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RESEARCH ARTICLE

Study the Effect of Neem Gum and Hydroxy Propyl Methyl Cellulose on Floating and Bioadhesive Gastroretentive Matrix Tablet Using Central Composite Design

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ABSTRACT

The main objective of this study was to develop a gastroretentive dosage form of Atorvastatin calcium with bioadhesion and floating properties. Thirteen matrix tablets were formulated using different ratios of hydroxypropylmethylcellulose (HPMC K4M) and Neem gum as release controlling agent. Also Sodium bicarbonate ($NaHCO_3$) was used as gas generating agent. The study discussed the application of Central composite design (CCD) and response surface methodology (RSM) for the optimization of process parameters i.e. concentration of Neem gum and HPMC K4M, affecting the drug release, floating and mucoadhesive properties. The range of values of the independent variable used were, f_{lag} time of as minimum as possible, mucoadhesive strength of > 20 g, drug release at 2 h of 20% to 25% and drug release at 8 h of 60% to 70%. The Predicted values were found to be in good agreement with experimental values for all three response variable. Drug release profiles of all formulations followed Higuchi model with non- fickian diffusion mechanism. The magnitude of the coefficient of correlation of the fitted quadratic equations revealed that both Neem gum and HPMC K4M has negative effect on the floating lag time and drug release profile, and positive effect on mucoadhesive strength.

KEYWORDS

Gastroretentive, Floating, Mucoadhesion, Central Composite, Neem Gum, HPMC K4M

INTRODUCTION

For systemic delivery, the oral route has been the perfect route of administration for many drugs due to the ease of administration, patient compliance and flexibility in formulation. However; it is a well-accepted fact that it is difficult to predict the real in-vivo time of release with solid, oral dosage form since the drug absorption in the gastrointestinal tract may be variable in certain circumstances. Thus a wide variety of approaches of drug delivery system (DDS) have been investigated for oral administration. However development process is precluded by several physiological difficulties, such as inability to restrain and localize the DDS within desired regions of gastrointestinal tract (GIT) due to highly variable nature of gastric emptying process. Recently several technical advancements resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, extending the duration of its activity and targeting the delivery of drug to tissue. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT). Prolonged gastric retention improves bioavailability, increase the duration of drug release, reduce drug waste, and improves the drug solubility that are less soluble in a high pH environment. Drug with prolonged GRT i.e. gastroretentive dosage form (GRDFs),

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will provide new and important therapeutic option. Various attempts have been made to retain the dosage form in the stomach by increasing the retention time. Gastroretentive dosage form (GRDFs) are designed on the basis of various approaches like, formulating high density (sinking) system that is retain in the bottom of the stomach, low density (floating) system that remain buoyant above gastric fluid, mucoadhesive system that cause bioadhesion to stomach mucosa, expandable, unflodable or swellable system which limits the emptying of dosage form through the pyloric sphincter of stomach, super porous hydrogels magnetic systems etc. The selected drug Atorvastatin calcium is the most preferred molecule among Statins, used to treat moderate to severe familial or non-familial hypercholesterolemia (HMG - CoA reductase inhibitors used in the treatment of hyperlipidaemia). It has oral bioavailability of less than 12%. It is highly soluble in acidic pH and absorb in upper part of GIT. In the current study an attempt has been made to formulate GRDFs of Atorvastatin calcium to improve absorption and its oral bioavailability.

The objective of the current study was to develop a floating and bioadhesive gastroretentive dosage form of Atorvastatin calcium using Neem gum and HPMC K4M polymers as well as to evaluate its effect on drug release profiles, mucoadhesion and floating properties. This study also involves modeling and optimization of process parameters i.e. concentration of Neem gum and HPM K4M, affecting the drug release, floating and mucoadhesive properties. Central composite design was used as a design of experiment for optimizing the formulation. The common practice for finding the important process parameters is by varying one parameter and keeping the others at a constant level. The major disadvantage of this method is that it does not include interactive effects among the variables and, hence, it does not represent the complete effects of various parameters involved in the process. In order to overcome this problem, optimization studies can be carried out using the response surface methodology (RSM) which explores the relationship between several independent variables and the response variable.

MATERIALS AND METHOD

Materials

Atorvastatin Calcium was obtained as a gift sample from Megsis Pharma Pvt Ltd. HPMC K4M was obtained from Vitas Pharma. Neem gum is a natural gum obtained from Neem tree. All other chemicals used in the study were purchased and were of analytical grade. Minitab statistical software package were used for the design of experiment and statistical analysis.

Methods

Preparation of Gastro Retentive Matrix Tablet

Matrix tablets of Atorvastatin Calcium tablets (10 mg) were prepared by wet granulation method. The various excipients used were listed in Table 1. All the excipients were passed through sieve no. 40, mixed and granulated with 5% PVP K30 dissolved in isopropyl alcohol. The wet mass was passed through sieve no. 14 and dried at 60^0 for 20 mins in hot air oven. The dried granules were passed through sieve no. 22/44. The granules passed from sieve no. 22 and retained on sieve no. 44 were used for tableting. 10% of fines of the total weight of granules, lubricant and glidant were mixed with retained granules and the blend was compressed using Cadmach single punch tablet machine.

Pre-Formulation Studies

Compatibility studies of Atorvastatin calcium and polymers, Hydroxy propyl methylcellulose and Neem gum were carried out using FT- IR spectra.

Pre-Compression Studies

Prepared granules were evaluated for angle of repose, Bulk density, Compressibility Index and Hausner's Ratio.

Post Compression Studies

Weight variation, Tablet Friability, Hardness, thickness Content uniformity, Swelling Index, Mucoadhesion studies were performed for prepared tablets.

In vitro Dissolution Studies

In-vitro drug release of all formulations was carried out using USP-Type II dissolution apparatus (Paddle type). The dissolution medium 900 ml (0.1 N HCl, pH 1.2) buffer was placed in the dissolution flask maintaining the temperature of 37±0.5^{0}C and the paddle was rotated at 50 rpm. One Atorvastatin calcium tablet was placed inside the dissolution medium. Dissolution studies were carried out for 12 h. 5 ml samples were withdrawn at specific time interval and the same volume was replaced to maintain sink condition. The sample was filtered 1 ml of the filtrate was diluted to 10 ml with 0.1 N HCl (pH 1.2) and analyzed for drug content spectrophotometrically at 245 nm.

The drug release mechanism of the formulation were determined by fitting its drug release data to various kinetic model such as zero order, first order, Higuchi model and Korsmeyer's-Peppas model.

In-vitro Buoyancy Determination

Buoyancy Lag Time (BLT): The time interval between introduction of Atorvastatin Calcium floating tablet into the dissolution medium and its flotation to the top of the dissolution medium was termed as BLT.

Duration of Buoyancy (DB): The duration up to, which the dosage form floats, was termed as duration of bouyancy.

In-vitro buoyancy was determined by placing randomly selected tablets in USP dissolution test apparatus, in 900 ml of 0.1 N HCl (pH 1.2) at 37±0.5^{0}C.

Swelling Index

The extent of swelling was measured in terms of percentage weight gain by the tablet. One tablet from each formulation was weighed and kept in a beaker containing 100 ml 0.1 N HCl (pH 1.2). After every 2 h time interval the tablets were withdrawn, blotted to remove excess water and reweighed. This process was continuous till the end of 12 h. The percentage weight gain by the tablet was calculated using the formula below.

$$\text{Swelling index (SI)} = \frac{\text{Weight of swollen tablet} - \text{Inital wieght of the tablet}}{\text{Initial weight of the tablet}} \times 100 \quad \ldots\ldots 1$$

Ex-vivo Mucoadhesion Studies

Mucoadhesion studies were conducted using goat intestinal mucosa as the model membrane. The mucosa was kept frozen in pH 6.8 phosphate buffer and thawed to room temperature before use. The mucosal membrane was removed, washed and was kept at 37±0.5^{0}C for 30 m in pH 6.8 phosphate buffer before the mucoadhesion evaluation studies. The tablet was stuck on to the mucosal membrane with a weight of 5 g for a total duration of 3 m. Mucoadhesive strength was determined in terms of weight in grams required to separate the tablet from the mucosa. Not more than three tablets were tested on each tissue obtained from the animal. Fresh tissue was used for each batch of the tablet

Experimental Design

For the optimization of the gastroretentive matrix tablet, a Central Composite Design (CCD) with α =1 was employed to investigate the effect of two independent variables, Neem gum (X_1) and HPMC K4M (X_2) on the response variables, f_{lag} time (Y1), mucoadhesive strength (Y2) , drug release at 2 h (Y3) and drug release at 8 h (Y4). In this experimental design, 2 factors were evaluated each at 3 level using Minitab statistical software package with all 13 possible combinations Table 3. The variables and there ranges studied are summarized in Table 2. The low and high values are proposed based on the experiments conducted so far.

Statistical Analysis

Experimental data shown in Table 3 were used for determining the coefficients of the second-order polynomial equation by the Minitab software. The response surface and contour plots were generated using the same software for different interactions of independent variables. Such three dimensional surfaces could yield accurate geometrical representation and provide useful information about the behavior of the system within the experimental design.

Table 1: Formulation composition of Atorvastatin matrix tablets according to Central Composite Design

Formula	Atorvastatin Calcium (mg)	Neem gum (mg)	HPMC 4KM 100 (mg)	Sodium Bicarbonate (mg)
F1	10	10	25	20
F2	10	30	25	20
F3	10	10	75	20
F4	10	30	75	20
F5	10	10	50	20
F6	10	30	50	20
F7	10	20	25	20
F8	10	20	75	20
F9	10	20	50	20
F10	10	20	50	20
F11	10	20	50	20
F12	10	20	50	20
F13	10	20	50	20

Table 2: Experimental range and level of independent variables in the formulation

Variable	Symbol	Coded variable level		
		Low	**Centre**	**High**
		-1	**0**	**1**
Neem Gum	A	10	20	30
HPMC K4M	B	25	50	75

Table 3: Formulation with Coded level of variables and observed responses

Std Order	Run Order	Formulation code	Coded level of variable		Observed			
			A	B	F_{lag} time (S)	Mucoadhesive strength (g)	Q_2 (h)	Q_8 (h)
1	1	F1	-1	-1	94	10	34.92	100
2	2	F2	1	-1	74	18	22.96	74.56
3	3	F3	-1	1	70	16	24.4	80.00
4	4	F4	1	1	52	28	16.64	49.00
5	5	F5	-1	0	78	14	27.16	89.66
6	6	F6	1	0	60	26	16.92	58.22
7	7	F7	0	-1	80	16	27.13	84.96
8	8	F8	0	1	56	25	18.78	60.33
9	9	F9	0	0	63	23	21.24	68.94
10	10	F10	0	0	62	24	21.12	68.52
11	11	F11	0	0	63	23	20.94	67.89
12	12	F12	0	0	63	23	21.4	69.5
13	13	F13	0	0	62	23	20.96	67.96

Table 4 : The desirable range for each response

Responses	Desirable range
f_{lag} time	As minimum as possible
Mucoadhesive strength	>20g
Q2 h	20%-25%
Q8 h	60%-70%

RESULTS AND DISCUSSION

Compatibility Studies

The principle IR absorption peaks of Atorvastatin calcium was observed in the spectra of the physical mixture of the drug and the excipients. The IR spectral study indicated no interaction between the drug and the excipients, confirming the stability of the drug in the formulation.

Evaluation of Granules

The values of angle of repose ranged from 26^0 – 30^0 compressibility Index ranged from 7% - 13% and Hausner's ratio ranges from 1.02 - 1.12. The LBD and TBD of the granules were ranged from 0.634 -0.688 and 0.675 – 0.741 respectively. The result of Angle of repose indicates good flow property and the values of Compressibility Index and Hausner's ratio gave support to the flow property.

Evaluation of Tablets

The shape of all tablets of all formulation remains circular with no visible cracks. The thickness ranged from 4.0 - 4.4 K/cm^2. The average weight variation of 20 tablets from each formulation remains within 250mg. The hardness of all batches remained within the range of 5.9 ± 0.79 and percentage friability was found to be less than 1%. The percentage of drug content was more than 98%.

All the formulations showed values within the specified limits for tests like hardness, friability, weight variation and assay which indicate that the prepared tablets are of standard quality.

Swelling Study

Swelling study was performed on all batches every 2 h up to 12 h. The results of swelling Index are shown in Fig. 1. From the evaluation of all the formulations it was observed that there is a linear relationship between swelling index and the concentration of polymers till 8 h. In the initial 8 h the swelling index of the matrix tablet increased due to the formation of viscous gel mass and then the swelling index were decreased due to dissolution of outermost gelled layer of the tablet

***In-vitro* Buoyancy Studies**

By immersing the tablets of each batch in 0.1N HCl (pH1.2) buffer at 37^o, all the tablet floated within 3 m and remain buoyant for > 12h without disintegration.

***In Vitro* Bioadhesion Studies**

The Fig. 2 shows the significant variation in the values of bioadhesive strength, obtained using different concentration of polymers. Maximum bioadhesive strength was observed for Neem gum and HPMC K4M at the highest level (+1).

In-Vitro Dissolution Studies

The data obtained from in-vitro dissolution studies of all the formulations was given in the Fig. 3. The release rate and percentage drug release for the entire 13 batch showed a wide variation. The results clearly indicate that the drug release is strongly affected by the variable selected for the study.

Data Analysis

Mathematical relationships for the measured dependent variable (response) and the independent variables were developed using statistical software Minitab. Thirteen tests were conducted as per the software. The four output variables (responses), such as Floating lag time (Y1), mucoadhesive strength (Y2) , drug release at 2 h (Y3) and drug release at 8 h (Y4), were evaluated, and the results are shown in Table 3 . The predicated and actual values of the responses were given in Table 5.

The experimental results in Table 3 were fitted to a polynomial quadratic model by applying multiple regression analysis for Floating lag time, drug release at 2 h, drug release at 8 h and mucoadhesive strength. To evaluate the effect of polymers on the response variables precisely, the drug and other excipients used in the formulations of the gastroretentive 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 Floating lag time (Y1), mucoadhesive strength (Y2), drug release at 2 h (Y3) and drug release at 8 h (Y4), to the transformed factor are given in equation 2 to 5 respectively.

The quadratic equation for the model in coded units is given below:

Y1 = 62.86 - 9.33*A -11.67*B + 0.50*AB + 5.48*A2 + 4.48*B2 ……..**2**

Y2 = 23.10 + 5.33*A + 4.17*B + 1.00*AB - 2.86*A2 - 2.36*B2 ……**3**

Y3 = 21.01 - 4.99*A - 4.20*B + 1.05*AB + 1.327*A2 + 2.242*B2……**4**

Y4 = 68.86 - 14.65*A - 11.70*B -1.39*AB + 4.348*A2 + 3.053*B2 ……**5**

The above equations represent the effect of variables (A, B) and their interactions on the response (Y1, Y2, Y3, Y4). A positive magnitude of the coefficient represents

increased effect, while a negative magnitude indicates decreased effect between the variable and response.

The statistical significance of Eq. 2 to 5 was checked by F-test, and the analysis of variance (ANOVA) for response surface model is shown in Table 6 and Table 7. The p value for the models is less than 0.05. This indicates that the model is considered to be statistically significant. The predicted values of responses obtained from Eq. 2-5 were given in Table 5. The value of the coefficient of multiple determination (r^2) for F lag time, Mucoadhesive strength, drug release at 2 h, drug release at 8 h were found to be 0.9837, 0.9404, 0.9853 and 0.9685 respectively which means the model could explain the total variations in the systems. The high value of r^2 indicates that the equation is capable of representing the system under the given experimental domain.

It can be observed from the Eq. 2 that both Neem and HPMC K4M have negative effect on the floating lag time. Though the increase in concentration of both polymers decreases the floating lag time, HPMC K4M shows more effect than the Neem gum. This is evident from the slightly higher coefficient value for B. In formulation where the HPMC K4M and Neem gum was at higher concentration (both +1) shown shorter lag time however the formulation with low (-1) to high (+1) ratio of HPMC K4M and Neem gum shown varied effect on lag time. This indicates that the effects of both polymers on lag time depend on the ratio of polymers taken. Considering only the minimum lag time F4 and F8 can be considered as a better formula compared to other.

The positive magnitude of coefficient for Neem gum (A) and HPMC K4M (B) in Eq. 3 indicates both polymers can enhance the mucoadhesive strength. However considering the higher magnitude of coefficient, Neem gum has slightly more effect on the mucoadhesive strength compared to Neem gum. F4 shows the highest mucoadhesive strength. This may be due to the high concentration of both polymers (+1) in the formula. The positive magnitude of AB in Eq.3 indicates that apart from the individual effect, the combinations of different ratio of polymers also contributed to the effect on mucoadhesive strength. This is also evident from figure 2.

The negative value of the coefficient for A and B in Eq. 4 and Eq. 5 suggests that both Neem gum and HPMC K4M has significant impact on controlling the release of drug from the matrix tablets. For response Y_3, Neem gum and HPMC K4M has got almost similar effect on controlling the release rate while for response Y_4 Neem gum has more impact when compared to HPMC K4M. For response Y3, the positive magnitude of AB indicates that individual effect of polymers are more significant when compared to the interactive effect. Formulation F2, F3, F10-F13 shown Q2 release of 20% to 25% and Formulation F8-F13 shown Q8 release of 60% to 70% which are within the desirable range.

Though F4 exhibit shorter lag time and high mucoadhesive strength however shown a very retard drug release and the main reason may be due to the very high concentration of both the polymers.

The interaction factors for A and B on response variables (Y1, Y2, Y3, Y4) are described by the response surface plot and contour plot in Figure 4 and Figure 5 respectively.

Release Kinetic Model

The drug releasing profile and its kinetic release model are important because they correlate the *in-vitro* and *in-vivo* dug responses. In order to derive the best fit kinetic model the cumulative drug release results were fitted in to various mathematical model. The results are shown in table 8 .The model that gives higher "r" value is considered as the best fit of release data. By comparing the correlation coefficient values, formulation gave good fit to Higuchi model. When analyzed according to the Peppas model, the release exponent "n" was found to be $0.5 < n < 1.0$ value, it was observed that it followed non- fickian anomalous transport diffusion mechanism.

Table 5: Observed and Predicted values for f lag time, Mucoadhesive strength, % drug release at 2 h and 8h

A	B	F_{lag} time (S)		Mucoadhesive strength (g)		Q8 (h)		Q2 (h)	
		Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
-1	-1	94	94.33	10	9.38	34.92	34.82	100	101.21
1	-1	74	74.66	18	18.05	22.96	22.74	74.56	74.70
-1	1	70	69.99	16	15.71	24.4	24.33	80	80.60
1	1	52	52.33	28	28.38	16.64	16.44	49	48.52
-1	0	78	77.68	14	14.91	27.16	27.33	89.66	87.85
1	0	60	59.01	26	25.57	16.92	17.35	58.22	58.56
0	-1	80	79.01	16	16.57	27.13	27.45	84.96	83.61
0	1	56	55.68	25	24.91	18.78	19.06	60.33	60.21
0	0	63	62.86	23	23.10	21.24	21.01	68.94	68.86
0	0	62	62.86	24	23.10	21.12	21.01	68.52	68.86
0	0	63	62.86	23	23.10	20.94	21.01	67.89	68.86
0	0	63	62.86	23	23.10	21.4	21.01	69.5	68.86
0	0	62	62.86	23	23.10	20.96	21.01	67.96	68.86

Table 6: Summary of ANOVA results for depended variables (f lag time and Mucoadhesive strength)

Source	DF	Sum of squares	Mean Square	F	P	
F lag time						
Regression	5	1562.87	312.575	502.26	0	Significant
Residual Error	7	4.36	0.622			
Lack-of-Fit	3	3.16	1.052	3.51	0.128	Not Significant
Pure Error	4	1.2	0.3			
Total	12	1567.23				
Mucoadhesive strength						
Regression	5	339.965	67.993	169.7	0	Significant
Residual Error	7	2.805	0.401			
Lack-of-Fit	3	2.005	0.668	3.34	0.137	Not Significant
Pure Error	4	0.8	0.2			
Total	12	342.769				

Table 7: Summary of ANOVA results for depended variables (Drug release at 2h and 8h)

Source	DF	Sum of squares	Mean Square	F	P	
Q2 h						
Regression	5	289.004	57.801	563.32	0	Significant
Residual Error	7	0.718	0.103			
Lack-of-Fit	3	0.568	0.189	5.05	0.076	Not Significant
Pure Error	4	0.15	0.038			
Total	12	289.722				
Q8 h						
Regression	5	2239.87	447.97	327.56	0	Significant
Residual Error	7	9.57	1.37			
Lack-of-Fit	3	7.73	2.58	5.61	0.065	Not Significant
Pure Error	4	1.84	0.46			
Total	12	2249.44				

Table 8: Mathematical modelling and drug release kinetics of matrix tablets

Formulation code	Zero order		First order		Higuchi		Koresmeyar- Peppas	
	K	r^2	K	r^2	K	r^2	n	r^2
F1	8.50	0.846	0.06	0.713	35.94	0.917	0.70	0.942
F2	8.32	0.988	0.07	0.875	36.53	0.995	0.84	0.998
F3	8.58	0.976	0.07	0.858	37.66	0.993	0.83	0.995
F4	5.74	0.987	0.08	0.829	25.24	0.991	0.88	0.985
F5	8.74	0.949	0.07	0.822	38.11	0.984	0.80	0.987
F6	6.63	0.996	0.08	0.900	29.27	0.986	0.86	0.999
F7	8.66	0.946	0.07	0.803	37.74	0.986	0.81	0.981
F8	6.93	0.993	0.07	0.887	30.43	0.991	0.84	0.999
F9	7.94	0.994	0.07	0.885	34.94	0.991	0.85	0.999
F10	7.89	0.994	0.07	0.885	34.72	0.991	0.85	0.999
F11	7.82	0.994	0.07	0.885	34.39	0.991	0.85	0.999
F12	8.01	0.994	0.08	0.885	35.23	0.991	0.85	0.999
F13	7.83	0.994	0.07	0.885	34.42	0.991	0.85	0.999
Average	7.81	0.97	0.07	0.85	34.20	0.980	0.83	0.99

Formula Optimization

Desirability function was calculated for Floating lag time (Y1), mucoadhesive strength (Y2) , drug release at 2 h (Y3) and drug release at 8 h (Y4) using response optimizer in Minitab Software. The desirability result shows 20:50 ratio of Neem gum and HPMC K4M is considered as optimum. However in the central composite design formula F9-F13 has the same ratio of polymers. So Based on the resulted data (Composite desirability of 1), analyzing the contour plots and also considering the value of lagtime, mucoadhesive strength and drug release, F10 was identified as the optimum formulation which has values within the desirable range (Table 4). The optimum process parameters were found to be 62 s as Floating lag time, 24 g for mucoadhesive strength, 21.12% drug release at 2 h and 68.52% drug release at 8 h.

CONCLUSION

The study discussed the effect of different ratios of Neem gum and HPMC K4M on drug release, floating and mucoadhesive properties by using Central composite design (CCD) as a design of experiment and response surface methodology (RSM) for the optimization of process parameters

Quadratic polynomial equations were derived for both concentration of Neem gum and HPMC K4M by using sets of experimental data and statistical software. 3D response surface plots which are simulations from the models were presented to describe the effect of the independent variables on response variable. Predicted values were found to be in good agreement with experimental values (r^2 values of 0.9837, 0.9404, 0.9853 and 0.9685 for F lag time, Mucoadhesive strength, drug release at 2 h, drug release at 8 h respectively). Drug release profiles of all formulations followed Higuchi model with non- fickian diffusion mechanism. The magnitude of the coefficient of correlation of the fitted quadratic equations revealed that both Neem gum and HPMC K4M has negative effect on the floating lag time and drug release profile and positive effect on mucoadhesive strength. Statistical optimization data revealed that tablets containing Neem gum (20 mg), HPMC K4M (50 mg) and NaHCO3 (20 mg) exhibits excellent floating properties, mucoadhesive strength and sustained drug release characteristics.

REFERENCES

1. Khan, F. N., & Dehghan, M. H. G. (2011). Enhanced bioavailability of atorvastatin calcium from stabilized gastric resident formulation. *AAPS PharmSciTech*, *12*(4), 1077-1086.
2. Yie W. Chein. (1992). Mucosal drug delevery potential route for non-invasive systemic administration. *Novel drug delivery*. 192-228.
3. Arora, S., Ali, J., Ahuja, A., Khar, R. K., & Baboota, S. (2005). Floating drug delivery systems: a review. *Aaps PharmSciTech*, *6*(3), E372-E390.
4. Nayak, A. K., Das, B., & Maji, R. (2013). Gastroretentive hydrodynamically balanced systems of ofloxacin. *In vitro* evaluation. *Saudi Pharmaceutical Journal*, *21*(1), 113-117.
5. Garg, S., & Sharma, S. (2003). Gastroretentive drug delivery systems.160-166.
6. Kulkarni Vishakha, S., Butte Kishor, D., & Rathod Sudha, S. Natural Polymers–A Comprehensive Review.
7. Jagdale, S. C., Patil, S., & Kuchekar, B. S. (2013). Application of Design of Experiment for Floating Drug Delivery of Tapentadol Hydrochloride.*Computational and mathematical methods in medicine*, *2013*. 1-7.
8. Meka, V. S., Nali, S. R., Songa, A. S., Battu, J. R., & Kolapalli, V. R. M. (2012). Statistical optimization of a novel excipient (CMEC) based gastro retentive floating tablets of propranolol HCl and it's in vivo buoyancy characterization in healthy human volunteers. *DARU Journal of Pharmaceutical Sciences*, *20*(1), 21.

9. Varshosaz, J., Tavakoli, N., & Kheirolahi, F. (2006). Use of hydrophilic natural gums in formulation of sustained-release matrix tablets of tramadol hydrochloride. *aaps Pharmscitech*, *7*(1), E168-E174.

10. Chavanpatil, M. D., Jain, P., Chaudhari, S., Shear, R., & Vavia, P. R. (2006). Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. *International Journal of Pharmaceutics*, *316*(1), 86-92.

11. Chen, Y. C., Ho, H. O., Lee, T. Y., & Sheu, M. T. (2013). Physical characterizations and sustained release profiling of gastroretentive drug delivery systems with improved floating and swelling capabilities. *International journal of pharmaceutics*, *441*(1), 162-169.

12. Rajamma, A. J., Yogesha, H. N., & Sateesha, S. B. (2012). Natural gums as sustained release carriers: development of gastroretentive drug delivery system of ziprasidone HCl. *DARU Journal of Pharmaceutical Sciences*, *20*(1), 58.

13. Mahendra Nakarari et al. (2010). Design and optimization of mucoadhesive hydrophilic matrix tablet containing Atenolol using central composite design. *Acta Pharmaceutica Sciencia*. *52*. 401-410.

14. Pund, S., Joshi, A., Vasu, K., Nivsarkar, M., & Shishoo, C. (2011). Gastroretentive delivery of rifampicin: *In vitro*mucoadhesion and *in vivo* gamma scintigraphy. *International journal of pharmaceutics*, *411*(1), 106-112.

