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Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin

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Abstract

Oral sustained release gastroretentive dosage forms offer many advantages for drugs having absorption from upper gastrointestinal tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new gastroretentive sustained release delivery system was developed with floating, swellable and bioadhesive properties. All these properties were optimized and evaluated. Various release retarding polymers like psyllium husk, HPMC K100M and a swelling agent, crosspovidone in combinations were tried and optimized to get the release profile for 24 h. 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. For the developed formulation, the value of n was found to be 0.5766 while for the marketed formulation the value was 0.5718 indicating the anomalous transport. The high water uptake leading to higher swelling of the tablet supported the anomalous release mechanism of ofloxacin. The similarity factor $f2$ was found to be 91.12 for the developed formulation indicating the release was similar to that of the marketed formulation (Zanocin OD). The swelling properties were increased with increasing crosspovidone concentration and contributed significantly in drug release from the tablet matrix. The bioadhesive property of the developed formulation was found to be significant ($P < 0.005$) in combination as compared to HPMC K100M and psyllium husk alone.

Keywords: Ofloxacin; Gastroretentive delivery; Sustained release; Bioadhesion

1. Introduction

Oral sustained release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems. One of the novel approaches in this area is gastroretentive delivery system (GRDS) (Deshpande et al., 1996; Singh and Kim, 2000) Prolonging the gastric retention of a delivery system is sometimes desirable for achieving therapeutic benefit of drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in or are degraded by the alkaline pH they encounters at the lower part of GIT. GRDSs are thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose. Apart from these advantages, these systems offer various pharmacokinetic advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics.

Gastrointestinal retention depends on many factors such as density of the dosage form, size of the dosage form, fasting and fed condition, nature of the meal taken, sleep, posture, etc. It also depends strongly on a complicated and unpredictable gastric emptying with migrating myoelectric complex motility of the stomach (Talukder and Fassihi, 2004). Various delivery systems like floating, swellable, mucoadhesive, high-density formulations, etc., have been developed to achieve gastroretention (Baumgartner et al., 2000; Li et al., 2003). The above-mentioned approaches for gastrointestinal retention work by one or more of these mechanisms (Chueh et al., 1995). Various formulations like floating microparticles, pellets, tablets, capsules, etc., were evaluated as a GRDS. Among these formulations, the multiparticulate systems (El-Kamel et al., 2001; Efentakis et al., 2000)

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like microparticles and pellets are more advantageous than single unit systems like tablets and capsules.

Our present work includes development of gastroretentive formulation of ofloxacin, and evaluation of floating, swelling and bioadhesive properties of the developed formulations. Ofloxacin exhibits pH dependant solubility. It is more soluble in acidic pH and slightly soluble at neutral or alkaline pH conditions (intestinal environment). Hence, an attempt was made to develop GRDS of ofloxacin which would increase the bioavailability of ofloxacin.

2. Materials and methods

2.1. Materials

Ofloxacin and psyllium husk were obtained as a gift sample from Macleoid Pharmaceuticals, India. HPMC K100M, PVP K30 and crosspovidone were gifted by M/s Rohm Pharma, Germany. Talc and magnesium stearate were gifted by M/s Bayer India Ltd., India. All other solvents and reagents were purchased from Ranbaxy Chemicals, India, and were of analytical grade.

2.2. Methods

2.2.1. Preparation of tablets

Tablets were prepared by conventional wet granulation method. The various excipients used were listed in Table 1. All the excipients were passed through sieve no. 40, mixed and granulated with PVP K30 (5%, w/v, in isopropyl alcohol). The dried granules were lubricated with magnesium stearate and talc and compressed into caplet sized tablets on a Cadmach single station tablet press.

2.2.2. Dissolution study

The release of ofloxacin from the tablets was studied using USP dissolution apparatus I. The dissolution medium was pH 1.2 buffer 900 ml. The temperature was maintained at 37 ± 0.5 °C. The rotation speed was 100 rpm. Five milliliters of aliquot was withdrawn at predetermined time intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 24 h. The medium was replenished with 5 ml of fresh buffer each time. Sample was analyzed by using UV spectroscopy at 291 nm.

The dissolution data obtained were plotted as percent cumulative drug release versus square root of time as per Higuchi equation.

$$Q = Kt^{1/2} \tag{1}$$

The release data were further treated by the Ritger and Peppas equation. The equation was treated logarithmically to determine the value of release exponent, n; the value of n is indicative of mechanism of drug release.

$$\frac{M_t}{M_\infty} = Kt^n \tag{2}$$

2.2.3. Water uptake study

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques (Agarwal and Mishra, 1999; Mohammed and Khedr, 2003). The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900 ml rotated at 50 rpm. The medium was maintained at 37 ± 0.5 °C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) (Gerogiannis et al., 1993) as

$$\mathrm{WU}\,(\%) = \frac{\text{weight of the swollen tablet} - \text{initial weight of the tablet}}{\text{initial weight of the tablet}} \times 100 \tag{3}$$

2.2.4. Bioadhesion study

In vitro tablet bioadhesion studies were done using rabbit stomach tissue (Betageri et al., 2001). The stomach tissue was used immediately for this study. The detachment force, i.e. the force required for separating the tablet from the tissue surface was determined. The study was done using a universal tensile tester (Lloyd Instruments, LR 50K model, UK). The stainless steel plate (L-shape) was fitted by one of its side into the upper and lower jaws of the instrument so as the other surfaces of the plates were facing each other. At the lower plate surface, rabbit stomach tissue was stuck with the glue and on the upper plate tablet was stuck. PBS, pH 7.4, was used as a medium and 20 μl was spread on the surface of contact of the tissue. Then the upper jaw with tablet stuck on the plate was lowered slowly so that it just touched the tissue surface. No external force was applied. The tablet was kept in contact with the tissue for 10 min and

Table 1
Formulation compositions to study the effect of different ingredients on in vitro release of ofloxacin

	Composition (mg/tablet)										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Ofloxacin	400	400	400	400	400	400	400	400	400	400	400
Psyllium husk	100	75	125	100	100	100	100	100	100	100	100
HPMC K100M	40	40	40	30	50	40	40	40	40	40	40
Crosspovidone	200	200	200	200	200	0	100	200	200	200	200
Sodium bicarbonate	70	70	70	70	70	70	70	60	80	70	70
Betacyclodextrin	100	100	100	100	100	100	100	100	100	0	50

then the upper jaw was slowly moved upward at the speed of 5 mm/min. The force required to separate the tablet surface from the tissue was measured. Tablets without any polymer were used as a control. The polymer was replaced by Avicel PH-101. All the experiments were done in triplicate.

3. Results and discussion

3.1. Drug release studies

In our previous work, we have shown the effect of polymers on in vitro drug release studies of ofloxacin by pH change method (Chavanpatil et al., 2005). We have also shown that our developed formulation was found to be bioequivalent to that of marketed formulation. The total amount of drug could not be released by pH change method since drug is less soluble in alkaline pH. Hence, we could not carry out drug release kinetics by pH change method. In this research work, we have carried out in vitro drug release studies in pH 1.2 buffer as a dissolution medium for 24 h in order to study the release kinetics of the developed formulation.

The compression force has a significant effect on in vitro drug release as well as on floating and swelling characteristics. So all the developed formulations were compressed at the compression force of 7–8 kg/cm^2.

Comparative in vitro drug release of various excipients used in different concentrations is shown in Fig. 1. Effect of different concentrations of psyllium husk on in vitro release of ofloxacin was as shown in Fig. 2. As the concentration of psyllium husk increased from 75 mg (F2) to 125 mg (F3) per tablet, initial drug release as well as drug release in the latter hours was decreased as compared to the marketed formulation. The percent cumulative drug release after 2 h for formulation F2 and F3 were 31.23 ± 1.32 and 24.84 ± 1.68%, respectively. The percent cumulative drug release for the formulation containing 100 mg psyllium husk (F1) was found to be 28.98 ± 1.08%. The higher initial drug release at lower concentrations of the polymer might be due to the erosion of the outer surface of the tablet at initial hours while the gelling properties of psyllium husk could have contributed to the slow release at latter hours.

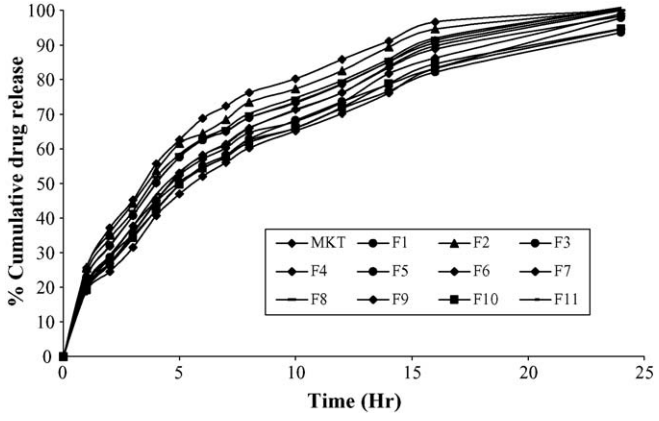

Fig. 1. Comparative in vitro release of ofloxacin from different developed formulations ($n = 6$). Standard deviation was found to be less than 2% in all the in vitro drug release profiles.

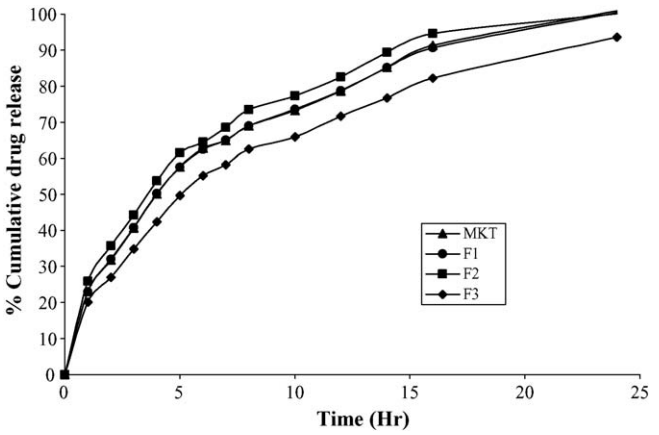

Fig. 2. Effect of different concentrations of psyllium husk on in vitro release of ofloxacin ($n = 6$). Standard deviation was found to be less than 2% in all the in vitro drug release profiles.

As the concentration of HPMC K100M was increased from 30 mg (F4) to 50 mg (F5), the burst drug release was decreased from 32.05 ± 1.92 to 25.65 ± 0.98% (Fig. 3). The burst drug release for formulation containing 40 mg (F1) HPMC K100M showed 28.98 ± 1.08%. This might be due to the increased polymer concentration could have increased the diffusion path length for the drug which could have retarded the drug release from the formulations.

To achieve the desirable floating and swelling properties with the comparable release profile to the marketed formulation, swelling and channeling agent were added.

Crosspovidone is a superdisintegrant, when comes into contact with an aqueous medium swells immediately to at least twice its original volume. Psyllium husk and HPMC K100M used simultaneously from a gel network due to which the swollen mass of crosspovidone is restrained in the tablet and the tablet does not disintegrate. The additional advantage of it is the maximum water uptake of the tablet can be achieved in a short period of time as water reaches deep into the core of the tablet. The effect of crosspovidone on drug release profile is as shown in Fig. 4. As the concentration of crosspovidone increases from 0 mg (F6) to

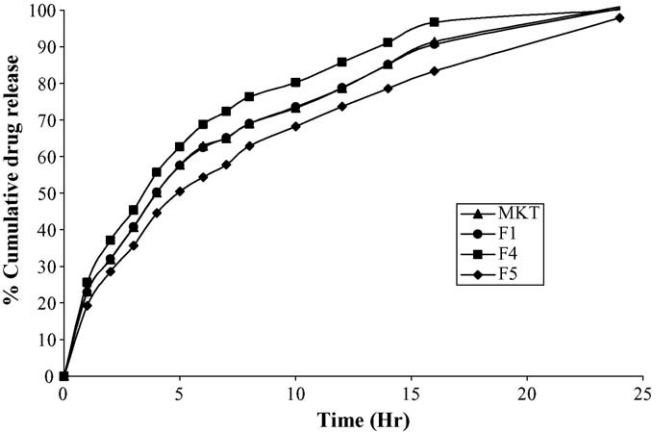

Fig. 3. Effect of different concentrations of HPMC on in vitro release of ofloxacin ($n = 6$). Standard deviation was found to be less than 2% in all the in vitro drug release profiles.

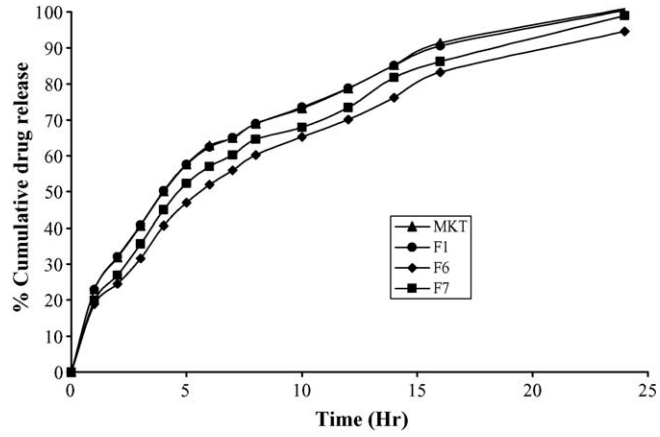

Fig. 4. Effect of different concentrations of crosspovidone on in vitro release of ofloxacin ($n = 6$). Standard deviation was found to be less than 2% in all the in vitro drug release profiles.

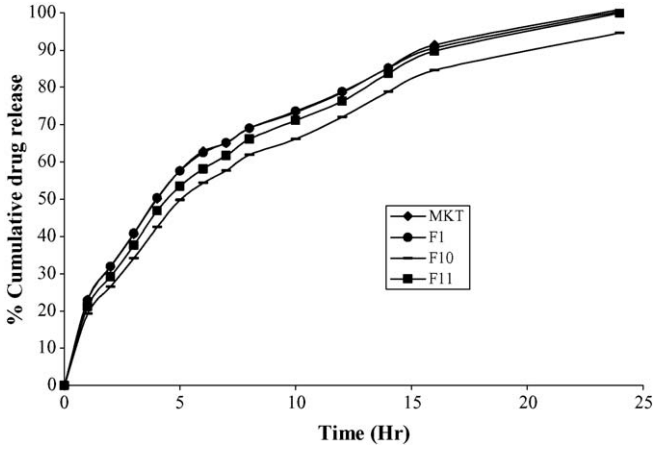

Fig. 6. Effect of different concentrations of betacyclodextrin on in vitro release of ofloxacin ($n = 6$). Standard deviation was found to be less than 2% in all the in vitro drug release profiles.

200 mg (F1), the percent cumulative drug release was increased from 34.98 ± 1.69 to $43.39 \pm 1.52\%$ at the end of 4 h. The percent cumulative drug release for formulation containing 100 mg (F7) crosspovidone was found to be $36.66 \pm 1.34\%$. As the concentration of crosspovidone increases, the water uptake capacity of the formulation increases which could have contributed to increase in the drug release from the formulation.

The effect of sodium bicarbonate concentration on in vitro drug release of ofloxacin is as shown in Fig. 5. In such systems, sodium bicarbonate acts as a gas generating agent. It generates gas when it comes into contact with an acidic environment of the stomach. This gas entraps into the matrix of water-soluble polymers and the formulation floats in an acidic environment of the stomach. As the concentration of sodium bicarbonate increases from 60 mg (F8) to 80 mg (F9) per tablet, the drug release was decreased from 31.55 ± 1.84 to $24.90 \pm 0.86\%$ at the end of 2 h. This could be because of the solubility of ofloxacin. It has good solubility in aqueous solution with pH between 2 and 5 and it is sparingly to slightly soluble in aqueous solution with pH 7. Sodium bicarbonate being alkaline in nature creates an alkaline microenvironment around the tablet and ofloxacin is less soluble in alkaline pH which decreased the drug release from the tablet matrix. The duration of floating for formulation (F1) was found to be 24 h in pH 1.2 buffer with the floating lag time of about 30 s.

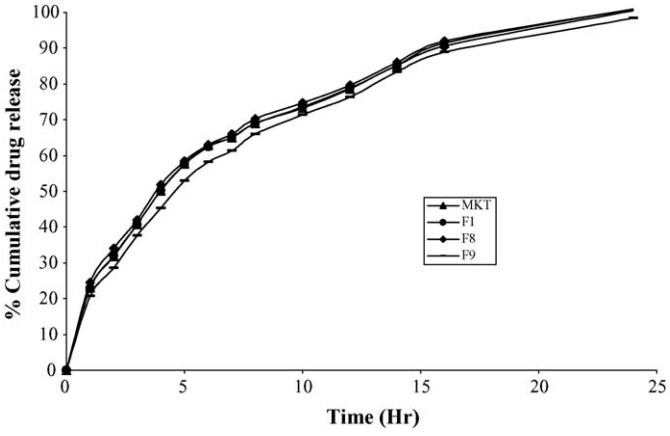

Fig. 5. Effect of different concentrations of sodium bicarbonate on in vitro release of ofloxacin ($n = 6$). Standard deviation was found to be less than 2% in all the in vitro drug release profiles.

The optimized formulation with the polymers, crosspovidone and sodium bicarbonate provided the release profile lesser than that of the marketed formulation. In order to increase the drug release in the latter period, channeling agents were tried. Different channeling agents like dextrose, potassium chloride, etc., were tried to get the desired release. Although they showed promising effect, the tablet physical integrity could not be achieved. Also the compressibility and the surface texture could not be achieved. Betacyclodextrin was tried to overcome all these problems. Being good and pH independent aqueous solubility, it dissolves rapidly forming fine channels in the tablet and thus promoting the drug release in the latter period (Fig. 6). Also good compressibility and fine particulate nature led to good hardness with glossy texture to the tablets. In case of formulation containing 0 mg (F10), percent cumulative drug release after 16 h was found to be $78.78 \pm 1.43\%$ whereas in case of formulation containing 100 mg (F1), percent cumulative drug release after 16 h was found to be $86.65 \pm 1.98\%$.

3.2. Water uptake study

The swelling of the polymers used (psyllium husk, HPMC K100M and crosspovidone) could be determined by water uptake of the tablet. The percent swelling of the tablet was determined by the method described in Section 2.2.3 at different time intervals. The complete swelling was achieved by the end of 8 h, so percent swelling was determined at the end of 8 h for all the developed formulations and for the marketed formulation. The percent swelling of F1 was found to be higher than that of the marketed formulation is as shown in Fig. 7. There was significant ($P < 0.005$) increase in percent swelling of the tablet with increase psyllium husk concentrations (formulations F1–F3). Similarly increasing concentrations of HPMC K100M also showed increase in swelling but not to that extent

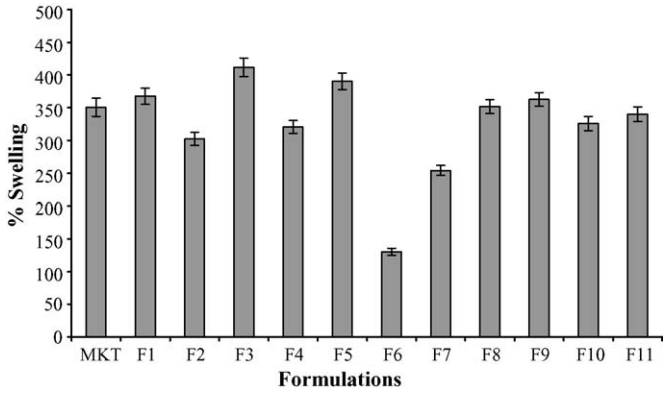

Fig. 7. Effect of various concentrations of excipients on swelling index ($n = 6$). Standard deviation was found to be less than 5% in all the in vitro drug release profiles.

of psyllium husk. The reason could be comparatively lower concentrations of HPMC K100M used for formulation development as compared to psyllium husk. Release retarding polymers could not be tried in higher concentrations for increasing the swelling property. The effect of swelling agent, crosspovidone was found to be very significant ($P < 0.005$) on swelling of the tablet. So the optimized formulation F1 and formulations with varying concentrations of crosspovidone, F6 and F7, were studied further at different time intervals. There was no significant difference observed on the swelling property by varying concentrations of sodium bicarbonate and betacyclodextrin.

F1, F6 and F7 were studied further for percent swelling at different time intervals up to 8 h and then at 12, 16 and 24 h. In all the formulations (Fig. 8), maximum swelling was observed in 8 h with very sharp increase up to 4 h in all the concentrations of crosspovidone. The values are 107.7 ± 10.12, 192.3 ± 9.62 and 335.9 ± 15.86 at the end of 4 h for 0 mg (F6), 100 mg (F7) and 200 mg (F1) of crosspovidone, respectively. There was significant ($P < 0.005$) increase in the swelling index of formulation F1 as compared to formulation F6 and F7. The percent swelling then gradually increased up to 8 h and then gradually decreased till 24 h. As discussed before, the swelling polymers, psyllium husk and HPMC K100M definitely have contributed in swelling properties apart from their release retarding property.

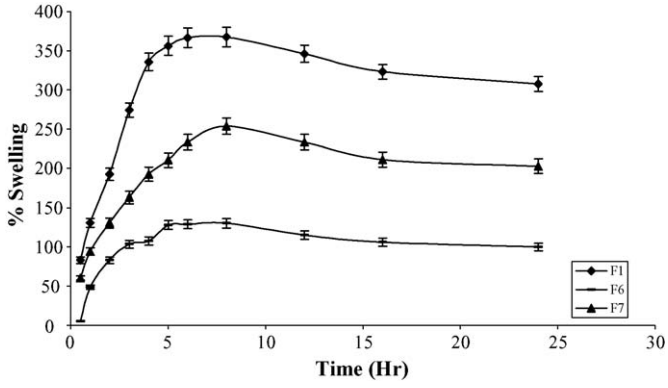

Fig. 8. Effect of different concentrations of crosspovidone on swelling behavior showing swelling indices (%) against time ($n = 6$). Standard deviation was found to be less than 5% in all the in vitro drug release profiles.

HPMC K100M swell immediately while psyllium husk swell completely in 3–4 h and this could be the reason that the faster swelling was observed in about 4 h with complete swelling in 8 h. About 60% of the drug was released at the end of 8 h and erosion process might have initiated attributing gradual decrease in percent swelling after 8 h. As described by Siepmann et al. diffusion of drug significantly depends on the water content of the tablet. This may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling of the system. Also from Figs. 4 and 8, it can be seen that the swelling of the tablet was much faster than the drug release from the tablet. At the end of 4 h the tablet was swollen almost to its maximum while about 50% drug was released. Also this higher water content could predict the higher penetration of the gastric fluid into the tablet leading to faster carbon dioxide gas generation and thus reducing the floating lag time. Consequently, faster and higher swelling of the tablet led to increase in dimensions of the tablet leading to increasing the diffusion pathways and thus decreasing diffusion rates. So the drug release was found to be high initially and then gradually decreased and complete release was obtained in 24 h.

3.3. Analysis of the drug release data

The drug release data were explored for the type of release mechanism followed. The data were treated with Eq. (1), i.e. Higuchi equation for all the developed formulations and it was found that the passage of drug through the hydrated gel matrix tablet is dependent on the square root of time. When the release profile was plotted versus square root of time, a linear relationship was observed with the regression coefficient close to 1 ($R^2 = 0.991$).

In controlled or sustained release formulations, diffusion, swelling and erosion are the three most important rate-controlling mechanisms followed. The drug release from the polymeric system is mostly by diffusion and is best described by Fickian diffusion. But in case of formulations containing swelling polymers, other processes in addition to diffusion play an important role in exploring the drug release mechanisms. These processes include relaxation of polymer chains, imbibition of water causing polymers to swell and changing them from initial glassy to rubbery state. Due to swelling, considerable volume expansion take place leading to moving diffusion boundaries complicating the solution of Fick's second law of diffusion (Siepmann and Peppas, 2001). So the release data were further treated by Eq. (2) given by Ritger and Peppas or also called as the Power law. This equation is a generalization of the observation that superposes two apparently independent mechanism of drug transport, Fickian diffusion and a case-II transport describes drug release from a swelling polymer. When n takes the value 0.5 it indicates diffusion-controlled drug release and for the value 1.0 indicates swelling-controlled drug release. Values of n between 0.5 and 1.0 can be regarded as an indicator for the both phenomena (anomalous transport). These extreme values for the exponent n, 0.5 and 1.0, are only valid for slab geometry and for spheres and cylinders different values have

Table 2
Formulation compositions to study the effect of different ingredients on in vitro release of ofloxacin

Formulations	Parameters	
	Release exponent, n	Regression coefficient, R^2
MKT	0.5718	0.9914
F1	0.5766	0.9934
F2	0.5380	0.9942
F3	0.5720	0.9910
F4	0.5496	0.9962
F5	0.5816	0.9963
F6	0.5912	0.9861
F7	0.6042	0.9891
F8	0.5429	0.9938
F9	0.5923	0.9941
F10	0.5855	0.9938
F11	0.5952	0.9860

been derived. For a matrix tablet, a cylindrical geometry is considered and as per Ritger and Peppas n takes values in the range of 0.45–0.89 for anomalous transport (Ritger and Peppas, 1987). The value of n with regression coefficient for all the formulations is shown in Table 2. For the optimized formulation (F1) the value of n was found to be 0.5766 while for the marketed formulation the value was 0.5718 indicating the anomalous transport. As discussed in Section 3.2, the high water uptake leading to higher swelling of the tablet supported the anomalous release mechanism of ofloxacin. As per our previous work, the physical integrity of the tablet was well maintained showing very slow and very less erosion of the swollen matrix. Formulations containing lower concentrations psyllium husk, HPMC K100M and sodium bicarbonate than that of F1 (F2, F4 and F8, respectively), the n value was slightly reduced while at higher concentrations (F3, F5 and F9, respectively) no significant change in n values was observed. In formulations F6 and F7, the values were slightly higher while the values were slightly increased in formulations F10 and F11. As discussed before, the value of n from 0.45 to 0.89 was used to show anomalous transport. So all these formulations were followed anomalous transport.

The developed optimized formulation F1 and the marketed formulation were found to have almost similar in vitro release profile. Dissolution profiles may be considered similar by virtue of overall profile similarity and by similarity at every dissolution sample point. The similarity factor for the two curves is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves. The two curves are to be considered similar when $f2$ value is close to 100. Generally $f2$ values greater than 50 (50–100) ensure sameness. The similarity factor $f2$ was found to be 91.12 for the developed formulation F1 and the marketed formulation, indicating the release was almost similar to that of the marketed formulation (Zanocin).

3.4. Bioadhesion study

Apart from the floating property of the tablet, bioadhesive tendency could be an important property for gastroretentive drug

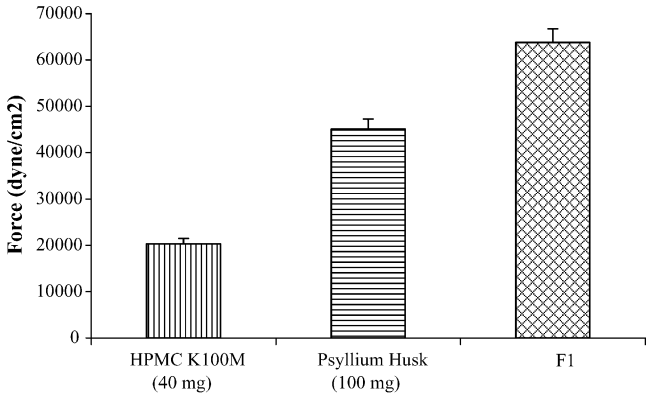

Fig. 9. Effect of different polymers on in vitro bioadhesion ($n = 3$). Standard deviation was found to be less than 5% in all the experiments.

delivery. HPMC polymers are reported to have the bioadhesive property. The developed formulation also contained psyllium husk known to have potential bioadhesive property. Crosspovidone, sodium bicarbonate and betacyclodextrin does not possess bioadhesive property, so only the polymers (HPMC K100M and psyllium husk) were studied for bioadhesive property. The bioadhesion study was carried out as described in Section 2.2.4. The control group, where polymers were replaced by Avicel PH101, showed no bioadhesion. The formulations containing only HPMC K100M and only psyllium husk were prepared with equal quantities to that present in formulation F1. As depicted in Fig. 9, the bioadhesive properties of the developed formulation was found to be significantly ($P < 0.005$) increased as compared to HPMC K100M and psyllium husk alone. HPMC is a long-chained, non-ionic polymer and the bioadhesive property could be due to formation of physical or hydrogen bonding with the mucus components. Psyllium husk contain large quantity of mucilage which contain two major polysaccharide fractions with equivalent weights about 700 and 4000. On hydrolysis they yield mostly D-xylose, L-arabinose and aldobiouronic acid. In contact with aqueous medium, the mucilage swell and thus could be responsible for bioadhesion by simple physical or hydrogen bonding with the mucus components. Hence, the bioadhesive property of the optimized formulation could assist the tablet to stay in the upper part of GIT and enhance the gastroretention along with the floating and swelling property.

4. Conclusion

We conclude that psyllium husk and HPMC K100M in combination can be promising polymers for gastroretentive drug delivery systems. The optimized formulation followed Higuchi kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix. Swelling studies were indicated significant water uptake and contributed in drug release and could be significant in gastroretention. Bioadhesive properties were also studied and the developed formulation showed significant bioadhesion as compared to that of the polymers alone. Thus, combining these approaches of gastroretention together the in vivo gastroretention could be predicted more reliably. Based on these promising

in vitro results, in vivo studies in healthy volunteers were carried out for determination of various pharmacokinetic parameters (Chavanpatil et al., 2005). However, in vivo studies for these gastroretentive parameters could not be done in animal models due to drastic anatomical and physiological differences between animal models and human being.

Acknowledgements

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