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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 tobe 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, dueto 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 andBioadhesive Drug Delivery System (FBDDS) [7-8]overcomes the problem of dose availability. Thesystems 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 andbioadhesive 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 andnanoparticles 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 3^2 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.

% of hydration = (W2-W1) X 100 / W1

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 ovensubsequently dried in desiccators for 2 days and reweighed (W3). Matrix erosion at 24h wascalculated by using following formula,

DS= (W1-W3) X 100 / W1

Where, W1- initial weight of tablet, W3 = Weight of tablets dried at 60o 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 Iapparatus). In this method, 900 ml of 0.1 N HCl was used as the dissolution media. The rateof stirring was 50 rpm. The Tablets were placed in dissolution media maintained at 37 ± 5°Cfor a period of 24 hours. At appropriate time intervals (every 2 hrs up to 24hrs), 5 ml of eachsample was taken and filtered. The dissolution media was then replaced by 5 ml of freshdissolution fluid to maintain a constant volume (sink condition). The samples were assayed bythe UV analytical method at 293.8 nm.

Stability study

The optimized formulation was wrapped in aluminum foil and subjected to 40 ±0.5°Ctemperature in oven for the period of one month. The formulation was analyzed fororganoleptic characteristics, hardness, drug content and dissolution. Similarity factor f2 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 + 2%. All results obtained were complies with the official standards.

Determination of Floating Behavior

An effervescent floating drug delivery was used to achieve in vitro buoyancy. All the batches(F1toF9) were prepared using HPMC K100M and SCMC; sodium bicarbonate was added as agas-generating agent. Sodium bicarbonate induced CO_2 generation in the presence ofdissolution 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 ofthe tablet falls below 1, the tablet becomes buoyant. All thetablets produced good gel strength, entrapping CO2 gas and imparting stable and persistentbuoyancy. All tablet batches (F1 toF9) exhibited satisfactory floatation ability and remainedbuoyant for more than 24 h in dissolution medium (0.1 N HCl). Floating lag time (FLT), forall batches (F1 to F9) was found to be 5.05 + 0.45 to 11 + 1 min (Table II). These resultsindicate that the buoyancy lag-time was satisfactory. The effect of HPMC on FLT was foundto 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 SCMCincreased, the detachment force increased.

Rotating Cylinder method

All tablet batches (F1 to F9) exhibited satisfactory adhesion duration ability and remainedadhered 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 highlysignificant.The percentage water uptake of the formulations (F1–F9) at 24 hr ranged from 322.87 to515.03%, shown in Table III. Because of hydrophilic nature of both the polymers thepercentage water uptake was found to be increased on increasing the concentration of HPMCK100M and SCMC in the formulations and, hence, the water uptake capacity increases. Drugdiffusion 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 thecase of high water content, polymer chain relaxation takes place with volume expansionresulting in marked swelling of the system. Also, higher water content could lead to greaterpenetration 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 thetablet would lead to an increase in the dimensions of the tablet leading to an increasing in thediffusion pathways and, thus, a reduction in diffusion rate.But the percentage matrix erosion was found to be increased with increasing the concentrationof SCMC in the formulations because SCMC get dissolve in water giving stable colloidaldispersion and thereby eroded to a greater extent and was found to be decreased on decreasingthe concentration of HPMC because HPMC forms matrix gel hence, the drug release rateincreases with increasing the concentration of SCMC and decreases with increasing theconcentration of HPMC.

In vitro Drug release study

HPMC and SCMC are hydrophilic polymers. When tablets containing these polymers comein 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 transitiontemperature of the polymers to the experimental temperature. At this temperature glassypolymer is transformed into a rubbery state. Mobility of polymeric chains is enhanced in thisstate. This favors the transport of water into tablet and consequently transport of thedissolved drug from tablet core to the

dissolution medium. Drug release from matrix tablet isdetermined 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 fordissolution studies. Ofloxacin was found to have 77.561 mg/ml solubility in 0.1 N HCl at25° C. Maintaining sink condition is important during the dissolution experiment forconsistent and accurate measurement of the dissolution rate. Sink conditions could bemaintained throughout the dissolution study and drug solubility could not be a factorresponsible for retardation of drug release from the formulations studied. Hence retardation ofdrug release from the formulations could be attributed to the properties of polymers used inthe 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 drugreleased. 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 absorbwater, thereby promoting the dissolution, and hence the release, of the drug i.e. ofloxacin. Moreover, the hydrophilic polymers would leach out andhence, create more pores and channels for the drug to diffuse out of the device.Whereas asincreasing the HPMC content of tablets decrease the percentage of drug released. Thesefindings are in compliance with the ability of HPMC to form complex matrix network whichleads 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 andKorsemayer-Peppas models. The coefficient of determination (R2) value was used as criteriato choose the best model to describe drug release from the tablets. The R2 values of variousmodels are given in Table IV. In case of all the formulations the R2 values were higher for Zeroorder model than for First order model indicating that the drug release from the formulationfollowed Zero order kinetics. The R2 value (R2>0.9712) obtained for fitting the drug releasedata to the Higuchi equation, indicated that the drug release mechanism from these tabletswas diffusion controlled. The values of 'n' in Peppas model also indicated that all theformulations followed diffusion and anomalous release; this indicated that the drug released iscontrolled by both diffusion and erosion.

Optimization data analysis

Response surface methodology (RSM) is a widely practiced approach in thedevelopment and optimization of drug delivery devices. Based on the principle ofdesign of experiments (DOE), the methodology encompasses the use of various types ofexperimental designs, generation of polynomial equations and mapping of the response overthe experimental domain to determine the optimum formulation(s). The technique requiresminimum experimentation and time, thus proving to be far more effective and cost-effectivethan the conventional methods of formulating dosage forms. Various RSM computations forthe current optimization study were performed employing Design Expert software.Polynomial models including interaction and quadratic terms were generated for all theresponse variables using multiple linear regression analysis (MLRA) approach. Thegeneral form of the MLRA model is represented as Equation below

$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 3X1X2 + \beta 4X1^2 + \beta 5X^2$

where, $\beta 0$ is the intercept representing the arithmetic average of all quantitative outcomes of 9runs; $\beta 1$ to $\beta 5$ are the coefficients computed from the observed experimental values of Y; andX1 and X2 are the coded levels of the independent variable(s). The terms X1X2 represents theinteraction. The polynomial equations can be used to draw conclusions after consideringthe magnitude of coefficient and the mathematical sign it carries (i.e., positive ornegative). The analysis of variance (ANOVA) is performed to identify the insignificantfactors 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 Linearmodel had been suggested by the software so as per this model the equation is as followsModel equation in coded terms

t50 = +6.31 + 4.37A – 1.04B

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

Model for t90

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

t90 = +18.31 + 4.61A – 1.13B

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

Model for Floating Lag Time (FLT)

After putting the data in Design Expert software, Fit summary applied to data in that Linearmodel 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.bicabonate	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		Korsemayer-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

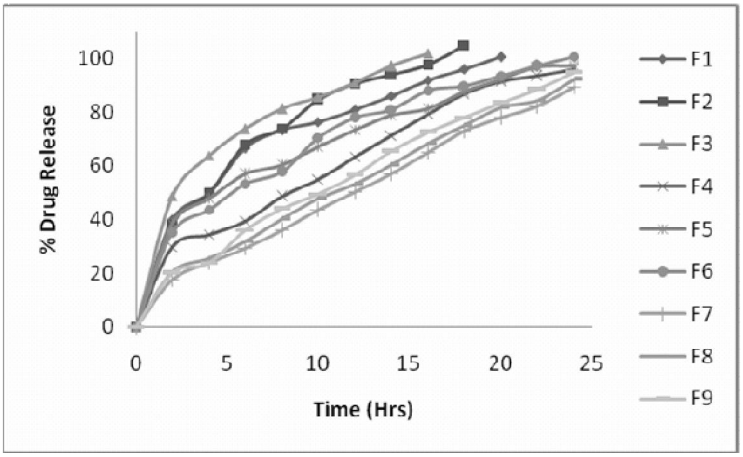

Figure 1: Dissolution profiles of formulations

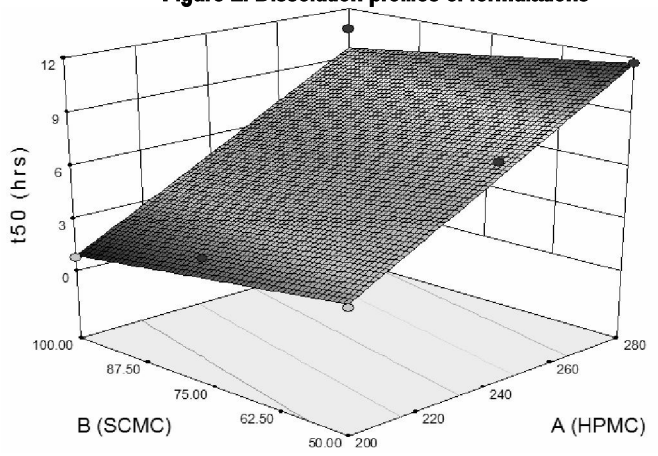

Figure 2: Response plot of t_{50}

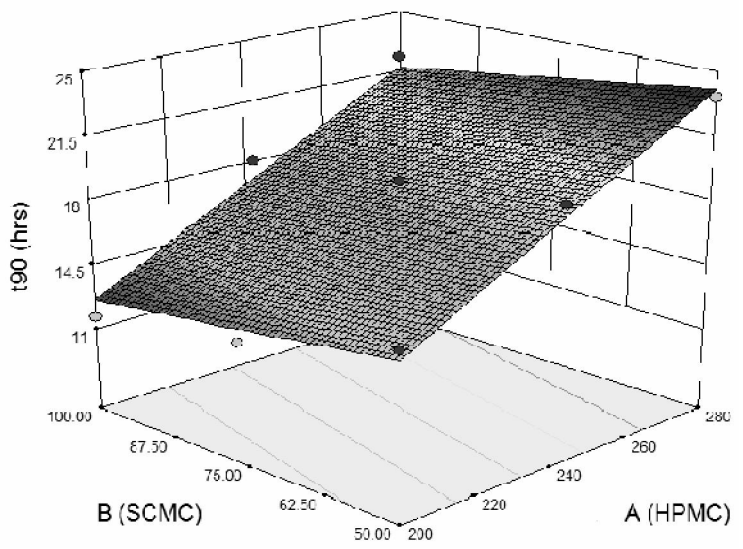

Figure 3: Response plot of t_{90}

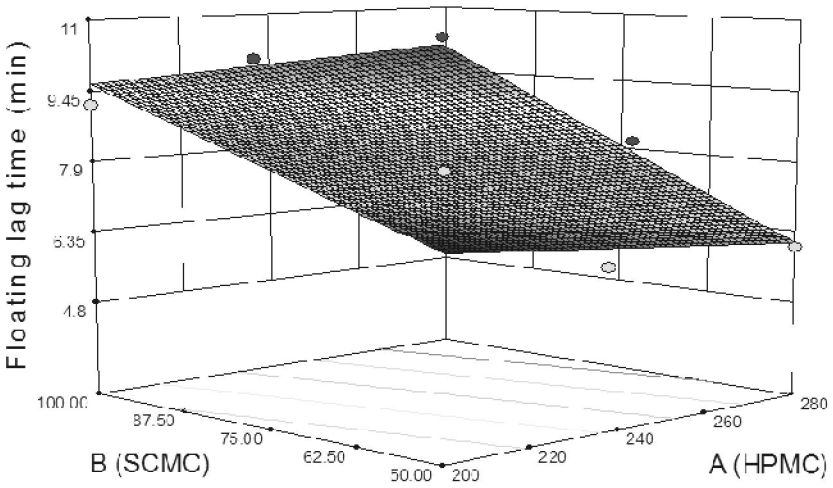

Figure 4: Response plot of floating lag time

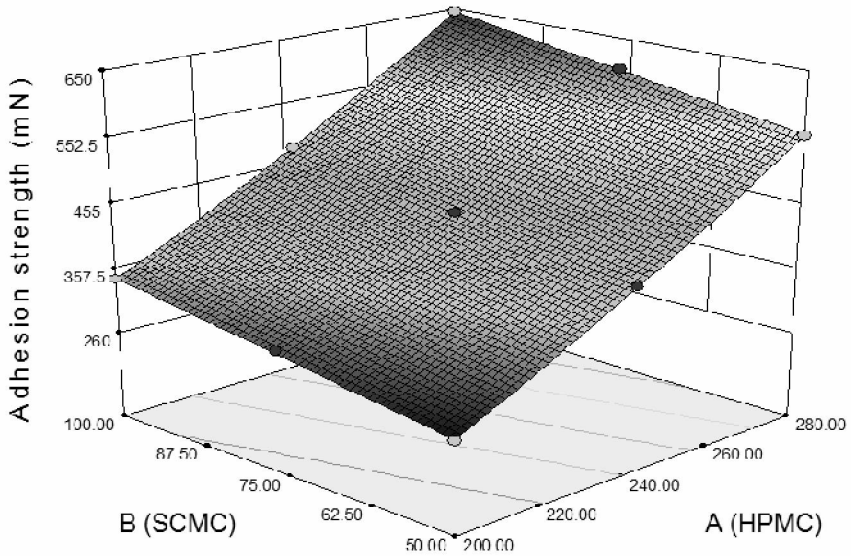

Figure 5: Response plot of adhesion strength

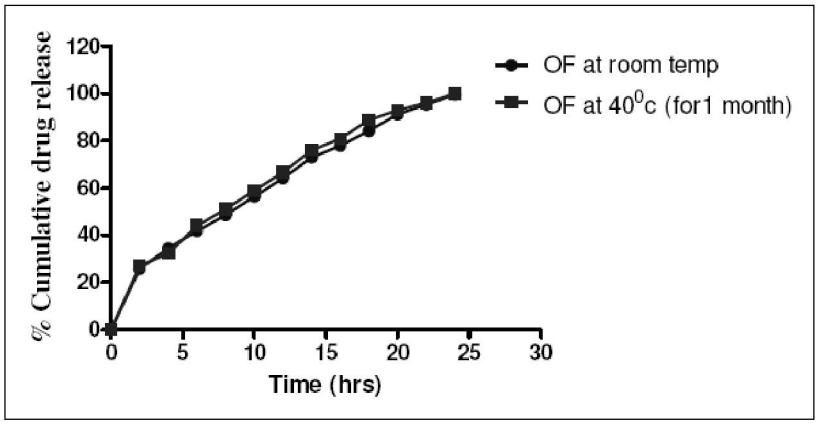

Figure.6: Dissolution profiles of optimized formulation at room temperature and at 40^{0}C

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

FLT = +7.87 – 2.37A – 0.63B

The result of multiple linear regression analysis (linear model) reveals that, on increasingconcentration 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 thatQuadratic model had been suggested by the software so as per this model the equation is asfollows

Model equation in coded terms

Adhesion strength = +443.33 +148.33A + 41.33B + 2.75AB + 10.67A2

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

Optimization Result

The optimization was performed on the basis of response surface modeling by using thenumerical and graphical optimization method. Desirability is an objective function thatranges from zero outside of the limits to one at the goal. The numerical optimizationfinds a point that maximizes the desirability function. The characteristics of a goal may bealtered by adjusting the weight or importance. For several responses and factors, all goalsget combined into one desirability function. The goal of optimization is to find a good setof 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 comparisonbetween predicted values and experimental values was carried outTable VI.

Stability Study

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 tobe 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 thedrug release study. The combination of floating system and bioadhesive system could be avery promising approach to increase gastric retention of dosage form with the use of polymersHPMC 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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