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Development of a prolonged-release gastroretentive tablet formulation of ciprofloxacin hydrochloride: Pharmacokinetic characterization in healthy human volunteers

Abolfazl Mostafavi [a], Jaber Emami [a,*], Jaleh Varshosaz [a], Neal M. Davies [b], Mahboubeh Rezazadeh [a]

[a] Department of Pharmaceutics, School of Pharmacy and Pharmaceutical Sciences and Isfahan Pharmaceutical Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[b] College of Pharmacy, Department of Pharmaceutical Sciences, Washington State University, Pullman, WA, USA

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ABSTRACT

The fluroquinolone anti-biotic ciprofloxacin is primarily dissolved and absorbed from the upper part of the GI tract. We, therefore, aimed to develop a prolonged release gastroretentive (GT) formulation of ciprofloxacin that could be administered once daily with a conventional tablet (CT). A variety of polymers and effervescent properties were utilized to optimize the desired disposition profile. Tablets were prepared by the direct compression technique and evaluated for physical properties, swelling, floating, and drug release. *In vivo* studies were also carried out on the optimized GT formulation and CT in healthy volunteers. A very sensitive and reliable HPLC method was developed to measure plasma concentration of ciprofloxacin. The duration of floating times were predominantly >24 h and floating lag times <20 s. The drug release mechanism followed zero order kinetics. C_{max}, T_{max}, and $AUC_{0-\infty}$ of GT *vs* CT were 0.945 ± 0.29 *vs* 2.1 ± 0.46 μg/ml, 6.0 ± 1.42 *vs* 1.42 ± 0.59 h and 8.54 ± 1.87 *vs* 9.45 ± 2.12 μg/ml/h, respectively. Pharmacokinetic parameters indicate that the developed GT formulation extended the pharmacokinetic profile achieved with CT. The C_{max}/MIC and $AUC_{0-\infty}$/MIC, which are indicative of eradication of pathogens, following co-administration of GT with CT were comparable to those of twice-daily administration of CT alone.

1. Introduction

Sustained release formulations can offer many pharmacokinetic and pharmacodynamic advantages over conventional dosage forms, including maintenance of constant therapeutic levels for a longer period of time and reduction of fluctuations in plasma drug concentrations. Sustained release formulations may reduce the risk of treatment failure and spreading of bacterial resistance especially in the case of antibiotics (Shweta et al., 2005; Trotta and Gasco, 1989). These drug delivery systems can also improve patient compliance by possible reduction in dosing frequency and total dose administered. However, sustained release drug delivery systems are not only developed to control drug release for a specific time period but also to prolong the residence time of the dosage form in the stomach or the proximal part of the small intestine. The presence of a dosage form in the upper part of the gastrointestinal tract is important especially for drugs that are degraded or metabolized in the intestine or for drugs with local activity in the stomach (Deshpande et al., 1996; Hawang et al., 1998; Shweta et al., 2005). Furthermore, for drugs with poor solubility in the intestine and those with site-specific absorption limitations, gastric retention may increase the overall gastrointestinal absorption (Rouge et al., 1996). Gastrointestinal retention depends on many factors such as density and size of the dosage form, the fasting or fed condition of the patient, the nature of the meal as well as posture (Khosla and Davis, 1990; Mojaverian et al., 1988). Several gastroretentive formulation approaches such as high density, expandable, swelling, mucoadhesive and floating systems have been developed (Bardonnet et al., 2006; Gange and Sharm, 2003; Klacsner et al., 2003). A gastric floating device is useful for drug delivery to the upper part of the GI tract. This system is most effective in the presence of sufficient fluid and food. The floating unit remains above the gastric contents without affecting the rate of gastric emptying and is protected from peristaltic waves (Brahma and Kwon, 2000; Rouge et al., 1996). Ciprofloxacin is available in conventional dosage forms for oral delivery and is considered as a broad spectrum antibiotic for the treatment of a wide range of bacterial infections, including urinary tract infections, respiratory and GI infections, as well as skin and bone infections (Clark, 2004; Martindale, 2005). Ciprofloxacin water solubility is strongly dependent on the acidic pH and mainly absorbed in the proximal areas of the GI tract. Therefore, conventional sustained release formulations liberating their drug contents

* Corresponding author. Tel.: +98 311 792 2586; fax: +98 311 668 0011/792 2586.
E-mail address: emami@pharm.mui.ac.ir (J. Emami).

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along with the intestine result in an incomplete release of the drug from the drug delivery system, leading to diminished efficacy of the administered dose. Therefore, an effective floating delivery system of this drug may offer pharmacokinetic and pharmacodynamic advantages. In order to develop a desire controlled release dosage form for ciprofloxacin it is necessary to optimize both the residence time of the system in the GI tract and the release rate of the drug from the system. Hence, the main focus in developing and optimizing gastroretentive formulations of ciprofloxacin is to compromise matrix integrity with the shortest possible bouncy lag time, with floating and release duration of up to 24 h. Floating alginate beads of ciprofloxacin were prepared to evaluate the formulation variables on the bead properties and to examine *in vitro* release in acidic environments (Srinath and Pandit, 2006). Some investigators have also developed floating microspheres of ciprofloxacin by using polymer mixtures such as HPMC and sodium alginate (Sahoo et al., 2007). Such multiparticulate systems are distributed over the length of the gastrointestinal tract releasing the drug at different locations. Single unit systems such as monolithic matrix tablets are more favorable because of their ease of the preparation and the large size of the dosage forms which restricts rapid passage through the gastric pylorus (Davis et al., 1986).

A ciprofloxacin effervescent floating tablet formulation has been previously developed using citric acid and sodium bicarbonate as effervescent agents (Varshosaz et al., 2006). In all the aforementioned studies, the main focus of the work has been to improve the bioavailability of ciprofloxacin by increasing the gastric residence time. However, no attempts have been made to prolong the drug release rate and consequently to reduce the dosing frequency. Conventional tablets of ciprofloxacin require twice-daily administration. Inconvenient drug dosing regimens, long duration of therapy, and possible side effects could result in poor patient adherence to the treatment which often leads to sub-therapeutic antibiotic concentrations at sites of infection. This consequently reflects in the prolonged pathogen persistence, clinical failure and/or selection of resistant organisms. Therefore, there has been significant interest in the development of a convenient once-daily formulation of ciprofloxacin. In this respect, two attempts have so far been made to deliver ciprofloxacin in a prolonged manner in order to extend its therapeutic effect for longer period of time (Arza et al., 2009; Bermúdez et al., 2008). However, these studies lack *in vivo* pharmacokinetic assessments. Because of the complex motility effect of the stomach in retaining of the dosage form in gastrointestinal tract, only *in vivo* studies can confirm the disposition efficacy of such systems (Baumgartner et al., 2000).

It has been clinically proven that delivery systems which are able to deliver a portion of ciprofloxacin immediately and the remaining fraction in a controlled fashion, such as matrix bilayer tablet containing two different salts of ciprofloxacin, could be administered once daily to enhance patient adherence to the treatment and thereby to improve clinical success rates. Additionally, therapeutic drug levels with these systems are achieved rapidly and lead to maintenance of concentrations over the 24 h, allowing very high rates of clinical cure and bacterial eradication especially in resistance complicated infections such as UTIs (Wagenlehner et al., 2006). The objective of the current investigation was, therefore, to develop a floating, swelling and prolonged release monolithic tablet formulation of ciprofloxacin that would increase gastric retention time of the dosage form and control the release of the drug over a 24 h period. This gastroretentive prolonged release segment could be co-administered with a 500 mg conventional immediate-release tablet, once daily to achieve desirable clinical effects and to reduce the total administered dose.

To manufacture the prolonged release floating tablets, the effects of different processing variables including polymer concentrations and effervescent agents on the drug release rate and buoyancy properties of the drug delivery system were investigated. The *in vivo* absorption and bioavailability of optimized gastroretentive formulations were compared to that of conventional tablet in healthy human volunteers.

2. Materials and methods

2.1. Materials

Ciprofloxacin HCL was obtained from Sigma (UK), hydroxypropylmethylcellulose (HPMC K100M) was a gift from Rhom pharma (Germany). Carbomer 971 P (CP 971P) was obtained from BF Goodrich, Xanthan gum, sodium carboxy methylcellulose, sodium bicarbonate and dichloromethane were provided by Merck (Germany), Crospovidone® (CRP) was purchased from Sigma (UK), and acetonitrile and methanol were purchased from Caledon (Canada).

2.2. Formulations of floating tablets

Prolonged-release gastroretentive tablets containing 582 mg ciprofloxacin hydrochloride (equivalent to 500 mg of ciprofloxacin) were prepared by a direct compression method using formula shown in Table 1. The tablets were prepared by mixing required quantities of HPMC K100M, CP 971P, xanthan gum, NaCMC, Crospovidone®, and sodium bicarbonate. All excipients were passed through sieve no.18, mixed using a mortar and pestle for 10 min, and lubricated with 1% (w/w) of magnesium stearate. The blended powders were compressed in to flat face tablets using a single punch tablet compression machine (GMBH-KS Kilian, Germany), fitted with 14 mm flat-faced punches with 60 N in hardness.

2.3. Physical properties of floating tablets

The thickness, hardness, weight variations, and content uniformity of fabricated tablets were determined by procedure stated in the US pharmacopoeia (USP, 2006).

2.4. In-vitro buoyancy studies

Floating characteristics of tablets were determined in a USP dissolution apparatus II in an acidic environment at $37 \pm 0.5\,^{\circ}C$ and 50 rpm (Mahesh et al., 2006). The floating lag time (FLT) as well as total floating time (TFT) were determined visually using a timing mechanism.

2.5. Swelling studies

The swelling behavior of tablets were measured in glass containing 200 ml of HCL (0.1 N) which was maintained at $37 \pm 0.5\,^{\circ}C$. At regular time intervals, the tablets were removed from glass and the percentage of swelling was calculated using the following equation (Dorozynski et al., 2004).

$$\%\text{swelling} = \frac{W_2 - W_1}{W_1} \times 100 \quad (1)$$

where W_2 is the weight of the swollen tablets, and W_1 is the initial weight of the tablets. The measurement was carried out in triplicate ($n = 3$).

2.6. In vitro bioadhesion study

Rabbit stomach tissue was used for the evaluation of bioadhesion (Betageri et al., 2001). The use of animal and surgical procedure was consulted and justified with a veterinarian for animal ethics

Table 1
Formulation composition of prepared floating gastroretentive ciprofloxacin tablets.

Developed formulations	Ciprofloxacin	HPMC K100M	Xanthan gum	Crospovidone®	Na CMC	Carbopol 971P	Na HCO_3
F1	500	50		100		50	50
F2	500	50		100		100	100
F3	500	50		100	50		50
F4	500	50		100	100		100
F5	500	50	40	100			50
F6	500	50	20	100			50
F7	500	50	10	100			50
F8	500	50		100			50
F9*	**500**	**75**		**100**			**50**
F10	500	100		100			50
F11	500	75		0			50
F12	500	75		50			50
F13	500	75		150			50
F14	500	75		100			100

* Lead formulation used in pharmacokinetic studies.

approval by the Animal Care and Use Committee of Isfahan University of Medical Sciences. A section of tissue was cut from the fundus of the healthy rabbit stomachs. The tissue was equilibrated at 37 ± 1 °C for 15 min in phosphate buffer solution (PBS) prior to the bioadhesion study. The study was performed using Universal Tensile Tester (HC 10, DARTEC model). After hydrating with PBS, the tissue was fixed on the stainless steel plate fitted to the lower grip of the instrument. The tablet was kept in contact with mucosa under the constant weight 5 g for 5 min. Then the upper blade of instrument was slowly lowered downward at the speed of 2 mm/min to separate the tablet from the tissue surface. The detachment force (Newton) was expressed as mean values ±SD for three tablets in each series.

2.7. Drug release studies

Six tablets of each formulation were used in the release experiment. The release rates of ciprofloxacin were determined using USP apparatus I (basket apparatus) at 37 °C in 900 ml 0.1 N HCL solution (pH, 1.2) with the rotation speed of 100 rpm. At appropriate time intervals 1, 2, 3, 4, 6, 8, 10, 12, 14 and 24 h, 5 ml of sample was withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were analyzed spectrophotometrically at 276 nm. A linear correlation ($r^2 > 0.999$) was obtained over the range of 2–20 μg/ml. High precision and accuracy were also obtained (CV: 1.49–5.68%, error: 1.21–4.62%). The dissolution data obtained were plotted as percent cumulative drug released versus time.

2.7.1. Analysis of release data

Different kinetic models (zero-order, first-order, Higuchi, and Hixson–Crowell) were applied to interpret the release from matrices and the Korsmayer–Peppas kinetics model was used to describe the release mechanism

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

where, M_t is the drug released at time t, M_∞ the drug released at infinite time, k the kinetic constant and n the release exponent (Costa and Lobo, 2001).

Mean dissolution time (MDT) and dissolution efficacy (DE) were used to compare the release rates amongst formulations. MDT was calculated by the following equation (Peppas, 1985).

$$\text{MDT} = \frac{\sum_{j=1}^{n} \widehat{t}_j \Delta M_j}{\sum_{i=1}^{n} \Delta M_j} \quad (3)$$

where j is the sample number, n the number of dissolution sample time, $\widehat{t}$ the time at midpoint between t_j and t_{j-1} and ΔM_j the additional amount of drug dissolved between t_j and t_{j-1}.

DE of profiles were calculated from the area under the curve at time t_j (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan and Rhodes, 1972).

2.8. In vivo studies

The study was conducted at the medical school hospital in Isfahan Iran, in accordance with ethical principles and standards described in the Declaration of Helsinki and the International Conference on Harmonization (ICH)/good Clinical Practice (GCP). Guidelines were approved by an independent Medical Bioethics Committee at the University of Isfahan. Written informed consent was obtained from all subjects prior to commencement of the study.

Twelve healthy adult male volunteers aged between 21 and 26 years and weighing from 56 to 70 kg participated in the study. Based on laboratory tests including hematology, blood biochemistry and urine analyses, subjects did not have an evidence of hepatic, renal, gastro-intestinal or hematological diseases. The subjects were instructed to abstain from taking any medications at least 2 weeks prior to and during the study period. Informed consent was obtained from the subjects after explaining the nature and purpose of the study. The protocol was the conventional, two-way, crossover study with 12 subjects. Thirty minutes before dosing, subjects were received standardized breakfast. A standard light lunch was served 5 h after drug intake. Volunteers were provided either optimized gastroretentive formulation (F9) or conventional formulation (500 mg immediate released tablet manufactured by Farabi Pharmaceutical Co. Iran) with 200 ml water. Volunteers were given extra 200, 250 and 400 ml water at 2, 4, and 8 h after administration of the tablet. The blood samples were taken in predetermined time intervals until 24 h post-dose. The samples were centrifuged at 3000 rpm for 20 min and plasma separated and kept frozen at −20 °C in coded glass tubes until HPLC analysis.

2.8.1. HPLC analysis

The concentration of ciprofloxacin in plasma was measured by the HPLC method developed in this laboratory. The method was validated for linearity, accuracy, and precision. A C_{18}-μ bondapak column (3.9 mm × 250 mm) was used. The mobile phase consisted of potassium dihydrogen phosphate (0.01 M)/acetonitrile (80:20) with final pH adjusted to 3.0 ± 0.1 with ortho-phosphoric acid. Phenacetin (100 μg/ml) was used as an internal standard. The mobile phase eluted at the flow rate of 1.5 ml/min and the effluent

was monitored at 276 nm using a UV detector. Column temperature was kept at 40 °C and 50 μl of sample was injected into the HPLC column. Drug and internal standard were extracted from the plasma with 5 ml dichloromethane. Sample tubes were vortexed for 30 s and were then centrifuged for 10 min. The upper aqueous layer was removed by aspiration and the organic layer evaporated to dryness under nitrogen gas. The residue was reconstituted with 75 μl of mobile phase and 50 μl aliquot was injected into the HPLC column.

The standard curve covering 25–4000 ng/ml concentration range was linear ($r^2 > 0.999$), the inter- and intra-day precision and accuracy were less than 12.87%, the detection limit was 15 ng/ml, and the mean recoveries were between 97.4% for calibration standard concentrations.

2.8.2. Pharmacokinetic analysis

Pharmacokinetic parameters were calculated using MS Excel software. The peak plasma concentration (C_{max}) and the corresponding peak time (T_{max}) were obtained directly from individual plasma concentration–time profiles. The AUC_{0-t} was calculated by the trapezoidal rule and the total $AUC_{0-\sim}$ was calculated according to the following equation.

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{K_E} \quad (4)$$

where C_t is the last measurable concentration and K_E is the elimination rate constant obtained from the least square fitted terminal log-linear portion of the plasma concentration–time profile (Shargel et al., 2005). The mean residence time (MRT) was calculated using following equation (Shargel et al., 2005).

$$MRT = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}} \quad (5)$$

where AUMC is the area under the first moment of the concentration time curves (Shargel et al., 2005).

2.9. Statistic analysis

All results are expressed as mean ± SD. Differences between two related parameters were performed by student's *t*-test or one-way ANOVA using software SPSS 17. Differences were considered significant at $P < 0.05$

3. Results

3.1. Physical characterization of the tablets

The floating tablets of ciprofloxacin showed uniform thickness, in the range of 3–3.3 mm. The weight variation for all formulations was within the acceptable limits. The hardness was maintained at 50–60 N.

3.2. In vitro buoyancy studies

FLT was less than 20 s for all formulations studied. FLT did not change significantly by increasing the sodium bicarbonate concentrations from 50 to 100 mg; thus 50 mg sodium bicarbonate was used in the optimized formulation. TFT was longer than 24 h for most formulations. In the optimized formulation (F9), CO_2 was generated after 13 s and floated for more than 24 h (Fig. 1).

Incorporation of Carbopol decreased TFT (2 h). Formulations (F3, F4) containing HPMC K100M/Na CMC demonstrated a total floating time of about 5–6 h. This value was increased in formulations contained HPMC K100M alone.

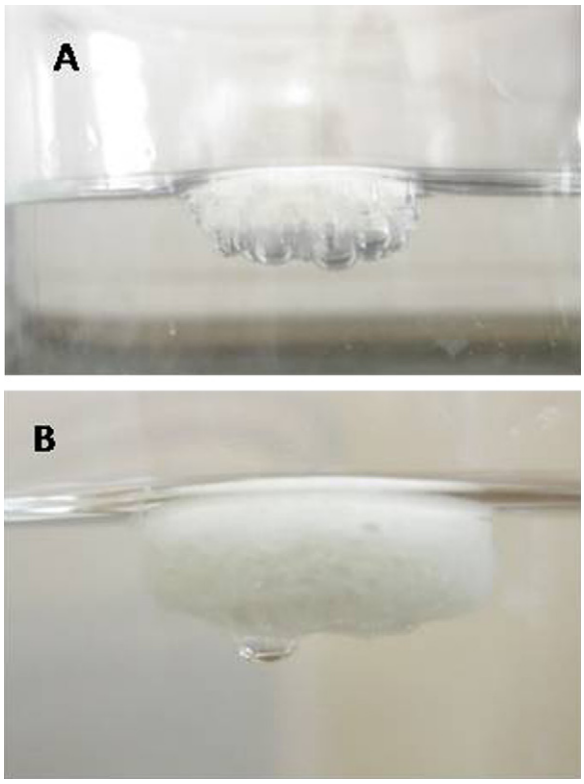

Fig. 1. Photographs of floating tablet in buffer HCL 0.1 N (A: 13 s after immersion, B: 24 h after immersion).

3.3. Swelling studies

The percent swelling of tablets were determined by the method described in Section 2.5 at different time intervals. Since the maximum swelling was observed after 8 h in most formulations, percent swelling was determined at the end of 8 h for all the developed formulations (Fig. 2).

For optimized formulation (F9) this value was 145.7 ± 5.5% at the end of 8 h. Formulations containing Carbopol (F1, F2) swelled immediately and then sank to the bottom of the beaker after 2 h. Formulations with NaCMC (F3, F4) swelled instantly which did not persist due to subsequent erosion. There was a significant ($P < 0.05$) increase in swelling of the tablet containing varying amount of HPMC (F8, F9, F10) with an increase in the HPMC content.

In formulations containing fixed amount of HPMC (F9, F11, F12, F13), increasing the concentration of Crospovidone® resulted in an increase in swelling index. ($P < 0.05$). Incorporation of varying amount of sodium bicarbonate or xanthan gum in the formulations had no impact on the swelling index. Crospovidone® and HPMCK100M had profound impact ($P < 0.05$) on swelling properties of the tablets. The swelling profiles of corresponding formulations

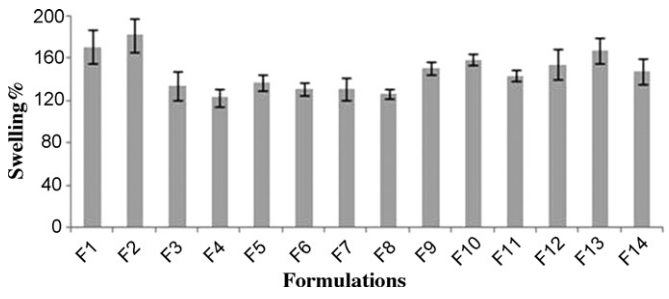

Fig. 2. Effect of various concentration of excipients on swelling percent ($n = 3$).

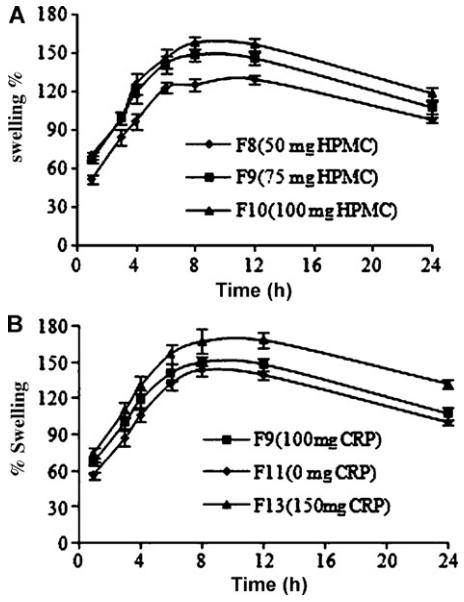

Fig. 3. Swelling percent of floating tablets with different amounts of HPMC K100M (A), and Crospovidone® (B).

up to 24 h are illustrated in Fig. 3A and B. Maximum swelling was achieved in 8 h maintained for about 4 h and gradually decreased till 24 h.

3.4. In vitro bioadhesion study

Carbomer 971P, Na CMC and HPMC K100M exhibiting inherent bioadhesion were chosen as retarding polymers. Fig. 4 shows the detachment forces of drug-free tablets with 100 mg bioadhesive polymers (positive controls) and adopted gastroretentive formulation.

The polymers showed significant differences in their bioadhesion in order of CP 971P > Na CMC > HPMC K100M ($P < 0.05$). Crospovidone®and sodium bicarbonate which were used as filler excipients do not possess bioadhesive properties. The adhesion force, in formulation F9 adopted as the most favorable formulation for *in vivo* studies was 0.68 ± 0.11 N.

3.5. Drug release kinetics

The effect of different amounts of excipients on drug release properties are shown in Fig. 5A–F. Formulations containing HPMC K100M/Carbopol (Fig. 5A), due to a rapid hydration, showed earlier

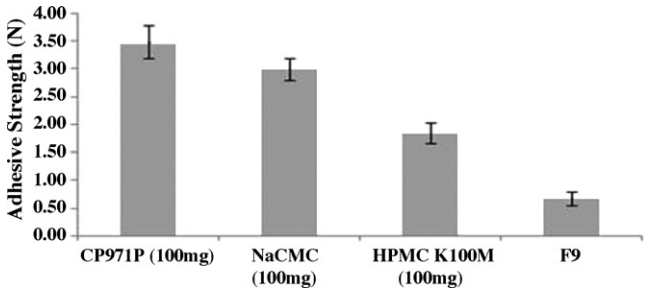

Fig. 4. Effect of different polymers on *in vitro* bioadhesion ($n = 3$).

release in dissolution medium. In formulations F3 and F4 the high viscosity of HPMC K100M seems to inhibit the initial burst effect of drug release but in later times due to the erodible properties of NaCMC, the tablets could not maintain their matrix integrity and the erosion of polymeric matrix in the higher rate than swelling properties could accelerate the drug release, hence the drug content was completely released before 24 h in these formulations. As shown in Fig. 5C, tablets containing HPMC K100M and xanthan gum exhibited constant drug release up to 24 h. As concentration of HPMC K100M and xanthan gum increased, the drug release rate was reduced (Fig. 5C and D). The drug release profiles from formulations containing different concentrations of Crospovidone® are shown in Fig. 5E. Higher concentration of Crospovidone® facilitates the drug release. Formulations (F9, F14) with different amounts of sodium bicarbonate did not show any significant effect ($P > 0.05$) on drug release rates.

The r^2 values obtained from different kinetics models (Table 2) suggest that the release from the formulations may follow any one of these models. When the higher correlation coefficient values are considered, the released data for the most formulations seem to fit better with zero order and Higuchi model. Optimized formulation (F9) fits to zero order kinetic ($r^2 = 0.992$). The release exponent ($n = 0.79$) also indicated that the combination effects of diffusion and polymer relaxation plays a role in drug release. MDT and DE were used to assess the effect of polymers on drug release profiles. The reverse order exists between MDT and release rate. MDT value is the highest (13.02 h) for F11 formulation and lowest (7.65 h) for F8 matrices. DE% changes directly with dissolution rate. For optimized formulation, the MDT and DE_{14h} were calculated to be 10.4 h and 52.7%, respectively.

3.6. Pharmacokinetic studies in healthy human volunteers

Pharmacokinetic studies were carried out in healthy human volunteers for optimized (F9) and conventional formulation. The

Table 2
Drug release kinetics of ciprofloxacin floating tablets.

Developed formulations	Zero order r^2	First order r^2	Higuchi r^2	Hixson–Crowell r^2	n	MDT	DE_{14h}
F1	0.810	0.963	0.989	0.983	0.59	5.86 ± 0.27	86.2 ± 1.6
F2	0.826	0.956	0.984	0.980	0.63	6.85 ± 0.39	73.2 ± 1.2
F3	0.846	0.991	0.982	0.991	0.84	6.65 ± 0.25	85.6 ± 1.3
F4	0.961	0.991	0.993	0.981	0.59	7.63 ± 0.29	79.3 ± 1.6
F5	0.965	0.998	0.996	0.994	1.16	16.1 ± 0.48	38.7 ± 0.5
F6	0.997	0.996	0.996	0.997	0.97	13.8 ± 0.18	42.1 ± 0.7
F7	0.964	0.985	0.991	0.993	0.84	11.9 ± 0.58	48.1 ± 1.2
F8	0.991	0.965	0.989	0.987	0.55	7.65 ± 0.38	71.3 ± 1.3
F9*	**0.992**	**0.851**	**0.982**	**0.939**	**0.79**	**10.4 ± 0.13**	**52.6 ± 1.2**
F10	0.962	0.988	0.997	0.996	0.92	12.6 ± 0.41	46.6 ± 1.4
F11	0.988	0.969	0.995	0.991	0.96	13.0 ± 0.36	38.5 ± 0.9
F12	0.966	0.995	0.995	0.996	0.99	10.1 ± 0.53	51.8 ± 0.6
F13	0.932	0.996	0.992	0.991	0.86	9.60 ± 0.46	58.0 ± 0.8
F14	0.973	0.996	0.996	0.993	0.71	9.73 ± 0.29	55.6 ± 0.7

* Lead formulation used in pharmacokinetic studies.

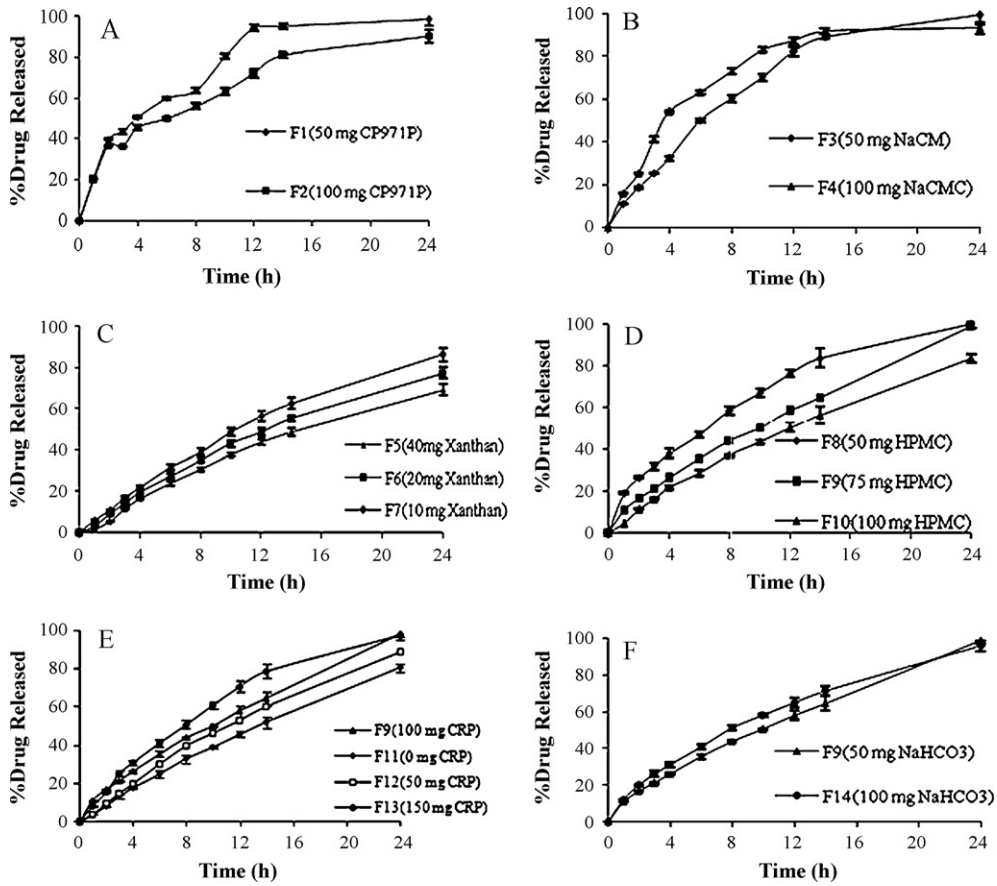

Fig. 5. Effect of different concentrations of excipients on the *in vitro* release of ciprofloxacin. (A) CP971P, (B) Na CMC, (C) Xanthan gum, (D) HPMC K100M, (E) Crospovidone®, and (F) Sodium bicarbonate ($n = 6$).

mean plasma concentration of ciprofloxacin versus time curve is illustrated in Fig. 6. C_{max} and T_{max} of optimized gastroretentive formulation (F9) were found to be 0.945 ± 0.29 μg/ml and 6.0 ± 1.41 h, respectively. C_{max} and T_{max} for conventional product were estimated to be 2.1 ± 0.46 μg/ml and 1.42 ± 0.59 h, respectively. The $AUC_{0-\infty}$ for optimized gastroretentive formulation and conventional product were 8.12 ± 1.8 and 9.45 ± 2 μg/ml/h, respectively (Table 3).

Fig. 6 also shows plasma concentrations after administration of a gastroretentive tablet formulation (F9, 500 mg) along with a 500-mg conventional tablet of ciprofloxacin. It is clearly evident that when two formulations are given simultaneously is able to maintain plasma levels within the therapeutic range. C_{max}, T_{max}, and $AUC_{0-\infty}$ for simulated profile are estimated to be 1.89 μg/ml, 2.98 h, and 17.32 μg/ml/h respectively.

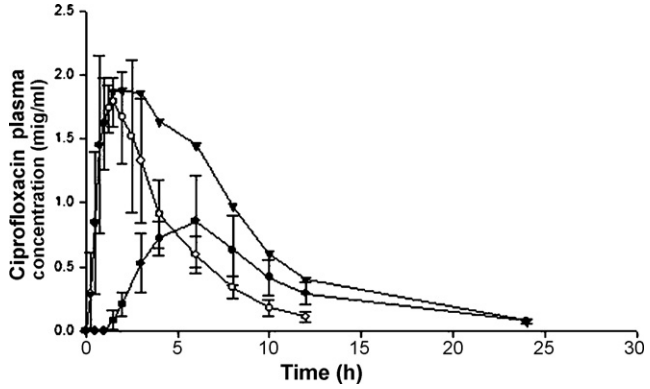

Fig. 6. Mean plasma concentration–time profile of ciprofloxacin after oral administration of 500 mg controlled release floating tablets (●), conventional immediate release tablets (○), and following co-administration of 500-mg conventional immediate release and controlled release floating tablets (▲) in healthy volunteers.

4. Discussion

This study was conducted to formulate a floating prolonged release form of ciprofloxacin to obtain a more optimal delivery of the drug in its absorption site. Several approaches of non-effervescent and effervescent systems have been used to achieve floating drug delivery systems to increase gastric residence time. Floating matrix tablets based on a gas forming agent in combination with the hydrogel polymers is one of the commonly used approaches to prepare floating delivery systems. Floating tablets which contained HPMC K4M and sodium bicarbonate immersed in simulated gastric fluid demonstrated CO_2 generation and floating properties (Wei and Yu, 2001). For soluble drugs such as sodium diclofenac, Carbapol gel significantly extends the release time but considerable fluctuations in the release profile were noted (Samani et al., 2003). In floating matrix tablets of phenoporlamine, HPMC K4M and Carbopol 971P have been used as hydrogel polymers (Xiaoqiang et al., 2006). All formulations containing Carbopol and HPMC K4M could release their drug content between 10 and 15 h.

The viscosity grade of the polymer is a critical feature in formulation development. HPMC K100M with the highest viscosity (2% solution, 100,000 mPa s) amongst HPMC polymers restrains CO_2 in the matrix leading to a density of less than unity. In addition, this feature can significantly retard the release of the drug from formulations. HPMC polymers are also reported to have bioadhe-

Table 3
Pharmacokinetic parameters of ciprofloxacin controlled release floating tablets and conventional immediate release tablets.

Tested Formulations	C_{max} (μg/ml)	K_a (h^{-1})	T_{max} (h)	MRT (h)	AUC_{0-t} (μg/ml/h)	$AUC_{0-\infty}$ (μg/ml/h)
Ciprofloxacin controlled release floating tablet (F9)	0.945 ± 0.29*	0.49 ± 0.13*	6.0 ± 1.42*	8.65 ± 0.81*	8.1 ± 1.57	8.54 ± 1.87
Ciprofloxacin conventional immediate release tablets	2.1 ± 0.49	2.31 ± 0.42	1.42 ± 0.59	3.75 ± 0.39	8.56 ± 1.87	9.45 ± 2.12

* $P < 0.05$.

sive properties (Li et al., 2003). Therefore, in the present study to achieve desirable floating, swelling, and drug release properties, HPMC K100M or Carbopol 971P or their combinations was incorporated in tablet formulations. Sodium bicarbonate was used as gas forming agent that generates carbon dioxide in contact with the acidic dissolution medium whose bubbles could be observed at the early stages of dissolution or during the floating test (Fig. 1). The generated gas is entrapped in the swollen hydrophilic polymer matrix, resulting in the buoyancy of the dosage form which can retain the system in the stomach for a longer time period and assist controlled released of the drug up to 24 h. In floating drug delivery systems, incorporation of an appropriate swelling agent such as Crospovidone® can both improve buoyancy and system integrity (Mahesh et al., 2006). In the light of the above considerations, the first formulation (F1) containing drug, HPMC K100, Carbopol 971P, Crospovidone®, and sodium bicarbonate was developed and evaluated. This formulation indicated a TFT of around 2 h. In the release medium, the hydrophilicity of Carbopol 971P promotes water penetration into the tablet matrices leading to an increase in density of the dosage form and a decrease in floating time. Increasing the amount of sodium bicarbonate (F2) had no significant effect on the duration of floating time in these series of formulations. Moreover, the Carbopol-containing formulations (F1, F2) could not maintain their matrix shape and swelling for 24 h. These formulations released their entire content within 14 h with MDT of 5.86 and 6.85 h, respectively. In domperidone floating tablets, TFT was reduced by increasing the concentration of Carbopol (Shailesh et al., 2008) Therefore, in subsequent formulations, Carbopol was replaced with another hydrogel polymer, Na CMC.

The gel layer formed by this polymer was not able to efficiently entrap the generated gas bubbles. Formulation F3 floated on the medium for a short period of time (6 h) and almost all the drug content was released during 14 h. An increase in Na CMC content or sodium bicarbonate contents (F4) could not significantly retard the release rate or augment the buoyancy duration. In addition, Na CMC was unable to withhold tablet shape and integrity efficiently for the intended period of time. In contrast, HPMC K100M which is a highly viscous polymer could not only restrain generated CO_2 in the matrices for an appreciable period, but also prevents tablet disintegration in the release medium.

It has been reported that incorporation of xanthan gum in the matrix may maintain constant drug release for a considerable period of time and preserve physical integrity of the tablets in the release medium (Patel et al., 2009). Therefore, floating tablets were formulated with HPMC K100M and xanthan gum to improve floating time and to achieve a desirable prolonged release pharmacokinetic profile. Formulations F5, F6, and F7 contained 40, 20, and 10 mg xanthan gum, respectively with an equal amount of HPMC K100M. F5 released only 60% of its drug content within 24 h. As the amount of xanthan gum was decreased, the drug release rate increased. Although, tablets containing xanthan gum showed a total bouncy time of longer than 24 h and constant drug release but even in formulation F7 containing the lowest amount of xanthan gum only 85% of the drug could be released in 24 h (Fig. 5C). Thus, xanthan gum was excluded from subsequent formulations and the optimized tablets were developed with HPMC K100M alone. Formulation F9 containing 75 mg HPMC K100M exhibited short bouncy lag time, floated for more than 24 h and released its drug content up to 24 h in a controlled manner without changing the physical integrity of the tablets in the release medium. Drug release was significantly retarded as the amount of HPMC K100M was increased. Formulations F8, F9, and F10 containing 50, 75, and 100 mg HPMC K100M showed MDT values of 7.56, 10.38, and 12.68 h, respectively. This change in MDT may be due to the gelling properties of HPMC K100M resulting in increased diffusion path length for the drug and retardation of drug release rate. As concentration of Crospovidone® increased from 0 mg to 150 mg (F11, F12, F13), the drug was released at faster rates. Crospovidone® with capillary effect, increases penetration of the release medium into the tablets producing micro channels in the polymeric matrix which accelerate drug release from interior part of the tablets. The DE_{14h} was calculated to be 38.59% for F11 and 58% for F13 formulations. The total duration of floating was observed to be more than 24 h. The effect of different amount of sodium bicarbonate on drug release properties was also investigated. As shown in Fig. 5F, in formulation F14 containing 100 mg sodium bicarbonate, no significant difference was observed in dissolution rate as compared with optimized formulation F9 which contained 50 mg of this substance.

Swelling is also a vital factor to ensure bouncy and drug dissolution and also can influence drug release kinetics. The swelling percent of developed gastroretentive tablets is shown in Figs. 2 and 3A and B. Swelling was observed up to 12 h in most formulations but decreased gradually after this time due to the drug release and in some cases by the erosion of polymeric matrix.

Maximum swelling was observed in formulation F13 with the highest amount of Crospovidone® and HPMC. The drug release rate significantly depends on both the water content and diffusion pathway (Siepmann and Peppas, 2001). Polymeric matrices in contact with water build a gel layer around the tablet core. Consequently, a greater extent of swelling at a higher amount of HPMC K100M led to an increase in tablet dimensions and increasing the diffusion pathways and thus decreasing dissolution rates. Crospovidone® with a capillary effect increases the penetration of water into the matrix tablet and because of the mobility of polymer chains depends on the water content of the system, at high water content, polymer chain relaxation takes place with volume expansion and shows high swelling index of these systems. As a result, in the series of formulations with equal amount of HPMC K100M, increasing the amount of Crospovidone® improved the dissolution rate and swelling index at the same time. Bioadhesive property of the optimized formulation (F9) was also studied and found to be 0.68 N. In general, it does not seem that mocuadhesive polymers are able to control and slow down significantly the GI transit time of solid dosage form (Streubel et al., 2006). Nevertheless, apart from floating properties of the tablet, the bioadhesion tendency of HPMCK100M could possibly, to some extent, assist the tablet to remain in upper part of the GI tract and enhance the gastroretention.

Prolonged drug absorption was achieved after administration of optimized formulation (F9) in human volunteers. The

K_a value of adapted formulation was significantly smaller than that of the marketed conventional dosage form which was used as reference ($0.418 \pm 0.13\ h^{-1}$ versus $2.3 \pm 0.42\ h^{-1}$, respectively). MRT values were significantly longer in the optimized formulation (8.65 ± 0.81 h) compared to the conventional formulation (3.75 ± 0.39 h). The pharmacokinetic parameters confirm that polymer content is able to sustain drug release from the matrix tablet. AUC_{0-24} and $AUC_{0-\infty}$ for F9 and conventional formulation were not statistically different ($P > 0.05$). The percent relative bioavailability of F9 formulation was found to be 94.5% which is comparable to that of the marketed product.

Bactericidal activity of ciprofloxacin is concentration-dependent and the $AUC_{0-\infty}$/MIC and C_{max}/MIC ratios are the key determinants in the development of bacterial resistance (Appelbaum and Hunter, 2000). It has been reported that the best therapeutic efficacy for ciprofloxacin is observed when the C_{max}/MIC is more than 10 and $AUC_{0-\infty}$/MIC value is greater than 125 (Schetag, 1999). The desired $AUC_{0-\infty}$/MIC and C_{max}/MIC values could be achieved via twice-daily administration of conventional dosage forms of ciprofloxacin. Where, the gastroretentive floating tablet developed in this study is administered along with an immediate release conventional dosage form once daily could preserve good therapeutic efficacy and safety profiles established for twice-daily of the conventional immediate release ciprofloxacin. Fig. 6 illustrates the plasma concentration time curve after co-administration of a gastroretentive tablet formulation (F9, 500 mg) with a 500-mg conventional tablet of ciprofloxacin. One of the major criteria in the development of this innovative therapeutic system was to obtain once-daily systemic exposure. It is evident that the AUC value following co-administration of developed floating formulation with conventional tablet would be equivalent to that achieved with twice-daily administration of conventional formulation and at least equally effective in medical practice. The second developmental criterion which was the fast achievement of C_{max} to provide rapid onset of action was also attained in our study. Additionally, lower fluctuations in drug plasma levels were observed. It is evident that once-daily co-administration of these two formulations are able to maintain plasma levels within the therapeutic range and also will provide AUC/MIC and C_{max}/MIC equivalent to those of twice-daily 500-mg tablets, thereby retaining activity against pathogens. Oral monolithic matrix of ciprofloxacin containing sodium alginate and xanthan gum as retardant polymers which was designed for once-daily administration has been previously reported (U.S. Patent No. 6, 261, 601, B1). Such systems which release their drug content with a constant manner would not provide the pharmacokinetic properties discussed above. Our results indicate that this developed therapeutic system may facilitate greater patient compliance, which can effectively translate into higher rate of clinical success while also reducing the spread of bacterial resistance.

5. Conclusion

Effervescent prolonged-released gastroretentive tablets of ciprofloxacin were successfully formulated. Tablets containing 75 mg HPMC K100 M as a retarding polymer showed desirable *in vitro* and *in vivo* kinetic properties. The optimized formulation released the drug in a zero-order fashion demonstrated a short buoyancy lag time, total floating time of at least 24 h and could maintain drug release for 24 h. Based on pharmacokinetic parameters, once-daily administration of this new formulation accompanied with a 500 mg immediate release tablet of ciprofloxacin promise to be a suitable alternative formulation dosing strategy compared to the twice-daily administration of a conventional release product.

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