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, xi, 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.

\[ \sum_{i=1}^{q} x_i = 1.0 \] (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 (x₁, x₂, . . . , xₖ) with a lower constraint, aᵢ, and an upper constraint, bᵢ, on each component such that 0 ≤ aᵢ ≤ xᵢ ≤ bᵢ, 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(x), may be described by the extreme vertices linear quadratic equation as follows (6):

$$E(x) = \sum_{i=1}^{q} \beta_i x_i + \sum_{i<j=q} \beta_{ij} x_i x_j$$  \hspace{1cm} (2)

where xᵢ is the fractional level of component i and βᵢ is the regression coefficient for component xᵢ.

### 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 x₁, x₂, x₃, and x₄ 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.

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-

<table>
<thead>
<tr>
<th>Component</th>
<th>Material type</th>
<th>Lower constraint fraction</th>
<th>Upper constraint fraction</th>
</tr>
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<tbody>
<tr>
<td>x₁</td>
<td>Soluble adhesive</td>
<td>0.100</td>
<td>0.300</td>
</tr>
<tr>
<td>x₂</td>
<td>Insoluble film-former</td>
<td>0.025</td>
<td>0.075</td>
</tr>
<tr>
<td>x₃</td>
<td>Insoluble adhesive</td>
<td>0.200</td>
<td>0.400</td>
</tr>
<tr>
<td>x₄</td>
<td>Insoluble excipient</td>
<td>0.200</td>
<td>0.500</td>
</tr>
</tbody>
</table>

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