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OPTIMIZATION OF A SLOW-RELEASE TABLET FORMULATION CONTAINING SODIUM SULFATHIAZOLE AND A MONTMORILLONITE CLAY

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ABSTRACT

A slow-release tablet formulation containing high levels of a montomorillonite clay, Veegum F®, was initially developed by trial and error. The present study was undertaken to utilize an approach involving statistics with the aid of computer science to develop a formula with desired characteristics. An experimental design for five factors was employed. The five factors consisted of levels of various components and the amount of compressional force applied while tableting. The response or dependent variables included tablet weight uniformity, hardness and friability; and percent drug in solution after 3 hours of dissolution testing. The response variables were fitted to a second-order polynomial with the five formulation factors as the independent variables. The resulting equations were used to optimize the formulation with respect to the response variables. The results indicated that a formulation with the desired characteristics could be predicted by the technique.

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INTRODUCTION

There is an increasing interest in the development and utilization of controlled release drug delivery systems. Oral dosage forms have received a great deal of attention, since they are the most convenient to administer.

In the previous reports (1-3) of this series, the development of a slow-release tablet formulation containing a high level of magnesium aluminum silicate was described. The release was found to follow first-order kinetics with several possible mechanisms involved. The mechanisms included hydration of the clay, diffusion of the soluble model drug (sodium sulfathiazole) through a hydrated gelatinous barrier and attrition of the gel barrier.

The term "optimized" in pharmaceutical product development has been used in the past to suggest that a product had been improved to satisfy the objectives of the development scientist. However, today this term usually implies that statistics and computers have been utilized to define the best possible product. There have been several reports (4-12) in the pharmaceutical literature on this subject. The major emphasis in these studies was the optimization of conventional dosage forms.

The formulation of the slow-release tablet characterized previously (1-3) resulted from a trial and error process. However, in this report the use of statistics with the aid of computer science to predict a formulation with the desired characteristics will be described.

EXPERIMENTAL

The materials and procedure to prepare tablets was reported earlier (1). To quantitate compressional force, the following procedure was used:

1. Three tablets of each formulation were compressed with a hydraulic press[1] using the same size punch and die set (7/16" flat face bevel edge) as in the tablet machine[2];
2. The amount of pressure used to compress tablets was measured with the aid of a load cell[3] calibrated to 2000 pounds;
3. The hardness of the three tablets was then measured[4] and a mean value calculated;
4. This mean value was then used to calibrate the single punch tablet machine.

Although this method of quantitating the force involved in the compression of tablets did not take into account the dwell times, hardness results (Table 1) were reproducible for tablets made with the same formulation and compression force. The pressures employed are shown in Table 2.

The experimental design (Table 3) required the preparation of 27 tablet formulations. Tablets made from each of the formulations were subjected to dissolution[5], hardness, friability[6] and uniformity tests. These tests represented the response variables. The independent variables (investigator controlled) included: compressional force (X_1), montomorillonite[7] level (X_2), dextrose-maltose[8] level (X_3), magnesium stearate[9] level (X_4), and starch[10] level (X_5). Calcium phosphate dihydrate[11] was used as the filler.

The translation of the levels in the experimental design into experimental values appears in Table 4. The experimental units were arbitrarily chosen. The zero level represented the level of the variables used to prepare the prototype formulation (1). The levels for additional experiments were then calculated by adding or subtracting the experimental unit. For

TABLE 1

HARDNESS OF THREE TABLETS

Formula	Hardness (kg) mean ± S. D.
1	5.58 ± 0.38
2	9.0 ± 0.0
3	6.16 ± 0.14
4	10.4 ± 0.63
5	5.6 ± 0.6
6	11.25 ± 0.0
7	7.6 ± 0.4
8	10.9 ± 0.38
9	6.2 ± 0.5
10	9.9 ± 0.38
11	6.7 ± 0.28
12	9.7 ± 0.72
13	6.1 ± 0.14
14	8.8 ± 0.14
15	7.0 ± 0.5
16	11.6 ± 0.57
17	4.7 ± 0.29
18	11.8 ± 0.52
19	8.1 ± 0.38
20	9.5 ± 0.0
21	8.2 ± 0.28
22	8.7 ± 0.28
23	9.6 ± 0.5
24	8.2 ± 0.14
25	7.1 ± 0.38
26	9.4 ± 0.38
27	9.25 ± 0.0

TABLE 2

EXPLANATION OF COMPRESSIONAL FORCE FACTOR**

Experimental Factor Level	Dial Reading*	Design Factor Level
0.25	1050	-1.547
0.5	1200	-1
1.0	1500	0
1.5	1800	+1
1.75	1950	+1.547

*read from a Load Cell, Enerpac Model LH-101

**Three tablets of the formulas were compressed at the dial reading corresponding to the specific level in the design for that formula. The tablets were tested for hardness and the values recorded. The average hardness was used to calibrate the single punch tablet machine.

example, + 1 in the design indicated that one experimental unit was added to the zero level and vice versa for -1. The $\pm$ 1.547 values represented extreme values for each factor and the experimental levels were calculated by adding or subtracting one-half experimental unit to or from the experimental levels corresponding to +1 or -1 in the design.

Each of the four responses was fit[12] to a second-order polynomial of the type:

$$Y = b_o + b_1X_1 \quad \ldots + b_5X_5$$
$$+ b_{12}X_1X_2 \quad \ldots + b_{45}X_4X_5$$
$$+ b_{11}X_1^2 \quad \ldots + b_{55}X^2_5$$

where Y = response variable

b = regression coefficient

X = independent variable

TABLE 3

EXPERIMENTAL DESIGN

	Factor Level in Experimental Units				
Trial	X_1	X_2	X_3	X_4	X_5
1	-1	-1	-1	-1	+1
2	+1	-1	-1	-1	-1
3	-1	+1	-1	-1	-1
4	+1	+1	-1	-1	+1
5	-1	-1	+1	-1	-1
6	+1	-1	+1	-1	+1
7	-1	+1	+1	-1	+1
8	+1	+1	+1	-1	-1
9	-1	-1	-1	+1	-1
10	+1	-1	-1	+1	+1
11	-1	+1	-1	+1	+1
12	+1	+1	-1	+1	-1
13	-1	-1	+1	+1	+1
14	+1	-1	+1	+1	-1
15	-1	+1	+1	+1	-1
16	+1	+1	+1	+1	+1
17	-1.547	0	0	0	0
18	+1.547	0	0	0	0
19	0	-1.547	0	0	0
20	0	+1.547	0	0	0
21	0	0	-1.547	0	0
22	0	0	+1.547	0	0
23	0	0	0	-1.547	0
24	0	0	0	+1.547	0
25	0	0	0	0	-1.547
26	0	0	0	0	+1.547
27	0	0	0	0	0

TABLE 4

TRANSLATION OF VARIABLES

Factor	Level in Design				
	-1.547	-1	0	+1	+1.547
			Experimental		Levels
Compressional Force Factor eu* = 0.5	0.25	0.5	1.0	1.5	1.75
Montmorillonite eu = 5%	22.5	25.0	30.0	35.0	37.5
Dextrose eu = 2.5%	10.5	11.5	14.0	16.5	17.75
Magnesium Stearate eu = 0.5%	0.25	0.5	1.0	1.5	1.75
Starch eu = 5%	12.5	15.0	20.0	25.0	27.5

*Experimental unit

The four response equations were subsequently fed into a computer optimization program[13]. The objective was to find the levels of the five independent variables that would provide tablets with the desired responses.

RESULTS AND DISCUSSION

The experimental design was of the orthagonol type for five factors (13). It enabled the five independent variables to be changed at the same time to study the effect of each variable as if they were changed one at a time. It also permitted the evaluation of the influence of interactions between the variables. The first sixteen trials represented a one-half factorial design for five factors and the factors were varied at two levels (+1 and -1). The remaining trials were designed to test the effect of each variable

at an upper and lower extreme while holding the other four at a constant level. This type of design was used previously in the optimization of a rapid release tablet formulation with success (5). Tablet weight uniformity, hardness, friability and percent drug in solution after three hours of dissolution testing were chosen as the response variables. The tablets made from each formulation were tested and the results appear in Table 5. Each response was fit to the second-order polynomial and the regression coefficients are shown in Table 6. The R^2 values for the four equations are also given and as can be seen, a reasonably good fit was obtained for the hardness, friability and dissolution responses. The poor fit for the weight uniformity response was probably due to the lack of variation of the parameter used. The coefficient of variation or relative standard deviation was the parameter and as shown in Table 5 it did not change significantly for the various formulations. Further examination of the other three equations revealed that the equation for friability may have been a less than desirable fit. An F test for the regression equations was performed and the calculated F value was significant at the 95% level for all except the friability equation (Table value of $F_{20,6,\alpha=0.05} = 3.87$). However, attempts to use other models for the friability data did not improve the results and the second order polynomial model was determined to be the best. The correlation coefficients for predicted and experimental values were also good for the dissolution, hardness and friability responses (see Table 7).

The optimum formulation could now be obtained. A formulation with the following characteristics was desired.

1) minimum amount of drug release after 3 hours;

2) hardness of 8-12 kg;

3) friability value less than 0.8%.

TABLE 5

RESPONSES FOR TWENTY-SEVEN FORMULAS

Formula	Weight Uniformity (C.V., %)n=20	Hardness (kg) mean, n = 6	Friability (%), n=10	Dissolution (%), n = 3
1	0.85	5.0	0.88	24.56
2	0.84	9.75	0.03	30.42
3	0.49	5.53	0.0005	42.98
4	1.45	9.9	0.12	24.69
5	0.68	5.5	0.41	47.1
6	0.94	11.33	0.07	27.98
7	0.64	6.68	0.42	31.24
8	0.88	8.95	0.09	47.84
9	0.67	4.93	0.7	34.67
10	0.66	9.7	0.12	24.84
11	0.89	6.1	0.27	25.84
12	0.88	8.18	0.12	37.11
13	0.7	4.83	0.67	29.69
14	1.09	7.6	0.16	40.93
15	0.88	6.08	0.33	48.27
16	1.07	10.4	0.13	82.26
17	0.37	4.48	0.88	34.27
18	0.98	10.7	0.09	28.55
19	0.61	8.88	0.15	30.78
20	1.53	6.45	0.06	37.91
21	1.59	6.58	0.52	32.7
22	0.45	7.18	0.1	39.5
23	0.87	7.68	0.11	34.83
24	1.8	6.48	0.29	35.56
25	0.83	5.95	0.28	46.36
26	0.76	8.4	0.17	28.77
27	0.7	7.78	0.16	32.36

Therefore, the objective was to minimize the dissolution function with the hardness and friability equations used as constraining functions. This was accomplished with the aid of an optimization computer program (GRG2) that was able to solve problems of this type.

As long as the dissolution function was continuous there would be a maximum or minimum value. The maximum or minimum value of the function

TABLE 6

REGRESSION COEFFICIENTS

Variable	Weight Uniformity	Hardness	Friability	Dissolution
	-1.41	16.7	2.14	-22.8
X_1	1.07	4.5	-2.227	1.8
X_2	-0.06	-0.749	0.24	2.76
X_3	0.136	0.14	-0.273	2.79
X_4	-1.25	-1.6	0.704	3.7
X_5	0.204	0.369	0.082	-0.54
X_1X_1	-0.632	0.74	0.439	-6.58
X_2X_2	0.0007	0.0088	-0.00237	-0.0136
X_3X_3	-0.0008	-0.0207	0.00512	0.0703
X_4X_4	0.541	-0.16	-0.068	0.15
X_5X_5	-0.00419	0.0001	-0.00023	0.0436
X_1X_2	0.0188	-0.127	0.043	0.035
X_2X_3	-0.00315	0.0126	0.0044	-0.0311
X_3X_4	0.0565	-0.114	0.006	-0.341
X_4X_5	-0.0297	0.0265	-0.027	0.188
X_1X_3	0.0075	0.039	0.004	0.015
X_1X_4	-0.223	-0.82	-0.01	1.91
X_1X_5	0.0017	0.157	0.019	0.279
X_2X_4	0.0112	0.1055	-0.001	-0.183
X_2X_5	0.00263	0.00315	-0.0001	-0.0503
X_3X_5	-0.00575	0.014	-0.0012	-0.1086
R^2 (%)	60.3	95.6	91.0	98.4
F	0.454	6.5	3.03	18.8

would occur at the point where the partial derivatives all equaled zero or where one of the partial derivatives became discontinuous. This point would be a stationary point. A single function could have many stationary points, e.g., local maximums or minimums. The task was even more difficult when the constraints were added to the problem.

TABLE 7

EXPERIMENTAL AND PREDICTED RESPONSES

Formula	Wt. Uniformity		Friability		Hardness		Dissolution	
	Exp.	Pred.	Exp.	Pred.	Exp.	Pred.	Exp.	Pred.
1	.85	.793	.88	.893	5.0	5.25	24.56	25.00
2	.84	.849	.03	.044	9.75	9.9	30.42	30.13
3	.49	.579	.012	.082	5.53	5.19	42.98	43.25
4	1.45	1.541	.12	.124	9.9	9.77	24.69	25.23
5	.68	.484	.41	.399	5.5	5.62	47.10	46.49
6	.94	.746	.07	-.018	11.33	11.66	27.98	27.65
7	.64	.526	.42	.400	6.68	6.52	31.24	31.46
8	.88	.832	.09	.071	8.95	8.69	47.84	47.33
9	.67	.779	.7	.765	4.93	4.99	34.67	34.91
10	.66	.771	.12	.108	9.7	9.97	24.84	25.36
11	.89	1.081	.27	.325	6.1	5.87	25.84	26.91
12	.88	1.137	.12	.177	8.18	7.85	37.11	37.45
13	.7	.606	.67	.633	4.83	5.07	29.69	29.89
14	1.09	1.062	.16	.125	6.08	5.72	40.93	40.40
15	.88	.932	.33	.362	10.4	10.25	48.27	48.29
16	1.07	1.124	.13	.085	4.48	4.72	28.26	28.56
17	.37	.41	.88	.768	10.7	10.65	34.27	33.24
18	.98	.838	.09	.178	8.88	7.79	28.55	28.73
19	.61	.863	.15	.217	6.45	7.72	39.78	31.23
20	1.53	1.175	.06	-.031	6.58	6.74	37.91	36.61
21	1.59	1.083	.52	.341	7.18	7.21	32.70	30.82
22	.45	.855	.1	.255	7.68	7.66	39.50	40.54
23	.87	1.177	.11	.133	6.48	6.69	34.83	35.22
24	1.8	1.391	.29	.243	5.95	6.46	35.56	34.33
25	.83	.694	.28	.164	8.4	8.08	46.36	47.28
26	.76	.794	.17	.262	7.6	7.74	28.77	27.00
27	.7	.98	.16	.226	7.78	7.26	32.36	34.69
Correlation Coefficient	.776		.954		.978		.992	

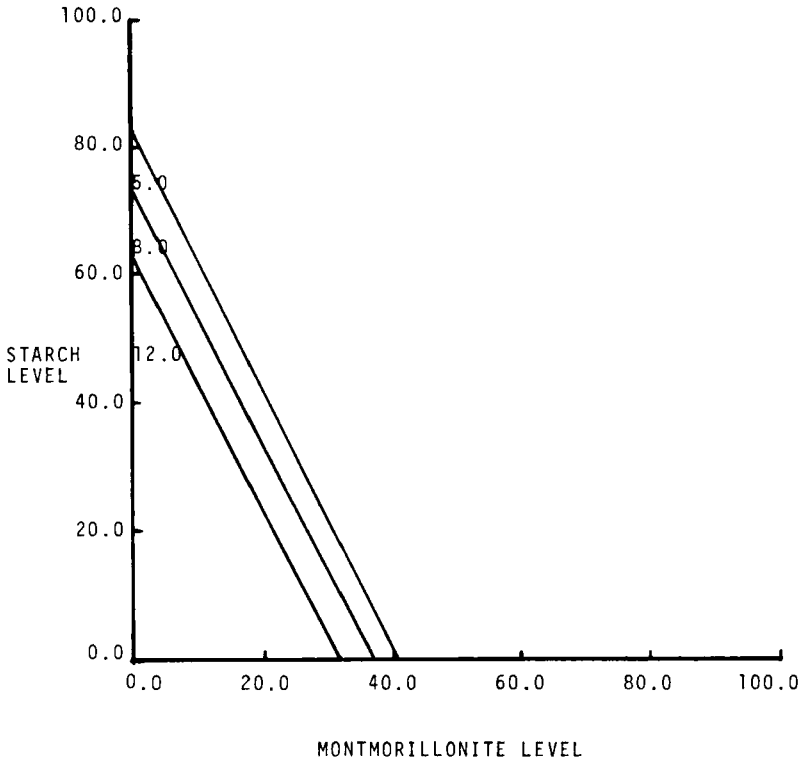

FIGURE 1

Interaction effects for montmorillonite and starch on tablet hardness: 5.0, 8.0 or 12.0 kg.

GRG2 was an optimization program that utilized a generalized reduced gradient method to search for the maximum or minimum of a function with or without constraints. The logic of these search techniques was to start at some base point and by iterative processes determine a new set of values for the variables. The function was analyzed at the new point and if the requirements for a maximum or minimum were not met, the process was continued. A more detailed discussion of optimization procedures can be found in references 14-18.

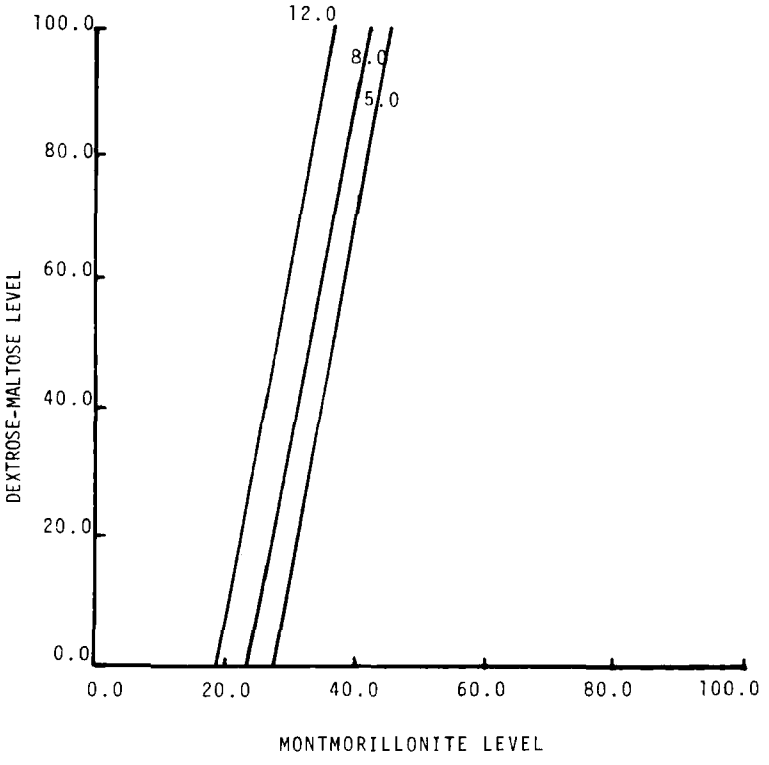

FIGURE 2

Interaction effects of dextrose-maltose and montmorillonite on tablet hardness: 5.0, 8.0, or 12.0 kg.

The objective and constraint functions were fed into the program. The ranges for the variables were:

force factor	0.25 - 1.75%
montmorillonite	5.0 - 50.0%
dextrose-maltose	0.0 - 80.0%
magnesium stearate	0.5 - 1.50%
starch	0.0 - 20.0%

After 13 searches the results were that a tablet formulation with the following levels of the variables:

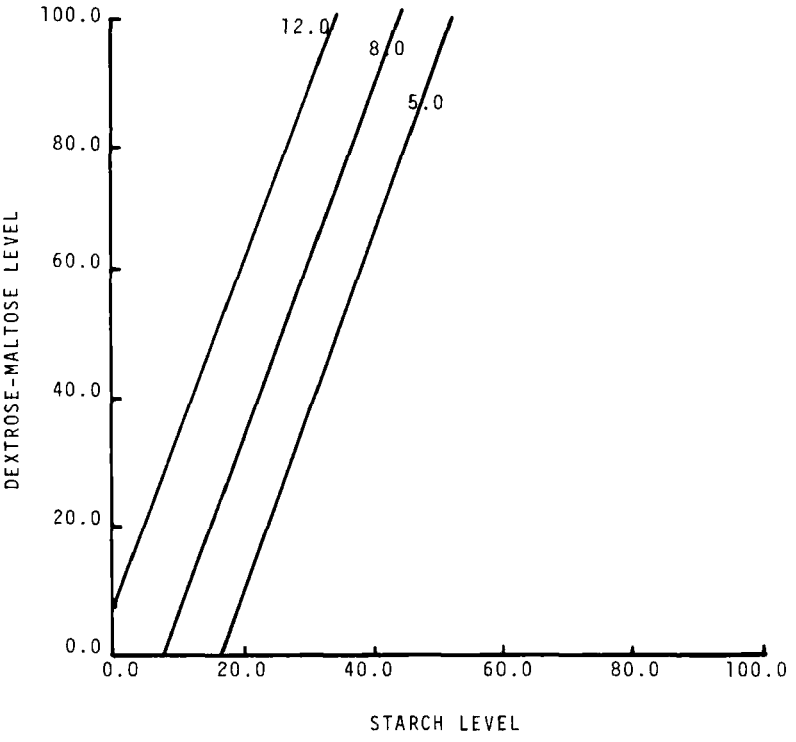

FIGURE 3

Interaction effects of dextrose-maltose and starch on tablet hardness: 5.0, 8.0 or 12.0 kg.

force factor	1.1
veegum	29.98%
dextrose-maltose	14.00%
magnesium stearate	0.96%
starch	20.00%

would release 33.25% drug in solution in three hours, have a friability value of 0.1% and a hardness of 7.76Kg. This formulation was essentailly the same as the prototype formulation which corresponded to number 27 in the experimental design. As can be seen in Table 7, the experimental and predicted results are in excellent agreement. Therefore, it was concluded that the prototype formula-

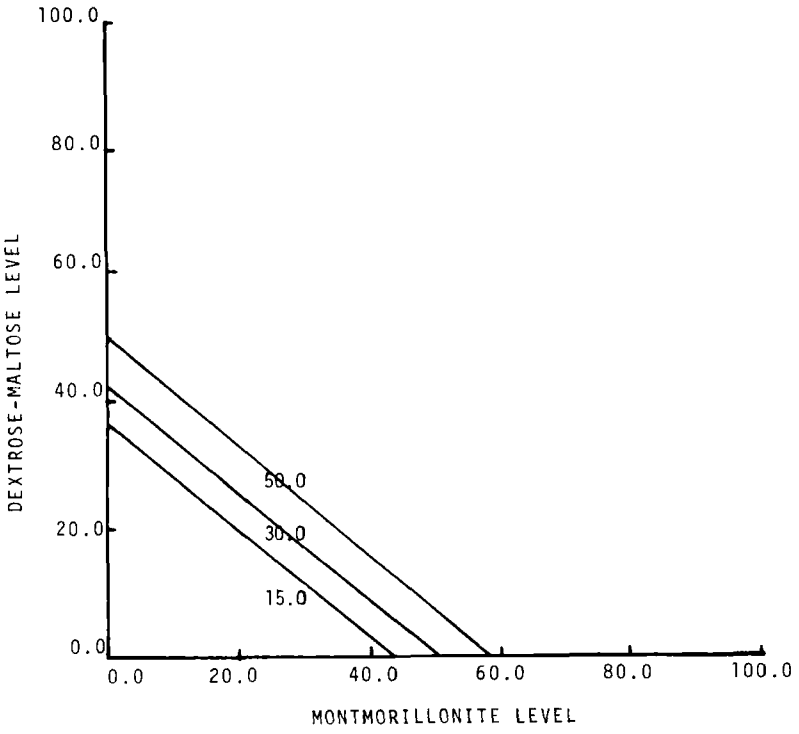

FIGURE 4

Interaction effects of dextrose-maltose and montmorillonite on tablet dissolution: 15, 30 or 50% dissolved in 3 hours.

tion developed by trial and error was the optimum formulation which was also predicted by a computer utilization.

The second-order polynomial model used to fit this data can be thought of as representing a surface. One way to geometrically illustrate this surface in two dimensions was to plot one independent variable vs. another while holding the response level and the other variables constant (19). The resulting curves are called contour lines. A second-order equation defined a quardric surface which would be difficult to represent in two dimensions (19). How-

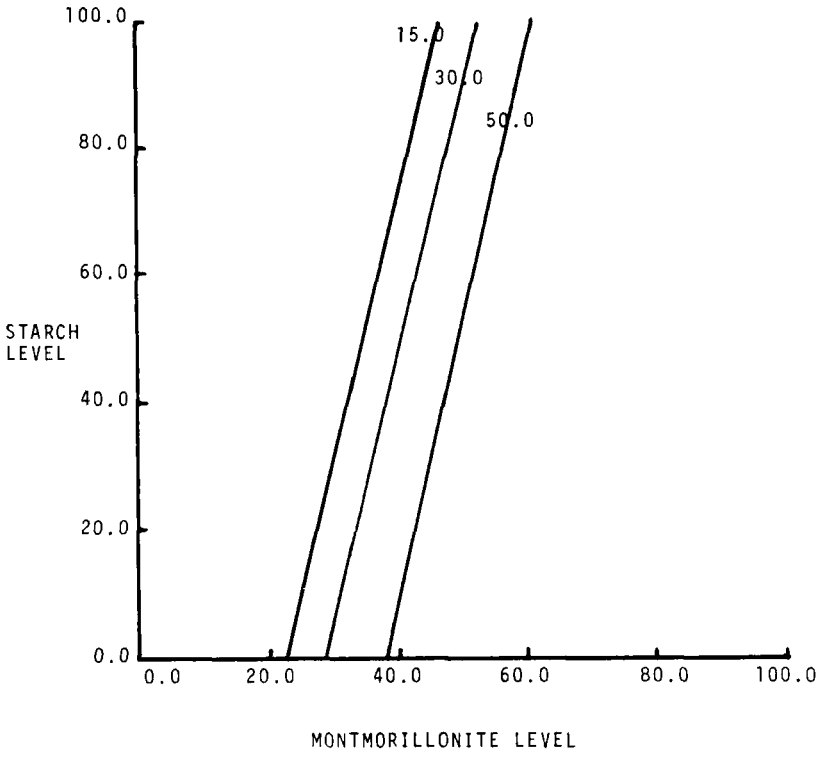

FIGURE 5

Interaction effects of starch and montmorillonite on tablet dissolution: 15, 30 or 50% drug dissolved in 3 hours.

ever, information regarding one factor's dependence upon another factor is obtainable from these plots. Contour plots for generated data in the reasonable experimental range are given in Figures 1-6. These plots indicated that:

1) To maintain the same tablet hardness, the starch level must be decreased and the dextrose-maltose level slightly increased when the montmorillonite level is increased (Figures 1 and 2); and that the dextrose-maltose level must be increased when the starch level is increased (Figure 3).

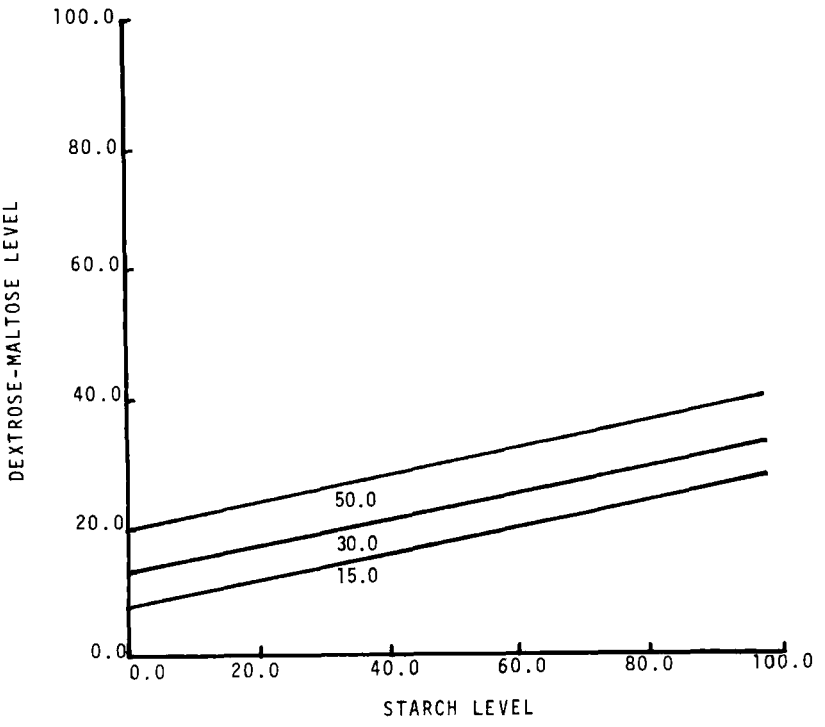

FIGURE 6

Interaction effects of dextrose-maltose and starch on tablet dissolution: 15, 30 or 50% drug dissolved in 3 hours.

2) To maintain a constant dissolution response the dextrose-maltose level should be decreased and starch level slightly increased when the montmorillonite level is increased (Figures 4 and 5); and that the dextrose-maltose level should be slightly increased when the starch level is increased (Figure 6).

As indicated by Down et al. (11), these plots were useful for gaining information about the formulation.

Another type of plot contains the response plotted as a function of each variable. To represent all five variables in one plot

TABLE 8

UNNORMALIZED AND NORMALIZED FACTOR LEVELS

Factor	Unnormalized Level	Normalized Level (%)
X_1	0.25	0.0
	0.5	16.7
	1.0	50.0
	1.5	83.3
	1.75	100.0
X_2	5.0	0.0
	10.0	14.3
	20.0	42.3
	30.0	71.4
	40.0	100.0
X_3	0.0	0.0
	20.0	40.0
	30.0	60.0
	40.0	80.0
	50.0	100.0
X_4	0.25	0.0
	0.5	14.3
	1.0	42.3
	1.5	71.4
	2.0	100.0
X_5	0.0	0.0
	10.0	20.0
	20.0	40.0
	40.0	80.0
	50.0	100.0

the factor levels had to be normalized (10). The following equation was used to normalize the different levels:

$$N = \frac{X - L}{H - L} \times 100 \qquad \text{Eq. 2}$$

where N is the normalized factor level, X is the unnormalized factor level, L and H are the lowest and highest levels for a specific factor respectively. The unnormalized and normalized levels for the

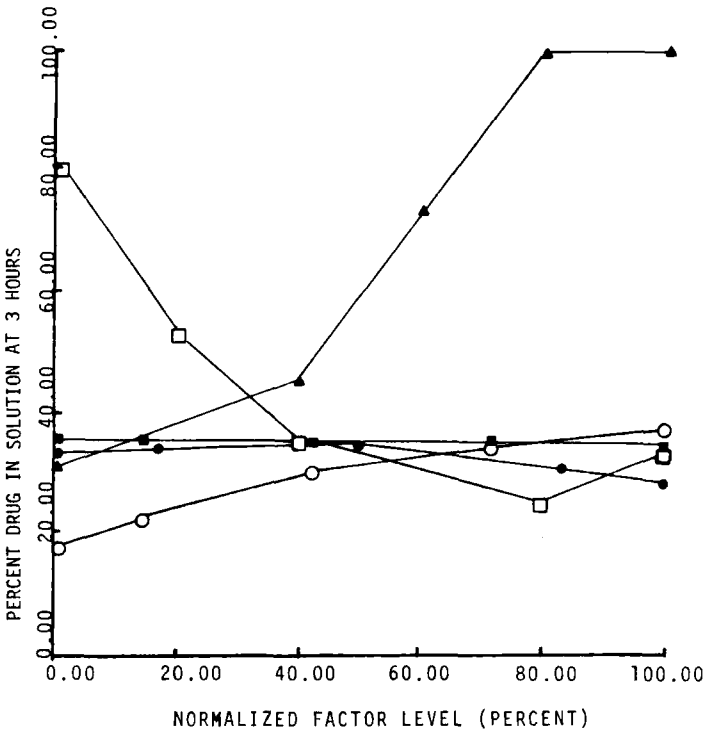

FIGURE 7

Percent drug in solution at 3 hours as a function of each independent variable. Key: ▲ montmorillonite; □ starch; ● compressional force; ○ dextrose-maltose; ■ magnesium stearate.

five factors are given in Table 8. The dissolution and hardness responses are plotted as a function of each independent variable in Figures 7 and 8 respectively. The other four variables were held constant at their optimum levels. As shown in Figure 7, the percent drug in solution at 3 hours decreased with increasing starch levels and increased with increasing montomorillonite levels. This response appeared to be influenced little by the change in compressional force and magnesium stearate levels. Figure 8 shows that tablet hardness decreased with an increase in montomorillonite level up to about 80 percent. Hardness also increased with an increase in starch

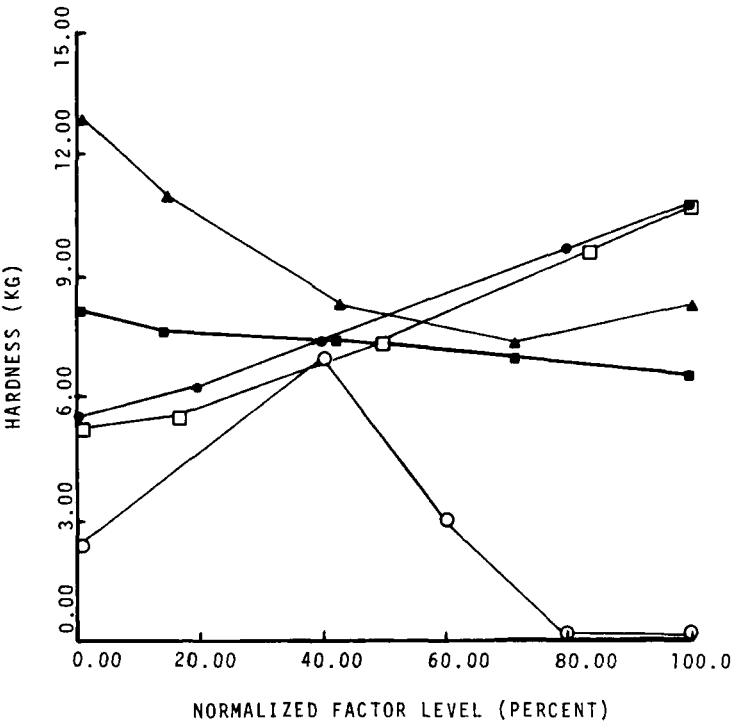

FIGURE 8

Tablet hardness as a function of each independent variable. Key: ▲ montmorillonite; ● starch; □ compressional force; ○ dextrose-maltose; ■ magnesium stearate.

level and compressional force. This response appeared to be independent of a change in the level of magnesium stearate. The plot shows that as the level of dextrose-maltose increased there was a point where a further increase caused the tablets to become softer. As is very evident, these plots were also an asset for gaining knowledge about the formulation.

The results of the optimization technique indicated that this procedure was very useful. It was possible to completely characterize the slow-release tablet by preparing twenty-seven trial formulations. The method not only enabled the prediction of a formulation with the desired characteristics, but also made it possible to gain important

information concerning the physicochemical properties of the dosage form.

FOOTNOTES

1. Carver Press
2. Stokes, Model F
3. Enerpac, Model LH-101
4. Herbelein
5. Hanson, Six Spindle Apparatus
6. Roche Friabilator, 100 Revolutions
7. Veegum F®, R. T. Vanderbilt
8. Emdex®, Edward Mendell Co., Inc.
9. City Chemical Corporation
10. Starch 1500®, Colorcon Co.
11. Emcompress®, Edward Mendell Co., Inc.
12. MINITAB Statistical Package
13. GRG2

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