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Optimization of hydrophilic matrix tablets using a D-optimal design

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Abstract

One method of achieving sustained drug release is by the use of hydrophilic polymeric excipients directly compressed with active ingredients into tablets. Hydrophilic polymers swell in the presence of water to form hydrogel structures from which drugs are released by slow diffusion. The release rate modulation is obtained by the use of different types of polymer alone or in combinations. Optimization of the release rate of propranolol hydrochloride from mixtures containing two hydrophilic polymers: hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (CMCNa) was made by mixture design. Mixing ratios of the two polymers with the active ingredient were selected as formulation factors. Experimental results were examined using a D-optimal quadratic model. Contour plots were formed based on the model to assess the change in the response surface in order to understand the relationship between dependent and independent variables. The results enabled the formulation of tablets with the desired dissolution characteristics together with a fairly complete characterization of the system. Optimization of release rate was performed applying constraints on the cumulative amounts of drug released after 1, 6 and 12 h release time intervals. Optimized formulations presented release rates that were close to the predicted values. Fitting the release data from optimized formulations was performed according to Korsmeyer et al. (1983) and Peppas and Sahlin (1989) kinetic models. Release from optimized formulations occurs mainly by Fickian diffusion but an important fraction of the drug is released by polymer relaxation. © 1997 Elsevier Science B.V.

Keywords: Sustained release; Hydrophilic polymers; Hydroxypropylmethylcellulose; Sodium carboxymethylcellulose; Propranolol hydrochloride; Optimisation; D-optimal; Dissolution

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1. Introduction

Swellable matrix systems with anomalous release kinetics are suitable solutions for drug release control for oral administration. The release rate modulation is achieved through the use of different types of polymer alone or in combinations. The drug release rate is linked to the properties and also the proportion of the drug, the gel and the thickness of gel through which the drug must diffuse (Papadimitriou et al., 1993).

In this study we considered mixtures of two hydrophilic polymers: hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (CMCNa), which could potentially be added to formulations to produce slow release dosage forms, as detailed by literature (Ford et al., 1985, 1987; Buri and Doelker, 1980; Ranga Rao et al., 1988). The active ingredient was propranolol hydrochloride that has appropriate pharmacokinetic and activity profiles which make it a suitable candidate for controlled release matrix systems (Ford et al., 1985; Taylan et al., 1996; Rekhi et al., 1995).

The present study deals with the optimization of formulation variables to improve dissolution characteristics of the matrix formulation. To design the best product under conditions of competitive objectives and interactive effects (non-linear properties) via a trial and error approach is time consuming and often unsuccessful. Optimization by means of an experimental design might be helpful in shortening the experimenting time. These experiments will lead to summarizing equations of each dependent variable within the optimum space from which all desired combinations of independent variables can be calculated.

The objective of this study was to evaluate the effect of formulation variables on the cumulative percentage of drug released at different time intervals, and to optimize the product using mathematical equations and response contour plots. The optimization procedure would aid in the preparation of controlled release tablets with predictable properties.

2. Materials and methods

2.1. Materials

Polymers used in this study were: hydroxypropylmethylcellulose (HPMC), (Methocel K1OOM Premium, Colorcon, Orpington, UK) and sodium carboxymethylcellulose (CMCNa), (Blanose 7MF, Aqualon, Paris, France). Propranolol hydrochloride was obtained from S&D Chemicals (Cunningham House, Harrow, UK) and magnesium stearate from Serva (Heidelberg, Germany).

2.2. Software

Fit of data to the model, evaluation of the quality of fit of the model and contour plots modelling were performed with MODDE 3 software (Umetri, AB, Umea Sweden).

2.3. Methods

2.3.1. Tablet manufacturing

Mixtures of 1000 g consisting of blends of the two polymers with the active ingredient and with 1% magnesium stearate used as lubricant were prepared for each position from the experimental design (Table 3).

The powders were thoroughly mixed for 15 min, using an Erweka RM 5 mixing device (Erweka Apparatebau, Heusenstamm, Germany) at maximum stirring speed.

Tablets were directly compressed on an EK 0 tabletting machine (Korsch, Berlin, Germany) at a tablet weight of 300 mg using concave punches of 9 mm diameter.

All tablets were stored at 37 ± 1°C and 65% relative humidity for 2 weeks prior to testing.

2.3.2. Dissolution tests in vitro

The dissolution studies were carried out following the USP XXIII paddle rotating method at 37°C and 60 rpm using Erweka DT dissolution tester (Erweka Apparatebau, Heusenstamm, Germany). Distilled water (1000 ml) was used as dissolution medium. Sink conditions were maintained during dissolution. Samples of 3 ml volume

Table 1
Experimental ranges for independent variables and constraints

Factors	Experimental ranges		
	Low values	High values	Constraints
X_1 (Fraction of HPMC)	0	0.66	
X_2 (Fraction of CMCNa)	0	0.66	$X_2+X_3\leq 0.80$
X_3 (Fraction of propranolol HCl)	0	0.66	$X_3\geq 0.34$

were collected at suitable time intervals, filtered, and assayed spectrophotometrically (Hitachi U 2000, Japan) at 289 nm for the drug content. The cumulative mass of drug released was calculated. Released fractions, Q_t/Q_0 (where Q_t is the cumulative mass of drug released at measuring time t and Q_0 is the total amount of propranolol loaded into the tablet) were considered.

2.3.3. Experimental design

In a mixture design where the composition is the factor of interest, the levels cannot be chosen arbitrarily. All fractions of the components must sum to unity (Snee, 1971). In a design so constrained a simplex lattice design is recommended (Huisman et al., 1984). In three component mixtures all mixture possible combinations can be graphically represented by the interior and the boundaries of an equilateral triangle using simplex lattice designs. The true value of the response can be represented as a distance orthogonal to the factor space (a vector).

It is often physically impossible to use a component over the full factor space. The range over which the components are varied may be restricted, resulting in a small area of interest. Such area is usually an irregular polyhedron delimited by extreme vertices. The only design available in this case is a D-optimal design (Lewis and Chariot, 1991). D-optimal designs maximize the information in the selected set of experimental runs with respect to a stated model.

For a special regression model: $\boldsymbol{y} = X\beta + \varepsilon$ where

$\boldsymbol{y}$ is a $(N \times 1)$ vector of observed responses

$\mathbf{X}$ is a $(N \times p)$ extended design matrix, i.e. the n experimental runs extended with additional columns to correspond to the p terms of the model

$\boldsymbol{\beta}$ is a $(p \times 1)$ vector of unknown coefficients to be determined by fitting the model to the observed responses

$\boldsymbol{\varepsilon}$ is a $(N \times 1)$ vector of residuals

the D-Optimal design maximizes the determinant of the $\mathbf{X}'\mathbf{X}$ matrix which is an overall measure of the information in $\mathbf{X}$. Geometrically this corresponds to the maximizing of the volume of $\mathbf{X}$ in a p dimensional space (Umetri, 1995).

Independent variables were different mixing ratios of the three components (Table 1) and dependent variables were cumulative percents of drug released after 1, 6 and 12 h sampling intervals (Table 2).

Preliminary experiments were performed to select the discrete set of potentially good runs and it was observed that formulations with HPMC fractions lower than 0.2 lead to high dissolution rates, releasing the entire drug content before 12 h. Therefore the experimental design was constrained to only include experimental runs where the sum of $X_2 + X_3 \leq 0.8$. The presence of propranolol hydrochloride in the formulations was constrained in order to remain at therapeutic levels specific for slow release formulations i.e. between 0.100 and O.200 g, therefore formulations containing fractions of propranolol HCl smaller than

Table 2
Dependent variables and the constraints applied on responses

	Dependent variables	Constraints
Y_1	Cumulative % dissolved in 1 h	$10\leq Y_1\leq 20$
Y_2	Cumulative % dissolved in 6 h	$45\leq Y_2\leq 55$
Y_3	Cumulative % dissolved in 12 h	$80\leq Y_3\leq 100$

Table 3
Experimental matrix for the D-optimal design and results

Run	Variable factors			Results		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
1	0.66	0	0.34	0.122	0.448	0.712
2	0.34	0	0.66	0.152	0.683	0.992
3	0.2	0.46	0.34	0.104	0.545	0.902
4	0.2	0.14	0.66	0.112	0.612	0.986
5	0.553	0	0.446	0.143	0.518	0.792
6	0.446	0	0.553	0.148	0.585	0.866
7	0.506	0.153	0.34	0.074	0.388	0.680
8	0.353	0.306	0.34	0.052	0.352	0.672
9	0.2	0.353	0.446	0.098	0.576	0.925
10	0.35	0.15	0.5	0.084	0.512	0.856
11	0.35	0.15	0.5	0.087	0.518	0.862
12	0.35	0.15	0.5	0.084	0.507	0.851
13	0.35	0.15	0.5	0.089	0.525	0.870

0.34 were eliminated from the matrix design. The percentages for variable terms $X_1 - X_3$ and the constraints are summarized in Table 1.

Previous experiments also suggested that a non-linear response function must be expected. Therefore a quadratic model was chosen for interpreting data results from the D-optimal design. The model was of the form:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad (1)$$

The coefficients b_1, b_2 and b_3 represent the estimation of the main effects of the factors **X**. Similarly b_{11}, b_{22} and b_{33} represent the estimation of the second order effects and b_{12}, b_{13} and b_{23} the estimation of interactions. The model generated contained quadratic terms which explained the non-linear nature of responses and multiple factor terms explaining interaction effects between factors.

The D-optimal experimental domain and the observed responses are shown in Table 3.

3. Results and discussion

3.1. Fitting of data to the model

Different propranolol HCl release rates and profiles were obtained based on the experimental design (Table 3). Dissolution profiles of all 13 formulations are shown in Fig. 1.

The model was fitted to the data for all responses simultaneously using Modde for Windows computer program. The normalized coefficients of the fitted model are related in Table 4. In normalized form the coefficients are divided by the standard deviation of their respective response.

The initial model was refined by excluding the terms for which the level of significance was greater than 0.05 ($P \geq 0.05$). The remaining terms were used to refit the data and the resultant equations are given below:

$$Y_1 = -0.015 + 0.145X_1 - 0.062X_2 + 0.168X_3 + 0.594X_2^2 - 0.691X_1X_2 \quad (2)$$

$$Y_2 = 0.279 - 0.100X_1 - 0.181X_2 + 0.626X_3 + 1.270X_2^2 - 0.963X_1X_2 \quad (3)$$

$$Y_3 = 0.629 - 0.246X_1 - 0.080X_2 + 0.653X_3 + 1.122X_2^2 - 0.841X_1X_2 \quad (4)$$

To show the quality of fit of the model, residual plots of the observed values versus the predicted values were depicted in Fig. 2. Plots showed the points fairly close to straight lines indicating good models.

3.2. Analysis of the fitted data

It can be seen in Eqs. (2)–(4) that X_2 has a remarkable negative effect on all responses, while a negative effect of X_1 was evident on the Y_2 and Y_3 responses. X_3 has a strong positive effect on all three responses and one can consider this being normal since X_3 represents propranolol HCl with high water solubility. One can also observe a significant negative interaction effect among X_1 and X_2 factors effective on all the analyzed responses. The quadratic nature of all the responses was determined by the presence of X_2^2 term.

Contour plots based on the Eqs. (2)–(4) were drawn with the aid of a computer program

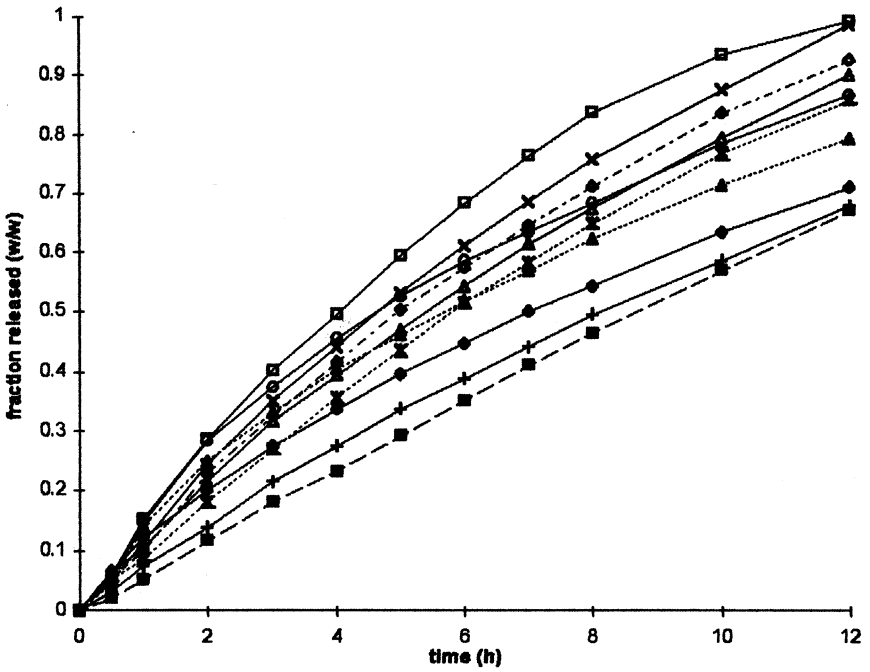


Fig. 1. Dissolution profiles of propranolol hydrochloride from formulations according to experimental design (Table 3) (– ◆ –) Form 1, (– □ –) form 2, (— △ —) form 3, (— x —) form 4, (· · · ▲ · · ·) form 5, (– ◦ –) form 6, (— + —) form 7, (— ■ —) form 8, (· · · ◇ · · ·) form 9, (· · · * · · ·) forms 10–13.

(Section 2.2). They are presented in Figs. 3–5. These diagrams describe the variation on $Y_1 - Y_3$ responses as a function of the composition of mixtures. The function is not linear and indicates the importance of interactions among X_1, X_2 and X_3 as mentioned before.

As can be seen both polymers show efficient retardatory action on all three responses while the presence of propranolol in formulations increases the release rate probably due to its high dissolution rate which generates pores in the polymeric mass facilitating water penetration. This conviction is in concordance with previous results indicating an increase in swelling rates of polymeric matrices in the presence of variable amounts of high water soluble drugs (Bodea et al., 1995).

During the analysis of the Y_2 and Y_3 responses one could see that HPMC proved to be more active in retarding the release of propranolol HCl while on Y_1 response CMCNa proved to be more effective. This observation is in agreement with visual observations that were made during the release experiments. It was observed that CMCNa presented a high swelling rate being strongly eroded in the dissolution medium compared with HPMC which is less eroded and has a moderate swelling rate.

Propranolol HCl release from HPMC matrices presented a burst effect in initial dissolution stages. The burst effect observed with HPMC formulations was probably caused by the fact that in the initial stages of dissolution the gel barrier that controls the release was not yet formed, allowing the rapid dissolution of propranolol hydrochloride from the tablet surfaces. As water penetrates the matrix a swollen gel barrier is formed on the matrix surface which becomes the rate limiting step that controls the release of the drug. The burst effect was less evident in formulations containing CMCNa and mixtures of CMCNa with HPMC.

Table 4
Normalized PLS (partial least squares) coefficients for propranolol dissolution after 1 h (Y_1), 6 h (Y_2) and 12 h (Y_3)

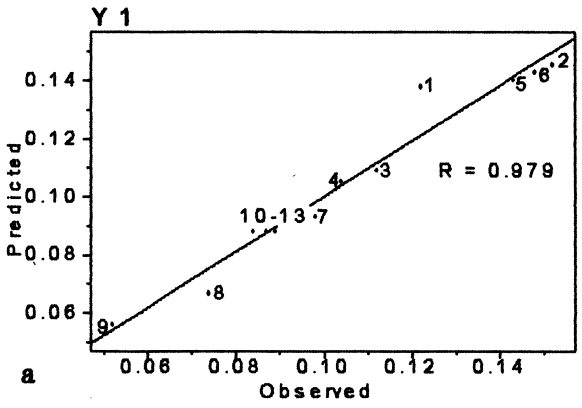
	Coefficient[a]	S.E.[b]	P[c]	Confidence interval ($\pm$)[d]
Y_1				
Constant	2.772	0.261	1.453×10^{-5}	0.618
X_1	−0.187	0.080	0.053	0.190
X_2	−1.058	0.093	8.993×10^{-6}	0.220
X_3	0.352	0.051	2.426×10^{-4}	0.122
X_1X_1	0.021	0.034	0.555	0.081
X_2X_2	0.475	0.053	4.403×10^{-5}	0.125
X_3X_3	-1.854×10^{-3}	0.018	0.919	0.042
X_1X_2	−0.261	0.078	0.013	0.185
X_1X_3	0.037	0.046	0.455	0.110
X_2X_3	−0.073	0.056	0.231	0.132
Y_2				
Constant	5.416	0.348	1.089×10^{-6}	0.823
X_1	−0.682	0.107	3.806×10^{-4}	0.253
X_2	−0.727	0.124	6.077×10^{-4}	0.292
X_3	0.555	0.068	8.357×10^{-5}	0.162
X_1X_1	0.016	0.046	0.740	0.108
X_2X_2	0.325	0.071	2.477×10^{-3}	0.167
X_3X_3	−0.016	0.023	0.509	0.055
X_1X_2	−0.295	0.104	0.025	0.246
X_1X_3	0.051	0.062	0.438	0.146
X_2X_3	0.016	0.074	0.836	0.176
Y_3				
Constant	7.850	0.304	3.362×10^{-8}	0.720
X_1	−0.826	0.094	4.887×10^{-5}	0.222
X_2	−0.457	0.108	3.911×10^{-3}	0.256
X_3	0.574	0.060	2.831×10^{-5}	0.142
X_1X_1	0.009	0.040	0.820	0.094
X_2X_2	0.144	0.062	0.052	0.146
X_3X_3	−0.029	0.020	0.199	0.048
X_1X_2	−0.302	0.091	0.013	0.216
X_1X_3	0.060	0.054	0.306	0.128
X_2X_3	0.104	0.065	0.154	0.154

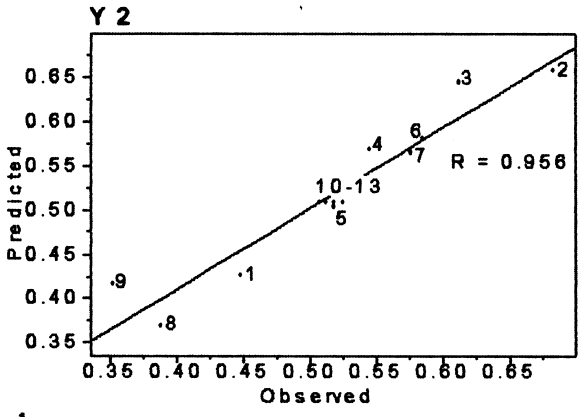
Coefficients are corrected at three decimal places.
[a]S.E. Standard error of the coefficient.
[b]P Probability to obtain the displayed value for the coefficient if it's true value was zero.
[c]Confidence interval The 95% confidence interval on the coefficient value.

The aim of the optimization was to maximize the response function on the response Y_3 with the respect of the constraints on the responses Y_1 and Y_2.

The responses were combined by superimposing the contour plots. The optimization procedure generated the region of interest; where the maximized point was found by non-linear programming using Lagrange multipliers (Fonner et al., 1970; Lipp and Heimann, 1996). The optimization procedure is depicted in Fig. 6. The optimal point is located at the intersection between 0.10 constraint on Y_1 and 0.55 constraint on the response Y_2 (point 0 on Fig. 6).

Optimized formulations predicted release values that were compared with observed values after preparing the slow release formulations in optimized conditions. Results concerning optimum levels for independent factors as well as comparative values of predicted and observed responses are reported in Table 5. The optimized formulations yielded responses that were close to the predicted values.





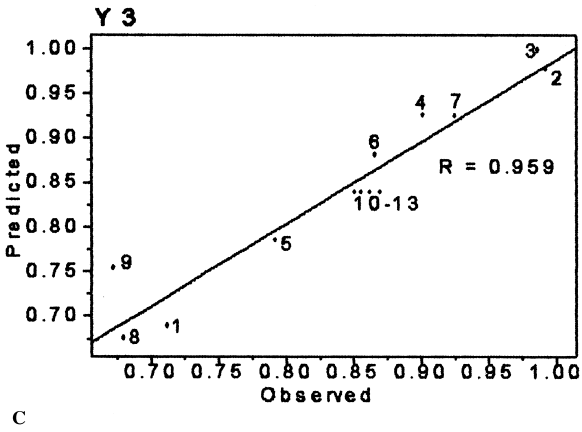


Fig. 2. Residual plots of the observed values versus the predicted values: (a) For Y_1; (b) For Y_2; (c) For Y_3.

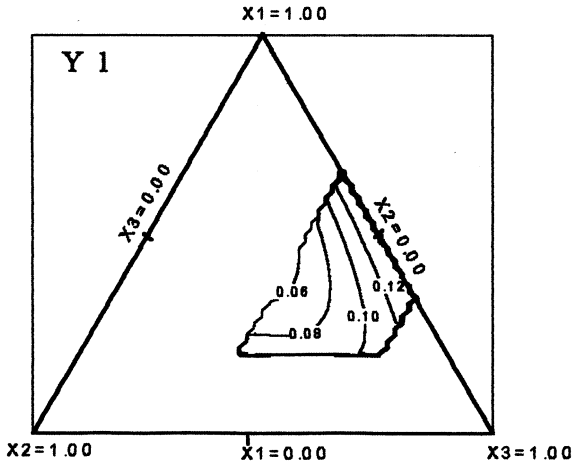


Fig. 3. Contour plots showing the effect of mixture composition upon Y_1 (fraction of propranolol HCl released after 1 h)

The kinetics and mechanism of drug release from the optimized system were investigated by fitting the release data into the simple relationship derived by Korsmeyer et al. (1983), which is often used to describe drug release from polymeric systems:

$$\frac{M_t}{M_\infty} = kt^n \tag{5}$$

where M_t/M_∞ is the fractional release of drug, t

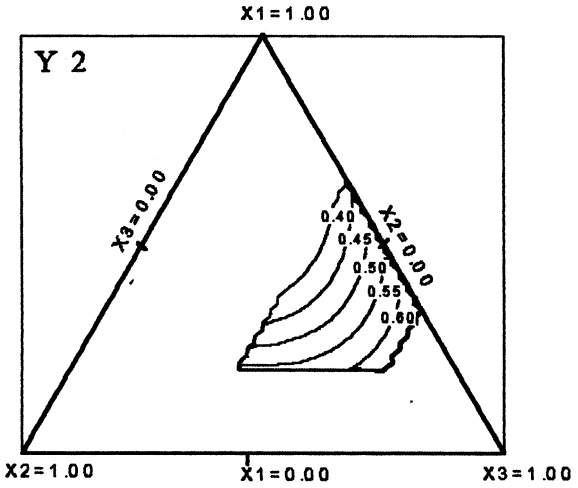


Fig. 4. Contour plots showing the effect of mixture composition upon Y_2 (fraction of propranolol HCl released after 6 h)

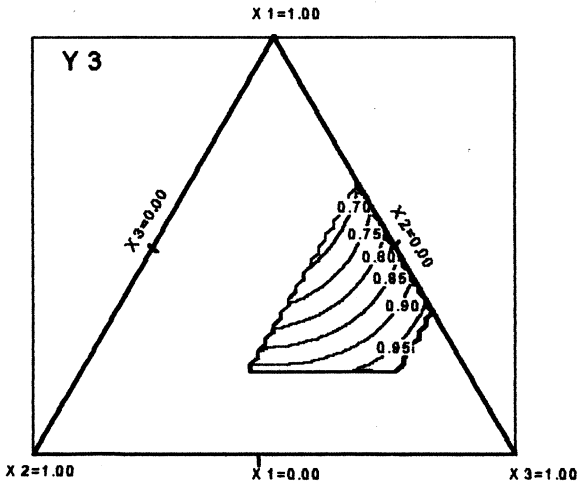


Fig. 5. Contour plots showing the effect of mucture composition upon Y_3 (fraction of propranolol HCl released after 12 h)

is the release time (expressed in hours), k is a constant that incorporates structural and geometric characteristics of the release device and n is the release exponent which indicates the kinetics of the release: being Fickian diffusion for $n = 0.5$; non-Fickian transport for n between 0.5 and 1; and constant zero order release (super case II) for $n = 1$.

Polymer swelling and drug diffusion through a HPMC–CMCNa matrix generally do not follow a

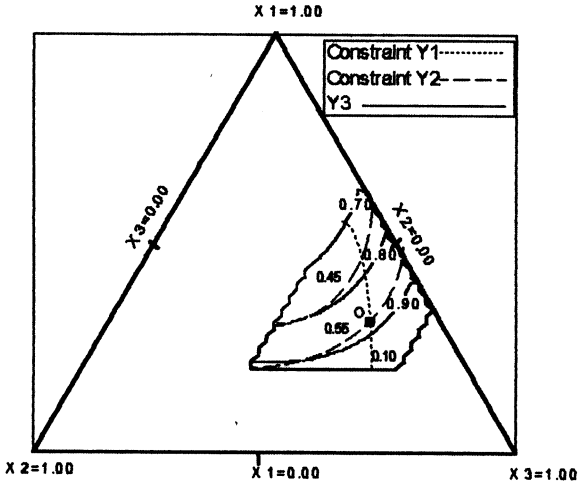


Fig. 6. Contour plot showing the optimization procedure. The optimal point is marked with a small black square noted with O.

Table 5
Optimized levels for independent variables and comparative levels of predicted and observed responses for optimized formulation

	X_1	X_2	X_3
X predicted	0.333	0.115	0.552
	Y_1	Y_2	Y_3
Y predicted	0.100	0.550	0.881
Y observed	0.107	0.542	0.872

Fickian release behavior, due to the existence of a molecular relaxation process which is believed to be responsible for this phenomenon.

Peppas and Sahlin (1989) proposed a heuristic model and derived an equation which is very useful for quantifying the approximate amount of drug released by Fickian diffusion and by polymer relaxation:

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} + k_2 t \tag{6}$$

where the first term of the right-hand side represents the Fickian contribution, and the second term is the case II relaxational contribution, k_1 and k_2 corresponding to the release rates of the Case I and Case II mechanisms respectively.

Table 6 shows the estimated parameters, which result from the fitting of dissolution data according to Eqs. (5) and (6). The value of n as a result from the fitting the data according to Korsmeyer model indicates a non-Fickian release of the drug. However the treatment of dissolution data according to the heuristical model proposed by Peppas and Sahlin (1989) indicates that the percent of drug released by Fickian diffusion still predominates.

4. Conclusions

A method to obtain good experimental mixture designs when the experimental factor space is not a simplex, is to use D-optimum criterion where a given number of experiments is selected out of many possible mixtures, in order to give a statistically optimized design.

Table 6
Evaluation of dissolution data from optimized formulation according to Korsmeyer model and Peppas heuristic model

Korsmeyer model				Peppas model			
Kinetic constant (k)($h^{-0.849}$)	Kinetic exponent (n)	R^{2a}	RMS[b]	Estimated $k_1(h^{-1/2})$	Estimated $k_2(h^{-1})$	R^{2a}	RMS[b]
0.114	0.849	0.997	0.022	0.190	0.030	1.000	0.014

[a]R^2, Correlation coefficient.
[b]RMS, Root mean square deviations between measured and calculated values.

HPMC proved to have the highest retardatory effect upon the release of propranolol HCl. The negative interaction effect was also evident between the two polymers upon the release of active ingredient.

Examination of the contour plots led to the determination of the region where acceptable values of the response are obtained. Optimum region respecting all the constraints applied to the results was found by superimposing contour plots. Maximized Y_3 response was found in the interior of this optimum zone by non-linear programming methods using the method of Lagrange multipliers.

An optimized formulation was prepared and subjected to dissolution. The observed results were close to the predicted values. Dissolution data for optimized formulation were treated according to the Korsmeyer model. Quantification of the amount of drug released by Fickian diffusion and by polymer relaxation was performed by fitting the release data into a polynomial expression proposed by Peppas and Sahlin (1989). Results are indicative of anomalous non-Fickian drug release behavior, Fickian diffusion being also important in governing the release of the active ingredient.

The information obtained on the influence of the different excipients would be expected to prove useful on further development when formulations of different dissolution characteristics might be required.

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