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Formulation Optimization of A Floating Once-Daily Matrix Tablet of Ofloxacin

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ABSTRACT

The purpose of the present study was to develop an optimized gastric floating once-daily matrix tablet of ofloxacin (FERMTs) using hydrophilic polymers such as HPMC K4M, HPMC 100M, isapagulha husk and sodium bicarbonate as buoyancy contributer. The formulation of FERMTs were designed by 2^3full factorial design taking amount of HPMC K4M, HPMC 100M and sodium bicarbonate as formulation variables and prepared by wet granulation method. The FERMTs were then evaluated for hardness, friability, weight variation, content uniformity, *in vitro* drug release and floating capacity. Finally, the floating lag time (FLT) and cumulative % drug release at 4h, 8h, 12h and 16h were taken as response variables and the FERMT formulation was numerically optimized by 2^3full factorial design using Design-Expert software (version 8.1). The optimized formula showed excellent floating efficiency over a 16 h period with FLT of 2.80 mins and drug release over a period of 16 hour. Analysis of dissolution data showed that the kinetic of drug release followed Korsemeyer-peppas model.

Keywords: Floating tablet; Extended-release; Factorial design; Ofloxacin

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INTRODUCTION

Peroral sustained release dosage forms have been popular for the past three decades due to their considerable therapeutic advantages with better patient compliance [1]. However, this approach has not been suitable for a variety of important drugs characterized by a narrow absorption window in the upper part of the gastrointestinal tract, i.e. stomach [2]. The relatively short transit time of the dosage forms in these segments of g. i. tract is responsible for the fact. Thus, after only a short period of time less than 2 to 3 hours, the sustained release device leaves the upper part of g. i. tract i.e. absorption window and the drug is released in non-absorbing distal segments of the g. i. tract. This results in a poor bioavailability of such drugs. Ofloxacin is such a drug that poorly soluble in intestinal pH and therefore it is mainly absorbed from the stomach. Due to its narrow absorption window the oral bioavailability of ofloxacin is around 50% [3]. Lodging of the delivery system of ofloxacin in the stomach for the entire period of drug release may improve the degree of absorption and bioavailability [4].

Gastric retention of the delivery device for entire period of drug release may be a potential approach for uniform drug release, plasma conc. Vs time profile and improvement of oral-bioavailability. Various techniques and approaches for gastroretentive device of different drugs with narrow absorption window including floating beads, floating tablets, floating microspheres, hydrodynamically balanced systems have been reported [5-12]. But no substantial work has been reported to achieve good floatability along with a once-daily release profile.

Ofloxacin is an important member of first generation fluoroquinolones, active against gram-negative and gram-positive bacteria and certain anaerobes. It is also active against *Chlamydia* and *Mycoplasma*. It is used in non-specific urethritis, cervicitis and atypical pneumonia. It also inhibits *Mycobacterium tuberculosis* and can be used in place of ciprofloxacin. It is highly active against *Mycobacterium laprae*. It is suitable for chronic bronchitis and other respiratory or ENT infections, gonorrhea. Usual dose is 200mg two times a day. Sustained formulation preferably once daily formulation may increase outcome of the therapy and also patient compliance. But the problem is its absorption is strongly dependent on the local physiology in the GI tract and it is absorbed in the higher sections of the GI tract. Ofloxacin is readily soluble in the acidic environment of the stomach. In the intestine, where neutral to slightly alkaline pH conditions prevail; however, precipitation of the drug occurs, which adversely affects the absorption in the lower segments of the intestine. There is a need for systems that reside in the stomach over a relatively long time and release the drug there in a sustained manner.

The objective of the present study is to develop a once-daily gastroretentive tablet formulation of ofloxacin in order to improve the oral bioavailability as well as patient compliance. The gastric retention technique used in our study is based on gas generation and subsequent entrapment within the tablet that makes it buoyant in the gastric fluid [13].

Hydroxypropylmethyl cellulose K4M (HPMC K4M) and HPMC 100M were used as matrix forming polymer and Sodium bicarbonate ($NaHCO_3$) as gas generating agent. Ispagulha husk was added to the formulation to prevent premature erosion of the matrix and introduce mechanical integrity to the matrix. HPMC K4M, HPMC 100M and $NaHCO_3$ were considered as formulation variables, where floating lag time (FLT) and Cumulative % drug release (CPR) at 4h, 8h, 12h and 16h were taken as response parameters.

2^3 full factorial design was applied to design the formulations and optimize using Design-Expert software (version 8.1). The optimized formula remained floated in 0.1N HCl over 16 hours and showed a drug release capacity over 16 hours. To the best of our knowledge, this work is not reported earlier.

MATERIALS AND METHODS

Materials

Ofloxacin was donated by La-Chemico Pharmaceuticals, India, as gift sample; Hydroxypropylmethyl cellulose K4M was donated by Colorcon Asia Pvt Ltd; ispagulha husk was purchased from Baidyanath, Kolkata, India; HPMC 100M, Talc and Magnesium stearate were purchased from Loba Chemie Pvt Ltd, Mumbai, India; Ethanol, conc. Hydrochloric acid, sodium bicarbonate anhydrous were purchased from Merck Specialties Pvt Ltd, Mumbai, India. The drug and excipients were used as received without further treatment and the reagents were of analytical grade.

Formulation Design of FERMTs

For formulation of FERMTs, Hydroxypropylmethyl cellulose K4M (HPMC K4M), HPMC 100M and $NaHCO_3$ were taken as formulation variables. Talc and magnesium stearate were used as lubricant. The amount of ofloxacin, ispagulha husk powder, talc and magnesium stearate were kept constant in all batches. The 2^3 full factorial design was adopted to design the experiment using Design-Expert software (version 8.1, Stat-Ease Inc., Minneapolis, USA)[14]. The low and high level of HPMC K4M, HPMC 100M and $NaHCO_3$ were set at (150 mg; 200mg), (30mg; 60mg) and (80mg; 120mg) respectively. The Design-Expert software designed the experiment giving 8 different formulas of FERMTs. The formulas of 8 batches were given in Table 1.

Table1: Formulation of different 8 batches of FERMTs designed by Design Expert software

Formulation code	Ofloxacin (mg)	HPMC K4M (mg)	HPMC 100M (mg)	$NaHCO_3$ (mg)	PVP K30 (mg)	Isabgul Husk (mg)	Magnesium Stearate (mg)	Talc (mg)	Total weight (mg)
F_1	400	150	30	80	50	50	10	10	780
F_2	400	150	30	120	50	50	10	10	820
F_3	400	150	60	120	50	50	10	10	850
F_4	400	150	60	80	50	50	10	10	810
F_5	400	200	60	120	50	50	10	10	900
F_6	400	200	60	80	50	50	10	10	860
F_7	400	200	30	80	50	50	10	10	830
F_8	400	200	30	120	50	50	10	10	870

Preparation of FERMTs

The **FERMTs** were prepared by wet granulation method[15]. At first, the drug, HPMC K4M, HPMC 100M, ispagulha husk powder (passed through 100 mesh) and $NaHCO_3$ were mixed together well by geometric mixing using pestle mortar. The powder mixture was wet-massed with ethanol. Then the mass was passed through a sieve (mesh no # 18) to obtain granules. Then the granules were dried in a hot air oven at 60°C for half an hour. The granules were passed through sieve #18 and then sieve #22. The granules those passed sieve #18 but retained on sieve #22, were taken for compression. Prior compression magnesium stearate and talc were mixed with the granules. Then the granules were compressed by tablet compression machine (LABPRESS, 10 Station, REMI, Mumbai, India) using flat shaped punches and 12 mm diameter.

Evaluation of FERMTs

Weight variation and content uniformity test

Weight variation and content uniformity test were carried out as per USP 2009 to check the uniformity of prepared FERMTs. In both cases relative standard deviation (RSD) and acceptance value (AV) were calculated for each formulation[16].

Hardness test

Crushing force was measured using Monsanto Hardness Tester for each formulation to check the mechanical strength of FERMTs. The measurement was repeated in triplicate. The average crushing force for each formulation was then calculated.

Friability test

This was carried out to test the friability of the floating tablets using Roche type friabilator. A tablet was weighed accurately and placed in the friabilator. Then it was rotated at 25 rpm for 4 minutes. After that, the tablet was taken out and reweighed. The % friability (f) was calculated

using the formula[17]:

$$f = (w_1 - w_2) \times 100\% / w_1$$

Where w_1 is the previous weight and w_2 is the weight after operation. The study was repeated in triplicate for each formulation and average was calculated.

In vitro floating test

In vitro floating test was carried out to evaluate floating property of the FERMTs. The floating lag time (FLT) is the time taken by the tablet to reach the surface of the floating medium after placing of the tablet in the floating medium. The floating time (FT) is time period throughout which the tablet remains buoyant in the floating medium. A tablet was placed in 0.1N HCl acid in a 100 ml beaker. Then the floating lag time and floating time were observed and noted[18]. The study was repeated three times for each formulation and average FLT and FT were calculated.

In vitro drug release test

In vitro drug dissolution tests from all eight batches of formulated tablets were carried out using USP dissolution test apparatus type-I (DS-800; 6+2; SC/TR, Lab India, Mumbai, India) in 900 ml 0.1N HCl acid (pH 1.2) maintained at 37^0C with a basket rotation speed of 50 rpm. 5 ml of aliquot was withdrawn at predetermined time points and same volume buffer was added to the dissolution medium each time. Drug released from the tablets at different time points were measured spectrophotometrically (UV-vis double beam spectrophotometer, Pharmaspec-1700, Shimazdu, Japan) at the λ_{max} value at 293 nm. The in vitro drug release data were fitted to various release kinetic models viz. zero order, first order, Higuchi model, Hixson-Crowell and Korsmeyer-Peppas model to understand the mechanism of drug release. The study was repeated in triplicate for each formulation.

Zero order model: $Q_t = K_0 t$ (Q_t is the amount of drug released in time, t, K_0 is zero order release constant)[19]

Firs order model: $\log Q_t = \log Q_0 + K_1 t/2.303$ (Q_0 is the initial amount of drug in solution)[20]

Higuchi model: $Q_t = K_H t^{1/2}$ [21].

Hixson-Crowell model: $(1-f_t)^{1/3} = 1 - K_\beta t$ (f_t is the fraction of drug released at time, t)[22]

Korsmeyer-Peppas model: $f_t = at^n$ (a is a release rate constant incorporating structural and geometric characteristics of the dosage form, n is the release exponent, indicative of the drug release mechanism)[23]

Higuchi model describes drug release as a diffusion process based on the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of

modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs[24].

Korsmeyer-Peppas model describes the *n* value in order to characterize different mechanism of drug release, when $n = 0.5$, $0.5 < n < 1$, $n = 1$ and $n > 1$ corresponds to Case-I (Fickian) diffusion or Higuchi kinetic, anomalous (non-Fickian) diffusion, Case-II transport and super Case-II transport respectively[25].

Analysis of the responses and formulation optimization

Finally the response variables: FLT, cumulative % drug release (CPR) at 4h, 8h, 12h and at 16h (CPR4h, CPR8h, CPR12h and CPR16h respectively) were analyzed and formulation was optimized numerically to obtain target FLT (1 min) and target CPR (25%, 40%, 60% and 80% at 4, 8, 12 and 16 hours respectively; Table 2) by Design-Expert software following the 2^3 full factorial design. After optimization, the floating tablets were prepared as per the optimized formula and evaluated. Then the observed responses were compared to the predicted and target values.

RESULTS AND DISCUSSION

The content uniformity and weight variation test showed that the acceptance values of all formulations in each case were within the limit prescribed in USP. The prepared FERMTs showed having sufficient mechanical strength. The tablets showed having hardness within the range of 4.5 kg/m^2 to 6.23 kg/m^2. The tablets were compressed with a constant compaction force. The % friability of all formulations was well below 1% (Table 2).

Table 2: Hardness, % friability, floating lag time and total floating time of different eight batches

Formulation code	Hardness(Kg/m^2) average ± s.d.	% friability average ± s.d.	FLT (min) average ± s.d.	TFT (hr)
F_1	4.5 ± 0.25	0.11 ± 0.02	5 ± 0.56	>16
F_2	5.5 ± 0.56	0.13 ± 0.06	1 ± 0.05	>16
F_3	5.2 ± 0.21	0.02 ± 0.003	4 ± 0.08	>16
F_4	5.25 ± 0.65	0.05 ± 0.002	5 ± 1.1	>16
F_5	6.23 ± 1.12	0.01 ± 0.005	3 ± 0.74	>16
F_6	5.5 ± 0.31	0.10 ± 0.03	7 ± 1.19	>16
F_7	5.13 ± 1.29	0.09 ± 0.007	4 ± 0.87	>16
F_8	5.5 ± 0.92	0.03 ± 0.002	2 ± 0.13	>16

FLT- floating lag time; TFT- total floating time

The in vitro floating test showed that the floating lag time (FLT) observed was within the range from 1 min to 7 mins on average (Table 2). The total floating time (TFT) for all formulations was observed greater than 16 hours. After reaching the tablet in the stomach, gastric fluid

penetrates the interior of the tablet resulting generation of CO_2 due to the reaction between $NaHCO_3$ of the tablet formulation and HCl acid of the gastric fluid. Simultaneously, the hydrophilic polymers HPMC K4M, HPMC 100M and ispagulha husk powder absorb water and form a continuous barrier gel layer at the outer surface of the tablet. As a result, CO_2 gas gets entrapped inside the tablet, and thus contributes the buoyancy to the tablet. Therefore, the resultant density of the tablet becomes lower than that of gastric fluid leading to the floatation of the tablet in the floating medium. The two parameters floating lag time (FLT) and total floating time (TFT) are generally used to define the magnitude of the floating efficiency of the device. The FLT was taken as response variable in this study as it changes with different formulations whereas TFT remains constant in all designed formulations (more than 16 hours) and it is not taken as response variable. The ANOVA study yielded the regression model for FLT, which was as follow:

FLT = +3.88 + 0.13A + 0.88B - 1.37C + 0.12AB-0.13AC+0.13BC-0.63ABC [A= HPMC K4M, B = HPMC 100M, C= $NaHCO_3$] (Table 5).

The values of the coefficients of different independent variables in the model equation for FLT indicate that floating lag time is mainly influenced by $NaHCO_3$ and comparatively less influenced by HPMC K4M and HPMC 100M. But the effect of the $NaHCO_3$ is negative that means increase in the concentration of sodium bicarbonate decreases the floating lag time whereas the effect of other two variables are positive. This may be due to the fact that more $NaHCO_3$ produces more CO_2 that enhance the buoyancy, but on the other hand, hydrophilic polymers HPMC K4M and HPMC 100M absorb water and thus increase the weight of the tablet and finally decrease the buoyancy. The influence of HPMC 100M is greater than that of HPMC K4M, because HPMC 100M has higher molecular weight and contains more hydrophilic groups and therefore absorb more water than HPMC K4M. Other coefficients in the model equation indicate there are interactions between the independent variables significantly. 3-D curve for FLT **(**Figure 2) showed the effects of independent variables on the floating lag time. The study also showed that the tablet once floated, maintains its buoyancy level over a long period of time (>16 hours). The tablet does not undergo disintegration because it contains hydrophilic polymers that absorb water and form a gel. Therefore there is no chance of escape of CO_2 from the interior bulk of the tablet to the outside. This ensures the continued floatability of the tablet in the floating medium.

In vitro dissolution study showed drug-release over 16 hour period from different designed formula (Figure 1). Fitting of the dissolution data into different release kinetic models revealed

that the kinetic of drug-release follows zero order and Korsmeyer-Peppas (KP) models (Table 3). The exponent values of KP model obtained were near 1.0 (0.5<n<1), which indicates drug-release by both fickian diffusion and subsequent erosion of the matrix[26]. A barrier gel layer was found to form around the outer surface of the tablets. The tablets were also found to swell up because of uptake of water by hydrophilic polymers such as HPMC K4M and HPMC 100M. This outer gel layer actually controls the drug release. Diffusion of drug occurs from this gel following Fick's first law of diffusion. The outer barrier gel layer was found to propagate gradually towards the interior of the tablets. The surface erosion was also found in later stage of dissolution when viscosity of the outer gel layer drops significantly. The great deviation of 'n' value of KP model from 0.5 (value indicating fickian diffusion) might be due to the surface erosion (Table 3). Cumulative percent drug release at 4h, 8h, 12h and 16h were considered as response variables. The ANOVA study yielded best fitting polynomial regression equations for each response variable.

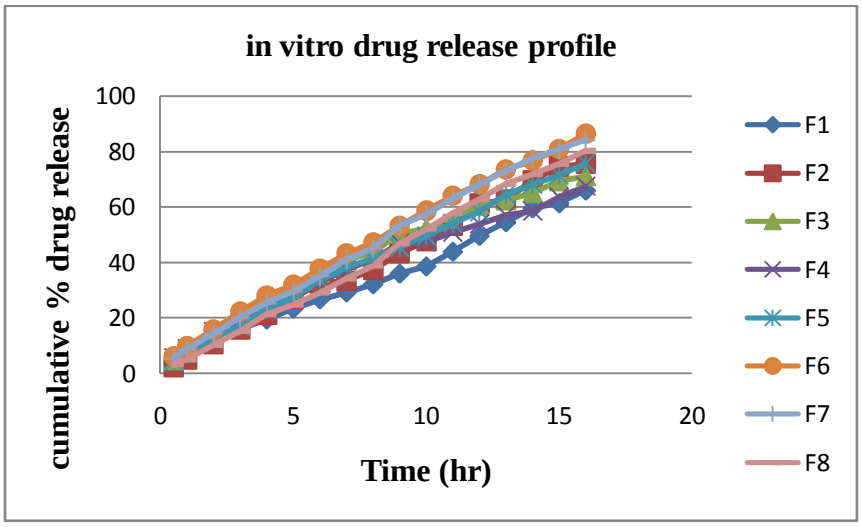

Figure 1: In vitro drug release profile (zero order)

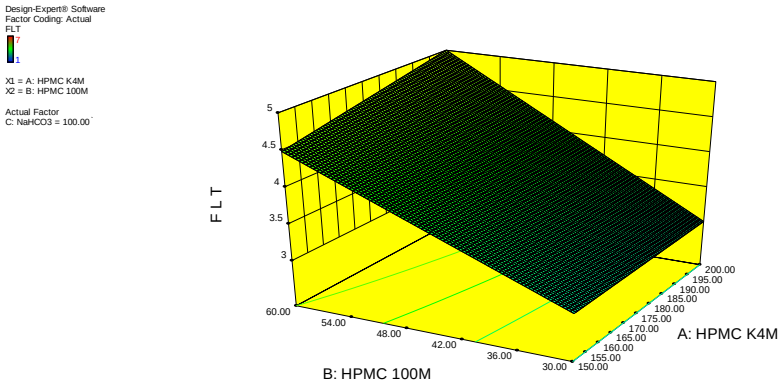

Figure 2: 3-D curve for response floating lag time

Table 3: R^2value of different kinetic models of in vitro dissolution data

Formulation code	Zero order	First order	Higuchi	Hixon-Crowell	Peppas-Koresmeyer R^2	n
F_1	0.9942	0.8639	0.9538	0.9789	0.9954	0.8119
F_2	0.9959	0.8065	0.9661	0.9815	0.9968	0.9988
F_3	0.9821	0.8100	0.9928	0.9980	0.9976	0.8005
F_4	0.9843	0.8261	0.9921	0.9955	0.9989	0.7238
F_5	0.9975	0.8499	0.9770	0.9917	0.9985	0.8397
F_6	0.9973	0.8603	0.9789	0.9853	0.9980	0.7775
F_7	0.9973	0.8667	0.9726	0.9870	0.9967	0.8212
F_8	0.9976	0.8583	0.9599	0.9823	0.9966	0.9635

The regression model of CPR4h was:

CPR_{4h} = +23.39 + 0.95A + 1.63B - 0.82C - 0.54AB - 1.47AC (Table 5)

The regression coefficients of the independent variables in the model equation demonstrate that the effects of HPMC K4M and HPMC 100M on CPR_{4h} are positive whereas the effect of $NaHCO_3$ is negative. HPMC 100M has 1.72 fold effects on CPR4h compared to HPMC K4M. HPMC 100M having higher molecular weight and more number of hydrophilic groups in its molecules, can uptake more water resulting formation of low-viscous gel layer which is rapid erosion-prone. This disable HPMC 100M to retard the drug release to a greater extent like HPMC K4M. Figure. 3 has demonstrated the effect of formulation variables on the CPR4h. The experiment also demonstrates the interaction effect of the formulation variables.

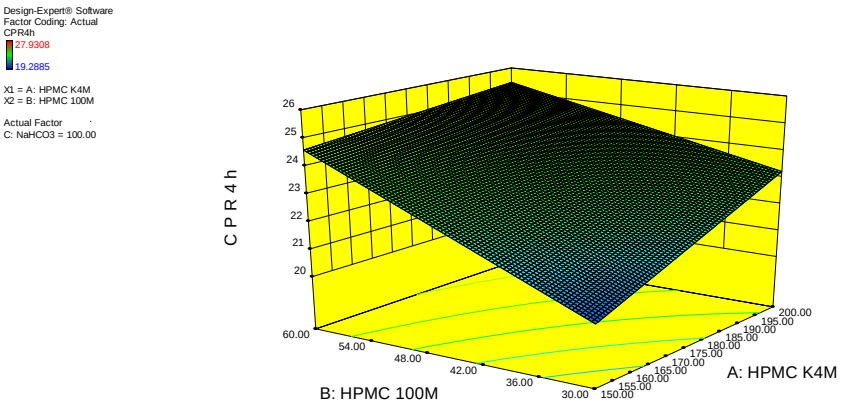

Figure 3: 3-D curve for response CPR_{4h}

The regression equation of CPR8h was:

CPR_{8h} = +40.79 + 2.3A + 2.49B - 0.49C - 1.31AB - 2.47AC (Table 5)

The effects of the formulation variables on the CPR8h demonstrated by the regression coefficients and figure. 4 are shown similar with their effects on CPR4h. It may be due to the fact that the water uptake kinetic was similar up to 8 hours period and the drug release kinetic is

greatly dependent on the water uptake and swelling kinetic of the hydrophilic components present in the formulation.

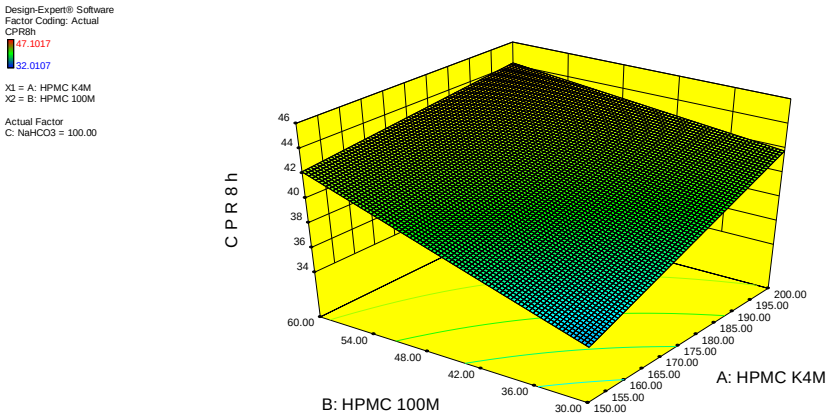

Figure 4: 3-D curve for response CPR_{8h}

The regression equation of CPR12h was:

CPR_{12h} = +60.31 + 4.06A - 0.077B + 0.38C - 1.02AB - 4.17AC - 1.22BC (Table 5) The effects of HPMC K4M and $NaHCO_3$ on CPR_{12h} are positive whereas the effect of HPMC 100M is negative. The regression coefficients in the model and Figure 5 demonstrate that there is a great effect of HPMC K4M on CPR12h compared to very little effect of HPMC 100M. This might be due to gradual drop in the rigidity of three-dimensional polymeric network in the later stage of dissolution. A significant interaction between HPMC K4M and sodium bicarbonate has also been demonstrated by the regression coefficient. The positive effect of sodium bicarbonate can be explained by the fact that in later stage of dissolution the water present in the matrix of the tablet dissolve CO_2 gas resulting drop in pH towards acidic that further increase the solubility of the drug in the more acidic fluid present in the interstitial channel of the matrix and thereby the rate of diffusion of the drug. The regression equation of CPR16h was:

CPR_{16h} = +75.82 + 5.84A - 0.66B - 0.16C - 3.46AC - 1.61BC (Table 5)

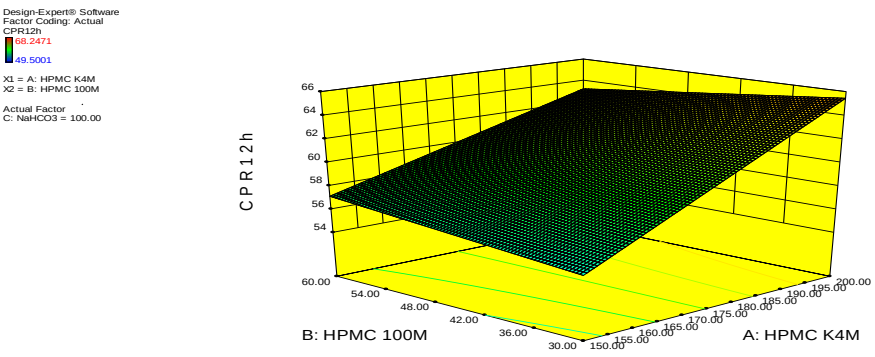

Figure 5: 3-D curve for response CPR_{12h}

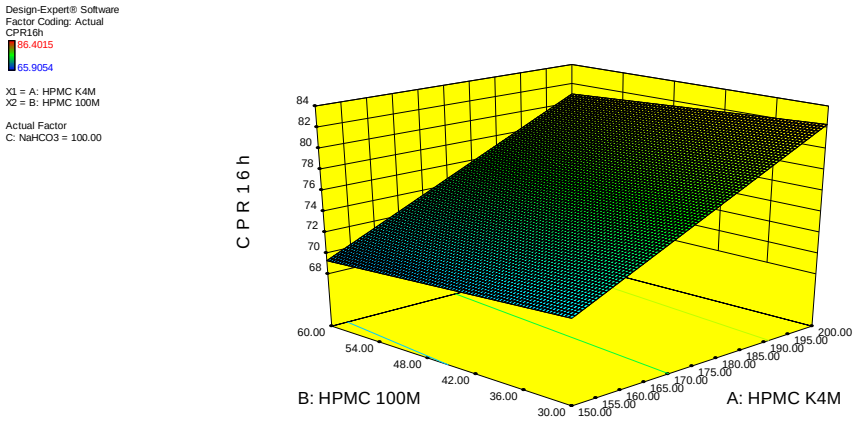

Figure 6: 3-D curve for response CPR_{16h}

The effects of the formulation variables on the CPR16h demonstrated by the regression coefficients and figure. 6 are shown similar with their effects on CPR12h with exception negative effect of sodium bicarbonate that can be explained by the fact that un-reacted $NaHCO_3$ may neutralize the acidic pH of the fluid present in tablet matrix and interstitial channel and thereby further decrease in the solubility of the drug resulting decrease in the rate of diffusion. In all cases of release response there are significant interactions between the independent variables.

The ANOVA study of each of the response variables yielded the best fitting polynomial model for that variable. Only those models were considered which had a high F-value corresponding to $p< 0.05$ (Table 5). The 5 polynomial models were then solved simultaneously by numerical methods keeping the target values as given in the Table 4 to obtain optimized formula. The target for CPR4h, CPR8h, CPR12h, CPR16h and FLT were set at 25%, 40%, 60%, 80% and 1 min respectively. The optimized levels of formulation-variables were HPMC K4M 200 mg, HPMC 100M49.22 mg and sodium bicarbonate 119.59 mg. After optimization, the floating tablets were prepared as per the optimized formula and evaluated. The study showed 21.9%, 41.32%, 62.67% and 76.82% drug release at 4h, 8h, 12h and 16h respectively resulted from the optimized floating tablet. The FLT observed was 2.80 mins. The comparison of observed values with the predicted and target values revealed closeness to the target and predicted values of the responses (Table 4).

Table 4: independent formulation variables and dependent variables with different values

Sr. no.	Independent variables	Dependent variables/response	Target value of response	Predicted value	Obtained value
1	HPMC K4M	FLT	1 min	2.67 min	2.80 min
2	HPMC 100M	CPR_{4h}	25%	22.4%	21.9%
3	$NaHCO_3$	CPR_{8h}	40%	40.52%	41.32%
4	-	CPR_{12h}	60%	60.0%	62.67%
5	-	CPR_{16h}	80%	77.49%	76.82%

Table 5: Polynomial equations of different response generated by Design-Expert (8.1)

Response	Best fitting polynomial equations(in terms of coded factors)
Floating lag time	FLT = +3.88 + 0.13A + 0.88B - 1.37C + 0.12AB-0.13AC+0.13BC-0.63ABC
CPR_{4h}	CPR_{4h} = +23.39 + 0.95A + 1.63B - 0.82C - 0.54AB - 1.47AC
CPR_{8h}	CPR_{8h} = +40.79 + 2.3A + 2.49B - 0.49C - 1.31AB - 2.47AC
CPR_{12h}	CPR_{12h} = +60.31 + 4.06A - 0.077B + 0.38C - 1.02AB - 4.17AC - 1.22BC
CPR_{16h}	CPR_{16h} = +75.82 + 5.84A - 0.66B - 0.16C - 3.46AC - 1.61BC

CONCLUSION

The purpose of the present study was to develop an optimized gastric floating once-daily matrix tablet of ofloxacin (FERMTs) using hydrophilic polymers such as HPMC K4M, HPMC 100M, isapagulha husk and sodium bicarbonate as buoyancy contributer. On the basis of in vitro evaluations, an optimized tablet formulation was obtained, that showed an optimum floatability and an excellent extended release profile that may be utilized to meet once-daily facilities of drug delivery device. In addition, it needs to be mentioned that future research work should include the evaluations of the in vivo gastric retention capacity as well as in vivo drug release profile both in animal and human models as well as elaborate clinical trials in order to place it as a marketable product.

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