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Optimization of propranolol hydrochloride sustained release pellets using a factorial design

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Abstract

A conventional pan coating method was used to prepare propranolol–HCl sustained release coated pellets. Eudragit RS was used for controlling release. A 3^2 full factorial design was selected and nine experimental runs were performed to improve dissolution characteristics of the sustained release formulation. The independent variables were: plasticizer concentration in the coating and volume of coating dispersion applied to the pellets in the coating pan. Optimization was performed in order to maximize the fraction of propranolol released after 12 h with respect to constraints applied to the model after 1 h and 6 h release period. The optimized formulation provided dissolution rates that were close to predicted values. A non-linear fitting of 'in vitro' dissolution data for the optimized formulation was performed. The kinetics of dissolution was shown to follow the Hixon–Crowell model. © 1997 Elsevier Science B.V.

Keywords: Pellets; Coating; Optimization; Factorial design; Propranolol HCl; Dissolution; Non-linear fitting

1. Introduction

The use of pellets as a drug vehicle in controlled release dosage forms has received significant attention (Hosny et al., 1994; Saettone et al., 1995; Sonaglio et al., 1995). This is because of several advantages which they possess: they reduce the risk of systemic toxicity due to dose dumping, they reduce local irritation and peak plasma fluctuations and they minimize potential side effects without appreciably lowering drug bioavailability (Follonier and Doelker, 1992).

Pellets are commonly coated in fluidized bed granulators but in some specific conditions satisfactory results can be obtained by using classical coating drums. In this particular case agglomeration of the beads during coating is a common problem. Therefore coating dispersions producing low agglomerations of beads in the pan and

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providing efficient and predictable release of drugs should be of considerable interest.

Propranolol, a non-selective beta adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. Because of its relatively short plasma half-life and extensive hepatic first pass metabolism following oral administration, it is a suitable candidate for incorporation into formulations with slow or sustained release (Ford et al., 1985; Taylan et al., 1996; Rekhi et al., 1995).

Optimization procedure involving factorial designs and analysis of response surfaces is powerful, efficient and also a systematic tool in developing sustained release formulations with ideal release properties (Singh et al., 1995; Karnachi and Khan, 1996; Bouckaert et al., 1996)

The aim of this study was to investigate the effects of formulation variables upon the release properties of propranolol HCl-containing pellets coated with Eudragit RS using a classical coating drum. The release of the active ingredient was optimized as a function of process variables using mathematical equations and response surface plots.

The optimization procedure would aid in the preparation of controlled release pellets with predictable properties. Two important coating parameters were considered in order to obtain an optimal formulation: plasticizer–polymer ratio in the coating and the volume of coating dispersion. The response surface method is a useful and efficient tool to obtain an appropriate model with minimum experiments. The range of each process variable was predetermined using preliminary experiments.

2. Materials and methods

2.1. Materials

The following materials were all utilized as received: propranolol (S&D Chemicals, Cunningham House, Harrow, UK), magnesium stearate (Serva, Heidelberg, Germany) polyvinylpyrrolydone K30 (Janssen Chimica, Belgium), lactose (S&D Chemicals, Cunningham House, Harrow, UK), Aerosil 200 (S&D Chemicals, Cunningham House, Harrow, UK), sucrose; Eudragit RS and Eudragit NE 30D (Röhm Pharma GmbH, Darmstadt, Germany) PEG 6000 (Merck-Schuchardt, München, Germany). All other ingredients and chemicals were of analytical grade while sucrose was of food grade.

2.2. Software

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

Release data for the optimized formulation were fitted to non-linear models using MSFIT. MSFIT is an integrated computer program developed for nonlinear fitting of dissolution data from controlled release devices (Lu et al., 1996). The use of this program eliminates the disadvantages associated with linear transformation and provides a more accurate fitting of data to the models.

2.3. Methods

2.3.1. 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 the application of a dusting powder containing a mixture of lactose, polyvinylpyrrolidone and propranolol. Process conditions and equipment are shown in Table 1.

2.3.2. Coating procedure

The pellets were coated by spraying a solution of Eudragit RS in acetone/isopropanol mixture (1:1) in a coating pan and drying using a stream of hot air. Coating equipment and process conditions are shown in Table 1.

2.3.3. Dissolution tests 'in vitro'

The dissolution studies were carried out using the USP XXIII rotating basket method at 37°C,

and 100 rpm using an Erweka DT dissolution tester. Distilled water (1000 ml) was used as dissolution medium. Sink conditions were maintained during dissolution. Samples of 3 ml volume were collected at suitable 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.

Table 1
Pelletization and coating equipment and process conditions

Pellets formulation	
Core material	
Sucrose beads (g, sieved 0.5–0.8 mm)	700
Dusting powder	
Propranolol HCl (g)	700
Lactose monohydrate (g)	650
Polyvinylpyrrolidone K30 (g)	40
Aerosil 200 (g)	10
Spray dispersion:	
Eudragit NE 30D (g)	200
Coating formulation	
Eudragit RS 12.5%	311.2 g
Magnesium stearate	34.6 g
PEG 6000	Variable
Distilled water	6.9 g
Isopropyl alcohol	to 700g
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 (rot/min)	35
Pan angle	30°
Coating process	
Inlet air temperature (°C)	40–45
Exhaust air temperature (°C)	30–35
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 (rot/min)	15
Pan angle	45°

Table 2
Independent variables: factors and levels for full factorial design

Factors	Levels		
	−1	0	1
Plasticizer concentration (% w/w) (X_1)	10	28	46
Volume of coating (ml/100 g pellets) (X_2)	80	200	320

2.3.4. Content uniformity

One hundred mg of each of the prepared batches was ground carefully and dissolved in 100 ml distilled water. The solutions were filtered and their propranolol content was determined spectrophotometrically. Three replicate experiments were performed.

2.3.5. Experimental design

A two factor, three levels full factorial design was used for the optimization procedure. This design provided an empirical second order polynomial model used for prediction of the effect of formulation variables on the dissolution characteristics using a small number of experimental runs.

The factorial design is a simplified representation in analytical form of a given reality. In this mathematical approach each experimental response Y can be represented by a quadratic equation of the response surface:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2 \quad (1)$$

The equation enables the study of the effects of each factor and their interactions over the considered responses.

The two factors as well as their levels are shown in Table 2. In Table 3 the analyzed responses and the constraints on the responses are presented. The matrix of the factorial plan and the results are represented in Table 4.

Table 3
Dependent variables and the constraints used

	Dependent variables	Constraints
Y_1	Cumulative % dissolved in 1 h	$10 \leq Y_1 \leq 20$
Y_2	Cumulative % dissolved in 6 h	$45 \leq Y_2 \leq 65$
Y_3	Cumulative % dissolved in 12 h	$80 \leq Y_3 \leq 100$

3. Results and discussion

3.1. Fitting of data to the model

Dissolution profiles of all nine formulations required by the experimental design are shown in Fig. 1. The model was fitted to the data for all responses simultaneously using Modde for Windows computer program. The initial model was refined by including in the model only those terms for which the level of significance was below or equal to $p \leq 0.05$ (Table 5). Exceptions were made only for terms which were essential to maintain the hierarchical model (X_1, for example).

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 response, with R^2 and Q^2 values close to the unity. For Y_2 and Y_3 responses the model was acceptable explaining more than 90% of the response variation and with a predictive ability of more than 60% for both responses.

Table 4
Experimental matrix and results

Run	Variable factors		Results		
	X_1	X_2	Y_1	Y_2	Y_3
1	−1	−1	69.51	93.02	99.38
2	0	−1	63.15	87.32	93.87
3	1	−1	65.26	86.24	92.17
4	−1	0	24.81	82.84	94.15
5	0	0	20.56	77.89	90.80
6	1	0	18.45	76.32	91.34
7	−1	1	10.11	48.46	82.85
8	0	1	7.42	62.35	88.81
9	1	1	5.86	68.36	89.32

3.2. Examining of the coefficients

The resultant equations of all responses are given below:

$$Y_1 = 116.972 - 0.138X_1 - 0.676X_2 + 1.084 \times 10^{-3}X_2^2 \quad (2)$$

$$Y_2 = 115.729 - 0.556X_1 - 0.208X_2 + 3.088 \times 10^{-3}X_1X_2 \quad (3)$$

$$Y_3 = 107.986 - 0.350X_1 - 0.078X_2 + 1.583 \times 10^{-3}X_1X_2 \quad (4)$$

The equations represent the quantitative effect of process variables (X_1 and X_2) upon the responses (Y_1; Y_2; Y_3)

Coefficients with more than one factor represent the interaction between factors while coefficients with second order terms indicate the quadratic nature of the phenomena. Positive signs indicate a synergistic effect while negative terms indicate an antagonistic effect upon the response.

Table 5 summarizes the normalized coefficients which resulted from the PLS (partial least squares) procedure. In normalized form the coefficients are divided by the standard deviation of their respective response.

One can conclude that the volume of coating has the largest antagonistic effect on all responses. Interaction is unimportant for Y_1 response while for Y_2 and Y_3 responses it has a marked positive effect. The effect of quadratic terms was relevant only on Y_1 response. The effect of plasticizer itself was insignificant, but the interaction between plasticizer and the volume of coating proved to be statistical significant.

3.3. Analysis of the fitted data

Three dimensional surfaces showing the influence of dependent variables X_1 and X_2 upon the responses Y_1, Y_2 and Y_3 were depicted in Fig. 3(a–c), following the resultant polynomial equa-

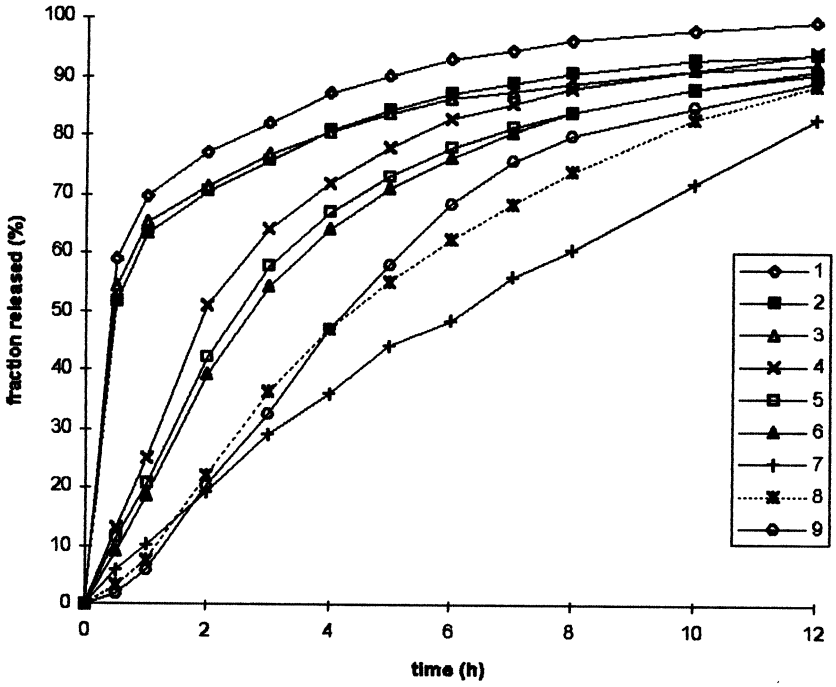

Fig. 1. Dissolution profiles of propranolol from pellets coated according to experimental matrix design (see Table 4).

tions. The rate of propranolol release was related inversely to the thickness of the coat, in all the studied responses, suggesting that the film thickness was the most effective factor in controlling drug release.

In Fig. 3b and 3c, one can see an increase in dissolution rates with a rise in the plasticizer level for high volume of coating and a decrease in dissolution rates with the rise of the plasticizer level for low volumes of coating. Plasticizers are added to the polymer coating of sustained-release granules in order to improve the mechanical properties of the coating film. When low volumes of coating are applied, plasticizers have a retarding effect on release kinetic through polymeric films due to their properties facilitating the formation of coherent films. When high volumes of coating are applied, the probability for the formation of coherent film increases due to increased film thickness. In thick film coatings, the presence of PEG 6000 may increase the rate of release due to its hydrophilic nature, producing supplementary pores into films.

Optimization was performed for the response Y_3 (cumulative percentage released in 12 h) with the respect of the constraints on the responses Y_2 and Y_1. The optimization was performed by superimposing contour plots and locating the area of interest (optimal surface). The procedure was depicted in Fig. 4. A pure mathematical optimum point was detected by non-linear programming methods at $X_1 = 10$ and $X_2 = 255$ (checkpoint O on Fig. 4).

In Table 6 the observed and predicted responses of design point 5 (which is the central point of the design), and six additional points (checkpoints A, B, C, D, E and O on Fig. 4) are presented to show the predictive value of the model. Four checkpoints were located symmetrically around the checkpoint 5 (checkpoints A, B, C and D), one checkpoint was randomly located inside the optimal surface (checkpoint E) and the last checkpoint was the pure mathematical optimum (checkpoint O).

It is evident that the responses measured at the pure mathematical optimum have inadequate val-

Table 5
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	0.803	0.037	3.857×10^{-6}	0.095
X_1	−0.093	0.026	0.016	0.067
X_2	−1.098	0.026	1.450×10^{-7}	0.067
X_2X_2	0.589	0.045	4.798×10^{-5}	0.116
Y_2				
Constant	5.405	0.115	8.278×10^{-8}	0.296
X_1	0.078	0.141	0.602	0.362
X_2	−1.038	0.141	7.265×10^{-4}	0.362
X_1X_2	0.475	0.173	0.040	0.444
Y_3				
Constant	20.286	0.124	1.604×10^{-10}	0.318
X_1	−0.131	0.152	0.426	0.390
X_2	−0.904	0.152	1.898×10^{-3}	0.390
X_1X_2	0.759	0.186	0.009	0.477

[a] Coefficient, value of the coefficient.
[b] S.E., standard error of the coefficient.
[c] P, probability to obtain the displayed value for the coefficient if its true value was zero.
[d] Confidence interval, the 95% confidence interval on the coefficient value.

ues, the amount of drug released after 6 h exceeding the constraints. This is due to the fact that the models predictions are statistical, i.e. these values have a specific confidence interval and the point was located exactly on the 65% constraint border. Therefore another point of the optimal surface was tested, that was checkpoint E. At checkpoint E the measured values were in concordance with the experimental requirements showing that the optimal surface was correctly estimated. The other predictions match rather well.

Release data for the formulation corresponding to checkpoint E were fitted to nonlinear models using an integrated computer program MSFIT. Four popular release models are implemented in the program: Baker–Lonsdale, Hixon–Crowell, Higuchi and first order release kinetic models.

The Baker and Lonsdale equation (Baker and Lonsdale, 1987) describe the drug release from spherical matrices. It is:

$$\frac{3}{2}[1-(1-F)^{2/3}]-F=k_{\mathrm{bl}}t \tag{5}$$

where F is the fraction of drug released at any time t, k_{bl} is the constant of the process, according to Baker and Lonsdale model. The value of k_{bl} could be calculated according to the following equation: $k_{\mathrm{bl}}=(3DC_{\mathrm{s}})/(r_0^2C_0)$, where D is the diffusion coefficient, C_{s} is the saturation solubility, C_0 the total concentration of drug dispersed and dissolved and r_0 the initial radius of the pellets.

Hixon and Crowell model (Hixon and Crowell, 1931) initially proposed as a kinetic model for the dissolution of powders, is based on the assumption that the dissolution of powder is independent of the initial particle diameter. The equation has been used by many researchers to describe the release of drugs from spherical matrices (Singh et al., 1995). It is:

$$1-(1-F)^{1/3}=k_{\mathrm{hc}}t \tag{6}$$

where, F is the fraction dissolved at any time t and k_{hc} is the kinetic process constant, according to Hixon–Crowell model.

The model for diffusion controlled release given by Higuchi (1963) is:

$$F=k_{\mathrm{h}}\sqrt{t} \tag{7}$$

where F is the percentage of the dissolved drug at any time t and k_{h} is the Higuchi dissolution rate constant.

Occasionally drug release data are fitted to a first order kinetic model described by the following equation (Shah et al., 1987; Mortada et al., 1988):

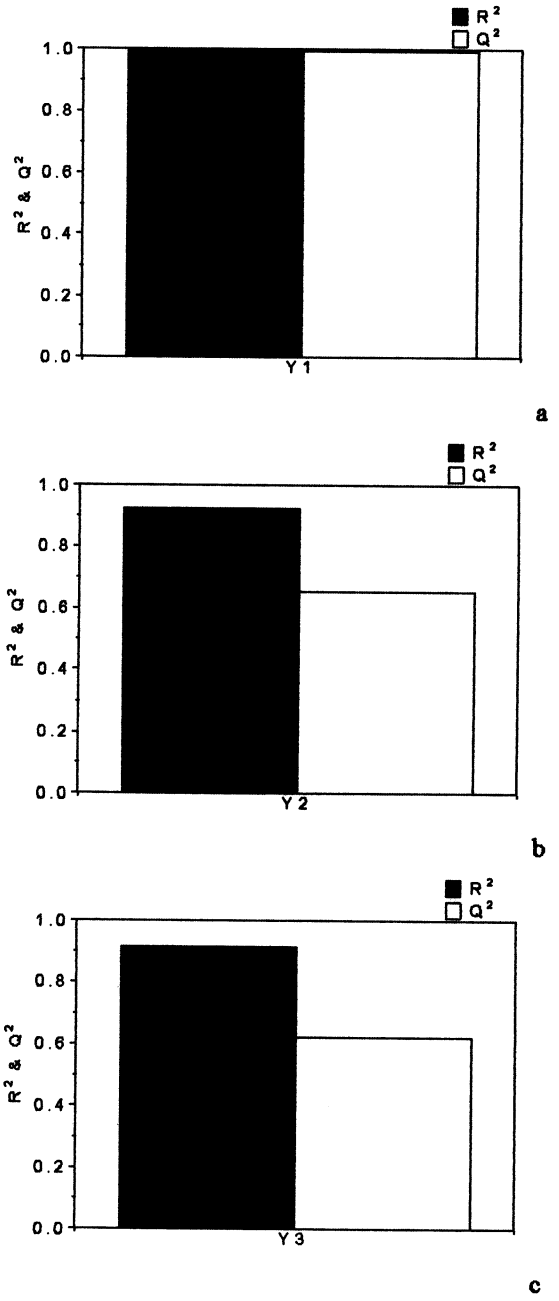

Fig. 2. Quality of the fit of the model for each response. R^2 is the fraction of variation of the response explained by the model and Q^2 is the fraction of the variation of the response that can be predicted by the model.

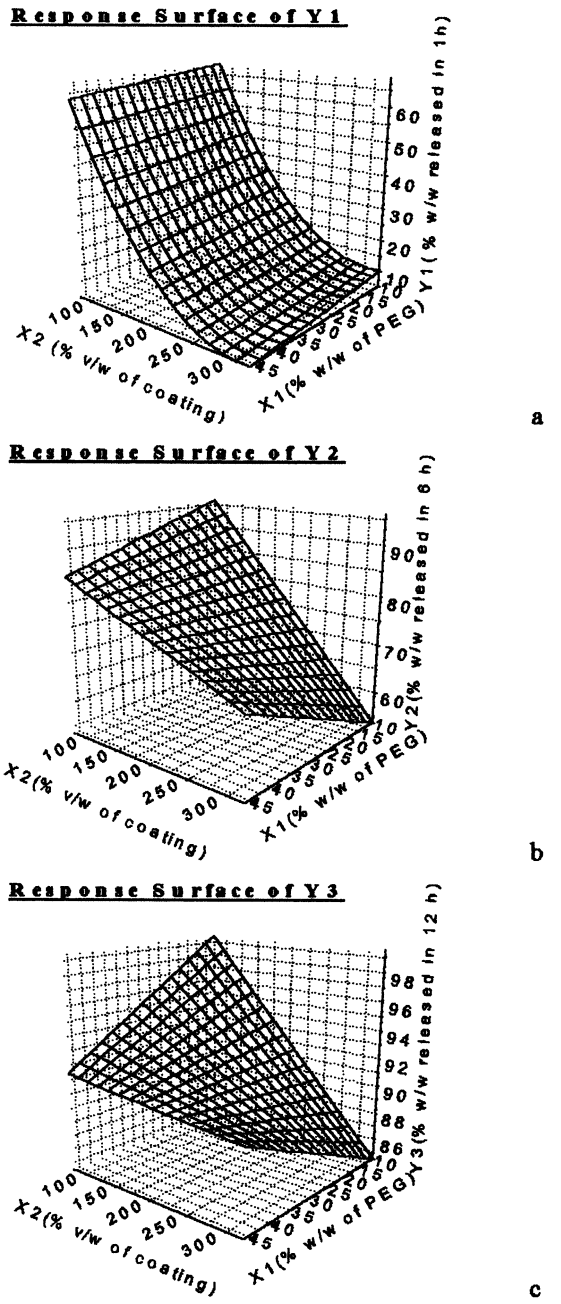

Fig. 3. (A–C): Three-dimensional plot for the evaluation of the effect of variable factors X_1 and X_2 on the response surfaces (a) Y_1; (b) Y_2; (c) Y_3.

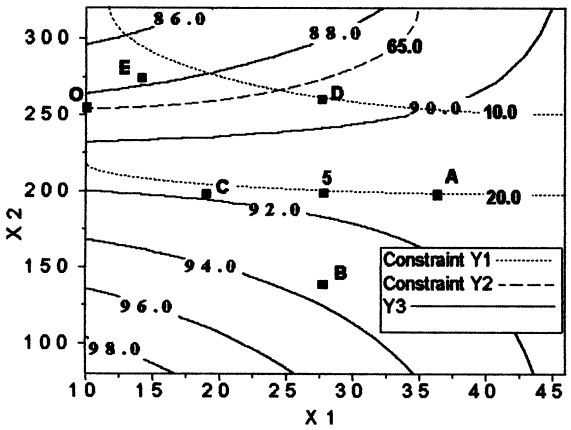

Fig. 4. Contour plot showing the optimization procedure.

$$F = 1 - e^{-k_1 t} \quad (8)$$

where F is the fraction of drug release at different sampling intervals t and k_1 is the first order process kinetic constant.

Results of fitting of the data to the above mentioned models are reported in Table 7. Statistical parameters for the value of the dissolution constant (k) in Hixon–Crowell model show smaller root mean square (RMS) deviations, small standard deviations and small confidence intervals. Visual examination of the fraction released versus time curve in the presence of the input data points corroborated with previously described statistical parameters leads us to the conclusion that the Hixon–Crowell model provides the best correlation.

4. Conclusions

The main objective of the study was to prepare coated propranolol HCl pellets with a predictable release rate. Data confirm the choice of an appropriate plasticizer/polymer combination and the amount of coating dispersion may be critical in

Table 6
Levels of factors, predicted and observed responses of the predicted optimal formulations (O and E) and some additional points

Formulation	Levels of variables		Y_1		Y_2		Y_3	
	X_1	X_2	Predicted	Observed	Predicted	Observed	Predicted	Observed
5	28	200	21.26	20.56	75.85	77.89	91.45	90.80
A	37	200	20.02	18.40	76.40	75.80	91.15	92.30
B	28	140	39.71	42.50	83.14	88.32	93.47	101.25
C	19	200	22.51	24.62	75.29	78.15	91.75	95.20
D	28	260	10.62	8.45	68.56	70.28	89.43	92.35
E	15	275	10.98	13.47	62.93	64.28	87.83	92.67
O	10	255	13.70	16.48	65.00	68.54	88.63	94.54

Table 7
Nonlinear data fitting parameters applied to dissolution of propranolol HCl from optimized formulation (standard deviations and confidence intervals are calculated for estimated parameters, k)

Dissolution models	k[a]	RMS[b]	Standard deviation	95% Confidence interval[c]
Baker–Lonsdale	0.0128	0.1129	0.0027	0.0065–0.0191
Hixon–Crowell	0.0480	0.0084	0.0005	0.0467–0.0494
Higuchi	0.2417	0.0783	0.0159	0.2049–0.2784
First order	0.1674	0.0280	0.0054	0.1549–0.1799

[a] k, constant of the process.
[b] RMS, root mean square deviations between measured and calculated values.
[c] Confidence intervals were computed using univariate method according to the Student's $t_{(\alpha,df)}$ statistics criterion: CI = Estimated parameter $\pm$ ($t_{(\alpha,df)} \times$ S.D.) (Lu et al., 1996).

determining the performance of sustained release pellets.

An experimental design was used to optimize the release of propranolol HCl from sustained release pellets. The tested parameters were: plasticizer concentration and volume of coating applied to the pellets in a classical coating pan. Using equations describing the model it was possible to derive isoresponse graphs and therefore to have an excellent tool for the interpretation of data. The most effective factor in determining the rate of release was the volume of coating.

A sustained release propranolol-loaded pellet formulation with satisfactory release characteristics was successfully prepared using Eudragit RS as coating agent. Data from the optimized pellets were fitted according to four well-known kinetic models. The best correlation of data was obtained with the Hixon–Crowell model.

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