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Application of simplex centroid design in formulation and optimization of floating matrix tablets of metformin

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ABSTRACT

The purpose of this research work was to develop the buoyant matrices of metformin by the direct compression method using mixture design as an optimization technique. The simplex Centroid design was practiced as an optimization technique by modifying the quantity of three elements simultaneously and holding back their total concentration constant.

Method: The amounts of HPMC K15M (X_1), kappa-Carrageenan (X_2) and sodium bicarbonate (X_3) were used as the independent variables while floating lag time (Y_1), % drug released after 1 hour(Y_2) and time required for 90% (t_{90}) were taken as the response variables. As per the simplex centroid design total 14 formulations were formulated. Matrices were evaluated for physical parameters, *in-vitro* buoyancy, swelling ability and adhesion retention period.

Results: The results of response variables were statistically evaluated using design expert software. Formulation M-SCD 7 was found to be the optimum having good floating lag time and also matching the desirability criteria for drug release. The formulation also gave reasonably high adhesion retention period and swelling index desirable for securing the retention of formulation in the abdomen.

Conclusion: It was concluded that the mixture of kappa carrageenan and HPMC K 15 M increases the flexibility in the release pattern of the drug. This study establishes the use of simplex centroid design in the development of floating matrix tablets with minimum experimentation.

INTRODUCTION

Metformin is among the drugs which require to be on the upper portion of the gastrointestinal tract for better drug delivery (Basak *et al*., 2007; Porta *et al*., 2008). Many advances have been successfully used for increasing the bioavailability of metformin by preparing gastro-retentive dosage forms (Yadav *et al.,* 2011; Priyadarshini *et al.,* 2015; Tack-on *et al.,* 2013). The objective of the present research work was to develop a gastroretentive drug delivery system containing metformin using simplex lattice design as an optimization technique.

Authors of this article have already checked the combined effect of HPMC and other polymers on the release and gastroretentive properties of the formulation. They found that the batches containing HPMC K15M and kappa-carrageenan polymer showed better release as compared to all other formulations (Patel *et al.,* 2016). The effect of the combination of HPMC K15M and kappa-carrageenan has not been explored earlier for metformin. However, a study conducted by Dorozynski *et al.*, 2011, had proved that the mixtures of carrageenan and HPMC, increase flexibility in the release characteristics of controlled release preparations. The combination can be used to modify the drug release properties of polymeric matrices, which can help in obtaining tailor-made materials for drug delivery system and therefore can be employed as a beginning spot for the formulation of controlled release dosage forms. Hence, the floating matrix tablet of metformin was prepared using these polymers and optimized using mixture design.

The evolution of a new pharmaceutical formulation by trial and error technique is very much time consuming and also calls for high cost. Due to these causes, the maturation of a novel drug molecule has diverted the pharmaceutical industry to

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investigate various strategies in the evolution of novel drug delivery systems (Colombo *et al.,* 1985). The optimization techniques, on the foundation of a few experiments and statistical analysis of the resolutions can provide an effective and economical method for the prognostication of the optimal composition. Recently, the use of Design of experiment (DoE) has increased immensely in R&D of drug due to its practical applicability in the industry. Even for the development of gastroretentive formulations statistical designs are applied for the optimization of dosage form. Recent example is the application of DoE for the optimization of floating drug delivery prepared by hot melt extrusion (Vo *et al.,* 2016). In the present research work mixture design has been employed for the optimization. Mixture design has been already explored for the optimization of transdermal (Duangjit *et al*., 2014), thin films (Gohel *et al.,* 2009), nanosuspensions (Suhesti *et al.,* 2016) and gastroretentive tablets (Prajapati *et al.,* 2009, Mandlik *et al*., 2012; Thakkar *et al*., 2014; Jivani *et al*., 2009; Patel *et al*., 2007). A simplex lattice is an arrangement of equally spaced points on a simplex (Lachman *et al*., 1970). When described by a polynomial equation the lattice can be referred to as {q, m}, where, q = Number of components, m = Degree of the polynomial, or in other words, the number of proportions assumed by each part. The simplex centroid design is based on the same rules as the simplex lattice design, with the exception that the design points are not only equally spaced but now also appear either in equal proportions or zero (on the boundaries). The number of design points is determined by 2q – 1. The design also has an overall centroid containing equal proportions, equally spaced.

MATERIALS AND METHODS

Materials

Metformin hydrochloride was obtained as a gift sample from Sanofi-Aventis Ltd., Ankleshwar. Sodium bicarbonate, was procured from Sulab Reagents, Suvidhinath laboratories, Baroda, HPMC K15M was procured from Astron Chemicals, Ahmedabad, kappa-carrageenan was procured from Rajesh Chemicals, Vadodara. Rest other excipients were obtained from the local market.

Methods

Formulation of Metformin floating tablets

Tablets containing 500mg of Metformin were made by direct compression technique. The active ingredient, Metformin, release-delaying polymers (HPMC K15M and kappa Carrageenan), a gas-forming agent, $NaHCO_3$, were passed through sieve no. 40, individually. The quantities of all the above mentioned solids were taken as per mentioned in Table 2 and powders blends were prepared and mixed in a mortar and pestle for 10 minutes. Then, microcrystalline cellulose and magnesium stearate were added to the above powder mixture and mixing was done for another 10 minutes. At last, 1000mg of mixture was weighed and fed into the die of Rotary tablet compression machine (Cronimach Instrument, India) manually, with capsule shaped punch die set. The width and length of produced caplet tablets with 8mm x 17mm with breakline. Using a Monsanto hardness tester (Monsanto Chemical, M. Shah and com., India), the hardness of the tablets was adjusted at 5 kg/cm^2.

Mixture design - Simplex Centroid Design

The studied carried out by Patel *et al.,* 2016, suggested that controlled release formulations prepared with the combination of HPMC K15 M and κ-Carrageenan, as release retarding polymers were giving satisfactory release, hence these polymers were considered for the formulation of buoyant matrix tablet of Metformin. The levels of the independent variable was decided based on the literature survey, (Dorozynski et al., 2011) and by the experimentation done by authors in the previous studies (Patel *et al.,* 2016). Mixture design was used to optimize the formulations with HPMC K15 M, κ-Carrageenan and sodium bicarbonate as independent elements. As the dose of the drug is very high, it was decided to develop floating matrix tablets containing metformin using **simplex centroid design** as the technique for optimization by changing the amount of three factors concurrently and keeping their total concentration constant.

Table 1: Factors and their examined levels in Simplex Centroid Design.

Independent Variables /Levels	Amount of HPMC K15M	Amount of k-Carrageenan	Amount of sodium bicarbonate
	X_1 (mg)	**X_2 (mg)**	**X_3 (mg)**
Low	150	50	150
High	200	100	200
Dependent Variables	**Y_1** - Floating lag time (sec)(F_{lag}) **Y_2** - Drug released after 1 hour (%) **Y_3** - Time required for 90% (t_{90})		
No. of replicates 4			

The Simplex Centroid design (SCD) for three-component system is presented by an equilateral triangle in two-dimensional space. In this study, the amounts of matrixing agent, HPMC K4 M (X_1), release retarding polymer, kappa-Carrageenan (X_2), gas-generating agent, sodium bicarbonate (X_3), were chosen as independent variable. The floating lag time (F_{lag}), drug released after 1 hour and time required for 90% drug release, were claimed as dependent variables (Table 1). The design was applied and evaluated using the Design-Expert® Software (version- 9.0.6, Stat-Ease) by running 14 experiments. The composition of the batches formulated by using this statistical design is given in table 2.

Table 2: Composition and Evaluation of the batches prepared by applying SCD.

Runs	Batch code	Transformed Fractions of Variables*			Floating lag time (sec)	Drug released after 1 hr (%)	Time required for 90% (hrs)
		X_1	X_2	X_3			
1	M-SCD 1	175	50	175	10	35.05	5.2
2	M-SCD 2	158.33	58.33	183.33	5	33.92	5.76
3	M-SCD 3	150	100	150	5	35.47	5.84
4	M-SCD 4	150	50	200	8	36.2	4.99
5	M-SCD 5	183.33	58.33	158.33	15	29.37	6.95
6	M-SCD 6	166.67	66.67	166.67	12	35.27	5.91

7	M-SCD 7	175	75	150	15	34.54	6.86
8	M-SCD 8	158.33	83.33	158.33	10	48.09	4.68
9	M-SCD 9	175	75	150	12	34.5	6.82
10	M-SCD 10	150	75	175	42	49.75	5.03
11	M-SCD 11	150	100	150	10	35.47	5.92
12	M-SCD 12	200	50	150	45	39.09	6.89
13	M-SCD 13	150	50	200	5	36.00	5.03
14	M-SCD 14	200	50	150	45	38.67	6.76

*In all the batches, each tablet contained 500mg Metformin, 90mg microcrystalline cellulose and 10mg magnesium stearate. X_1 represents the amount of HPMC K15M (mg); X_2 represents the amount of kappa-carrageenan (mg); X_3 represents the amount of sodium bicarbonate (mg).

Physical properties of floating tablet

All the floating matrix tablets, prepared by applying SCD were subjected to check their physical properties. The tests like weight uniformity, hardness, drug content and friability studies were performed as per IP 2007.

Tablet swelling ability

The swelling performance of the tablets was evaluated, in triplicate. A tablet was weighed (W_1) and positioned in in a petri dish with 20 ml of HCl (0.1 N), maintained at 37±0.5 ºC. After 8 hours the tablets were taken away from the petri dish and the swollen tablet was then reweighed (W2) (Dorozynski *et al.,* 2004 and Patel *et al.,* 2009). The swelling index (SI) was calculated using following formula.

$$Swelling\ Index = \frac{W2 - W1}{W1}$$

Where, W2 stands for the weight of the swollen tablets, and W1 stands for the initial weight of the tablets.

Size of tablets, before and after swelling, was also measured.

***In-vitro* floating studies**

The buoyant behaviour of the tablets was found visually, in triplicate. Briefly, a tablet was resting in a glass beaker, holding 200 ml of 0.1 N HCl, which was placed in a water bath at 37 ± 0.5ºC. Then floating lag time i.e., the time required for the tablet to float on the 0.1N HCl and total floating period, i.e., the time period for which the tablet remained buoyant", were noted (Rosa *et al.,* 1994).

Tablet adhesion retention period

The adhesion retention period of the tablets was evaluated, on an agar petri plate (2%, w/w), made in 0.1 N HCl (pH 1.2). One side of the tablet was moistened with 0.1 N HCl and then placed on the agar plate by slightly pressing it with a finger. After some time, the agar plate was attached to a USP disintegration test apparatus (DBK Disintegration apparatus, Ahmadabad) and moved up and down in 0.1 N HCl (pH 1.2) at 37 ± 0.5ºC. The tablet attached on the plate was dipped into the solution and then taken out and the process was continued till the tablet got detached from the agar plate. The retention period of the tablet on the plate was measured visually (Nakamura *et al.,* 1996; Perioli *et al.,* 2009).

Drug release studies

USP Dissolution Tester Apparatus, type-II (Paddle method) (Electro lab instrument) was used to study the drug release from the prepared floating tablets, in triplicate. The temperature was maintained at 37 ± 0.5 ºC and the paddles rotated at a speed of 100 rpm. The prepared tablets were placed into 900 ml of 0.1N HCl solution (pH 1.2) and aliquots of 5 ml were withdrawn from the dissolution flask at regular interval of time. The aliquots were filtered through a cellulose acetate membrane (0.45 µm). The amount of the drug present in each sample was determined spectrophotometrically at a wavelength of 230 nm. To maintain the sink condition, at each time of withdrawal, 5 ml of fresh medium was replaced into the dissolution flask.

RESULTS AND DISCUSSION

Physical properties of floating tablet

All the prepared formulations complied the weight uniformity study. The hardness of all the batches was found to be in the range of 4.1 to 5.7. Drug content of all the batches was near 100 %, which proved to have good content uniformity in the prepared batches. Friability was also found within the limit for all the batches. All the prepared batches were floating for more than 8 hours, but formulations M-SCD 12and M-SCD 14 were sinking in between the flotation time study, this may be due to the high concentration of HPMC K15M and minimum level of the gas generating agent.

The tablet adhesion retention time was in the range of 64.22 to 120.30 minutes. It was found that as the amount of kappa carrageenan increased in the formulations, the tablet retention also increased, which was expected because Carrageenan is high molecular weight sulfated polysaccharides and its high adhesion period may be due to hydrogen bonding or ionic interaction with agar. However, increased levels of sodium bicarbonate decreased the tablet adhesion retention period. Swelling index was found to be in the range of 2.18 to 3.51. In this case, it was also observed that the increase in amount of kappa carrageenan increased the swelling index. This is credited to the capacity of the polymer to get hydrated quickly and high water uptake, which eventually cause the swelling of the polymeric matrix. The results for all these parameters is given in table 3.

Experimental responses of the batches prepared by applying SCD

The result of all the dependent variables is given in table 2. A statistical model incorporating 14 interactive terms was used to assess the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

Table 3: Results of the physical properties of the batches prepared by applying SCD.

Batch code	Weight uniformity	Hardness (kg/cm^2)	Drug content (%)	Friability (%)	Floating Time (hrs.)	Tablet adhesion retention period (min.)	Swelling index (ratio)
M-SCD 1	Conforms	4.1±0.28	98.92±0.94	0.23±0.16	> 8	74.25	2.36
M-SCD 2	Conforms	5.7±0.95	100.91±0.43	0.22±0.17	> 8	73.37	2.32
M-SCD 3	Conforms	5.7±0.43	99.04±0.74	0.29±0.08	> 8	120.30	3.41
M-SCD 4	Conforms	5.2±0.55	99.62±0.31	0.29±0.21	> 8	69.52	2.23
M-SCD 5	Conforms	5.2±0.95	99.43±0.65	0.13±0.14	> 8	81.41	2.56
M-SCD 6	Conforms	4.7±0.54	99.56±0.42	0.19±0.11	> 8	88.43	2.82
M-SCD 7	Conforms	4.7±0.38	100.83±0.27	0.23±0.10	> 8	97.52	3.16
M-SCD 8	Conforms	4.8±0.75	99.56±0.29	0.24±0.08	> 8	102.34	2.91
M-SCD 9	Conforms	4.6±0.65	100.18±0.54	0.31±0.28	> 8	96.55	3.10
M-SCD 10	Conforms	4.2±0.62	99.16±0.63	0.23±0.12	> 8	85.27	2.98
M-SCD 11	Conforms	5.2±0.67	100.54±0.54	0.32±0.09	> 8	118.24	3.51
M-SCD 12	Conforms	4.8±0.34	100.3±0.51	0.32±0.18	> 8	85.20	3.01
M-SCD 13	Conforms	5.6±0.95	101.17±0.41	0.14±0.10	> 8	64.22	2.18
M-SCD 14	Conforms	4.6±0.62	100.46±0.95	0.32±0.13	> 8	80.21	2.94

Table 4: Analysis of Variance table for dependent variables with Simple centroid design model.

Source	Sum of Squares	Degree of freedom	Mean Square	F Value	p-value Prob > F
Floating lag time (sec) (F_{lag})					
Model	2801.58	6	466.93	29.89	0.0001
Residual	109.34	7	15.62		
Corrected Total	2910.93	13			
Drug released after 1 hour (%)					
Model	384.88	8	48.11	1932.94	< 0.0001
Residual	0.12	5	0.025		
Corrected Total	385.01	13			
Time to release 90% of drug (t_{90})					
Model	8.92	8	1.11	354.38	< 0.0001
Residual	0.016	5	3.146E-003		
Corrected Total	8.93	13			

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the 14 runs, and bi is the estimated coefficient for the factor Xi. The master effects (X_1, X_2, and X_3) represent the average result of changing one element at a time from its low to high value. The interaction terms (X_1X_2, X_2X_3, X_1X_3, and $X_1X_2X_3$) give the information about how the response changes when two or more factors are simultaneously modified. The values for F_{lag}, drug released in 1 hour, and t_{90} for all 14 batches (M-SCD1- M-SCD14) is presented in table 2. The outcomes indicated that the values of subject variables are dependent on independent variables. All the formulations gave satisfactory floating lag time in the range of 5 to 45 seconds, which means that the chosen. The formulations gave percentage drug release in 1 hour in the range of 29.37 to 49.75%. The formulations released 90% of the drug in the time range of 4.68 to 6.95hrs. Using analysis of variance (ANOVA), the significance ($p < 0.05$) of the ratio of mean square variation due to the regression coefficient, and the residual error were tested (Table 4). The special Cubic Mixture model was found to be significant for floating lag time, whereas Special Quartic Mixture model was followed by other two responses. The high values of correlation coefficients for F_{lag} (R^2 = 0.9624), drug release at 1hr (R^2 = 0.9997), and t_{90} (R^2 = 0.9982) indicated a good fit (ie, good agreement between the dependent and independent variables). Lack of Fit F-value for Y_1, Y_2 and Y_3 was found to be about 5.45, 0.57 and 0.75 respectively, which suggests the desirable, insignificance of Lack of Fit.

Floating lag time

The result can be expressed for model analysis by Special Cubic Mixture model. The fitted equation for the responses are given as follows:

$$F_{lag} = +45.17X_1 + 7.22X_2 + 5.73X_3 - 51.21X_1X_2 - 66.59X_1X_3 + 133.70X_2X_3 - 388.68X_1X_2X_3$$

The polynomial equations can be applied to find the conclusions after looking at the magnitude of coefficient and the mathematical sign it carries (i.e. positive or minus). By looking into the above equation, it is apparent that all the three factors, Amount of HPMC K15M (X_1), kappa-carrageenan (X_2) and sodium bicarbonate (X_3) show positive effects on floating lag time of the formulated floating tablets of metformin. But it was observed that X_1 had significant effect on the lag floating time. This means, more the concentration of HPMC K15M, more floating time is experienced by the formulation. The interaction was found to be more significant and the proper combination of the three variables is required to get the desired minimum floating lag time. Observed and predicted values of the floating lag time were found to be comparable, which additionally validates the suitability of the model. The three dimensional response surface graphs for a

floating lag time are given in Figure 1 (shows the obtained contour plot) and Figure 2 (shows response surface plots). This give the information about the main and interaction effects of the independent components.

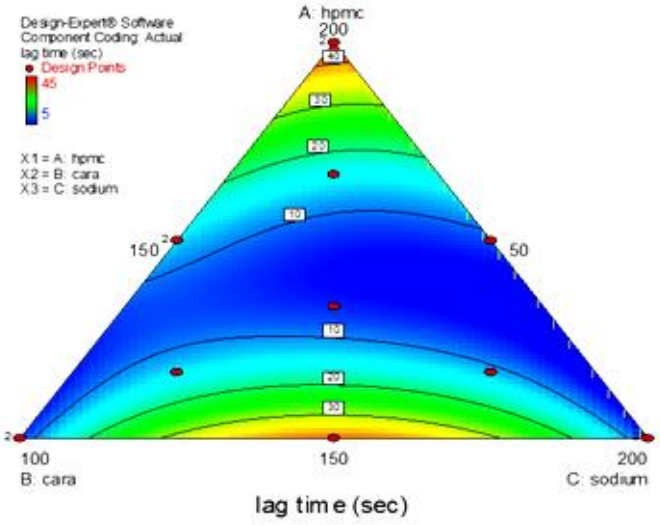

Fig. 1: Contour plot for floating lag time.

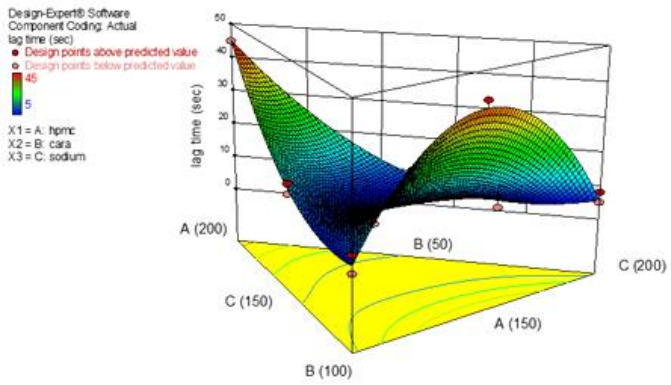

Fig. 2: Response surface plot for floating lag time.

On looking into the results of F statistics, it was observed that model probability was greater than F value i.e. 29.89, which confirms the significance of the model. There is only a 0.12% chance that an F-value this large could occur due to noise. Significance of the model was also proved by the p-value less than 0.0500. In this case A, AB, BC, ABC are significant model terms.

Drug released after 1 hour

The results of ANOVA for the applied model on percentage drug released after 1 hour are shown in Table 4. On looking into the results of F statistics, it was observed that model probability was greater than F value i.e. 1932.94, which confirms the significance of the model. There is only a 0.01% chance that an F-value this large could occur due to noise. Significance of the model was also proved by the p-value less than 0.0500.

In this case A, B, C, AB, BC, A^2BC, AB^2C, ABC^2 are significant model terms. The predicted and adjusted R^2 values were found to be 0.9941 and 0.9992 respectively, that means the difference was less than 0.2, which shows the good agreement between dependent and independent variables. The result can be expressed for model analysis by Special Quartic Mixture model using following equation:

$$Drug\ released\ after\ 1hr\ = +38.88X_1 + 35.47X_2 + 36.10X_3 - 10.60X_1X_2 - 9.71X_1X_3 + 55.91X_2X_3 - 699.29X_1^2X_2X_3 + 916.03X_1X_2^2X_3 - 656.40X_1X_2X_3^2$$

By looking into the above equation, it is evident that all the three factors, Amount of HPMC K15M (X_1), kappa-carrageenan (X_2) and sodium bicarbonate (X_3) show positive effects on percentage drug released after 1 hour of the prepared floating tablets of metformin. The interaction effect was observed between the independent variables. There is strongest synergistic effect shown by a ternary interaction of $X_1X_2X_3$ at higher level of kappa carrageenan (X_2). This means that as the concentration of X_2 is more in the three dimensional plane, the percentage of drug released after 1hr will increase, which can be attributed to the rapid hydration and erosion of kappa carrageenan. The regression coefficient obtained for Y_2 was 0.9997, which shows that the model is best fitted. Here also, observed and predicted values for percentage drug released after 1 hour were found to be comparable, which additional validates the suitability of the model. The three dimensional response surface graphs for percentage drug released after 1 hour are given in Figure 3 (shows the obtained contour plot) and Figure 4 (shows response surface plots). This give the information about the main and interaction effects of the independent components.

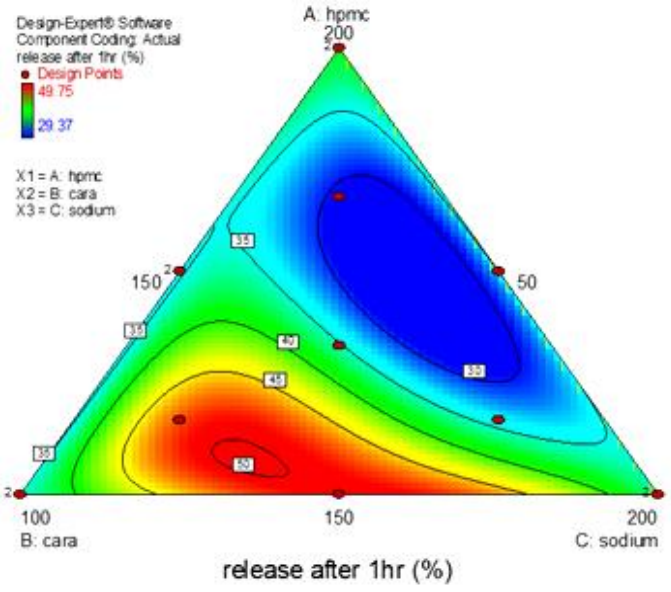

Fig. 3: Contour plot for Drug released after 1 hour.

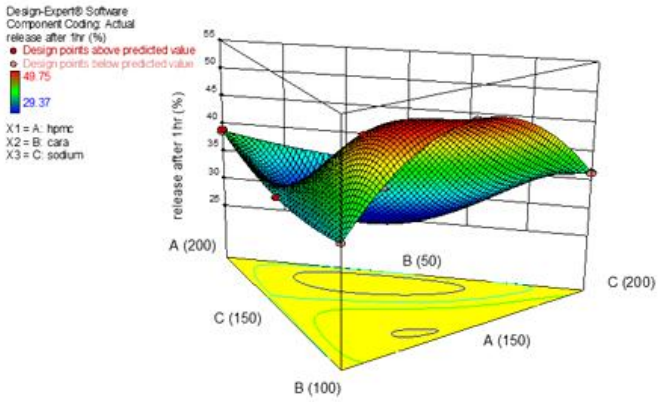

Fig. 4: Response surface plot for Drug released after 1 hour.

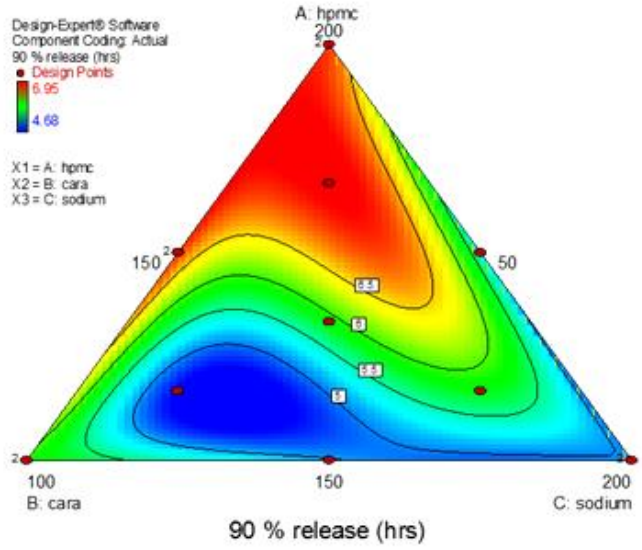

Fig. 5: Contour plot for Time to release 90% of drug.

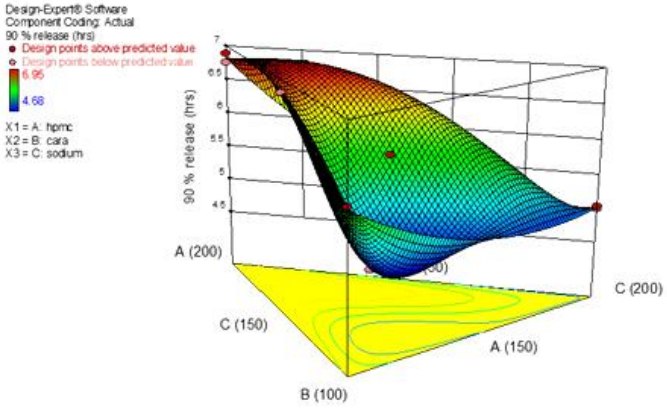

Fig. 6: Response surface plot for Time to release 90% of drug.

Time to release 90% of drug

The results of ANOVA for the applied model on time to release 90% of drug are shown in Table 4. On looking into the results of F statistics, it was observed that model probability was greater than F value i.e. 354.38, which confirms the significance of the model. There is only a 0.01% chance that an F-value this large could occur due to noise. Significance of the model was also proved by the p-value less than 0.0500. In this case A, B, C, AB, BC, A^2BC, AB^2C, ABC^2 are significant model terms.

The predicted and adjusted R^2 values were found to be 0.9609 and 0.9954 respectively, that means the difference was less than 0.2, which shows the good agreement between dependent and independent variables. The result can be expressed for model analysis by Special Quartic Mixture model using following equation:

$$t_{90} = +6.82X_1 + 5.88X_2 + 5.01X_3 + 1.94X_1X_2 - 2.89X_1X_3 - 1.68X_2X_3 + 74.85X_1^2X_2X_3 - 130.17X_1X_2^2X_3 - 76.96X_1X_2X_3^2$$

By looking into the above equation, it is evident that all the three factors, Amount of HPMC K15M (X_1), kappa-carrageenan (X_2) and sodium bicarbonate (X_3) show positive effects on time to release 90% of drug of the prepared floating tablets of metformin. There is strongest antagonistic effect shown by a ternary interaction of $X_1X_2X_3$ at higher level of kappa carrageenan (X_2). This means that as the concentration of X_2 is more in the three dimensional plane, the time required for the release of 90% drug will decrease, which means early release of the drug from the formulation due to rapid hydration and erosion property of kappa carrageenan. The regression coefficient obtained for Y_3 was 0.9997, which shows that the model is best fitted. The three dimensional response surface graphs for time to release 90% of drug are given in Figure 5 (shows the obtained contour plot) and Figure 6 (shows response surface plots). This give the information about the main and interaction effects of the independent components.

Validation of Model

An additional three formulations, suggested by the design expert, was formulated to check and validate the reliability of the mathematical models built here with Simple centroid design The prepared formulation was evaluated and the experimentally obtained results were compared to those predicted by the mathematical models. Table no. 5 shows the values of the selected factors used for development of the validation batch, taken from the software, keeping the amount of all other ingredients constant. The actual and predicted values of the responses is shown in Table no. 6 and it is evident that the predicted values were close to the actual values which validates the model successfully.

Table 5: Formula for validation runs.

Factors	Values		
	F 1	**F 2**	**F 3**
X_1 : Amount of HPMC K15M	**191.82**	**185.14**	**183.33**
X_2 : Amount of k-Carrageenan	**56.73**	**64.62**	**66.66**
X_3 : Amount of sodium bicarbonate	**151.45**	**150.24**	**150.01**

Table 6: Predicted and actual values of the responses for validation run.

Responses	F1		F2		F3	
	Predicted values	Actual values	Predicted values	Actual values	Predicted values	Actual values
Floating lag time	30.786	35.74	22.946	25.33	21.145	23.74
Drug released after 1 hr	35.560	35.31	35.516	35.19	35.392	34.97
Time required for 90%	6.940	6.89	6.940	6.79	6.940	6.84

The overlay plot gives the regions not meeting the specifications as greyed out, leaving an operating window or sweet spot in yellow colour (Figure 7). This means that within the yellow region the formulation prepared will give desired lag time and release profile. It is evident from the overlay plot that the minimum amount of gas generating agent is sufficient to give the desired effect. Medium to high concentration of HPMC K15 M is required, whereas the amount of kappa carrageenan should be medium. However, other studies showed that the presence of high amount kappa carrageenan increases the adhesion retention period and swelling index of the formulation, which insures the presence of the formulation in stomach even with low level of fluid by enabling swelling and mucoadhesion technique.

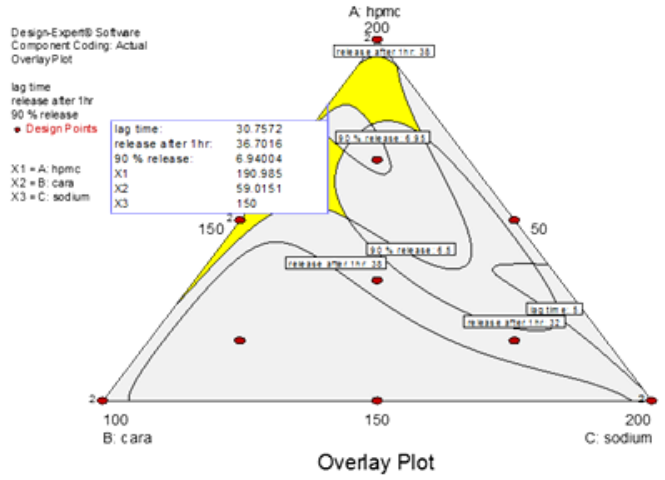

Fig. 7: Overlay plot.

It was found that the fomulation M-SCD 7 and M-SCD 9 (with same composition) fullfilled the desiarablity criteria and hence can be considered as optimized formulation. Moreover, the formulation showed resonably high adhesion retention period and swelling index desirable for ensuring the retetion of formulation in stomach.

CONCLUSION

In the present work, a gastroretentive drug delivery system of metformin was developed,by applying a statistical design, using HPMC K15M, kappa carrageenan and sodium bicarbonate as independent variables. The effect of the combination of HPMC K15M and kappa-carrageenan has not been explored earlier for metformin. Hence, the floating matrix tablet of metformin was prepared using these polymers and optimized using mixture design. A simplex centeroid design was applied to inspect the combined effect of the three variables in the formulations. The result of multiple regression analysis indicated that medium to high levels of X_1, medium level of X_2 and low level of X_3 should be used for the manufacturing of the floating matrix tablet with desired in vitro floating time and release profile. There was strongest synergistic and antagonistic effect shown by a ternary interaction of $X_1X_2X_3$ at higher level of kappa carrageenan (X_2) on amount of drug released in 1hr and t_{90}, respectively. Formulation M-SCD 7 was found to be the optimum having good floating lag time and also matching the desirability criteria for drug release. The formulation also gave reasonably high adhesion retention period and swelling index desirable for ensuring the retention of formulation in the stomach. Hence, it was concluded that the mixture of kappa carrageenan and HPMC K 15 M increases the flexibility in the release pattern of the drug. However, increase amount of kappa carrageenan is not desirable as it hinders the controlled release of the drug by increasing the hydration of the formulation and hence fastens the release of drug from the formulation.

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