Research Article

Statistical Optimization of Intra-gastric Floating tablets of Cefixime Trihydrate Using Mixture Design

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ABSTRACT

The objective of this study was to optimize intra-gastric floating tablets using statistical mixture-design based on three formulation variables such as Guar gum, Sod. alginate, and Sod. CMC. Ten formulations from the experimental design were determined for the time required to release 50% of drug ($t_{50\%}$), drug release at 2 h (R_{2h}), mean dissolution time (MDT) and dissolution efficiency at 10 h (DE_{10h}). All data were analyzed by using statistical programs. Results showed that selected independent variables significantly affect the above variables. Contour plots of each response were depicted, based on the equation given by the statistical-fitted models. With the optimization of more than one criterion, a combined contour plot was made so that the optimum formulation to satisfy the overall goal was obtained. The scale up formulation was selected from the optimized area of the combined properties. The interaction and quadratic terms were also found to affect the formulation variables. An excellent agreement was found between the actual value and predicted value. The optimized experimental conditions for preparation composition comprised 50% CT with 6.755% guar gum, 5.60% Sod. alginate, 7.64% Sod. CMC, which exhibit 4.732 h, 4.552h, 33.022 % and 54.438% of $t_{50\%}$,MDT, R_{2h}, and DE_{10h} respectively. In conclusion, it can be said that mixture design is a valuable second-degree design to develop and optimize gastro floating tablets (GFT) of Cefixime Trihydrate which in turn provides a basis to localize the drug release in the gastric region which in turn increase the oral bioavailability.

Keywords: Dissolution efficiency, Fickian diffusion, Intra-gastric, Mean dissolution time, Mixture Design.

INTRODUCTION

Intra-gastric dosage forms are designed to remain in the stomach for prolonged period of time and enable to promote the continuous input of the drug to the gastric region. Therefore, different approaches have been proposed to retain the dosage form in the stomach, including bioadhesive systems, swelling and expanding systems, floating systems, and delayed gastric emptying devices.[1] Among these, the floating dosage form has been used most commonly. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach, and for drugs that are poorly soluble or unstable in the intestinal fluid.[2] The floating systems include single, multiple, and raft forming systems. The principle of these systems offer simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The present investigation is concerned about the development of mix matrix floating drug delivery systems by wet granulation technique that generates CO_2, thus reduces the density of the system in the stomach for prolonged period of time and releases the drug slowly at the desired rate.[3]

Cefixime Trihydrate (CT) with pKa value of 2.5 (weak acid) remain unionized at acidic pH, thus promotes more absorption of drug in the gastric region. Moreover, the absolute bioavailability of oral cephalosporin is below 50-60%, which suggests an absorption mechanism through the mucosa with limited capacity.[4,5] Further, the biological half-life is 3.0±0.4 h, thus necessitating frequent administration to maintain constant therapeutic drug levels. From the above characteristics CT was considered as model drug for formulation of floating tablet, which would remain in stomach or upper part of GIT for prolonged period of time, therefore the maximum drug release is maintained at desired site.

The objective of this study was to exhibit the application of statistical experimental design to find out optimum formulation for compressed floating tablets using CT as model drug. Guar gum (viscoelastic agent), sodium alginate (gel forming polymer) and Sod. CMC (swelling agent) were selected as the independent variables. In this study, a concentration of polymer mixture in the tablet was fixed at a specific amount. A suitable design for this restriction is statistical mixture design.[6] All mixture designs have a constraint, that is, the sum of all component proportions must add up to one. As a result of this constraint, a change in the amount of one component requires an adjustment in the amount of other components to keep the sum of the components equal to one. The Simple centroid design was applied for optimization of the study formulations. This method can find optimization areas for overall objectives, using a combined contour plot of dependent variables such as $t_{50\%}$, MDT, R_{2h} and DE_{10h}.

MATERIALS AND METHODS

Cefixime Trihydrate was provided by Lincon Pharmaceutical, Ahmadabad, Guar gum, Sodium

bicarbonate, Sod. alginate, Sod. CMC were provided by Cipla limited (Goa, India). Lactose, Magnesium stearate and other chemicals were analytical grade and used as received.

Research Design (The Mixture Design)

Mixture experiment is a special type of design of experiment, in which the factors are the components or ingredients of a mixture, and consequently, their levels are not independent.[7] The sum of all components is 100%. Mixture factors are expressed as fraction of total amount. For the three-component mixture, then

$$0 \le X_i \le 1 \quad \text{..... (1)}$$

Where i = 1, 2, 3 and

$$X_1 + X_2 + X_3 = 1 \quad \text{..... (2)}$$

This means that they cannot be changed independently of one another. A mixture factor can be a formulation factor or a filter factor. Only one mixture factor can be defined as filter.

Formulation factors are the usual mixture factors used in formulations and have specifically defined experimental ranges. The filter is a mixture component, usually of little interest, making up a large percentage of the mixture and added at the end of a formulation to bring the mixture total to the desired amount.

The Augmented Simplex Centroid Design

To accommodate a polynomial equation to represent the response surface over the entire mixture region, a natural choice for the design would be one whose points are spread evenly over the whole mixture factor space.

Simplex designs are used to study the effects of mixture components on the response variable.[8] The simplex centroid design has 2^p-1 points, corresponding to the p permutations of (1, 0, 0,..., 0), the $\frac{p}{2}$ permutations of (1/2, 1/2, 0, ..., 0), the $\frac{p}{3}$ permutations of (1/3, 1/3, 1/3, 0, ..., 0), and the overall centroid $\frac{1}{p}, \frac{1}{p}, \frac{1}{p}, \frac{1}{p} \ldots . \frac{1}{p}$. In Figure 1, the simplex centroid design consists of the point numbers 1, 2, 3,4,5,6, and 10. A criticism of the simplex centroid design is that most of the experimental runs occur on the boundary of the region and, consequently, include only p-1 of the p components. It is usually desirable to augment the simplex centroid with additional points in the interior of the region where the blends will consist of all p mixture components. In augmented simplex centroid design (JMP Statistics and Graphic Guide, Version 3.1, 1995), the point numbers 7, 8 and 9 are added into the design. The response can be related to the mixture composition with the use of a special cubic equation.[9]

$$y = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{123} X_1 X_2 X_3 \quad \text{.....(3)}$$

Where y is the modeled response, β_1 to β_{123} are the regression coefficients and X_1, X_2, and X_3 are the fractions of the three mixture components.

The seven regression coefficients in this model can be estimated by use of multiple regressions. This requires at least seven measurements of each response, located in the experimental space. After calculating the models for each criterion, the values of the response can be predicted at every mixture composition within the experimental space.

It should be noted that in this model, the intercept, present in normal model equations, has disappeared. As a consequence, it is not possible to evaluate Scheffe' models with linear regression, using standard regression software.

Formulations

The mixture design, based on augmented simplex centroid design, was employed. This design has 10 formulations that spread evenly over the whole mixture factor space. Floating matrix tablet formulations containing 50% of CT were prepared by wet granulation method. Cefixime trihydrate (CT) 200 mg was mixed with the required quantities of polymer blend (5-10%) each of guar gum, Sod. CMC, Sod. alginate with total 20% wt./tab. Sodium bicarbonate (15%) and lactose q.s. to made 400mg/tab by geometric mixing (Table 1). Damp mass of the mixture was prepared by aqueous solution, followed by wet sieving in 12mm sieve and dried up to 1 h at 40^0 C. The dried granules were lubricated with magnesium stearate (2%) and compressed on a 10-station rotary tablet machine (Rimek, Ahmadabad, India) using a 10-mm standard flat-face punch.

Evaluation of the GFT

The prepared tablets were evaluated for parameters like hardness, friability, weight variation, thickness, *in vitro* drug release, *in vitro* floating lag time and total buoyancy time.

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by measuring floating lag times and duration of buoyancy according to the method described by *Rosa et al.*[10] The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

***In vitro* release studies**

The release of the drug was studied using USP Type II dissolution apparatus using 900 ml 0.1N HCl as dissolution media maintained at 37 ± 0.5^0C with rotation speed of 50 RPM. Aliquots of 1 ml were collected at pre-determined time intervals and were replenished with an equivalent volume of fresh medium. The samples were filtered and diluted to a suitable concentration with 0.1N HCl. They were analyzed by using UV–Visible double beam spectrophotometer at 278 nm (V-670, Jasco, Japan). The results were expressed as mean ± S.D. (n = 3). The cumulative percentage drug release was calculated using

an equation obtained from the standard curve. The times for 50% drug release, drug released at 2 h were calculated based on the Korsmeyer and Peppas model.[11]

Mechanism of drug release

To evaluate the mechanism of drug release from floating matrix tablets, data of drug release were plotted in Korsmeyer *et al's* equation.[12] The release exponent 'n' characterizes the mechanism of drug release from polymeric matrix system. Mean dissolution time (MDT) value is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer.[13] Further, the dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to certain time t, expressed as % of the area of the rectangle described by 100 % dissolution in the same time.[14] It can be calculated by the following equation:

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100 - - - (4)$$

Where y is the % of drug dissolved at time t. y_{100} is the 100 % drug release at time t.

Table 1: Experimental range and level of independent variables

Coded	Variable	Range and level	
		0	1
X_1	Guar Gum (%)	5	10
X_2	Sod.Alginate (%)	5	10
X_2	Sod. CMC (%)	5	10

Table 2: The percentage composition of the component with experimental results

No.	X_1	X_2	X_2	t_{50}% (h)	MDT (h)	R_{2h} (%)	DE_{10h} (%)	FLT (min)	TFT (hr)
F1	10	5	5	4.54	4.99	31.38	51.466	8	11
F2	5	10	5	4.272	4.7	31.97	51.876	15	14
F3	5	5	10	4.231	4.69	33.28	55.838	12	12
F4	7.5	7.5	5	5.1	4.54	31.02	50.113	17	12
F5	7.5	5	7.5	5.01	4.722	30.9	51.7	11	11
F6	5	7.5	7.5	4.55	4.11	33.67	57.86	13	12
F7	6.66	6.66	6.66	4.25	4.48	36.22	57.24	13	13
F8	8.33	5.833	5.833	4.26	4.49	35.23	56.22	12	12
F9	5.833	8.33	5.833	4.99	4.69	33.59	52.27	11	14
F10	5.833	5.833	8.333	4.71	4.899	30.89	53.21	12	12

Table 3: Regression equation of response variables

Response	Regression equation	R square
t_{50}%	4.595 Guar Gum % + 4.327 Sod. Alginate % + 4.286 Sod. CMC % + 1.66 Guar Gum % *Sod. Alginate % + 1.384 Guar Gum % *Sod. CMC % + 0.08 Sod. Alginate % *Sod. CMC %	0.77
MDT	4.98 Guar Gum % + 4.69 Sod. Alginate % + 4.68 Sod. CMC % - 1.036 Guar Gum % *Sod. Alginate % - 0.288 Guar Gum % *Sod. CMC % -2.156 Sod. Alginate % *Sod. CMC %	0.974
R_{2h}	31.075 Guar Gum % + 31.665 Sod. Alginate % + 32.975 Sod. CMC % + 3.478 Guar Gum % *Sod. Alginate % + 0.378 Guar Gum % *Sod. CMC % + 10.278 Sod. Alginate % *Sod. CMC %	0.74
DE_{10h}	51.195 Guar Gum % + 51.605 Sod. Alginate % + 55.567 Sod. CMC % - 0.83 Guar Gum % *Sod. Alginate % - 2.48 Guar Gum % *Sod. CMC % + 21.413Sod. Alginate % *Sod. CMC %	0.834

Statistical Analysis

The data of all dependent variables were used to evaluate for the model response and R square by using SAS® software program (Version 6.12, USA). The model search was started with a full model as shown in Equation 3.

The non-significant terms of the model were excluded. Only significant terms (α = 0.05) were used in the fitted model. The contours of response model were plotted by using JMP® software (Version 11, USA). Then, the range of optimal value of each property was selected. All selected response surface areas were superimposed and the optimal range for all properties was obtained.

RESULTS AND DISCUSSION

All GFT passed physicochemical tests for weight variation, drug content and friability as per the specification of Indian Pharmacopoeia. Floating lag time of all formulations was within the range 8-16 min (Table 2). All formulations floated in the 0.1N HCl for more than 11 h showing good matrix integrity during this extended period of time. From the data it was revealed that as the

concentration of polymer increased, the floating lag time decreased due to the increasing hydrophilic nature of the polymer allowing penetration of liquid through pores formed on the surface of the tablet, and the total floating time increased due to swelling of the tablet which keeps it intact for a longer period of time.[15]

The results of the evaluation of dependable variables for different batches of floating tablets (F1 –F10) are given in Table 2. To evaluate the effect of polymers on the response variables precisely, the drug and other excipients used in the preparation of the floating tablets were not considered in the development of polynomial models. The effect of formulation variables on different dependent or response variables was assessed by the generated regression coefficients and r^2 values. The fitted quadratic equations relating the responses such as, time required to release 50% of drug ($t_{50\%}$), mean dissolution time (MDT) drug release at 2 h (R_{2h}) and Dissolution efficiency at 10 h (DE_{10h}) and r^2 were summarized in Table 3.

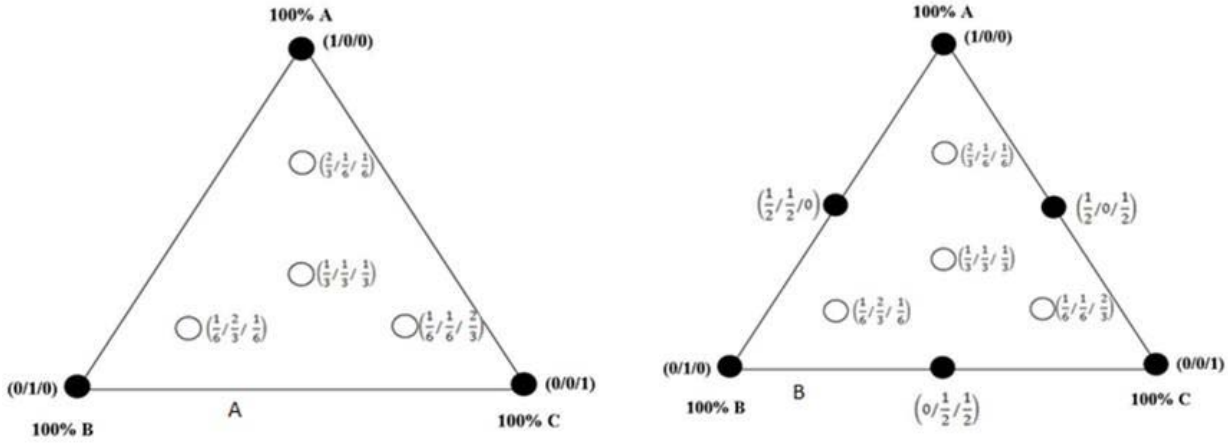

Figure 1: The mixture design (a) belongs to the axial family and supports a linear model and the design (b) belongs to the simplex centroid family and supports a quadratic model. The full circles represent mandatory experiments and the open circles optional experiments. The designs are for mixtures of three components and the fraction of each component is given for each experiment.

Table 4: Observed response of the formulations in central composite design

Formulations	Zero order	1st order	Higuchi	Peppas	
	R^2	R^2	R^2	n	R^2
F1	0.975	0.918	0.976	0.615	0.987
F2	0.972	0.905	0.982	0.631	0.995
F3	0.996	0.91	0.979	0.605	0.985
F4	0.943	0.966	0.993	0.583	0.996
F5	0.973	0.906	0.982	0.654	0.997
F6	0.964	0.788	0.981	0.562	0.985
F7	0.963	0.899	0.985	0.568	0.993
F8	0.956	0.896	0.977	0.594	0.994
F9	0.966	0.901	0.981	0.612	0.988
F10	0.964	0.885	0.988	0.586	0.989

The correlation coefficients (r^2) for variables $t_{50\%}$ (h), MDT (h), R_{2h} (%), DE_{10h} (%) were found to be 0.77, 0.97, 0.83, 0.74 respectively, which are approaching to one indicating the good model characteristics. Further, lower values for the variables $t_{50\%}$ (h) and DE_{10h} (%) signify the partial explanatory of the model. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (positive or negative). The interaction terms and quadratic terms also show a significant effect on the response variables.

A rigorous study of dissolution profile for all formulations gave an insight in to the effect of polymeric filler on release profile of the formulations. From the dissolution profile it was revealed that as the increased concentration of guar gum decreased the drug release characteristics as shown in Figure 2. Significant decrease ($p<0.05$) in release of drug with 5 to 15% range of guar gum as seen in F1 to F10, this attribution due to the formulation containing large concentration of high viscosity polymers. Guar gum induced formation of strong viscous gel layer that leads to decreased water diffusion into the tablet matrix which results in decrease drug release. The gel strength of the swollen matrix formulation might be too high to release the drug from the formulation. The hydration of guar gum is independent of the pH of the dissolution medium.[16]

Moreover, incorporation of Sod. alginate increasing the gelling characteristics which attributed longer tortuous path thus provides more diffusion path length of the dissolved drug. Hence, providing diffusion predominant drug release rather erosion. Sodium CMC was used as a channelling agent, which guides water into the tablet by forming pores due to its swelling property.

The data of drug dissolution have been fitted to Korsmeyer *et al's* equation Table 4. The release exponent

(n) of different formulations are within 0.55 to 0.65 which are close approximation to 0.5 reflecting diffusion predominant characteristics of drug release rather than erosion of the polymer. Since Fickian diffusion was the dominant dissolution mechanism, hence both $t_{50\%}$ and MDT increase in higher concentration of polymer level due to movement of drug to a longer distance before being released into surrounding liquid.

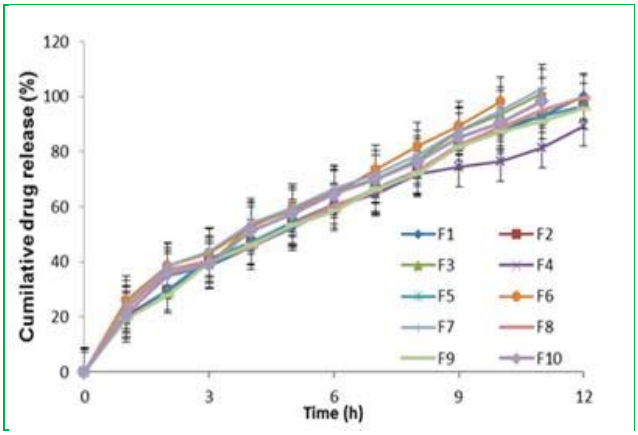

Figure 2: Cumulative percent release of the formulation F1 to F10

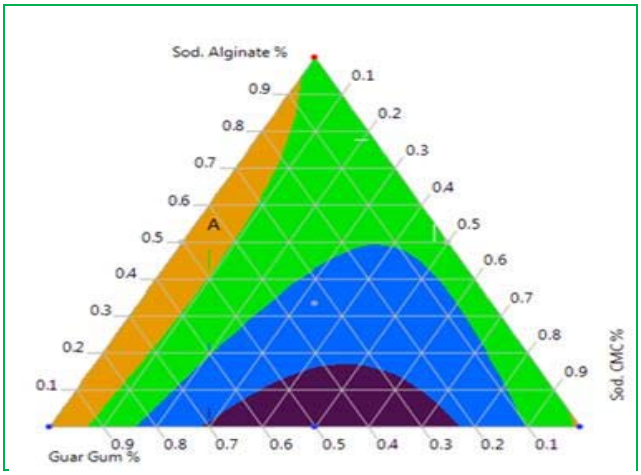

Figure 3: Contour Plot of the time required to release 50% of drug ($t_{50\%}$)

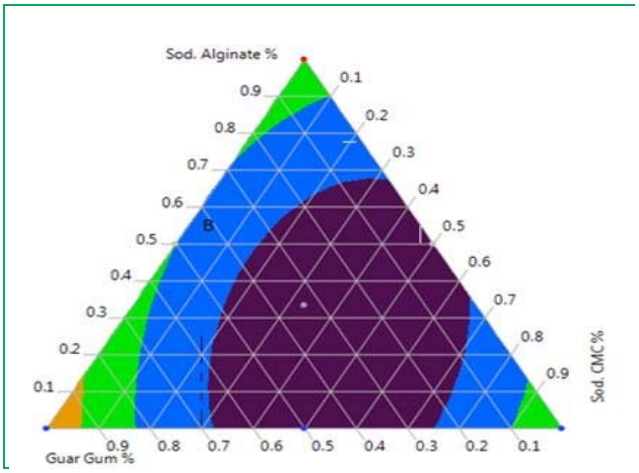

Figure 4: Contour Plot of mean dissolution time (MDT)

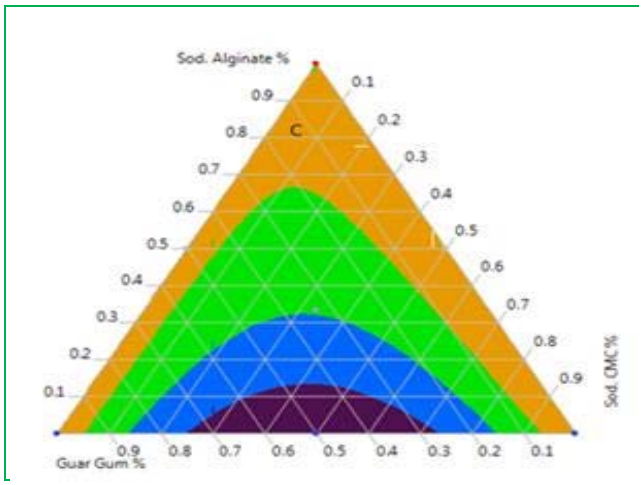

Figure 5: Contour Plot of the drug release at 2 h (R_{2h}), and

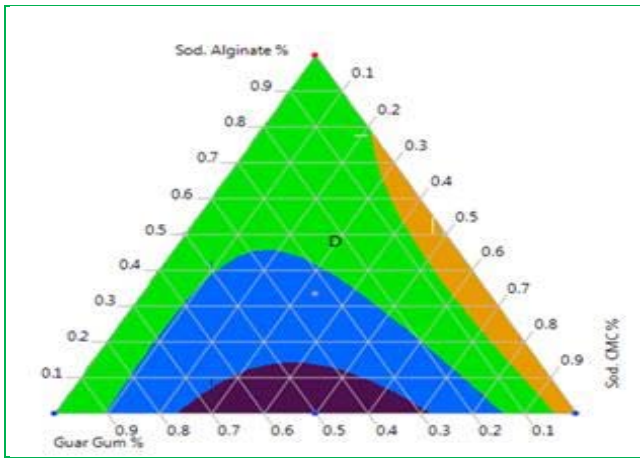

Figure 6: Contour Plot of the dissolution efficiency at 10 h (DE_{10h})

The effect of polymer on dependent variables such as t_{50}% was depicted on the ternary graph. The selected area of the above parameter (area A) was chosen for the range within the desirable 4.4 to 5 h, Figure 3. Similarly for the parameter MDT the area B for the range 4.3 to 5.1 ranges Figure 4. Further other parameters such as R_{2h}, DE_{10h} also depicted in the Figure 5 and 6. The desirable range both the case (Area C, D) 31 to 33.5 and 52.5 to 57.5.

To optimize all the responses with different targets, a multi criteria decision approach (a numerical optimization technique by the desirability function and a graphical optimization technique by the overlay plot) was used. The recommended concentrations of the independent variables were calculated by the JMP software from the above plots which has the highest desirability near to 1.0. The extensive grid and feasibility searches provided that the optimum formulations and the respectively desired function response plot and overlay plot are as shown in Figure 7 and 8, where one solution was found with a highest desirability (prediction = 0.9657). Figure 8 shows the optimized area which had all properties in the selected criteria. The point X is the selected point for scale up formulation. At this point, the proportion of Guar gum: Sod. Alginate: Sod CMC was found to be 35.11:12.08:52.808 % respectively.

On the basis of dependent variables the optimized experimental conditions for preparation composition comprised 50% CT with 6.755% guar gum, 5.60% Sod. alginate, 7.64% Sod.CMC, 15% sodium bicarbonate, 2% magnesium stearate with quantity sufficient lactose to form 400mg/tab which exhibit 4.732 $t_{50\%}$ (h), 4.552 MDT (h), 33.022 R_{2h} (%) and 54.438 DE_{10h} (%).

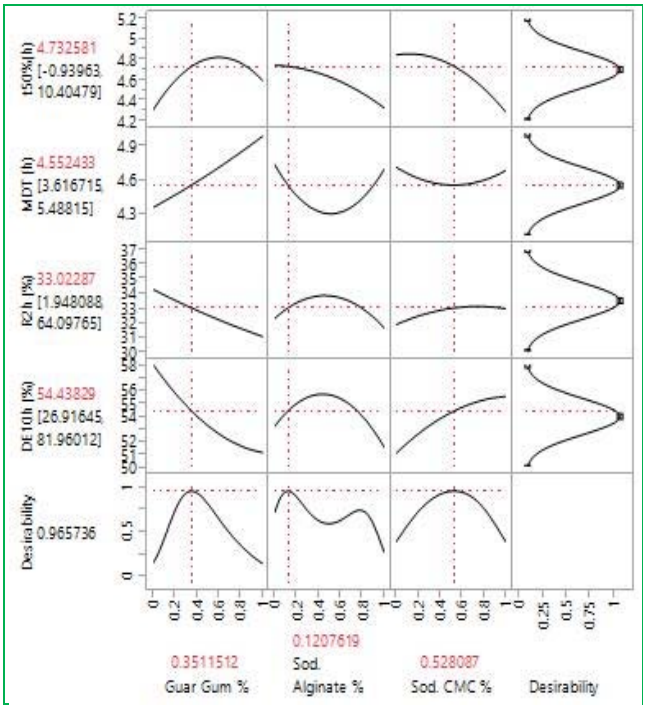

Figure 7: Prediction profiler of optimization of gastric floating tablets of CT using independent variables (desirability plot)

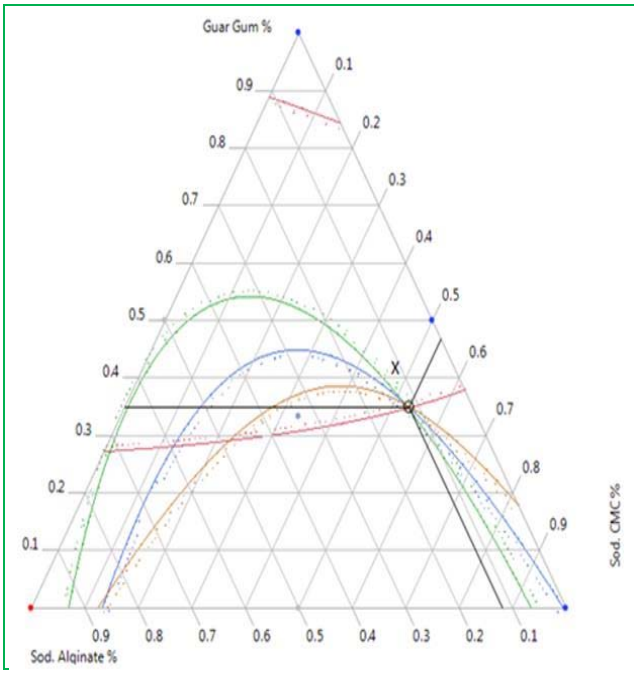

Figure 8: The overlay plot showing the optimized area of floating tablet and the selected point. (X = the selected point).

CONCLUSION

The statistical mixture design has the advantage of performing a small number of experiments and the fitted model from the statistical analysis can be used to predict values of responses at any point inside the experimental space. The mixture design can be successfully used to optimize the floating formulations. The graphical procedure is an important tool for understanding the change of responses and locating the area of interest. A graphical method can be easily used to locate the overall optimum zone. The formulation containing 6.755% Guar gum, 5.60% Sod. alginate, 7.64% Sod. CMC, was in the optimum zone and was considered as an optimum formulation. The design and evaluation of the formulations in this study resulted in successful product development. Hence floating tablets were prepared and optimized effectively by RSM. RSM can be used to reduce the time and cost of the development of the experimental procedure. Further RSM is that the response surface is fitted by a continuous function and can be drawn as a contour plot. The optimal area in each contour plot can be located easily by reading the value from the plot. The combination of each response can be made and the overall optimal zone can be obtained, using the intersection area of each optimal response. Hence floating tablets of CT effectively increase the gastric residence time and prolong the drug release in the stomach, which, in turn, improves the local availability of the drug.

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