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Optimization of Tablet Formulations Containing Talc

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Abstract - An optimized direct compression tablet formulation of a conventional theophylline tablet was developed using the technique of response surface methodology and successive quadratic programming (SQP). The response surfaces were obtained from fitting data generated from a second-order uniform-precision rotatable hexagonal experimental design. The tablet formulation was optimized for mean in vitro dissolution time using disintegration time, ejection force, friability and hardness, as constraints within the experimental region by the SQP technique. The response surface model was validated by preparing and evaluating the predicted formulation. The characteristics of the tablet formulation were analyzed by principal component analysis. Sensitivity analysis for the optimal solution was performed for each constraint, while all remaining constraints were held constant. The

robustness of the response surface model was evaluated by simulation for error in the compression force values.

Introduction

This paper reports studies of the application of mathematical techniques, novel to the pharmaceutical industry, for the optimization of tablet formulations containing talc as a major component. Previous papers have indicated that tablets containing talc have advantages as compared with tablets containing magnesium stearate in terms of both reduced liability to capping and good compaction (1,2). it is well established that mathematical optimization techniques are of considerable value in pharmaceutical formulation (3).

From the experimental data obtained from an appropriate statistical design a mathematical model can be derived, which can then be solved by an optimization technique to give an optimal solution.

Experimental Design-Response surface methodology are sets of efficient experimental designs for use in the optimization process (4-7). Response Surface methodology (RSM) attempts to model unknown functional relationships between the response variable and the independent variables by appropriately designed experiments. Suitable approximation to the true functional relationship can usually be achieved by a low order polynomial fitted to the relatively small region of interest as defined by the experimental range of the independent variables. A response

surface obtained from an experimental design can be of the first order and therefore follow the properties of proportionality and additivity. Available response surface designs for fitting first order model include simplex (8), super modified simplex (9), fractional factorial (10), Plackett-Burman (4) and Koshal (4) experimental designs. If significant curvature is present in the true surface then a second order polynomial is fitted. The complete second order response surface (Y) can be written as follows for n variables:

$$\hat{Y} = b_O + [\sum_{h=1}^{n} b_h X_h = [\sum_{h,k=1}^{n} b_{hk} X_h X_k \qquad h \leq k. \qquad (1)$$

Where X_h and $_k$ are independent variables, b_O and b_h are first order regression coefficients, while $b_{hk}(h \_ k)$ are second order regression coefficients.

A second order response surface design requires that each of the quantitative factors, must assume at least three levels (4,5). In addition the number of experimental runs must be greater than or equal to the number of coefficients in the second order model, for a given set of independent variables (4-7). At the same time it is desirable to use a design that allows a maximal return for minimum number of experiments. The ratio of the number of the experimental runs, to the maximum number of coefficients in the second order response surface model is termed redundancy (6). The second order response surface designs include factorial (11), computer-optimized (12), Box-Behnken (4), and a central composite design based on a factorial (13,14), fractional factorial (3, 15-17) and simplex (18) designs.

Experimental designs are further classified into orthogonal, rotatable and uniform-precision types according to the variance properties of the predicted response (4-7). Although estimators of regression coefficients would be uncorrelated, that is the covariances between the pure second order coefficients would be zero, the variance of predicted response is a function of both distance and direction from center of an orthogonal non-rotatable design (4-7). Whereas, except at the design center, the variance of predicted response for a rotatable design is less than that of orthogonal design and is only a function of distance but not of the direction from the center of the design (4-7). Therefore, from the point of view of precision of the predicted value, the property of rotatability is more desirable than orthogonality in an experimental design. Furthermore, the rotatable designs are valuable in canonical analysis of response surfaces where rotation of a design around its center would not change the variance of the predicted response. Therefore it is always useful to use a rotatable experimental design. The rotatable design property is obtained by choice of peripheral points locci and does not depend on the number of center points. Equiradial type designs, such as pentagon, hexagon and octagon, consist of points equally spaced at an unit distance from the origin of a circle and are rotatable (5,7). Conditions to be met for any experimental design to be rotatable (4-7) are specified in (Eqs. 1-4).

$$\left[\sum_{i=1}^{n} X_{hi} X_{ki} = 0 \quad (h,k = 1,2,.....1;\ h = k) \right. \tag{1}$$

$$\left[\sum_{i=1}^{n} X_{gi} X_{hi} X_{ki} = 0 \right. \tag{2}$$

$$\left[\sum_{i-1}^{n} X_{fi} X_{gi} X_{hi} X_{ki} = 0 \qquad \{(f,g) = (h,k)\} \right. \tag{3}$$

$$\left[\sum_{i=1}^{n} X_{hi}^4 = 3\left[\sum_{i=1}^{n} X_{hi}^2 X_{ki}^2 \quad (h = k) \right. \right. \tag{4}$$

To obtain a design which is both rotatable and orthogonal the number of center points required becomes large (4-7). For example, a 3*3 factorial is a non-rotatable, orthogonal experimental design and it would require seven additional center points with modified axial spacing of ± 1.414 to achieve properties of rotatability and orthogonality. However, with a smaller number of central points it is possible to obtain an uniform-precision rotatable design (5,7). Repetition of an experimental trial under same controllable conditions allows determination of the estimate of mean sum of square pure error for the lack of fit test and a better estimate of the response at the design center. Additionally, replication of center points can allow experiments to be run in orthogonal blocks (4-7). The order of experiment should be randomized to assist in minimizing effect of any uncontrollable factors that exert a consistent bias (6).

The use of unconstrained optimization methods such as steepest descent technique has been reported for enteric film coating of tablets (10). The purpose of constrained non-linear optimization is to obtain values of independent variables that will produce the desired optimum response for the chosen objective function subject to various constraints

(6,19). With constrained optimization problems, the optimal values for independent variables must simultaneously satisfy the constraints (6,19). Constrained non-linear optimization techniques have also been reported in the pharmaceutical literature. These include (a) Grid Search technique as applied to tablet formulations (3,13,15,16) and solid dispersions (14,17), (b) a classical Lagrangian method (11) as applied to tablet formulation, and more recently (c) a successive unconstrained minimization technique (SUMT) for a solid dispersion (18). Using sequential prediction analysis procedure and Grid Search technique, Bohidar et. al. (16) optimized multiple potency tablets. These constrained nonlinear optimization techniques are accesible on microcomputers (13,15,20) and they are compared with the successive quadratic programming (SQP) technique in Table I. Data on efficiency and reliability have been reported (21). The shortest time required to obtain the final optimal solution (efficiency) and the ability to converge to final optimal solution (reliability), for a wide variety of problems (21) are important requirements of any successful optimization technique (19). Where as the Lagrangian, SUMT or SQP give an unique solution, the Grid Search method provides multiple solutions which have to be further evaluated to give an unique solution (15,18). Hence, the Grid Search method is the slowest. Although the SQP, Lagrangian and SUMT all use the gradient method, such as the method of steepest descent, which is fast when the search starts far away from the optimum, only the SQP uses the

Table 1

Comparison of different optimization techniques

Properties	Constrained Grid Search	Non-Linear Lagrangian Method	Optimization Techniques SUMT	SQP
Accessible	Yes	Yes	Yes	Yes
Efficiency	Slowest	Fast	Slow	Fastest
Reliability	Very Good	Good	Moderate	Very Good

Newton method near the optimum and is thus able to converge faster (19,22). The Newton method requires the use of the inverse of hessian matrix. The successive quadratic programming method can employ the Newton method near the optimum in the Broydon-Fletcher-Goldfarb-Shano (BFGS) Method. The BFGS is a quasi Newton technique (19,22) in that it is able to update the Lagrangian hessian matrix of the quadratic subproblem (19,22) at each iteration such that it approaches the inverse of hessian matrix near the optimum. The BFGS method is most successful at keeping the Lagrangian hessian matrix positive definite for the minimization problem, provided the initial update matrix is also positive definite such as the identity matrix (19,22). The reliability of the Grid Search method is very good because, it does not require a continuously differentiable function (15), unlike the Lagrangian, SUMT or SQP (19,22). The reliability of SQP is improved because it combines the

concepts of Lagrange multipliers (as in the Lagrangian method), with the penalty function (P) approach (as in SUMT), to achieve optimum solution (19,22). The algorithm for the SQP method is shown in Fig 1. The objective of the present study was to evaluate an efficient and a reliable optimization technique for obtaining a solution to a non-linear optimization problem. The technique consists of an uniform-precision rotatable hexagonal equiradial type experimental design and successive quadratic programming. The aim was to increase the drug dissolution rate from the tablet without adversely affecting other properties of the tablet. It is believed that this work represents the first publication dealing with these specific optimization methods for pharmaceutical purposes.

Experimental Section

Materials - The direct compression formulations had the following percentage (w/w) composition:
Theophylline 25.0% (Sigma Chemical, St. Louis, Missouri), Alpha Press 300 talc 15.0% (Cyprus Industrial Minerals Compnay, Mobile, Alabama), corn starch 2 to 4% (Sigma Chemical, St. Louis, Missouri) and direct tableting lactose 56 to 58% (Scheffield Products, Norwich, New York).

Choice of Second Order Designs - The two factor uniform-precision rotatable hexagonal equiradial type design required the same number of experimental runs as the 3*3 factorial and the central composite design, but provided improved design properties, see Table II. The two

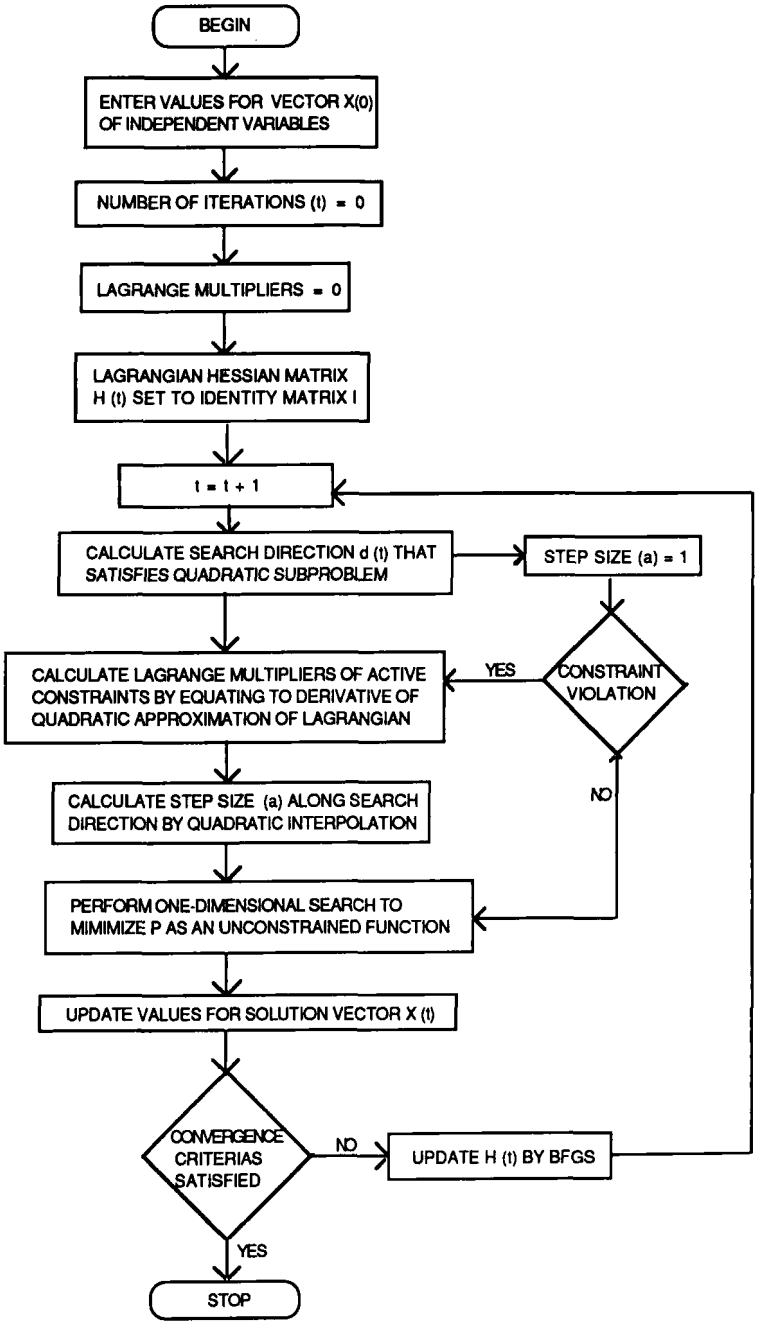

Fig 1 SQP algorithm

Table II

Second Order Design

Properties	Experimental Design 3 * 3 Factorial	Central Composite	Equiradial Hexagon
Runs	9	9	9
Redundancy	1.5	1.5	1.5
Orthogonal	Yes	No	No
Rotatable	No	Yes	Yes
Uniform-Precision	No	No	Yes

independent variables studied consisted of compression force (X_1) and the percent of disintegrant (X_2), which are a process and formulation variable, respectively. All other processing and formulation variables were kept constant. The effect of these two independent variable were studied using the uniform-precision rotatable hexagonal experimental design as shown in Table III.

Formulations and Preparation - The controlled conditions for material storage, processing and manufacturing were maintained at 24 $\pm$ 2°C and at relative humidity of 26 $\pm$ 3%. All powders were sieved through a mesh 20 sieve. The components of the various tablet formulations, each batch weighing 150 grams, were mixed for 1.5 minutes in a WAB type T2C turbula mixer. The tablet formulations were compressed, according their random order number, on an instrumented Stokes B-2 rotary tablet press

Table III

Experimental design for two factors

Experimental Unit	Random Order Number	Factor Levels Coded X1	Form X2	Physical Units X1 (KN)*	X2 (%w/w)
1	2	1.0	0.000	15.11(0.30)	3
2	5	0.5	0.866	13.38(0.31)	4
3	6	-0.5	0.866	9.99(0.22)	4
4	8	-1.0	0.000	8.45(0.18)	3
5	1	-0.5	-0.866	9.97(0.23)	2
6	9	0.5	-0.866	13.58(0.35)	2
7	3	0.0	0.0	11.95(0.19)	3
8	4	0.0	0.0	11.84(0.27)	3
9	7	0.0	0.0	11.77(0.29)	3

*Value in parenthesis is standard deviation.

which was used as described previously (23). The tooling consisted of a single standard concave set of punches of size 3/8 inch. The press speed was set at twenty five r.p.m. The compression and the ejection forces data were collected for thirty tablets per formulation, in three runs. Each run comprised of ten tablets. No tablet capping or laminating problems occurred during tablet manufactur.e All the tablets were manufactured on the same day.

Determination of In Vitro Properties - Ten tablets were evaluated for crushing strength (Erweka Hardness Tester; Chemical and Pharmaceutical Industry, New York, New York). Six tablets were evaluated for friability, during which no tablet capping or lamination occurred (Erweka Friabilator;

Chemical and Pharmaceutical Industry, New York, New York). Six tablets were evaluated for disintegration time using discs (U.S.P. Disintegration Time Tester, Vanderkamp; Vankel Industries, Chatham, New Jersey). The dissolution apparatus (Paddle method, U.S.P.; Vanderkamp; Van-kel Industries, Chatham, New Jersey). The medium and procedure described in the U.S.P. were applied to three tablets per formulation. Dissolution samples of 10 ml were withdrawn at 5, 10, 15, 20, 30, and 45 minute time points intervals. The dissolution medium volume was kept constant by adding the same volume of fresh (37^{o}C) solvent. Additionally, to ensure total release of drug, the agitation speed was increased to 150 r.p.m. for an additional 45 minutes after all the times samples had been obtained, this sampling time is referred to as T_{∞}. The samples were diluted and the concentration were measured on a Diode Array Spectrophotometer (Hewlett Packard; Loveland, Colorado) at a wavelengths of 272 nm as specified in the U.S.P. (24). The predicted formulation tablets were analyzed similarly.

Analysis of Data - The dependent response variables consisted of ejection force and the resultant drug delivery system characteristics such as tablet mean in vitro dissolution time (MDT in vitro), crushing strength, disintegeration time and friability.

Both Weibull model (25,26) and Gompretz model (27) are empirical models that are useful for fitting data to sigmoid shaped curves. The Weibull model requires an estimate of lag time term, which is not known with accuracy. With the

Gompretz model no assumption is necessary for the lag time value, and at time zero the percentage release intercept is almost zero. In addition at the upper tail of these sigmoid shaped curves the Gompretz model approaches and maintains the asymptotic values as is the case with experimental dissolution data. The dissolution data were therefore fitted to Gompretz model (Eq. 23) (27):

$$= \alpha \exp \{ -\beta e^{-kt} \} \quad (23)$$

where is the percent drug dissolved at time t, α is the final value of percent drug dissolved, β is the scale parameter and k is the shape parameter. The Gompretz model was fitted to dissolution data using non-linear regression analysis technique (28). The MDT in vitro is the ratio of the first to zero moments of dissolution rate-time curve (29). Since the first moment curve could not be readily integrated in terms of elementary functions, both moments were calculated by use of the trapezoidal rule using computer with programming in basic. The response surface equations for MDT in vitro and friability were calculated using least squares multiple regression analysis (30). The least squares multiple regression analysis (30). The least squares criteria for estimating coefficients for the equation weights observed data points that have large residuals, which tend to have large sample variances, in order to minimize the sum os squares error. The reciprocal of the variance were used in the weighted least squares multiple regression analysis (27,30) for ejection force, hardness, and disintegration time data. The weighted least

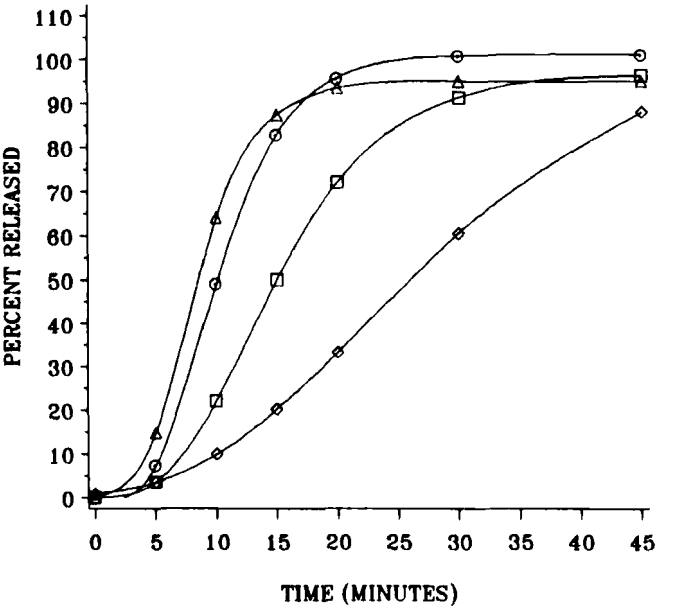

Fig 2 Dissolution curves of theophylline from tablets of formulation 1 (o), 4 (△), 8 (□), 9 (◇).

squares gives weight to those points that have lowest sample variances and therefore overcomes the limitations of the least squares method. The optimization was carried out using fortran subroutines, for the SQP algorithm (31). The characteristics of the tablet formulation was evaluated using principal component analysis (32,33). The simulation study was carried using a program written in SAS basic (34).

Results and Discussion

Response Variables - The dissolution profiles for the tablets are shown Figure 2, and the parameters for the Gompretz model are shown in Table IV. The tablet properties obtained from the experimental design are shown in Table V.

Table IV

Gompretz Model Parameters

Formulation Number	Gompretz Model Parameters α	β	k
1	103.996	6.421	0.1054
2	100.657	8.748	0.1806
3	101.216	7.853	0.2700
4	95.206	8.705	0.3089
5	101.336	9.444	0.257
6	107.805	4.819	0.0707
7	98.001	6.771	0.1555
8	97.007	7.369	0.1607
9	101.767	8.078	0.1479
Optimized	95.242	5.249	0.1125

Regression Models - the response surface equations (Table Vi) for the MDT in vitro, the hardness, and disintegration time were linear, while those for ejection force and friability were non-linear and therefore the problem was solved for the optimum solution by a non-linear optimization technique. The p values indicated that the equations are highly statistically significant. The R square and the R square with adjusted degrees of freedom values, and the lack of fit test at the 5% significance level for the regression equations indicate that the goodness of fit were satisfactory. The relationship between the response variable and the controllable variables are shown in Figures 3-6, by means of three dimensional plots (35).

Table V

Tablet Properties

Experimental Unit	Ejection Force (N)*	Weight % RSD	Hardness (Kg)*	Percent Friability	Disintegration Time (Minutes)*	MDT in vitro (hr)
1	613.1(10.8)	0.3531	13.48(1.58)	0.294	8.63(0.28)	0.3573
2	581.1(26.7)	0.4224	11.82(1.32)	0.344	6.01(0.30)	0.2536
3	450.5(18.6)	0.4066	8.99(0.90)	0.419	3.44(0.09)	0.1646
4	397.1(21.8)	0.3674	7.65(0.66)	0.496	3.37(0.15)	0.1496
5	462.8(21.8)	0.3633	8.97(0.69)	0.422	5.44(0.21)	0.1847
6	603.9(14.3)	0.4045	13.17(1.70)	0.291	9.13(0.48)	0.4038
7	542.4(27.7)	0.3042	10.67(1.27	0.353	6.07(0.35)	0.2652
8	533.5(28.9)	0.4072	10.71(1.01)	0.296	5.68(0.31)	0.2657
9	533.0(30.2)	0.3616	10.25(1.34)	0.328	6.53(0.21)	0.2963

*Value in parenthesis is standard deviation.

Table VI

Response surface data

Parameters/ Summary	Ejection Force (N)	Hardness (Kg)	Percent Friability	Disintegration Time (minutes)	MDT in vitro (hr)
B0	537.838	10.596	0.3395	6.0105	0.2601
B1(X1)	118.262	3.039	-0.1017	2.7426	0.1206
B2(X2)	-	-	-	-1.3497	-0.0492
B11(X1*X1)	-38.780	-	0.0624	-	-
B22(X2*X2)	-	-	-	-	-
B12(X1*X2)	-	-	-	-	-
R Square	0.9774	0.9739	0.8888	0.9812	0.8693
ADJ R-SQ.	0.9699	0.9702	0.8518	0.9749	0.8257
F Value	130.038	261.544	23.989	156.586	19.945
Prob>F	0.0001	0.0001	0.0014	0.0001	0.0022

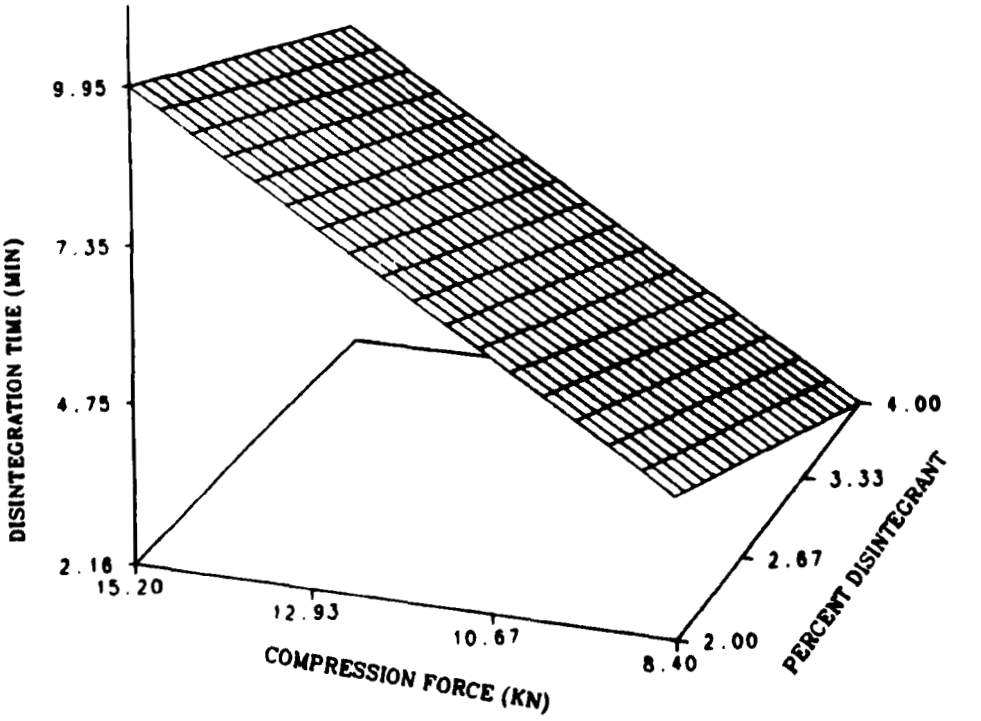

Fig 3 Three dimensional plot of ejection force data.

Optimization - The objective function of MDT in vitro was minimized so as to obtain rapid dissolution rate. The constraints used were that tablet hardness should be ≤ 12 kg, the disintegration time should be ≤ 7.5 minutes, the friability should be ≤ 0.3 percent, and the ejection force should be ≤ 605 Newtons. Additional constraints were the experimental limits placed on values of compression force (X_1) and percent disintegrant (X_2).

Optimal Solution - the optimum solution values for the independent variables satisfied all the constraints simultaneously and provided an optimal value for the

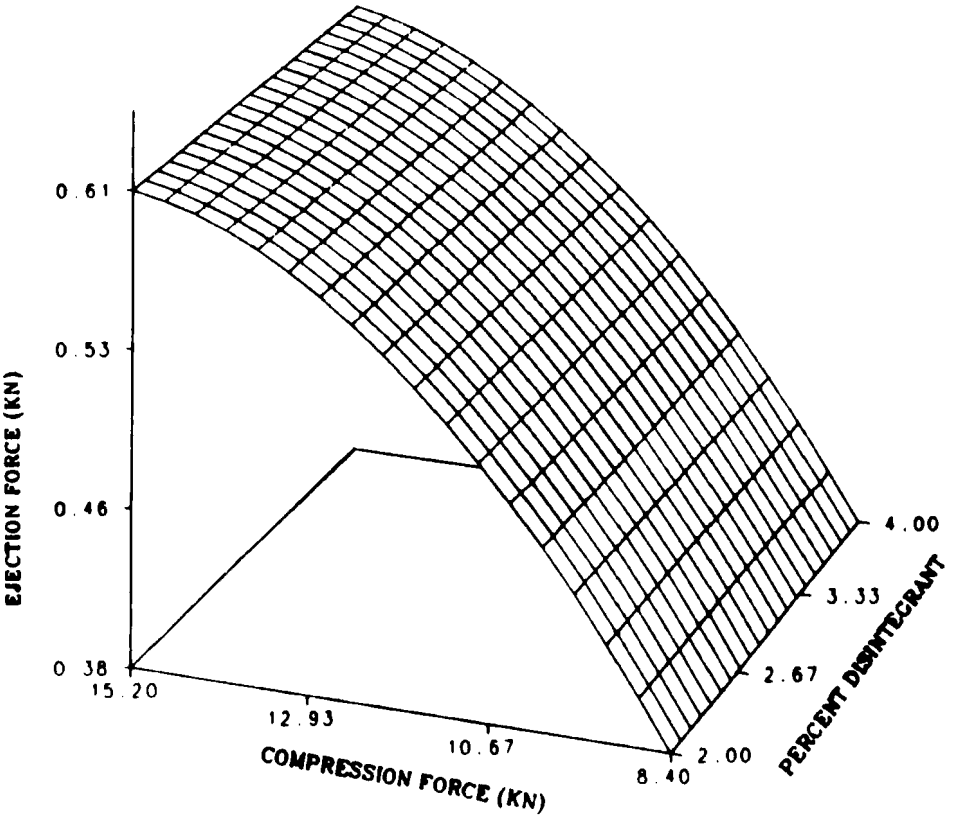

Fig 4 Three dimensional plot of percent friability data.

objective function. The formulation according to the optimal solution was prepared as shown in Table VII. The comparison of predicted and experimental values for the optimum formulation showed very good agreement and are shown in Table VIII. A model is valid if despite its inexactness in representing the system, it can give a reasonable prediction of a systems performance.

Sensitivity Analysi - In the vicinity of the optimal solution, the change in the objective function values were

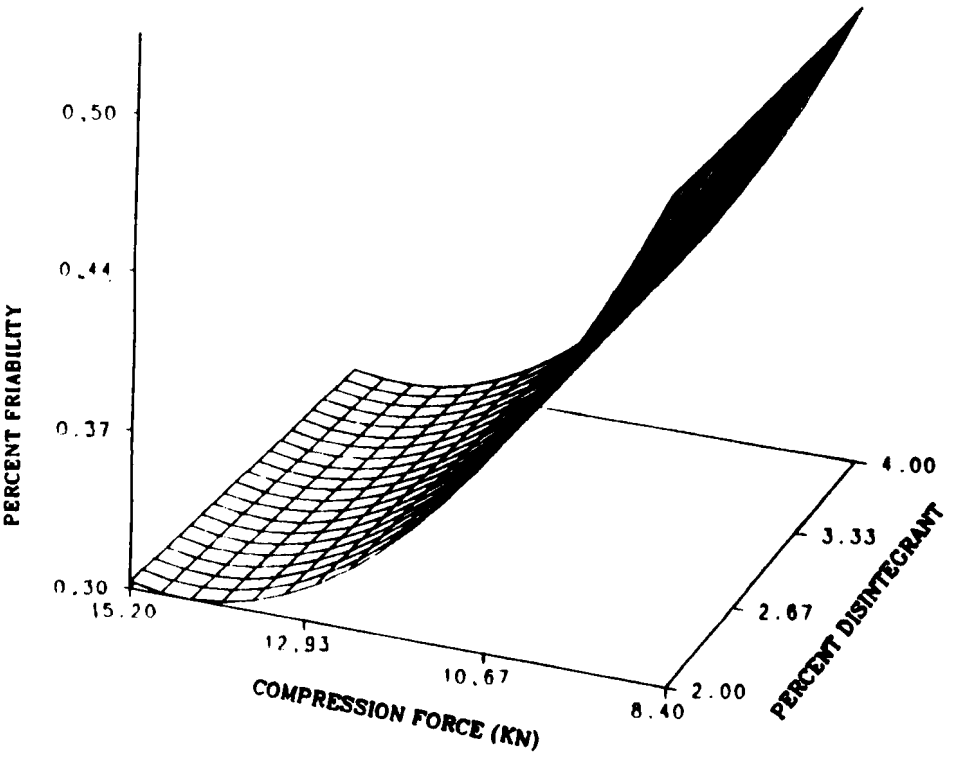

Fig 5 Three dimensional plot of disintegration time data.

monitored in response to minor modifications in each of the constraints values, while all the other constraint values were held constant. The MDT in vitro values were then calculated from the solutions obtained for X_1 and X_2 by SQP. For hardness constraint the values that could be altered ranged from 12.54 to 12.85 kg but values below 12.54 kg did not alter X_1 and X_2. For disintegration time constraint the values below 6.593 minutes produced infeasible solution, while values above 6.593 minutes produced no change in X_1 and X_2. For ejection force constraints the values below 597.55 Newtons produced infeasible solution, while values

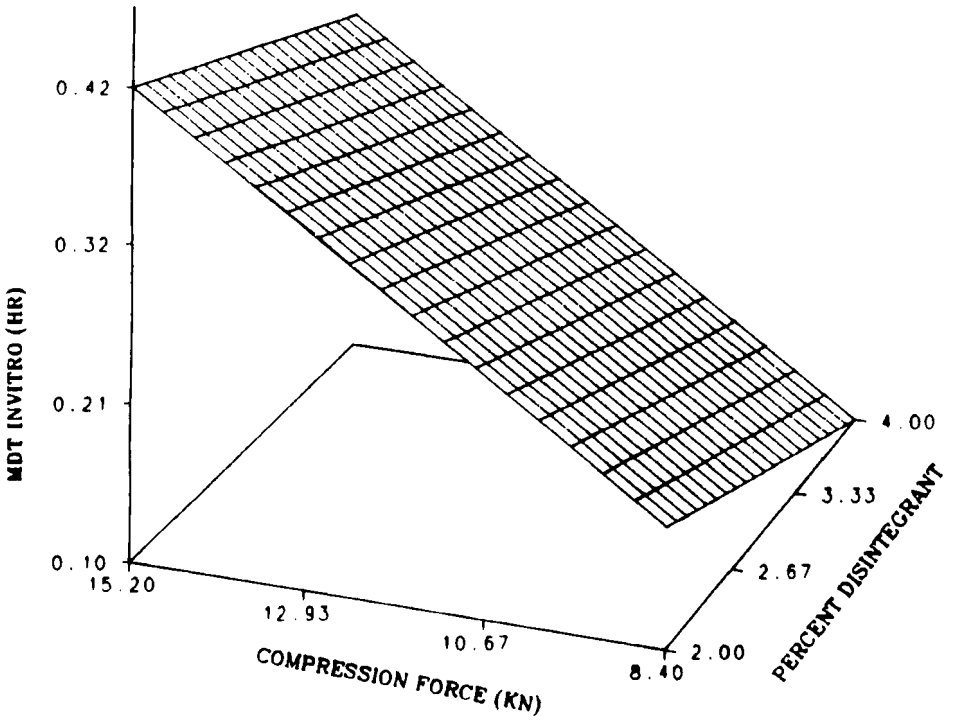

Fig 6 Three dimensional plot of mean in vitro dissolution time data.

Table VII

Optimized Formulation

Ingredients	Percent w/w
Theophylline	25.0
Beaverwhite 300	15.0
Corn Starch	4.0
Lactose	56.0

Table VIII

Comparison of experimental and predicted tablet properties

Optimum Formulation	Ejection Force (N)*	Hardness (Kg)*	Percent Friability	Disintegration Time (minutes)*	MDT in vitro (hr)
Constraints	≤605	≥12.0	≤ 0.3	≤7.5	
Predicted	597.55	12.54	0.2999	6.593	0.2945
Experimental	584.15(17.93)	12.17(1.44)	0.2323	6.57(0.29)	0.3154

*Value in parenthesis is standard deviation.

above 597.55 Newtons produced no change in X_1 and X_2. For friability constraint the values altered ranged from 0.2984 to 0.3060 percent. Friability values below 0.2984 produced infeasible solution, while values above 0.3060 produced no further change in X_1 and X_2. Similar relationship between friability and drug dissolution from tablets have been reported (11). Using the rate method the sensitivity coefficients at the optimal solution were found to be 1.02 and - 1.43 with respect to hardness and friability respectively. From these results it is clear that the MDT in vitro was more sensitive to changes in friability than hardness. The negative sign of the sensitivity coefficient indicated that increase in friability results in decreased MDT in vitro, while increase in tablet hardness increases the MDT in vitro as expected.

Principal Component Analysis - Principal component analysis was performed using standardized scores for the in vitro tablet properties of crushing strength, disintegration time, percent friability and MDT in vitro. The first, second and third principal components, which correspond to the eigenvalues, in descending order of magnitudes respectively, could explain 92.8%, 4.5% and 2.1% of the overall information about these tablet formulations. The first principal component represented the overall tablet physical properties since the entries of the eigenvector for the first principal component were of similar magnitude. In other words measurements of all these tablet properties are

Table IX

Simulations of variations in compression force

Parameters* Summary	Ejection Force (N)	Hardness (Kg)	Percent Friability	Disintegration Time (minutes)	MDT in vitro (hr)
B0	533.556(5.173)	10.604(0.090)	0.3388(0.004)	6.0186(0.087)	0.2605(0.003)
B1(X1)	115.335(4.621)	3.006(0.127)	-0.0999(0.005)	2.7268(0.124)	0.1202(0.005)
B2(X2)	-	-	-	-1.3578(0.159)	-0.0494(0.005)
B11(X1*X1)	-31.423(8.220)	-	0.0635(0.011)	-	-
B22(X2*X2)	-	-	-	-	-
B12(X1*X2)	-	-	-	-	-
R Square	0.9798	0.9648	0.8859	0.9791	0.8719
ADJ R-SQ.	0.9731	0.9598	0.8479	0.9721	0.8292
F Value	179.772	218.890	24.209	166.417	21.203
Prob>F	0.0001	0.0001	0.0016	0.0001	0.0023

*Value in parenthesis is standard deviation.

of approximately equal importance in defining the characteristic of these tablet formulations.

Simulation of Variations in Compression Forces - In regression analysis it is assumed that a cause and effect relationship exist between dependent variable (Y) which is measured with experimental error, and the independent variables (X_1....,X_k) whose values are measured without error. The compression force values were randomly perturbed according to the experimentally observed standard deviations to study their effects on the values of response surface equations coefficients in a simulation study (34). If the optimum value is unaffected by minor changes in value of a coefficient, then that coefficient has low sensitivity, and therefore having a precise value for that parameter will not be crucial to finding the true optimum (34). The equations obtained from the simulation study had coefficients in close agreement with those actually obtained from experiment. The coefficient values obtained from the simulation experiment are shown in Table IX. Furthermore, these equations were used for obtaining the optimal solution using the same constraints as with the acual experiment. The optimal solution obtained was very similar, suggesting the use of 4% corn starch and 14.21 KN of compression force. This suggests that the response surface model generated by an uniform-precision rotatable hexagonal design is a robust one.

Conclusions

A mathematical optimization technique, novel to the pharmaceutical sciences, has been applied to obtain an optimum formulation of conventional theophylline tablets. The uniform-precision rotatable hexagonal equiradial type experimental design provided a robust response surface model. The constrained nonlinear optimization problem was efficiently optimized by use of the SQP technique. Properties of the optimal formulation agreed well with the predicted profile. Sensitivity analysis performed showed that the optimal solution was sensitive to changes in hardness and friability.

References and Notes

1. Jarosz, P. L., Parrott, E. L., Drug Dev. Indus. Pharm. 1984, 4, 259-273.
2. Williams III, R. O., McGinity, J. W., J. Pharm. Sci. 1989, 78, 1025-1034.
3. Schwartz, J.B., Flamholz, J.R., Press, R.H., J. Pharm. Sci. 1973, 62, 1518-1519.
4. Box, G.E.P., Draper, N.R., Smith, H., Empirical Model Building and Response Surface, Wiley: New york, 1987, pp 505-515.
5. Myers, R.H., Response Surface Methodology; Allyn and Bacon: Boston, 1971; pp 126-173.
6. Biles, W.E., Swain, J.J., Optimization and Industrial Experimentation, Wiley: New York, 1980, pp 135-147.

7. Montgomery, D.C., Design and Analysis of Experiments; Wiley, New York, 1984, pp 460-463.
8. Shek, E., Ghani, M., Jones, R.E., J. Pharm. Sci, 1980, 69, 1135-1142.
9. Routh, M.W., Swartz, P.A., Denton, M.B., Anal. Chem. 1977, 49, 1422-1428.
10. Dincer, S., Ozdurmus, S.J., Pharm. Sci. 1977, 67, 1070-1073.
11. Fonner, Jr., D.E., Buck, J.R., Banker, G.S., J. Pharm. Sci. 1970, 59, 1587-1596.
12. Gordon, M.S., Chatterjee, B., Chowhan, Z.T., J. Pharm. Sci., 1990, 79, 43-47.
13. Down, J.R.B., Miller, R.A., Chopra, S.K., Millar, J.F., Drug Dev. Indus. Pharm. 1980, 6, 311-330.
14. Takayama, K., Nambu, N., Nagai, T., Chem. Pharm. Bull. 1983, 31, 4496-4450.
15. Schwartz, J.B., Flamholz, J.R., Press, R.h.J., Pharm. Sci. 1973, 62, 1165-1170.
16. Bohidar, N.R., Bavitz, J.F., Shiromani, P.K., Drug Dev. Indus. Pharm. 1986, 12, 1503-1510.
17. Takai, T., Takayama, K., Nambu, N., Nagai, T., Chem. Pharm. Bull. 1984, 32, 1942-1947.
18. Takayama, K., Imaizumi, H., Nambu, N., Nagai, T., Chem. Pharm. Bull. 1985, 33, 292-300.
19. Reklatis, G.V., Ravindran, A., Ragsdell, K.M., Engineering Optimization: Methods and Applications, Wiley: New York, 1983, pp 438-458.

20. Wasil, E., Golden, B., Liu, L., Computers Opns. Res. 1989, 16, 497-512.

21. Schittkowski, K., Annals of Operation Research 1986, 5, 485-500.

22. Powell, M.J.D., In Lecture Notes in mathematics, Vol. 630, Watson, G.A., Ed., Springer-Verlag, New York, 1978, pp 144-157.

23. Dawoodbhai, S., Chueh, R.R., Rhodes, C.T. Drug Dev. Indus. Pharm. 1987, 13, 2441-2457.

24. U.S. Pharmacopeia, 21st rev., U.S. Pharmacopeial Convention, Rockville, MD, 1985, pp 1042-1043.

25. Grant, E.I., Leavenworth, R.S., Statistical Quality Control, McGraw Hill, New York, 1972, pp 581-583.

26. Lagenbucher, F., J. Pharm. Pharmac. 1972, 24, 979-981.

27. Draper, N.R., Smith, H., Applied Regression Analysis, Wiley, New York, 1980, pp 108-111, 511-512.

28. The NLIN Procedure, SAS Technical Report P115, SAS Institute, Inc., Cary, NC, 1982, pp 7.1-7.14.

29. Tanigawara, Y., Yamaoka, K., Nakagawa, T., Uno, T., Chem. Pharm. Bull. 1982, 30, 1088-1090.

30. The REG Procedure, SAS Version 5.0; SAS Institute, Inc., Cary, NC, 1985, pp 656-709.

31. The NCONF Optimization Routine, IMSL Version 1.0, IMSL Inc., Math/Library, Houston, 1981, pp 895-902.

32. Bohidar, N.R., Schwartz, J.B., Restaino, F.A., J. Pharm. Sci. 1975, 64, 966-969.

33. The PRINCOMP Procedure, SAS Version 5.0, SAS Institue, Inc., Cary, NC, 1985, pp 622-637.

34. Chatterjee, S., Hadi, A.S., Sensitivity Analysis in Linear Regression, Wiley, New York, 1988, pp 261-261.

35. The RSREG Procedure, SAS Technical Report P115, SAS Institute, Inc., Cary, NC, 1982, pp 10.1-10-12.