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RESEARCH PAPER

A Mixture Experiment Approach for Controlling the Dissolution Rate of a Sustained-Release Tablet

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ABSTRACT

Several sustained-release tablet formulations with acceptable pharmacokinetic properties were found to be unstable because of the effects of lactose. Because the pharmacokinetic properties were acceptable, an attempt was made at developing stable formulations that reproduced the in vitro drug release characteristics of the unstable formulations. Through the use of a statistically designed mixture experiment, alternative formulations were generated and tested for dissolution. The dissolution data collected in the mixture experiment were used to develop a statistical regression model for identifying formulations with dissolution rates equal to those of the unstable formulations. The form of the regression model was based on the Higuchi equation. The data analysis indicated that it is possible to generate dissolution profiles that reproduce those of the original formulations by adjusting the ratios of Methocel® K4MCR Premium and Methocel K100MCR Premium and by replacing the detrimental lactose with calcium phosphate dibasic anhydrous.

INTRODUCTION

A development program was initiated for the manufacture of a sustained-release matrix tablet formulation of a potent water-soluble drug. Release profiles for two of the four formulations tested in a biostudy are shown in Figs. 1 and 2. Table 1 shows the composition of the general formulations.

The dissolution rate of matrix release tablets can be modeled according to the Higuchi equation (1) which states:

$$Q = [(D\varepsilon/\tau)\,(2A - \varepsilon C_s)\,C_s]^{1/2}\,\text{time}^{1/2} \qquad (1)$$

where Q = amount of drug released per unit area at an elapsed time; D = diffusion coefficient of the drug in the

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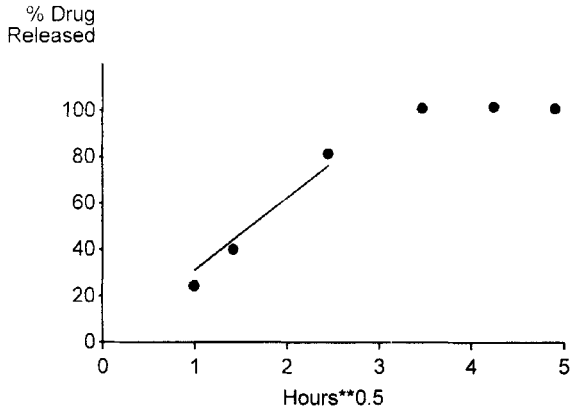

Figure 1. Existing formulation with lactose = 64.5% and Methocel K100MCR = 20.0%. Drug release rate (slope) = 31.1% drug released/$hr^{1/2}$.

matrix; A = concentration of drug present in the matrix at time 0 and at any time beyond the moving boundary; ε = porosity of the matrix; τ = tortuosity of the matrix; and C_s = solubility of the drug in the matrix.

For the purposes of empirical modeling, this equation can be further simplified to

$$\text{Percent drug released} = k[\text{time}]^{1/2} \qquad (2)$$

where $k = [(D\varepsilon/\tau)\,(2A - \varepsilon C_s)\,C_s]^{1/2}$. Thus, percent drug released can be modeled as a straight line function of the square root of time, with the intercept of the line equal to zero and the model parameter k representing the slope of the line (drug release rate).

As is often the case during the development process, the formulations originally developed did not have sufficient stability to warrant commercialization. An incompatibility was noted with the lactose in the formulations. Therefore, alternative formulations which included calcium phosphate dibasic anhydrous as the main diluent were suggested.

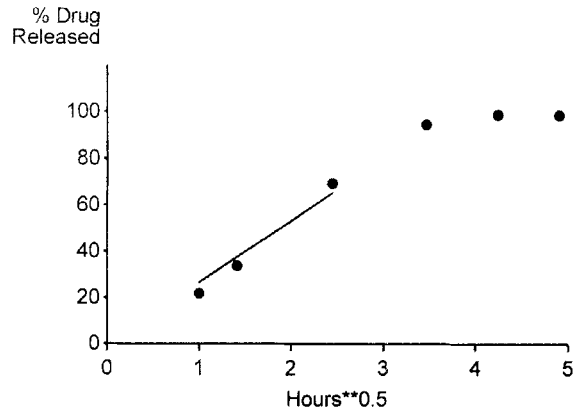

Figure 2. Existing formulation with lactose = 44.5% and Methocel K4MCR = 40.0%. Drug release rate (slope) = 26.6% drug released/$hr^{1/2}$.

Table 1

Existing Tablet Formulation

Ingredient	Amount
Buffer salt in water	5.0% w/w
Microcrystalline cellulose, drug mixture	10.0% w/w
Magnesium stearate NF	0.5% w/w
Total	15.5% w/w
Lactose (diluent)	Varies[a]
Methocel K4MCR Premium (polymer 1)	Varies[a]
Methocel K100MCR Premium (polymer 2)	Varies[a]
Total	84.5% w/w

[a] Determines drug release rate.

An experiment was conducted in an attempt to develop calcium phosphate dibasic anhydrous formulations that would mimic the release rates of pre-existing lactose formulations. The four lactose formulations that were targeted produced release rates of 20, 27, 31, and 48 (% drug released/$time^{1/2}$), respectively. Previous studies have shown that compression force, drug particle size, viscosity grade of polymer, and tablet thickness do not influence the release rate in the ranges studied, but that the drug-to-polymer ratio does alter the release rate. Therefore, the investigation focused on using the drug-to-polymer ratio as the method of generating the desired drug release rates.

Table 2

Design Constraints for the Mixture Experiment

Ingredient	Amount
Methocel K4MCR Premium	0–33.8% w/w
Methocel K100MCR Premium	0–16.9% w/w
Calcium phosphate dibasic anhydrous	q.s.[a]
Total	84.5% w/w
Buffer salt in water	5.0% w/w
Microcrystalline cellulose, drug mixture	10.0% w/w
Magnesium stearate NF	0.5% w/w
Total	15.5% w/w

[a] q.s.: Quantity sufficient to attain a total of 84.5% w/w.

Through the use of a mixture design, calcium phosphate dibasic anhydrous formulations were manufactured using varying polymer levels to determine the effect on the release rate of the drug substance. The polymers used were Methocel® K4MCR Premium and Methocel K100MCR Premium. The formulation required the sum of the polymers and calcium phosphate dibasic anhydrous to equal 84.5% w/w of the formulation. The formulation constraints for development are given in Table 2.

EXPERIMENTAL DESIGN

The 11-run (11 granulation batches) experimental design was a mixture design (2) in three formulation ingredients: calcium phosphate dibasic anhydrous, Methocel K4MCR Premium, and Methocel K100MCR Premium.

The feasible experimental region (Fig. 3) was defined by the following constraints on the two polymers (as percent of total batch weight): Methocel K4MCR Premium $\leq$ 33.8% w/w, and Methocel K100MCR Premium $\leq$ 16.9% w/w. The sum of the relative percentages of the three experimental ingredients was held fixed at 84.5% w/w.

The 11 experimental runs are listed in Table 3. Four runs were vertices of the constrained experimental region, four were edge centroids, and three were replicates of the overall centroid (see Fig. 3). The 11-run design was set up in two blocks, with the four vertices and three centroid replicates in block 1 and the four edge centroids in block 2.

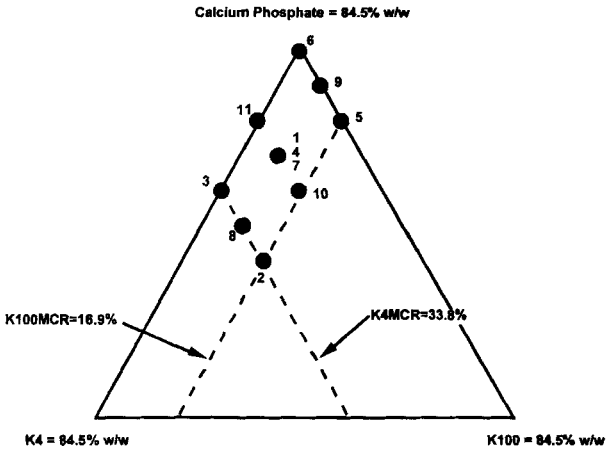

Figure 3. Feasible experimental region with locations of design points and run numbers.

MATERIALS AND METHODS

Methocels K4MCR Premium and K100MCR Premium were obtained from The Dow Chemical Co. (Midland, MI); calcium phosphate dibasic anhydrous was obtained from Edward Mendell Co. (Patterson, NY); magnesium stearate NF was obtained from Mallinckrodt

Table 3

Eleven-Run Experimental Design

Run	Calcium Phosphate (% w/w)	K4 (% w/w)	K100 (% w/w)	x_1[a]	x_2[a]	x_3[a]	Description
1	59.15	16.90	8.45	0.7	0.2	0.1	Centroid
2	33.80	33.80	16.90	0.4	0.4	0.2	Vertex
3	50.70	33.80	0.00	0.6	0.4	0.0	Vertex
4	59.15	16.90	8.45	0.7	0.2	0.1	Centroid
5	67.60	0.00	16.90	0.8	0.0	0.2	Vertex
6	84.50	0.00	0.00	1.0	0.0	0.0	Vertex
7	59.15	16.90	8.45	0.7	0.2	0.1	Centroid
8	42.25	33.80	8.45	0.5	0.4	0.1	Edge
9	76.05	0.00	8.45	0.9	0.0	0.1	Edge
10	50.70	16.90	16.90	0.6	0.2	0.2	Edge
11	67.60	16.90	0.00	0.8	0.2	0.0	Edge

[a] x_1 = Calcium phosphate/84.5; x_2 = K4/84.5; x_3 = K100/84.5.

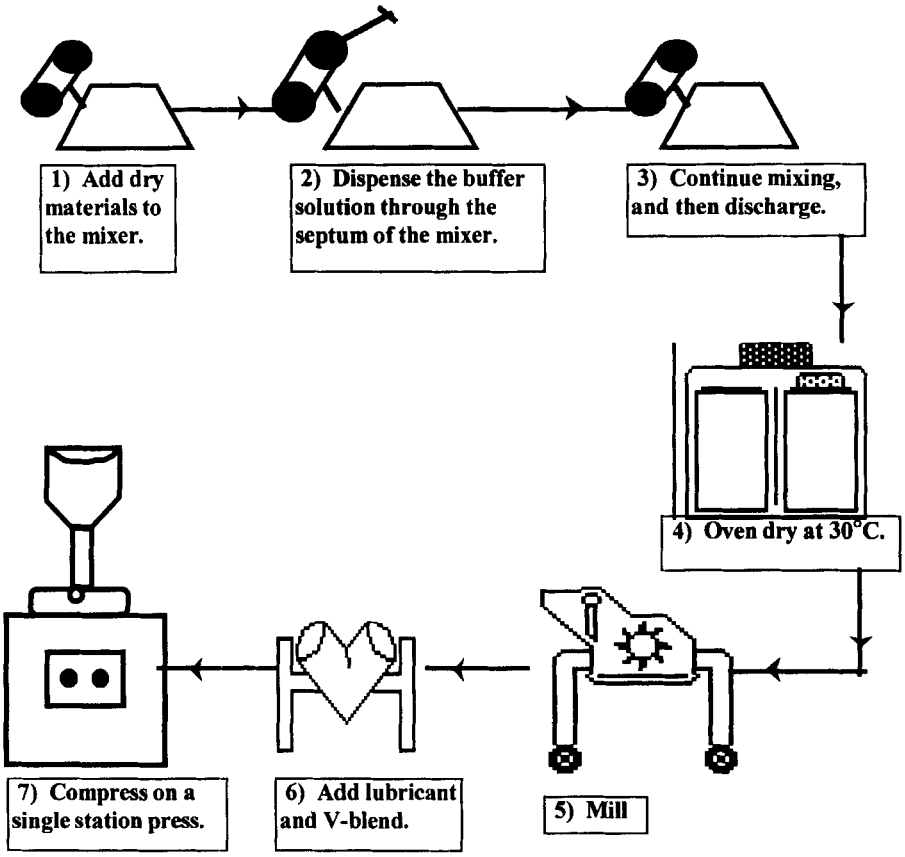

Figure 4. Process flow diagram.

(Chesterfield, MO); and microcrystalline cellulose NF (PH 101) was obtained from FMC (Princeton, NJ).

Preparation of the Granulation

Drug dissolved in water was the granulating solution. This solution was slowly injected through the septum of a CBM Lightnin' mixer containing the Avicel. The mixer and chopper blades were set at the maximum rotational speed (44–46 rpm). After the granulating solution was dispensed, the granulation was mixed for an additional 5 min. The granulation was oven-dried at 30°C until moisture levels were below 3%. The dried batches were milled and screened.

Preparation of the Final Blends

The flow diagram in Fig. 4 shows the steps in preparing the final blends. Fifty grams of the granulation was added to the CBM Lightnin' mixer. The goal was to obtain a final batch weight of 0.5 kg. For each batch, the appropriate amounts of excipients were weighed and placed into the CBM Lightnin' mixer. The buffer salt was slowly dissolved in 105 ml of water, dispensed in the CBM Lightnin' mixer, and mixed for 11 min. After the mixture was discharged, the batch was placed in an oven at 30°C until moisture levels were below 3%.

The dried granulation was milled and blended with 0.5% w/w magnesium stearate for 2 min. in a Patterson-Kelley V-blender (East Stroudsburg, PA). Tablets of 250 mg fill weight were compressed from the final blends on a single-station press to a tablet hardness between 8 and 10 kps. Previous experimentation showed that the dissolution was not significantly affected by tablet hardness.

Physical Testing

Tablet hardness was measured on the Schleuniger (Marion, IA) hardness tester and an average hardness of 10 tablets was calculated.

Table 4

Dissolution Data (Percent Drug Released)

Run	1 hr	3 hr	6 hr	9 hr	12 hr	18 hr	24 hr
1	23.6	44.6	62.3	74.7	81.6	90.4	91.8
2	11.8	26.1	40.6	50.2	57.7	69.2	75.1
3	24.0	39.5	54.6	65.2	75.0	81.3	86.5
4	20.8	39.6	55.9	66.7	74.6	81.8	84.7
5	31.2	52.6	67.1	75.0	79.4	81.8	81.5
6[a]	88.8	104.7	104.7	104.5	104.3	104.6	103.5
7	23.8	44.7	62.7	74.7	82.0	89.9	91.7
8	18.3	32.6	46.4	55.9	64.6	74.4	79.6
9[a]	76.8	94.8	99.9	99.2	99.3	99.0	98.2
10	18.2	36.1	49.7	60.0	67.4	76.7	82.7
11	35.4	57.9	74.8	83.9	88.0	91.2	91.5

[a] Not used in model fitting (drug release too rapid).

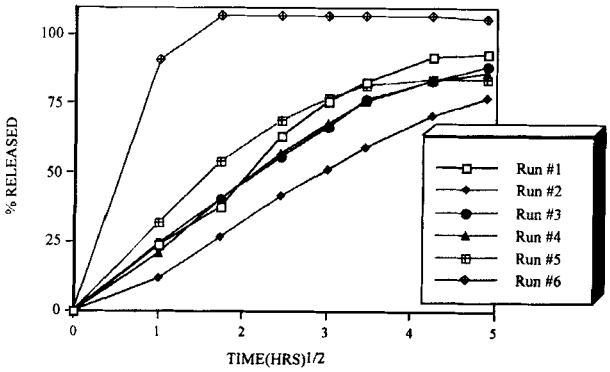

Figure 5. Dissolution profiles for experimental runs 1–6.

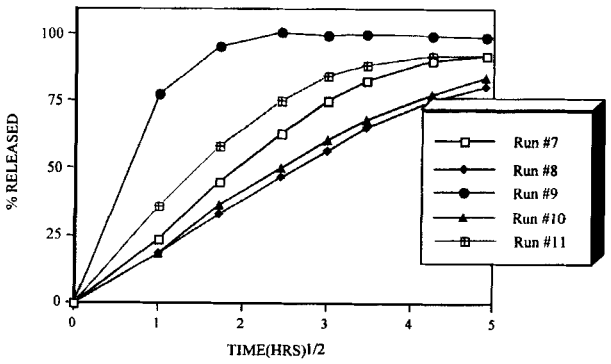

Figure 6. Dissolution profiles for experimental runs 7–11.

Dissolution

Percent drug release was measured at 1, 3, 6, 9, 12, 18, and 24 hr. The dissolution data are listed in Table 4. Dissolution profiles are shown in Figs. 5 and 6.

DATA ANALYSIS

The statistical analysis for the 11-run design was performed on the 1-, 3-, and 6-hr dissolution data only because the primary interest was in the dissolution rate early in the dissolution profile, that is, before the profile began to plateau. This approach made it possible to calculate and compare the release rates of the experimental calcium phosphate dibasic anhydrous formulations to the release rates of the reference lactose formulations which were calculated from 1-, 2-, and 6-hr dissolution data.

The statistical analysis consisted of fitting a regression model to the dissolution data as a function of the proportions of the three experimental formulation ingredients and the square root of time ($hr^{1/2}$). For fitting the model, the formulation ingredient proportions were coded as follows: x_1 = calcium phosphate dibasic anhydrous (w/w%)/84.5%; x_2 = Methocel K4MCR Premium (w/w%)/84.5%; and x_3 = Methocel K100MCR Premium (w/w%)/84.5%, so that $x_1 + x_2 + x_3 = 1$ (see Table 3). The candidate model fitted to the data (2) was a second-order Scheffé polynomial with a first-order term in the square root of time ($hr^{1/2}$):

$$\text{Percent released} = (\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3) hr^{1/2} \quad (3)$$

For ease of interpretation, the model in Eq. (3) can be thought of as a linear regression model [see Eq. (2)] in which the slope is defined as

$$\text{Slope} = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3$$

The slope is a function of the proportions of the three ingredients in the experimental formulations through x_1, x_2, and x_3. The release rate (slope) can be estimated as a function of the proportions of the three ingredients in the experimental formulations through x_1, x_2, and x_3 after the model parameters (βs) have been estimated from the data.

The model fitting was done using the JMP® version 3.0.2 statistical analysis package (SAS Institute, Inc., Cary, NC).

RESULTS AND DISCUSSION

The Higuchi equation was developed as a way of modeling drug release (dissolution) as a straight line function of the square root of time for sustained-release formulations. It is inappropriate to use the Higuchi equation for immediate-release formulations. Therefore, data from 2 of the 11 experimental runs (runs 6 and 9) were omitted from the data analysis because they were essentially immediate-release formulations (dissolution reached nearly 100% before 6 hr) that could not be reliably modeled by a straight line.

The data from the remaining seven design points (nine runs including three replicates at the centroid) were used to fit the model in Eq. (3). A simpler model was determined to provide an adequate fit to the data and was taken as the final model. The model in Eq. (3) was reduced to the simpler model based on F-tests for groups of model parameters ($p < 0.10$), t-tests on individual model parameters ($p < 0.10$), F-tests for model lack of fit ($p < 0.10$), adjusted R^2, and residual plots. The final fitted model was

$$\text{Percent released} = (36.65x_1 + 2.94x_2 - 7.66x_3)\text{hr}^{1/2} \quad (4)$$

The fit of the model to the data (adjusted $R^2 = 96.1\%$) can be evaluated visually in Figs. 7–9, in which the fitted

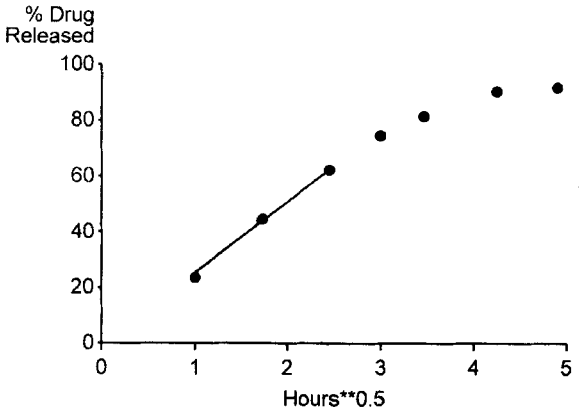

Figure 8. Run 1: calcium phosphate = 59.15%, K4 = 16.9%, K100 = 8.45% ($x_1 = 0.7$, $x_2 = 0.2$, $x_3 = 0.1$). Model: % drug released = $(36.7x_1 + 2.9x_2 - 7.7x_3)\text{hr}^{1/2}$.

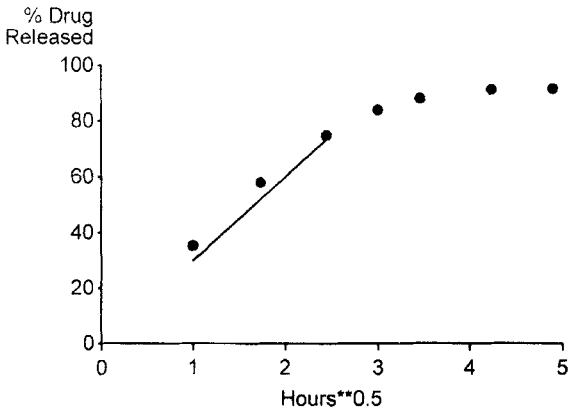

Figure 7. Run 11: calcium phosphate = 67.6%, K4 = 16.9%, K100 = 0% ($x_1 = 0.8$, $x_2 = 0.2$, $x_3 = 0$). Model: % drug released = $(36.7x_1 + 2.9x_2 - 7.7x_3)\text{hr}^{1/2}$.

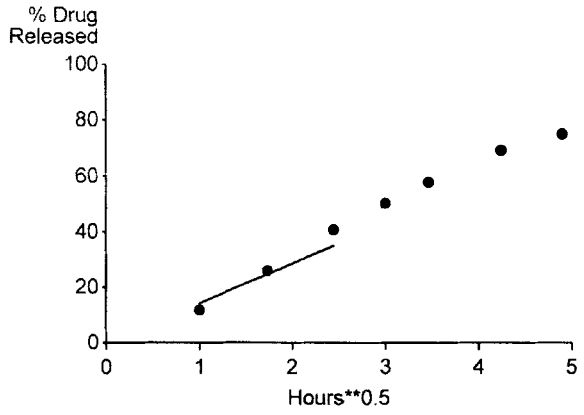

Figure 9. Run 2: calcium phosphate = 33.8%, K4 = 33.8%, K100 = 16.9% ($x_1 = 0.4$, $x_2 = 0.4$, $x_3 = 0.2$). Model: % drug released = $(36.7x_1 + 2.9x_2 - 7.7x_3)\text{hr}^{1/2}$.

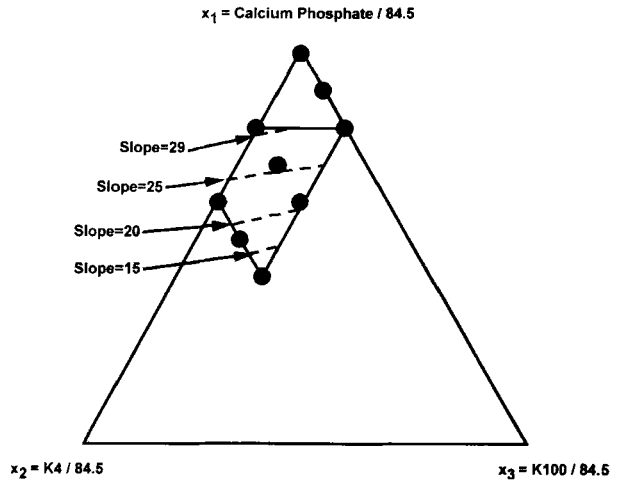

Figure 10. Model predicted drug release rate (slope). Model: slope = $36.7x_1 + 2.9x_2 - 7.7x_3$.

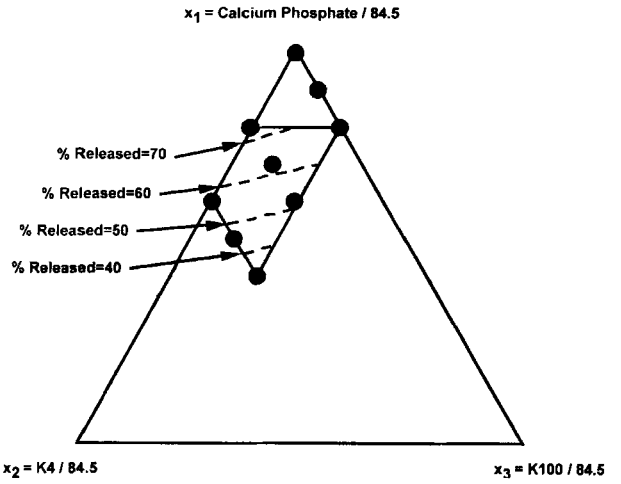

Figure 11. Model predicted percent drug released at 6 hr. Model: % drug released = $(36.7x_1 + 2.9x_2 - 7.7x_3)\text{hr}^{1/2}$.

model is overlaid on the data values from experimental runs 11, 1, and 2, respectively.

Based on the model in Eq. (4), the estimated release rate (slope) for any point within the region defined by the seven design points used to fit the model was

$$\text{Release rate (slope: \% released/hr}^{1/2}) = 36.65x_1 + 2.94x_2 - 7.66x_3 \quad (5)$$

A contour plot that indicates how the release rate (slope) is predicted by the model in Eq. (5) to change as the proportions of the three formulation ingredients change within the region defined by the seven points used to fit the model is shown in Fig. 10. Table 5 shows examples of two formulations that are predicted by the model in Eq. (5) to reproduce the target release rates of 20 and 27, respectively. In theory, an infinite number of formulations exist that would reproduce a slope of 20, that is, all points on the contour corresponding to a slope of 20 in Fig. 10. Likewise, all points on the contour having a value of 27 in Fig. 10 correspond to formulations that are predicted to reproduce a slope of 27. The other two target slopes (31 and 48) were not reproducible within the region where the model in Eq. (5) can be applied. Additional experimentation outside that region, that is, experiments with formulations containing slightly lower proportions of the polymers, would have to be conducted to determine how to reproduce slopes of 31 and 48. A

Table 5

Example Model-Predicted Calcium Phosphate Formulations for Reproducing Target Release Rates

Target Release Rate (Slope: % Released/hr$^{1/2}$)	Calcium Phosphate (% w/w)	K4 (% w/w)	K100 (% w/w)	x_1[a]	x_2[a]	x_3[a]
20	44.66	33.80	6.04	0.53	0.40	0.07
	48.08	19.52	16.90	0.57	0.23	0.20
27	60.31	24.19	0.00	0.71	0.29	0.00
	65.62	1.98	16.90	0.78	0.02	0.20
31	Not reproducible within region where prediction model applies					
48	Not reproducible within region where prediction model applies					

[a] x_1 = Calcium phosphate/84.5; x_2 = K4/84.5; x_3 = K100/84.5.

contour plot of the percent drug released at 6 hr, which is predicted by the model in Eq. (4), is shown in Fig. 11.

CONCLUSIONS

Through the use of a statistically designed mixture experiment and an accompanying regression model based on the Higuchi equation, a methodology for identifying new sustained-release tablet formulations was developed. The methodology successfully reproduced the dissolution rates of existing formulations with known pharmacokinetic properties. Formulations with release rates of 20 and 27% $hr^{1/2}$ were identified for further development.

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