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Research paper

Once-daily propranolol extended-release tablet dosage form: formulation design and in vitro/in vivo investigation

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Abstract

The purpose of this study was to develop and optimize the propranolol once-daily extended release formulations containing HPMC, Microcrystalline cellulose (MCC) and lactose. In vitro studies, the response surface methodology and multiple response optimization utilizing the polynomial equation were used to search for the optimal formulation with specific release rate at different time intervals. The constrained mixture experimental design was used to prepare systematic model formulations, which were composed of three formulation variables: the content of HPMC (X_1), MCC (X_2), and lactose (X_3). The drug release percent at 1.5, 4, 8, 14 and 24 h were the target responses and were restricted to 15–30, 35–55, 55–75, 75–90 and 90–110%, 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 matrix tablets followed non-Fickian diffusion. In the vivo study, the MRT was prolonged for matrix tablets when compared with commercial immediate release tablets. Furthermore, a linear relationship between in vitro dissolution and in vivo absorption was observed in the beagle dogs.

Keywords: Extended release dosage form; Mixture experimental design; Response surface methodology; Dissolution; In vivo absorption; In vitro–in vivo correlation

1. Introduction

The 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 as not to be affected by intra- and inter-subject variations of both gastric pH and GI transit time. The 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 extended release dosage forms such as promethazine and acetaminophen [3–5]. In addition, some studies [6–8] report insufficient drug absorption from controlled release products in in vivo studies 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 such as polyethylene glycol, lactose and surfactants into the gel-forming matrix can improve the phenomenon of insufficient drug release and/or absorption because these excipients can stimulate the water penetration into the inner parts of the matrix, thus resulting in drug release from matrix [9–12]. Microcrystalline cellulose (MCC) is often regarded as one of the best excipients for direct compression [13]. Incorporated MCC into the formulation was shown to increase dissolution rates and compressibility of tablets made by high shear granulation [14]. Lactose is a soluble excipient and has been widely used in tablet dosage form. In this study for once-daily propranolol extended-release dosage forms, HPMC 4000

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was used as a retardant, and the MCC as well as lactose were used to modify the drug release and ensure that most of drug is released in a period time comparable to the gastrointestinal residence time.

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, its bioavailability is very limited (30%) due to the hepatic first-pass effect. Its elimination half-life is also relatively short (about 2–6 h) [15–19]. Therefore, it was chosen as a model drug for preparation of the once-daily extended-release dosage form.

It is well-known that traditional experimentation involves a good deal of effort and time especially when complex formulations are to be developed. In order to readily reach our goal, a computer optimization technique, based on a response surface methodology (RSM) utilizing polynomial equation [19–23] was used to search for the optimal propranolol extended-release formulation and efficiently quantify the influences of formulation variables on the drug release. Furthermore, the pharmacokinetics of the extended-release matrix tablets were evaluated using beagle dogs to explore the relationship between in vitro release and in vivo absorption.

2. Materials and methods

2.1. Materials

The following reagents were used: propranolol hydrochloride, *p*-hydroxybenzoate butyl ester (TCI, Japan), hydroxypropylmethylcellulose (HPMC), viscosity 4000 (Shin Etsu, Japan), Magnesium stearate (Ajax, Australia), Lactose (New Zealand Lactose Co., New Zealand) and Microcrystalline cellulose (MCC) (Asahi, Japan). All other chemicals and solvents were of analytical reagent grade.

2.2. Preparation of model formulations

In order to easily optimize the formulation and evaluation of the influence of each additive on the dissolution rate, the constrained mixture experimental design [24] was used to prepare systematic model formulations which were composed of three formulation variables: the content of HPMC (X_1), MCC (X_2), and lactose (X_3). The total amount of the varying ingredients (HPMC, MCC and lactose) was maintained at 300 mg. The causal factors and measured responses are listed in Table 1. The range of each process variable was predetermined using preliminary experiments [25]. According to D-optimal mixture model, 14 model formulations including 6 estimate formulations, 4 estimate lack of fit formulation and 4 replicates formulations were randomly arranged by Design-Expert® software. The compositions of all model formulation are summarized in Table 2. The drug release percent at 1.5, 4, 8, 14 and 24 h were selected as response variables to detect the burst effect and ensure complete drug release.

Table 1
Variables in the mixture design

Formulation variables	Levels	
	Low	High
X_1 = fraction of HPMC in total excipients	0.3	0.8
X_2 = fraction of MCC in total excipients	0	0.35
X_3 = fraction of Lactose in total excipients	0	0.35
Response variables	**Constraints**	
$Y_{1.5\ h}$ = percent dissolved in 1.5 h	$15\% \le Y_1 \le 30\%$	
$Y_{4\ h}$ = percent dissolved in 4 h	$35\% \le Y_2 \le 55\%$	
$Y_{8\ h}$ = percent dissolved in 8 h	$55\% \le Y_3 \le 75\%$	
$Y_{14\ h}$ = percent dissolved in 14 h	$75\% \le Y_4 \le 90\%$	
$Y_{24\ h}$ = percent dissolved in 24 h	$90\% \le Y_5 \le 110\%$	

The amount of propranolol was fixed at 100 mg. The amount of total excipients was fixed at 300 mg. $X_1 + X_2 + X_3 = 1$.

The drug and additives were weighed and mixed well. Water was added to make a wet mass. Then the wet component was granulated through a 40 mesh sieve. The granules were dried in an oven for 3 h at 40 °C, and then blended with 1% of 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.

Table 2
The composition and responses of model formulations of propranolol extended release tablets

Run	X_1 HPMC	X_2 MCC	X_3 Lactose	$Y_{1.5\ h}$	$Y_{4\ h}$	$Y_{8\ h}$	$Y_{14\ h}$	$Y_{24\ h}$
1	0.30	0.35	0.35	31.3	53.8	75.3	91.6	100.9
2	0.65	0.00	0.35	22.1	45.4	66.3	82.8	95.6
3	0.80	0.20	0.00	18.1	32.4	49.9	66.0	82.8
4	0.65	0.35	0.00	19.1	35.8	53.5	71.1	87.6
5	0.64	0.09	0.27	22.3	38.3	57.7	75.1	90.1
6	0.72	0.14	0.14	20.5	38.4	59.2	76.0	92.2
7	0.55	0.18	0.27	23.1	40.3	59.7	76.7	92.6
8	0.80	0.20	0.00	16.9	31.0	49.7	65.2	81.7
9	0.80	0.00	0.20	17.8	34.7	54.1	72.4	88.0
10	0.47	0.30	0.18	26.0	44.3	63.2	80.9	94.8
11	0.65	0.35	0.00	19.7	34.3	53.3	70.9	86.5
12	0.80	0.00	0.20	19.5	35.5	54.0	72.5	87.6
13	0.64	0.27	0.09	21.4	37.6	55.8	73.7	91.3
14	0.30	0.35	0.35	31.0	53.4	75.9	91.5	101.5

1. The amount of propranolol was fixed at 100 mg; 2. The amount of total excipients was fixed at 300 mg; 3. Yi: responses, the drug release percent at 1.5 h ($Y_{1.5\ h}$), 4 h ($Y_{4\ h}$), 8 h ($Y_{8\ h}$), 14 h ($Y_{14\ h}$) and 24 h ($Y_{24\ h}$); 4. The composition of each run was random and arranged according to the D-optimal model provided Design-Expert® software.

2.3. Determination of the release of propranolol from HPMC matrix tablet

The United States Pharmacopoeia [26] basket method was used for all the in vitro dissolution studies. The simulated gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) without enzymes were used as a dissolution medium. The rate of stirring was 100 rpm. The propranolol tablets were placed in 900 ml of gastric fluid and maintained at 37 °C. Five millilitres 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 for the time specified. The samples were analyzed by ultraviolet/visible spectrophotometry at 290 nm. At least 6 tablets of each formulation were determined. The mean and SD of dissolved percent were calculated.

2.4. Data analysis

The released drug percents at 1.5, 4, 8, 14 and 24 h (responses) of all model formulations were treated by Design-Expert® software. Suitable models for mixture designs consisting of three components include linear, quadratic and special cubic models. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual sum of square (PRESS), proved by Design-Expert software. Among them, PRESS indicates how well the model fits the data, and for the chosen model it should be small relative to the other models under consideration [27].

Linear model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3$$

Quadratic model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3$$

Special cubic model:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

In order to propose the possible release mechanism, the drug release from HPMC matrix tablets was fitted to the following power model [28].

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

where M_t/M_∞ is the fractional drug release percentage at time t. The 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. A value of $n = 0.45$, indicates Case I (Fickian) diffusion, $0.45 < n < 0.89$ indicates anomalous (non-Fickian) diffusion and $n = 0.89$ indicates Case-II transport.

2.5. In vivo absorption study

Six male beagle dogs weighing 8–14 kg were used in this study in accordance with a protocol approved by the Institutional Review Board-Use and Care of Animals at Kaohsiung Medical University. All dogs were fasted 12 h prior to the experiment but water was allowed. The legs were shaved and a forefoot vein was cannulated using an 18 gauge cannula. After oral administration of experimental extended-release matrix tablets and commercial immediate release tablets (40 mg, Zeneca), 3 ml of blood samples were taken at appropriate intervals. The samples were centrifuged

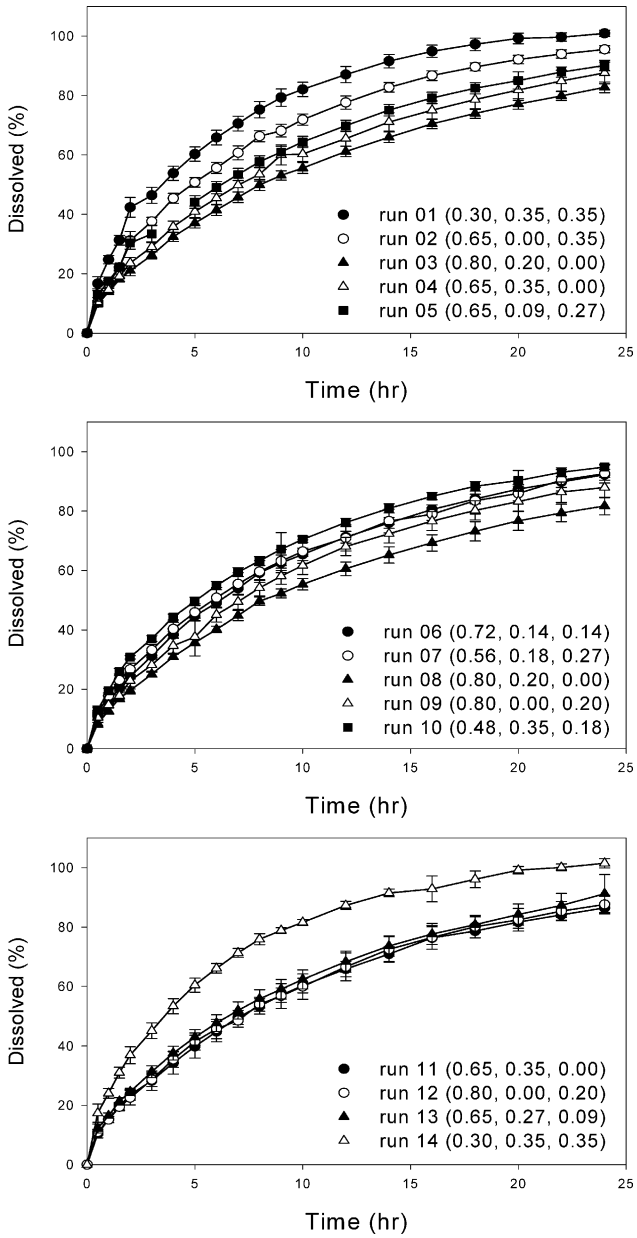

Fig. 1. Dissolution profiles of all model formulations.

for 10 min, and plasma was kept frozen pending analysis. The propranolol plasma concentration was determined according to a previous study [29].

The measured plasma concentrations were used to calculate the area under the plasma concentration-time profile from time zero to the last concentration time point (AUC_{0-t}). The AUC_{0-t} and AUMC were determined by the trapezoidal method. The $AUC_{0-\infty}$ was determined by the following equation:

$$AUC_{0-\infty} = AUC_{0-t} + Ct/k_{el}$$

k_{el} was estimated by fitting the logarithm of the concentrations versus time to a straight line over the observed exponential decline. The *C*max and *T*max were obtained directly from the data. Oral clearance (Cl) was calculated as dose divided by $AUC_{0-\infty}$. The mean residence time was determined by AUMC divided by AUC. The Wanger-Nelson model [30] was used to calculate the percentage of the propranolol dose absorbed profiles [31–33].

$$FAt = (Ct + k_{el} \times AUC_{0-t})/k_{el} \times AUC_{0-\infty}$$

where FA*t* is the fraction of drug absorbed at time *t*, *Ct* is the concentration of drug in the plasma at time *t* and *k* is the elimination rate constant. The elimination rate constant, k_{el}, was calculated from the mean plasma concentration-time profile after administration of immediate release tablets. The in vivo absorption values were directly related to in vitro dissolution data to complete the in vitro–in vivo correlations. All other comparisons were performed by using ANOVA.

3. Results and discussion

3.1. In vitro release study

The dissolution profiles of all model formulations required by the mixture experimental design are shown in Fig. 1. The responses of these formulations are summarized in Table 2. The wide variation indicated that the factor combinations resulted in different drug release rates. The drug release rate and burst effect decreased with the increase in the tablet content of HPMC. It was also noted that the drug released at later stage was incomplete ($Y_{24\ h} < 90\%$), while the added amount of HPMC was at high level. Incorporated MCC and lactose into the HPMC matrix could increase the drug release rate. The increment effect of release rate of lactose was higher than hat of MCC while the HPMC was at a moderate level (compared with run 2 and 4). These findings concurred with the results of previous studies which reported that added water-soluble excipients into the gel-forming matrix can improve drug release from controlled release product [11,12].

In order to evaluate the effect of formulation ingredients on the dissolution pattern, the causal factor and response variables were related using polynomial equation with statistical analysis. As shown in Table 3, the approximations of response values ($Y_{1.5\ h}$, $Y_{4\ h}$, $Y_{8\ h}$, $Y_{14\ h}$ and, $Y_{24\ h}$) based on the linear model was most suitable because its PRESS was smallest. The values of the coefficients X_1, X_2 and X_3 are related to the effect of these variables on the response. The contour plots illustrating the simultaneous effect of

Table 3
Optimal regression equation for each response variable

Model	Coefficient	$Y_{1.5\ h}$	$Y_{4\ h}$	$Y_{8\ h}$	$Y_{14\ h}$	$Y_{24\ h}$
	$b_1(X_1)$	12.22	24.75	41.86	59.38	78.75
	$b_2(X_2)$	29.48	48.67	67.99	83.81	97.01
	$b_3(X_3)$	31.68	56.19	79.57	96.73	105.24
	$b_{12}(X_1X_2)$	–	–	–	–	–
	$b_{13}(X_1X_3)$	–	–	–	–	–
	$b_{23}(X_2X_3)$	–	–	–	–	–
	$b_{123}(X_1X_2X_3)$	–	–	–	–	–
Linear	CV	5.08	6.87	5.63	4.05	2.66
	R^2	0.9488	0.8787	0.8678	0.8791	0.8592
	Adjusted R^2	0.9395	0.8566	0.8438	0.8571	0.8336
	PRESS	24.31	139.40	206.94	175.52	107.41
Quadratic	CV	4.09	7.36	5.88	4.09	2.77
	R^2	0.9759	0.8987	0.8950	0.9101	0.8887
	Adjusted R^2	0.9609	0.8354	0.8293	0.8539	0.8191
	PRESS	21.73	217.22	302.46	246.69	158.90
Special cubic	CV	4.36	7.84	6.24	4.29	2.82
	R^2	0.9761	0.8995	0.8968	0.9136	0.8993
	Adjusted R^2	0.9556	0.8133	0.8083	0.8395	0.8130
	PRESS	38.11	254.66	371.19	276.24	159.56

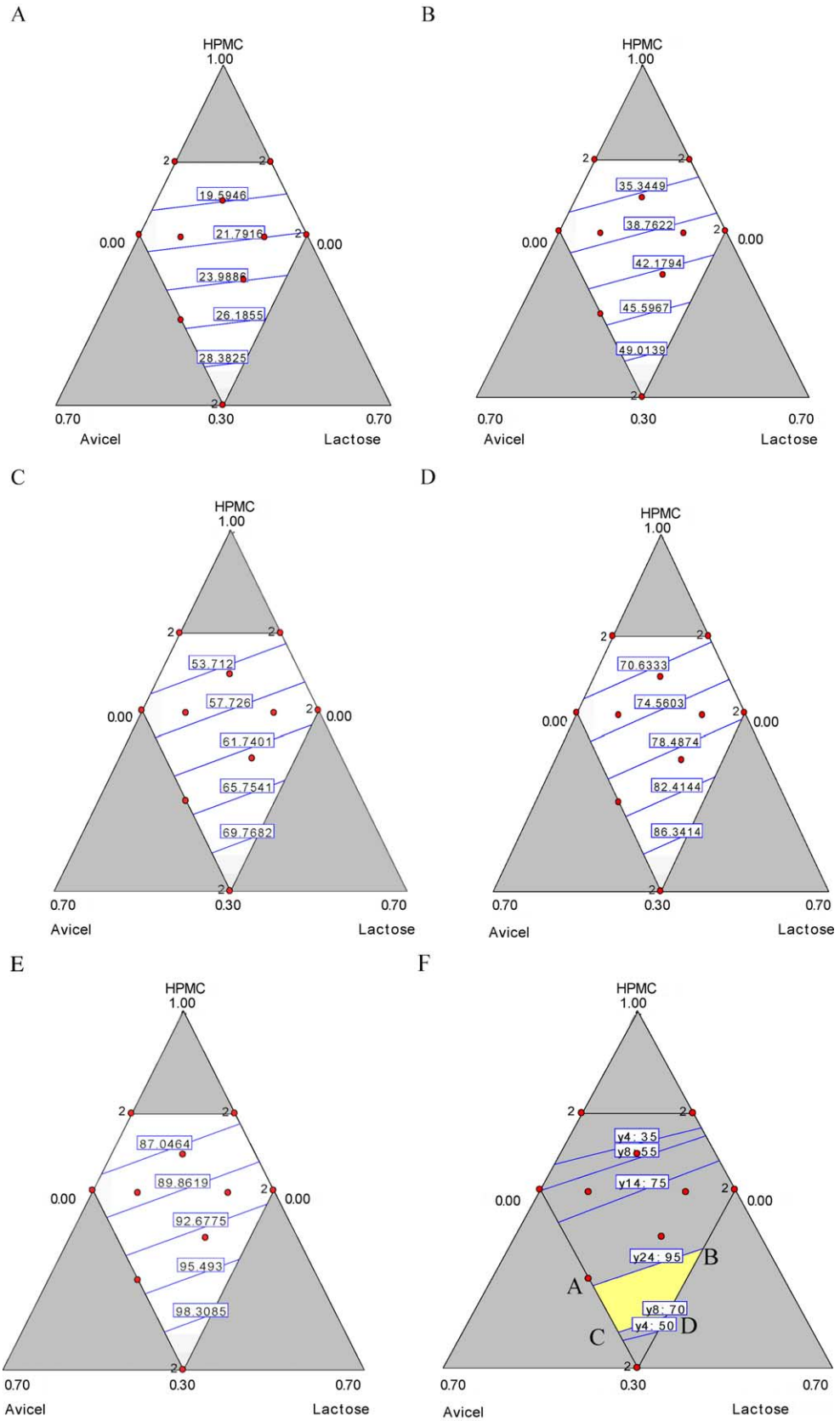

Fig. 2. The triangular-dimensional contour diagrams illustrating the effect of HPMC (X_1), MCC (X_2) and lactose (X_3) on the release of propranolol from matrix tablets. (A) 1.5 h drug release percent, (B) 4 h drug release percent, (C) 8 h drug release percent, (D) 14 h drug release percent, (E) 24 h drug release percent, (F) Overlay plot.

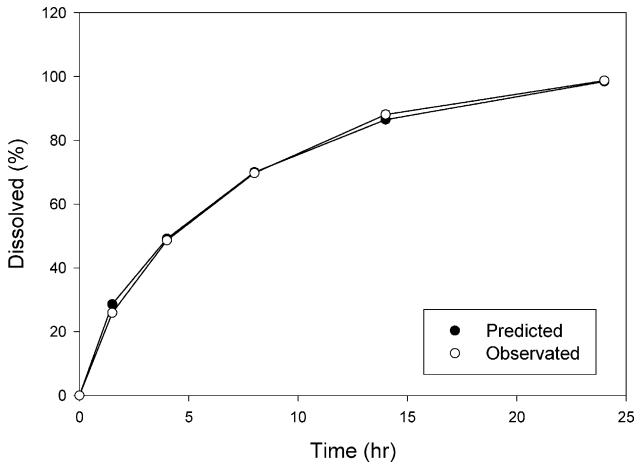

Fig. 3. Comparison of the observed dissolution profile with the predicted profile.

the causal factors on individual and combined response variable are represented in Fig. 2. The amount of the different constituents was fixed ($X_1 + X_2 + X_3 = 1$), since the term of $X_3 = 1 - X_1 - X_2$, $X_2 = 1 - X_1 - X_3$ or $X_1 = 1 - X_2 - X_3$ could be substituted into the obtained polynomial equations shown in Table 3 for comparing the effect of these variables on the drug release at different time points. For example, we can get the equations of $Y_{1.5\ \mathrm{h}} = 32 - 19X_1 - 2X_2$ and $Y_{24\ \mathrm{h}} = 105 - 27X_1 - 12X_2$, when $X_3 = 1 - X_1 - X_2$ is substituted. The results showed that the HPMC (X_1) was the main retardant for the propranolol extended-release tablet, and the decrement on the percent drug release at early stage was higher than at later stage, thus indicating that the burst effect of formulation could be lessened by increasing the amount of HPMC. In the case of substitution with $X_1 = 1 - X_2 - X_3$, $Y_{1.5\ \mathrm{h}} = 12 + 17X_1 + 19X_3$ and $Y_{24\ \mathrm{h}} = 79 + 19X_2 + 27X_3$, it was found that both MCC and lactose can increase the release rate, and the enhancement effect of lactose was higher than MCC.

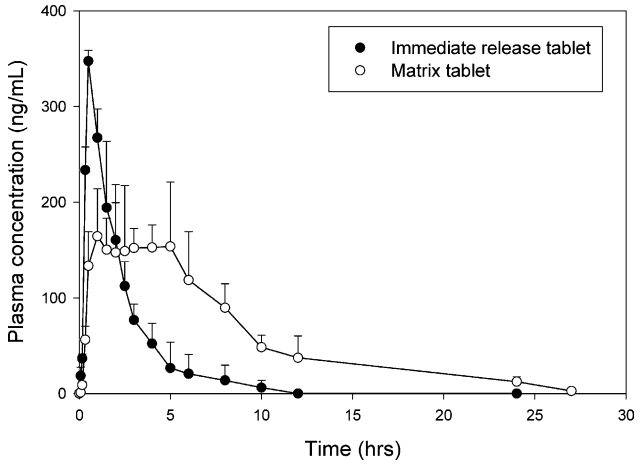

Fig. 4. In vivo plasma concentration-time profiles following oral administration of the matrix tablets and commercial immediate release tablets (Zeneca). Error bars represent means ± SD for each observation.

Table 4
Pharmacokinetic parameters of propranolol after oral administration of experimental matrix tablets and commercial immediate release tablets

	Matrix tablets	Immediate release
*T*max (h)	1.25 ± 0.42	0.50 ± 0.00
*C*max (ng/ml)	187.17 ± 43.34	347.33 ± 11.37
$AUC_{0-24\ \mathrm{h}}$ (ng/ml h)	1597.14 ± 192.10	735.18 ± 214.65
$AUC_{0-\infty}$ (ng/ml h)	1694.71 ± 244.54	758.06 ± 243.96
MRT (h)	6.57 ± 0.46	2.12 ± 0.57
Cl (l/h)	60.01 ± 8.36	56.28 ± 16.59

Moreover, the influence on drug release of lactose at the later stage was higher than that at the early stage. This result might contribute to the water-soluble material, lactose, which can stimulate the water penetration into the inner parts of the matrix, thus resulting drug release from matrix [11,12].

In general, an optimal extended-release dosage form must have a minimal burst effect within most of the drug being released in a specific time period. The USP monographs for drug extended drug release dosage forms specify the percent of drug released after more than one time point [26]. Therefore, the percent of drug release after 1.5, 4, 8, 14 and 24 h were selected as the response variables. These time points were used to detect the burst effect at an earlier stage and to ensure that most of the drug is released in a period of time comparable to the gastrointestinal residence time. The range of these responses were restricted to $15\% < Y_{1.5\ h} < 30\%$; $35\% < Y_{4\ h} < 55\%$; $55\% < Y_{8\ h} < 75\%$; $75\% < Y_{14\ h} < 90\%$; $90\% < Y_{24\ h} < 110\%$ (Table 1). Under these conditions, these five responses were then combined to determine an all over optimum region. Fig. 2F shows an acceptable region (ABCD) met the requirement of these responses. An optimum response was found with $Y_{1.5\ h}$, $Y_{4\ h}$, $Y_{8\ h}$, $Y_{14\ h}$, and $Y_{24\ h}$ of 28.6, 49.2, 70.0, 86.5

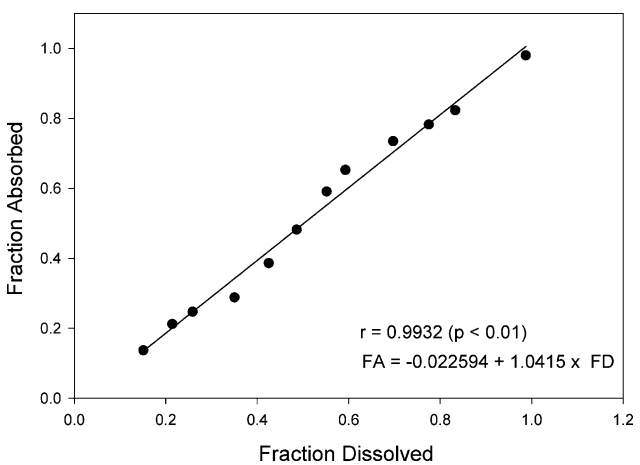

Fig. 5. Relationships between the percent release and the percent absorbed for matrix tablets in beagle dogs.

and 98.4% at X_1, X_2 and X_3 values of 0.37, 0.35 and 0.28, respectively. To verify these values, the optimum formulation was prepared according the above values of the factors and subjected to the dissolution test. The dissolution profiles of the optimum formulation and the predicted profile are shown in Fig. 3. Both profiles were compared using the FDA recommended similarity factor (f_2) [34]. The values of f_2 was 88 and above the critical value (50) indicating an equivalence to the release profile of the optimum formulation and the predicted profile. The release mechanisms of propranolol from predicted HMPC matrix tablet were also evaluated on the basis of a power model [28]. The correlation coefficients (r) of all HPMC tablets were above 0.9870 ($P < 0.01$). The values of exponent constants (n) were between 0.4607 and 0.5990 indicting that the mechanism of drug release from HMPC matrix tablets was by non-Fickian diffusion.

3.2. In vivo absorption study

The drug plasma concentration-time profiles following oral administration of the experimental extended-release formulation and commercial immediate release tablets are shown in Fig. 4. The pharmacokinetic parameters are listed in Table 4. The administration of matrix tablets resulted a significant different ($P < 0.05$) improvement of the plasma drug level, a significantly ($P < 0.05$) prolongation of the action of the formulation as the *T*max was extended from 0.5 to 1.25 h and the MRT prolonged for 2.12–6.57 h. The result indicated that the experimental matrix tablets indeed possessed extended-release effects, relative to the commercial immediate release formulation.

Exploring a relation between the in vivo absorption and in vitro drug release from a controlled-release dosage form is an important part of the dosage form development process [35]. The apparent in vivo absorption profiles from the single dose study were calculated using the Wagner-Nelson method. The absorption profile versus percent release in vitro at the same point is shown in Fig. 5. There was significant correlation ($P < 0.05$) between the fraction dissolution (FD) and fraction absorbed (FA) using concordance analysis. However, the linear regression analysis showed that a statistically significant relationship ($r = 0.993221, P < 0.001$) existed between the FD and FA for the matrix tablets and was best described by the equation $\mathrm{FA} = 1.042(\mathrm{FD}) - 0.023$. The slope and intercept were close to 1 and 0, respectively, indicating that the in vivo fraction absorbed could be predicted from in vitro dissolution data.

In summary, a once-daily extended-release tablet dosage form with the desired in vivo performance was successfully designed. However, further investigations in human are required to prove the clinical usability of the experimental extended-release formulation.

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