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EVALUATION OF CHITOSAN CITRATE COMPLEXES AS MATRICES FOR CONTROLLED RELEASE FORMULATIONS USING A 3^2 FULL FACTORIAL DESIGN.

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ABSTRACT

Chitosan citrate complexes of several viscocity grades were synthesized, isolated, purified and identified. These complexes were found to form viscous gels of varying viscosities, upon dispersion in water. The ability of these complexes in sustaining drug release from matrix tablets was evaluated using a two factor three level full factorial design with theophylline as the model drug. Viscosity and concentration of the polymer complexes were optimized to achieve the desired in-vitro release profile. In-vitro dissolution characteristics were evaluated in deionized water as the dissolution medium. Data were fit to a quadratic model and polynomial equations were generated and used to predict the optimum formulation composition with desired release characteristics. These complexes were found to be very effective in sustaining the release of theophylline and were directly compressible. The release mechanism appears to be diffusion controlled. Excellent correlation

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was obtained between predicted and actual release profiles of the optimum formula.

INTRODUCTION

Chitosan is an amino polysaccharide obtained by alkaline deacetylation of chitin. Chitosan has a molecular weight ranging from $1x10^5$ to $3x10^5$. It is a cationic polyelectrolyte and gels in acid media differing from commercially available hydrophilic matrix systems which are nonionic or polyanionic[1].

Chitosan has an excellent ability to absorb water and has been investigated as a disintegrant. Sawayanagi et al. used chitosan at levels of 30-60% in tablets as a disintegrant and sustained release vehicle for water soluble drugs such as propranolol hydrochloride[2]. It was also reported that tablets containing chitosan at levels below 60% passed the disintegration test of the Japanese Pharmacopeia X[3]. Miyazaki et al. reported the usefulness of chitosan as a drug carrier for indomethacin and papaverine hydrochloride[4].

Sawayanagi et al. reported that chitosan enhances the dissolution properties of poorly soluble drugs[5,6]. Nambu et al. also showed that the ground mixtures of poorly soluble drugs such as phenytoin with chitosan exhibited significantly higher bioavailability than the drug alone[7].

Nigalaye et al. investigated the sustained release characteristics of chitosan in presence of citric acid or carbomer-934P in tablets, containing theophylline as the model drug[8]. The rate of drug release was slower in the tablets containing citric acid or carbomer-934P than chitosan alone.

The purpose of this study was to prepare and isolate chitosan citrate complexes and investigate their usefulness as hydrophilic matrix systems.

MATERIALS AND METHODS

Materials

Chitosan (Betachem Inc., NJ), citric acid, anhydrous granular (Pfizer Inc., New York, NY), theophylline, anhydrous (Knoll Fine Chemicals, New York, NY), stearic acid (Mutchler chemical Inc., Westwood, NJ), magnesium stearate (Mutchler Chemical Inc., Westwood, NJ), and silca gel (W. R. Grace and Co., Baltimore, Maryland). Except for chitosan and citric acid, the materials were used as received without further treatment.

Preparation of Chitosan Citrate Complexes

Chitosan citrate complexes with different viscosities were prepared, isolated and characterized[9].

Viscosity Study

Two (2) % w/v dispersions of the chitosan citrate complexes were prepared by dispersing the complex in purified water with stirring. These dispersions were allowed to stand for 24 hrs and their viscosity was measured using a Brookfield viscometer equipped with appropriate spindles.

Experimental Design

A 3^2 full factorial design was utilized in this investigation. Concentration of the complex per tablet and the viscosity of the complex (transformed) were used as the independent variables. The experimental design is presented in Table I.

Values for the variable X_1 range from 1080cps to 15000 cps and for variable X_2 range from 75 mg to 225 mg per tablet. Transformed values as shown in the table 1 were obtained by using the following equation[10].

$$T = \frac{(A) - (1/2)(Max + Min)}{(1/2)(Max - Min)} \quad \text{....Equation 1.}$$

Where T is the transformed value, A is the actual value of the factor being transformed, max and min are

TABLE I

Experiment #	Viscosity of the Complex (X_1)	Concentration of the Complex (X_2)
1	-1.0	-1.0
2	-0.192	-1.0
3	1.0	-1.0
4	-1.0	0.0
5	-0.192	0.0
6	1.0	0.0
7	-1.0	1.0
8	-0.192	1.0
9	1.0	1.0

the maximum and minimum values in the range of the factor being transformed[10].

Dependent variables were the percent drug dissolved at hours 1,6,12 and 24. The data obtained were fit to a quadratic model and polynomial equations were generated. Contour plots and response surface plots were generated based on these equations. Levels of independent variables were predicted to achieve the desired release profile to that of a marketed dosage form.

Data Analysis

The experimental design and data analysis were achieved using X-STAT (John Wiley & Sons) and Statgraphics (Statistical Graphics Corporation inc.,) software packages.

Compression of Tablets

Tablets were directly compressed using different combinations of chitosan citrate complexes at different levels according to the full factorial design. Magnesium stearate (0.5% w/w), stearic acid (0.5% w/w), silica gel (0.25% w/w) were incorporated as lubricants and glidants prior to compression. Tablets were compressed at a constant compression force of 3000 pounds.

TABLE II

RUN #	Controleed Factors X_1	X_2	Measured Characteristics HR1	HR6	HR12	HR24
1	-1.000	-1.000	17.2	47.4	64.4	84.0
2	-0.192	-1.000	13.1	35.2	57.6	86.7
3	1.000	-1.000	7.9	26.6	50.9	77.3
4	-1.000	0.000	13.8	96.4	97.0	98.3
5	-0.192	0.000	4.7	66.8	97.5	97.6
6	1.000	0.000	3.9	38.9	75.6	94.5
7	-1.000	1.000	16.2	99.2	100.6	102.4
8	-0.192	1.000	4.5	53.0	96.2	102.3
9	1.000	1.000	3.5	32.5	59.2	82.2

In-vitro release studies

In-vitro release studies were conducted on tablets using USP XXI dissolution apparatus II (Distek, Inc., New Jersey) at 50 RPM and 37°C. 900 ml of deionized water was used as the dissolution media. Dissolution samples were collected at predetermined times, and replaced with fresh media, thus maintaining sink conditions. Samples were filtered and analysed using a U.V Spectrometer at 271 mm. Percent drug released was calculated from the absorbance values using a dissolution analysis program on an IBM PC.

RESULTS AND DISCUSSION

The three polymer complexes used in this study were found to have the viscosities of 1080, 6700 and 15000 cps. The dissolution data are presented in Table 2. The polynomial equations based on the quadratic model are given below.

$$Y_1 = 4.3001 - 5.317*X_1 - 2.3752*X_2 - 0.6526*X_1*X_2 + 4.1610*X_1^2 + 2.9333*X_2^2 \quad \text{-Eqn...2}$$

$$Y_2 = 58.89 - 24.167*X_1 + 11.878*X_2 - 10.985*X_1*X_2 + 10.197*X_1^2 - 18.383*X_2^2 \quad \text{-Eqn...3}$$

$$Y_3 = 93.94 - 12.717*X_1 + 13.375*X_2 - 7.408*X_1*X_2 - 6.960*X_1^2 - 18.550*X_2^2 \quad \text{-Eqn...4}$$

$$Y_4 = 99.83 - 5.117 * X_1 + 6.261 * X_2 - 3.4590 * X_1 * X_2 - 4.9484 * X_1^2 - 7.650 * X_2^2 \quad \text{-Eqn...5}$$

Where Y_1 to Y_4 are percent dissolved in 1,6,12 and 24 hours respectively. The responses in the above equations Y_1 thru Y_4, are the quantitative effect of the formulation components or independent variables X_1 and X_2, which represent the viscosity and concentration per tablet of the chitosan citrate complexes, respectively. The values of the coefficients of the independent variables (X_1 and X_2) relate to the effect on the particular response. The coefficients of the combination terms such as X_1X_2 are a measure of the effect of interaction between the corresponding factors on the response. The positive and negative values indicate synergistic and antagonistic effects respectively.

The negative signs for coefficients for X_1 and X_2 in equation 2 for 1st hour show that both components X_1 and X_2 are reducing the release rate, whereas in equations 3, 4 and 5 for hours 6, 12 and 24 X_1 (viscosity) reduces the release rate while X_2 (concentration per tablet) is increasing the release rate. The negative sign for interaction term X_1X_2 suggests that there is an antagonistic interaction between X_1 (viscosity) and X_2 (concentration per tablet). This interaction is quite small and insignificant in the first hour and increases several fold in the sixth hour and slowly decreases in 12th and 24th hours.

The contour plots of the dependent variables that are represented by equations 2-5 are shown in Figures 1-4. Contour plots illustrate the response on a two dimensional surface. These contour plots are extremely useful to visualize the effects of independent variables on dependent variables and also to estimate the formulation composition or the values of the independent variables to achieve the desired characteristic values

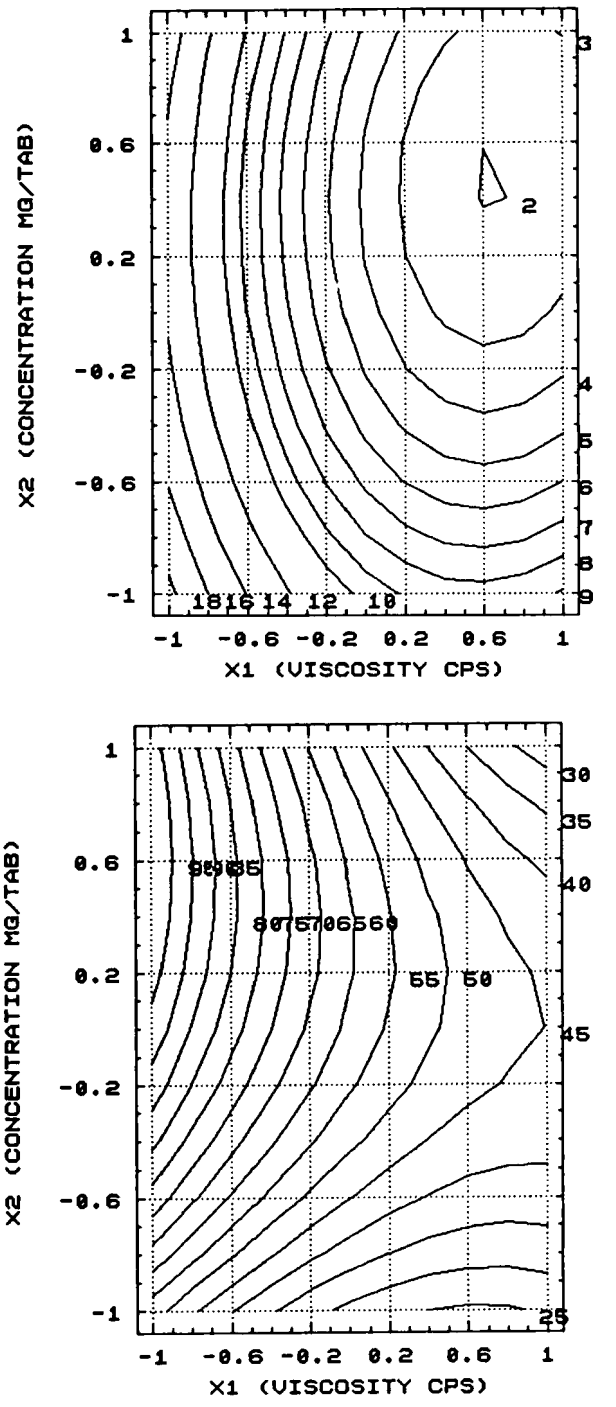

FIGURE I & II: Contour plots for percent theophylline dissolved as a function of viscosity and concentration in 1 and 6 hours respectively.

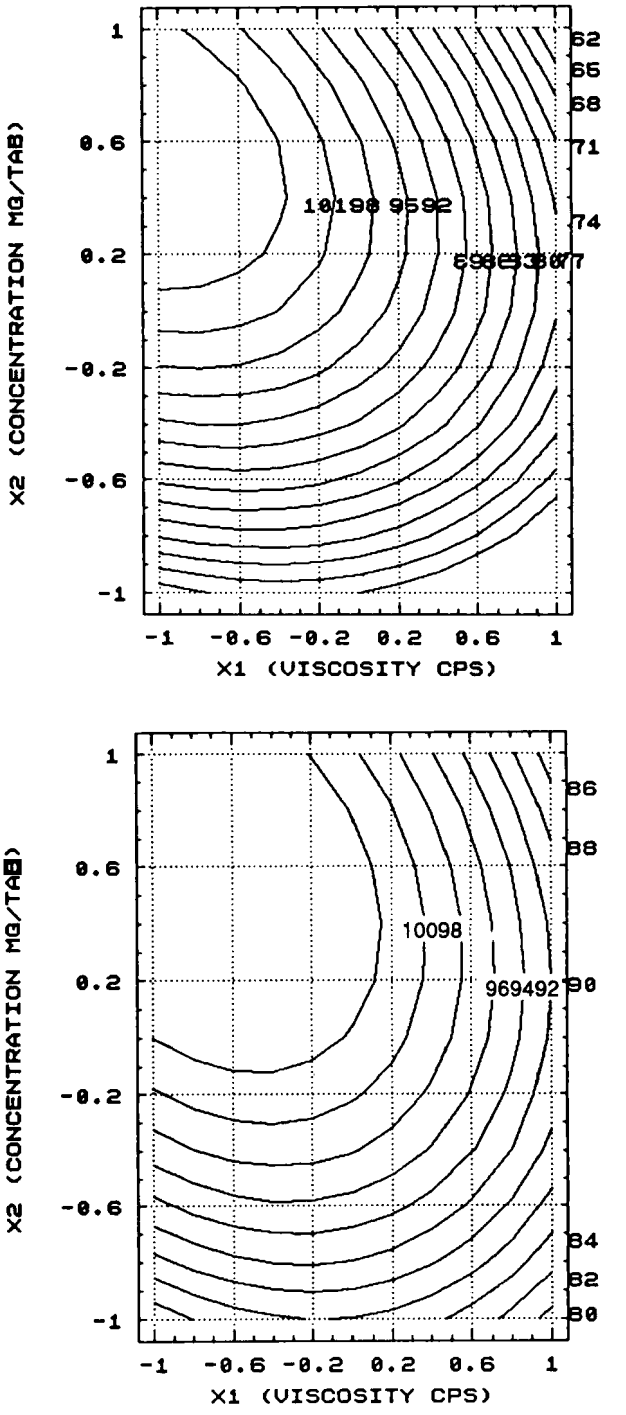

FIGURE III & IV: Contour plots for percent theophylline dissolved as a function of viscosity and concentration in 12 and 24 hours respectively.

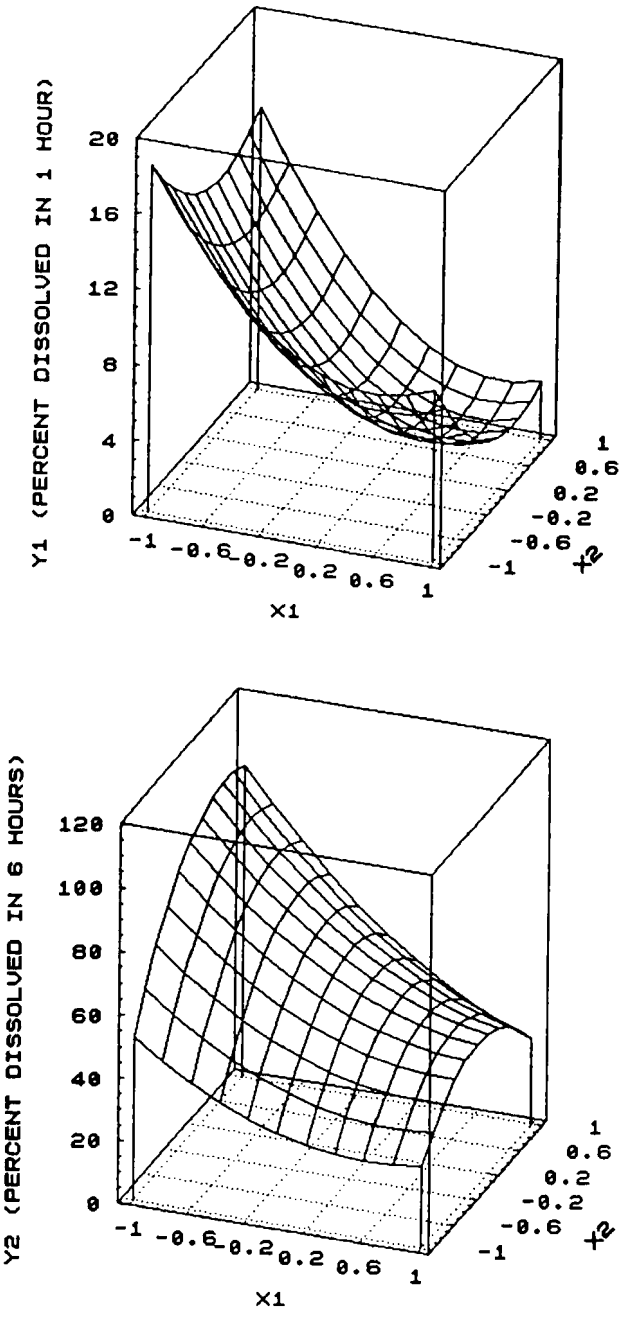

FIGURE V & VI: Response surface plots for percent theophylline dissolved as a function of viscosity and concentration in 1 and 6 hours respectively.

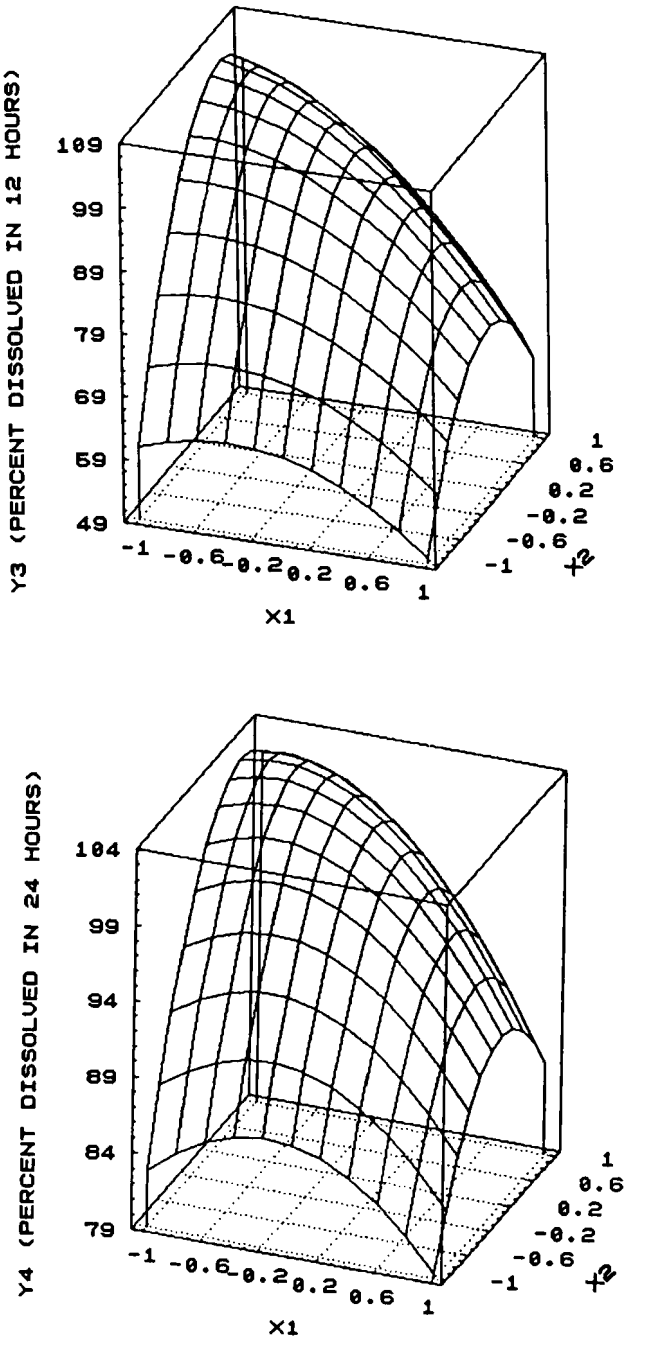

FIGURE VII & VIII: Response surface plots for percent theophylline dissolved as a function of viscosity and concentration in 12 and 24 hours respectively.

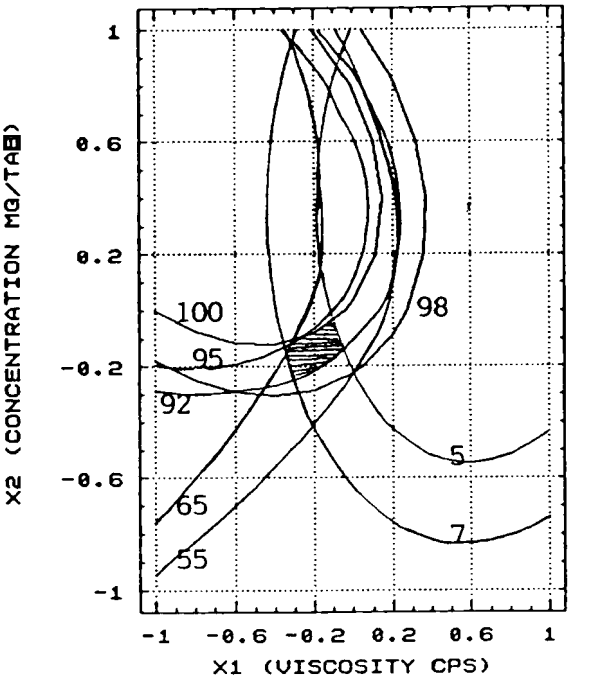

FIGURE IX: Overlaid contour plots for selection of optimum theophylline formulation.

(dependent variables). The numbers printed next to the lines in the contour plots represent the percent drug dissolved at their respective time interval.

The response surface plots present the responses in a three dimensional view. In equations 2 to 5 the terms X_1^2 and X_2^2 indicate the presence of curvature in the response surface. The response surface plots for all the dependent variables are presented in Figures 5-8. The smooth curved surface is predicted from the equations based on the experimental data.

Lines 7 and 8 in Figure 1 indicate that decreasing viscosity, coupled with increasing concentration of the complex will cause the percent released to remain the same. Whereas, Figure 2 for the 6th hr, indicates that

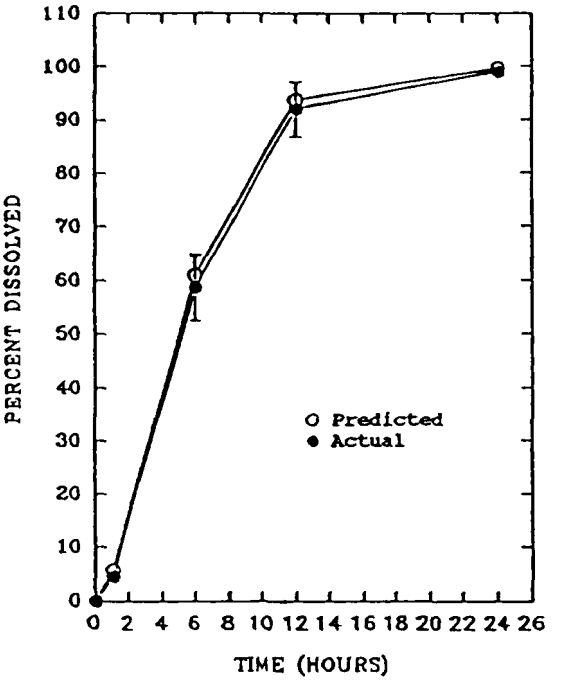

FIGURE X: Predicted and actual dissolution profiles of theophylline from the optimum formulation.

both increased viscosity and concentration keep the release constant. The same is true of contour plots representing hours 12 and 24 (Figures 3 and 4).

The desired percent dissolved values for various time points were chosen and the contour plots (Figures 1-4) were superimposed. The superimposed contour plot is presented in Figure 9. Percent dissolved values of 5 to 7 for 1st hour, 55 to 65 for 6th hour, 92 to 95 for 12th hour and 98 to 100 for the 24th hour were chosen for the superimposed contour plot. The shaded region in the middle of the plot is the optimum region and the X_1 and X_2 values corresponding to that region represent the optimum formulation. The optimum ranges obtained from the plot for X_1 and X_2 are -0.25 to -0.05 and -0.22 to

TABLE III

TIME HRS.	PREDICTED VALUES	ACTUAL VALUES
1	5.67	4.7 (± 0.15)
6	61.1	58.7 (± 6.1)
12	93.6	91.9 (± 5.2)
24	99.5	98.9 (± 0.6)

0.0, respectively. Boundary and constraint equations for independent and dependent variables, respectively, can force the optimization software program to look for the optimal regions only in the areas of interest. The following constraint equations were used to obtain the optimum formulation composition.

Constraint Equations

$Y_1 > 5.5$; $Y_2 < 62.0$; $Y_3 > 92.0$; $Y_4 > 99.0$

Upon execution of the search the values of -0.169 and -0.133 were obtained for the independent variables X_1 and X_2, respectively. These values were fit to equations 2-5 and the values of 5.67, 61.1, 93.6, 99.5 were obtained for Y_1 to Y_4 respectively. The values obtained for X_1 and X_2 were back transformed using equation 1 to obtain 6864 cps and 140 mg/tablet respectively.

Theophylline tablets were manufactured using the composition obtained from the optimization and analyzed, in the same manner as the experimental batches. Table 3 presents the actual percent dissolved values obtained and the predicted values. These values are also plotted in Figure 10. The actual values obtained were found to be in excellent agreement with the calculated values. It is

also evident from this data, that the full factorial design enabled accurate prediction of the properties of the chitosan citrate complexes in theophylline tablets.

CONCLUSION

Chitosan citrate complexes are excellent directly compressible hydrophilic matrix systems. Increasing the viscosity of the polymer, retarded the diffusion of the drug from the matrix and yielded slower release profiles, at constant concentrations of polymer per tablet. A 3^2 full factorial design was used to obtain an optimal formulation using response surface methodology. This economical procedure is useful in predicting formulation properties in product development.

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