Mathematical Optimization Techniques in Drug Product Design and Process Analysis

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Abstract □ Optimization techniques represent analytical tools available to the researcher in his search for the best possible solution to a particular problem. Methodologies have been developed for structuring typical pharmaceutical development problems into a framework whereby sophisticated mathematical techniques can be employed to arrive at an optimal solution. Pharmaceutical product and process design problems were structured as constrained optimization problems and subsequently solved by the Lagrangian method of optimization. This optimization method was employed to generate optimal formulations in typical tablet design problems and to locate optimizing levels of processing variables in a typical encapsulation design problem.

Keyphrases □ Drug product design—mathematical optimization techniques □ Process analysis—mathematical optimization techniques □ Lagrangian method—optimization, drug design □ Optimum tablet design—techniques □ Tablets, optimization design—phenylpropanolamine HCl

Pharmaceutical product and process design problems are normally characterized by multiple objectives. In designing a product, for example, the pharmaceutical scientist must often meet prespecified control limits which define or influence such dosage form characteristics as the unit cost, physical stability, chemical stability, or physiological availability of the active ingredient. The parameters describing these dosage form characteristics represent response or dependent variables, and any limits or conditions placed on these response variables represent objectives. The magnitude of the observed value for each response variable generally depends upon levels of one or more of the controllable (independent) variables. Mathematically speaking, the jth response variable is measured as y_j, and the responses obtained are a function of levels of one or more of the controllable variables, X_1, X_2, ..., X_n. Thus,

$$y_j = f_j(X_i), \quad j = 1,2,\ldots,r; \quad i = 1,2,\ldots,n \quad \text{(Eq. 1)}$$

where f_j is the relationship between the one or more X_i controllable variables and each response variable y_j. The geometrical representation of y_j as a function of possible combinations of levels of the controllable variables defines a response surface (Fig. 1). The task of the pharmaceutical scientist frequently involves locating levels of the one or more X_i controllable variables that meet limits or conditions placed on each y_j response variable.

The response variables of product and process design problems are often affected differently by particular combinations of the controllable variables due to interaction effects (1–5). If the response variable effects are nonadditive, the response surface is highly complicated. Unless the program of experimentation is statistically well designed and an extensive series of experiments is conducted, accurate estimates of the response variable from a fixed set of controllable variables are virtually impossible (6).

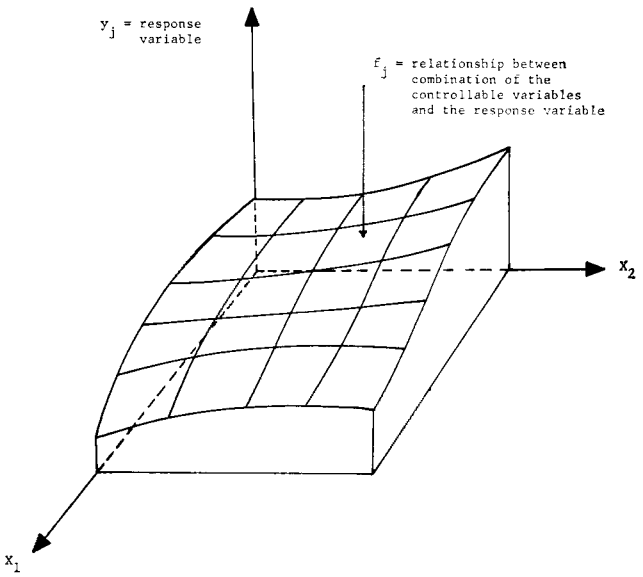

Figure 1—*Representative graph of Eq. 1 for two controllable variables,* X_1 *and* X_2.

Design problems are further complicated when objectives are competing. As a particular controllable variable is increased in most pharmaceutical design problems, one response variable tends to improve while another response variable is degraded. For example, compressional force or the concentration of granulating agent employed may produce competing effects on tablet friability and disintegration time or on tablet hardness and drug-release rate. Achievement of the best product or process design under conditions of competing objectives and interactive effects by guesswork or trial and error is time consuming, unreliable, costly, and often unsuccessful. Furthermore, the pharmaceutical researcher who employs such techniques may not recognize how close a particular solution lies to the optimal solution.

One way of dealing with complex pharmaceutical design problems is to structure them as constrained optimization problems. Problems structured in this way can be solved by any one of a number of existing techniques; one of the more versatile techniques is the Lagrangian method. This study investigated the usefulness of a systematic optimization approach in solving pharmaceutical product and process design problems.

Constrained mathematical optimization methods would appear to be broadly applicable to many pharmaceutical product design and process analysis problems. Data which are currently being generated by preformulation research programs during drug product design

should permit the use of optimization techniques in an increasing number of product design or process analysis programs.

Optimization techniques have the capability in pharmaceutical research of: (*a*) saving time and minimizing costs in achieving the desired product design; (*b*) improving the reliability of the research effort to achieve the optimal or near optimal product or process design solution; and (*c*) improving quality and assuring quality of the final drug product as affected by product and/or process design.

THEORY

Optimization problems may be broadly classified as either unconstrained or constrained. Unconstrained optimization involves the maximization or minimization of a function in which no restrictions or limits have been placed on the controllable variables or functions of the controllable variables. For example, optimization of

$$y = f(X_i), \quad i = 1,2,\ldots,n \qquad \text{(Eq. 2)}$$

represents an unconstrained optimization problem and can be solved by classical calculus techniques (7). For a function of n controllable variables, the location of relative optima requires solving a set of n simultaneous equations. The n simultaneous equations result from partially differentiating Eq. 2 with respect to the n controllable variables. The global optimum is then established by evaluating $f(X_i)$ at the relative optimum points and selecting the most extreme of all the solutions obtained.

A constrained optimization problem (7) is one in which a function is optimized subject to restrictions or limits placed on the controllable variables. Mathematically, the problem is to optimize

$$y = f(X_i), \quad i = 1,2,\ldots,n \qquad \text{(Eq. 3)}$$

such that:

$$g_j(X_i) = \alpha_j, \quad j = 1,2,\ldots,p \leq n \qquad \text{(Eq. 4)}$$

$$g_j(X_i) \geq \alpha_j, \quad j = p+1,\ldots,m \qquad \text{(Eq. 5)}$$

Equation 3 represents the function to be optimized and is generally referred to as the objective function. Equations 4 and 5 are referred to as equality and inequality constraints for the specified constants α_j. Only the greater than or equal to relationship is represented, since $h(X_i) \leq 0$ may be written as $g(X_i) = -h(X_i) \geq 0$. Thus, the constrained optimization problem involves locating levels of X_i that produce an optimal response in $f(X_i)$ such that the constraints of the problem are not violated. If the objective function and constraints are linear, the problem can be solved by linear programming techniques (8–10). If nonlinearities exist in the objective function and/or one or more of the constraints, the constrained optimization problem of Eqs. 3–5 becomes a nonlinear programming problem. Several techniques capable of dealing with nonlinear programming problems have been developed (11–13). Since systems of pharmaceutical interest are often characterized by the presence of many interactions, nonlinear models frequently result.

The Lagrangian Method—Of the techniques available for solving the constrained optimization problem in its general form (Eqs. 3–5), the most versatile method appears to be the Lagrangian method (7, 14, 15). *Appendix A* contains two numerical examples illustrating this method of optimization. The Lagrangian method has many desirable properties because this method: (*a*) locates the optimum directly and does not search infeasible points; (*b*) generates only feasible solutions; (*c*) efficiently handles inequality as well as equality constraints; and (*d*) deals with nonlinearities in the objective function and/or constraints.

Inequality constraints are converted to equality constraints by incorporating a slack variable, q_j, which must be nonnegative to assure that its value is positive in the Lagrange function (16). Thus, Eq. 5 may be written as follows:

$$g_j(X_i) - q_j^2 = \alpha_j, \quad j = p+1,\ldots,m \qquad \text{(Eq. 6)}$$

The slack variable, q_j, in effect absorbs the slack created by the original inequality relationship. For a less than or equal to constraint, the minus sign in Eq. 6 is replaced with a plus sign. Once the inequality constraints have been converted to equality constraints, the next step is to form the Lagrange function, F, which is equal to the objective function plus the products of the Lagrange multiplier, λ_j, and the constraint (7). For the general constrained optimization problem (Eqs. 3–5), the Lagrange function becomes

$$F = f(X_i) + \sum_{j=1}^{p} \lambda_j[g_j(X_i) - \alpha_j] + \sum_{j=p+1}^{m} \lambda_j[g_j(X_i) - q_j^2 - \alpha_j] \qquad \text{(Eq. 7)}$$

As shown in Eq. 7, one Lagrange multiplier is introduced for each constraint, and one slack variable is introduced for each inequality constraint.

If the task is to minimize the objective function, then the Lagrange function is minimized with respect to the controllable variables X_i and maximized with respect to the Lagrange multipliers λ_j, giving a so-called minimax solution (17, 18). In maximizing the objective function, the resulting solution is a maximin solution relative to X_i and λ_j, respectively. Either form of the resulting solution is a stationary point in which the tangent of the Lagrange function is zero with respect to each X_i and λ_j. Therefore, the values of the controllable variables which jointly satisfy each partial derivative of the Lagrange function with respect to X_i ($i = 1, 2, \ldots, n$), λ_j ($j = 1, 2, \ldots, p, \ldots, m$), and q_j ($j = p+1, \ldots, m$), each set equal to zero, provides stationary points including a constrained extreme of the objective function. These satisfying values, X_i^*, can be obtained by the simultaneous solution to the $n + m$ equations. Each set of X_i^* values obtained is a root to this set of equations and denotes a stationary point. If a set of equations gives multiple roots, then each root may be substituted into the objective function to find the one that is the desired extreme. If the equations obtained from partially differentiating the Lagrange function result in a set of simultaneous nonlinear equations, then numerical methods must be used to locate the simultaneous solution point (14).

The Lagrange multiplier has an interesting interpretation directly relating to optimization problems (19). The numerical value of λ_j represents a measure of the instantaneous rate of change of the objective function with a change of the constraint's limiting value. Thus, the value of λ_j is useful in projecting the expected gain or loss in the objective function accompanying a change in constraint of one unit.

The Lagrangian method of solving constrained optimization problems assumes that a mathematical relationship exists which relates the response variable to levels of the controllable variables. Theoretically, mathematical models can be derived from a knowledge of the natural laws governing the system. However, underlying mechanisms in pharmaceutical product and process design problems are often so complicated that the formulation of an analytical mathematical model is out of the question. If an analytical model is impossible to derive, then an empirical mathematical model may be developed by using multiple-regression techniques (4, 20). Thus, it is usually possible to fit a polynomial to the response surface which can be expected to give an adequate approximation of the response surface over the region of experimentation. The Lagrangian method has been applied to a constrained optimization problem involving polynomial models generated by multiple-regression techniques (21).

EXPERIMENTAL

A typical product design problem was studied in this investigation. It involved locating levels of the binder and disintegrant that optimized tablet physical properties and drug availability in a model tablet formulation. An optimization method was used to solve a constrained tablet design problem involving a restriction placed on the urinary elimination rate of the drug. A process design problem was also analyzed utilizing regression models describing powder encapsulation (4).

Model Tablet Design, Preparation, and Evaluation—A model tablet system was employed to demonstrate the advocated design procedure. Tablets containing various concentrations of a disintegrant and binder were prepared. The effect of the binder and dis-

integrant concentration on tablet hardness, friability, volume, *in vitro* release rate, and urinary excretion rate of drug in human subjects was recorded. Phenylpropanolamine hydrochloride[1] was the drug chosen based on its relatively low dose, safety, quantitative urinary excretion reflecting drug availability, and ease of assay from the urine. The model tablet system employed: (*a*) represented commonly used ingredients in tablet formulations; (*b*) produced tablets that did not split or fracture during the friability test; and (*c*) contained levels of binder and disintegrant that significantly affected tablet hardness, friability, volume, and *in vitro* release rate of the drug. The tablet formulas studied were all contained within the following limits:

Phenylpropanolamine hydrochloride	50 mg.
Dicalcium phosphate dihydrate[2]	*q.s.*
Corn starch[3]	1–41%
Stearic acid USP[4]	5–45%
Tablet weight =	400 mg.

To achieve reproducible friability and *in vitro* $t_{50\%}$ release rate data, it was necessary to control the moisture content of the tablets. The starch, therefore, was dried for 4 hr. at 120°, and all tablet ingredients were individually stored in a vacuum desiccator containing anhydrous calcium sulfate[5] for 24 hr. prior to compression. Tablets were individually compressed, utilizing 0.95 cm. (3/8 in.) standard cut tooling, to a load of 3000 lb. on a pneumatic press.[6] The load was maintained for 10 sec., and all tablets were stored in a vacuum desiccator for at least 24 hr. prior to use. Karl Fischer moisture determinations were conducted to ensure that the moisture content of the tablets remained below 1%. At least five replicate tablets, each based on a separate powder mixture of a particular formulation, were used to obtain a measure of tablet volume, hardness, friability, and *in vitro* $t_{50\%}$ release rate for all nine tablet formulations studied.

Tablet hardness in kilograms was determined using a Pfizer hardness tester.[7] Since tablet moisture content affected tablet friability, a special friabilation apparatus was fabricated in which humidity control was possible. This apparatus consisted of a 1.5-oz. amber, dry square bottle whose bottom was covered with a 0.25-in. layer of Wood's metal (soft solder). A 0.08-cm. (1/32-in.) thick piece of Teflon was dried over the Wood's metal to provide a smooth standard surface for tablet contact. A silica gel bag,[8] wrapped in muslin, was attached to the cap of the bottle. Attrition was provided to the tablet in the bottle by placing the entire unit in an Eberbach shaker unit[9] oscillating at 275 ± 3 c.p.m., with a stroke length of 3.8 cm. (1.5 in.). Friability was measured as the percent weight loss of an individual tablet after 40 min. of shaking. The conditions selected for the friabilation test were found to give reproducible data and to distinguish real friability differences existing among the nine different tablet formulations.

Tablet volume was computed from the cylindrical tablet volume and the spherical segment volume of the standard cup punches used. The volume of the spherical segment was calculated as (22)

$$V = 1/6\pi h(3r^2 + h^2) \qquad \text{(Eq. 8)}$$

where r is the radius of the segment and h is its depth. Punch diameter [0.94 cm. (0.3720 in.)] and punch depth [0.10 cm. (0.0410 in.)] were measured with calipers. The volume of each spherical segment was calculated to be $V = 0.037$ cm.^{3} (0.0023 in.^{3}). The crown thickness of the tablets was measured using an Ames micrometer.[10]

The *in vitro* release rate tests were conducted in a 250-ml., three-necked, round-bottom flask, utilizing 200 ml. of distilled water as the solvent, at 37 ± 1°. Agitation was provided by a model 12 Stedi-Speed adjustable stirrer[11] equipped with a two-bladed, 3.18-cm. (1.25-in.) diameter stainless steel impeller, which was operated at 130 ± 2 r.p.m. This agitation level provided solvent circulation but did not disturb the particles formed by the disintegrating tablet at the bottom of the flask. Five-milliliter aliquots were removed at selected time intervals for analysis, with each aliquot being replaced by 5 ml. of distilled water. The concentration of drug in the bulk solvent was corrected for drug lost from the previous samples. Each aliquot was filtered through a Millipore filter (0.65-μ pore opening), and its absorbance was determined at 256.4 mμ. Cumulative percent of drug released *versus* time plots were prepared for each of the replicate tablets of each formulation. The time for 50% of the drug to be released ($t_{50\%}$) was determined graphically from each plot.

Table I—Tablet Formulations Used in the Optimization Study

Formulation No.	Mg. of Ingredient per Tablet: Phenylpropanolamine HCl	Dicalcium Phosphate $\cdot 2H_2O$	Starch	Stearic Acid
1	50	326	4 (1%)	20 (5%)
2	50	246	84 (21%)	20
3	50	166	164 (41%)	20
4	50	246	4	100 (25%)
5	50	166	84	100
6	50	86	164	100
7	50	166	4	180 (45%)
8	50	86	84	180
9	50	6	164	180

The nine tablet formulations listed in Table I define a full 3^2 factorial design. Levels of stearic acid and starch were equally spaced to permit a trend analysis of the data in the framework given by Davies (6). Replication provided an estimate of the experimental error involved, and experiments were randomized to prevent systematic biasing of the estimates of experimental effects.

Urinary Excretion Rate—The urinary excretion rate of phenylpropanolamine hydrochloride was determined for four different tablet formulations (Formulations 1, 3, 4, and 7 of Table I) and for a control solution of the drug. The control solution contained 47.66 mg. of drug in 200 ml. of distilled water. Five healthy human male subjects were used. Each subject was separately administered all four of the dosage forms and the control solution of drug at time intervals of $7 \times t'_{50\%}$ or longer, where $t'_{50\%}$ represents a measure of the urinary elimination rate half-life in hours of the last formulation administered. The order of administration of the dosage forms and the order in which the individuals were tested were randomized. A modification of the assay of Heimlich *et al.* (23) was used for the drug urinalysis in which cyclohexane was employed as the extracting solvent. Three standards were run during each assay in which three known amounts of drug were added to a blank urine sample; the sample had been collected from each subject prior to administration of the dosage form. Semilog plots of cumulative percent drug remaining in the body *versus* time were made, the least-squares equation for each line was solved, and the $t'_{50\%}$ value was calculated.

RESULTS AND DISCUSSION

The effects of varying concentrations of stearic acid and starch, the controllable variables X_1 and X_2, on the tablet response variables of hardness (y_1), *in vitro* $t_{50\%}$ release rate (y_2), friability (y_3), and volume (y_4), are presented in Table II. A two-factor analysis of variance (24) for homogeneity of variances disclosed that the *in vitro* $t_{50\%}$ release rate (y_2) and friability (y_3) data appearing in Table II were not homoscedastic at the 99% confidence level. A transformation was found which, when applied to the $t_{50\%}$ and friability data, resulted in statistically equal variances at the nine different experimental conditions. An arithmetic plot was prepared showing the combination of standard deviation and mean value for each experimental condition of the *in vitro* release rate and of the friability. In both cases the standard deviations were found to be proportional to the mean values, as indicated in the least-squares proportions of Eqs. 9 and 10, with correlations of fit exceeding 0.99:

$$S_{y_2} = (0.7356 \times 10^{-1})\bar{y}_2 \qquad \text{(Eq. 9)}$$

$$S_{y_3} = (0.8274)\bar{y}_3 \qquad \text{(Eq. 10)}$$

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Monsanto Chemical Co., St. Louis, MO 63166
[3] A. E. Staley Mfg. Co., Decatur, IL 62525
[4] Ruger Chemical Co., Irvington-on-Hudson, N. Y.
[5] Drierite, W. A. Hammond Drierite Co., Xenia, OH 45385
[6] Fred S. Carver, Inc., Summit, N. J.
[7] Chas. Pfizer & Co., Inc., Brooklyn, NY 10017
[8] W. R. Grace Chemical & Co., Baltimore, MD 21203
[9] Eberbach Corp., Ann Arbor, Mich.
[10] B. C. Ames Co., Waltham, MA 46518
[11] Fisher Scientific Co., Chicago, Ill.

Table II—Effect of Stearic Acid and Starch Concentration on Certain Physical and Chemical Properties of the Tablets

Stearic Acid, X_1	Percentage of Starch (X_2): 1 — Response Variables				21 — Response Variables				41 — Response Variables			
	y_1[a]	y_2[b]	y_3[c]	y_4[d] × 10^2	y_1	y_2	y_3	$y_4 \times 10^2$	y_1	y_2	y_3	$y_4 \times 10^2$
5	11.7	52.5	4.49	2.36	5.4	15.0	13.12	2.53	1.5	5.1	40.03	2.72
	12.0	44.3	4.68	2.37	4.0	14.2	13.71	2.56	1.3	5.4	47.20	2.72
	10.8	47.9	4.43	2.37	4.4	15.7	15.07	2.56	1.3	5.9	41.21	2.69
	10.2	56.3	5.28	2.38	4.2	17.3	15.88	2.54	1.0	6.0	47.92	2.69
	9.5	51.0	4.33	2.37	5.8	15.8	14.80	2.55	2.5	5.4	42.74	2.70
Mean	10.8	50.4	4.64	2.37	4.8	15.6	14.52	2.55	1.5	5.6	41.82	2.70
SD	1.04	4.56	0.378	0.005	0.79	1.15	1.102	0.012	0.71	0.38	3.498	0.010
25	15.0	118.0	1.13	2.52	11.0	27.2	1.55	2.67	6.5	12.5	4.74	2.82
	16.2	141.9	0.99	2.53	9.5	25.2	1.69	2.66	5.4	11.8	5.03	2.85
	16.4	123.5	1.10	2.53	9.8	23.2	1.48	2.66	6.7	13.5	5.17	2.84
	14.6	116.0	1.21	2.53	10.3	28.3	1.78	2.66	6.4	12.0	4.79	2.82
	15.5	123.0	1.09	2.53	11.2	24.0	1.64	2.64	7.2	11.1	5.75	2.83
Mean	15.5	124.5	1.10	2.53	10.4	25.6	1.63	2.66	6.4	12.2	5.10	2.83
SD	0.77	10.25	0.080	0.001	0.74	2.14	0.115	0.010	0.61	0.89	0.406	0.013
45	17.1	300.0	0.08	2.73	13.5	36.2	0.49	2.86	9.8	19.6	0.88	3.00
	17.7	270.0	0.08	2.74	13.0	39.2	0.45	2.87	9.2	18.2	0.95	3.01
	17.8	324.0	0.10	2.73	13.1	43.1	0.40	2.85	9.8	20.7	0.79	2.99
	17.8	285.0	0.10	2.71	13.0	38.4	0.38	2.86	10.2	19.8	0.84	2.97
	16.1	281.0	0.08	2.73	12.8	41.7	0.38	2.86	11.0	21.7	0.74	2.97
Mean	17.3	292.0	0.09	2.73	13.1	39.7	0.42	2.86	10.0	20.0	0.84	2.99
SD	0.73	20.88	0.011	0.008	0.46	2.73	0.049	0.005	0.66	1.32	0.081	0.016

[a] The y_1 is tablet hardness in Pfizer kilogram units. [b] The y_2 is *in vitro* release rate as measured by time in minutes for 50% of the drug to be in solution ($t_{50\%}$). [c] The y_3 is tablet friability as measured by percentage weight loss. [d] The y_4 is tablet volume in cubic inches.

Brownlee (25) has shown that when $S_y = k\bar{y}$, the natural logarithmic transformation stabilizes the variances. This transformation was applied to the release rate and friability data; the results appear in Table III. Three units were added to each transformation of friability datum to eliminate negative logarithmic values. The test for homogeneity of variances was then applied to the transformed data, and the existence of homoscedasticity could not be rejected at the 99% confidence level.

Regression Models—In stepwise regression, there are two basic versions: forward and backward (26). In this study, a backward stepwise regression analysis program[12] was utilized to generate polynomial models relating the response variables to the controllable variables. The results of the regression analysis appear in Table IV. Although the multiple-correlation coefficients for the regression models were high (Table IV), the predictive power of each model required further evaluation. A valid means of extending the polynomial evaluation is to select experimental conditions or treatments not included in the original set of experimental conditions and to compute both the predicted response and its associated confidence interval. The result of a new experiment can then be compared with the prediction to determine if the new experimental result is contained within the confidence interval. Four new experimental conditions were tested, and these formulations corresponded to the possible combinations of $X_1 = 15$ and 35% and $X_2 = 11$ and 31%. The predictions from the polynomial models were determined, and the 95% confidence intervals about a single prediction were computed. Construction of confidence intervals associated with multiple regression can be found in Chew (20). Next these formulations were prepared and the responses in question experimentally determined. Results of these analyses are given in Table V. The experimental response values all fell within the 95% confidence interval about a single prediction (Table V), with one exception. Thus, acceptance of the regression models in Table IV for predictive purposes in this study appears to be reasonable.

Contour Graphs—Contour graphs illustrate combinations of the controllable variables producing the same response. For each predesignated response of y_j, X_2 was solved at values of $X_1 = 2, 4, 6, \ldots, 40$. A computer program for this purpose for use on the IBM 7090 was written, and contours were set by interpolation from the X_1 and X_2 values obtained in the program output. The generated contour graphs are presented in Figs. 2–5. Contour graphs not only give various combinations of the controllable variables which produce the same response, but they also provide other interesting and useful information. For example, from the contour graph for tablet hardness (Fig. 2), it can be seen that to maintain a tablet hardness of 6.0 kg., the ratio of starch to stearic acid must be about 2:1; for a tablet hardness of 12.0 kg., the ratio needs to be about 1:2. For the sake of illustration, assume that the requirements on the final tablet are that hardness be 8–10 kg. and *in vitro* $t_{50\%}$ be 20–33 min. The solution to this problem is readily

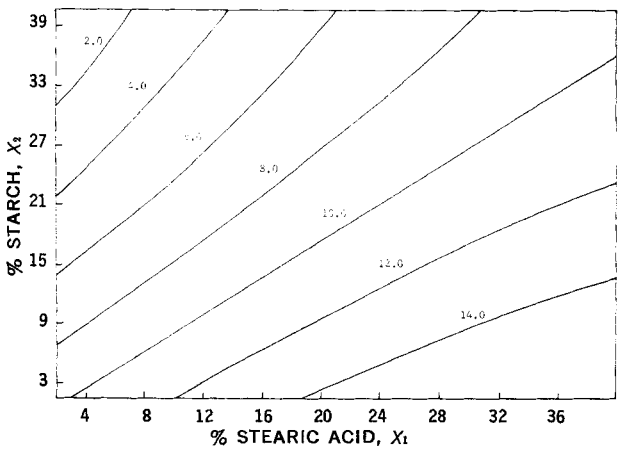

Figure 2—*Contour curves for tablet hardness (kilogram), illustrating levels of starch and stearic acid producing similar responses.*

[12] This regression analysis program was developed for use on the IBM 7090 by M. Dale Fimple of the Sandia Corp.

Table III—Stabilizing Effect of the Logarithmic Transformation on *In Vitro* Release Rate (y_2) and Friability (y_3)

% Stearic Acid (X_1)	% Starch (X_2)	—ln y_2[a]— Mean	*SD*	—ln y_3[b] + 3.0— Mean	*SD*
5	1	3.901	0.1212	4.533	0.0789
5	21	2.745	0.0729	6.674	0.0770
5	41	1.714	0.0686	6.731	0.0821
25	1	4.822	0.0796	3.100	0.0729
25	21	3.239	0.0835	3.485	0.0729
25	41	2.498	0.0776	4.626	0.0776
45	1	5.675	0.0843	0.563	0.1218
45	21	3.580	0.0690	2.127	0.1129
45	41	2.994	0.0657	2.822	0.0967

[a] The *in vitro* $t_{50\%}$ release (y_2) is measured in minutes. [b] The tablet friability (y_3) is measured by percentage weight loss.

Table IV—Results of Multiple Regression Analyses[a]

Coefficients and Trend Components	Trend Component Name	Regression Coefficient Value: Tablet Hardness, y_1	*In Vitro* $t_{50\%}$, ln y_2[b]	Tablet Friability, ln y_3 + 3.0[b]	Table Volume, $y_4 \times 10^2$
B_{i0}	y-Intercept	0.96089×10^1	0.37657×10^1	0.45164×10^0	0.23441×10^1
$B_{i1}X_1$	Linear in X_1	0.31689×10^0	0.45581×10^{-1}	0.0	0.49647×10^{-2}
$B_{i2}X_2$	Linear in X_2	-0.33759×10^0	-0.55720×10^{-1}	0.72057×10^{-1}	0.83571×10^{-2}
$B_{i3}X_1^2$	Quadratic in X_1	-0.29915×10^{-2}	0.0	-0.20254×10^{-2}	0.79259×10^{-4}
$B_{i4}X_2^2$	Quadratic in X_2	0.21832×10^{-2}	0.0	0.0	0.0
$B_{i5}X_1X_2$	Linear × linear interaction	0.12626×10^{-2}	-0.17935×10^{-2}	-0.77965×10^{-2}	-0.52103×10^{-4}
$B_{i6}X_1X_2^2$	Linear × quadratic interaction	0.0	0.45949×10^{-4}	0.11249×10^{-3}	0.11770×10^{-5}
$B_{i7}X_1^2X_2$	Quadratic × linear interaction	0.0	0.0	0.18878×10^{-3}	0.0
$B_{i8}X_1^2X_2^2$	Quadratic × quadratic interaction	0.0	-0.20698×10^{-6}	-0.30361×10^{-5}	-0.19681×10^{-7}
Multiple correlation coefficient		0.9899	0.9982	0.9975	0.9983

[a] These analyses were performed on a polynomial of the form $y_i = B_{i0} + B_{i1}X_1 + B_{i2}X_2 + B_{i3}X_1^2 + B_{i4}X_2^2 + B_{i5}X_1X_2 + B_{i6}X_1X_2^2 + B_{i7}X_1^2X_2 + B_{i8}X_1^2X_2^2$, where i = 1, 2, 3, and 4. [b] Since the logarithmic transformation was applied to *in vitro* $t_{50\%}$ and tablet friability data to stabilize the variances, trend and regression analyses were performed on the transformed data.

available by superimposing the contour graphs for tablet hardness and *in vitro* $t_{50\%}$ on each other. Figure 6 illustrates the desired solution space (shaded portion of graph). Figure 6 points out the fact that there are many combinations of X_1 and X_2 producing responses which meet these restrictions on tablet hardness and *in vitro* release rate. When this is the case, the final selection of levels of X_1 and X_2 can be based on some other criterion such as cost. The reader interested in the different types of contour graphs and their physical interpretation is referred to Box (27).

Constrained Optimization—Since a reasonably rapid release rate of drug is generally an important objective in the design of solid dosage forms, optimization of this parameter was employed in studying the applicability of constrained optimization to a pharmaceutical product design problem. The problem was thus to locate levels of stearic acid (X_1) and starch (X_2) that minimized the *in vitro* release rate, such that the average tablet volume did not exceed 0.442 cm.^{3} (0.0270 in.^{3}) and the average friability value did not exceed 2.72%. Expressed mathematically, this constrained optimization problem was to minimize

$$y_2 = f_2(X_1,X_2) \qquad \text{(Eq. 11)}$$

such that the following constraints were not violated:

$$5 \leq X_1 \leq 45 \qquad \text{(Eqs. 12–13)}$$

$$1 \leq X_2 \leq 41 \qquad \text{(Eqs. 14–15)}$$

$$y_3 = f_3(X_1,X_2) \leq 2.72 \qquad \text{(Eq. 16)}$$

$$y_4 = f_4(X_1,X_2) \leq 0.0270 \qquad \text{(Eq. 17)}$$

Equations 12–15 serve as constraints to keep the X_1 and X_2 values in the known experimental region.

Figure 7 represents a graphical analysis of the constrained optimization problem defined by Eqs. 11–17. The shaded portion of the graph defines the region of feasible solutions where none of the constraints is violated. Any pair of X_1 and X_2 values within the shaded region meets the friability and volume constraints as well as the minimum starch percentage (Eqs. 14, 16, and 17), without consideration of such nonbinding constraints as those of Eqs. 12, 13, and 15. The dashed contour lines of Fig. 7 represent *in vitro* $t_{50\%}$ responses of 12, 20, and 33 min. Since this family of contour lines is decreasing in the direction of Point A, it is also evident that the minimum starch percentage of Eq. 14 will not be binding in a minimization problem. By eliminating obviously nonbinding inequality constraints, the optimization problem of Eqs. 11–17 reduces to the following: minimize

$$\ln y_2 = B_{20} + B_{21}X_1 + B_{22}X_2 + B_{25}X_1X_2 + B_{26}X_1X_2^2 + B_{28}X_1^2X_2^2 \qquad \text{(Eq. 18)}$$

such that

$$B_{30} + B_{32}X_2 + B_{33}X_1^2 + B_{35}X_1X_2 + B_{36}X_1X_2^2 + B_{37}X_1^2X_2 + B_{38}X_1^2X_2^2 + q_1^2 - (\ln 2.72 + 3.0) = 0 \qquad \text{(Eq. 19)}$$

$$B_{40} + B_{41}X_1 + B_{42}X_2 + B_{43}X_1^2 + B_{45}X_1X_2 + B_{46}X_1X_2^2 + B_{48}X_1^2X_2^2 + q_2^2 - (0.0270 \times 10^2) = 0 \qquad \text{(Eq. 20)}$$

Table V—Verification of Generated Polynomial Models

New Experimental Conditions: % Stearic Acid, X_1	% Starch, X_2	Variable	Predicted y_i from Polynomial	95% CI about the Single Prediction	Experimental Results
15.0	11.0	Hardness (y_1), kg.	10.4	8.8 – 12.1	9.4
15.0	31.0		5.9	4.3 – 7.5	4.4
35.0	11.0		14.1	12.4 – 15.7	14.6
35.0	31.0		10.1	8.4 – 11.7	9.6
15.0	11.0	*In vitro* $t_{50\%}$ (y_2), min.	37.3	31.7 – 43.8	34.4
15.0	31.0		12.3	10.4 – 14.4	12.9
35.0	11.0		68.0	57.9 – 80.2	72.8
35.0	31.0		19.9	16.9 – 23.4	19.9
15.0	11.0	Tablet friability (y_3), % wt. loss	3.18	2.32 – 4.36	4.14
15.0	31.0		7.04	5.13 – 9.66	6.64
35.0	11.0		0.55	0.40 – 0.78	0.51
35.0	31.0		1.21	0.88 – 1.66	1.21
15.0	11.0	Table volume (y_4), in.^{3}	0.0252	0.0249 – 0.0255	0.0254
15.0	31.0		0.0268	0.0266 – 0.0271	0.0272[a]
35.0	11.0		0.0269	0.0266 – 0.0272	0.0270
35.0	31.0		0.0283	0.0281 – 0.0286	0.0284

[a] This value fell slightly outside the 95% confidence range for a single prediction.

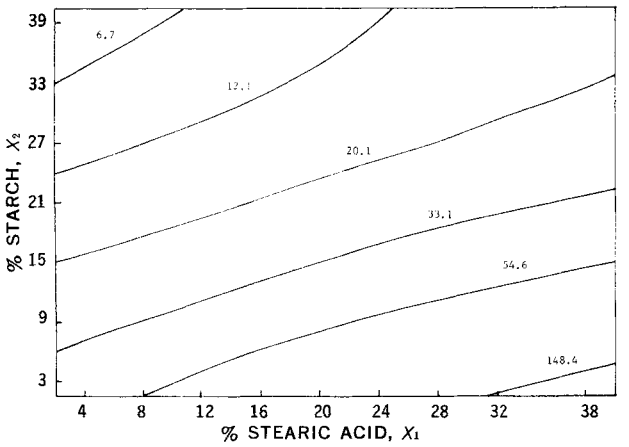

Figure 3—*Contour curves for* in vitro $t_{50\%}$ *(minute), illustrating levels of starch and stearic acid producing similar responses.*

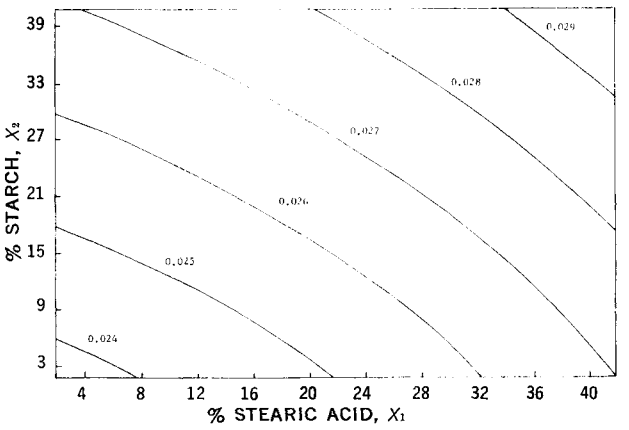

Figure 5—*Contour curves for tablet volume (cubic inch), illustrating levels of starch and stearic acid producing similar responses.*

In Eqs. 18–20, the regression models developed earlier (Table IV) have been substituted into Eqs. 11, 16, and 17. The slack variables q_1 and q_2 have been included in Eqs. 19 and 20 in order that these constraints may be written as equality constraints. The formulated Lagrange function is then

$$F = B_{20} + B_{21}X_1 + B_{22}X_2 + B_{25}X_1X_2 + B_{26}X_1X_2^2 + B_{28}X_1^2X_2^2 + \lambda_1(B_{30} + B_{32}X_2 + B_{33}X_1^2 + B_{35}X_1X_2 + B_{36}X_1X_2^2 + B_{37}X_1^2X_2 + B_{38}X_1^2X_2^2 + q_1^2 - 4.000) + \lambda_2(B_{40} + B_{41}X_1 + B_{42}X_2 + B_{43}X_1^2 + B_{45}X_1X_2 + B_{46}X_1X_2^2 + B_{48}X_1^2X_2^2 + q_2^2 - 2.70) \quad \text{(Eq. 21)}$$

where λ_1 and λ_2 are terms known as Lagrange multipliers. As can be seen from Eq. 21, one is introduced for each constraint.

The original constrained optimization problem involving three equations has now been converted into an unconstrained minimax problem involving one equation. The minimax solution of Eq. 21 defines values of X_1 and X_2 which minimize the *in vitro* $t_{50\%}$ value subject to the constraints on tablet friability and volume. When this Lagrange function is partially differentiated with respect to each variable, each differentiation is set equal to zero, and the set of six equations is solved simultaneously, the values of each variable are

$$X_1^* = 22.5\% \quad \lambda_1 = 0.50 \quad q_1 = 0.0$$
$$X_2^* = 26.8\% \quad \lambda_2 = 2.90 \quad q_2 = 0.0$$

By substituting these values of X_1 and X_2 into Eq. 18, $t^*_{50\%}$ = 17.9 min., which is the best release rate that can be achieved under the restrictions involved. Since $q_1 = q_2 = 0.0$, both previously described constraints are binding as indicated by Fig. 7, where it is evident that the contour line for $t^*_{50\%}$ = 17.9 min. would pass through Point A, where the contour lines for y_3 = 2.72% and y_4 = 0.442 cm.^{3} (0.0270 in.^{3}) cross.

Sensitivity Analysis—The solution to a constrained optimization problem may depend heavily upon the restricting values assigned to the secondary objectives or constraints. Consequently, minor modifications in these restricting values may result in a substantial improvement in the primary objective. Sensitivity analysis serves to identify the changes in the primary objective resulting from such modifications of the restricting values. Sensitivity analysis involves solving the constrained optimization problem for systematic changes of the restricting values assigned to the secondary objectives. Mathematically, the problem is to minimize ln y_2, such that

$$\ln y_3 + 3.0 \leq \ln \alpha_k + 3.0 \quad \text{(Eq. 22)}$$

$$5 \leq X_1 \leq 45, \text{ and } 1 \leq X_2 \leq 41 \quad \text{(Eqs. 23–24)}$$

The restraining values of percent friability (α_k) were allowed to assume the following values: 0.3, 0.4, 0.5, 0.6, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0. These results are shown in Fig. 8, and they demonstrate that substantial improvements in $t^*_{50\%}$ can be obtained for values of α_k up to about 1–2%. Beyond 2%, the rate of decrease of $t^*_{50\%}$ is very low. Consequently, the scientist designing the drug product can evaluate the potential gains in the primary objective which accrue from modifications of restraining values on secondary objectives. An objective decision on whether or not restraining values on secondary objectives should be relaxed (or tightened), and by how much, is thus made possible. Also, the locus of X_1^* and X_2^* points may be shown as a function of α_k, as demonstrated by Fig. 9, so that any decision on the revision of α_k can immediately provide a revised solution in terms of the tablet formulation.

Frequently, it is useful to consider the sensitivity of multiple constraints which requires a Lagrangian solution for each different combination of restricting values. For example, if the friability restriction was retained as α_k and a tablet volume constraint of

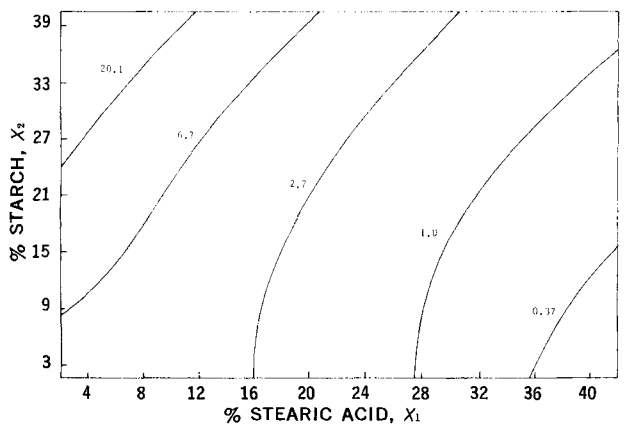

Figure 4—*Contour curves for tablet friability (percent weight loss), illustrating levels of starch and stearic acid producing similar responses.*

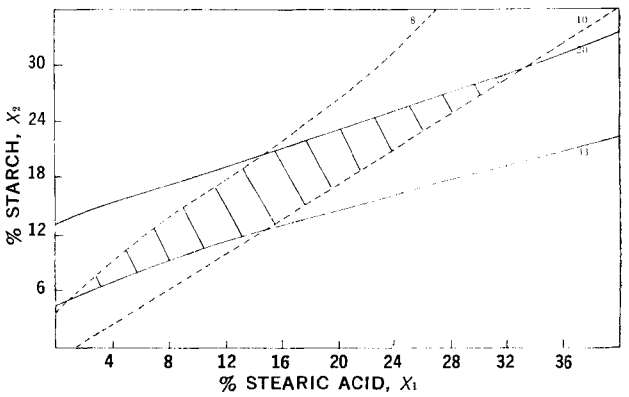

Figure 6—*Feasible solution space defined by hypothetical restrictions on tablet hardness and* in vitro $t_{50\%}$ *release rate. Key: - - -, hardness contours (kilogram); and —,* in vitro $t_{50\%}$ *contours (minute).*

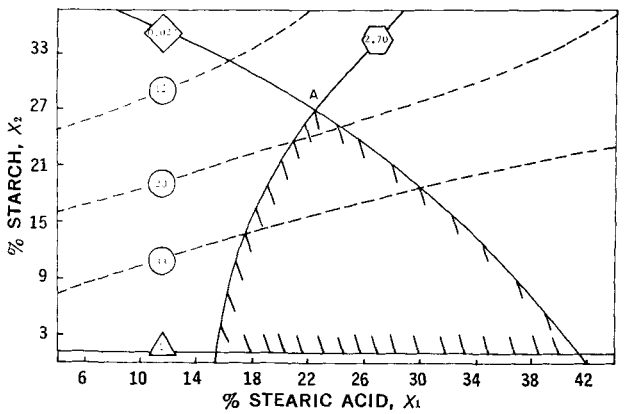

Figure 7—*Graphical analysis of constrained optimization problem defined by Eqs. 26–32. Key:* O, in vitro $t_{50\%}$ *(minute);* ◇, *volume (cubic in.);* ○, *hardness (kilogram); and* △, *percent starch.*

β_k' was added, then each α_k, β_k' combination requires a new solution that provides $t^*_{50\%}$, X_1^*, and X_2^* values. The results for nine combinations of α_k and β_k' for this example are shown in Table VI. An examination of the X_1^* and X_2^* values indicates that none of the experimental condition constraints was binding. Figure 10 provides a graphic illustration of $t^*_{50\%}$ as a function of α_k and β_k'. Figure 10 demonstrates that a sizable improvement in $t^*_{50\%}$ can be achieved by relaxing α_k and β_k' values, but the rate of improvement drops off sharply past the midvalue of $\alpha_k = 2.70$ and $\beta_k' = 0.0270$.

Constrained Optimization and *In Vivo* Studies—Clinical trials performed on a new drug in its various dosage forms or dosage form modifications may result in information on the relationship between blood levels, level of therapeutic action, duration of action, toxicity properties, and the absorption rate or possibly the consequent elimination rate of the drug. Establishment of such relationships could lead to criteria being established on the absorption rate or consequent elimination rate in order that the best therapeutic response and/or duration of effect and minimal toxicity be achieved. The results of urinary elimination-rate studies performed on certain formulas used in this investigation are presented in Table VII. The time in hours for 50% of the drug to be eliminated ($t'_{50\%}$) was used as a measure of the urinary elimination rate of the drug as modified by the availability from the respective formulation. The linear correlation coefficients for the semilog plots of drug retention *versus* time all exceeded 0.98, indicating that the excretion of phenylpropanolamine hydrochloride followed an apparent first-order process. A comparison of the mean *in vitro* ($t_{50\%}$) and *in vivo* ($t'_{50\%}$) data showed that the rank order of the formulations was the same for each criterion. Further analysis revealed that the logarithm of the mean *in vivo* $t'_{50\%}$ data correlated very highly ($r = 0.993$) with the mean *in vitro* $t_{50\%}$ data on a linear scale. Figure 11 depicts this plot and illustrates the correlation. The confidence bands about the $t'_{50\%}$ values represent 95% confidence intervals. It would appear that prediction of the *in vivo* $t'_{50\%}$ response from a knowledge of the *in vitro* $t_{50\%}$ response can be made fairly accurately for the tablet system used in this study, employing the correlation curve appearing in Fig. 11.

To illustrate the utility of the constrained optimization approach as applied to *in vivo* data, a sample constrained optimization problem was formulated and solved using the Lagrangian method.

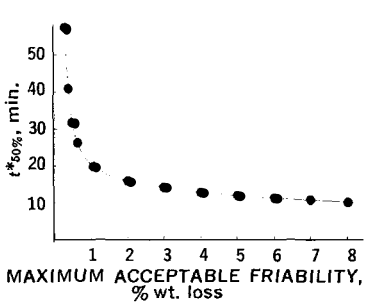

Figure 8—*Optimum* in vitro $t_{50\%}$ *release rate as a function of restrictions on tablet friability.*

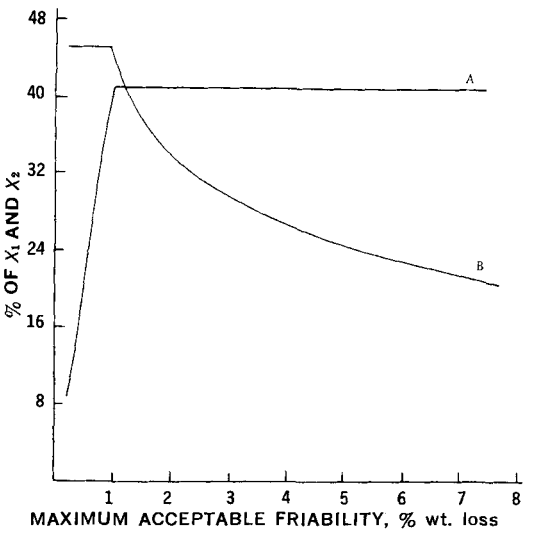

Figure 9—*Optimizing values of stearic acid and starch as a function of restrictions on tablet friability. Key: A, percent starch; and B, percent stearic acid.*

The following situation was assumed to exist in this illustrative example:

1. The primary objective was to minimize tablet friability or its equivalent ($\ln y_3 + 3$).
2. Secondary objectives were to maintain a reproducible fill in the packaging container and to avoid noticeable differences in tablet size so that the tablet volume (y_4) is held within the interval 0.0261–0.0269.
3. Another secondary objective was to keep the *in vivo* elimination half-life below 6.5 hr. for the desired therapeutic effect of this drug.

In constrained optimization form, the problem may be mathematically stated as: minimize

$$(\ln y_3 + 3.0) = f_3(X_1, X_2) \qquad \text{(Eq. 25)}$$

such that

$$2.61 \leq y_4 \times 10^2 \leq 2.69, \text{ and} \qquad \text{(Eqs. 26–27)}$$

$$0.69937 + (0.1908 \times 10^{-2})(e^{\ln y_2}) \leq \log 6.5 \qquad \text{(Eq. 28)}$$

In Eq. 28, the left-hand side of the equation represents the least-squares estimate of the curve appearing in Fig. 11, and $\ln y_2$ as a function of X_1 and X_2 can be found in Table IV.

Employing the Lagrangian method, the solution to the constrained optimization problem (Eqs. 25–28) was found to be as follows: $X_1^* = 34.1\%$, $X_2^* = 13.3\%$, and $y_3^* = 0.64\%$ wt. loss. The volume constraint of Eq. 26 was nonbinding, and the other two constraints (Eqs. 27–28) were binding. To demonstrate further the validity of this approach to tablet design, a formulation was prepared using the optimal percentages of stearic acid and starch (34.1 and 13.3%, respectively) and the empirical test results were

Table VI—Optimizing Percentages of Stearic Acid and Starch and the Corresponding Optimal *In Vitro* Release Rate as a Function of Simultaneous Restraining Values on Tablet Friability and Volume

Maximum Acceptable Constraints		Optimizing Values of Controllable Variables		Optimum *In Vitro* Release Rate
Friability, % wt. loss	Volume, cm.³ (in.³)	% Stearic Acid, X_1^*	% Starch, X_2^*	($t^*_{50\%}$), min.
1.00	0.426 (0.0260)	27.9	7.9	71.6
	0.442 (0.0270)	30.7	18.2	34.9
	0.459 (0.0280)	23.8	26.5	23.8
2.70	0.426 (0.0260)	18.7	17.7	26.0
	0.442 (0.0270)	22.5	26.8	17.9
	0.459 (0.0280)	27.1	34.8	14.8
7.40	0.426 (0.2060)	10.9	23.9	15.4
	0.442 (0.0270)	32.6	32.8	11.6
	0.459 (0.0280)	20.6	40.4	10.6

Table VII—Results of Urinary Excretion Studies for Tablets Containing Various Concentrations of Starch and Stearic Acid

Formulation No.[a]	Subject	Urinary Excretion Rate ($t'_{50\%}$), hr.	Mean ($t'_{50\%}$), hr.	*SD*
Solution of Drug	1	6.30		
	2	4.09		
	3	4.38	4.95	0.853
	4	5.09		
	5	4.88		
3	1	4.62		
	2	4.57		
	3	6.71	5.20	0.874
	4	5.05		
	5	5.07		
1	1	5.70		
	2	5.94		
	3	7.34	6.23	0.641
	4	6.07		
	5	6.09		
4	1	9.13		
	2	7.00		
	3	11.77	9.14	1.723
	4	9.17		
	5	8.62		
7	1	22.68		
	2	13.48		
	3	16.54	18.00	6.878
	4	17.66		
	5	19.65		

[a] See Table I.

compared with the theoretical values predicted. These results appear in Table VIII, and the *in vivo* urinary elimination rate curves appear in Fig. 12. The mean tablet volume of 0.442 cm.^{3} (0.0270 in.^{3}) and the mean $t'_{50\%}$ excretion of 6.4 hr. were very close to the theoretical predictions of 0.0269 and 6.5, respectively. By optimizing the tablet friability, a cohesive tablet was formed, with an average friability weight loss of about 0.58%, which is sufficiently close to the theoretical prediction of 0.64%.

Pharmaceutical Process Optimization—Reier *et al.* (4) have recently quantified the weight and weight variation of filled capsules with controllable process variables. They found the significant set

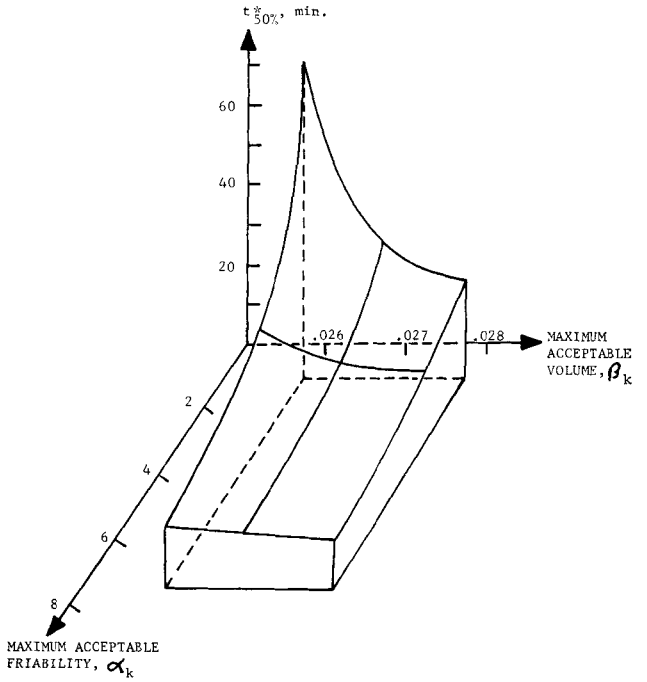

Figure 10—*Optimum* $t_{50\%}$ *as a function of restrictions on tablet friability and volume.*

Table VIII—Experimental Response Values for the Optimal Tablet Formulation of 34.1% Stearic Acid and 13.3% Starch

Volume, cm.^{3} (in.^{3})	Tablet Friability, % wt. loss	Urinary Excretion Rate ($t'_{50\%}$), hr.
0.442 (0.0270)	0.58	5.0
0.442 (0.0269)	0.55	5.9
0.442 (0.0270)	0.57	7.1
0.442 (0.0270)	0.63	7.8
0.444 (0.0271)	0.55	6.3
Mean: 0.442 (0.0270)	0.58	6.4

of controllable variables to be: (*a*) machine speed, r.p.m. (X_1); (*b*) capsule size, cm.^{3} (X_2); (*c*) specific volume, ml./g. (X_3); (*d*) flowability, in.^{2} (X_4); and (*e*) presence or absence of talc (X_5). Regression models relating these controllable variables with mean gross capsule weight (y_1), capsule weight standard deviation (y_2), and capsule weight coefficient of variation (y_3) were given. These regression models can be employed to formulate an unconstrained optimization problem for determining levels of machine speed (X_1), specific volume (X_3), and flowability (X_4), which minimize the capsule weight coefficient of variation (y_3). Assuming that talc is present in the formulation, the model for y_3, using the data of Reier *et al.* (4), becomes

$$y_3 = 4.15 + 0.04X_1^2 + 0.23X_3^2 - 1.86X_4 + 0.45X_4^2 - 0.15X_1X_3 - 0.11X_1X_4 \quad \text{(Eq. 29)}$$

Taking the first partial derivatives of Eq. 29 with respect to X_1, X_3, and X_4, setting these expressions equal to zero, and solving this set of three simultaneous linear equations produced the following: X_1^* = 13.3 r.p.m., X_3^* = 4.34 ml./g., and X_4^* = 3.75 in.^{2} At this global minimum, y_3^* = 0.78%. However, the values for X_1^* and X_3^* far exceed values used by the authors in deriving Eq. 29 and may, therefore, not be valid. An interesting point is, however, that this information would suggest using a light, free-flowing powder and a high machine speed to minimize capsule weight variation. Since the maximum machine speed used by Reier *et al.* (4) was 8.7 r.p.m., the optimization problem may be reformulated using this maximum machine speed as fixed, or:

$$y_3 = 7.18 - 1.31X_3 - 2.82X_4 + 0.23X_3^2 + 0.45X_4^2 \quad \text{(Eq. 30)}$$

The solution to Eq. 30 is a global minimum at X_3^* = 2.85 ml./g. and X_4^* = 3.13 in.^{2}, with the criterion of y_3^* = 0.90% at this minimum. Insofar as these regression models hold for various possible formulations, which appear to be reasonably general, the values X_1^* = 8.7, X_3^* = 2.85, and X_4^* = 3.13 for the controllable variables minimize the capsule weight coefficient of variation. If y_3 is independent of capsule size, which appears valid for at least moderate variations, then the solution to this optimization problem holds for various capsule sizes.

However, it may not always be practical to utilize these optimum operating conditions. Often the bulk formulation, capsule size, and weight are specified in advance. As an example, assume the following information has been prespecified: (*a*) capsule size = No. 0, or X_2 = 0.699; (*b*) capsule weight = 400 mg., or y_1 = 400; (*c*) specific volume of powder = 2.80 ml./g., or X_3 = 2.80; and (*d*) talc is present, or X_5 = +1. The objective is to locate levels of machine speed (X_1) and flowability (X_4) which minimize the capsule weight

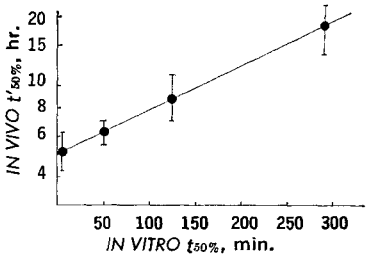

Figure 11—*Correlation of* in vivo *and* in vitro *release rate data.*

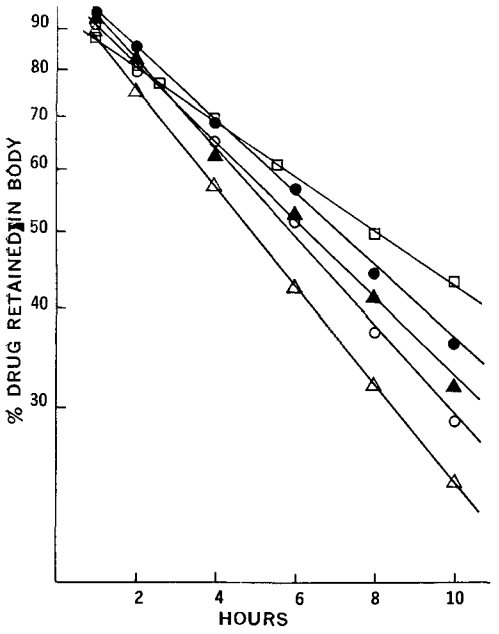

Figure 12—*Urinary excretion data from five humans for the optimal tablet formulation of 34.1% stearic acid and 13.3% starch. Key:* O, *Subject 1;* △, *Subject 2;* □, *Subject 3;* ●, *Subject 4; and* ▲, *Subject 5.*

coefficient of variation. This represents a constrained optimization problem which may be formulated as follows: minimize

$$y_3 = 6.09 - 1.86X_4 + 0.04X_1^2 - 0.45X_4^2 - 0.42X_1 - 0.11X_1X_4 \quad \text{(Eq. 31)}$$

such that

$$548.49 - 32.27X_1 - 11.20X_2 + 1.92X_1^2 = 400 \quad \text{(Eq. 32)}$$

The Lagrangian expression then becomes

$$F = 6.09 - 1.86X_4 + 0.04X_1^2 + 0.45X_4^2 - 0.42X_1 - 0.11X_1X_4 + \lambda(148.49 - 32.27X_1 - 11.20X_2 + 1.92X_1^2) \quad \text{(Eq. 33)}$$

By partially differentiating Eq. 33 and solving this set of nonlinear equations, it was found that $X_1^* = 5.63$ r.p.m., $X_4^* = 2.47$ in.^{2}, and $y_3^* = 1.62$. Thus, for a 400-mg. No. 0 capsule, whose contents have a specific volume of 2.8 ml./g., the minimum coefficient of variation possible is 1.62, and this is achieved at a machine speed setting of 5.63 r.p.m. and a flowability value of 2.47 in.^{2}

SUMMARY

The use of constrained optimization techniques, employing the Lagrangian method, has been successfully applied to complex pharmaceutical product and process design problems involving many competing objectives. Location of optimal solutions to pharmaceutical design problems by this analytical–mathematical approach has been demonstrated. In most situations the location of the theoretical optimal solution point can provide the starting reference for adjustments due to other practical considerations, thereby permitting more rapid and accurate solution of the design problem. The steps involved in solving a design problem *via* the constrained optimization approach may be summarized as follows:

Identify important response variables y_j, $j = 1, 2, \ldots, r$, the significant set of controllable variables X_i, $i = 1, 2, \ldots, n$, and measures on both classes of variables.

Determine a mathematical relationship between each y_j as a function of X_i, either analytically or empirically.

Select the response variable which is of greatest importance as the principal objective to be optimized and place control limits on the remaining response variables.

Solve the resultant constrained optimization problem by one of the several existing techniques.

In addition to finding optimal solutions to constrained pharmaceutical problems, the application of sensitivity analysis studies to such problems was also illustrated. The rate of change of the optimal response in the principal objective to changes of restrictions on the competing or lesser important objectives was analyzed for a product design problem.

The mathematical and statistical techniques described in this paper are suggested as an improvement over the trial-and-error approach widely employed today in pharmaceutical product and process design. Improved reliability of the research effort and a saving in time and money are the direct results of this sophisticated approach to pharmaceutical research problems.

APPENDIX A

Example 1—Locate the levels of X_1 and X_2 which maximize

$$y = X_1X_2 \quad \text{(Eq. A-1)}$$

such that

$$X_1 + X_2 = 4 \quad \text{(Eq. A-2)}$$

Since the constraint in Eq. A-2 is already in the form of an equality constraint, the Lagrangian function can be formed immediately:

$$F = X_1X_2 + \lambda(X_1 + X_2 - 4) \quad \text{(Eq. A-3)}$$

Taking the first partial derivatives of the Lagrangian function (Eq. A-3) and setting the resulting equations equal to zero,

$$\partial F/\partial X_1 = X_2 + \lambda = 0 \quad \text{(Eq. A-4)}$$

$$\partial F/\partial X_2 = X_1 + \lambda = 0 \quad \text{(Eq. A-5)}$$

$$\partial F/\partial \lambda = X_1 + X_2 - 4 = 0 \quad \text{(Eq. A-6)}$$

Solving these three equations simultaneously, $X_1^* = 2$, $X_2^* = 2$, and $\lambda = -2$. Substituting these values of X_1 and X_2 back into the objective function (Eq. A-1), it was found that $y^* = 4$. Thus, the maximum response in y that can be obtained subject to the constraint of $X_1 + X_2 = 4$ is 4 units. This constrained optimization problem is represented graphically in Fig. A-1. Contour curves for objective function responses of 2, 4, and 6 units are shown. The dashed, straight line in Fig. A-1 represents the constraint (Eq. A-2), and Point A depicts the optimal solution point ($X_1^* = 2$, $X_2^* = 2$).

Example 2—Locate the levels of X_1 and X_2 which minimize

$$y = X_1^2 + X_2^2 \quad \text{(Eq. A-7)}$$

such that

$$X_1 + X_2 \geq 4 \quad \text{(Eq. A-8)}$$

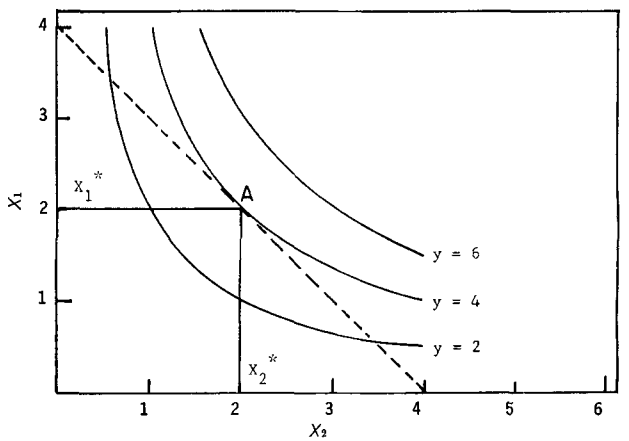

Figure A-1—*Graphical solution for constrained optimization problem of Eqs. A-1 and A-2. Key:* - - -, *contour line for* $X_1 + X_2 = 4$.

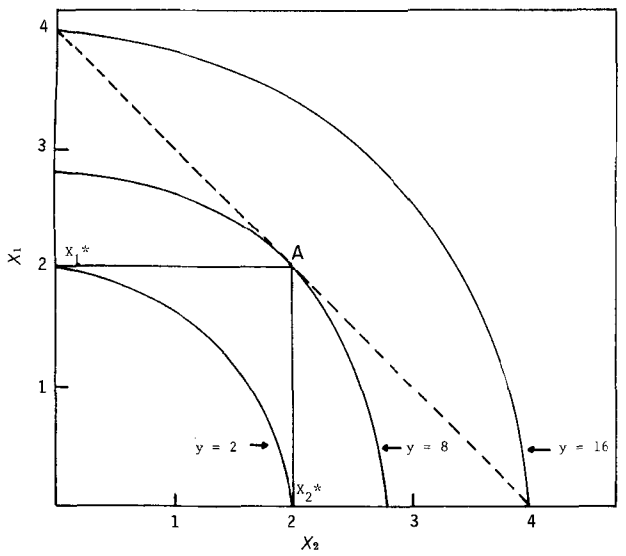

Figure A-2—*Graphical solution for constrained optimization problem of Eqs. A-7 and A-8. Key: - - - -, contour line for* $X_1 + X_2 = 4$.

The inequality constraint of Eq. A-8 must first be converted to an equality constraint by introducing a slack variable, q. Thus, Eq. A-8 may be written as

$$X_1 + X_2 - q^2 = 4 \qquad \text{(Eq. A-9)}$$

and the Lagrangian function becomes

$$F = X_1^2 + X_2^2 + \lambda(X_1 + X_2 - q^2 - 4) \qquad \text{(Eq. A-10)}$$

Taking the first partial derivatives of Eq. A-10 and setting these expressions equal to zero,

$$\partial F/\partial X_1 = 2X_1 + \lambda = 0 \qquad \text{(Eq. A-11)}$$

$$\partial F/\partial X_2 = 2X_2 + \lambda = 0 \qquad \text{(Eq. A-12)}$$

$$\partial F/\partial \lambda = X_1 + X_2 - q^2 - 4 = 0 \qquad \text{(Eq. A-13)}$$

$$\partial F/\partial q = -2\lambda q = 0 \qquad \text{(Eq. A-14)}$$

Solving these four equations simultaneously, $X_1^* = 2$, $X_2^* = 2$, $q = 0$, and $\lambda = -4$. At this optimal solution point, $y^* = 8$ units. This constrained optimization problem is represented graphically in Fig. A-2. Point A in Fig. A-2 illustrates the minimum response in y that can be achieved under the restriction that $X_1 + X_2 \geq 4$. At the simultaneous solution point for Eqs. A-11–A-14, it is noted that $q = 0$. Thus, at the optimal solution point, $X_1 + X_2 = 4$.

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