DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(1), 27-37 (1991)

WATER BASED SILICONE ELASTOMER CONTROLLED RELEASE TABLET FILM COATING V - A STATISTICAL APPROACH

Luk Chiu Li[+] and Garnet E. Peck[*]

[+] University of Oklahoma
College of Pharmacy
1110 N. Stonewall
P.O. Box 26901
Oklahoma city, Oklahoma 73190

[*]Purdue University
Department of Industrial and Physical Pharmacy
West Lafayette, Indiana 47906

ABSTRACT

The silicone elastomer latex formulated with polyethylene glycol and colloidal silica produced a controlled release film coating on potassium chloride tablets. The release rate of potassium chloride was controlled by the total amount of polyethylene glycol and the weight fraction of polyethylene glycol 8000 and 1450 incorporated in the coating. A mathematical model was developed to quantitate the effect of coating components on the drug release rate using the statistical extreme vertices design. The predictive capability of this functional relationship was tested and validated experimentally.

INTRODUCTION

A novel silicone elastomer latex has been evaluated as a controlled release tablet film coating (1). Polyethylene glycols (PEGs) of different molecular weights have been incorporated in the coating system as the water soluble component. The release of potassium chloride from the silicone elastomer coated tablets showed evidence of a

[*] For correspondence

membrane controlled process. Studies of the effect of the coating composition on the release rate of potassium chloride from coated tablets have shown that an increased release rate was achieved at a higher PEG level. For the same PEG content coatings consisting of high molecular weight PEG demonstrated enhanced drug permeability (1). The aim of this study was to determine the feasibility of using mixtures of PEG 8000 and PEG 1450 to produce silicone elastomer coated potassium chloride tablets with different release characteristics by using a statistical response surface approach. The cause-effect relationship between the coating component levels and the drug release rate was quantitatively defined by a multiple linear regression model. The capability of the model to predict the drug release rate, at different levels of each soluble component in the coating formulation was also tested.

EXPERIMENTAL

Materials:

The coating components and potassium chloride were obtained from the same source as reported previously (1).

Methods:

Preparation of Coated Tablets:

The compression and coating of potassium chloride tablets followed the procedures reported previously (1).

In Vitro Drug Release Testing:

The release of potassium chloride from coated tablets was determined using the USP dissolution method II for a period of 6 hours or 12 hours, depending on the release rate. For the 6-hour dissolution testing a 20.0 ml sample of the dissolution medium was withdrawn at a half hour interval for the first three hours and at hourly intervals for the remaining 3 hours. The sampling interval for the 12-hour dissolution testing was one hour for the first 6 hours and two hours for the remaining six hours. The volume of the dissolution medium was kept constant by adding 20.0 ml of fresh degassed deionized water each time a sample was withdrawn. The conductivity of the sample was measured using a conductivity meter (Conductivity Bridge Model PM-70C13, Barnstead Company) and the

amount of potassium chloride in the sample was calculated by means of a calibration curve. The amount of potassium chloride in a sample withdrawn at each sampling interval was accounted for in the computation of the cumulative amounts of potassium chloride released. The release profile of potassium chloride was obtained by plotting the cumulative percent of total dose released against elapsed time. The cumulative percent release data (up to 85% of the total amount released) were correlated with the time elapsed using the method of least squares. The regression was not forced through the origin and the zero time point was not included in the regression. The slope of the best fitted equation represents the zero order release rate of potassium chloride from the tablet system at steady state.

Extreme Vertices Experimental Design:

The components (X_i) in a coating formulation are subject to the constraint that the sum of all component proportions add up to 1.0.

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

Additionally, an upper constraint (b_i) and a lower constraint (a_i) of the formulation are shown by the following:

$$0 \leq a_i \leq X_i \leq b_i \leq 1.0 \qquad (2)$$

The extreme vertices design (2,3) has been shown to be highly efficient for experiments with the above constraints (4,5). The experimental space is uniquely determined for this design by the intersection of all constraint planes. One experimental point is taken at each extreme point of vertex, one from the center of each planar face, and one at the geometric center of the entire space. Anderson and McLean (2) have developed a detailed algorithm for identifying the experimental points.

The coating formulations considered in this experiment had a fixed silicone to silica ratio of 2 to 1, hence the silica filled silicone elastomer can be considered as a single component. Thus, the number of components in the coating formulation is reduced to three. In terms of weight fraction the constraints for these three components are: 0.06 to 0.32 for PEG 8000, 0.06 to 0.32 for PEG 1450 and 0.6 to 0.7 for silicone elastomer. An

Table 1

Component levels and pseudocomponent levels for the coating formulations evaluated in the extreme vertices design.

Formulation Number	Silicone Elastomer		PEG 8000		PEG 1450	
	(1)	(2)	(1)	(2)	(1)	(2)
1	0.700	0.357	0.060	0.000	0.240	0.643
2	0.700	0.357	0.240	0.643	0.060	0.000
3	0.600	0.000	0.320	0.929	0.080	0.071
4	0.600	0.000	0.080	0.071	0.320	0.929
5	0.700	0.357	0.150	0.321	0.150	0.321
6	0.600	0.000	0.200	0.500	0.200	0.500
7	0.650	0.179	0.175	0.411	0.175	0.411

(1) Actual level in weight fraction.
(2) Pseudocomponent level.

additional constraint on the weight ratio of PEG 1450 to PEG 8000 was set from 1:4 to 4:1 for all the coating formulations evaluated in this study. With these three experimental factors and the two constraints, a total of seven formulations were generated using the algorithm. The compositions of the coating formulations are listed in Table 1. The zero order release rate of potassium chloride from the coated tablets was used as the dependent variable in this design. The levels of each coating component in the coating formulation and the zero order release rate of potassium chloride obtained were subsequently fitted to a quadratic model shown as follows:

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_5 + b_6X_6 + \epsilon \quad (3)$$

where Y is the drug release rate, X_1 is the percent of PEG 8000, X_2 is the percent of PEG 1450, X_3 is the percent of silicone elastomer, X_4 is the interaction between X_1 and X_2, X_5

is the interaction between X_1 and X_3, X_6 is the interaction between X_2 and X_3 and ϵ is the error term.

The development of a mathematical model usually involves the use of computer fitting. Since the independent variables in the equation are fractions, cumulative rounding errors may be significantly large in the computer data fitting and the estimated equations may become less accurate (6). Kurotori (7) proposed a transformation of component levels (X_i) to pseudocomponent levels (X'_i) which involves a shift of coordinates to bring the origin to the geometric center of the factor space as shown in equation 4.

$$X'_i = \frac{X_i - a_i}{1 - \sum_{i=1}^{q} a_i} \qquad (4)$$

where X'_i is the calculated pseudocomponent level for X_i, X_i is the actual level for the variable, a_i is the lower constraint for variable X_i, and $\Sigma\, a_i$ is the sum of the lower constraints for all independent variables.

The pseudocomponent levels for the corresponding actual variable levels are also presented in Table 1. The best fitted model correlating the pseudocomponent of the independent variables and the zero order release rate was subsequently developed using the SAS (Statistical Analysis System) step-wise multiple regression procedures (Stepwise). A minimum number of variables would remain in the best fitted model. The predicting capability of the model was validated using predicted and experimental data from formulations that had not been used for the model development.

RESULTS AND DISCUSSION

Figure 1 depicts the release profiles of potassium chloride from tablets coated with four different coating formulations represented in the extreme vertices design. Despite the difference in the slope, these release profiles showed evidence of a membrane-controlled process. The cumulative percent of potassium chloride released exhibited a linear relationship ($R > 0.995$) with time elapsed for up to 85% of the dose released. The slope of the release profile represented the zero order release rate of potassium chloride from the coated tablets at steady state.

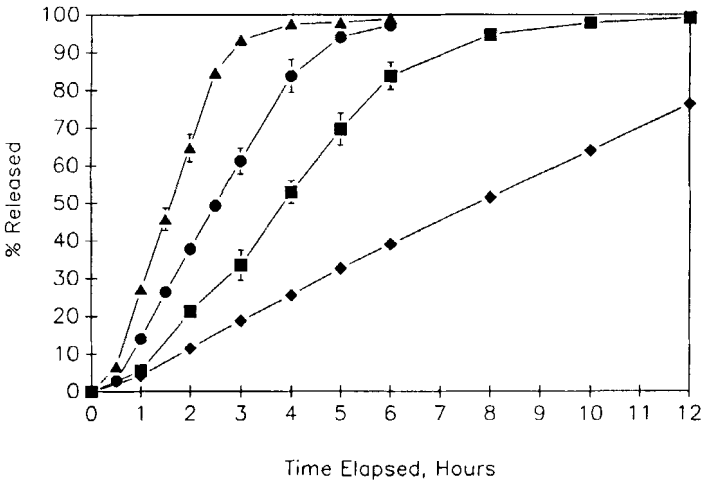

FIGURE 1

The release profile of potassium chloride from tablets coated with various coating formulations*. (◆) 1; (■) 7; (●) 6 and (▲) 3.

* Refer to Table 1.

The zero order release rate for potassium chloride from tablets coated with formulations evaluated in the extreme vertices design is given in Table 2. A mathematical relationship between this parameter and the pseudocomponent levels of the three formulation variables was derived using the SAS step-wise multiple regression procedures. A best fitting quadratic model with a R^2 value of 0.9928 was developed. In other words, the regression model accounted for 99.28 percent of the total variation, which indicates an excellent fit. The random coefficient of variability was 12.323 percent and the standard error was 2.104. The analysis of residuals did not indicate any problems which would have impeded the modeling process. No data point deviated from the predicted values by more than two standard errors. The equation of best fit is as follows:

$$Y = 42.454\ X'_1 + 16.183\ X'_2 - 19.990\ X'_4 - 58.049\ X'_5 \qquad (5)$$

where Y is the drug release rate at steady state (% per hour), X'_1 is the fraction of PEG 8000 expressed as pseudocomponent, X'_2 is the fraction of PEG 1450 expressed as pseudocomponent, X'_4 is the interaction between PEG 8000 and PEG 1450, and X'_5 is the interaction between PEG 8000 and silicone elastomer.

Table 2

Zero-order release rate of potassium chloride from tablets coated with coating formulations evaluated by an extreme vertices design.

Formulation Number	Zero-Order Release Rate (percent per hour)
1	6.53 (0.057) [a]
2	13.86 (0.374)
2-1 [b]	13.68 (0.269)
3	39.69 (1.082)
4	19.76 (1.290)
4-1	16.67 (0.967)
5	10.79 (0.203)
5-1	10.38 (0.419)
6	23.30 (1.308)
7	16.03 (0.968)

[a] Mean and standard deviation for three samples.
[b] Replication.

This model is capable of quantifying the effect of coating formulation changes and relating these changes mathematically to the resulting drug release rate. Most importantly, this model can also be used for the prediction of the drug release rate for all the formulations having a composition within the factor space defined by the design. In the validation of the predictive capability of this model, four coating formulations were generated for evaluation. The composition of these four testing formulations is given in Table 3, along with the experimental and predicted drug release rate. The differences between the experimental and predicted values for the drug release rate are less than 2 standard errors of the model indicating an acceptable predictive capability of the model (8).

Table 3

Experimental and predicted zero-order release rate of potassium chloride for tablets coated with coating formulations generated within the extreme vertices design factor space.

Coating Composition (Fraction)			Zero-Order Release Rate (percent per hour)		
PEG 1450	PEG 8000	Silicone Elastomer	Experimental Value	Predicted Value	Difference
0.2000	0.1000	0.70000	8.91 * (0.221)	9.77	0.86
0.24375	0.08125	0.67500	11.21 (0.567)	11.66	0.45
0.07000	0.28000	0.65000	27.28 (1.633)	25.23	-2.05
0.09375	0.28125	0.62500	31.90 (0.430)	29.50	-2.40

* Mean and standard deviation for three samples.

The predicted drug release rate for other coating formulations with the composition within the factor space of this design was computed using equation 5. Thirteen equally spaced weight fractions of total PEG content ranging from 0.3 to 0.4 and six different weight ratios (from 1:4 to 4:1) of PEG 1450 to PEG 8000 were used in the calculation; hence a total of seventy eight data points were generated. The effect of the three formulation components on the release rate is illustrated by a three dimensional presentation (Figure 2) with the percent of total PEG content and the weight fraction of PEG 1450 in total PEG content as the two independent variables and the drug release rate as the dependent variable. The percent of total PEG content was used instead of the percent of silicone elastomer in the presentation because of the following two considerations. PEGs were incorporated in the silicone elastomer coating as a pore forming agent which modified and enhanced the permeability of the coating to hydrophilic and ionic species. From the formulation standpoint, it appears to be more practical to use the percent of total PEG content than

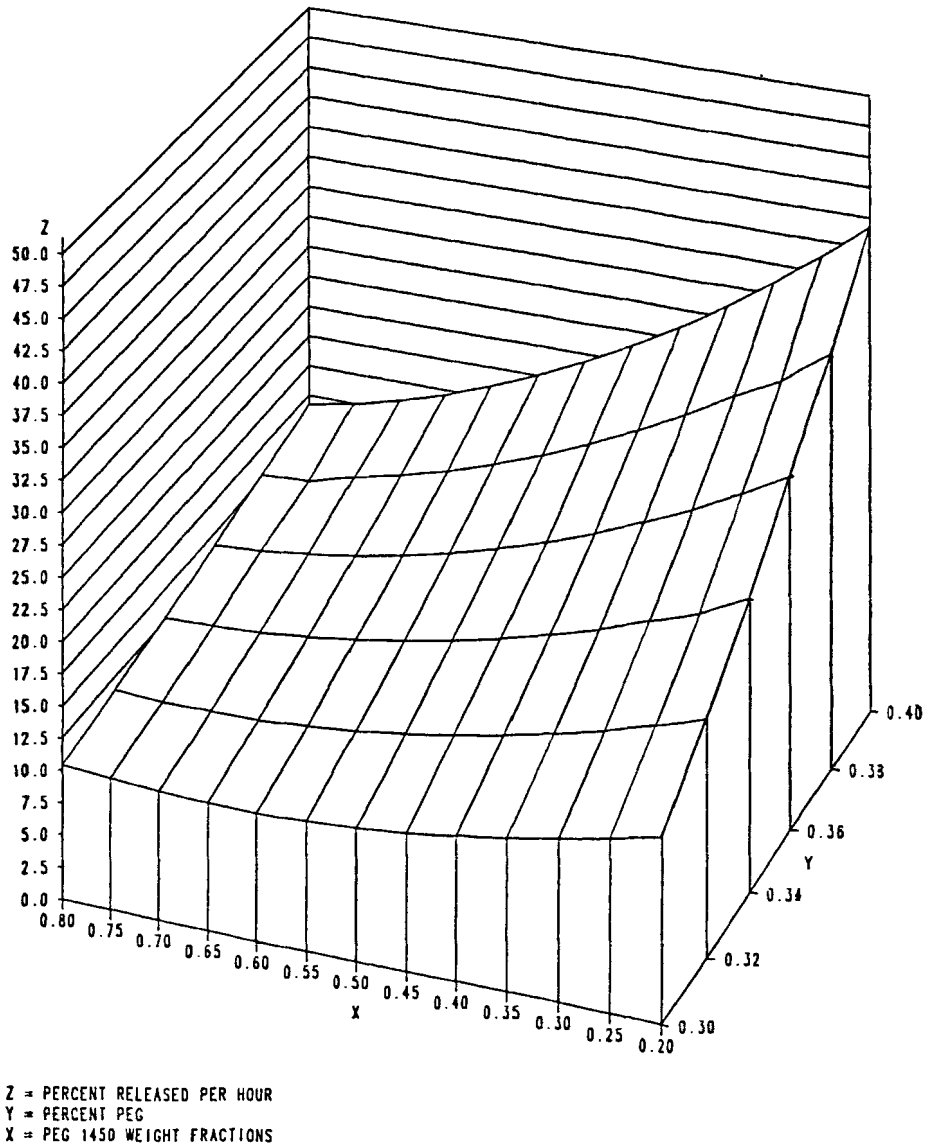

FIGURE 2

The effect of weight fractions of polyethylene glycol 1450 and the total polyethylene glycol loading level on the mean release rate of potassium chloride from coated tablets.

the percent of silicone elastomer in the presentation. Furthermore, since all component levels (weight fractions) for a specific formulation are added up to one, the fraction of the silicone elastomer is actually reflected by the fraction of the total PEG content in the coating. As a matter of fact the composition of the tablet coating formulation corresponding to each data point in Figure 2 was uniquely defined by the two independent variables used in this presentation.

For a fixed weight fraction of PEG 1450, a higher drug release rate was obtained with coatings containing greater amounts of PEG. It is also noted that at a specific PEG level, the drug release rate decreased as the weight fraction of PEG 1450 was increased. The enhancing effect of the total PEG content on the drug release rate was attributed to the increasing extent of pore formation in the coating as a result of leaching of the water soluble components into the dissolution medium (1). In addition to the extent of pore formation, the morphology of the PEG loaded silicone elastomer tablet coating was shown to affect the permeability of the coating. It has been concluded that the influence of PEG molecular weight on the drug permeability of the silicone elastomer tablet coating was associated with its impact on the morphology of the coating (1). PEG 1450 has a melting point of 42°C and a relatively low solution viscosity. The incorporation of this component in the coating formulation would facilitate the formation of a tablet coating with a more compact and less porous film structure which would exhibit a low drug permeability. For coating formulations containing PEG 8000 which has a melting point of 60°C and a higher solution viscosity, a less continuous and more porous film structure would be formed, which showed a high drug release rate from the resultant tablet coating (1). Therefore, an increase in the weight fraction of PEG 1450 in the coating formulation would probably facilitate the formation of coatings with a more compact structure and a lower drug permeability. This may provide a plausible explanation for the gradual decrease in release rate of potassium chloride from tablet coatings containing a higher fraction of PEG 1450.

CONCLUSION

This study has shown that the use of mixtures containing PEG 8000 and PEG 1450 is a feasible approach to formulate a silicone elastomer tablet film coating with

variable controlled release characteristics. The relationship between the release rate of potassium chloride and the composition of the coating consisting of the PEG mixture has been established using a mathematical model developed through the use of the extreme vertices design. The model also allows the accurate prediction of the drug release rate for a specific coating formulation.

ACKNOWLEDGMENT

This study was supported by a grant from the Dow Corning Corporation.

REFERENCES

1. L.C. Li and G.E. Peck, Drug Dev. Ind. Pharm., 15 (1989) 499.

2. V.L. Anderson and R.A. McLean, "Design of Experiments, A Realistic Approach", Marcel Dekker, New York, 1974.

3. R.A. McLean and V.L. Anderson, Technometrics, 8 (1966) 447.

4. A.D. Johnson, "A Mixed Polymer Tablet Matrix for Oral Controlled Release of Dextromethorphan Hydrobromide", Ph.D. Thesis, Purdue University, West Lafayette, IN, 1987.

5. 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.

6. J.W. Gorman, Technometrics, 8 (1966) 455.

7. I.S. Kurotori, Ind. Quality Control, 22 (1966) 592.

8. N.H. Nie, C.H. Hull, J.G. Jenkins, K. Steinbrenner and D.H. Bent, "SPSS, Statistical Package for the Social Sciences", 2nd edition, McGraw-Hill Book Co., New York, 1970.