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Influence of Sodium CMC and HPMC on the Physical Characteristics of Ofloxacin Floating Matrix Tablets

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Authors' contributions

This work was carried out in collaboration between all authors. Author PK has designed the study, author BRC has written the protocol and managed the literature survey, author VD has drafted the manuscript and author NTH has managed the analyses of the study. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Sustained release floating drug delivery systems or gastro retentive drug delivery systems enables prolonged and continuous input of drug to the upper part of gastrointestinal tract and improves the bioavailability of medication. A new strategy is proposed for the development of floating drug delivery systems of Fluoroquinolone antibiotic, Ofloxacin, a potent moiety for treating UTI's.
Methodology: Various rate retarding polymers like HPMC K4M, HPMC 5 cps and swelling agent as Sodium carboxymethyl cellulose in different proportions were tried and optimized to achieve the drug release for 8 hr. All the formulations were evaluated for floating properties, swelling characteristics and *in vitro* drug release studies. The *in vitro* drug release was found to be matrix diffusion controlled. Optimized formulation was subjected to intermediate stability studies at various combinations of temperature and humidity according to ICH guidelines.
Results: Lower hardness and higher thickness decreased the floating lag time and increased floating duration. Based on drug release studies, formulation F5 was optimized as the best formulation because it released about 89.27 ±2.6% of the drug at the end of 8

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hr while other formulations released not more than 80 ±2.2%. This may be due to high NaCMC content which might have caused excessive channeling, thereby giving a burst release. Optimized formulation F5 was found to follow zero order kinetics with r^2 value of 0.993.

Conclusion: In conclusion we have been proved that HPMC K4M has retarded the drug release, while HPMC 5cps has facilitated high buoyancy time for the tablets. NaCMC has influenced as channeling agent. Formulation F5 was optimized for its long buoyancy time, prolonged duration of drug release, zero order and diffusion controlled drug release kinetics which can assure 100% bioavailability.

Keywords: Floating drug delivery; diffusion controlled; HPMC; Sodium CMC; ofloxacin.

1. INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation especially for sustained release [1]. The de novo design of an oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. Floating drug delivery system (FDDS) exerts buoyancy in stomach for extended period of time thereby offer prolonged gastric residence time ensuring favourable bioavailability [2]. These attempts include introducing floating dosage forms (gas generating systems and swelling or expanding systems) [3-6], mucoadhesive systems [7], high density systems, modified shape systems, gastric emptying delaying devices and co-administration of gastric emptying delaying drugs. Swelling systems are also referred to as plug type systems [8,9].

The principle of floating preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [5]. Floating drug delivery system also known as hydrodynamically balanced system, have a bulk density lower than gastric fluids and thus remain buoyant in the gastric fluids for a prolonged period of time without affecting the gastric emptying rate. The presence of polymers in the systems promotes their swelling to a size that prevents their passage through pyloric sphincter resulting in prolonged GRT. However, a balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to achieve optimum benefits and to avoid unwanted side effects [9,10]. Ofloxacin is a fluoroquinolone antibacterial agent which is highly effective against gram positive and gram negative bacteria [11]. While the solubility of ofloxacin in water is 60 mg/ml at acidic pH of 2-5, it shows as low as 4 mg/ml at pH 7. Earlier studies reported on the formulations of ofloxacin gastroretentive systems using natural polymers and various grades of HPMC [12-14]. We have also reported on the formulation and evaluation of lamivudine multiunit floating dosage forms using novel lipoidal polymers [15]. There are no reports found on the influence of NaCMC along with HPMC on the characteristics of ofloxacin floating matrix tablets. Hence, in the present investigation we have studied the influence of various hydrophilic polymers such as sodium carboxymethyl cellulose (NaCMC), HPMC K4M and HPMC 5 cps on the *in vitro* characteristics of floating matrix tablets of ofloxacin.

2. MATERIALS AND METHODS

Ofloxacin, polyvinyl pyrollidone K-30 (PVP K30), hydroxypropyl methyl cellulose (HPMC K4M and HPMC 5 cps) were gratis samples from Alkem Labs, Mumbai. Sodium carboxymethyl cellulose (NaCMC), sodium bicarbonate, citric acid anhydrous, magnesium stearate, and isopropyl alcohol were purchased from SD Fine Chemicals, Mumbai, India. All other chemicals used were of analytical grade.

2.1 Formulation of Floating Tablets of Ofloxacin

Floating tablets of ofloxacin were prepared by wet granulation method as per the formulation design shown in Table 1. The intra-granular ingredients were blended and mixed with the solution of PVP K30 in isopropyl alcohol to make a wet mass. The granules were prepared by passing the wet mass through No. 18 mesh and drying 50ºC for 1 hr in a hot air oven. The dried granules were passed through No. 22 mesh and the extra-granular mass was added and blended for 5 min. Matrix tablets were compressed on 8-station mini rotary tableting machine (Cadmach, India) with 12 mm flat shaped punches. Tablets of batches F1-F4 did not contain intra-granular NaCMC.

Table 1. Composition of the formulations F1 to F10

Name of excipients	Weight of excipients (mg)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Intra granular										
Ofloxacin	200	200	200	200	200	200	200	200	200	200
HPMC K4M	100	50	50	65	65	65	65	65	65	65
HPMC 5cps	150	200	125	90	90	86	100	80	90	90
Na CMC	-	-	-	-	8	10	8	8	8	8
NaHCO3	25	25	25	27.5	27.5	27.5	22.5	32.5	27.5	27.5
Citric acid anhydrous	19	19	19	22.5	22.5	22.5	22.5	22.5	22.5	22.5
PVP K-30	40	40	20	25	25	25	25	25	25	25
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular										
Na CMC	12	12	12	16	8	10	8	8	8	8
$NaHCO_3$	25	25	25	27.5	27.5	27.5	22.5	32.5	27.5	27.5
Citric acid anhydrous	19	19	19	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Magnesium stearate	6	6	5	4	4	4	4	4	4	4
Tablet weight	596	596	500	500	500	500	500	500	500	500

2.2 Physical Properties of Tablets

All prepared floating tablets were evaluated for their thickness, weight variation, hardness and friability according to official methods [16]. The weight variation was determined by taking 20 tablets using an electronic balance (Shimadzu, Japan). Tablet hardness (n=6) was determined using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics).

FTIR spectroscopic analysis of ofloxacin and formulation (F5) was conducted using Perkin Elmer Spectrum RX (Thermo Scientific, Mumbai, India). Finely powdered dry samples were

blended with KBr (1:100 ratio w/w) to make a pellet. The detector was purged using nitrogen gas. The spectra were collected in the 400-4000 cm^{-1} with 8 cm^{-1} resolution, 60 scans and beam spot size of 10-100 µm.

2.3 Drug Content Uniformity

Ten tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with 0.1N HCl (pH 1.2 buffer) and the solution was filtered through 0.45 µ membranes. Each extract was suitably diluted and analyzed at 294 nm using UV-visible spectrophotometer (Aquamate, Thermo Scientific, Mumbai, India) [13].

2.4 *In vitro* Buoyancy Study

The randomly selected tablets (n=6) from each formulation were placed in a 900 ml glass basket containing simulated gastric fluid USP maintained at 37±0.5ºC. The time taken for the tablet to rise to the surface and float was taken as floating lag time. The overall floating time was calculated during the dissolution studies [17]. The floating lag time and the floating duration were reported. The formulations which did not float or which did not have a long floating duration were exempted from further drug release studies.

2.5 *In vitro* Drug Release Studies

In vitro drug release studies (n=3) were carried out using USP XXII dissolution apparatus type II (Labindia, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of 0.1N HCl, maintained at 37 ±0.5ºC. A 5 ml of dissolution samples were drawn at every 1 hour interval and replaced with an equal volume of 0.1N HCl to maintain the volume constant. The sample solution was diluted sufficiently and analyzed at 294nm using an UV-visible spectrophotometer (Aquamate, Thermo Scientific, Mumbai, India) [13]. Out of the 10 formulations, seven formulations were taken for the dissolution studies. Dissolution for F1, F2 and F10 was not done since they were not meeting the specific characteristics for floating tablets.

2.6 Kinetic Model Fitting of the Dissolution Data

The dissolution data obtained was fitted into various models and the formulation best followed which type of model was decided based on the regression value. The mechanism of the drug release and rate kinetics of the dosage form was fitted into zero order, first order and Higuchi release models [18].

2.7 Stability Studies

The short-term stability studies were carried out for a period of three months for the optimized formulation F (5) according to ICH guidelines. The optimized formulation was subjected to stability study at 25 ± 2ºC and 60 ± 5% RH 40 ± 2ºC and 75 ± 5% RH for 90 days. The samples were evaluated for physical changes, hardness, friability, drug content, buoyancy study and percentage drug release during the stability studies [19]. The dissolution profile values were compared using similarity factor (f2).

2.8 Comparison with Marketed Formulation

In vitro dissolution study of the marketed product (Zanocin – OD 400mg) was carried out to compare the drug release profile with that of the formulated ofloxacin floating tablets. The same dissolution method used for the formulations was used for the marketed formulation. In addition dissolution was also carried out in pH 6.8 phosphate buffer to study the release of the drug [20].

3. RESULTS AND DISCUSSION

The gastro retentive formulations of F1 to F10 were prepared using wet granulation method and the influence of polymers and other physical parameters were evaluated in the present study. HPMC K4M was used as the rate retarding polymer while HPMC 5cps was used because its low density helps in floating of the tablet due to its swelling property which decreases the tablet density in solution and gives buoyancy. NaCMC was used as a channeling agent which guides water into the tablet by forming pores due to its swelling property. Sodium bicarbonate and citric acid anhydrous together were used as the effervescent agents which give a quick thrust to the tablet to float immediately. Magnesium stearate was used as the lubricant while PVP K30 and IPA were used in as binding solution. The effervescent agent was added in equal amounts both in the intra granular and the extra granular parts so as to provide continuous thrust throughout the floating time of the tablet. NaCMC was used totally in the extra granular part up to F4 and then divided equally in to both phases from F5 to F10. Formulations from F1 to F6 were prepared for optimizing the formula. Further optimization was done by varying sodium bicarbonate levels (F7 and F8) and varying the hardness (F9 and F10). FTIR studies showed the characteristic stretching peaks for C-F (1457.70), C=C-O-C (C-O 1072.31), -CH3 (C-H 2968.12),-COOH (C=O 1711.55) - COOH (O-H 2755.71) and aromatic (Ar-H 3042.49) groups were observed in both the spectra of pure drug and formulation F5 which revealed that there is no drug-polymer interaction (Fig. 1).

3.1 Physical Properties of Tablets

The tablet parameters i.e., weight variation, hardness, thickness and friability and the assay values were all found to be within the specified limits. The floating lag time for all the formulations was found to be less than 15 seconds, except for F1 and F2. The formulations F1 did not float and F2 took 9 ±0.5 min to float. The floating duration in all the formulations was found to be more than 24 hr except in F1, F2 and F10 while F1 and F2 did not have the required thrust while F10 had high hardness. The formulation F5 has shown 24.2 ±0.3 hr buoyancy time. Each batch of the tablets was analyzed for the drug content and all the batches were found to be within the limits of 98.67 ±2.18 to 104.93 ±4.84% as shown in Fig. 2.

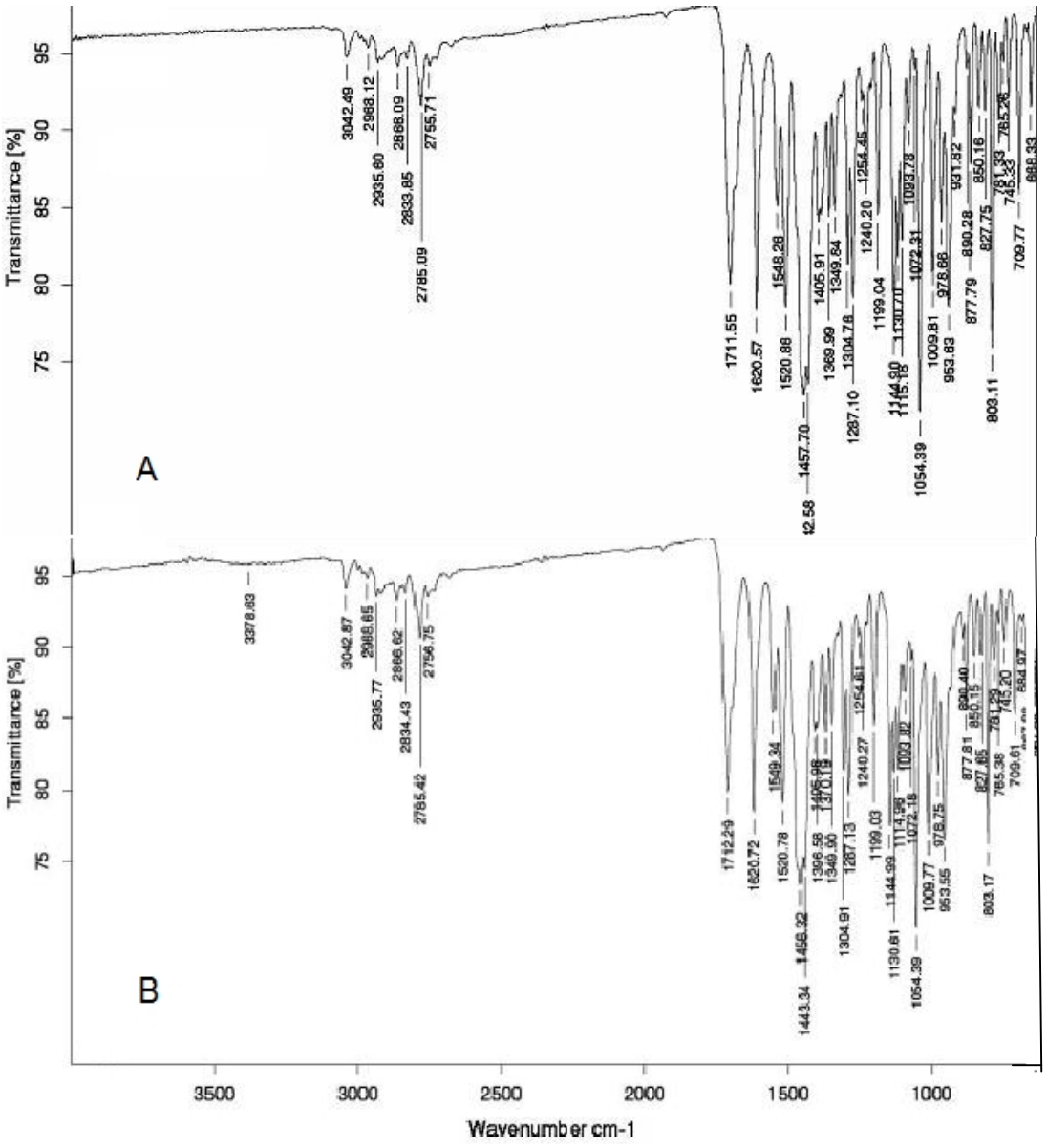

Fig. 1. FTIR spectra of (A) ofloxacin and (B) formulation F5

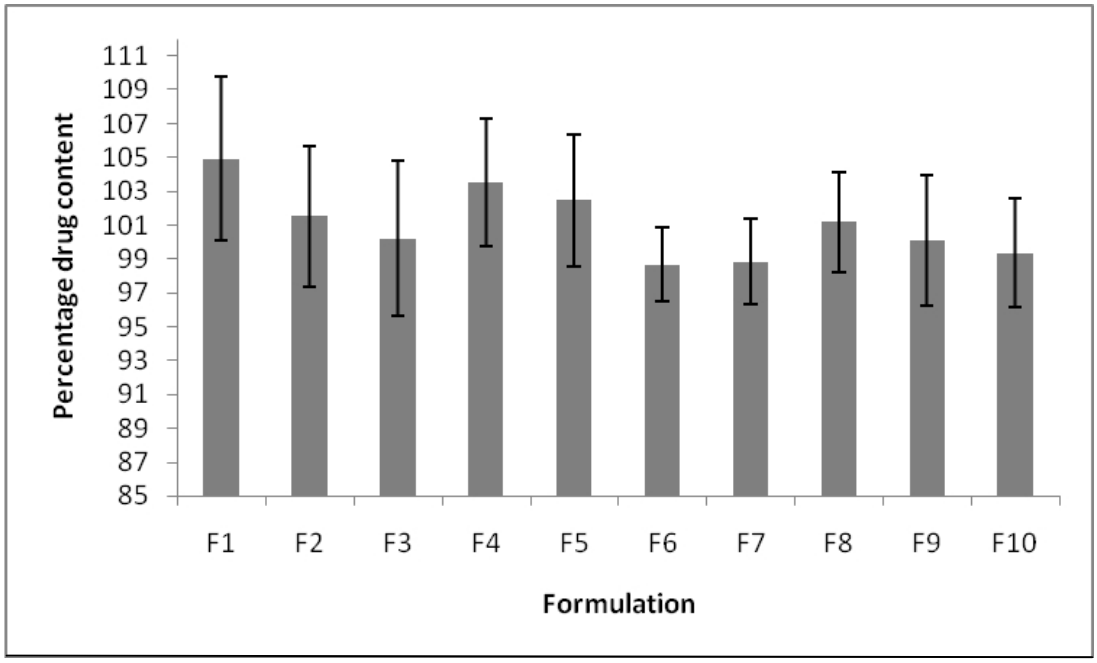

Fig. 2. Comparison of assays of different formulations

It was observed that the hardness and thickness of the tablets influenced floating properties and summarized in Figs. 3 and 4. Lower hardness and higher thickness decreased the floating lag time and increased floating duration. Formulations F9 and F10 were prepared with decreased and increased hardness respectively to study its effect on the dissolution with comparison to the hardness of the optimized formulation (F5). Formulation F10 failed to pass the floating duration hence was exempted from the dissolution study.

Matrix integrity of the tablets is an important parameter that needs to be studied in case of oral sustained release tablets. If the tablet does not maintain its physical integrity, it could be broken down into smaller fragments and escape from the upper part of the GI tract [21]. We found that all the formulations maintained integrity during the total floating duration. Earlier studies showed that >15% w/w concentration of HPMC K4M was needed to maintain the integrity of the floating tablets [22]. But the combination of HPMC K4M and HPMC 5cps in the concentrations of >8.4% w/w (F2) and >16.77 w/w (F8) respectively could have contributed for maintenance of tablet integrity in this study (Table 1). Further, HPMC 5cps exerts excellent water retaining property and could have further maintained the integrity of tablets. Although <10% w/w of $NaHCO_3$ was found optimum to maintain integrity of tablets [22], we have used 8-13% w/w of $NaHCO_3$ which was equally divided in the intra and extragranular levels of the tablets. This has helped the formulations to maintain integrity.

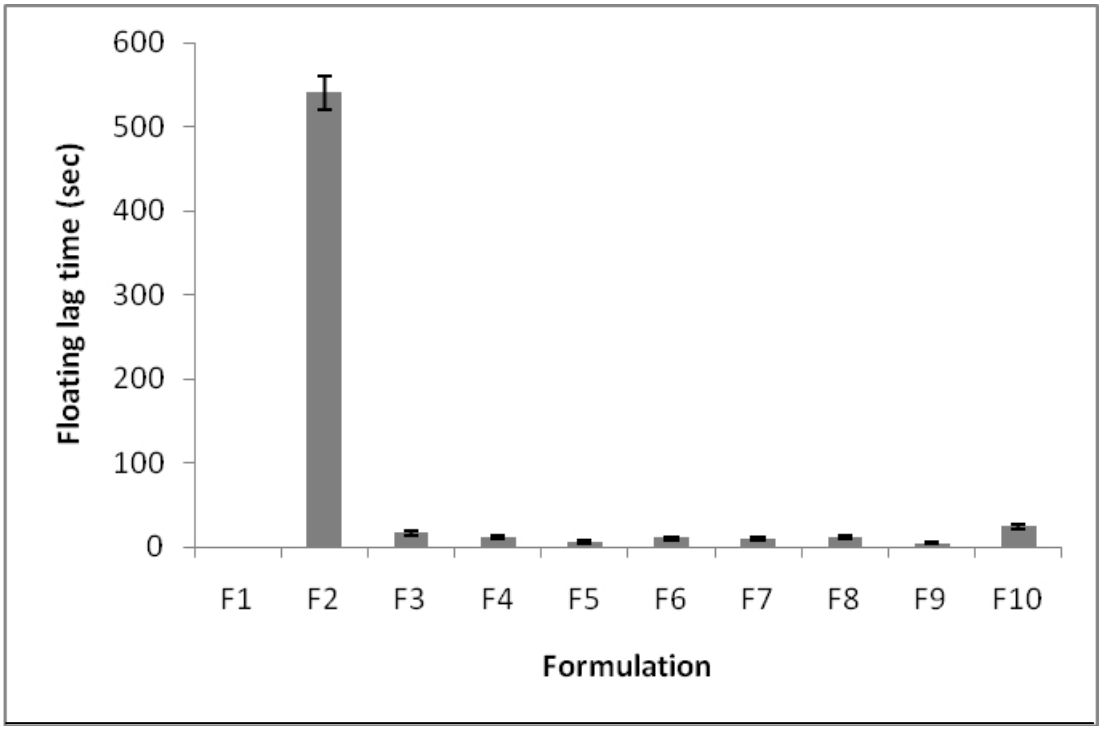

Fig. 3. Floating lag time of the formulations

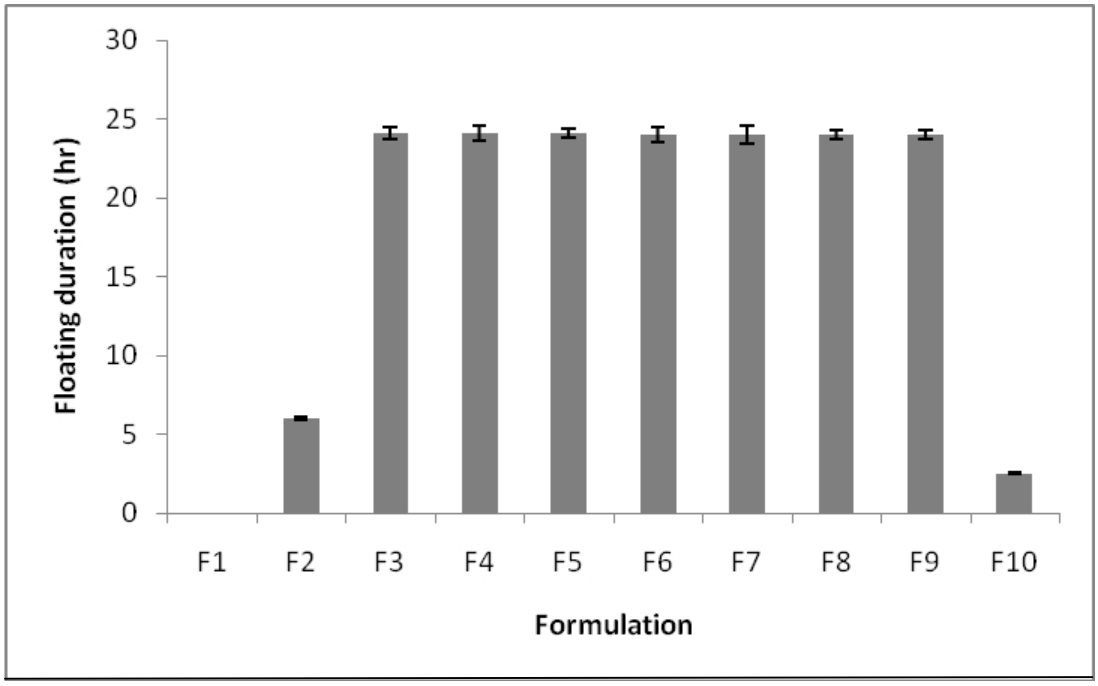

Fig. 4. Floating durations of the formulations

3.2 *In vitro* Drug Release Studies

In vitro drug dissolution studies of the formulations were carried out and the results are summarized in Fig. 5. After conducting the drug release studies, formulation F5 was optimized as the best formulation because it released about 89.27 ±2.6% of the drug at the end of 8 hr while other formulations released not more than 80% ±2.2. All the formulations showed a good linearity except F6 which showed burst effect and released 50.93 ±1.9% within 0.5 hr. This may be due to high NaCMC content which might have caused excessive channeling, thereby giving a burst release. Formulations F1 did not float and F2 and F10 had very small floating duration (6 and 2.5 hr). Hence, were exempted from drug release studies. Formulations F7 and F8 were prepared with a 2% decrease and increase of sodium bicarbonate levels respectively in the two formulations to study its effect on the dissolution with comparison to the optimized formulation F5.

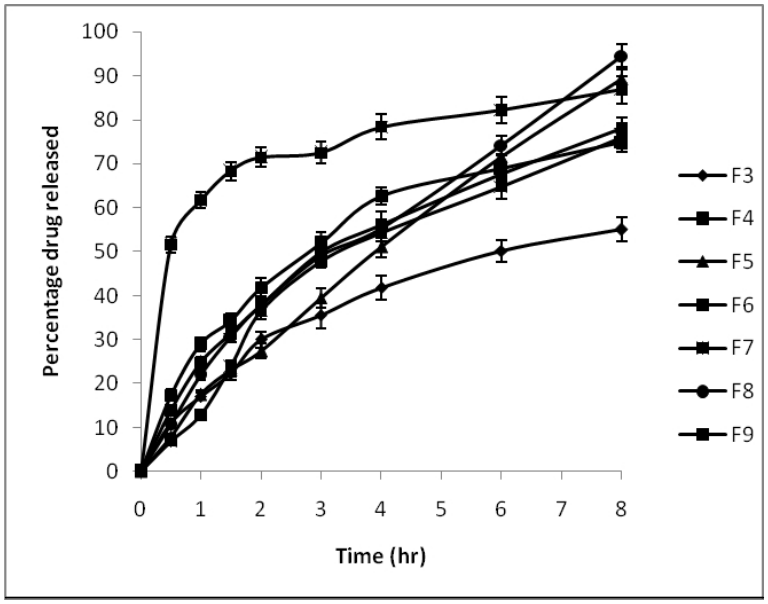

Fig. 5. Dissolution profile of formulations

3.3 Kinetic Model Fitting of the Dissolution Data

Modeling of the drug release was done using the best-fit method. The release was plotted according to the zero order, First order and Higuchi's equations graphically and the regression coefficient values were studied. Optimized formulation F5 was found to follow zero order kinetics with r^2 value of 0.993 (Figs. 6-8). Formulations F3, F4, F7 and F9 were found to follow first order kinetics as well as Higuchi's kinetics showing that drug release took place through porous matrix systems with freely soluble drug since ofloxacin is freely soluble at low pH conditions. Formulation F6 failed to follow any release mechanism since there was burst release which might be due to excessive channeling and swelling because of higher NaCMC. The formulation F8 was nearly following Higuchi's kinetics since the r^2 value was 0.973. The effect of sodium bicarbonate on the drug release was studied with low and high contents in F7 and F8 respectively. The formulation F7 showed slightly reduced drug release while F8 showed slightly higher release while both were following Higuchi's

release kinetics. This may be because F7 had lower sodium bicarbonate levels which provided lesser channeling for the drug to release and the opposite is the case for F8 (Fig. 9).

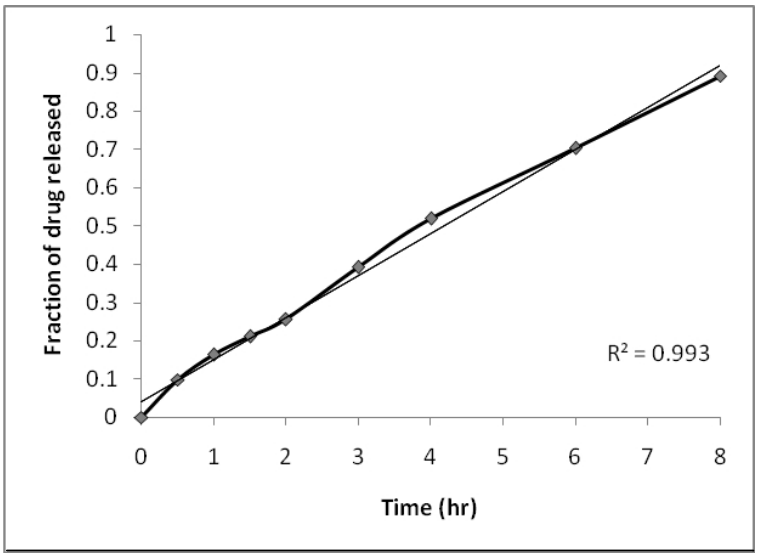

Fig. 6. Zero order release kinetics of optimized formulation (F5)

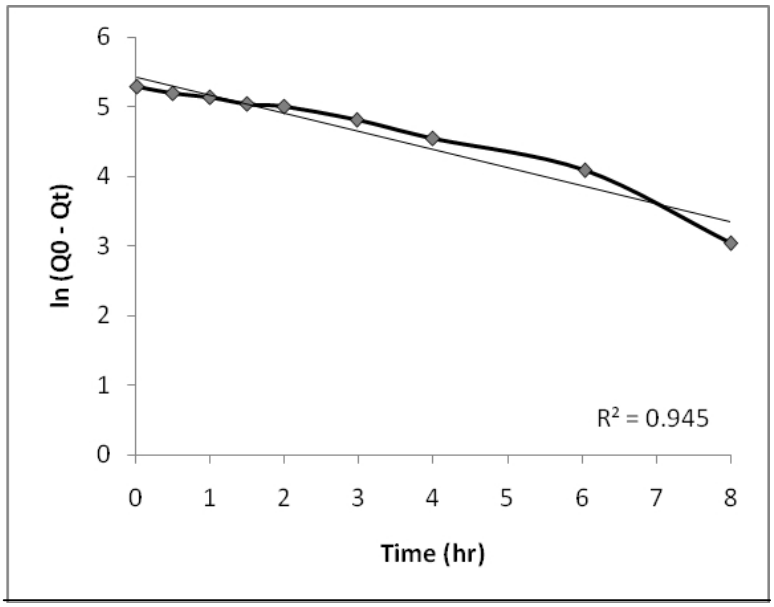

Fig. 7. First order release kinetics of optimized formulation (F5)

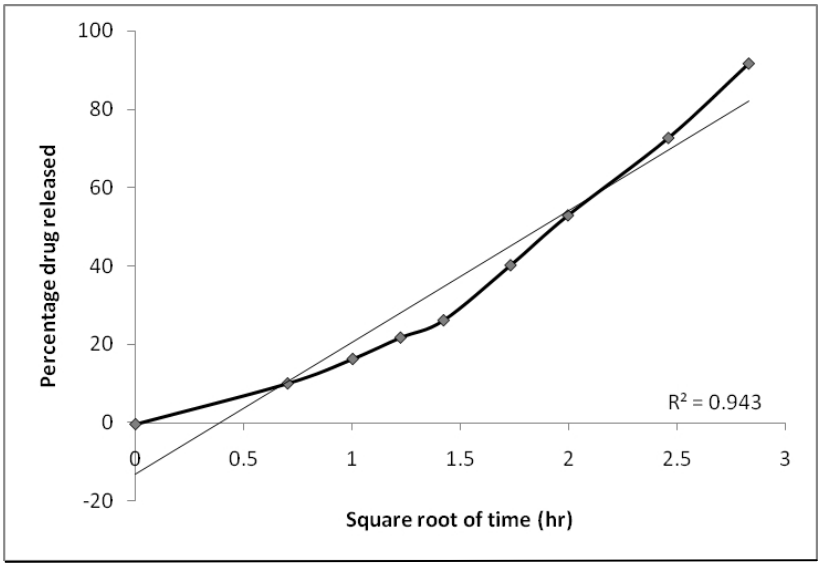

Fig. 8. Higuchi's release kinetics of optimized formulation (F5)

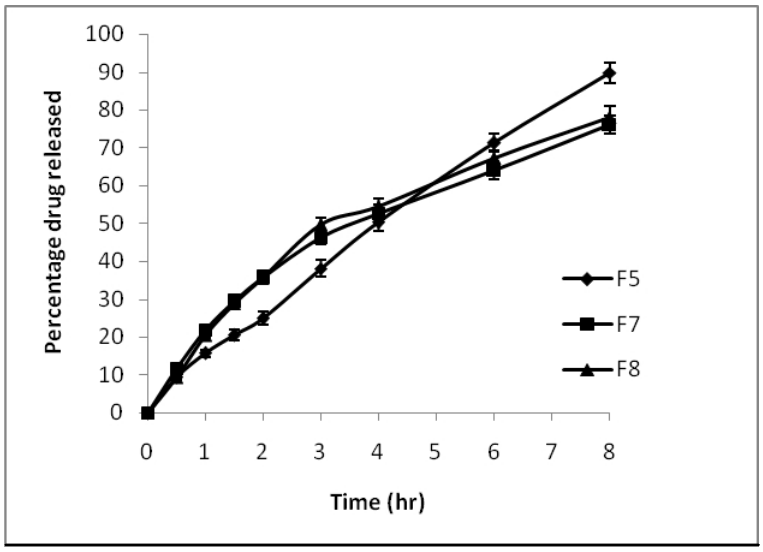

Fig. 9. Effect of sodium bicarbonate on dissolution

3.4 Effect of Hardness on Floating Properties and Drug Release

The effect of hardness showed an impact on floating properties of the tablets as shown in Fig. 10. The formulation with higher hardness (11.29±0.18) i.e. F10 though having a short lag time (15 ±3 sec), floated only for 2.5 hr. The formulation with lower hardness F9 showed release similar to F5 up to 4 hr. Last two time points showed reduced release which might be due to excessive swelling of the polymer thereby retarding the drug release after 6 hr.

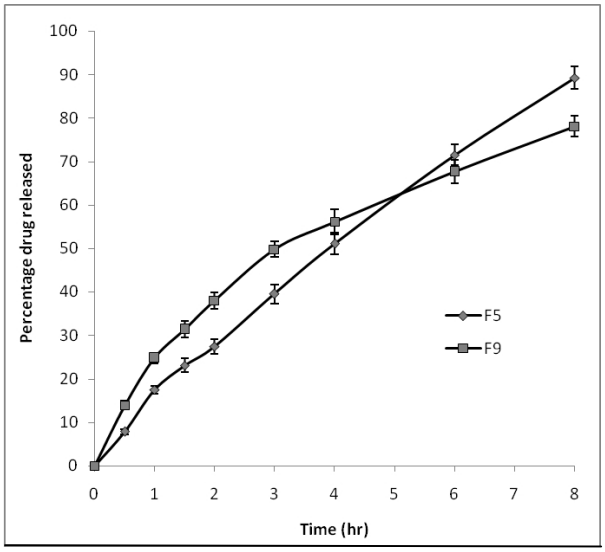

Fig. 10. Effect of hardness on dissolution

3.5 Stability Studies

The stability studies were carried out with the optimized formulation (F5) for three months under two conditions i.e. 25ºC/60% RH and 40ºC/75% RH for 90 days as per ICH guidelines. The physical parameters, assay and dissolution data were found to be similar to those of the optimized formulation F5 (Figs. 5, 11 and 12). An average difference of 10% at all measured time points results in a f2 value of 50. Calculating of similarity factor (f2) is a measure of finding similarity in drug release profiles of different formulations during dissolution study. The similarity factor obtained between the stability samples and formulation F5 was 57.6 ±6.9% which indicates that the variation in dissolution profiles were below <10%. This demonstrated the stability of the formulation.

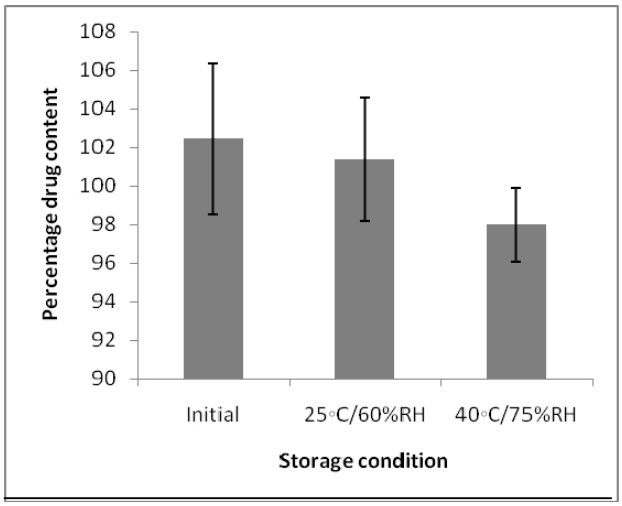

Fig. 11. Stability data of optimized formulation F5

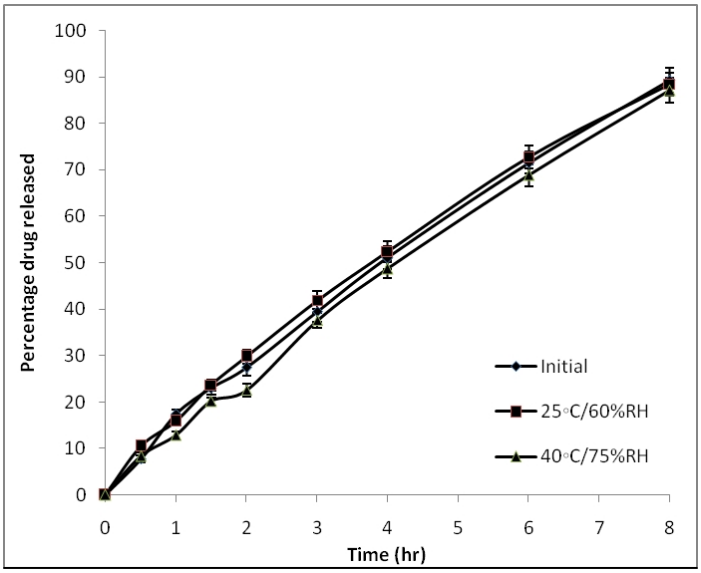

Fig. 12. Stability of dissolution profile for optimized formulation F5

3.6 Comparison with Marketed Formulation

There is no available marketed floating formulation of ofloxacin and hence the marketed extended release formulation (Zanocin-OD) was chosen for comparison of the dissolution profile. Dissolution in 0.1N HCl showed a release of 63.5 ±2.1% at the end of 8 hr where as dissolution in pH 6.8 phosphate buffer showed a release of only 13.39 ±0.7% which clearly shows that ofloxacin is poorly soluble in higher pH conditions (Fig. 13). Zanocin-OD being given as once daily tablet might not release the drug efficiently after entering small intestine due to high pH. This might lead to lower bioavailability of the drug in this formulation.

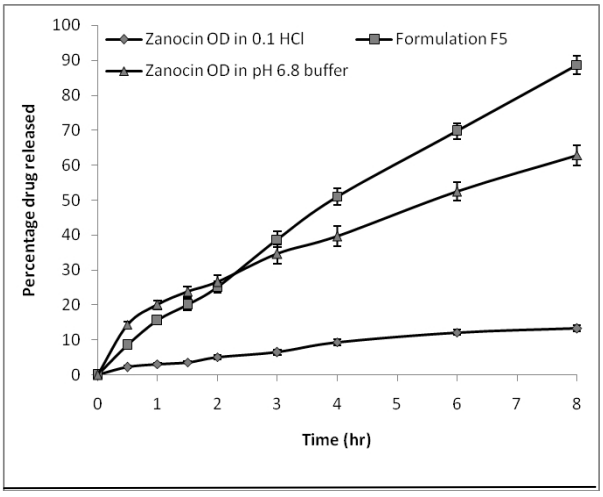

Fig. 13. Dissolution profile of marketed formulation

4. CONCLUSION

In conclusion from the present study we reveal that employed polymers influence for fabrication of successful gastro retentive tablets of ofloxacin. It has been proved that HPMC K4M has retarded the drug release, while HPMC 5cps has facilitated high buoyancy time for the tablets. NaCMC has influenced as channeling agent. Formulation F5 was optimized for its long buoyancy time, prolonged duration of drug release, zero order and diffusion controlled drug release kinetics which can assure 100% bioavailability. Further, imaging studies, pharmacokinetic and pharmacodynamic studies and clinical trials can be performed to develop a marketed formulation of gastro retentive ofloxacin for effective therapy.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

ACKNOWLEDGEMENTS

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COMPETING INTERESTS

The authors declare that there are no competing interests related to this research work.

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