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RESEARCH PAPER

Optimization of Propranolol Hydrochloride Sustained-Release Pellets Using Box-Behnken Design and Desirability Function

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ABSTRACT

The objective of the present study was to evaluate three process parameters for the application of ethylcellulose films from organic solutions to obtain multiparticulate controlled drug delivery of propranolol hydrochloride. The coating process was developed in a classical coating pan.

A Box-Behnken central composite design was used to evaluate the effect of the film thickness (expressed as the amount of lacquer applied on pellets' surface unit), concentration of lacquer in the coating dispersion, and the plasticizer concentration on the independent variables. Those were t_{85}*, the degree of sticking in the coating pan, and the duration of the coating process. Contour and response surface plots were depicted based on the equation given by the model. Because the results were competitive, i.e., improving one response had an opposite effect on another one, an overall desirability function was described to ameliorate the interpretation of the results. The optimization procedure generated the maximum overall desirability value. A formulation was prepared under the optimized conditions yielding response values which were close to the predicted values.*

To understand the mechanism of drug release from the optimized pellets various models were used to fit the dissolution data. The Higuchi model appears to provide the best correlation.

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INTRODUCTION

The pellet-based multiple unit extended release dosage forms are gaining more importance as a result of their several advantages: they reduce the risk of systemic toxicity due to dose dumping, reduce local irritation, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering drug bioavailability (1).

Though most of pelletization and coating techniques are developed in fluidized-bed devices, in some specific conditions satisfactory results could be obtained using classical coating drums. In this particular case agglomeration of the beads during coating is a common problem. Therefore coating dispersions that provide an efficient and predictable release of drugs should be of considerable interest.

Ethylcellulose is probably the most widely used water-insoluble polymer to control the release rate of the drugs from solid dosage forms (2–5). It is soluble in many organic solvents, it has good film-forming properties, and enables flexible coatings.

Propranolol, a nonselective beta adrenergic blocking agent, was chosen as a model because of its short half-life, and increased dosing frequency, suggesting the need for a controlled release dosage form (6–8).

Optimization by means of factorial designs and analysis of the response surfaces is a powerful, efficient, and systematic tool for shortening experiment time in the design of pharmaceutical dosage forms and technological processes (9–11). During the optimization procedure some of the response variables are to be maximized and some are to be minimized, and they could have an opposite effect on one another. Several approaches have been used to solve this particular problem. An interesting approach to solving the problem is through the use of a desirability function that combines all the responses into one measurement (12). The desirability functions were used by many authors to solve complicated situations which occurred during optimization techniques (13–16).

One of the most popular experimental designs employed in optimization techniques is the Box-Behnken design (17). The design was used to construct a second-order polynomial model to describe the reciprocal dependency of the studied parameters.

MATERIALS AND METHODS

Materials

The following materials were all used as received: propranolol (S&D Chemicals), ethylcellulose N22 (Aqualon), magnesium stearate (Serva), polyvinylpyrrolydone K30 (Janssen), lactose (S&D Chemicals), Aerosil 200 (S&D Chemicals), sucrose; Eudragit NE 30D (Röhm Pharma, GmbH), PEG 6000 (Merck-Schuchardt), and butylstearate (Merck-Schuchardt). All other ingredients and chemicals were of analytical grade and sucrose was of food grade.

Software

Response surface modeling and evaluation of the quality of fit of the model were performed with the Modde 3 software package (Umetri, AB, Umea, Sweden).

Release data for the optimized formulation were fitted to nonlinear models using MSFIT, an integrated computer program developed for nonlinear fitting of dissolution data from controlled-release devices (18). The use of this program eliminates the disadvantages associated with the linear transformation and provides a more accurate fitting of data to the models.

Methods

Preparation of Pellets

Pelletization was accomplished in a classical coating pan. The core material was 700 g sucrose, sieved to 0.5–0.8 mm. The core material was placed in the pan and Eudragit NE 30D dispersion was sprayed continuously onto the falling particles concomitantly with dusting with a powder containing a mixture of lactose, Kollidon, and propranolol. Process conditions and equipment are reported in Table 1.

Coating Procedure

The pellets were coated by spraying the organic dispersion containing ethylcellulose as film forming agent in a coating pan and drying it using a stream of hot air. Butylstearate was used as plasticizer. The initial coating (containing 3% ethylcellulose) was diluted to the desired ethylcellulose content according to the experimental plan. Plasticizer concentration was considered as a percentage from the ethylcellulose content. Coating equipment and process conditions are reported in Table 1.

Particle Size Analysis

Pellets and coated pellets were sieved using a set of sieves (Prolabo) with different apertures (500, 630, 800, 1000, 1250, and 1600 μm). All samples were analyzed in duplicate. The percentage weight size frequency of distribution of particle and the arithmetic mean (in micrometers) were determined. Most of the uncoated pel-

Table 1

Pelletization and Coating Equipment and Process Conditions

Pellets formulation		
Core material	Sucrose, sieved, 0.5–0.8 mm	700 g
Dusting powder	Propranolol HCl	700 g
	Lactose monohydrate	650 g
	Polivinylpyrrolidone K30	40 g
	Aerosil 200	10 g
Spray dispersion	Eudragit NE 30D	200 g
Initial coating formulation		
	Ethylcellulose	50 g
	Butylstearate	variable
	Magnesium stearate	90 g
	Ethanol	305 g
	Ethylacetate to	1666 g
Coating pan	Erweka (capacity 9 liters)	
Pelletization process		
Batch size (g)		700
Spray rate (ml/min)		4
Dusting rate (g/min)		25
Atomizing air pressure (bar)		1
Spray nozzle diameter (mm)		1.2
Rotation speed (rpm)		35
Pan angle		30°
Coating process		
Inlet air temperature (°C)		35–40°C
Exhaust air temperature (°C)		25–30°C
Atomizing air pressure (atm)		1.4
Spray nozzle diameter (mm)		1.2
Batch size (g)		500
Spray rate (ml/min)		4
Baffles		2
Rotation speed (rpm)		15
Pan angle		45°

lets fell in the diameter range 600–1250 μm. All fines and agglomerates were discarded. The fraction of beads remaining between sieves with apertures of 630 and 1000 μm was collected and subjected to the coating procedure. Coated pellets with diameter size higher than 1600 μm were the stuck pellets and their fraction, calculated as a percentage from the total mass, and were introduced into the optimization procedure.

Dissolution Tests In Vitro

The dissolution studies were carried out following the USP XXIII rotating basket method at 37°C and 100 rpm, using Erweka DT dissolution tester. Distilled water was used as dissolution medium. Samples of 3 ml volume were collected at suitable time intervals, filtered, and assayed spectrophotometrically (Hitachi U 2000) at 289 nm for the drug content. The cumulative mass of drug released was calculated. At the end of each release study, the beads were removed, ground, and assayed to determine the residual drug content. The total amount of drug present in the beads was calculated as the sum of the cumulative mass of drug released at the last sample and the mass of drug remaining in the beads. Three replicate experiments were performed.

Estimating the Surface Area of Small Particles

The surface area of the beads to be coated was estimated by gas permeametry using the method described by Lehmann et al. (19). The estimation allowed us to calculate the amount of coating to be applied on the pellets to obtain a particular thickness of diffusion shell following the experimental plan.

Content Uniformity

One hundred milligrams of each of the prepared batches was grinded carefully and dissolved in 100 ml

distilled water. The solutions were then filtered and their propranolol content was determined spectrophotometrically. Three replicate experiments were performed.

Optimization Through the Use of the Desirability Function

The measured responses (Y_1, Y_2, and Y_3) were combined in one desirability function after computing individual desirability functions. Different desirability functions were employed to best describe the importance of each response to the global optimization of the process.

t_{85} was the critical response in the optimization procedure, therefore, the Harrington's exponential function (13) with one-sided specification was used to find individual desirability values. The exponential dependence of desirability values on the t_{85} increases the probability of obtaining high values for t_{85}. The desirability function was calculated as follows: t_{85} of 16.0 hr was given a desirability value (d) of 0.8 and t_{85} of 8 hr was given a value of 0.4 in a desirability scale with a maximum of 1.0. Each of these two desirability values (d) was transformed to a dimensionless response Y' using the equation

$$Y' = -[\ln(-\ln d)] \tag{1}$$

To find the linear relationship between the t_{85} values and their correspondent desirability, the following linear transformation equation was described using the two paired values of Y and Y' at t_{85} of 16.0 and 8.0 hr:

$$Y' = b_0 + b_1 Y \tag{2}$$

where b_0 and b_1 are constants, and in this case they were found to be equal to −1.3251 and 0.1765, respectively.

The desirability of each t_{85} value that resulted from the experimental plan was calculated from the Y' value using the exponential equation:

$$d = e^{-(e^{-Y'})} \tag{3}$$

Y_2 and Y_3 responses were minimized in the optimization procedure. For both responses a linear desirability function described by Derringer and Suich (14) was applied. The equation was of the form:

$$d = \frac{Y_{max} - Y_i}{Y_{max} - Y_{min}} \tag{4}$$

where Y_{max} and Y_{min} are the maximum and minimum acceptable values and Y_1 is the experimental result. The maximum response was chosen so that the desirability value for the worse response was close to 0, while the minimum response was chosen to produce individual desirability values close to 1. The overall desirability values were calculated from the individual values according to the following equation:

$$D = (d_1 d_2 \ldots d_k)^{1/k} \tag{5}$$

Experimental Design

The independent factors selected for observations are shown in Table 2.

Table 3 lists the evaluation results of each formulation in terms of the individual responses together with the calculated desirability.

For the three-factor and three-level design, a total of 15 experimental runs are needed. These runs, along with the response variables of t_{85}, percentage of sticking, and duration of coating process are presented in Table 4.

A second-order polynomial model was used to generate appropriate regression models for Y_1, Y_2, and Y_4 responses using statistical software for experimental design. The polynomial equation employed to fit the data from the experimental design was of the form

Table 2

Independent Factors; Minimum and Maximum Desirable Levels

Response Variables	Measured Responses	Levels		Desirability Function
		Minimum	Maximum	
t_{85} (hr)	Y_1	-	-	Exponential
Stuck pellets % (w/w)	Y_2	6	80	Linear
Duration of coating process (min)	Y_3	100	1200	Linear
Overall desirability	Y_4	0	1	-

Table 3

Independent Variables; Factors and Levels for Box-Behnken Design

Factors	Levels		
	-1	0	1
Amount of lacquer applied on pellets surface (mg/cm^2) (X_1)	1	2.5	4
Concentration of lacquer in the coating dispersion (% w/w) (X_2)	1	2	3
Plasticizer concentration (% w/w) (X_3)	10	20	30

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad (6)$$

where Y_1, Y_2, and Y_4 are the dependent variables and X_1, X_2, and X_3 are the independent variables. The coefficients b_i represent the estimation of the main effects of the factors X_{ijk}. Similarly b_{ii} represents the estimation of the second-order effects and b_{ij} and b_{ijk} are the estimation of interactions between X_i and X_j. The model generated contained quadratic terms which explained the nonlinear nature of responses and multiple factor terms which explained the interaction effects between factors.

The dependence of Y_3 response, i.e., the duration of coating process on experimental factors, was linear being a consequence of the experimental conditions, i.e., the spray rate, the amount of coating to be applied, and the polymer concentration in the coating dispersion. The dependence of Y_3 on variable factors is described by the following linear equation:

$$Y_3 = \frac{260X_1}{X_2} \quad (7)$$

RESULTS AND DISCUSSION

Dissolution profiles of all 15 formulations required by the experimental design are shown in Fig. 1. t_{85} values were detected directly on this figure.

The model was fitted to the data for all responses simultaneously using Modde for Windows computer

Table 4

Experimental Matrix and Results

Run	Variable Factor			Results			
	X_1	X_2	X_3	Y_1	Y_2	Y_3	Y_4
1	1	1	20	1.2	6.2	290	0.340
2	4	1	20	16.2	49.5	1160	0.229
3	1	3	20	0.5	8.5	96.6	0.314
4	4	3	20	10.1	78.6	386.6	0.195
5	1	2	10	0.25	6.9	145	0.296
6	4	2	10	12.5	58.2	580	0.479
7	1	2	30	1.8	7.1	145	0.394
8	4	2	30	12.9	63.1	580	0.444
9	2.5	1	10	4.2	11.8	725	0.405
10	2.5	3	10	3.3	33.7	241.6	0.405
11	2.5	1	30	9.3	15.2	725	0.567
12	2.5	3	30	4.2	35.3	242	0.444
13	2.5	2	20	5.2	20.2	362.5	0.515
14	2.5	2	20	5.4	23.6	362.5	0.514
15	2.5	2	20	5.1	19.5	362.5	0.513

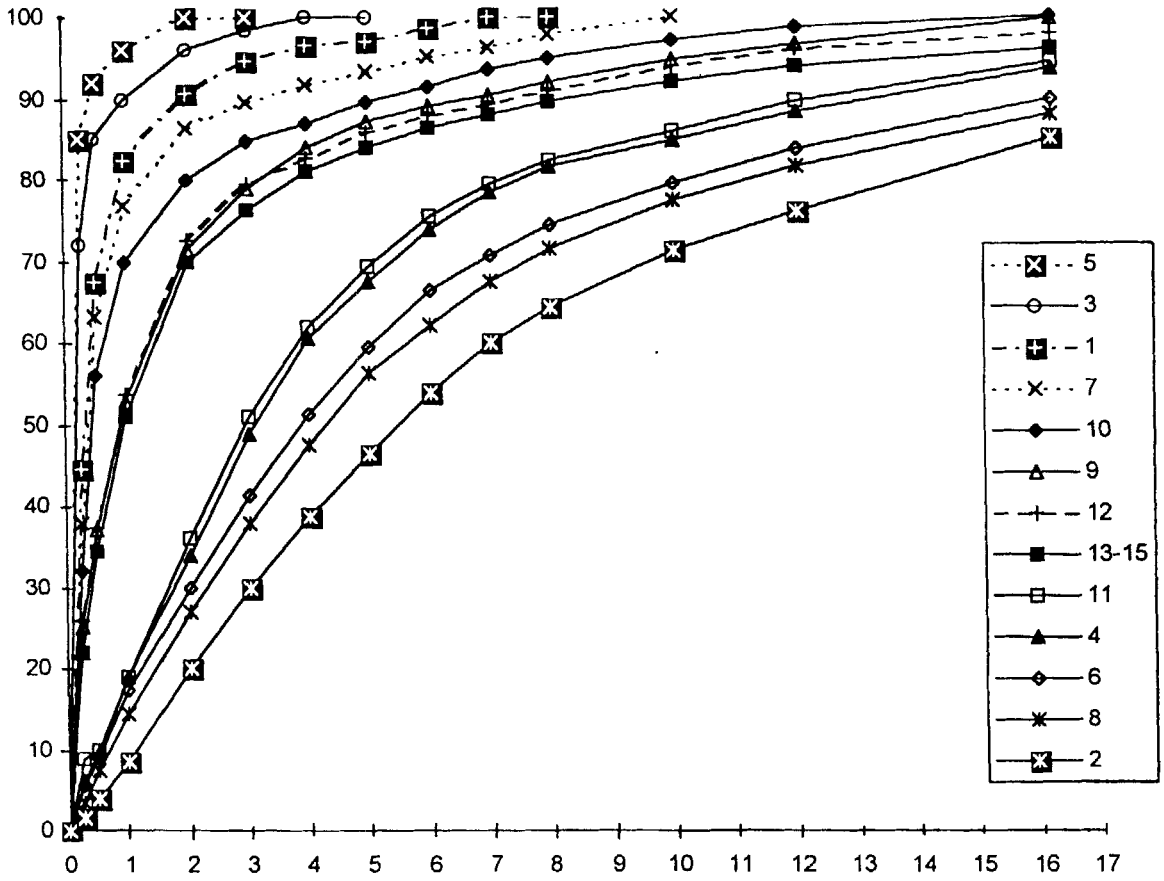

Figure 1. Dissolution profiles of propranolol from pellets coated according to the experimental matrix design.

program. The initial model was refined by excluding terms that are insignificant for responses. In Fig. 2 the quality of fit of the model for each response is plotted. R^2 is the fraction of variation of the response explained by the model and Q^2 is the fraction of the variation of the response that can be predicted by the model. R^2 is an overestimated measure, and Q^2 is an underestimated measure of the goodness of fit of the model. The model was found to be statistically excellent for Y_1 and Y_2 responses. It was acceptable for the overall desirability (Y_4) explaining more than 70% of the response variation and with a predictive ability of more than 20%.

The regression procedure according to the second-order polynomial model generated the equations describing mathematical relationships between dependent and independent variables. The resultant equations are given below.

$$Y_1 = -7.544 + 2.044X_1 + 2.750X_2 + 0.309X_3 + 0.750X_1^2 - 0.900X_1X_2 - 0.105X_2X_3 \quad (8)$$

$$Y_2 = 11.585 - 17.220X_1 - 1.992X_2 + 0.126X_3 + 5.336X_1^2 + 4.467X_1X_2 \quad (9)$$

$$Y_4 = -0.300 + 0.336X_1 + 0.373X_2 + 0.003X_3 - 0.067X_1^2 - 0.099X_2^2 \quad (10)$$

Figure 3 summarizes the scaled and centered coefficient plot for all responses. This plot provides a picture of the relative contributors of every term in the model on all responses.

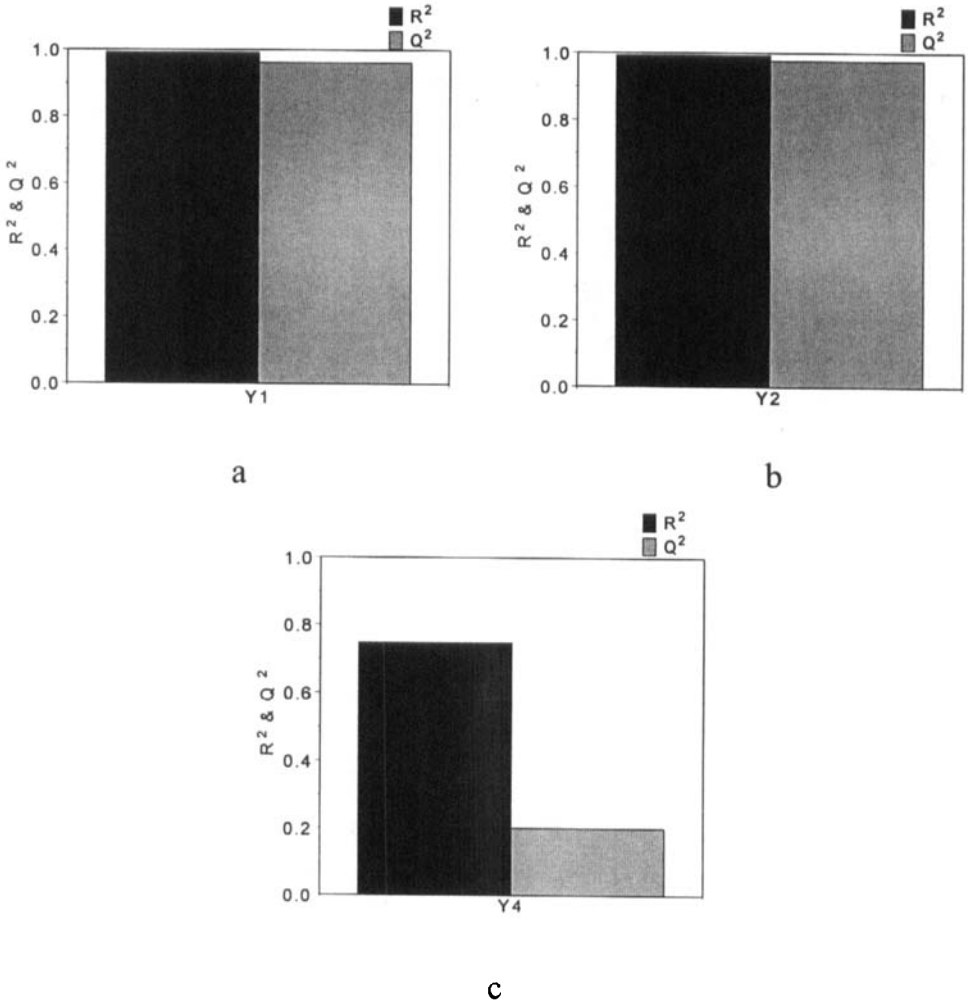

Figure 2. Quality of fit of the model for each response. R^2 is the fraction of variation of the response explained by the model and Q^2 is the fraction of the variation of the response that can be predicted by the model.

As it can be seen in Fig. 3, X_1 and X_3 had a positive influence upon Y_1, while X_2 had a negative influence on this response. In other words by increasing the amount of film on pellet surfaces we obtained a remarkable effect in retarding the release of propranolol. The same effect but to a smaller extent was obtained by increasing the amount of plasticizer and decreasing the concentration of ethylcellulose in the coating dispersion. The quadratic nature of the response was determined by the presence of the significant X_1^2 term. Interactions were detected between X_1 and X_2 and between X_2 and X_3 terms. X_1 and X_2 factors proved to have a positive effect on Y_2. When the thickness of film and the concentration of the lacquer in coating dispersion were increased, an increase in the degree of sticking of pellets in the coating pan was observed. Changes on X_3 proved to be unimportant on Y_2. The nonlinear nature of the Y_2 response was confirmed by the presence of X_1^2 term. Interactions between X_1 and X_2 proved to have an effect on Y_2.

Three-dimensional plots for the measured responses were formed based on the model to assess the change

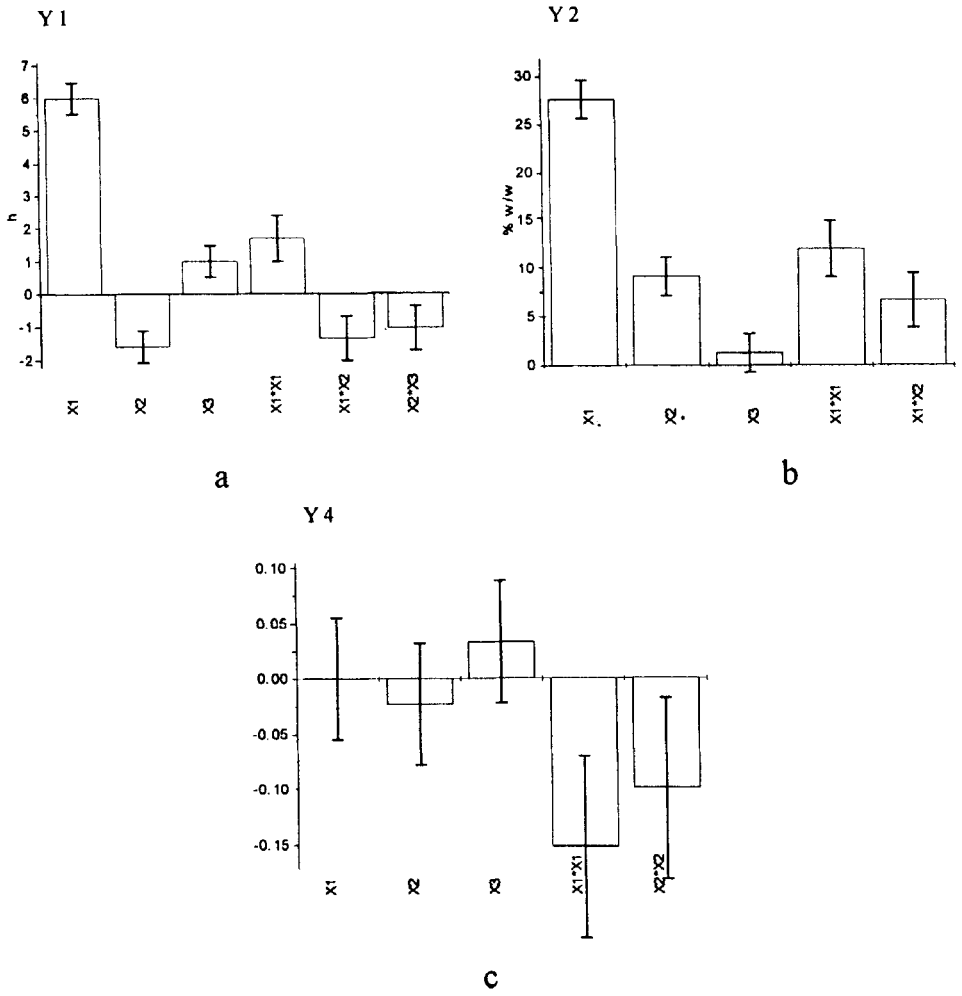

Figure 3. Scaled and centered PLS (partial least squares) coefficients. The coefficients were corrected for values introduced into the PLS procedure and thus the ordinate scale is comparable to *Y*-units (i.e., percent of propranolol released). Histograms correspond to the change in response (ordinate scale) estimated for a relative increase of the indicated descriptor variable, i.e., from median to high level in the original factorial design. The bars indicate confidence interval.

of the response surface. The relationship between the dependent and independent variables can be further understood by these plots. Figure 4(a) shows the effect of X_1 and X_2 on Y_1. t_{85} value increased with film thickness (X_1) and with the application of less-concentrated coating dispersions (X_2). This could be explained since the application of less-viscous dispersion allows a better spread of lacquer on the particle surface, producing more compact films. The effect becomes more evident when thick films are applied.

Figure 4(b) shows the effect of X_1 and X_3 on the response Y_1. The figure shows an increase in the t_{85} when the film thickness and plasticizer content are increased. Physically a plasticizer affects the interactions between polymer chains, softening the polymer and facilitating the formation of more flexible film.

Figure 4(c) demonstrates the effect of X_2 and X_3 on the response Y_1 showing an increase of t_{85} when plasticizer content into films is increased and ethylcellulose content in the dispersion to be applied is decreased. The effect is much more pronounced at high plasticizer concentrations resulting from an interaction effect between X_2 and X_3.

Figure 5 shows the effect of X_1 and X_2 on the response Y_3. As can be seen, the degree of sticking is very much increased when higher amounts of lacquer are

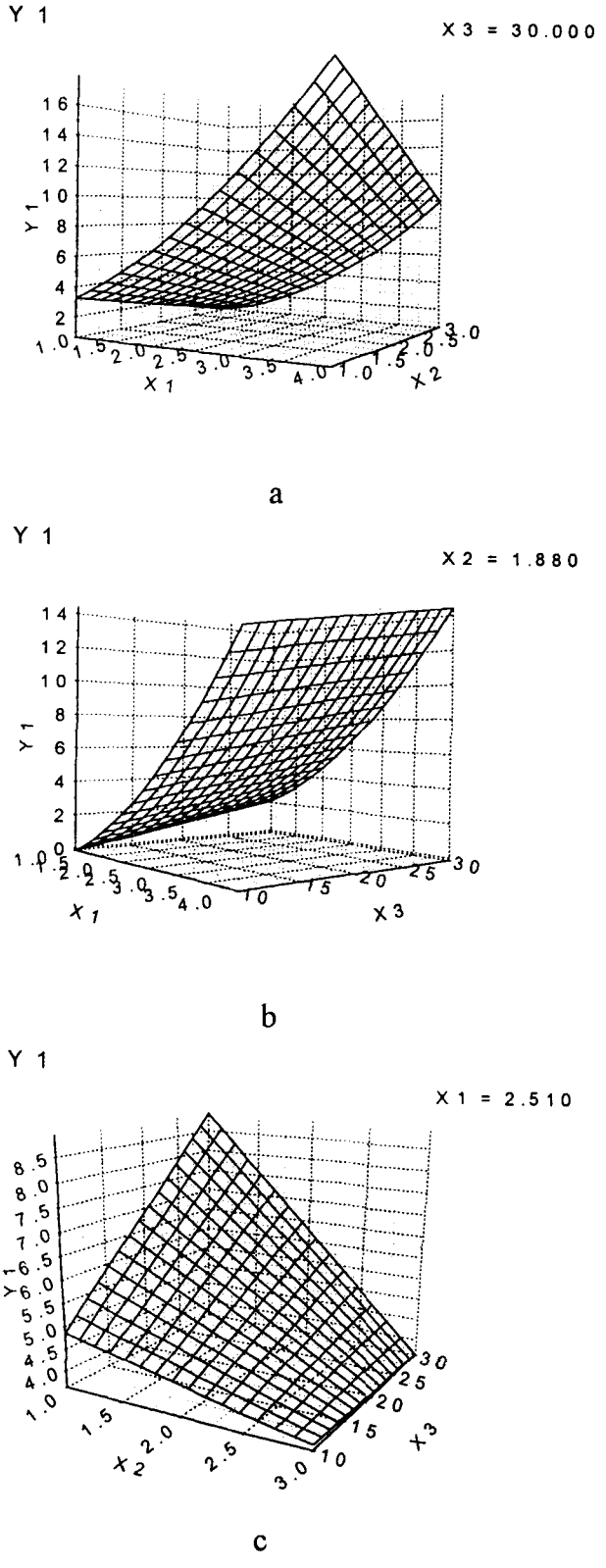

Figure 4. Contour plots showing the effect of the X_1, X_2, and X_3 on Y_1.

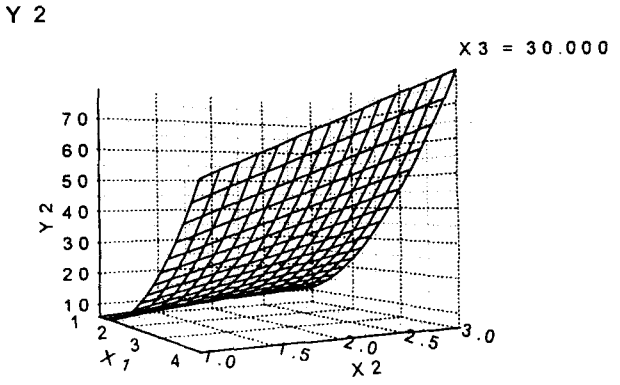

Figure 5. Contour plots showing the effect of X_1 and X_2 on Y_2.

applied on pellets, and to a smaller extent, by the increase in ethylcellulose content in the dispersion to be applied.

As a conviction of these results to attain significant retarding effects, higher amounts of ethylcellulose should be applied on the pellets. It should be also pointed out that application of higher amounts of lacquer increases the degree of sticking and duration of application procedure. The degree of sticking could be minimized by the use of more diluted coating dispersion, but this further increases the time of application, requiring more solvents and generating more costly procedures.

In such conditions of competing objectives, all the measured responses were combined in one overall response that is the overall desirability. Overall desirability responses were calculated from the individual desirability responses. The results were included in the optimization procedure and an equation was found to describe the effect of independent variables upon overall desirability [Eq. (10)]. The scaled and centered coefficient plot showed the important quadratic nature of the relationship. X_1^2 and X_2^2 being the most effective terms influencing the overall desirability [Fig. 3(c)].

Table 5

Predicted Optimum Levels for Independent Variables

Independent Variable	Optimum Levels
X_1 (mg/cm^2)	2.51
X_2 (% w/w)	1.88
X_3 (% w/w)	30

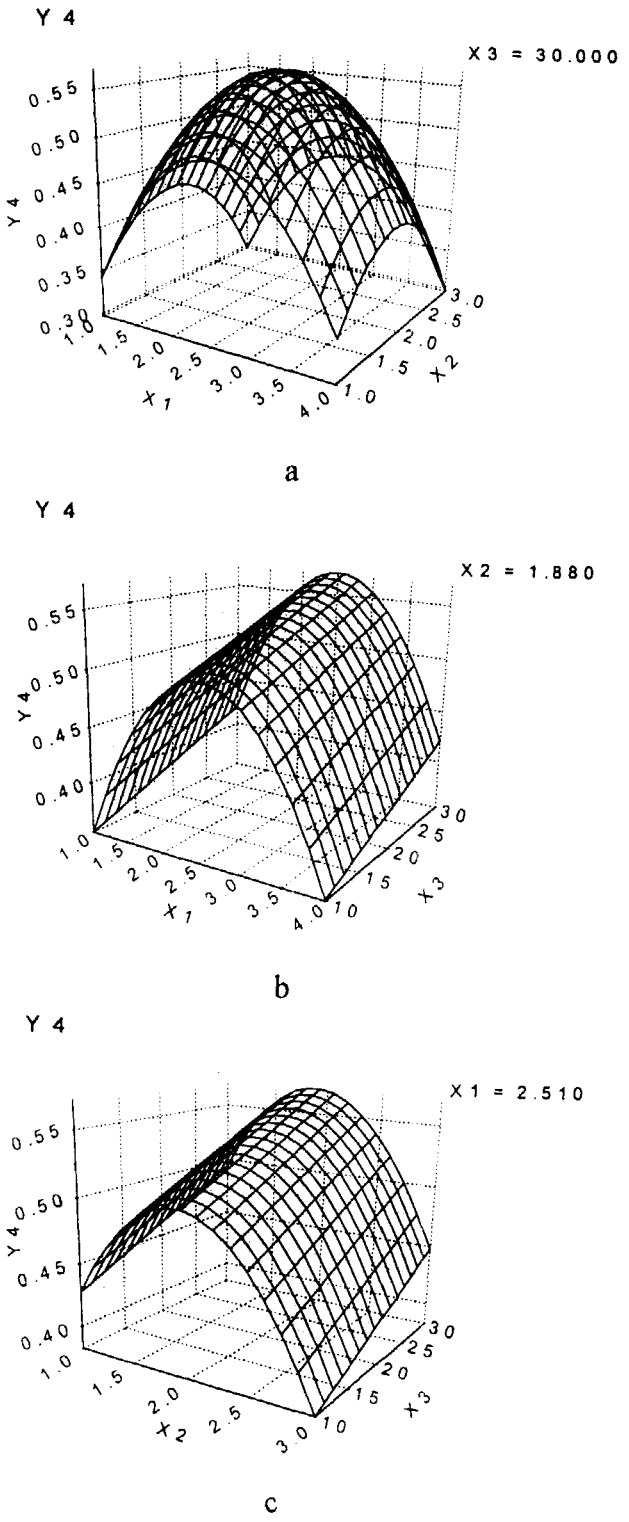

Figure 6. Contour plots showing the effect of X_1 and X_2, X_1 and X_3, and X_2 and X_3 on Y_4.

Table 6

Comparison of the Observed and Predicted Values

Response Variable	Predicted	Error of Observed	Prediction
Y_1 (hr)	6.58	6.58	0
Y_2 % (w/w)	23.09	24.27	5.11%
Y_3 (min)	387	387	0
Y_4	0.57	0.548	3.85%

The effect of independent variables on the overall desirability is shown in Fig. 6. The plots illustrate that high values must be used for X_3 and moderate values for X_1 and X_2 to achieve the best overall desirability values.

The optimal value for the overall desirability was found by nonlinear programming procedure. The prediction of the ranges of formulation variables where the optimum formulation may occur is related in Table 5.

Table 6 illustrates the predicted and observed responses for the optimum formulation.

Release data for the optimized formulation were fitted to nonlinear models using an integrated computer program MSFIT. The release models are: Baker-Lonsdale, Hixon-Crowell, Higuchi, and first-order release kinetic models.

Results of fitting of the data to the above-mentioned models are reported in Table 7. Visual examination of the fraction released versus time curve in the presence of the input data points corroborated with statistical data lead us to the conclusion that the square root of time (Higuchi) model provided the best correlation.

CONCLUSIONS

The investigated variables were found to be highly dependent on the formulation variables. Because the responses were competitive to one another, an overall desirability function was utilized to combine all the responses into one measurement. The overall desirability values were included into the optimization procedure and a general equation was deduced to describe the relationship between variable factors and the overall desirability. The results allowed the determination of the optimum experimental conditions. The application of the optimized formulation to the pellets provided responses which were close to those of the predicted values. The analysis of the release mechanism from the optimized

Table 7

Nonlinear Data Fitting Parameters[a] Applied to Dissolution of Propranolol HCl from Optimized Formulation

Dissolution Models	Equation of the Model[b]	k	Uncertainty[c]	Standard Deviation	95% Confidence Interval[d]
Baker-Lonsdale (20)	$\frac{3}{2}[1-(1-F)^{2/3}]-F=kt$	0.0295	0.0005	0.0029	0.0231–0.0360
Hixon-Crowell (21)	$1-(1-F)^{1/3}=kt$	0.0936	0.0011	0.0078	0.0766–0.1107
Higuchi (22)	$F=kt^{1/2}$	0.3139	0.0021	0.0153	0.2805–0.3473
First-order (23)	$F=1-e^{-kt}$	0.3942	0.0067	0.0276	0.3340–0.4544

[a]Uncertainty, standard deviations, and confidence intervals are calculated for estimated parameter k.
[b]F is the fraction of drug released at a time t and k is the constant of the process.
[c]The uncertainty of the estimated parameter is calculated as a square root of the diagonal elements of the matrix $[\alpha]^{-1}$, where $[\alpha]$ is a matrix of sums of crossproducts of certain partial derivatives (24,25).
[d]Confidence intervals were computed using univariate method according to the Student's $t_{(\alpha,df)}$ statistics criterion: CI = estimated parameter $\pm$ ($t_{(\alpha,df)}$ × SD).

formulation proved that best correlations exist with Higuchi model.

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