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Original Article

Optimization of the Gastroretentive Controlled Release Drug Delivery System of Clarithromycin

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ABSTRACT

The The present study investigates the development of an optimized Gastroretentive controlled release drug delivery system. Statistical experimental design and data analysis using response surface methodology is also illustrated. A Box Behnken Design (BBD) was selected and the three factors were evaluated at 3 levels respectively. the amount of HPMC K4M(X1), HPMC E15LV (X2) and sodium bicarbonate (X3) were selected as independent variables and the dependent variables were floating lag time (Y1),T50%(Y2) and T90%(Y3). Fifteen BBD formulations were formulated and dissolution studies and floating characteristics were performed on these formulations. The dissolution data obtained were then fitted to the PCP disso version 2.08 software. Linear regression analysis and model fitting depicted that the formulations followed zero order and Korsmeyer-Peppas kinetic models. The optimized formulation variable was found to be significant for the release properties ($P < 0.05$) and floating lag time.

Key words: Clarithromycin, gastroretentive, Box Behnken Design, Floating lag time (FLT), response surface plot.

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1. INTRODUCTION

Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most possible approaches for achieving extended and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). Dosage form with prolonged GRT or

gastro-retentive drug delivery system (GRDDS) provides an important therapeutic option. Gastroretentive drug delivery system can improve the controlled delivery of drugs that have an absorption window, by continuously releasing the drug for prolonged period of time before it reaches to its absorption site. Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drug that are having site specific absorption from the stomach or upper part of small intestine. Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems, swelling and expanding system, floating systems and delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [1, 2]*Helicobacter pylori* is a prevalent human specific pathogen, which is now believed to be the causative bacterium for chronic gastritis, peptic ulcer and adenocarcinoma, one of the most common forms of cancer in humans and its eradication requires high concentration of drug within the gastric mucosa for long duration.[3]Clarithromycin is an advanced generation macrolide antibiotic used in treatment of *H. pylori* and respiratory infection. In controlled release formulation, if the concentration of antibiotic is maintained above MIC, drug resistance can be reduced. To achieve the desired therapeutic profile with maximum drug utilization and improve the patient compliance present study was applied to develop the Gastroretentive drug delivery system for Clarithromycin.[4]

2. MATERIALS AND METHODS

Clarithromycin was received as gift sample from Cipla Ltd, HPMC K4M,HPMC E15LV sodium bicarbonate, and magnesium stearate were received from Colorcon Asia Ltd.,Goa.Folin Ciocalteu Phenol Reagent was purchased from Qualigens chemicals, Mumbai.

2.1 Preformulation studies

In preformulation studies at first drug identification was done by determining melting point,UV spectral analysis[5], infra red spectral analysis[6] and Differential Scanning Calorimetry (DSC)[6].

Physical properties like Bulk density[7], Tapped density, Hausner's ratio[9], Carr's index[8] , and Angle of repose [9] of the drug and excipients were determined .

2.2 Acid stability in 0.1N HCl

Accurately weighed 100 mg of drug was dissolved in adequate amount of 0.1N HCL and volume made up to 100 ml. The stock solution was diluted to obtain a concentration of 100µg/ml. 5ml of aliquot was withdrawn and 2 ml of Folin Ciocalture reagent [5] added to it and 2ml of 20% sodium carbonate solution. The volume was made up to 10 ml using 0.1N HCL to obtain the concentration of 50 µg/ml. The resultant solution was scanned from 200 to 800 nm and the spectrum was recorded.

2.3 Study of interferences by various additives

The various excipients used in the gastoretentive tablets may interfere with the drug inference at the estimating wavelength of drug, so it is necessary to study the interferences. Each excipient weighing accurately 50 mg was separately added in 50ml of 0.1N HCl solution. Each excipient solution were filtered and diluted to obtain final concentration of 50 µg/ml. to each of this added 2 ml of Folin Ciocalture reagent and 2 ml of 2% sodium carbonate solution and shaken gently for 5 mins. The resultant solutions were then analyzed at 760 nm and absorbance were recorded.

2.4 Preparation of floating matrix tablets

All the materials were weighed accurately as per formula. At first materials were shifted through 40 no. sieve except magnesium stearate,it were shifted through 60 mesh. the drug and polymer were mixed

properly by geometrical mixing in a double poly bag for few min. then sodium bicarbonate added to this mixture as a gas generating agent. Mixture once again blended for 5 min.Above mixture had been lubricated with magnesium stearate and mixed for 3 min. Finally mixture was compressed by using punch (18.5 x 9 mm).

2.5 Evaluation of Tablets

The tablets were evaluated for various parameters like Appearance and shape[10], Uniformly of thickness and diameter, Hardness[11], Weight variation[10], Friability, Drug content readings were recorded. The tablets were also evaluated for In Vitro Buoyancy Study[12], Dissolution studies, Swelling study, Kinetics of drug release[13] and summarized in the table

3. RESULT AND DISCUSSION

3.1 Drug identification

The average melting point of Clarithromycin was determined by capillary method and was found to be 228^0 c, which was similar reported melting point. The UV –Visible of Clarithromycin solution (50 µg/ml) exhibited wave length of absorbance maximum at 760 nm which complies with the reported. The IR spectrum of Clarithromycin was in accordance with the reported peaks.

The IR spectra of clarithromycin showed the characteristic band of hydrogen bonds between -OH groups vibration at 3466 cm^{-1} characteristic band C=O vibration of lactone group at 1733 cm^{-1} and strong absorption band at 1691 cm^{-1} belonging to the carbonyl ketone ,peak for N-CH3 stretching of aromatic ring at 1424 cm^{-1} .the IR spectra of drug +HPMC ;drug + $NaHCO_3$ and blend for compression showed all the above mentioned peaks for Clarithromycin. These result showed that there is no Interaction between drug and excipients. Differential scanning calorimetry studies indicated a sharp endothermic peak at 227^0C and 275^0C for pure Clarithromycin .This was as per the reported.

3.2 Drug and polymer flow properties

The angle of repose of drug and polymer blend which include Talc and Magnesium Stearate was found to be 31.64 ±1.34,carr's index was found to be 21.43±0.44 and Hausner's ratio found 1.18±0.06.the angle of repose was found to be less than 35^0.the Carr's index and Hausner ratio values for good flowability should be below 25% and below 1.25,respectively.the results showed that the Drug and polymer blend had Carr's index value less than 25% and Hausner ratio greater than 1.25,confirming good flow properties.

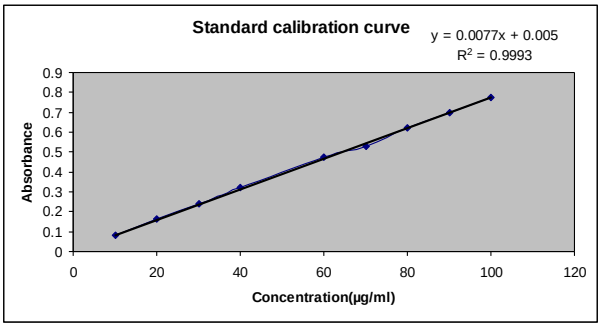

Fig 1: Standard Calibration Curve of Clarithromycin

3.3 Study of Interferences by Various Additives

No colour was developed with excipients and F.C reagent, thus indicating no interference of excipients with analysis.

3.4 Evaluation of Tablets

All tablets of the Formulations were off white coloured with smooth surface; caplet shaped with good texture.Uniform thickness of the tablets throughout the batches ensures good tablet strength and shape and is also important with respect to packaging and handling. The thickness of the tablets should be restricted within 5% or less of an established standard value. Excessive variation in the tablet thickness can result in problems with packaging as well as consumer acceptance. There was no marked variations in the thickness of tablets within each formulation (<5%) indicating good flow properties of blend throughout the compression

process. the thickness of the batches was found in the range of 5.71 and 6.0mm.

After compression, a tablet requires a certain amount of mechanical strength to withstand the shock of handling in the manufacturing, packaging, shipping and dispensing. The hardness of the tablet was found to be in the range of 8.2 to 8.8 kg/cm^2.this ensures good mechanical strength. Friability of the tablet is the measure of the tablets strength. Tablets with friability less than 1% of their weight are acceptable. The friability of the BBD batches was in the range of 0.39 to 0.59, which was within the specified limits.

A tablet is designed to contain a specific amount of tablet formula. To check labeled amount of drug, it is necessary to note the tablet weight. The average weight of tablets within each formulation was found to be uniform. This indicates uniform filling of the die cavity during tablet compression.. The percent deviation in weight variation from average value for all formulations batches were within limit.

The drug content of the formulations was found to be within the limits and the value ensures good uniformity of the drug content in the tablets.

The tablets were evaluated for various parameters of floating properties and release properties and readings were recorded in table.

Table 1: Formulation and dissolution characteristics of Box Behnken Design Formulations

F. code	Floating lag time(sec) (Y_1)	$T_{50\%}$ release(hrs) (Y_2)	$T_{90\%}$ release(hrs) (Y_3)	Floating (duration (hrs)	Matrix integrity (Visual)	Swelling index (%)
F1	181	5.158	9.704	11	Excellent	164.52
F2	121	5.696	10.484	12	Excellent	163.94
F3	170	3.647	6.396	07	Excellent	159.22
F4	118	3.46	6.23	07	Excellent	160.8
F5	210	4.08	10.661	11	Excellent	167.35
F6	118	3.647	9.86	11	Excellent	165.84
F7	179	5.989	10.944	>12	Excellent	169.15
F8	154	4.08	7.366	8	Excellent	157.27
F9	171	5.348	9.876	11	Excellent	159.33
F10	150	3.433	6.238	7	Excellent	154.13
F11	124	6.263	11.118	>12	Excellent	168.35
F12	119	5.7	10.423	12	Excellent	162.87
F13	124	5.572	10.972	12	Excellent	162.49
F14	112	5.378	9.818	11	Excellent	154.92
F15	168	5.837	10.755	12	Excellent	166.95

To find out the optimum concentration of sodium bicarbonate for the floating properties, formulation containing 100 mg of sodium bicarbonate was prepared. These formulations were analyzed for the floating behavior i.e. floating lag time and floating time. the formulation containing 100 mg of the sodium bicarbonate showed maximum floating time i.e. more than 12 hours and minimum floating lag time i.e. less than 180 seconds. So sodium bicarbonate concentration 100 mg selected for medium level for the further studies.

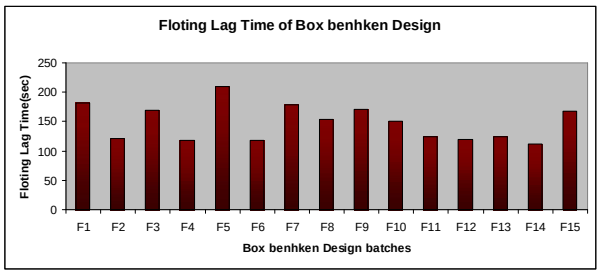

Fig 2: floating lag time of Formulations

Formulations F3, F4, F8 and F10 containing 112mg of HPMC K4M concentration showed higher drug release after 12 hrs. Formulations F5, F7, F11 and F15 containing 162 mg of HPMC K4M concentration showed lower drug release after 12 hrs. Formulations F8 shows lower release than F10 showed considerable effect of concentration of HPMC E15LV since these two formulations differs in only HPMC E15LV concentration.

The responses from the dissolution study were taken T50% release and T90% release. the response T50% release and T90% release of the formulation F7 andF8 containing 162 mg and 112 mg HPMC K4M showed significant difference indicating the rate retarding effect of polymer. the T50% release of formulation F7 and F8 were 5.989 and 4.08 hrs . Also the T90% release of the formulation F7 and F8 were 10.944 and 7.366 hrs. the response T50% and T90% release of the formulations F7 and F15 containing 55mg and 35mg HPMC E15LV showed very less difference indicating the low retarding effect of polymer. The T50% release

of formulation F7 and F15 were 5.989 and 5.837 hrs. Also the T90% release of formulations F7 and F15are 10.944 and 10.755 hrs.

However, with constant polymer concentration of HPMC K4M and HPMC E15LV in formulation F1 and F6 bearing medium level HPMC K4M and high level of HPMC E15 LV and increased sodium bicarbonate concentration (80 and 120 mg respectively) showed increased T 90% release .Same fashion was observed for formulations F9 and F14 bearing medium level HPMC K4M and low level of HPMC E15LV and increased sodium bicarbonate concentration (80 and 120 mg).. This depicts the considerable effect of sodium bicarbonate on release profile of the drug.

Table 2: Kinetic models of the Box Behnken Design formulations

Formulation	Zero Order	First Order	Matrix	Korsemeyer Peppas	Hixon Crowell	n
F1	0.9962	0.9558	0.9364	0.9974	0.984	1.0279
F2	0.9950	0.9433	0.9308	0.9967	0.9978	0.9922
F3	0.9983	0.9083	0.9231	0.9984	0.9558	1.022
F4	0.9955	0.9125	0.9102	0.99	0.9554	1.0703
F5	0.9981	0.968	0.938	0.9969	0.9874	0.9055
F6	0.9935	0.9573	0.9533	0.9972	0.9863	0.8420
F7	0.9948	0.938	0.9101	0.9829	0.9676	0.9627
F8	0.9974	0.9338	0.9301	0.9904	0.9689	0.9052
F9	0.9942	0.9516	0.9471	0.9978	0.9848	0.9205
F10	0.9988	0.9385	0.9394	0.9965	0.9739	0.9258
F11	0.9961	0.9623	0.9401	0.9978	0.9863	0.9296
F12	0.9947	0.9366	0.9327	0.9966	0.9761	0.9751
F13	0.9951	0.9405	0.9272	0.9960	0.9758	0.9967
F14	0.9951	0.9327	0.9424	0.9971	0.9723	0.9185
F15	0.9907	0.9590	0.9370	0.9922	0.9833	0.9268

3.5 Experimental Design

A three-factor,three-level BBD with three replicates at the center point was selected to build response surface models.Three factors, HPMC K4M content(X_1),HPMC E15LV content(X_2) and sodium bicarbonate (X_3),were used in the design and the responses were floating lag time (FLT)(Y_1),time required for cumulative 50% release($T_{50\%}$ release)(Y_2) and time required for cumulative 90% release ($T_{90\%}$ release)(Y_3).below table summarizes the factors, the levels tested, and the responses. HPMC K4M content, HPMC E15LV content, and $NaHCO_3$ were determined in the range of 112-162 mg,35-55 mg and 80-120 mg respectively.

Table 3: Variables in Box-Behnken Design

Formulation variables	Levels Used		
	-1	0	1
X_1=HPMC K4M content	112	137	162
X_2=HPMC E15LV content	35	45	55
X_3=$NaHCO_3$ content	80	100	120

Response variables

Y_1=floating lag time - FLT (sec)

Y_2=time required for cumulative 50% release - $T_{50\%}$ release (hrs)

Y_3= time required for cumulative 90% release - $T_{90\%}$ release (hrs**)**

Table 4: Formulation coded values and weight of Box Behnken Design batches

Formulation Code	coded values x1	x3	x2	total weight of tablet(mg)
F1	**0**	**1**	**-1**	**790**
F2	**0**	**0**	**0**	**800**
F3	**-1**	**0**	**-1**	**755**
F4	**-1**	**0**	**1**	**795**
F5	**1**	**0**	**-1**	**805**
F6	**0**	**1**	**1**	**830**
F7	**1**	**1**	**0**	**835**
F8	**-1**	**1**	**0**	**785**
F9	**0**	**-1**	**-1**	**770**
F10	**-1**	**-1**	**0**	**765**
F11	**1**	**0**	**1**	**845**
F12	**0**	**0**	**0**	**800**
F13	**0**	**0**	**0**	**800**
F14	**0**	**-1**	**1**	**810**
F15	**1**	**-1**	**0**	**815**

3.6 Data analysis by design expert software

The experimental runs with independent variables and corresponding responses for the 15 formulations tested are presented in table 16.the dependent variables were the floating lag time (FLT) (Y_1),cumulative 50% release ($T_{50\%}$ release) (Y_2) and cumulative 90% release

($T_{90\%}$ release) (Y_3). In this study, a three factor, three level Box Behnken design was used and the design consists of replicated center points and a set of points lying at the midpoints of each edge of a multidimensional cube that defines the interesting area. PRESS is a measure of the fit of the model to the points in design; the smaller PRESS the better the model fits to the data points. The quadratic model generated by the design is on the form:

$Y=\beta_0+ \beta_1X_1+ \beta_2X_2+ \beta_3X_3+ \beta_{12}X_1X_2+ \beta_{13}X_1X_3+ \beta_{23}X_2X_3+ \beta_{11}X_1^2+ \beta_{22}X_2^2+ \beta_{33}X_3^2$

Where β_0 is an intercept and β_1- β_{33} are the coefficients of relevant factors and their interaction terms. Mathematical relationships in the form of quadratic equations for all responses and their standardized main effects are shown below with contour plot and response surface plot Two dimensional contour plots and three dimensional response plots are presented in figure, which are very useful to study of the effects of two factors on the responses. These types of plots are useful in the study of the effects of two factors on the responses at one time. In all the presented figures, the third factor was kept at a constant level. The fitted regression equations relating the responses floating lag time (FLT), $T_{50\%}$ release and $T_{90\%}$ release are shown in the following equations, respectively.

Final Equation in terms of coded Factors-

$FLT=+121.33+11.12X_1+3.87X_2-32.50X_3+1.75X_1X_2-8.50X_1X_3-1.00X_2X_3+25.71X_1^2+15.71X_2^2+8.46X_3^2$

Final equation in terms of actual factors-

FLT=+121.33+11.12 HPMC K4M+3.87HPMC E15LV-32.50$NaHCO_3$+1.75(HPMC K4M)(HPMC E15LV) -8.50 (HPMC K4M)($NaHCO_3$)-1.00(HPMC E15LV)($NaHCO_3$+25.71 (HPMC K4M)^2+15.71 (HPMC E15LV)^2+8.46 ($NaHCO_3$)^2

(R^2=0.9965)

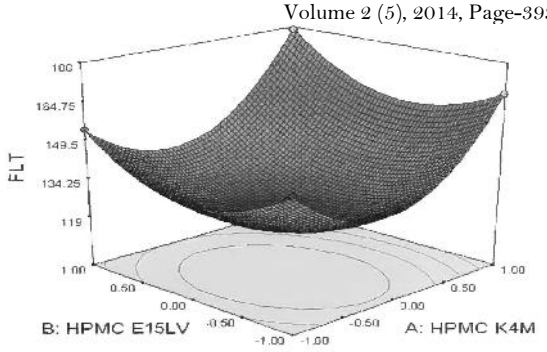

Fig 3: Response surface plot for floating lag time

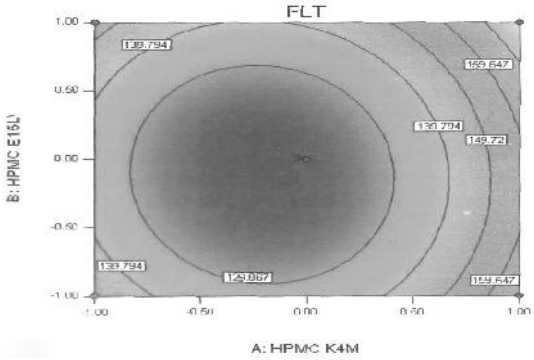

Fig 4: contour surface plot for floating lag time

The above figure shows the FLT increases with increasing concentration of either HPMC K4M or HPMC E15LV at constant concentration of NaHCO3.

Final Equation in terms of coded Factors-

$T_{50\%}=+5.66+0.94X_1-0.1X_2+0.064X_3-0.12X_1X_2+0.59X_1X_3-0.39X_2X_3-0.67X_1^2-0.15X_2^2-0.62X_3^2$

Final equation in terms of actual factors-

$T_{50\%}$=+5.66+0.94 HPMC K4M-0.1HPMC E15LV+0.064$NaHCO_3$-0.12(HPMC K4M)(HPMC E15LV) +0.59 (HPMC K4M)($NaHCO_3$)-0.39(HPMC E15LV)($NaHCO_3$-0.67 (HPMC K4M)^2-0.15 (HPMC E15LV)^2-0.62 ($NaHCO_3$)^2

(R^2=0.9255)

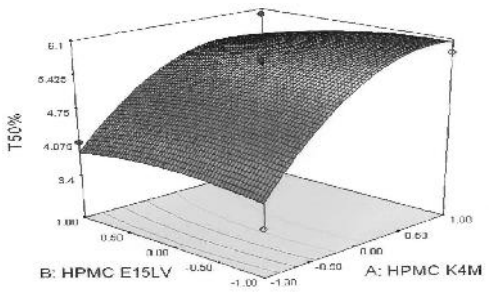

Fig 5: Response surface plot for $T_{50\%}$

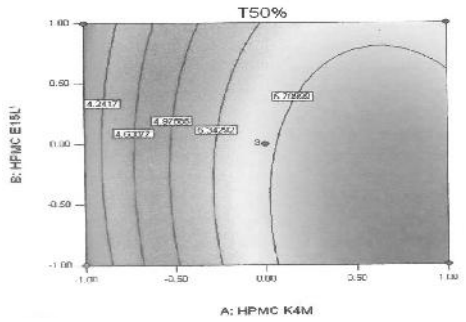

Fig 6: Contour surface plot for $T_{50\%}$

This above figure shows that $T_{50\%}$ increases with increasing concentration of either HPMC K4M or HPMC E15LV at constant concentration of NaHCO3.

Final Equation in terms of coded Factors-

$T_{90\%}$=+10.63+2.16X_1+0.15X_2+0.049X_3-0.23X_1X_2+0.16X_1X_3+0.053X_2X_3-1.51X_1^2-0.29X_2^2-0.52X_3^2

Final equation in terms of actual factors-

$T_{90\%}$=+10.63+2.16 HPMC K4M-+0.15HPMC E15LV+0.049$NaHCO_3$-0.23(HPMC K4M)(HPMC E15LV) +0.16 (HPMC K4M)($NaHCO_3$)+0.053(HPMC E15LV)($NaHCO_3$-1.51 (HPMC K4M)^2-0.29 (HPMC E15LV)^2-0.52 ($NaHCO_3$)^2

(R^2=0.9876)

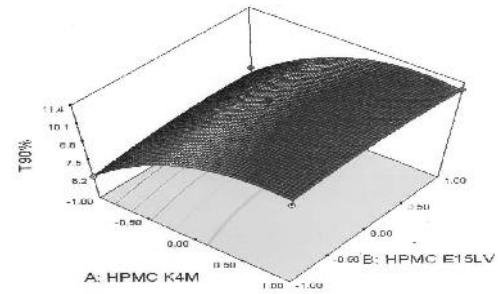

Fig 7: Response surface plot for $T_{90\%}$

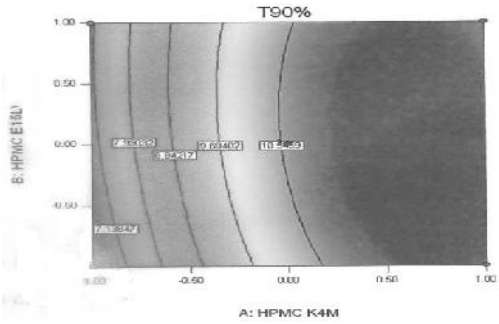

Fig 8: Contour surface plot for $T_{90\%}$

This above figure shows that $T_{90\%}$ increases with increasing concentration of either HPMC K4M or HPMC E15LV at constant concentration of NaHCO3..The positive coefficient of variable X_1 i.e HPMC K4M in case of responses FLT,$T_{50\%}$ and $T_{90\%}$ indicates that as the HPMC K4M concentration was increasesd the FLT,$T_{50\%}$ and $T_{90\%}$ value was also increased.the positive coefficient of variable X_2 i.e HPMC E15LV in case of responses FLT and $T_{90\%}$ indicates that HPMC E15LV concentration was increased the value of FLT and $T_{90\%}$.however, the negative coefficient for $T_{50\%}$ shows opposite effect indicating the increased concentration of HPMC E15LV leads to decreased $T_{50\%}$ value. The negative coefficient of variable X_3 i.e. $NaHCO_3$ in case of response FLT indicates that as the $NaHCO_3$ concentration was increased the FLT value was decreased. However, the positive coefficient for $T_{50\%}$ and $T_{90\%}$ indicating the increased concentration of $NaHCO_3$ leads to increased $T_{50\%}$ and $T_{90\%}$ value.

3.7 ANOVA study

Below Table shows ANOVA for the dependent variables FLT,$T_{50\%}$ and $T_{90\%}$ respectively. The coefficient X1,X2,X3 were found to be significant at $p<0.05$,hence conformed that significant effect of independent variables on the selected responses,Increasing the concentration of the HPMC K4M resulted in the decrease in the realease of Clarithromycin and increase in FLT of the tablet. However ,the icrease in concentration of the $NaHCO_3$ resulted in decrease in FLT and increase in drug realease . overall both variables caused significant change in the responses. ANOVA and Multiple regression analysis were done using state Ease Design Expert software. However, all three independent variables favour the preparation of controlled release floating tablets of clarithromycin.

Table 5: Results of analysis of variance for measured response

parameters	Degree of fredom	Sum of suare	Mean sum of square	Fischer's ratio	Significance P
For Floating lag time (FLT)					
Regression	9	13119.02	1457	158.73	<0.0001
Residual	5	45.92	9.18		
Total	14	13164.93			
For cumulative 50% release					
Regression	9	12.26	1.36	14.26	0.004
Residual	5	2.59	0.52		
Total	14	14.85			
For cumulative 90% release					
Regression	9	46.78	5.20	44.24	0.0003
Residual	5	0.59	0.12		
Total	14	47.37			

Model validation

The formulations were evaluated for tablet properties and response study.

Table 6: Tablet properties evaluations of optimized batch

Formulation	Appearance	Thickness (mm)	Hardness Kg/cm^2	Weight variation	Friability (%)	Drug Content(%)
Optimized formulation	**Off white,caplet shaped**	**5.82±0.03**	**8.3±0.41**	**803±1.14**	**0.46±0.04**	**99.26±0.99**
		Mean±SD, n=5	**Mean±SD, n=6**	**Mean±SD, n=20**	**Mean±SD, n=6**	**Mean±SD, n=5**

Table 7: Predicted and observed responses of the optimized formulation

Responses	Predicted (A)	Observed (B)	Residual (A-B)
Y1	**162.88**	**163.45±2.15**	**0.57**
Y2	**5.70**	**5.5914**	**-0.1086**
Y3	**11.023**	**10.997**	**0.026**

4. CONCLUSION

The investigation carried out so far has encouraged for drawing the following conclusion-A Box Behnken design was performed, and the desired release of clarithromycin from the floating tablets was achieved through careful monitoring of the selected formulation variables. Further the release from the floating studies suggested that the desired floating profile of gastroretentive floating drug delivery system could be achieved while maintaining the desired release properties of formulation. The statistical approach for formulation optimization is useful tool, particularly when two or more variables are to be evaluated simultaneously. The mathematical model generated by regression analysis can be used to predict and optimize the formulation variables. The prediction from the model conforms to the experimental results, thus indicating the validity of the method. The formulated formulation controlled the release, avoided the dose dumping, extended the duration of action of drug with prolonged floating time. Overall, a controlled release intragastric floating system for clarithromycin has been successfully developed using the Box Behnken design with minimum experimentation. The statistical method has been illustrated in this study which can be extrapolated to the development of gastro retentive drug delivery system containing other drug.

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