimum regression equation ($p>0.05$). *b*) Multiple correlation coefficient. *c*) Standard deviation of residual. *d*) Observed F value. *e*) $p<0.01$.

response surfaces obtained illustrating the simultaneous effect of the causal factors on each response variable are presented in Fig. 2. The equations of all responses (Table 2) represent the quantitative effect of process variables (X_1, X_2) upon the responses (Y_1; Y_2; Y_3; Y_4; Y_5). The values of the coefficients X_1 and X_2 are related to the effect of these variables on the response. Coefficients with more than one factor represent the interaction between factors while coefficients with second order terms indicate the quadratic nature of the phenomena. A positive sign indicates a synergistic effect while a negative term indicates an antagonistic effect upon the responses. The results showed that the X_1 (HPMC/drug ratio) and the interaction of X_1X_2 were the major factors influencing the earlier release phase (Y_1, Y_2, Y_3) and the later release phase (Y_4, Y_5), respectively. However, the effect of the HPMC/drug ratio on the drug release was greater than avicel in the experimental time period. The effect of avicel was more important in the later stage.

In order to obtain an optimal formulation with an adequate release percent at different time points, multiple response optimization was performed to search for the level which fitted the following constraints: $Y_1 \leq 25\%$; $35\% < Y_2 < 50\%$; $55\% < Y_3 < 70\%$; $75\% < Y_4 < 90\%$; $95\% < Y_5 < 110\%$. Under these conditions, the model predicted Y_1, Y_2, Y_3, Y_4, and Y_5 values of 24.99%, 47.21%, 67.57%, 86.79% and 102.17% at X_1 and X_2 values of −0.312 and −0.999, respectively. This optimum formulation was a predicted point, thus, in order to validate the predictive ability of the hypothesized model for each response around the optimized conditions, the agreement between predicted and measured responses was verified. Therefore, the propranolol extended release formulation was prepared according to the optimized conditions and sub-

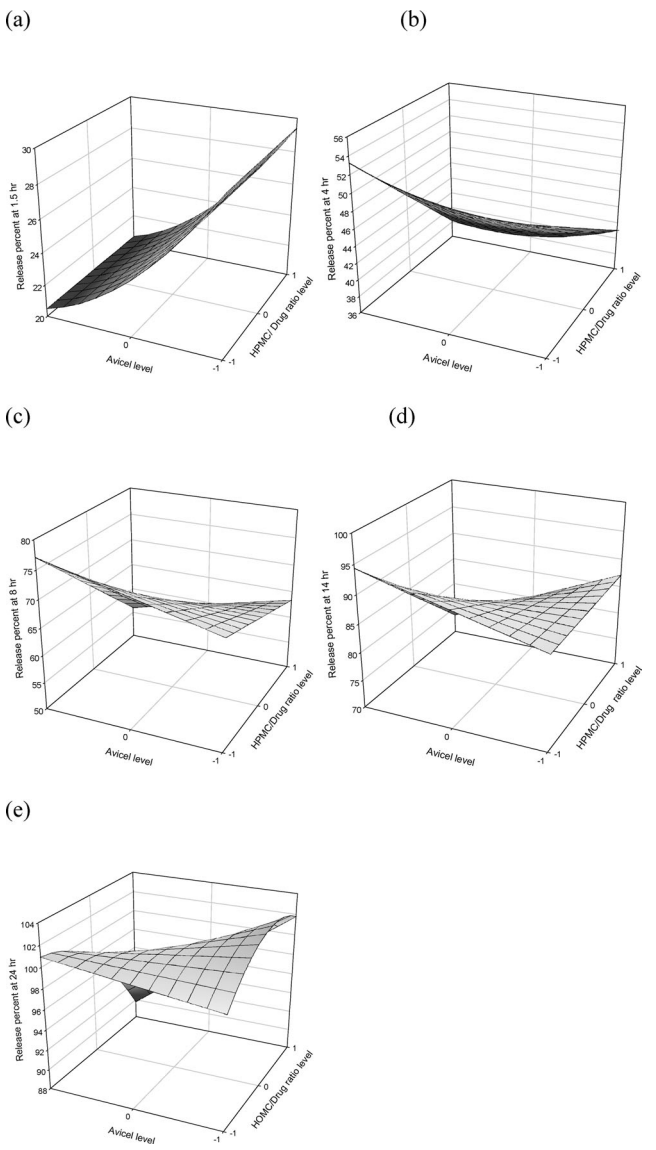

Fig. 2. Response Surface Plots Obtained by Plotting HPMC/Drug Ratio against Avicel Level

(a) 1.5 h drug release percent, (b) 4 h drug release percent, (c) 8 h drug release percent, (d) 14 h drug release percent, (e) 24 h drug release percent.

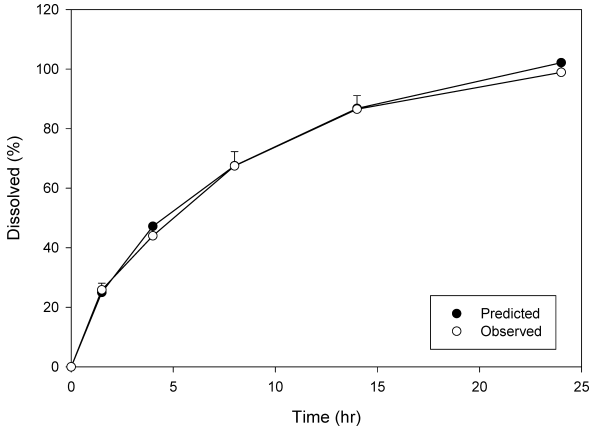

Fig. 3. Comparison of Observed Dissolution Profile and Predicted Dissolution Profile of the Optimal Formulation Obtained from the Response Surface Methodology

jected to the release test. The dissolution profiles of the optimum formulation and the predicted profile are shown in Fig. 3. Both profiles were compared using the FDA[15] recommended similarity factor (f_2). The values for f_2 were 94, 80, 83, 86, and 82 at 1.5, 4, 8, 14, and 24 h, respectively, which indicated equivalence to the release profile of the optimum formulation and the predicted profile. The release mechanisms for propranolol from the predicted HMPC matrix tablets were also evaluated on the basis of a simple exponential model.[16] The correlation coefficient, release rate constant (k), and exponent constant (n) were 0.9933 ($p<0.01$), 21.3 ± 1.8, and 0.52 ± 0.02, respectively. The value of the exponent constant (n) was close to 0.5, indicting that the mechanism of drug release from HMPC matrix tablets was a quasi-Fickian diffusion.

It was concluded that the response surface methodology (RSM) and multiple response optimization utilizing a polynomial equation can be successfully used to design an extended release formulation containing water-soluble drug for a predetermined release profile. A sustained release propranolol formulation with satisfactory release characteristics was successfully prepared with HPMC and avicel.

Acknowledgement The authors would like to thank Professor Takayama of Hoshi University for providing the software.

REFERENCES

1) Gao P., Meury R. H., *J. Pharm. Sci.*, **85**, 725—731 (1996).
2) Gohel M. C., Amin A. F., *J. Control Release*, **51**, 115—122 (1998).
3) Ford J. L., Rubinstein M. H., Hogan J. E., *Int. J. Pharm.*, **24**, 327—338 (1985).
4) Ford J. L., Mitchell K., Rowe P., Armstrong D. J., Elliott P. N. C., Rostron, C., Hogan J. E., *Int. J. Pharm.*, **71**, 95—104 (1991).
5) Sako K., Sawada T., Nakashima H., Yokohama S., Sonobe T., *J. Control Release*, **81**, 165—172 (2002).
6) Rekhi S. G., Porter S. C., Jambhekar S. S., *Drug Dev. Ind. Pharm.*, **221**, 709—729 (1995).
7) Taylan B., Capan Y., Guven O., Kes S., Hincal A., *J. Control Release*, **38**, 11—20 (1996).
8) Eddington N. D., Ashraf M., Augsburger L. L., Leslie J. L., Fossler M. J., Lesko L. J., Shah V. P., Rekhi G. S., *Pharm. Dev. Tech.*, **3**, 535—547 (1998).
9) Sonaglio D., Bataille B., Ortigosa C., Jacob M., Khan M., *Int. J. Pharm.*, **115**, 53—60 (1995).
10) Bouckaert S., Massart D. L., Massart B., Rremon J. P., *Drug Dev. Ind. Pharm.*, **22**, 321—327 (1996).
11) Karnachi A. A., Khan M. A., *Int. J. Pharm.*, **131**, 9—17 (1996).
12) Wu P. C., Obata Y., Fujikawa M., Li C. J., Higashiyama K., Takayama K., *J. Pharm. Sci.*, **90**, 1004—1014 (2001).
13) USP XXIII, United States Pharmacopeial Convention, Inc., Rockville, MD, 1995, p. 1328.
14) Takayama K., Fujikawa M., Nagai T., *Pharm. Res.*, **16**, 1—6 (1999).
15) United States Food and Drug Administration (FDA), Guidance for industry, dissolution testing of immediate release solid oral dosage forms, August 1997.
16) Ritger P. L., Peppas N. S., *J. Control Release*, **5**, 37—42 (1987).
17) Huang Y. B., Tsai Y. H., Yang W. C., Chang J. S., Wu P. C., *J. Appl. Polym. Sci.*, **93**, 1886—1890 (2004).
18) Cressman W. A., Summer D., *J. Pharm. Sci.*, **60**, 132—134 (1971).
19) Uchida T., Kawata M., Goto S., *J. Pharmacobio-Dyn.*, **9**, 631—637 (1986).
20) Katori N., Okudaria K., Aoyagi N., Takeda Y., Uchiyama M., *J. Pharmacobio-Dyn.*, **14**, 567—575 (1991).
21) Feely L. C., Davis S. S., *Int. J. Pharm.*, **41**, 83—90 (1988).
22) Efentakis M., Al-Hmound H., Choulis N. N., *Acta Pharm. Technol.*, **36**, 237—239 (1990).
23) Vlachou M., Hani N., Efentakis M., Tarantili P. A., Andreopoulos A. G., *J. Biomater. Appl.*, **15**, 65—77 (2000).
24) Nokhodchi A., Norouzi-Sani S., Siahi-Shadbad M. R., Lotfipoor F., Saeedi M., *Eur. J. Pharm. Sci.*, **54**, 349—356 (2002).