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Floating tablets for controlled release of ofloxacin via compression coating of hydroxypropyl cellulose combined with effervescent agent

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ABSTRACT

To prolong the residence time of dosage forms within gastrointestinal trace until all drug released at desired rate was one of the real challenges for oral controlled-release drug delivery system. Herein, we developed a fine floating tablet via compression coating of hydrophilic polymer (hydroxypropyl cellulose) combined with effervescent agent (sodium bicarbonate) to achieve simultaneous control of release rate and location of ofloxacin. Sodium alginate was also added in the coating layer to regulate the drug release rate. The effects of the weight ratio of drug and the viscosity of HPC on the release profile were investigated. The optimized formulations were found to immediately float within 30 s and remain lastingly buoyant over a period of 12 h in simulated gastric fluid (SGF, pH 1.2) without pepsin, indicating a satisfactory floating and zero-order drug release profile. In addition, the oral bioavailability experiment in New Zealand rabbits showed that, the relative bioavailability of the ofloxacin after administrated of floating tablets was 172.19%, compared to marketed common release tablets TaiLiBiTuo®. These results demonstrated that those controlled-released floating tables would be a promising gastro-retentive delivery system for drugs acting in stomach.

1. Introduction

Oral route was one of the most convenient and preferable ways for drug administration (Kagan and Hoffman, 2008), when the bioavailability of peroral drug delivery systems was determined by various factors, including the retention time of those dosage forms within the gastrointestinal tract (GIT). It has been reported that the extent of drug absorption from the GIT was related to their contact time with the small intestinal mucosa (Deshpande et al., 1996; Hirtz, 1985), while most of the conventional oral delivery systems have shown some limited bioavailability due to fast gastric-emptying time (Acharya et al., 2014). Thus, the real challenge of developing a controlled drug delivery system was not just to sustain the drug release but also to prolong the residence time of the dosage form in the stomach or the upper small intestine until all drug released at the desired rate (Zhu et al., 2014). Hence, an optimum gastro retentive dosage forms (GRDF) system could be defined as a system which would retain in the stomach for a sufficient time interval against physiological barriers with drug releasing in a controlled manner, and finally be easily metabolized in the body (Pawar et al., 2011). Currently, GRDF may be broadly classified into: high-density (sinking) systems, low-density (floating) systems, expandable systems, superporous hydrogel systems, mucoadhesive systems and magnetic systems (Bardonnet et al., 2006).

Among them, floating drug delivery system (FDDS) could basically float in the gastric fluid and prolong GRT to obtain sufficient drug bioavailability (Baumgartner et al., 2000; Sauzet et al., 2009; Singh and Kim, 2000), because of their lower bulk density compared to that of the aqueous medium. Typically, FDDS could be divided into two types: effervescent drug delivery systems which depended on the generation of carbon dioxide gas upon contact with gastric fluids and non-effervescent drug delivery systems. According to previous report, FDDS was desirable for those drugs: (i) act locally in stomach; (ii) have a narrow absorption window in the small intestinal region; (iii) are unstable in the intestinal environment and (iv) have poor solubility in a high pH environment (Bardonnet et al., 2006; El Gamal et al., 2011; Nagarwal et al., 2010; Talukder and Fassihi, 2004).

Ofloxacin is a fluoroquinolone antibacterial agent, which has a broad antimicrobial spectrum against both gram-positive and

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gram-negative bacteria, which has been approved for use in the treatment of gastrointestinal infections, respiratory tract infections and urinary tract infections (Zivanovic et al., 2006). Ofloxacin was readily soluble in stomach of acidic environment, but prone to precipitate in the intestine of neutral or slightly alkaline pH values, which affected their absorption in the lower section of the intestine. Apart from solubility, the absorption site is the upper part of the gastrointestinal tract (Chavanpatil et al., 2005). Therefore, various floating systems for ofloxacin have already been investigated. Chavanpatil et al. (2005) have developed ofloxacin sustained release tablet using psyllium husk, HPMC K100 M, crospovidone and sodium bicarbonate. However, when the tablets were immersed in simulated gastric fluid, the floating tablets showed burst drug release in the first 2 h. Zhang et al. (2012) reported a floating multi particulate system for ofloxacin based on a multilayer structure by coating with a release retarding film (EC), an effervescent layer ($NaHCO_3$) and a gas-entrapped polymeric membrane (Eudragit® RL 30D), respectively. The analysis of the release mechanism showed a zero-order release for the first 8 h. However, the film coating technique is complicated and expensive (Zhang et al., 2012).

In order to overcome those drawbacks mentioned above, we combined floating drug delivery systems with controlled release systems to realize simultaneous control of drug release rate and location. Moreover, researchers found that compression-coated tablet was promising candidate to control drug release rate. A novel compression coating tablet is design to achieve zero-order release by similar release manner with the osmotic systems (Guo and Shi, 2009). Drawing on the concept, we design a novel floating drug delivery system based on the compression coating technology combined with effervescent agent.

The aim of this study were to prepare fine floating tablets via compression coating and investigate the possibility of those tablets as a delivery system for controlled release of ofloxacin. The hydrophilic polymer (hydroxypropyl cellulose) combined with effervescent agent (sodium bicarbonate) was used as the functional materials, while the sodium alginate was also utilized in the coating layer to control the drug release rate. The effects of formulation factors on the *in vitro* drug release behavior of those zero-order released floating tablets were studied, as well as the swelling and floating ability. Moreover, the oral bioavailability evaluation was executed in rabbits compared with market tablets TaiLiBiTuo®.

2. Materials and methods

2.1. Materials

Ofloxacin (OFLX) was obtained from Yangtze Pharmaceutical Co., Ltd. (Taizhou, China). Three viscosity grades of hydroxypropyl cellulose (HPC) (HPC-SL: 4.0 mPa s; HPC-L: 8.0 mPa s; HPC-M: 350 mPa s) were gifted from Nippon Soda Co., Ltd. (Yokyo, Japan), and were used as a binder and hydrophilic materials to control the release rate of the compression-coated tablet. Sodium bicarbonate was obtained from Lingfeng Chemical Reagent Co., Ltd. (Shanghai, China). Magnesium stearate was obtained from Sunhere Pharmaceutical Excipients Co., Ltd. (Anhui, China). Sodium alginate was obtained from Huanghai Pharmaceutical Co., Ltd. (Qingdao, China). All other materials were of reagent grade and used as received. The marketed immediate release tablets TaiLiBiTuo® were used as the reference.

2.2. Method

2.2.1. Preparation of compression-coated floating tablet

2.2.1.1. Preparation of core tablets. The core tablets were prepared by a conventional wet granulation method. The powder mixture of ofloxacin and HPC were passed through a 80-mesh sieve to obtain a well-dispersed mixture and wet massed with ethanolic solution as the binder. The soft material was forced through a 40-mesh sieve. The granules were dried for 2 h at 60 °C in the oven (DHG-9245A, Shanghai Huiyi Technology Co., Ltd., China) and resized by passing through a 24-mush sieve. Magnesium stearate was added into the granules as a lubricant and mixed for 10 min. Tablets were prepared by 7 mm flat-face punch with single press tableting machine (Shanghai Pharmaceutical Machinery Factory, China). The hardness of the tablets was adjusted as 40–50 N using a Monsanto hardness tester (Shanghai Huanghai drug test instrument Co., Ltd., China). As shown in Table 1, optimized batch containing ofloxacin 80 mg, HPC 10 mg and magnesium stearate 0.5 mg in 90.5 mg tablet.

2.2.1.2. Preparation of compression-coating layer. A wet granulation method was applied to prepare the partial granules of the compression-coated layer (Huang et al., 2013). The compression-coating layer was prepared according to the design depicted in Table 1. The respective powder, namely ofloxacin, release-retarding polymer (sodium alginate), and a gas-forming agent ($NaHCO_3$) were mixed homogeneously and kneaded with binder solution. 5% HPC-SL was added to the mixture of ethanolic and water (9:1) to prepare the binder solution. The formed dough was passed through 40-mush sieve, dried and received through 40-mush sieve. The mixture of HPC-L and HPC-M was passed through 80-mush sieve, and then mixed with the granules and magnesium stearte as the coating layer.

2.2.1.3. Compression coating of core tablet. Half mount of prepared granules used for shell formation in each tablet, and 7 mm diameter tablet cores were compression-coated into 11 mm diameter tablets. The compression-coated tablets were prepared by first filling one-half of the coating layer powders into the die to form a powder bed. In the center, the tablet core was positioned on the powder bed followed by filling the remaining half of the compression-coated layer on top and then tablet under force of 70 N.

Table 1
The core tablet and coating layer Formulation of the floating controlled-release tablets of ofloxacin.

Formula code	Core tablet		Coating layer							
	f1	f2	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	80	80	120	120	120	120	120	120	120	120
HPC-L (mg)	10	–	50	90	120	90	90	90	90	90
HPC-M (mg)	–	10	120	80	50	80	80	80	80	80
Na alginate (mg)	–	–	30	30	30	10	45	30	30	-
$NaHCO_3$ (mg)	–	–	70	70	70	70	70	50	90	70
Mg stearate (mg)	0.5	0.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total (mg)	90.5	90.5	391.5	391.5	391.5	371.5	406.5	371.5	416.5	361.5

2.2.2. In vitro buoyancy study

The floating behavior of the compressed-coated tablets was visually determined in triplicate. The tablets were placed in a 250 ml beaker, containing 200 ml of 0.1 M HCl, maintained in a water bath at 37 ± 0.5 °C. The time required for the compressed-coated tablet to rise to the surface and float was determined as floating lag time (FLT) and the time period up to which the tablet remained buoyant is determined as total floating time (TFT).

2.2.3. Determination of compression-coated tablets swelling ability

The swelling property of the compression-coated was determined according to the method described by Dorożyński et al. (2011). Briefly, the tablets were weighed individually (designated as W_0) and placed in a glass beaker, containing 200 mL of 0.1 M HCl and incubated at 37 ± 0.5 °C. At regular 2 h time intervals until 12 h, the tablets were removed and the excess surface liquid was carefully removed by a filter paper (Dorożyński et al., 2011). The swollen floating tablets were then reweighed (W_t) and the selling index (SI) was calculated using the following formula:

$$\mathrm{SI} = \frac{W_t - W_0}{W_0}$$

2.2.4. In vitro *release study*

In vitro dissolution study of ofloxacin from the compression-coated tablet was performed using USP dissolution apparatus II (Paddle method) at a rotation speed of 100 rpm in 900 mL of 0.1 M HCl at 37 ± 0.5 °C (Tadros, 2010). Ten milliliter of aliquot were withdrawn at predetermined time intervals of 0.5, 1, 2, 4, 6, 8, 10 and 12 h. Collected samples were filtered through a cellulose acetate membrane (0.45 μm) and assayed at 294 nm on a UV spectrophotometer after suitable dilutions. At each time of withdrawal, 10 mL of fresh medium was replenished into the dissolution flask. All tests were carried out in triplicate.

The mechanism of the drug release was evaluated using zero-order model, first-order model, Higuchi model and Korsmeyer–Peppas model. The data were evaluated according to the following equations:

Zero-order model:

$$\frac{M_t}{M_\infty} = kt$$

First-order model:

$$\ln\left(1 - \frac{M_t}{M_\infty}\right) = -kt$$

Higuchi equation:

$$\frac{M_t}{M_\infty} = kt^{1/2}$$

Korsmeyer–Peppas model:

$$\frac{M_t}{M_\infty} = kt^n$$

where $M_t/M_\infty$is the fraction of drug released, k is a constant incorporating structural and geometric characteristics of drug dosage form, and n is the diffusional exponent. The equation was treated logarithmically to determine the value of release exponent, n; the value of n is indicative of mechanism of drug release. For a matrix tablet, when n takes the value of 0.45 it indicates diffusion-controlled drug release and for the value 0.89, it indicates swelling-controlled drug release. Values of n between 0.45 and 0.89 can be regarded as an indicator for both the phenomena (anomalous transport) (Donbrow and Samuelov, 1980; Korsmeyer et al., 1983).

2.2.5. In vivo evaluation of the floating tablets in New Zealand rabbits

All the animal experiments were approved and supervised conducted by the China Pharmaceutical University Ethics Committee of Care and Use of laboratory Animals, and the animals were house and handled according to the University Unit for Laboratory Animal Medicine guidelines.

Three healthy New Zealand rabbits (weighting 2.0–2.5 kg) were fasted overnight with free access to water. In addition, 20 mL water was given to every rabbit until 8 h after the test preparation administration (Zhang et al., 2012). After oral administration of the test preparation, 2.5 mL of venous blood samples were collected from the ear vein and placed in heparinized tubes at predetermined time intervals. The blood samples were prepared by centrifugation at 4000 × *g* for 10 min in an Nr. 12154 rotor (Sigma 3K30). The plasma was separated and then kept frozen at −20 °C until determination. A washout period of at least 1 week between two consecutive administrations was allowed to eliminate the effect of the prior doses before the nest drug administration.

The analytical method using to determine ofloxacin concentration in the plasma was undergoing some modification. 200 μL of plasma was thoroughly mixed with 40 μL of tinidazole methanol solution (20 μL/mL) as the internal standard solution, then 500 μL of acetonitrile was added and vortexed for 2 min to precipitate plasma proteins, followed by centrifugation (10,000 rpm) for 10 min. The supernatant was removed and evaporated to dryness under nitrogen at 45 °C. The enrichment was reconstituted in 200 μL mobile phase by vortex-mixing for 10 min. Then, 20 μL resulting aqueous solution was injected (Cui et al., 2008).

Chromatography was carried out by HPLC using the LC-10AT liquid chromatograph (Shimadzu, Kyoto, Japan). Separation was obtained using a reversed-phase column (Inertsil ODS-3, 4.6 × 250 mm i.d. 5 μm, GL Science, Japan) with a protective column and UV detection (Shimadzu, Kyoto, Japan) was performed at 294 nm. The mobile phase was a mixture of 0.05 mol/L citric acid (pH of the aqueous triethylamine to 4.0): acetonitrile (82:18, v/v) pumped at a flow rate of 1 mL/min. Methodological studies, such as linearity, specificity, precision of with-in and between days were demonstrated to satisfy the requirements of the methodology. Pharmacokinetic data analysis was carried out using non-compartmental pharmacokinetics data analysis software (Kinetic 4.4.1TM, Thermo Electron Corporation, USA). The area under the plasma concentration-time curve $AUC_{(0\rightarrow t)}$ was calculated. The maximum plasma concentration (C_{max}) and time to reach the maximum plasma concentration (T_{max}) were obtained actual observations.

2.2.6. Data statistical analysis

The results were analyzed by ANOVA with Bonferroni post *t*-tests using Graph Pad Instat Software-1.13 (Graph Pad Software, San Diego, CA, USA) and $p < 0.05$ was considered statistically significant.

3. Results and discussion

3.1. Physicochemical characteristics of tablets

Controlled-release ofloxacin effervescent floating tablets were investigated using release-retarding gel-forming polymer like HPC and sodium alginate and a gas-forming agent like $NaHCO_3$. In the previous work, hardness was a determining factor to the buoyancy ability of the tablets but had little effect on the drug release profile (Singh et al., 2014). Increasing the hardness would possibly lead to prolongation of the floating lag time by affecting the rate tablet penetration by the dissolution medium. Based on these conclusions, the hardness of the floating was adjusted, in the current work, which was ranging between 60–70 N.

Table 2
The floating lag time and total floating time of the prepared ofloxacin floating controlled-release tablets (mean ± SD, $n = 3$).

Formula code	Floating lag time (s)	Total floating time(h)
F1	27.07 ± 2.04	>12
F2	19.25 ± 0.81	>12
F3	15.33 ± 1.65	8
F4	24.35 ± 1.06	>12
F5	20.47 ± 1.25	>12
F6	36.23 ± 0.90*	>12
F7	10.43 ± 1.14*	>12
F8	37.81 ± 0.27	>12

* $p < 0.05$ *vs.* F2.

3.2. In vitro buoyancy study

The investigated gastro-floating tablet employed $NaHCO_3$ as a gas-forming agent, sodium alginate as release-retarding agent dispersed in a hydrogel matrix (HPC-L and HPC-M). The carbon dioxide gas is produced by the acidity of the gastric content and is entrapped in the hydrocolloid, so the tablets float upon in the stomach. Thus, there are three main influencing factors about the floating lag time and duration: the ratio of hydrogel matrix (HPC-L and HPC-M), the amount of $NaHCO_3$ and sodium alginate.

Most test tablets could float in the fluid for more than 12 h, but their values of FLT varied between different formulations (Table 2 and Fig. 1). HPC-L or HPC-M was a sustain-release material and its density became lower when the polymer was swelling in the fluid. The ratio of HPC-L/HPC-M has effect both on the floating lag time and the floating duration. Increasing the ratio of HPC-L/HPC-M from 5:12 to12:5 (F1, F2 and F3), the FLT decreased from 27.07 ± 2.04 to 15.33 ± 1.65 s. However, the total floating time shortened from 12 to 8 h at the same time. Thus, when the ratio of HPC-L/HPC-M in the tablets increased, the FLT increased and the floating duration decreased, suggesting that the hydration and gas forming process of the tablets shortened. To adjust the floating lag time and floating duration, 9:8 was choose as the optimal ratio of HPC-L/HPC-M.

One of the factors influencing the FLT is the amount of $NaHCO_3$. The FLT for the formulations F2 (19.25 ± 0.81 s) had significantly shorter ($p < 0.05$) than that of F6 (36.23 ± 0.90 s). Similar behavior was observed with the F7 and F2 (10.43 ± 1.14 and 19.25 ± 0.81 s, respectively). Thus, increasing the amount of $NaHCO_3$, the FLT decreases. This phenomenon might be due to the larger amount of $NaHCO_3$ lead to an increase in the rate of pore formation and consequently rapid hydration of the hydrogel matrix (Choi et al., 2002). As shown in Table 2, the amount of sodium alginate also has no significantly effect on the floating lag time prepared with a constant $NaHCO_3$. Moreover, there was no significant difference between F2 and F5 (19.25 ± 0.81 and 20.47 ± 1.25 s). This could be explained with the rate of the test medium penetration into these matrices, may be external sodium alginate need shorter the time to form external gel compared with HPC. Thus, the density of the tablets reduced more quickly with the increasing amount of sodium alginate and consequently the floating lag time was decreased to some extent.

3.3. Swelling indices

The swelling hydration ability of the formula has a significantly effect on the tablet buoyancy and drug release kinetics. As shown in Fig. 2, the uptake of the prepare matrices depends on the type of polymer. The percent swelling of F2 gradually increased up to 8 h and then gradually decreased till 12 h. However, the formulation without Sodium alginate had the maximum swelling at 4 h after which polymer started eroding slowly in the medium. As Viridén et al. (2009) reported, the swelling behavior of the hydrophilic tablets starts with water diffusion into the glassy material, then a highly concentrated polymer solution is formed. The solvent continues to penetrate the tablet, and the gel layer and dimensions of the swollen tablet increase, a process normally referred to as the swelling process. Thus, the phenomenon shown in Fig. 2 may due

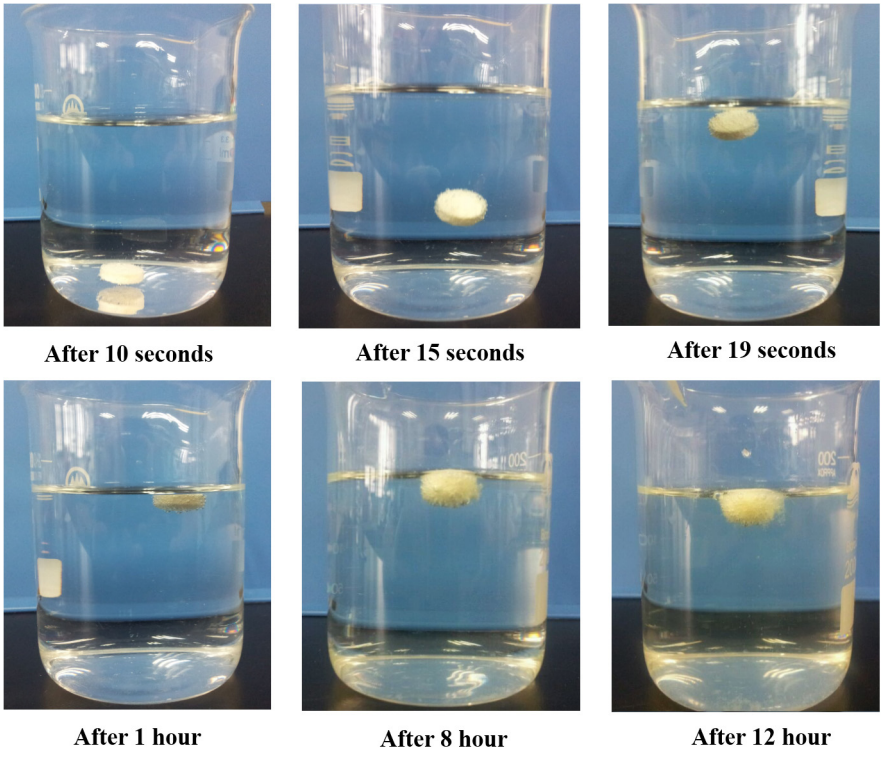

Fig. 1. Photographs taken during *in vitro* buoyancy study of formula F2 in 200 mL 0.1 N HCl at different time intervals.

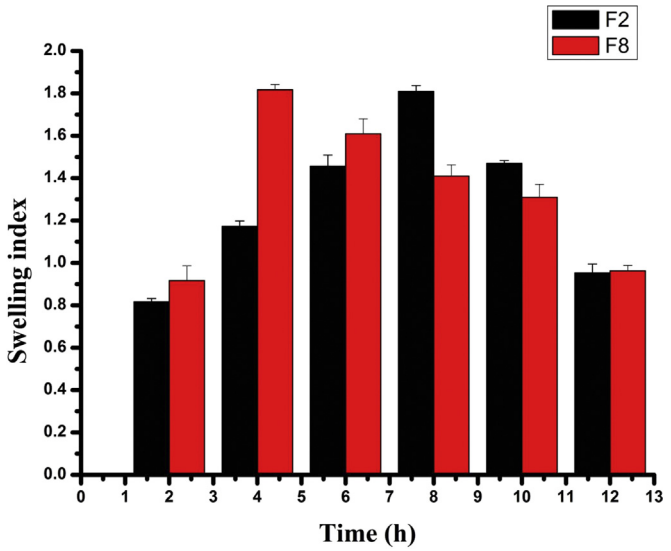

Fig. 2. Effect of different kinds of hydrogel matrix material on swelling behavior (mean ± SD, $n = 6$).

to the property of Sodium alginate to retain water and create a hydrocolloidal layer of high viscosity in the presence of 0.1 M HCl solution. The thick swollen Sodium alginate hydrocolloidal layer decreased the migration of small molecules such as water or drug, hence the swelling rate was slowed and corresponding with the studies *in vitro* release.

3.4. Drug release studies

The weight ratio of ofloxacin in the core and the coating layer is an important factor of the designing tablets to achieve a zero-order release. Different ratio might cause flexible extent drug release profiles such as pulsatile, sigmoidal, decreasing/increasing rates with time. It was shown in Fig. 3 that different ratio of ofloxacin in the core and the coating layer had different release profiles. The weight ratio 1:1 or 2:3 (core: coating layer) can be achieved a zero-order release of the floating tablets, while the release of weight ratio 1:1 was not stable (the coating layer was too thin to control drug release). Thus, the weight ratio 2:3 (core: coating layer) was choose for the further.

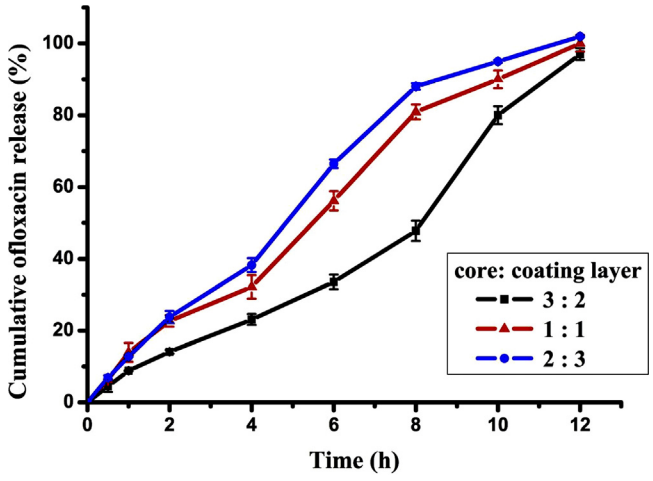

Fig. 3. Dissolution profiles of ofloxacin releasing from the floating tablets with different drug ratio in the core tablet and the coating layer under the condition of 0.1 M HCl at 37 °C (mean ± SD, $n = 6$).

It is commonly used a hydrophilic matrix, rate-controlling polymer to control the release of oral drugs (Tiwari and Rajabi-Siahboomi, 2008). HPC is a non-ionic water soluble cellulose ether with a remarkable combination of properties. A compression-coated tablets system was made with HPC in the outer layer display a zero-order controlled release function (Huang et al., 2013). The influence of viscosity grade of the HPC on the coating layer and core tablets drug release rate was investigated. As was shown in Fig. 4a, the drug release profiles of core tablets with different viscosity grades have a significant difference. HPC-L with a low viscosity showed a quick water uptake rate so the dissolution of the hydrogel layer was rapid. As the viscosity grade of HPC-M was higher, it showed a relatively high swell tendency. Thus, the release rate decreased in the order of HPC-L and HPC-M. In this paper, HPC-M might be more appropriate for the core tablet to achieve a zero-order release of the floating tablets. In order to adjust the release rate, mixtures of HPC-L and HPC-M were utilized in the coating layer to modify the viscosity of the gel. The water penetrating rate decreased with increasing HPC-M ratio, causing slower drug release. In this paper, zero-order release could be achieved by the weight ratio of 9:8 (HPC-L:HPC-M) in the coating layer (Fig. 4b).

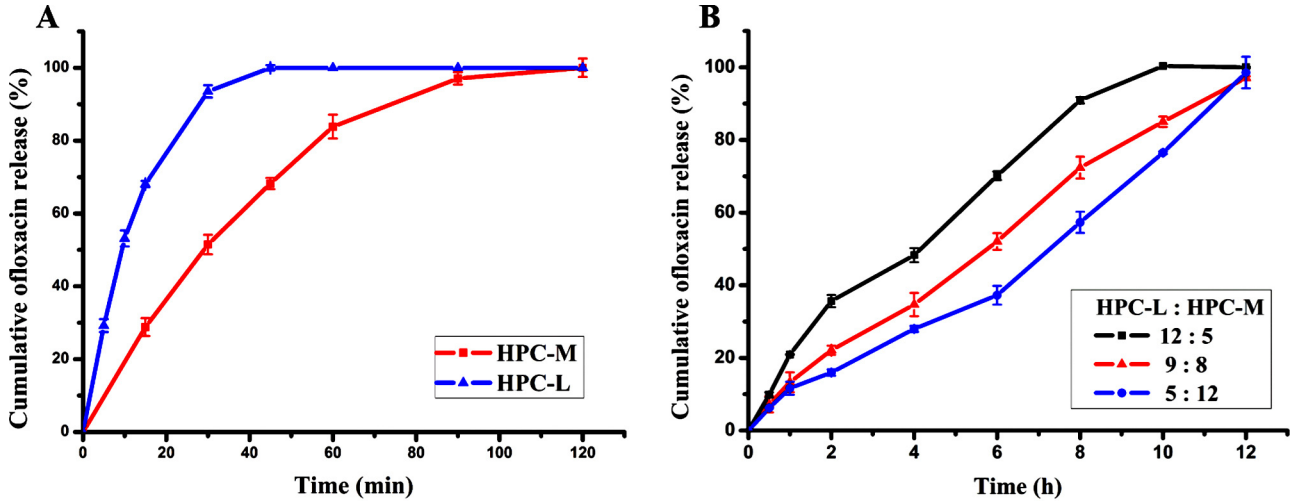

Fig. 4. Dissolution profiles of ofloxacin releasing from the core tablets (a) and floating tablets(b) with different viscosity grade HPC under the condition of 0.1 M HCl at 37 °C (mean ± SD, $n = 6$).

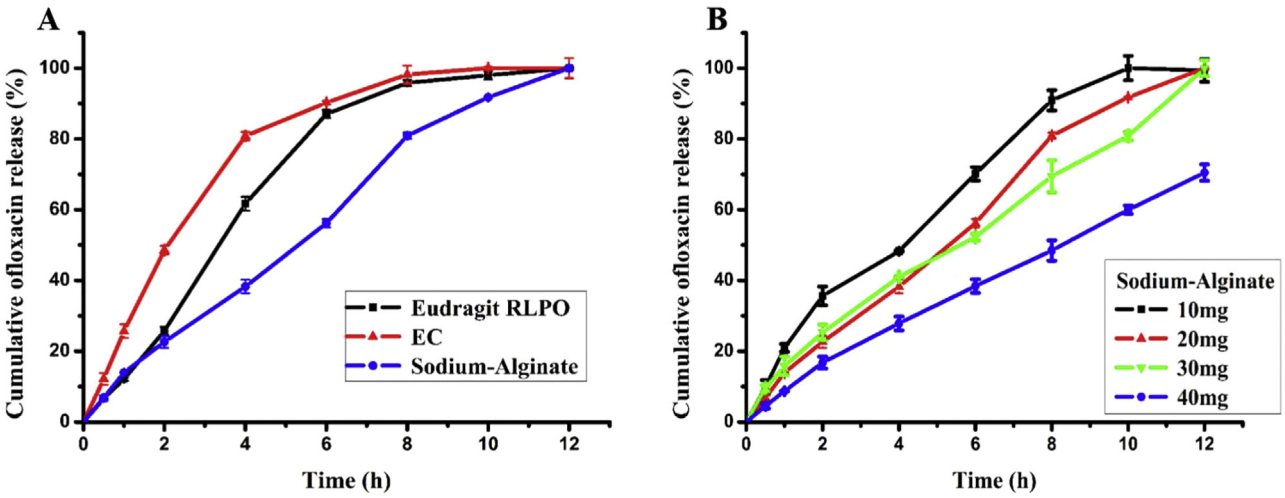

Fig. 5. Dissolution profiles of ofloxacin releasing from the floating tablets with different kind (a) and concentration (b) of release-retarding agent under the condition of 0.1 M HCl at 37 °C (mean ± SD, $n = 6$).

The influence of the release-retarding agent type (sodium alginate, Eudragit® RL PO or EC) and dosage (10–45 mg) on the release of the drug from the floating tablets was shown in Fig. 5a and b, respectively. In identical quantities, sodium alginate, Eudragit® RL PO or EC significantly influence the release profiles. It is well known that water-soluble drugs are mainly released based on diffusion through gel layer. EC and Eudragit® RL PO could not dissolve in 0.1 M HCl, they can decrease the erosion rate of the gel. Then, the diffusion rate of drug was reduced in some way. However, at low pH hydration of sodium alginate leads to the formation of a high-viscosity acid gel. The alginate molecule will undergo an almost immediate hydration to create a hydrocolloidal layer. This makes up a diffusion barrier extremely decreasing the drug molecules release from the tablets (Tønnesen and Karlsen, 2002). Moreover, the influence of the concentration of sodium alginate on drug release rate was investigated. Dissolution studies showed that drug release at 8 h markedly decreased from 90% to 48% as the amount of Sodium alginate increased from 10 mg to 45 mg. An inverse relationship was observed between the amount of sodium alginate and drug release rates. Along with the increase of Sodium alginate, thickness of the polymeric gel layer increased with decreased porosity, therefore decreased the drug release from the tablet.

Sodium bicarbonate acted as a gas generating agent in the formulation, it generated gas when contacted with an acidic environment of the stomach. The influence of $NaHCO_3$ concentration on drug release was shown in Fig. 6. As the amount of $NaHCO_3$increased from 50 mg to 100 mg per tablet, the drug release rate did not have a significant different in the first 2 h, but obviously increased in the next 8 h.This phenomenon might be due to the higher $NaHCO_3$ percentage in the formulation. This would lead to an increase in the rate of pore formation and consequently rapid hydration of the tablets matrices, followed by quickly drug release (Gambhire et al., 2007).

Taking the aim of the work of achieving a compromise between excellent floating behavior (short floating lag time and prolonged floating duration) and controlled drug release characteristics, F2 was chosen for further studies. The drug release from the polymeric systems is mostly by diffusion and is best described by Fickian diffusion. However, the factors affecting the drug release of matrix tablets seemed very complicated, hydration of the polymer, water penetration into polymer matrix, erosion of the gel layer etc., those in the process of drug release could be involved (Chavanpatil et al., 2006). Korsmeyer and Peppas equation superposes two apparently independent mechanism of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer (Korsmeyer et al., 1983). The results of release kinetics analyses of the drug from the floating controlled release tablets are shown in Table 3. The floating controlled release tablets fit the zero-order model well *in vitro* dissolution test. The diffusional exponent n for the floating controlled-release tablets was found to be 0.827, which is between the range of 0.45–0.89. Thus, the drug release should be ascribed to an anomalous transport, which indicate the drug release is controlled by more than one process: diffusion and erosion.

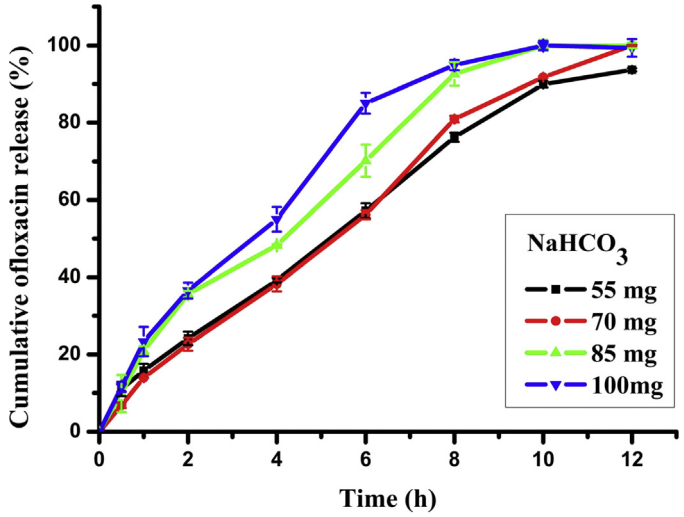

Fig. 6. Dissolution profiles of ofloxacin releasing from the floating tablets with different concentrations of $NaHCO_3$ under the condition of 0.1 M HCl at 37 °C (mean ± SD, $n = 6$).

Table 3
Mathematical modeling and release kinetics of ofloxacin from the prepared tablets.

Model	K	R^2	n
Zero-order model	0.082	0.995	–
First-order model	0.298	0.789	–
Higuchi	0.302	0.960	–
Korsmeyer–Peppas	0.127	0.999	0.827

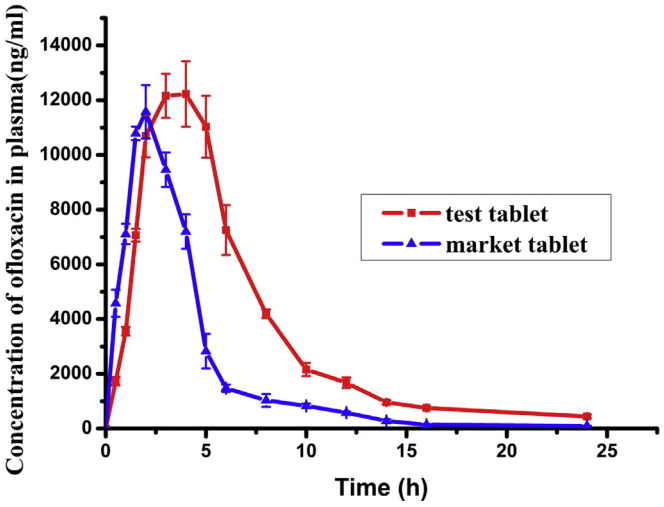

Fig. 7. Mean plasma concentration-time profiles of ofloxacin from the test and the marketed tablets following oral administration (mean ± SD, $n = 3$).

3.5. In vivo *study*

The floating tablet exhibit excellent *in vitro* floating behavior and dissolution study, then the bioavailability was studies to affirm the pharmacokinetic parameters. The plasma concentration-time profiles of the gastro-floating and market tablets in three New Zealand rabbits are illustrated in Fig. 7 and the main pharmacokinetic parameters are presented in Table 4. The mean value of C_{max} was 12,298.85 ± 1193.56 ng/mL and the T_{max} was 3.15 ± 0.56 h after oral administration of floating controlled-release tablets. However, the after oral administration of market tablets the average value of C_{max} was 11,575.37 ± 973.23 ng/mL and the T_{max} was 1.80 ± 0.23 h. The C_{max} of the test was similar with that of the market tablet, while the drug concentration of the test tablet maintained a higher level than that of the market tablet. The AUC_{0-t} values of the test and market preparation were 83,009.05 ± 1057.53 and 48,208.61 ± 1955.21 h ng/mL. The higher drug concentration and AUC_{0-t} was due to the slow release and sustained absorption, or the prolonged grastric residence time (Hu et al., 2011). Moreover, Marier has reported that oflocxacin exhibits concentration-dependent antibacterial activity (Marier et al., 2006), thus the test tablets may be more effective than the market tables. Table 4 also shows that the value of MRT had a significant difference ($p < 0.05$) between the test preparation (6.60 ± 0.13 h) and the market tablets (4.23 ± 0.27 h). While MRT representing the resistance time *in vivo*, it indicated that the test preparation really had a longer gastro retention time than the market tablet. In conclusion, the floating controlled-release tablets were efficient to improve the oral bioavailability since it prolongs the residence time in the major absorption site.

Table 4
Pharmacokinetics parameters obtained following oral administration of marketed Tailibituo® and the floating controlled-release tablets containing ofloxacin to rabbits (mean ± SD, $n =$).

Parameters	Unit	Test	Market
$AUC_{(0-t)}$	h ng/ml	83009.05 ± 1057.53	48208.61 ± 1955.21**
$AUC_{(0-\infty)}$	h ng/ml	85386.67 ± 1253.97	48720.57 ± 2048.05**
T_{max}	h	3.15 ± 0.56	1.80 ± 0.23**
C_{max}	ng/ml	12298.85 ± 2620.04	11808.71 ± 736.81
MRT	h	6.60 ± 0.13	0.12**

* $p < 0.05$.
** $p < 0.01$.

4. Conclusion

In the present study, controlled-release floating tablets of ofloxacin were successfully formulated by employing $NaHCO_3$ as a gas-forming agent, Na alginate as retarding agent and HPC as matrix. The tablets could float on the surface of artificial gastric fluid over 12 h and control the drug release for 12 h. Furthermore, the controlled-release floating tablets could improve the bioavailability without increasing the fluctuation of plasma concentrations. In summary, the controlled-release floating tablets can prolong the residence time of drug in the major absorption site and achieved a controlled-release effect and excellent bioavailability.

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