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Development and optimization of a novel sustained-release dextran tablet formulation for propranolol hydrochloride

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Abstract

A novel oral controlled delivery system for propranolol hydrochloride (PPL) was developed and optimized. The in vitro dissolution profiles of sustained-release matrix tablets of racemic PPL were determined and compared with the United States Pharmacopeia (USP) tolerance specifications for Propranolol Hydrochloride Extended-Release Capsules. The influence of matrix forming agents (native dextran, hydroxypropyl methylcellulose (HPMC), cetyl alcohol) and binary mixtures of them on PPL release in vitro was investigated. A central composite design was applied to the optimization of a sustained-release tablet formulation. The sustained-release matrix tablets with good physical, mechanical and technological properties were obtained with a matrix excipient:PPL ratio of 60:40 (w/w), with a dextran:HPMC ratio of 4:1 (w/w) and with a cetyl alcohol amount of 15% (w/w). A comparative kinetic study of the present matrix tablets and commercial SUMIAL RETARD capsules (Spain) was established. The value for the similarity factor ($f_2 = 69.6$) suggested that the dissolution profile of the present two sustained-release oral dosage forms are similar. Higuchi (diffusion) and Hixon–Crowell (erosion) kinetic profiles were achieved and this codependent mechanism of drug release was established.

Keywords: Native dextran; Sustained release; Optimization; Propranolol; Tablets

1. Introduction

Propranolol hydrochloride (PPL) is a β-adrenergic blocking agent, i.e. a competitive inhibitor of the effects of catecholamines at β-adrenergic receptor sites. It is widely used in therapeutics for its antihypertensive, antiangorous and antiarrhythmic properties. Furthermore, it has a short elimination half-life of 3 h, which makes it a suitable candidate to be delivered at a controlled rate (Kwong et al., 1988).

Controlled release dosage forms improve patient compliance and decrease incidences of adverse drug reactions. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in the peak/nadir concentration ratio (Yacobi and Walega, 1988). Hydrogels have attracted considerable attention in recent years as controlled release devices for the delivery of water-soluble drugs (Woodford and Hsieh, 1988). Hydroxypropyl methylcellulose has been employed extensively as hydrophilic matrix former in oral controlled-release dosage forms for different drugs including propranolol. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading (Ganga et al., 1992; Taylan et al., 1996; Chattaraj and Das, 1996).

Other hydrogels such as dextran can also be used for oral controlled release systems. Hydrogels of dextrans crosslinked with di-isocyanate, have been applied for colon-specific drug

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delivery as a chemical barrier for the diffusion release of drugs (Hovgaard and Brondsted, 1995). To date, dextrans of high molecular weight between 5,000,000 and 40,000,000 have not been reported as matrix controlled release system compound yet. B110-1-2, is a native dextran of high molecular weight (more than 5,000,000), that is mainly composed (95%) of (1-6)-linked α-D-glucose. Dextran is synthesized from sucrose by various strains of *Leuconostoc mesenteroides*.

The aim of the present study was to develop a new oral controlled delivery system using a natural derivative of sugar cane (native dextran) as a main adjuvant of the matrix for a water-soluble drug (propranolol hydrochloride). HPMC and sodium carboxy methylcellulose (CMC) were studied as a co-adjuvant with native dextran (DT). For optimization of the formulation, central composite design was used as an experimental design.

2. Materials and methods

2.1. Materials

Racemic propranolol hydrochloride (PPL) was obtained from Sigma (Saint Louis, USA). High molecular weight native dextran (more than 5,000,000) was obtained from the Center of Studies of Sugar Cane, Havana, Cuba. Hydroxypropyl methylcellulose (HPMC) with a viscosity grade 4000 cP (Methocel K4M) was obtained from Colorcon (Kent, England). Stearic acid, sodium carboxy methylcellulose (CMC), polyvinylpyrrolidone (PVP), magnesium stearate, and talc were USP 25/NFXX quality. Spanish commercial SUMIAL RETARD, Zeneca capsules (Lot. R 005) were used as a reference product. Other chemicals and reagents were analytical grade.

2.2. Matrix preparation

In the preliminary step, three different polymers (DT, HPMC, and CMC) and binary combinations of them were used. In all cases the ratio between polymers (or their combinations) and PPL was constant (1:1, w/w) and a 10% PVP solution was used as a binder solution. The drug and the excipients were sieved (80 mesh). The amount of lubricants (talc and magnesium stearate) was constant in all cases to prevent their effect on release of PPL from matrix. Compression was performed after granulation process with a single punch press applying a compression force of 9 (preliminary work) or 12 kN (experimental design), equipped with a 7.9 and 9.5 mm convex punches, respectively. For the preliminary work, batches of 100 tablets were prepared. Each batch of experimental design consisted of 1000 tablets (drug content in the tablet was 160 mg). PPL and polymers (DT and HPMC) were mixed for 10 min, granulated with an ethanolic solution of cetyl alcohol and passed through a 0.8 mm sieve. Granules were dried at 45 °C. The dried granules (moisture content below 2%) were passed through a 0.8 mm sieve. The granules were then lubricated for 2 min and press to tablet with indicated compression force (Castellanos et al., 2004).

The hardness of tablets ($n = 10$) was measured using a Pharma Test PTB-311 instrument (Germany). The friability of tablets was measured according to the USP 25 using 20 tablets and 100 rotations during 4 min.

2.3. Dissolution testing

The in vitro dissolution tests were performed on the USP dissolution apparatus 1 (basket) (Sotax AT7 Smart, Teknokroma, Spain), using 900 ml of each dissolution medium (pH 1.2 or pH 6.8, prepared according to USP Propranolol Extended Release Capsules Monograph, 2002) with a rotation speed of 100 rpm. Amount of drug dissolved (as racemate), was measured by using an UV–vis spectrophotometer (PC controlled Pharmacia LKB BioChrom 4060 Spectrophotometer, Sweden) at 290 nm. Seven diluted standard solutions of PPL, each medium (3.2, 8, 16, 24, 32, 40, 48 μg/ml) in a range from 10 to 150% of a theoretical concentration of 32 μg/ml were prepared twice a day during 3 days from a matrix solution of 1 mg/ml for calibrate curves.

The obtained experimental data were used to determine the required analytical parameters such as linearity (calibrate curves: $y = 19.370x - 0.001$, for pH 1.2 and $y = 19.187x - 0.004$, for pH 6.8 were obtained with coefficient of correlation $r = 0.999$ and 0.998, respectively), sensitivity, precision (repeatability: within-day repeatability, R.S.D. = 1.5% and 1.1% for both pH, respectively, and the intermediate precision assay: day to day repeatability, RSD = 1.8%, 1.5% and 1.4% for 24, 32 and 40 μg/ml, respectively (pH 1.2) and R.S.D. = 1.5%, 1.3% and 1.1%, respectively, for the same three concentrations (pH 6.8), 3 days, $n = 18$) and accuracy, according to Rampazoo (1990). Selectivity was checked by comparing the data obtained from pure substance and from samples spiked with excipients.

The tablets and capsules (18 replicates for each batch of tablets and commercial SUMIAL RETARD capsules) were kept the first hour and a half in a simulated gastric fluid at 37 °C, and subsequently in a simulated intestinal fluid at 37 °C (according to the Drug Release Test 1 of USP 25 specification for Propranolol Hydrochloride Extended-Release Capsules) for up to 24 h. Samples were collected at suitable time intervals. Two millilitres of aliquot was removed from each dissolution vessel and filtered through a 45 μm filter (Millipore Corp., Bedford, MA, USA). The same amount of fresh dissolution fluid was added to replace the amount withdrawn. The total amount of drug present in the tablets and capsules was calculated as the sum of the cumulative mass of drug released at the last sample and the mass of drug remaining (residue).

2.4. Experimental design and optimization of the formula

Experimental design and optimization of formulation were performed using Modde 4.0 software (Umetri, Umea, Sweden). A central composite design was applied to the optimization. This experimental design required 17 experiments in total ($2^k + 2k + 3$, k is the number of variables) including three center points.

Three variables and five responses (according to USP 25 tolerances for dissolution profile for Propranolol Hydrochloride Extended-Release Capsule) were involved in the experimental design. The variables and their ranges studied are summarized in

Table 1
Levels of formulation variables (central composite design)

Parameter	Low value (−1)	Central value (0)	High value (+1)
Ratio DT:HPMC (w/w)	1:1	4:1	7:1
Cetyl alcohol (%, w/w)	10	15	20
Ratio excipients:PPL (%, w/w)	30	50	70

Nominal values corresponding to −1, 0 and +1 levels.

Table 1. The high and low values of each variable were defined based on preliminary experiments. The critical responses were $t_{100\%}$ and $t_{30\%}$ corresponding to the time when 100% and 30% of drug contained in the tablets is delivered to the dissolution medium, respectively, because this system was developed to release drug in 24 h ($t_{100\%} \sim 24$ h) and to prevent an overdose for first minutes ($t_{30\%} > 1.5$ h). The other responses were in the amount of PPL dissolved at 4, 8 and 14 h.

Table 2 shows results obtained for every formula development according to Modde 4.0 software. The collected experimental data were fitted by a multi linear regression (MLR) model with which several responses can be dealt with simultaneously, to provide an overview of how all the factors affect all the responses. The responses of the model, R^2 and Q^2-values were over 0.99 and 0.93 for $t_{100\%}$ and 0.98 and 0.89 for $t_{30\%}$, respectively, implying that the data fitted well with the model. Here, R^2 is the fraction of the variation of the response that can be modeled and Q^2 is the fraction of the variation of the response that can be predicted by the model. The relationship between a response y and the variables x_i, x_j... can be described by a polynome:

$$y = \beta_0 + \beta_i x_i + \beta_j x_j + \beta_{ij} x_i x_j + \beta_{ii} x_i^2 + \beta_{jj} x_j^2 + \cdots + E$$

where, β_j's are coefficients to be determined and E is the overall experimental error.

2.5. Kinetic analysis

In order to characterize the drug release mode from the optimum matrix and SUMIAL RETARD capsules, the experimental data were fitted to the Peppas, Hixon–Crowell, Higuchi and zero-order equation (Eqs. (1)–(4), respectively) by using the WINNONLIN program (Scientific Consulting Inc., PCNonlin, NC, USA):

$$M_t/M_\infty = Kt^n \quad (1)$$

$$M_t/M_\infty = 1 - (1 - k_1 t)^3 \quad (2)$$

$$M_t/M_\infty = b + k_2 t^{1/2} \quad (3)$$

$$M_t/M_\infty = a + k_3 t \quad (4)$$

In Peppas equation (Eq. (1)), M_t/M_∞ is the fraction of drug released up to time t, K is the kinetic constant and n is the release exponent indicative of the release mechanism (Peppas, 1985). In Hixon–Crowell equation (Eq. (2)) (Tahara et al., 1995), Higuchi equation (Eq. (3)) and zero-order release equation (Eq. (4)), k_1, k_2 and k_3 are constants. The Hixon–Crowell equation indicates an erosion-depended release mechanism. On the other hand, the Higuchi equation expresses a diffuse release mechanism. For the analysis of the residuals, we select the relative error (Re) expressed by Eq. (5):

$$\text{Relative error}\,(\%) = \frac{|\text{residual}|}{|\text{experimental value}|} \times 100 \quad (5)$$

Table 2
Matrix of central composite design and results

Run order	cEx:PPL	DT:HPMC	Ce	$t_{100\%}$[a]	$t_{30\%}$[a]	t_2[a]	t_3[a]	t_4[a]
10	30	1:1	10	10	0.5[b]	71[b]	90[b]	–[b]
7	70	1:1	10	15	2.1[c]	44[c]	73[c]	97[b]
1	30	7:1	10	11	0.5[b]	63[b]	82[b]	–[b]
11	70	7:1	10	14	2.2[c]	40[c]	76[c]	99[b]
9	30	1:1	20	14	1.3[b]	49[c]	70[c]	99[b]
8	70	1:1	20	16	2.2[c]	46[c]	62[c]	96[b]
5	30	7:1	20	14	1.6[c]	49[c]	70[c]	99[b]
15	70	7:1	20	16	2.4[c]	43[c]	60[c]	96[b]
3	30	4:1	15	20	1.2[b]	54[c]	79[c]	94[c]
16	70	4:1	15	26	2.6[c]	39[c]	56[c]	72[c]
17	50	1:1	15	15	1.6[c]	45[c]	63[c]	98[b]
4	50	7:1	15	16	1.7[c]	43[c]	65[c]	96[b]
2	50	4:1	10	21	1.4[b]	52[c]	71[c]	93[c]
12	50	4:1	20	24	2.2[c]	45[c]	63[c]	82[c]
6	50	4:1	15	24	2.1[c]	48[c]	65[c]	85[c]
14	50	4:1	15	23.5	2.2[c]	49[c]	66[c]	86[c]
13	50	4:1	15	24	2.1[c]	48[c]	66[c]	86[c]

Exp., number of experiments; cEx:PPL, ratio excipients:propranolol; DT:HPMC, ratio native dextran:hydroxypropyl methylcellulose; ce, percentage of cetyl alcohol (w/w) in the tablets; $t_{100\%}$, time (h) when 100% of PPL is dissolved to the dissolution medium; $t_{30\%}$, time (h) when 30% of PPL is dissolved to the dissolution medium; t_2, amount in % of PPL dissolved at 4 h; t_3, amount in % of PPL dissolved at 8 h; t_4, amount in % of PPL dissolved at 14 h.

[a] Values presented are the average of 18 replicates for each batch.

[b] Out of the USP range.

[c] Inside of the USP range.

2.6. Comparison of dissolution profiles

A similarity factor can be defined as:

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

In the equation above f_2 is the similarity factor, n is the number of time point, R_t is the mean percent drug dissolved of e.g. the current formulation, and T_t is the mean percent drug dissolved of e.g. the changed composition.

The evaluation of similarity is based on the conditions of:

- a minimum of three time points,
- 12 individual values for every time point,
- not more than one mean values of >85% dissolved, and
- that the standard deviation of the mean should be less than 10% from the second to last time point.

An f_2 value between 50 and 100 suggests that two dissolution profiles are similar (Annon, 1999). In this studies experimental data corresponding to (1.5, 4, 8, 14, 24 h) were considered.

3. Results and discussion

3.1. Development of the formula

Application of CMC polymer alone exhibited an increase in the release rate of PPL for the first few hours (Fig. 1). This may be attributed to the increase in the erosion rate of the CMC polymer. Later, the polymer swelling (i.e. an increase in the diffusional path length) retards the rate of release. When dextran of high molecular weight with a lot of ramifications was used, a decrease in the release rate of drug was observed. This may be attributed to an increase in diffusional path length for the drug, which in turn may be due to the slower erosion rate of the rubbery layer and faster advancement of the swelling of the glassy polymer. HPMC also decreases the release rate of PPL. Its mechanism is well known as a swelling controlled release system (Colombo et al., 2000). Release of soluble drugs as PPL

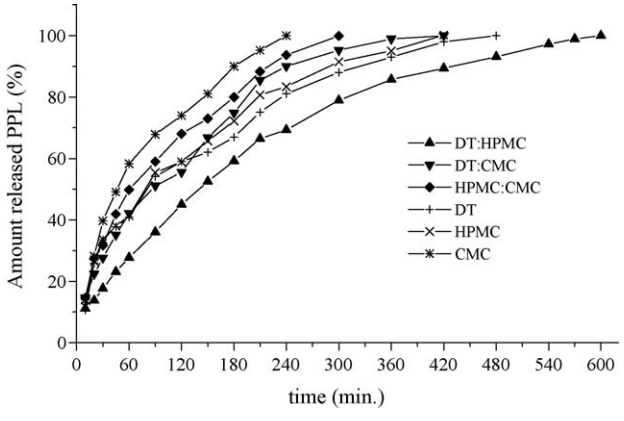

Fig. 1. Dissolution profiles for propranolol hydrochloride obtained in preliminary work.

from the HPMC matrix involves sequential processes of infiltration of medium into the matrix, hydration and swelling of the matrix, dissolution of drug in the matrix, and the leaching of the solubilized drug through the interstitial channels. The main driving force for drug release would be the medium infiltration into the tablet matrix and HPMC (4000 cP) can be used for PPL tablet matrix (Tahara et al., 1995). Medium infiltration rate can be adjusted by changing the polymer content or mixing various polymers.

The HPMC:CMC:PPL ratio 0.5:0.5:1 (w/w/w) showed the lower $t_{100\%}$ (time when 100% of PPL dosage contained in tablets is release) and the amount of PPL released at 1.5 h was higher. The combination DT:HPMC showed higher values for $t_{100\%}$ and lower amounts of PPL were released from the tablets at 1.5 h. In this case the time required for the edges to hydrate and reach equilibrium before erosion and the advance of solvent front through the matrix occur is shortened. In all cases, slow diffusion of drug is due to the increase in gel viscosity at the periphery, which consequently leads to decrease in the rate of formation of the swelling front into the matrix.

Previously it has been demonstrated that the increase of gel viscosity is synergistic when mixtures of these polymers are used. The ratio of the total gum to the drug and the ratio between hydrogels in the tablets are very important (Harris and Sellassie, 1989). In the following experiments, only combinations of dextran and HPMC were used. The values for $t_{100\%}$ increased dramatically when PVP was replaced by cetyl alcohol and the amount of it was increased up to 15% (w/w) in the matrix system. On the other hand, inclusion of stearic acid did not improve dissolution of PPL.

Fig. 2 represents the dissolution profiles all 17 trials generated from central composite design. The response surface plots formed by plotting the values for $t_{30\%}$ and $t_{100\%}$ as a function of the most important variables are shown in Fig. 3. In Fig. 3, the optimum condition obtained by the model can be seen. The optimum DT:HPMC ratio of 4:1 (w/w) gave $t_{100\%}$ equal to 24 h. With the tablet formulations composing of matrix excipient and PPL at a ratio ranging from 40:60 to 70:30 (w/w), the values for $t_{100\%}$ were satisfactory (around 24 h). However, the respective values for $t_{30\%}$ increased as a ratio of matrix excipient and PPL was ranging from 40:60 to 70:30 (w/w), thus showing that the early drug release was demanded and the initial dose required for pharmacological effect could be not sufficient. The sustained-release matrix tablets with good properties were obtained with a dextran:HPMC ratio of 4:1 (w/w), with a matrix excipient:PPL ratio of 60:40 (w/w) and with a cetyl alcohol amount of 15% (w/w). Ratio hydrophilic polymers:PPL 60:40 (w/w) is more robustness for any manufactured variability than 50:50 (w/w), because the central point of the design is near to the lowest desired area (Fig. 3). Under the optimal conditions, the mean value of hardness was 106 ± 3 N and the friability was less than 1% (0.2%).

Cetyl alcohol (ce in Fig. 4) has a significant positive effect on both responses in the range studies. This may be because the hydrophobic polymer prevents the fast release of PPL for the first few hours, meanwhile an increase in the diffusional path length of the drug, because the hydrophilic polymers swelling

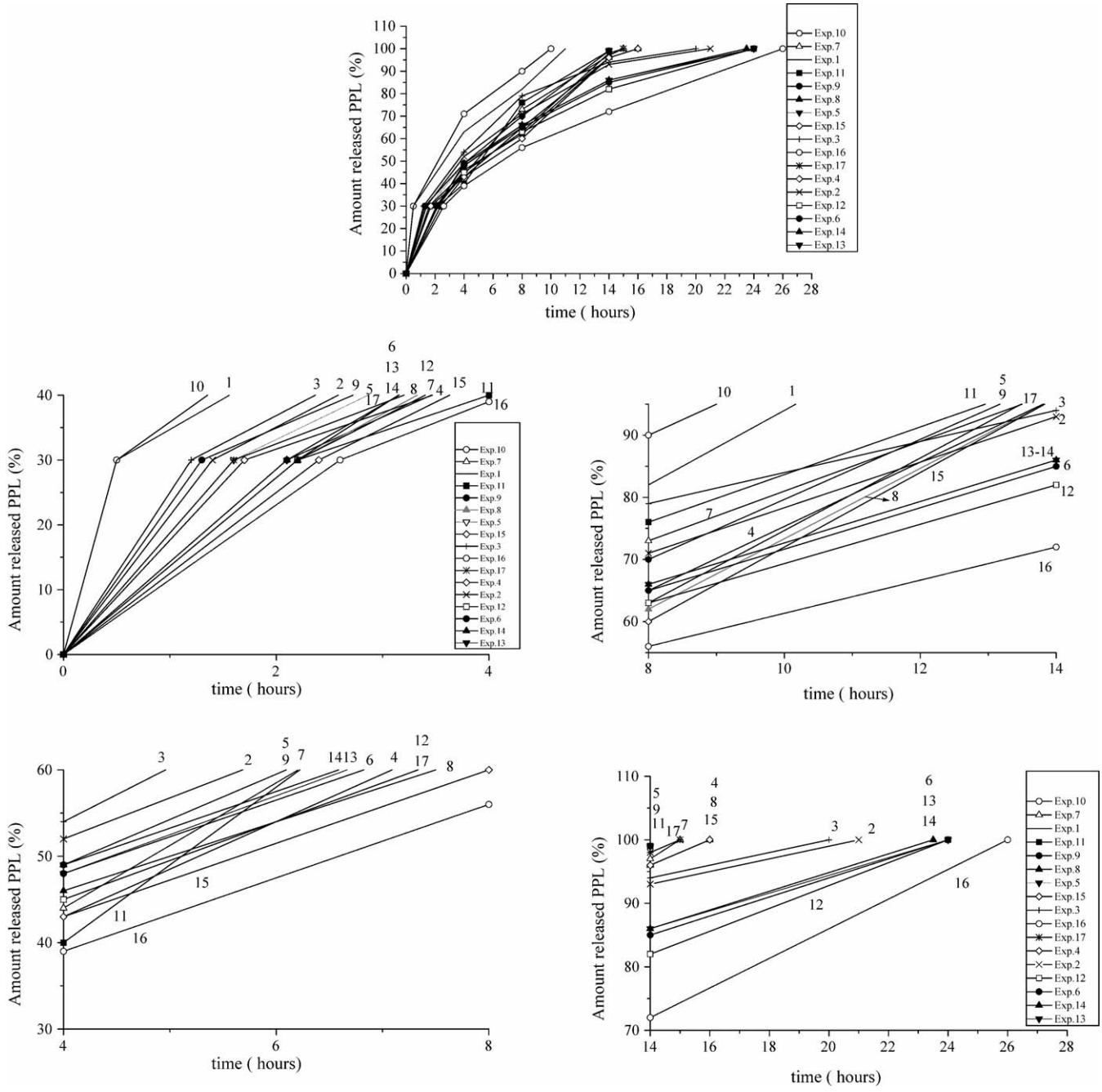

Fig. 2. Dissolution profiles of all 17 trials generated from central composite design.

(DT and HPMC) retard the rate of release. An interaction of cetyl alcohol and ratio hydrophilic polymers:PPL was observed for $t_{30\%}$. If a prolonged release rate is desired on this period, ratio of hydrophilic to cetyl alcohol can be increased, resulting in a decreased interspace volume after erosion of cetyl alcohol. Different to other product such as lactose (Tahara et al., 1995), cetyl alcohol as hydrophobic polymer could be increased. The viscosity and texture of the gel layer and some modifications of interaction polymer–polymer and polymer–solvent are present.

Fig. 5 shows dissolution profiles for optimum formula (tablets), which come from previous experiments and for SUMIAL RETARD capsules. The value for relative standard deviation (CV) was less than 6% for all points measured ($n = 18$). The dissolution profiles were in the range of tolerance established in USP 25 for Propranolol Hydrochloride Extended-Release Capsules, as shown in Table 3.

Three release mechanisms (Higuchi, Hixon–Crowell and zero order release equation) were applied to study the dissolution data of the optimum formulation and SUMIAL RETARD capsules. The parameters and correlation coefficient of each equation as well as the values for non-linear equation (Peppas) are shown in Table 4. The dissolution data best fit the Higuchi and Hixon–Crowell equation. This indicates that the dissolution is both diffusion and erosion dependent. On the other hand, the values obtained from Peppas model indicate that the main mech-

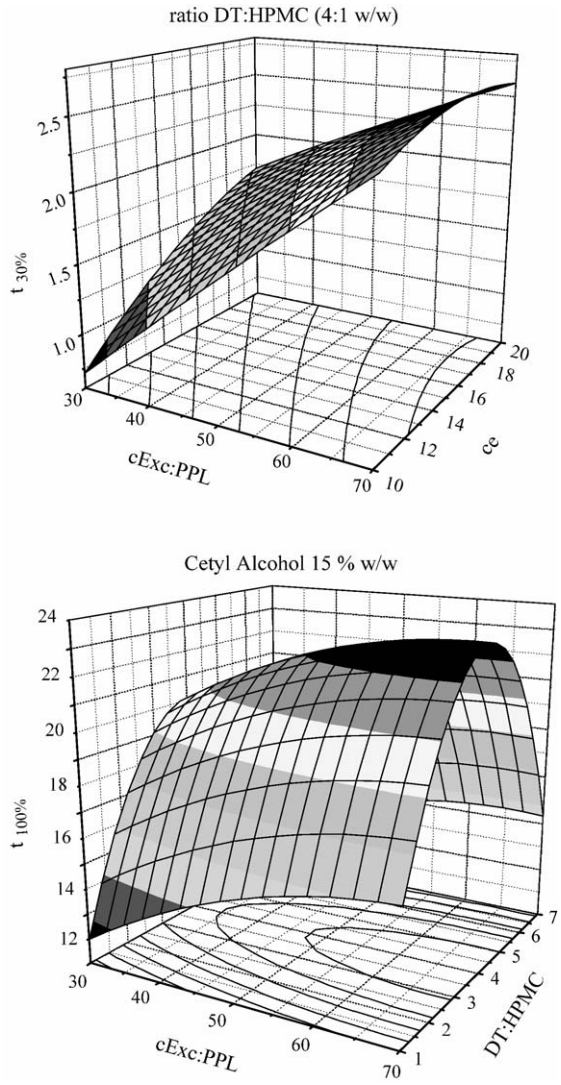

Fig. 3. Response surface plot showing the $t_{30\%}$ and $t_{100\%}$ as a function of correlation DT:HPMC, ratio Exc:PPL and percentage of cetyl alcohol in the formula.

anism is diffusion ($n = 0.48$) for the first part of the release curve (up to 60% of drug dissolve).

Plot of experimental values, Higuchi and Hixon–Crowell models for release of PPL from tablets is shown in Fig. 6. Both curves (diffusion and erosion) are similar to experimental values (Fig. 6A) and when experimental values versus predicted values by the models are plotted (Fig. 6B), the regression lines for each model almost superpose indicating that both mechanisms are predictive. However, the analysis of relative error (Table 4) indicate that diffusional model have been more predictive with better fit in the early parts of the release curve (up to 4 h) but later that is not so clear (from 4 up to 24 h) because values for Re are similar and both mechanisms are operative. The erosion and dissolution of HPMC and cetyl alcohol explains this combination. According to the literature, a drug release from hydrophilic matrix system is governed sequentially by the following processes: (1) hydration or swelling of the matrix which results in the formation of a gel; (2) dissolution of the drug into that hydrated matrix/gel; (3) diffusion of the drug molecules through

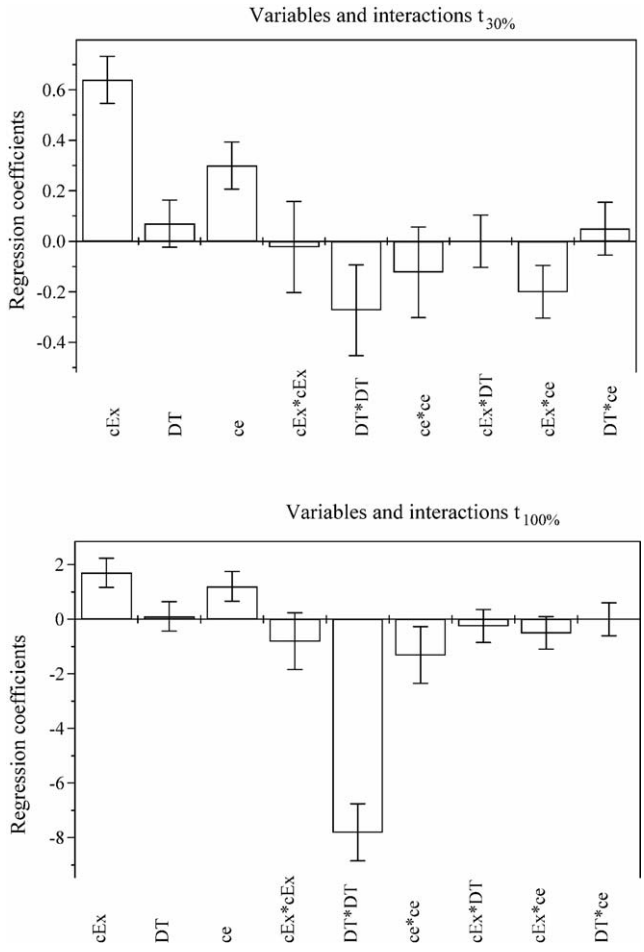

Fig. 4. Regression coefficient plot for the $t_{30\%}$ and $t_{100\%}$: DT, ratio dextran:HPMC (w/w); cEx, ratio excipients:propranolol (w/w); ce, percentage of cetyl alcohol (w/w) in the tablets.

that hydrated matrix; and finally (4) surface erosion and/or dissolution of the formed gel–matrix (Talukdar and Kinget, 1997).

3.2. Similarity

On several occasions dissolution profiles have to be compared for similarity, e.g. after scale-up or changes in composition

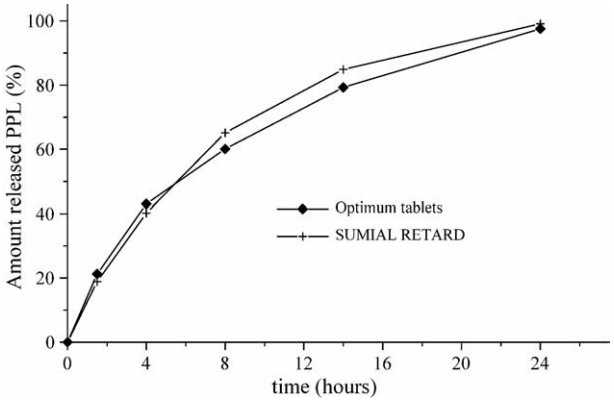

Fig. 5. Dissolution profiles of PPL for optimum formula (sustained-release tablets) and for SUMIAL RETARD sustained-release capsule.

Table 3
The percentage of the labeled amount of hydrochloride propranolol dissolved at the times specified conform to Acceptance Table 1 of Test 1 for Propranolol Hydrochloride Extended-Release Capsule USP 25 tolerance

Time (h)	Amount dissolved (%)			Similarity factor
	USP 25 tolerances	Tablets (optimum)	Capsule SUMIAL RETARD	
1.5	<30	21.3 ± 4.4[a]	18.9 ± 4.1[a]	
4	35–60	43.1 ± 4.2[a]	40.2 ± 3.1[a]	(f_2)
8	55–80	60.1 ± 3.1[a]	65.2 ± 2.8[a]	69.6
14	70–95	79.3 ± 2.8[a]	84.9 ± 2.6[a]	
24	81–110	97.6 ± 2.9[a]	99.1 ± 2.1[a]	

Amounts dissolved of propranolol hydrochloride are expressed as average values of 12 samples.
[a] Relative standard deviation obtained for 12 samples.

Table 4
Parameters and correlation coefficient obtained from kinetic equations for the matrix tablets (optimum) and SUMIAL RETARD capsule

Parameter	Higuchi	Hixon–Crowell	Zero order	Peppas
Tablets (optimum)				
k	0.208	0.035	0.049	22.828
r	0.999	0.997	0.943	0.999
n	–	–	–	0.484
Capsule (SUMIAL RETARD)				
k	0.215	0.029	0.051	22.914
r	0.998	0.987	0.961	0.999
n	–	–	–	0.501

TIME (h)	Percent dissolved	HIX.	HIG.	HIX_RES	HIG_RES	HIX-Re	HIG-Re
Predicted values for Higuchi and Hixon–Crowell models							
1.5	21.30	14.55	25.14	6.75	−3.84	31.68	18.03
4	43.10	35.54	41.05	7.56	2.05	17.53	4.75
8	60.10	61.48	58.06	−1.38	2.04	2.29	3.40
14	79.30	85.66	76.80	−6.36	2.50	8.03	3.15
24	97.60	99.39	100.56	−1.79	−2.96	1.83	3.03

Residuals and relative error (Re) (for tablets). All values are expressed as average values for 18 samples. k, kinetic constant; r, coefficient of correlation; n, release exponent; HIX., predicted values Hixon–Crowell model; HIG., predicted values Higuchi model; HIX_RES, residuals Hixon–Crowell model; HIG_RES, residuals Higuchi model; HIX-Re, relative error Hixon–Crowell model; HIG-Re, relative error Higuchi model.

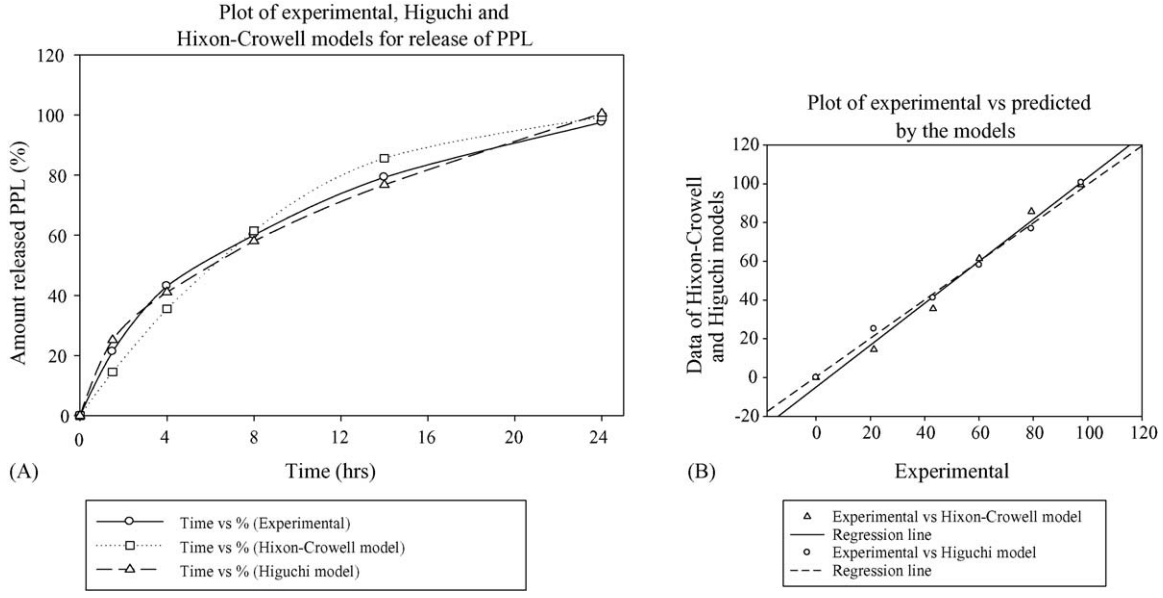

Fig. 6. (A) Plot of experimental values, Higuchi and Hixon–Crowell models for release of PPL from tablets. (B) Plot of experimental vs. predicted by the models.

and/or manufacturing process. The similarity of the profiles may be compared by model-independent or model-dependent methods, e.g. linear regression of the percentage dissolved at specified time points, by statistical comparison of the parameters of the Weibull function or by calculating a similarity factor. We calculated this last one and the value obtained for SUMIAL RETARD capsule and optimum tablet (see Table 3) established that dissolution profiles are similar even when different polymers were used and different manufacturing processes were performed.

4. Conclusions

The optimal formula was obtained through a central composite experimental design. Under optimal ratio of matrix compound and drug (60:40, w/w), optimal ratio of native dextran and HPMC (4:1, w/w) and 15% of cetyl alcohol, the new system presented is suitable for controlled release of PPL for 24 h and it fulfil the USP 25 Drug Release Test 1 for Extended-Released Hydrochloride propranolol capsule. Similarity factor $f_2 = 69.6$ obtained between tablets and SUMIAL RETARD capsule, suggests that the two prolonged release oral dosage forms dissolution profiles are similar. Higuchi (diffusion) and Hixon–Crowell (erosion) kinetic profiles were achieved, and consequently, codependent diffusion/erosion mechanism is suggested as a main release mechanism of PPL from the present tablets.

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