

Original Research Article

Formulation & Development of Gastroretentive Optimized once A Day Floating and/or Bioadhesive Tablet of Ofloxacin

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Abstract

A novel extended release Ofloxacin tablet formulation which possesses a unique combination of floatation and bioadhesion for prolonged residence in the stomach has been developed. Ofloxacin is mainly absorbed from proximal areas of the gastrointestinal tract thus the purpose of our study was formulation of floating-bioadhesive (FBDDS) tablets to increase the stay period of drug in its absorption area and decrease the dosing interval by increasing the bioavailability. Floating-bioadhesive tablets were prepared by direct compression technique using polymer like Hydroxy propyl methyl cellulose (HPMC K100M), Sodium carboxy methyl cellulose (SCMC), Ethyl cellulose & Sodium bicarbonate in different ratios. As the concentration of HPMC increased, drug release was found to be decreased and vice versa in case of SCMC. Sustained drug release with floating duration up to 24hrs and high bioadhesive strength was observed in case of Optimized formulation. The swollen tablet also maintains its physical integrity during the drug release study. Formulations were evaluated for in vitro drug release profile, swelling characteristics and in vitro bioadhesion property. The in vitro drug release followed Higuchi kinetics and the drug release mechanism was found to be of anomalous or non-fickian type and both diffusion and erosion..

Keywords: Ofloxacin, FBDDS, Factorial design, optimized.

Introduction

Oral sustained release systems continue to be the most popular ones among all drug delivery systems due to their several advantages over the conventional systems like; Improved patient compliance, less frequent dosing, reduction in fluctuation of steady state plasma levels, reduction in health care cost through improved therapy and shorter treatment period [1, 2] and patentability and opportunity for extending product life-cycle [3]. However, the problem frequently encountered with oral sustained release dosage forms is inability to increase the residence time of the dosage form in stomach and proximal portion of the small intestine, due to the rapid gastrointestinal transit phenomenon of stomach which may consequently diminish the extent of absorption of many drugs since most of the drug entities are absorbed from the upper part of intestine. Therefore it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. Several approaches have emerged to prolong the residence time of the dosage form at the absorption

site and oral sustained release bioadhesive floating system are one of the approach.

Ofloxacin, a 4- quinolone derivative is effective against wide variety of gram-positive and gram-negative bacteria. The half- life of Ofloxacin is [5-6] hrs, which is required in multiple doses to maintain a constant plasma concentration for a good therapeutic response [4-6]. A Floating and Bioadhesive Drug Delivery System (FBDDS) [7-8] overcomes the problem of dose availability. These systems are able to prolong the retention time of a dosage form in stomach, thereby improving the oral bioavailability of the drug. The present study was aimed to develop gastro retentive sustained release floating and bioadhesive drug delivery system (FBDDS) of ofloxacin which will remain in stomach for 24 hours while sustaining drug release to achieve target release profile using a combination of SCMC, HPMC K100M, EC and sodium bicarbonate.

Particulate floating or bioadhesive drug delivery systems like microspheres and nanoparticles have advantage of higher efficiency due to greater effective surface area for floating and bioadhesion as compared to systems like tablets. But particulate

floating orbioadhesive drug delivery systems have disadvantages like higher cost and use of organic solvents in their preparation. Overall benefit: cost ratio of floating and/or bioadhesivetablets may be higher than that of particulate floating or bioadhesive drug delivery systems. Considering this point, tablet dosage form was selected to design FBDDS in the present work.

Experimental

Materials

Ofloxacin was obtained as gift sample from Blue cross Pharmaceuticals Ltd., Nashik.HPMC K100M from Colorcon Ltd., Goa, SCMC from Lupin Pharmaceuticals, Pune.WhileEC from Alembic Pharmaceuticals Ltd. Vadodara, Gujarat. Other materials used were of ARGrade and were purchased from Modern Scientifics, Nasik.

Experimental design⁽⁹⁻¹⁰⁾

Formulation & development

A 3² full-factorial design was applied in the present study. In this design two factors were evaluated at 3 different levels and experimental trials were performed at all 9 possible combinations. The amount of release rate modifying HPMC K100M (X1) and amount ofbioadhesive polymer SCMC (X2) were selected as independent variables while t50%, t90%,floating lag time and detachment force were selected as dependent variables. The formulations are shown in Table 1.

Preparation of Tablets

Mixing of drug, polymers and other ingredients was done by geometric mixing. Tablets were prepared by direct compression method using rotary press (Rimek, India) with 13 mm flat tooling. Compression force for all the tablets was adjusted to get tablets of hardness 7- 9kg/cm².

Evaluation of Tablets

Evaluation of Tablet characteristics

All tablets were tested for appearance, colour and odour. The tablets were assayed for drug content using 0.1N HCl as the extracting solvent, and the samples were analyzedspectrophotometrically (Shimadzu 2450 PC, Japan) at 293.8 nm. Tablets were also evaluatedfor hardness (Pfizer type hardness tester Cadmach, Ahmedabad, India), friability (RocheFriabilatorRemi Electronics, Mumbai, India), content uniformity and thickness.

Determination of Floating Behavior of Tablets⁽⁸⁾

Floating (buoyancy) lag time (FLT) of tablets

The buoyancy lag time was determined using a 500 ml beaker containing 0.1N HCl. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time (FLT).

The buoyancy (Floating) duration

Duration of buoyancy is the time for which the tablet constantly floats on the surface of the medium. The duration of buoyancy was measured using a 500 ml beaker containing 0.1NHCl.

Ex-vivo Mucoadhesion Measurement of Tablets: (11-12)

Mecmesin Ultra tester (Detachment force) flag type

In evaluation of adhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. In the present study, goat intestine was used as model mucosal surface for bioadhesion testing. The detachment force (the force required to separate tablet from tissue surface) was reported as bioadhesive strength. The bioadhesive strength was reported in terms of Millinewton (mN).

Rotating Cylinder method

Rotating Cylinder method was used for measurement of adhesion time of formulations which was determined by using USP type VI (rotating cylinder method) apparatus, DISSO 2000LABINDIA at 37 ± 0.50C at 50 rpm using 0.1N HCl as a medium for 24 hrs. The goat gastric mucosa was adhered to the cylinder by using cynoacrylate glue. The tablet was pressed on the mucosa gently with the finger for 1 minute. The tablet was observed visually for 24 hours at1hour interval.

Determination of Swelling Index of Tablets

The swelling index of preweighed tablet was determined using USP type I dissolution apparatus (DISSO 2000 LABINDIA) at 50 rpm and 0.1 N HCl was used as medium; temperature was maintained at 37± 0.5oc 25,26. At selected time intervals, the specimens were removed, wiped gently with a tissue paper to remove surface water and weighed. Swelling characteristics of the tablet was expressed in terms of swelling index which was calculated by using following formula.

$$\% \text{ of hydration} = (W_2 - W_1) \times 100 / W_1$$

Where W1:- initial weight of tablet, W2:- weight of disc after specified time interval.

Determination of Matrix erosion

The swollen tablets in swelling study at 24 hours were dried at 600C in vacuum oven subsequently dried in desiccators for 2 days and reweighed (W3). Matrix erosion at 24h wascalculated by using following formula,

$$DS = (W_1 - W_3) \times 100 / W_1$$



Where, W_1 - initial weight of tablet, W_3 = Weight of tablets dried at 60°C for 24 hrs in vacuum oven.

Dissolution: Drug release from tablets

In vitro dissolution of formulation was studied using the rotating basket method (USP Type I apparatus). In this method, 900 ml of 0.1 N HCl was used as the dissolution media. The rate of stirring was 50 rpm. The tablets were placed in dissolution media maintained at $37 \pm 5^\circ\text{C}$ for a period of 24 hours. At appropriate time intervals (every 2 hrs up to 24 hrs), 5 ml of each sample was taken and filtered. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume (sink condition). The samples were assayed by the UV analytical method at 293.8 nm.

Stability study

The optimized formulation was wrapped in aluminum foil and subjected to $40 \pm 0.5^\circ\text{C}$ temperature in oven for the period of one month. The formulation was analyzed for organoleptic characteristics, hardness, drug content and dissolution. Similarity factor f_2 was calculated to determine the variation in drug release pattern after the storage period.

Results and Discussion

Evaluation of tablets

Hardness of tablets was in the range of 7-9 kg/cm². Thickness of tablets was found to be 6.7 ± 0.4 mm. Tablet weights varied between 795 mg to 803 mg. Percent weight loss in the friability test was found to be less than 0.5% in all the cases. Content uniformity was found within $100 \pm 2\%$. All results obtained were comply with the official standards.

Determination of Floating Behavior

An effervescent floating drug delivery was used to achieve in vitro buoyancy. All the batches (F1 to F9) were prepared using HPMC K100M and SCMC; sodium bicarbonate was added as gas-generating agent. Sodium bicarbonate induced CO₂ generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet becomes buoyant. All the tablets produced good gel strength, entrapping CO₂ gas and imparting stable and persistent buoyancy. All tablet batches (F1 to F9) exhibited satisfactory floatation ability and remained buoyant for more than 24 h in dissolution medium (0.1 N HCl). Floating lag time (FLT), for all batches (F1 to F9) was found to be 5.05 ± 0.45 to 11 ± 1 min (Table II). These results indicate that the buoyancy lag-time was satisfactory. The effect of HPMC on FLT was found to be highly significant and effect of SCMC was found to be significant.

Ex-vivo Mucoadhesion Measurement

Mecmesin Ultra tester (Detachment force):

The results of the detachment force of ofloxacin floating and/or bioadhesive tablets are given in Table II. In all the formulations, as the concentration of HPMC K100 M and SCMC increased, the detachment force increased.

Rotating Cylinder method

All tablet batches (F1 to F9) exhibited satisfactory adhesion duration ability and remained adhered for more than 20 hrs in dissolution medium (0.1N HCl).

Determination of Swelling Index and Matrix erosion

The effect of HPMC and SCMC on swelling index and % erosion was found to be highly significant. The percentage water uptake of the formulations (F1–F9) at 24 hr ranged from 322.87 to 515.03%, shown in Table III. Because of hydrophilic nature of both the polymers the percentage water uptake was found to be increased on increasing the concentration of HPMC K100M and SCMC in the formulations and, hence, the water uptake capacity increases. Drug diffusion depends significantly on the water content of the tablet. This may be because the mobility of the polymer chains is very dependent on the water content of the system. In the case of high water content, polymer chain relaxation takes place with volume expansion resulting in marked swelling of the system. Also, higher water content could lead to greater penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation, thereby reducing the floating lag-time (FLT). Consequently, faster and greater swelling of the tablet would lead to an increase in the dimensions of the tablet leading to an increasing in the diffusion pathways and, thus, a reduction in diffusion rate. But the percentage matrix erosion was found to be increased with increasing the concentration of SCMC in the formulations because SCMC get dissolve in water giving stable colloidal dispersion and thereby eroded to a greater extent and was found to be decreased on decreasing the concentration of HPMC because HPMC forms matrix gel hence, the drug release rate increases with increasing the concentration of SCMC and decreases with increasing the concentration of HPMC.

In vitro Drug release study

HPMC and SCMC are hydrophilic polymers. When tablets containing these polymers come in contact with water, hydrophilic polymers allow gradual hydration of the tablet matrix, leading to swelling of the tablet as discussed before. Water decreases the glass transition temperature of the polymers to the experimental temperature. At this temperature glassy polymer is transformed into a rubbery state. Mobility of polymeric chains is enhanced in this state. This favors the transport of water into tablet and consequently transport of the dissolved drug from tablet core to the

dissolution medium. Drug release from matrix tablet is determined by drug characteristics, delivery system and destination (site of drug release). Drug content of each tablet was 300 mg and 900 ml of dissolution medium was used for dissolution studies. Ofloxacin was found to have 77.561 mg/ml solubility in 0.1 N HCl at 25° C. Maintaining sink condition is important during the dissolution experiment for consistent and accurate measurement of the dissolution rate. Sink conditions could be maintained throughout the dissolution study and drug solubility could not be a factor responsible for retardation of drug release from the formulations studied. Hence retardation of drug release from the formulations could be attributed to the properties of polymers used in the formulations.

Drug release studies were made to determine whether the release of the drug is slow enough, i.e., which polymer percentage is enough to sustain the release of the drug for at least 24 hr. As Figures 1 show, increasing the SCMC content of tablets increases the percentage of drug released. This is because of rapid swelling and erosion of CMC in contact with water. Further, the increase in rate of drug release could be explained by the ability of the SCMC to absorb water, thereby promoting the dissolution, and hence the release, of the drug i.e. ofloxacin. Moreover, the hydrophilic polymers would leach out and hence, create more pores and channels for the drug to diffuse out of the device. Whereas as increasing the HPMC content of tablets decrease the percentage of drug released. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to increase in the diffusion path so the amount of drug released decreases.

Data treatment

The dissolution data of batches F1 to F9 was fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas models. The coefficient of determination (R²) value was used as criteria to choose the best model to describe drug release from the tablets. The R² values of various models are given in Table IV. In case of all the formulations the R² values were higher for Zero order model than for First order model indicating that the drug release from the formulation followed Zero order kinetics. The R² value (R²>0.9712) obtained for fitting the drug released data to the Higuchi equation, indicated that the drug release mechanism from these tablets was diffusion controlled. The values of 'n' in Peppas model also indicated that all the formulations followed diffusion and anomalous release; this indicated that the drug released is controlled by both diffusion and erosion.

Optimization data analysis

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DOE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to

determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms. Various RSM computations for the current optimization study were performed employing Design Expert software. Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as Equation below $Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_1X_2 + \beta_4X_1^2 + \beta_5X_2^2$ where, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 9 runs; β_1 to β_5 are the coefficients computed from the observed experimental values of Y; and X₁ and X₂ are the coded levels of the independent variable(s). The terms X₁X₂ represents the interaction. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). The analysis of variance (ANOVA) is performed to identify the insignificant factors and reduce the equation in order to get better fit and the best formulation possible.

Model assessment for the dependent variables

Model for t₅₀

After putting the data in Design Expert software, Fit summary applied to data in that Linear model had been suggested by the software so as per this model the equation is as follows Model equation in coded terms

$$t_{50} = +6.31 + 4.37A - 1.04B$$

The result of multiple linear regression analysis (linear model) reveals that, on increasing the concentration of HPMC t₅₀ is increased and reverse is true for SCMC as the signs are positive and negative respectively.

Model for t₉₀

After putting the data in Design Expert software, Fit summary applied to data in that Linear model had been suggested by the software so as per this model the equation is as follows Model equation in coded terms

$$t_{90} = +18.31 + 4.61A - 1.13B$$

The result of multiple linear regression analysis (linear model) reveals that, on increasing the concentration of HPMC t₉₀ is increased and reverse is true for SCMC as the signs are positive and negative respectively.

Model for Floating Lag Time (FLT)

After putting the data in Design Expert software, Fit summary applied to data in that Linear model had been suggested by the



Table 1: Formulations of Factorial design

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ofloxacin	400	400	400	400	400	400	400	400	400
HPMC K100M	200	200	200	240	240	240	280	280	280
SCMC	50	75	100	50	75	100	50	75	100
EC	50	50	50	50	50	50	50	50	50
Sod.bicarbonat	65	65	65	65	65	65	65	65	65
Mg-Stearate	5	5	5	5	5	5	5	5	5
DCP	130	105	80	90	65	40	50	25	---
Total	900	900	900	900	900	900	900	900	900

Table 2: Floating lag time (FLT) of different formulations (n=3)

Formulation	Floating Lag Time (FLT) (min) Mean + SD	Detachment force (mN) Mean + SD
F1	11.00 ± 1.00	265 ± 10.81
F2	10.38 ± 0.98	309 ± 12.28
F3	9.16 ± 1.04	343 ± 9.53
F4	8.71 ± 0.51	402 ± 11.53
F5	7.71 ± 0.56	445 ± 13.28
F6	7.56 ± 0.73	483 ± 17.08
F7	6.03 ± 0.56	557 ± 7.54
F8	5.05 ± 0.45	604 ± 13.52
F9	5.26 ± 0.92	646 ± 10.53

Table 3: Swelling indices & percent erosion of different formulations

Formulations	Swelling indices				% Erosion After 24 hr
	After 4 hr	After 8 hr	After 16 hr	After 24 hr	
F1	157.92	211.85	81.46	322.87	55.09
F2	167.16	246.06	338.52	381.40	49.91
F3	181.27	264.21	347.32	420.23	46.32
F4	159.63	222.44	329.31	434.00	43.88
F5	165.99	261.78	365.97	452.35	38.38
F6	196.10	298.30	367.85	471.74	35.87
F7	172.86	245.56	392.46	488.44	33.16
F8	184.06	333.05	430.53	499.79	30.2
F9	224.27	353.88	466.38	515.03	27.7



Table 4: Drug release kinetics of different formulations

Optimized formulation	Ofloxacin	HPMC K100M	SCMC	EC	Sod. bicarbonate	Mg stearate	DCP	Total
Quantity (mg)	400	254.76	75.27	48	70	05	46.97	900

Table 5: Composition of optimized formulation

Formulations	Zero Order		First Order		Higuchi		Korsmayer-Peppas	
	R ²	K ₀	R ²	K ₁	R ²	K _H	R ²	N
F1	0.9445	3.1961	0.9417	-0.068	0.9846	19.72	0.9867	0.4086
F2	0.9431	4.033	0.9488	-0.102	0.9853	23.84	0.9881	0.4713
F3	0.9649	3.687	0.9179	-0.101	0.9712	20.62	0.9954	0.3579
F4	0.9795	3.3621	0.9422	-0.059	0.9963	21.84	0.9573	0.5412
F5	0.9799	2.699	0.8984	-0.062	0.9893	17.77	0.9925	0.3935
F6	0.9987	3.3695	0.9249	-0.039	0.9711	21.07	0.9837	0.6926
F7	0.998	3.1961	0.9417	-0.068	0.9846	19.72	0.9867	0.4086
F8	0.9991	3.451	0.8761	-0.048	0.9736	22.24	0.9756	0.6580
F9	0.9915	3.55	0.9449	-0.045	0.9849	22.35	0.9839	0.6701

Table 6: Predicted and experimental values obtained for different responses of optimized formulation

Responses	Predicted values	Experimental values
t ₅₀ (hrs)	7.91	8.60
t ₉₀ (hrs)	19.99	20.31
Floating Lag Time (min)	6.99	6.25
Adhesion strength (mN)	500	492

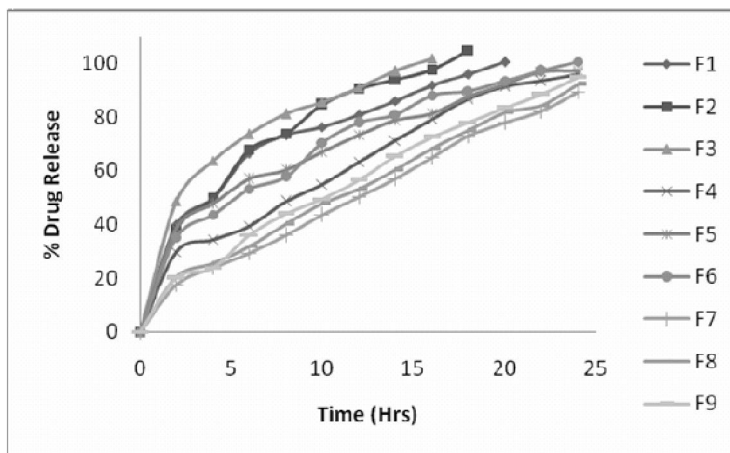


Figure 1: Dissolution profiles of formulations

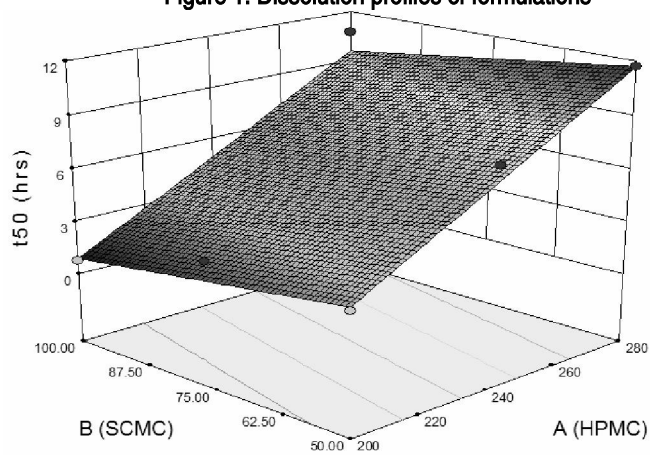


Figure 2: Response plot of t_{50}

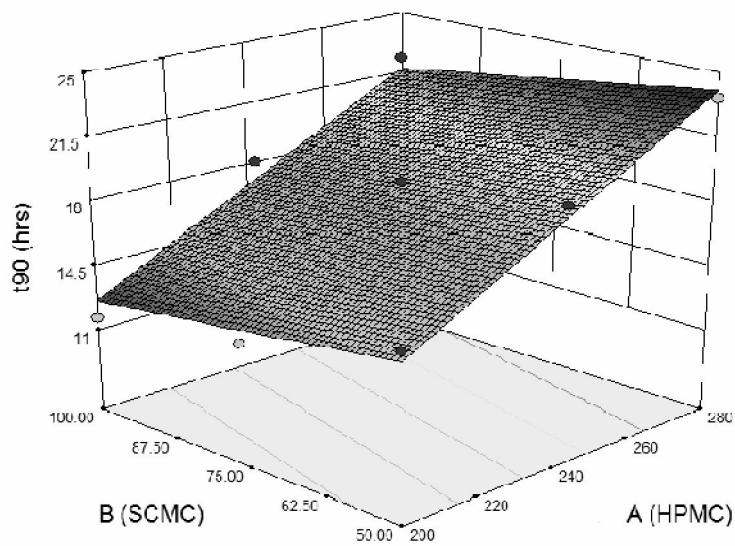


Figure 3: Response plot of t_{90}



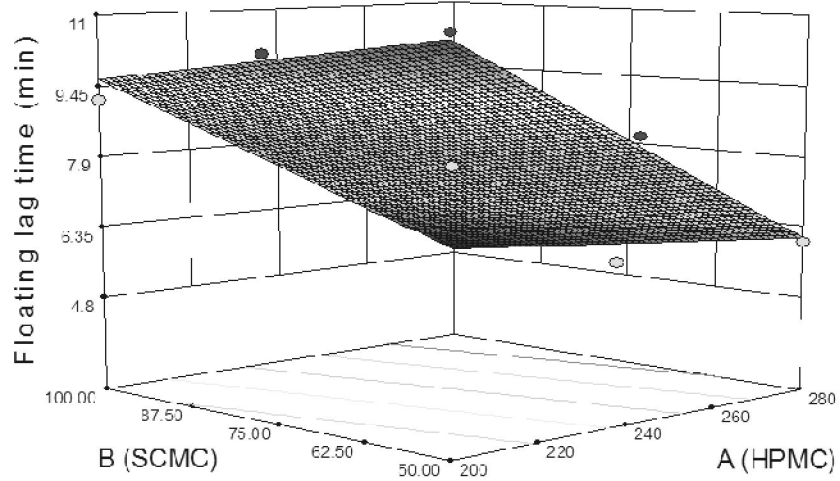


Figure 4: Response plot of floating lag time

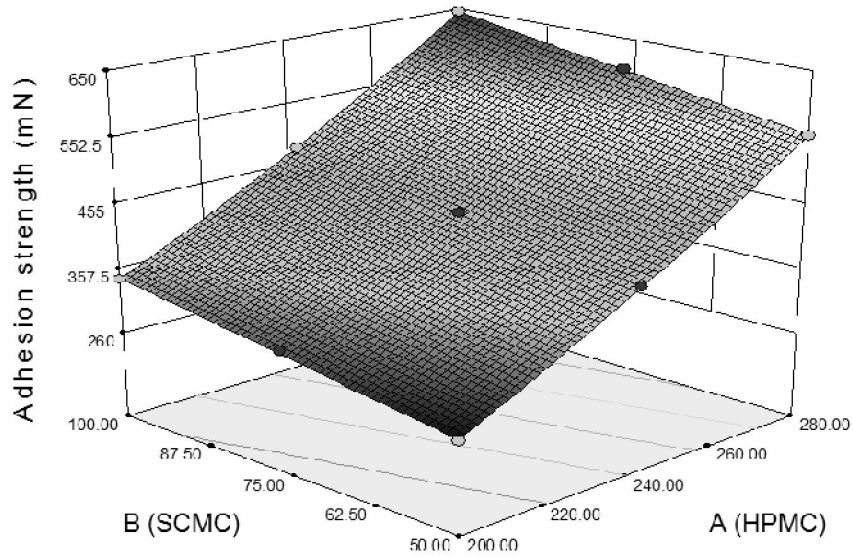


Figure 5: Response plot of adhesion strength

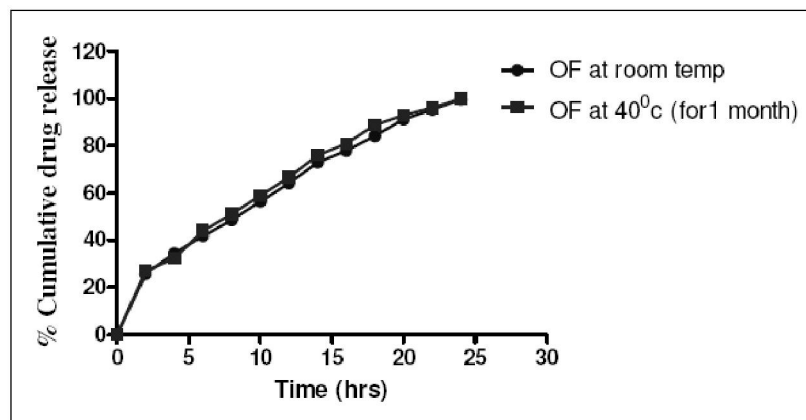


Figure.6: Dissolution profiles of optimized formulation at room temperature and at 40°C



software so as per this model the equation is as follows
Model equation in coded terms

$$FLT = +7.87 - 2.37A - 0.63B$$

The result of multiple linear regression analysis (linear model) reveals that, on increasing concentration of HPMC and SCMC, FLT was decreased.

Model for Adhesion strength

After putting the data in Design Expert software, Fit summary applied to data in that Quadratic model had been suggested by the software so as per this model the equation is as follows

Model equation in coded terms

$$\text{Adhesion strength} = +443.33 + 148.33A + 41.33B + 2.75AB + 10.67A^2$$

The result of multiple linear regression analysis (linear model) reveals that, both HPMC and SCMC increase the Adhesion strength of tablet.

Optimization Result

The optimization was performed on the basis of response surface modeling by using the numerical and graphical optimization method. Desirability is an objective function that ranges from zero outside of the limits to one at the goal. The numerical optimization finds a point that maximizes the desirability function. The characteristics of a goal may be altered by adjusting the weight or importance. For several responses and factors, all goals get combined into one desirability function. The goal of optimization is to find a good set of conditions that will meet all the goals. Tablets were compressed with hardness 8 kg/cm². Thickness of tablets was found to be 6.7 ± 0.6 mm. Tablet weight was found to be 900 mg. Content uniformity was found to be 99.92 ± 2%. All results obtained were complies with the official standards. The comparison between predicted values and experimental values was carried out Table VI.

Stability Study

References

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Hardness was found to be 8 kg/cm². Thickness of tablets was found to be 6.7 ± 0.6 mm. Tablet weight was found to be 900 mg. Content uniformity was found to be 98.92 ± 3%. Short-term stability testing was carried out for the optimized formulation (OF). The results for the dissolution profile are as depicted in the figure 6. Short-term accelerated stability data obtained for optimized formulation revealed that drug content, thickness, hardness, in-vitro dissolution were within the acceptable limit. The similarity factor f₂ for the same was found to be 77.50. Thus the formulation can be said to be stable. All results obtained were complies with the official standards.

Conclusion

Floating duration up to 24hrs and high bioadhesive strength of the formulation are likely to increase its GI residence. As the concentration of HPMC increased, drug release was found to be decreased and reverse was observed in case of SCMC. Sustained drug release with floating duration up to 24hrs and high bioadhesive strength was observed in case of optimized formulation. The swollen tablet also maintained its physical integrity during the drug release study. The combination of floating system and bioadhesive system could be a very promising approach to increase gastric retention of dosage form with the use of polymers HPMC and SCMC.

Authors' contributions

- i) AYP have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. Also he is involved in drafting the manuscript or revising it critically for important intellectual content
 - ii) DNL participated in the design of the study and performed the experimental work.
 - iii) DVD have participated in its design and coordination and helped to draft the manuscript.
- All authors have read and approved the final manuscript.

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