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*Report*

# A Statistical Approach for the Development of an Oral Controlled-Release Matrix Tablet

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Tablet matrix compositions for optimized prolonged release were selected by surface response methodology. The extreme vertices experimental design was used to develop a surface response model which mathematically defined the release of active component from the tablet matrix as controlled by the percentage of the excipient components. The model, a statistical quadratic equation with a standard error of 3.3, was validated for accurate prediction of drug release profiles and used to identify optimum formulations. This study demonstrated a new application of the extreme vertices experimental design, an efficient method for evaluating a complex mixture system for controlled release, where specific constraints are placed on one or more of the components.

KEY WORDS: controlled release; extreme vertices; surface response modeling; optimization.

## INTRODUCTION

The objective of this study was to optimize a tablet matrix for controlled release and to demonstrate a new application of the extreme vertices experimental design. The extreme vertices method is a fixed design for surface response modeling developed by McLean and Anderson (1) specifically for mixture systems where constraints are placed on the quantity of one or more components of the formulation. McCurdy (2) used this approach to evaluate the effect of sugar coating solution composition of the physical properties of coated tablets. In this study the extreme vertices experimental method was used to model the effect of the percentages of four tablet excipients on the release of an active component from the tablet matrix.

Initial experiments were conducted to establish approximate lower and upper limits on the percentage of each component required for the tablet matrix to function as a prolonged release dosage form. These constraints were used in an algorithm to determine experimental treatment combinations, or tablet formulations. Tablet compositions defined by the algorithm were manufactured, including duplication of two compositions for an independent estimate of error. Using dissolution test data from these tablets, a model was developed which mathematically defined the effect of tablet composition on release of the active component. The model was validated by testing its capability of predicting the dissolution profiles of five tablet compositions selected at random from the experimental inference space as defined by the extreme vertices algorithm. After model validation had been completed, a predicted optimum formulation was manufactured on a rotary tablet press. When tested in human subjects, the optimized tablet formulation demonstrated the required prolonged serum levels and 93% bioavailability compared to multiple doses of a commercially available solution dosage form.

## STATISTICAL THEORY

The measured response of a mixture system, such as a tablet, composed of $q$ components depends only on the fractional proportions of each component, $x_{ij}$, and not on the total amount of the mixture (3). A universal constraint on all mixture systems is that the sum of all component proportions add to 1.0.

$$\sum_{i=1}^{q} x_i = 1.0 \qquad (1)$$

As a result of this constraint, a change in the level of one component requires an adjustment in the level of at least one other component, thus, the proportion of a single component may not be adjusted independently of all other components. Factorial experimental designs may not be suitable for surface response modeling of mixtures because the experimental treatment combinations are determined by independent adjustments of each component level, a condition which is impossible to achieve for mixture systems with constant weight. Other types of surface response models may provide a more appropriate approach to the design of experiments for mixture formulations.

Some of these surface response modeling methods

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which have been applied to the study of mixture systems include the polynomial models, the ratio models, the simplex methods, and the extreme vertices design. Several criteria were important in selecting the best method. The experimental design selected for surface response modeling should efficiently characterize the entire mixture space. The polynomial modeling methods were inappropriate for this study because they would not cover the entire mixture space adequately (4). Snee (5) demonstrated the effectiveness of the ratio model, but computational complications are prohibitive for systems composed of more than three components. The simplex method has been widely used for mixture analyses, but this method cannot accommodate constraints on the mixture component levels unless the ranges of each component are equal (6). The extreme vertices experimental design of McLean and Anderson was developed specifically for mixtures with constraints on the proportions of one or more components and was selected for this study because the entire mixture space could be covered with a reasonable number of formulations. Computations, data analysis, and modeling were straightforward, and the unequal range of constraints on the tablet matrix components could be factored into the experimental design.

A description of the extreme vertices design helps to explain its application. Given a mixture of $q$ components ($x_1$, $x_2$, . . . , $x_q$) with a lower constraint, $a_i$, and an upper constraint, $b_i$, on each component such that $0 \leq a_i \leq x_i \leq b_i$, then the experimental treatment combinations for the extreme vertices design are uniquely determined as described by the algorithm of Anderson and McLean (1,6), as demonstrated in the Appendix. After the treatment combinations are prepared, the experimental samples are tested, the data are collected, and a model is fit to the data. The model, or surface contours, then is examined to determine the regions where the best response values may be obtained (7). The surface response of interest, $E(y)$, may be described by the extreme vertices linear quadratic equation as follows (6):

$$E(y) = \sum_{i=1}^{q} \beta_i x_i + \sum_{\substack{i=1 \\ i<j\leq q}}^{q} \beta_{ij} x_i x_j \qquad (2)$$

where $x_i$ is the fractional level of component $i$ and $\beta_i$ is the regression coefficient for component $x_i$.

## MATERIALS AND METHODS

All materials were pharmaceutical or food grade, and no organic solvents were used. Each tablet contained 17.14% active ingredient and 5.00% lubricant. Some characteristics of the experimental components $x_1$, $x_2$, $x_3$, and $x_4$ are summarized in Table I.

Eighteen experimental formulations were determined by the algorithm of Anderson and McLean (6), using the constraint levels shown in Table I as demonstrated in the Appendix. Of the 18 formulations, 16 were unique and 2 were replicates for an independent estimate of the error mean square for batches, which was the experimental inferential unit. Eight extreme vertices, or extrema, were identified which defined the geometric boundaries of a seven-sided hyperpolyhedron which represents the experimental mixture space as shown in Fig. 1. Eight additional experimental points were determined, one at the center of each of the seven faces of the heptahedron and one at the geometric center of the mixture space, designated the centroid point in Table II.

Table I. The Constraint Limits and General Characteristics of the Experimental Components of the Tablet Matrix

| Component | Material type | Lower constraint fraction | Upper constraint fraction |
|---|---|---|---|
| $x_1$ | Soluble adhesive | 0.100 | 0.300 |
| $x_2$ | Insoluble film-former | 0.025 | 0.075 |
| $x_3$ | Insoluble adhesive | 0.200 | 0.400 |
| $x_4$ | Insoluble excipient | 0.200 | 0.500 |

The materials were processed using conventional pharmaceutical equipment and compressed on a motorized laboratory press (Fred S. Carver Inc.). Drug release profiles for each formulation were determined for six tablets using USP Dissolution Method II, the paddle method. The equipment setup included a six-station multiple-spindle drive and dissolution drive control (Hanson Research Corp.) for stirring six standard Teflon-coated paddles at 100 rpm. The dissolution vessels were USP standard 1000-ml round-bottom flasks (Pyrex) which were filled with 900 ml of the appropriate dissolution medium. The schedule and compositions of the dissolution media are given in Table III. The temperature of the test media was maintained at 37°C by a constant-temperature water bath. Samples of 4.0 ml of the dissolution fluid each were collected and immediately filtered through a 0.45-μm filter at 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 8.0, 10.0, and 12.0 hr. The sample volume was replaced with 4.0 ml of fresh solution. Dilution effects were accounted for in the calculations of the concentration of the active ingredient. Evaporation of the dissolution fluid was minimized by covering the dissolution flasks during the test. Sink conditions were main-

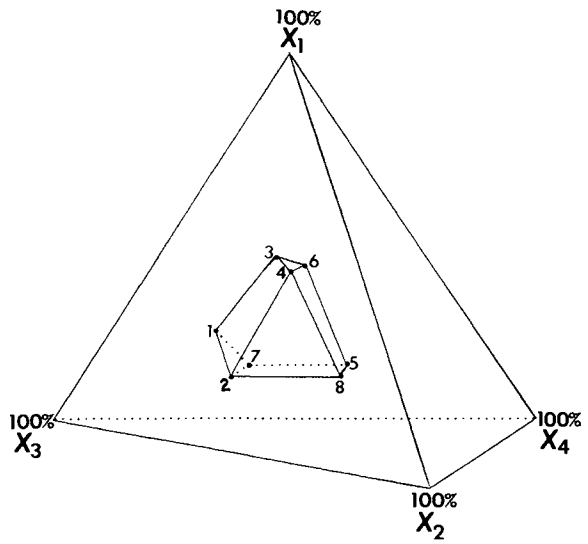


Fig. 1. A geometric representation of the mixture space of the extreme vertices experiment.

Table II. The Experimental Treatment Combinations for the Extreme Vertices Surface Response Experiment

| | Treatment combination | Percentage of each component | | | |
|---|---|---|---|---|---|
| | | $X_1$ | $X_2$ | $X_3$ | $X_4$ |
| Extrema | 1 | 15.4 | 2.5 | 40.0 | 20.0 |
| | 2 | 10.2 | 7.5 | 40.0 | 20.2 |
| | 3 | 30.0 | 2.5 | 25.4 | 20.0 |
| | 4 | 30.0 | 7.5 | 20.2 | 20.2 |
| | 5 | 10.0 | 2.5 | 20.0 | 45.4 |
| | 6 | 30.0 | 2.5 | 20.0 | 25.4 |
| | 7 | 10.0 | 2.5 | 40.0 | 25.4 |
| | 8 | 10.0 | 7.5 | 20.0 | 40.4 |
| Midpoints of facial planes | 9 | 19.1 | 2.5 | 29.1 | 27.2 |
| | 10 | 16.7 | 7.5 | 26.7 | 26.9 |
| | 11 | 21.4 | 5.0 | 31.4 | 20.1 |
| | 12 | 11.8 | 4.2 | 40.0 | 21.8 |
| | 13 | 20.0 | 5.0 | 20.0 | 32.8 |
| | 14 | 10.0 | 5.0 | 30.0 | 32.8 |
| | 15 | 30.0 | 4.2 | 21.9 | 21.8 |
| Centroid | 16 | 18.2 | 4.4 | 28.2 | 27.1 |

tained with solubility exceeding maximum concentration by a factor of at least 125.

The concentration of the active ingredient in the dissolution samples was determined by UV detection using a spectrophotometer (Beckman Model DU-7).

## RESULTS AND DISCUSSION

Three criteria were established for the target drug release profile: (i) a loading dose of 17–33% of the total drug released within the first 0.5 hr, followed by (ii) prolonged release of the remaining drug over the next 10–12 hr, preferably at a relatively constant rate, and (iii) at least 90% of the total dose dissolved after 12 hr.

The three example profiles in Fig. 2 represent the fastest and slowest release profiles observed as well as one of the intermediate profiles. Drug dissolution from different experimental formulations was complete in as little as 4.0 hr to a maximum of more than 12.0 hr. The amount of active ingredient released during the first 0.5 hr of the dissolution test was similar for all formulations, varying from 18.6 to 25.9% of the total dose, which is within the recommended loading dose of the compound (8). The cumulative percentage of the dose released from the systems after 12.0 hr ranged from 65 to 100%. The intermediate curve in Fig. 2, for example, met the criteria for the target drug release profile. A loading dose was released by 0.5 hr, followed by prolonged release for the

Table III. Schedule of Media for the Dissolution Test

| Time (hr) | pH | Dissolution medium |
|---|---|---|
| 0.0 to 1.5 | 1.2 | Simulated gastric fluid, USP[a] |
| 1.5 to 3.5 | 4.5 | Simulated intestinal fluid, USP[a,b] |
| 3.5 to 12.0 | 6.8 | Simulated intestinal fluid, USP[a,b] |

[a] Without enzymes, adjusted to equivalent ionic strength with NaCl.
[b] Adjusted to pH shown by the addition of 10% HCl solution sink conditions maintained for all media; no common ion effect.

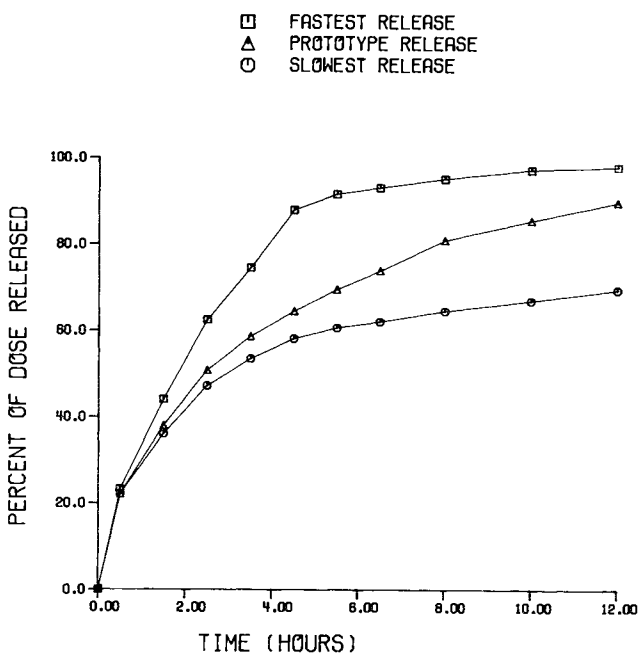


Fig. 2. Drug dissolution profiles representing the range of release patterns obtained from the extreme vertices experiment.

remainder of 12.0 hr. The cumulative percentage of the dose released over 12.0 hr exceeded the 90% minimum.

All formulations contained 17.1% active ingredient and 5.0% lubricant by weight. The formulation which released the active ingredient the most rapidly, extremum No. 6 in Table II, was composed of 30.0, 2.5, 20.0, and 25.4% of components $x_1$, $x_2$, $x_3$, and $x_4$, respectively. This formulation contained the lower limit of the water insoluble components $x_2$ and $x_3$ and the upper limit of the water-soluble component $x_1$. The 12-hr dose of drug was completely released from the tablet by 5.5 hr, so release of the active ingredient from this formulation was too rapid. By comparison, the formulation which released the active ingredient most slowly, extremum No. 2 in Table II, contained 10.2% $x_1$, 7.5% $x_2$, 40.0% $x_3$, and 20.2% $x_4$, which was the lower limit of the water-soluble component $x_1$ and the upper limit of the water-insoluble components $x_2$ and $x_3$. Only 65% of the total amount of active ingredient was released after 12.0 hr of the dissolution testing.

The dissolution data from all formulations of the extreme vertices experiment were fit by a quadratic polynomial [Eq. (2)] by computer-assisted multiple regression analysis using the stepwise method of SPSS (Statistical Package for the Social Sciences). The $F$-test ratio for including a regressor into the equation was initially set at 0.01 ($F_{IN} = 0.01$) and the $F$-test ratio for deleting or excluding a regressor from the model was set at 0.005 ($F_{OUT} = 0.005$). These values were set low to assure that all significant regressors were included in the initial model. For the final model the values of $F_{IN}$ and $F_{OUT}$ were set at 4, which approximates the 95% confidence level for inclusion of a regressor term in the model (9). The best fit of a model to the data had an $R^2$ of 0.85. The low $R^2$ value was caused by ill conditioning of the matrices used to estimate the regression coefficients of the model.

Kurotori (10) described the computational precision problems associated with multiple regression analysis of highly constrained independent variables with fractional numerical values and recommended transforming the data to pseudocomponents to circumvent this complication using the following equation:

$$x_i' = \frac{x_i - a_i}{1 - \sum_{i=1}^{q} a_i} \quad (3)$$

where $x_i'$ is the pseudocomponent level of component $x_i$ which has the lower constraint limit of $a_i$ for $q$ components from $i = 1, 2, \ldots, q$. When the independent variables were transformed to pseudocomponents and fit to the dissolution data, a transformed model with the $R^2$ of 0.97 was obtained. This value indicated an excellent fit since the standard error was only 3.3 and the coefficient of variability was 4.5%. The $F$ ratio for the lack of fit for the model by the method of Snee (5) was 1.08, which was less than 2.08 ($\alpha = 0.05$), the critical $F$ ratio for significant lack of fit. At a 95% confidence level the lack of fit for the model, therefore, was concluded to be statistically nonsignificant.

The analysis of residuals also indicated that the model accurately described the data. Only 2 data points of a total of 180 deviated from the model by more than two standard deviations. The numbers of positive and negative residuals were approximately equal, at 53 and 55, respectively, but the 30 runs of signs value was lower than the expected number of 55. An uneven number of positive and negative residuals or a large number of runs of signs may indicate autocorrelation or time-series correlation of the data. The Durbin–Watson test statistic of 0.89 was inconclusive for autocorrelation. Examination of the variation of the data within each treatment combination revealed no apparent correlation of the variation for the data taken between 1.5 and 12.0 hr inclusive. The variation of the 0.5-hr data, however, was consistently lower than the variation from 1.5 to 12.0 hr by a factor of 1.9. Tablet composition had less effect on dissolution during the first 0.5 hr because drug was dissolving from the surface of the tablet. This extent of autocorrelation did not disturb the fit of the model according to an evaluation proposed by Anderson and McLean (6) since the two variations differ by a factor which is substantially less than the critical value, calculated to be 9. The pseudocomponent model was concluded to quantitate accurately the functional relationship between the drug dissolution profiles and the composition of the tablets.

The transformed model in terms of pseudocomponents is given by the following equation:

$$Y = -49.7 + 85.3t^{1/4} - 1.93t + 33.7x_1' - 79.3x_2' - 16.2x_3' + 137x_2'x_3' - 41.2x_1'x_3' \quad (4)$$

where $Y$ is the percentage of the dose released at time $t$, and $x_i'$ represents the pseudocomponent level of component $x_i$, where $i = 1,2,3,4$. The regression equation included the pseudocomponent levels of the three polymeric components $x_1$, $x_2$, and $x_3$ and two interaction terms but not the pseudocomponent level of the inorganic component $x_4$. Component $x_4$, used as an inert, insoluble filler in the compositional range of 20 to 45% of the total tablet weight, apparently had no effect on drug dissolution which could not be modeled by the levels of the other components.

Equation (4) may be mathematically converted to a more easily used form by expressing the model in terms of the actual component levels instead of pseudocomponents. The transformed (pseudocomponent) model is back-transformed to a model expressed in terms of the actual component levels by the following equations of Gorman (11):

$$\beta_0 = K + \beta_0' \quad (5)$$

$$K = \frac{1}{L}\left(\sum_{1 \le i \le j < q}^{q} \beta_{ij}' a_i a_j\right) - \frac{1}{L}\left(\sum_{i=1}^{q} \beta_i' a_i\right) \quad (6)$$

$$L = 1 - \sum_{i=1}^{q} a_i \quad (7)$$

$$\beta_i = K - \frac{1}{L^2} \sum_{\substack{i<j<q \\ i \neq j}}^{q} \beta_{ij}' a_j + \frac{\beta_i'}{L} \quad (8)$$

$$\beta_{ij} = \frac{\beta_{ij}'}{L^2} \quad (9)$$

where $\beta_{ij}'$ and $\beta_{ij}'$ are the regression coefficients of the transformed model terms $x_i'$ and $x_i'x_j'$ and where $\beta_i$ and $\beta_{ij}$ are the regression coefficients of the back-transformed model terms $x_i$ and $x_jx_j$. The back-transformed model was determined as follows:

$$Y = -46.5 + 85.3t^{1/4} - 1.93t + 111x_1 - 285x_2 - 34.7x_3 - 182x_1x_3 + 607x_2x_3 \quad (10)$$

The transformed and back-transformed models return the same numerical value for any formulation, but the confidence intervals on the coefficients of the transformed model may not be used for the back-transformed coefficients. Any projections of confidence levels on the regression coefficients are restricted to the transformed (pseudocomponent) model.

In addition to descriptive capabilities, surface response models may be used to predict the response, or drug dissolution profiles, for tablet formulations prior to their preparation and evaluation. This predictive capability enables the formulation scientist to select the formulations for study which have the highest probability of achieving a target response.

Five formulations with compositions as given in Table IV were selected randomly from the mixture space of the extreme vertices experiment to validate the predictive capabilities of the model. The average difference between the profiles predicted by the model and the profiles determined experimentally was 2.05, which is well within experimental error (4.5%). An example comparison between the predicted and the experimental drug release profiles for a validation batch is shown in Fig. 3. Full data sets for numerical comparisons are given in Table V. Based on these comparisons, it was concluded that the model validly predicts the percentage of active drug which would be dissolved at time, $t$, for any formulation selected from the extreme vertices mixture

Table IV. Composition of Tablet Formulations Randomly Selected for Validation of the Predictive Capability of the Model

| Formulation no. | Percentage of each component | | | |
|---|---|---|---|---|
| | $X_1$ | $X_2$ | $X_3$ | $X_4$ |
| 1 | 12.9 | 4.7 | 29.5 | 30.8 |
| 2 | 16.0 | 6.2 | 31.0 | 24.7 |
| 3 | 16.0 | 4.5 | 31.0 | 26.4 |
| 4 | 25.0 | 7.4 | 24.0 | 21.5 |
| 5 | 26.0 | 4.1 | 27.0 | 20.8 |

space. Calculated drug dissolution profiles, however, require experimental verification.

A computer program was written to calculate the predicted drug release profiles for formulations in the mixture space represented by 2% increments in the levels of $x_1$ and $x_3$ and by 0.5% increments in the level of $x_2$ within the constraint limits of each component. Component $x_4$ did not appear in the model and, for this reason, was allowed to vary as required within the allowed range. Each candidate prototype formulation was required to release (as calculated by the equation) approximately 15 to 30%, less than 65%, believed to improve the manufacturability of the final dosage form on a rotary tablet press.

The tableting properties of this formulation were confirmed by manufacturing four scale-up batches greater than 1 kg using either an 8-station (Stokes) or a 16-station (Colton) rotary tablet press. Excellent content uniformity (±1.0%) and low weight variation (±1.0%) were determined for all tablet batches.

Although it is beyond the scope and intent of this discussion, a brief statement regarding the bioavailability performance of this formulation compared to an equivalent dose

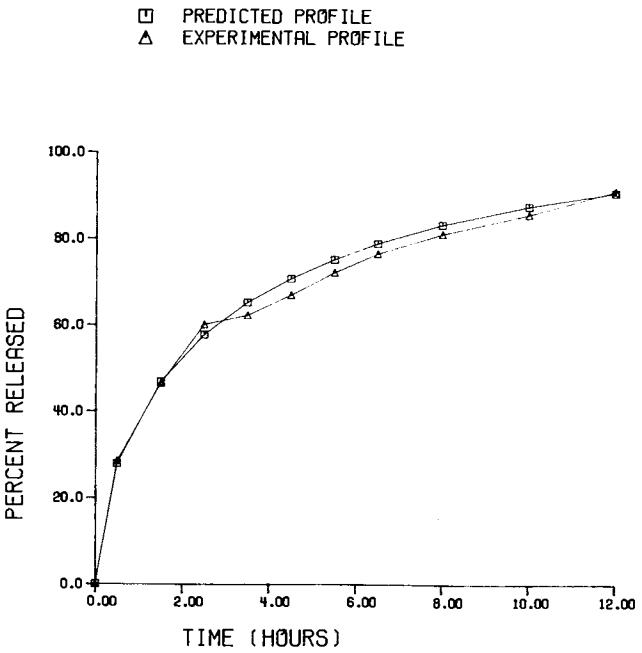


Fig. 3. Comparison of the dissolution profiles for a validation formulation as predicted by the model and as determined experimentally.

Table V. The Average Difference Between the Drug Dissolution Time Profiles Predicted by the Model and the Experimental Validation Profiles

| Time (hr) | Average difference for each formulation | | | | |
|---|---|---|---|---|---|
| | No. 1 | No. 2 | No. 3 | No. 4 | No. 5 |
| 0.5 | 8.10 | 6.11 | 5.20 | 3.76 | 0.57 |
| 1.5 | 6.06 | 0.73 | −0.78 | −0.49 | −0.29 |
| 2.5 | 7.74 | 2.84 | 1.37 | 1.76 | 2.40 |
| 3.5 | 2.62 | −1.98 | −3.83 | −2.62 | −2.99 |
| 4.5 | 0.24 | −4.84 | −6.04 | −3.11 | −3.78 |
| 5.5 | −0.18 | −6.04 | −7.01 | −3.48 | −3.01 |
| 6.5 | 0.38 | −5.20 | −6.37 | −1.61 | −2.34 |
| 8.0 | −1.73 | −6.29 | −8.25 | −3.21 | −2.13 |
| 10.0 | −1.27 | −7.26 | −6.50 | −0.99 | −1.89 |
| 12.0 | 0.90 | −2.59 | −2.95 | 2.81 | 0.43 |
| Avg. difference | 2.29 | −2.45 | −3.52 | −0.72 | −1.29 |
| SD | 3.69 | 4.42 | 4.29 | 2.64 | 1.97 |

of a commercial oral solution of the same drug human subjects is appropriate to demonstrate the practical applicability of this formulation as developed using the extreme vertices methodology. In a two-way, open-label, complete crossover study in eight normal healthy fasted males, bioavailability of the optimized controlled-release tablet was 93% compared to the oral solution, which was equivalent to the percentage dissolved by in vitro dissolution. Sustained serum levels of the active material were achieved by the controlled release dosage form for the 12-hr period.

The extreme vertices experimental design was demonstrated by this study to be an effective and efficient method for the design, evaluation, and optimization of a complex mixture for controlled release with performance-related compositional constraints. The relationship between the composition of the tablet matrix and the drug dissolution time profile was described quantitatively by surface response modeling, using a mathematical model validated for both descriptive and predictive capabilities. A prototype formulation was selected on the basis of model predictions and secondary manufacturability less than 75%, and approximately 90% of the dose at 0.5, 4.5, 6.5, and 12.0 hr, respectively. The acceptable range of these criteria was set arbitrarily at ±0.5%. The program identified 589 candidate formulations which achieved the standards required for a candidate prototype formulation. The extreme vertices experimental formulation five was included by the program in the list of candidate prototype formulations. All 589 formulations selected by the program came from the region around the extreme vertex labeled 5 in Fig. 1.

Although selection criteria could have been refined to narrow further the selection of optimal formulations, additional fine tuning of the formulation outside the identified range offered no obvious practical advantages since all targeted criteria could be met with any number of formulations within a limited range. Secondary criteria such as experimental data, reproducibility of the dissolution profiles, and projected tablet manufacturability were then used to select one formulation. When the secondary criteria were applied, formulation 5 was selected as the prototype formulation. First, experimental validation that the drug release profile

achieved the targeted dissolution criteria was already available from the extreme vertices experiment. Second, the standard deviation between the dissolution profiles for all tablets from the batch of formulation 5 was 50% lower than the average for all formulations from the extreme vertices design. This formulation also contained the maximum amount of the least expensive excipient $x_4$ and the minimum amount of the remaining three excipients $x_1$, $x_2$, and $x_3$. Component $x_4$ was also known to have excellent flow and compressibility properties, which was criteria, scaled up to pilot lab equipment, and shown to give the targeted release by dissolution testing and bioavailability in human subjects.

## APPENDIX: ALGORITHM FOR DETERMINING EXPERIMENTAL TREATMENT COMBINATIONS

After the constraints on the components were established as shown in Table AI, the experimental mixture space was uniquely determined by the intersection of the resulting constraint planes. As many as 32 extreme vertices, $q(2^{q-1})$, could be derived using a four-factor algorithm, where $q$ is the number of factors.

All possible two-level treatment combinations using the upper and lower constraint levels for three of the four factors were written down with the fourth factor level left blank. The three factors levels were added together and subtracted from 1.0 minus the level of active and lubricant [1.000 − (0.171 + 0.050) = 0.779]. If the remaining portion was within the constraint level for the fourth component level left blank, then this combination of points described one extreme point or experimental formulation as shown in the table below.

Table AI.

| Extremum formulation no. | Fraction of each component | | | | Experimental formulation no. |
|---|---|---|---|---|---|
| | $x_1$ | $x_2$ | $x_3$ | $x_4$ | |
| | — | 0.025 | 0.20 | 0.20 | |
| (1) | 0.154 | 0.025 | 0.40 | 0.20 | 1 |
| | — | 0.025 | 0.20 | 0.50 | |
| | — | 0.025 | 0.40 | 0.50 | |
| | — | 0.075 | 0.20 | 0.20 | |
| (2)* | 0.104 | 0.075 | 0.40 | 0.20 | 2* |
| | — | 0.075 | 0.20 | 0.50 | |
| | — | 0.075 | 0.40 | 0.50 | |
| | 0.10 | — | 0.20 | 0.20 | |
| | 0.30 | — | 0.20 | 0.20 | |
| | 0.10 | — | 0.40 | 0.20 | |
| | 0.30 | — | 0.40 | 0.20 | |
| | 0.10 | — | 0.20 | 0.50 | |
| | 0.30 | — | 0.20 | 0.50 | |
| | 0.10 | — | 0.40 | 0.50 | |
| | 0.30 | — | 0.40 | 0.50 | |
| | 0.10 | 0.025 | — | 0.20 | |
| (3) | 0.30 | 0.025 | 0.254 | 0.20 | 3 |
| | 0.10 | 0.025 | — | 0.50 | |
| | 0.30 | 0.025 | — | 0.50 | |
| | 0.10 | 0.075 | — | 0.20 | |
| (4)* | 0.30 | 0.075 | 0.204 | 0.20 | 4* |
| | 0.10 | 0.075 | — | 0.50 | |
| | 0.30 | 0.075 | — | 0.50 | |
| (5) | 0.10 | 0.025 | 0.20 | 0.454 | 5 |
| (6) | 0.30 | 0.025 | 0.20 | 0.254 | 6 |
| (7) | 0.10 | 0.025 | 0.40 | 0.254 | 7 |
| | 0.30 | 0.025 | 0.40 | — | |
| (8) | 0.10 | 0.075 | 0.20 | 0.404 | 8 |
| (9)* | 0.30 | 0.075 | 0.20 | 0.204 | 4* |
| (10)* | 0.10 | 0.075 | 0.40 | 0.204 | 2* |
| | 0.30 | 0.075 | 0.40 | — | |

Since extrema 9 and 10 were approximately equivalent to extrema 4 and 2, respectively, the duplicated points were used to calculate an error mean square for batches, the experimental inferential unit. Minor differences of $\leq 0.004$ ($\leq 4\%$) for components $x_1$, $x_3$, and $x_4$ for duplicate points 4 and 9, and 2 and 10, were considered insignificant. To obtain the actual experimental points 2 and 4 listed in Table II required averaging 10.4 and 10.0 to obtain $x_1 = 10.2\%$ for point 2 and averaging 20.4 and 20.0 to obtain $x_4 = 20.2\%$ for points 2 and 4. The eight unique points defined a seven-sided space. To complete the list of experimental points, the center of each facial plane was calculated as well as the centroid of the entire space.

Each facial plane was isolated by identifying all points with one component level constant. For example, points 1, 3, 5, 6, and 7 all have $x_2 = 0.025$. By averaging all five values of each component, the center of that facial plane was calculated to obtain treatment combination 9 from Table II. Points 2, 4, and 8 ($x_2 = 0.075$) were used to determine point 10; points 1, 2, 3, and 4 ($x_4 = 0.20$ or 0.202) to determine point 11; points 1, 2, and 7 ($x_3 = 0.40$) to find point 12; points 4, 5, 6, and 8 ($x_3 = 0.20$) to find point 13; points 2, 5, and 7 ($x_1 = 0.10$) to find point 14; and points 3, 4, and 6 ($x_1 = 0.30$) to find point 15. The average of all eight extremum points (1 through 8) determined the centroid of the polyhedron, treatment combination 16.

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## REFERENCES

1. R. A. McLean and V. L. Anderson. *Technometrics* 8:447–454 (1966).
2. V. E. McCurdy. *The Effect of Microcrystalline Cellulose in a Sugar Coating Suspension on the Coating Process and on the Physical Properties of the Coated Tablets,* Ph.D. thesis, Purdue University, West Lafayette, IN, 1985.
3. R. D. Snee and D. W. Marquardt. *Technometrics* 16:399–408 (1974).
4. R. D. Snee. *J. Qual. Tech.* 3:159–169 (1971).
5. R. D. Snee. *Technometrics* 15:517–528 (1973).
6. V. L. Anderson and R. A. McLean. *Design of Experiments: A Realistic Approach,* Marcel Dekker, New York, 1974, pp. 342–347.
7. J. B. Schwartz. *J. Soc. Cosmet. Chem.* 32:287–301 (1981).
8. *Handbook of Nonprescription Drugs,* 6th ed. American Pharmaceutical Assoc., Washington, D.C., 1977, p. 90.
9. D. P. Montgomery and E. A. Peck. *Introduction to Linear Regression Analysis,* John Wiley & Sons, Homewood, IL, 1983.
10. I. S. Kurotori. *Ind. Quality Control* 22:592–596 (1966).
11. J. W. Gorman. *J. Qual. Tech.* 2:186–194 (1970).