Drug Development and Industrial Pharmacy, 25(11), 1167–1176 (1999)

RESEARCH PAPER

Optimization of a Tablet Containing Chlorthalidone

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ABSTRACT

In pharmaceutical technological research, optimization studies generally deal with the search for the formulation that is as effective and as functional as possible. The effect of a formulation parameter (the amount of lactose in the composition of the tablets) and of a technological parameter (compression pressure) on four physical characteristics (tablet thickness, friability, hardness, and drug dissolution rate) of tablets containing the antihypertensive drug chlorthalidone were studied. The results obtained indicate that, in the development of a tablet formulation, it is possible to identify the most suitable formulation by applying a simple optimization method. The effect of the microclimatic stress (temperature and humidity) was also evaluated, and it was found that the optimized tablets were no longer within limits that had been established for them. This may indicate that it is opportune to keep the storage conditions of the excipients under control before their use.

INTRODUCTION

In pharmaceutical technological research, optimization studies generally deal with the search for the formulation that is as effective and as functional as possible. This does not mean that the formulation that is developed is the best, but rather that it is the most suitable in the adopted experimental conditions. Therefore, such studies are in continuous evolution as to the function of the operational conditions and equipment.

During the development of a formula, many composition and manufacturing variables should be considered. These variables can be classified in two groups: the independent variables, referring to the formulation and the manufacturing process (which are under the formulator's control), and the dependent variables or responses, which are related to the chemical and physical properties of the tablets.

Therefore, optimization is obtained by establishing a relationship among the various types of variables; the

values for the independent variables should be fixed, while the values of the dependent variables are linked immediately to the former by means of a mathematical model. Optimization techniques for pharmaceutical formulation and processing, as well as theoretical and practical aspects, can be found in the pharmaceutical literature (1–3).

This optimization study uses statistical methods, such as the experiments using factorial design models (4–6), central composite design (7,8), the sequential simplex technique (9,10), and other derived methods (11,12).

EXPERIMENTAL

Experimental Design

In this paper, the optimization study of tablets containing an antihypertensive drug (chlorthalidone) was carried out using factorial designed experiments by choosing two independent variables: X_1, the relative amounts of total lactose and microcrystalline cellulose, and X_2, the compression pressure expressed in kN. In our case, the two preparation variables (the lactose content and the compression pressure) were selected with three levels (high, medium, low).

Since the variables were interconnected, the experimental design in this case was a full 3^2 factorial, and nine formulations were prepared. The tablet formulations, chosen according to the experimental design, are reported in Table 1.

The amounts of chlorthalidone and magnesium stearate remained constant, while the percentages of lactose and microcrystalline cellulose changed.

Every mixture was pressed with a different compression pressure, and then we chose three values of compression pressure (high, medium, low) that determined an adequate hardness of the tablets. In Table 1, the compression pressure values are also shown.

The value of the dependent variables (or responses) Y is influenced by the two independent variables (X_1 and X_2). The dependent variables Y include tablet thickness, friability, hardness, and drug dissolution rate.

Polynomial models relating the response variables to the independent variables were generated by a backward stepwise regression analysis program. The analysis may be performed on a polynomial of the form

$$y = a_0 + a_1x_1 + a_2x_2 + a_3x_1^2 + a_4x_2^2 + a_5x_1x_2 + \cdots \quad (1)$$

where the terms are retained or eliminated according to standard stepwise regression techniques.

In this case, it was possible to reduce the system using the following simple equation:

$$y = a_0 + a_1x_1 + a_2x_2 \quad (2)$$

where y = dependent variable, x_1 = lactose/lactose + microcrystalline cellulose, and x_2 = compression pressure (KN).

Y represents any given response (tablet thickness, friability, hardness, and drug dissolution rate), and a_0, a_1, and a_2 represent the regression coefficients for the various terms containing levels of the independent variables. One equation is generated for each dependent variable. The values of the dependent variables Y are mean ± SD; statistical analyses were performed, and a p value of .05 was considered significant.

Table 1

Tablet Formulations Performed According to the Adopted Experimental Design

Batch Number	X_1: Lactose Content (Lactose/Lactose + Microcrystalline Cellulose)	X_2: Compression Pressure	Composition (%)			
			Chlorthalidone	Lactose	Microcrystalline Cellulose	Magnesiun Stearate
1a	0.1 (low)	9.75 (low)	20	7.95	71.55	0.5
2b	0.1 (low)	10.00 (medium)	20	7.95	71.55	0.5
3c	0.1 (low)	10.50 (high)	20	7.95	71.55	0.5
2a	0.5 (medium)	10.00 (low)	20	39.75	39.75	0.5
2b	0.5 (medium)	10.50 (medium)	20	39.75	39.75	0.5
2c	0.5 (medium)	11.00 (high)	20	39.75	39.75	0.5
3a	0.7 (high)	10.00 (low)	20	55.65	23.85	0.5
3b	0.7 (high)	10.25 (medium)	20	55.65	23.85	0.5
3c	0.7 (high)	10.50 (high)	20	55.65	23.85	0.5

The statistic technique of the minima squares was applied, allowing us to obtain an equation that is able to interpolate the experimental data and reduce experimental errors. The simple chosen model adequately fit our experimental data.

The effect of the microclimatic stress (temperature and humidity) on the responses was also evaluated. The objective was to verify if the resulting tablets were able to maintain their characteristics after stress.

Materials and Equipment

The following materials were used: chlorthalidone, micronized and screened (USP XXIII/NF XVIII); dried β-lactose (EP III); magnesium stearate (EP III); and microcrystalline cellulose (USP XXIII/NF XVIII).

The following equipment was used: high-speed mixer (Roram); hardness tester (Schlenninger Tecnogalenica); micrometer (Mitutoyio Italiana); rotary tablet machine (Manesty); granulometry tester (Alpine Air Screen); friability tester (Erweka); dissolution apparatus (Prolabo, USP XXIII/NF XVIII); analytical balance (Mettler AE 100); and spectrophotometer (Perkin-Elmer).

METHODS

Mixing of the powders to be compressed was performed at a rotation speed of 90 min^{-1} for 15 min. The mixtures were compressed into 6.3–6.4 mm diameter tablets at a weight of 100 ± 5 mg. The tableting machine was equipped with an apparatus for the compression pressure control.

All technological tests were performed on 10 samples for any formulation, with the exception of dissolution tests (6 samples).

Tablets were checked for diameter and thickness. Friability was checked after a 5-min rotation at 20 rpm, and the percentage weight loss was determined. Hardness was measured using an electronic instrument and is expressed in Kg.

The drug dissolution rate was determined using a beaker containing 900 ml of deionized water in a thermostatic bath (T = 37°C ± 0.5°C). Nets of stainless steel placed on the bottom of the beaker kept the tablets from sticking to the walls. Stirring (100 ± 2 rpm) allowed the circulation of the solvent, but did not influence the particles formed during tablet disaggregation. Of the solution, 5 ml was collected at intervals of 5, 10, 20, 30, 40, 50, and 60 min, and the volume of the solution was restored by adding 5 ml of fresh solvent at the same temperature. The solution was filtered through a Millipore filter (0.45 μm), and the concentration of the released chlorthalidone was recorded at 275 nm. The concentration of the released drug was extrapolated from the calibration curve obtained by standard solutions. The dissolution rate was expressed as percentage of the drug released as a function of time.

Microclimatic stress was performed on tablets in blister packaging stored at 37°C and 75% relative humidity (RH) for 30 days.

RESULTS AND DISCUSSION

In Table 2, the resulting dependent variables (thickness, friability, hardness, and drug dissolution rate) of the

Table 2

Dependent Variables of the Different Tablet Formulations

Formulation	Thickness (cm)	Friability (% Weight Loss)	Hardness (kg)	Drug Dissolution Rate (% Drug Released in 1 hr)
1a	3.022 (SD 0.201)	0.201 (SD 0.035)	4.80 (SD 0.125)	86.50 (SD 1.29)
2a	2.790 (SD 0.302)	0.147 (SD 0.045)	5.66 (SD 0.235)	92.34 (SD 1.284)
3a	2.386 (SD 0.123)	0.079 (SD 0.007)	11.82 (SD 0.235)	82.50 (SD 1.237)
1b	2.704 (SD 0.304)	0.154 (SD 0.024)	3.70 (SD 0.145)	90.78 (SD 2.35)
2b	2.362 (SD 0.215)	0.129 (SD 0.055)	9.28 (SD 0.124)	78.75 (SD 1.412)
3b	2.170 (SD 0.365)	0.067 (SD 0.047)	12.28 (SD 0.154)	65.25 (SD 2.356)
1c	2.694 (SD 0.178)	0.300 (SD 0.056)	3.14 (SD 0.156)	94.97 (SD 2.319)
2c	2.492 (SD 0.123)	0.170 (SD 0.024)	5.04 (SD 0.099)	78.75 (SD 1.237)
3c	2.338 (SD 0.312)	0.122 (SD 0.056)	7.86 (SD 0.165)	83.25 (SD 2.359)

Table 3

Equation Coefficients Obtained by Regression Analysis for the Dependent Variables

Dependent Variable	a_0	a_1	a_2	R
Thickness	9.18 (SD 0.604)	−0.19 (SD 0.087)	−0.64 (SD 0.060)	.979
Friability	1.69 (SD 0.380)	0.13 (SD 0.054)	−0.15 (SD 0.037)	.871
Hardness	−81.45 (SD 7.061)	−6.04 (SD 1.011)	8.86 (SD 0.697)	.983
Drug dissolution rate	293.30 (SD 52.106)	2.69 (SD 7.465)	−20.51 (SD 5.141)	.856

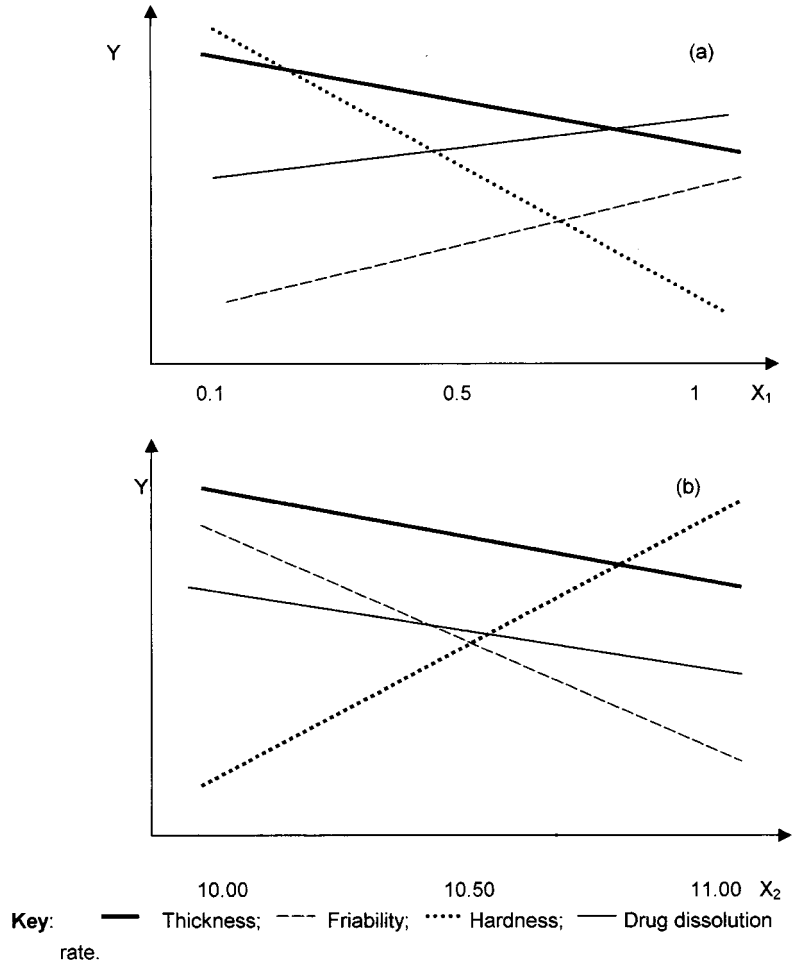

Figure 1. In these graphs, the dependent variables Y are obtained as a function of X_1 and of X_2; in the first graph (a), X_2 is maintained constant, and X_1 is changed; in the second graph (b), X_1 is maintained constant and X_2 is changed.

different tablet formulations are shown. In the mathematical dimension optimization calculation, we used the thickness values due to the fact that the diameter variables showed no significant difference (6.37 ± 0.01 cm).

The resulting a_0, a_1, and a_2 regression coefficients are shown in Table 3. In Fig. 1, by maintaining constant X_2 first and changing X_1 and then maintaining constant X_1 and changing X_2, the dependent variables Y were obtained, respectively, as a function of X_1 and of X_2. As shown in the same figure and as we can see from the positive or negative regression coefficients, by increasing the amount of lactose, thickness and hardness decrease, while friability and drug dissolution rate increase. In contrast, by increasing the compression pressure, thickness, friability, and drug dissolution rate decrease, while hardness increases.

Thus, it was possible to build up the contour plots for each dependent variable (Fig. 2). The figure shows the contour plots for the tablet thickness, friability, hardness, and drug dissolution rate. Contour plots illustrate combinations of the independent variables that produce the same response.

In Fig. 3, the contour plot obtained by superimposing the limits of acceptability of the dependent variables is

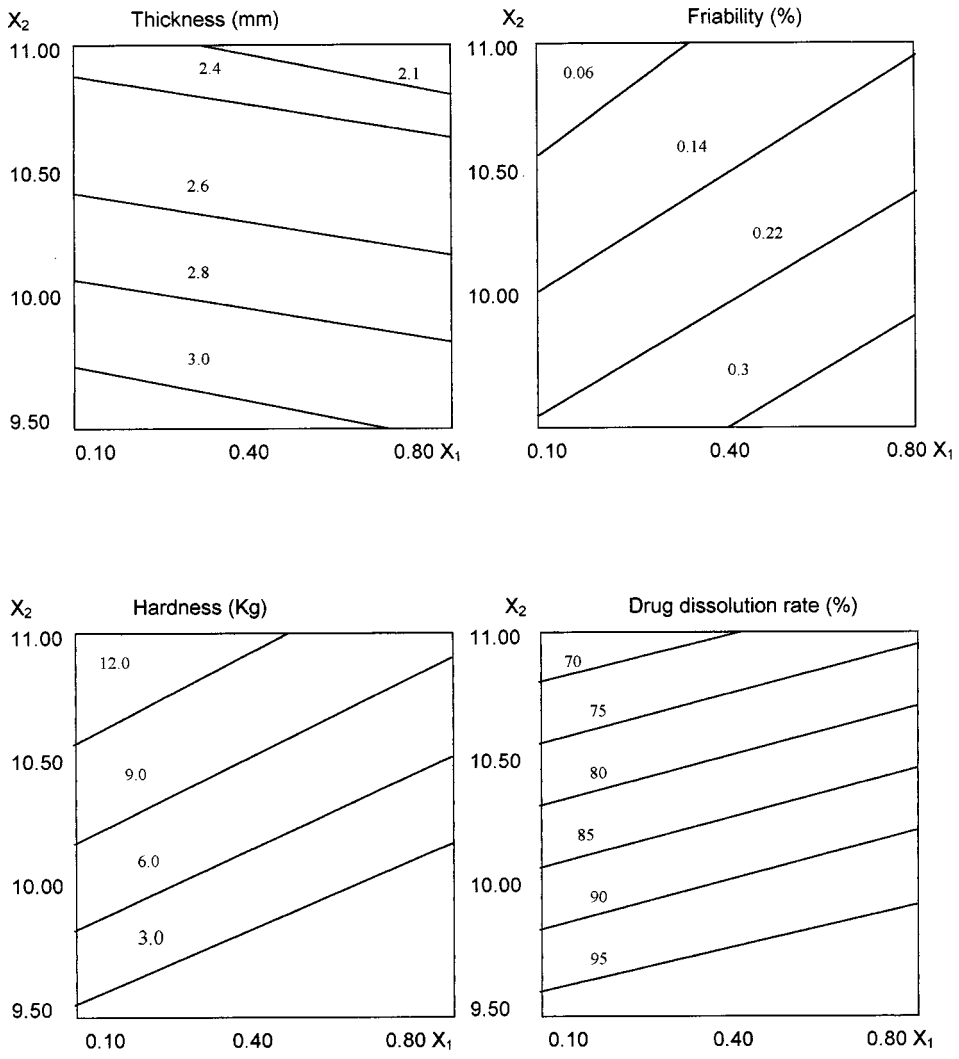

Figure 2. Contour plots for each dependent variable.

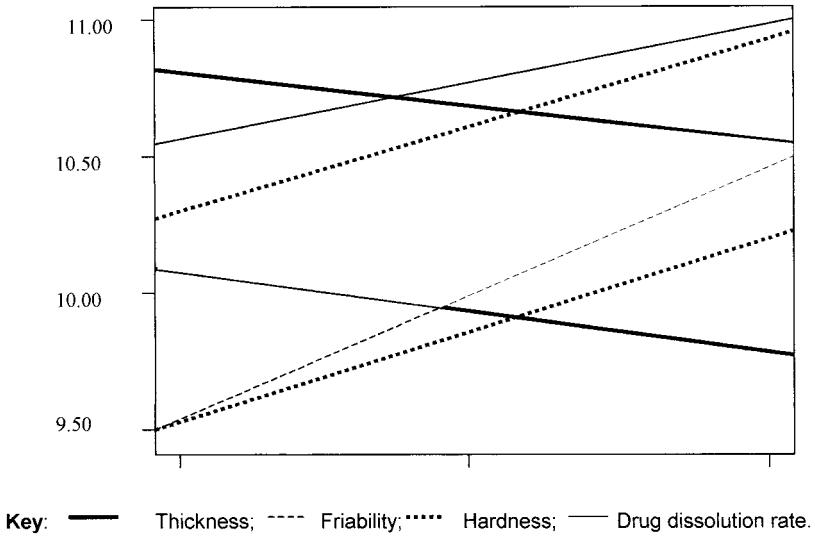

Figure 3. Superimposed contour plots.

represented. These limits are derived both from the contour plots (2.4–2.8 mm for thickness, 3–9 Kg for hardness) and from technological considerations (the maximum acceptable limit for friability was 0.22%, and the minimum acceptable limit for dissolution was 75%).

In this graph, an area appears that delimits the characteristics (dependent variables) that satisfy the established limits. Thus, the most likely optimal formulations may be evaluated: the 1b, 2a, and 3b formulations shown in Table 1 are included in the optimal area. When the tablets obtained were stored in blister packaging at 37°C and 75% RH for 30 days, the values of some characteristics were changed. In Table 4 the dependent variables (thickness, friability, hardness and drug dissolution rate) of the different tablet formulations after storage are shown. The a_0, a_1, and a_2 regression coefficients of the tablets after storage are shown in Table 5.

Figure 4 shows the graphs of the dependent variables Y after storage, obtained as a function of X_1 and of X_2. As shown in the same figure and as we can see from the positive or negative regression coefficients, by increasing the amount of lactose, the thickness, hardness, and dissolution rate decrease, while friability increases. As we increased the compression pressure, the thickness, friability, and drug dissolution rate decreased, while hardness increased. When compared to the data regarding the tab-

Table 4

Dependent Variables of the Different Tablet Formulations After Storage

Formulation	Thickness (cm)	Friability (% Weight Loss)	Hardness (kg)	Drug Dissolution Rate (% Drug Released in 1 hr)
1a	3.110 (SD 0.302)	0.287 (SD 0.001)	3.96 (SD 0.221)	90.95 (SD 3.271)
2a	2.871 (SD 0.123)	0.203 (SD 0.099)	4.48 (SD 0.235)	95.00 (SD 2.199)
3a	2.451 (SD 0.201)	0.065 (SD 0.031)	9.96 (SD 0.145)	87.65 (SD 4.241)
1b	2.764 (SD 0.254)	0.292 (SD 0.028)	2.88 (SD 0.176)	86.65 (SD 3.361)
2b	2.385 (SD 0.117)	0.176 (SD 0.054)	8.24 (SD 0.188)	83.30 (SD 2.399)
3b	2.246 (SD 0.221)	0.181 (SD 0.041)	9.88 (SD 0.271)	67.81 (SD 2.341)
1c	2.714 (SD 0.178)	0.377 (SD 0.039)	1.62 (SD 0.221)	92.65 (SD 4.321)
2c	2.512 (SD 0.123)	0.263 (SD 0.044)	3.73 (SD 0.109)	87.32 (SD 2.212)
3c	2.368 (SD 0.312)	0.083 (SD 0.014)	5.98 (SD 0.214)	82.01 (SD 3.401)

Table 5

Equation Coefficients Obtained by Regression Analysis for the Dependent Variables After Storage

Dependent Variable	a_0	a_1	a_2	R
Thickness	9.23	−0.28	−0.63	.971
	(SD 0.755)	(SD 0.108)	(SD 0.074)	
Friability	2.18	0.17	−0.20	.763
	(SD 0.732)	(SD 0.105)	(SD 0.072)	
Hardness	−71.24.45	−6.05	7.73	.971
	(SD 8.152)	(SD 1.168)	(SD 0.804)	
Drug dissolution rate	276.73	−2.39	−18.47	.918
	(SD 5.180)	(SD 5.040)	(SD 3.471)	

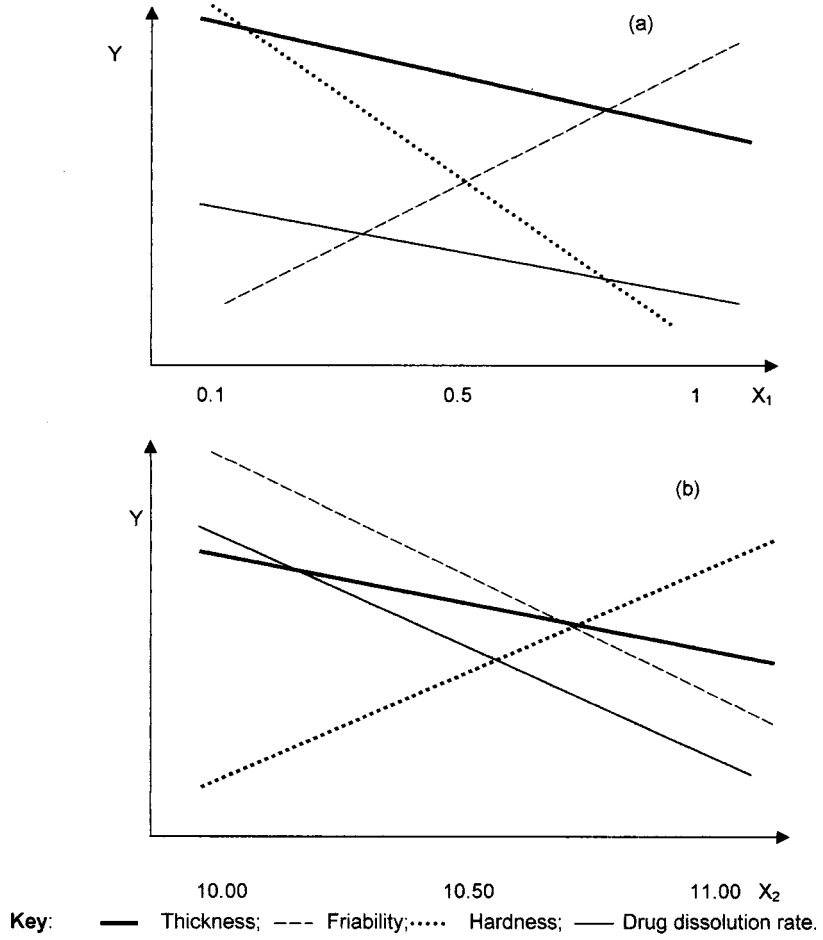

Figure 4. In these graphs, the dependent variables Y are obtained as a function of X_1 and of X_2; in the first graph (a), X_2 is maintained constant, and X_1 is changed; in the second graph (b), X_1 is maintained constant, and X_2 is changed. Y is obtained after storage.

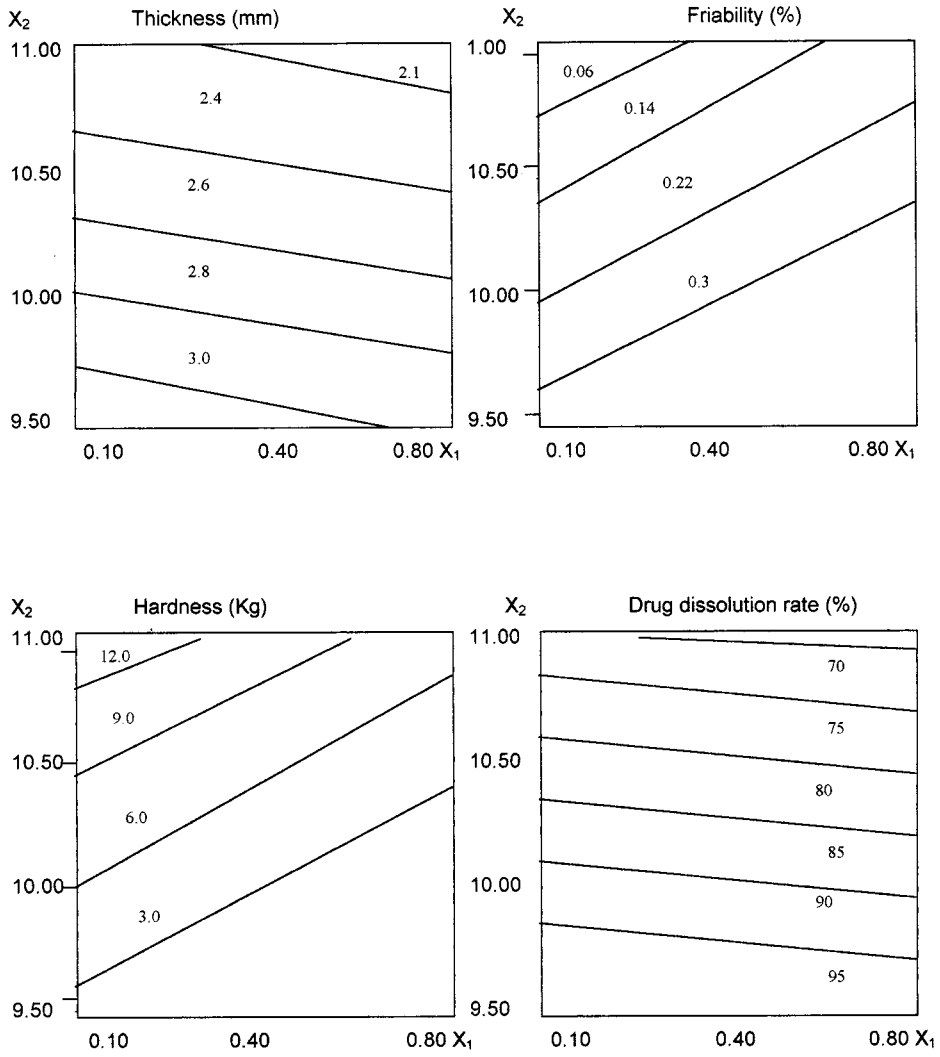

Figure 5. Contour plots for each dependent variable after storage.

lets that had not been stored, we found that the only parameter that changed its positive or negative regression coefficients was the dissolution rate: In the tablets that had not been stored, the dissolution rate decreased as the amount of lactose increased, while after storage, the dissolution rate increased as the amount of lactose increased.

Figure 5 shows the contour plots obtained for the same dependent variables studied after storage. The most severe storing conditions decreased the mechanical characteristics such as friability and hardness. As a consequence of these modifications, a more rapid tablet disaggregation and a faster drug dissolution rate were observed. The tablet thickness did not present significant changes.

The overlap of these contour plots allowed us to identify a new optimal formulation area (Fig. 6). In fact, the 1b, 2a, and 3b formulations did not drop into the area as a consequence of the changes induced in the dependent variables by the stress conditions. On the contrary, the 2b formulation fell into the optimal area with a good relationship between experimental and theoretical values after storage (Table 6).

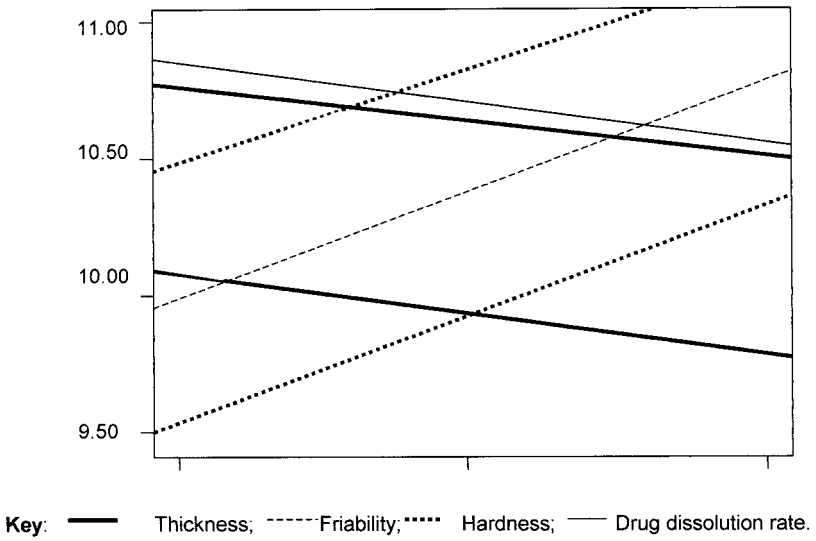

Figure 6. Superimposed contour plots after storage.

CONCLUSIONS

The results obtained in the present study indicate that, in the development of a tablet formulation, it is possible to determine the most suitable formulation by applying a simple optimization method. Such a method foresees the use of a simplified equation that, by establishing a relationship between two independent variables, allows us to obtain the dependent variable. Building up and superimposing the contour plots for the different independent variables (thickness, friability, hardness, and drug dissolution), it is possible to determine an area that delimits the characteristics of the dependent variables, satisfying all the established limits in order to obtain acceptable tablets.

When the obtained tablets were stored in blister packaging for 30 days at 37°C and 75% RH, the values of some characteristics changed. Therefore, by superimposing the relative contour plots, a new optimal formulation area was delimited; in this area, it was possible to identify the new conditions in order to obtain acceptable tablets. This may indicate that it is opportune to keep the storage conditions of the excipients under control before using them as they could be modified with consequent formation of tablets that no longer respect the previous optimization conditions.

Table 6

Comparison Between the Experimental and the Theoretical Values for the Most Probable Optimal Formulation, After Storage

y = Dependent Variable		Batch 2b
Thickness	E	2.385 ± 0.117
	T	2.44
Friability	E	0.176 ± 0.054
	T	0.18
Hardness	E	8.24 ± 0.188
	T	7.00
Dissolution	E	83.30 ± 2.399
	T	79.6

E = experimental value; T = theoretial value.

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