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Research paper

Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and *in vitro–in vivo* evaluation in healthy human volunteers

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ABSTRACT

Ciprofloxacin hydrochloride has a short elimination half-life, a narrow absorption window and is mainly absorbed in proximal areas of GIT. The purpose of this study was to develop a gastroretentive controlled-release drug delivery system with swelling, floating, and adhesive properties. Ten tablet formulations were designed using hydroxypropylmethylcellulose (HPMC K15M) and/or sodium alginate (Na alginate) as release-retarding polymer(s) and sodium bicarbonate ($NaHCO_3$) or calcium carbonate ($CaCO_3$) as a gas former. Swelling ability, floating behaviour, adhesion period and drug release studies were conducted in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C. The tablets showed acceptable physicochemical properties. Drug release profiles of all formulae followed non-Fickian diffusion. Statistical analyses of data revealed that tablets containing HPMC K15M (21.42%, w/w), Na alginate (7.14%, w/w) and $NaHCO_3$ (20%, w/w) (formula F7) or $CaCO_3$ (20%, w/w) (formula F10) were promising systems exhibiting excellent floating properties, extended adhesion periods and sustained drug release characteristics. Both formulae were stored at 40 °C/75% RH for 3 months according to ICH guidelines. Formula F10 showed better physical stability. Abdominal X-ray imaging of formula F10, loaded with barium sulfate, in six healthy volunteers revealed a mean gastric retention period of 5.50 ± 0.77 h.

1. Introduction

The real challenge in the development of an oral controlled-release drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form within the gastrointestinal tract (GIT) until all the drug is completely released at the desired period of time [1]. Indeed, gastric drug retention has received significant interest in the past few decades. Most of the conventional oral delivery systems have shown some limitations related to fast gastric-emptying time [2].

Garg and Gupta [3] classified the gastroretentive dosage forms into four main classes: (i) floating systems [4], (ii) expandable systems [5], (iii) bioadhesive systems [6] and (iv) high density systems [7]. Floating systems are of two types: (A) effervescent systems, depending on the generation of carbon dioxide gas upon contact with gastric fluids, and non-effervescent systems. The latter systems can be further divided into four sub-types, including hydrodynamically balanced systems [8], microporous compartment systems [9], alginate beads [10] and hollow microspheres/microballons [11]. In addition, super-porous hydrogels [12] and magnetic systems [13] were described.

As suggested by Singh and Kim [14], floating drug delivery is of particular interest for drugs which: (a) act locally in the stomach; (b) are primarily absorbed in the stomach; (c) are poorly soluble at an alkaline pH; (d) have a narrow window of absorption; and (e) are unstable in the intestinal or colonic environment.

Ciprofloxacin hydrochloride (Cipro HCl) is a broad spectrum fluoroquinolone antibiotic. It is approved for use in the treatment of bone and joint infections, infectious diarrhea, lower respiratory tract infections, urinary tract infections, hospital-acquired infections and meningococcal prophylaxis [15]. Since the drug is freely soluble in water (1 g in 25 mL) and has a short elimination half-life of about 4 h, various sustained-release preparations were prepared aiming to enhance its antibacterial activity [16,17]. It has a narrow absorption window [18] and is mainly absorbed in the proximal areas of GIT [19]. Therefore, certain Cipro HCl floating systems were developed by some research groups [18–20].

The objective of the present investigation was the design and *in vitro*/*in vivo* evaluation of more promising Cipro HCl effervescent floating tablets based on: (i) release-retarding gel-forming polymers like hydroxypropylmethylcellulose (HPMC K15M) and/or sodium alginate (Na alginate) and (ii) a gas-former like sodium

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bicarbonate ($NaHCO_3$) or calcium carbonate ($CaCO_3$). The optimum formula that combined excellent floating behaviour, extended adhesion period, sustained drug release characteristics and showed good physical stability after storage at 40 °C/75% RH for 3 months was chosen for further *in vivo* investigations in six healthy human volunteers to determine the mean gastric retention period.

2. Materials and methods

2.1. Materials

Ciprofloxacin hydrochloride and hydroxypropylmethylcellulose K15M were kindly provided by Egyptian Int. Pharmaceutical Industries Co. (EIPICO) (10th of Ramadan city, Egypt). Low viscosity sodium alginate was purchased from SD Fine Chemicals Ltd. (Mumbai, India). Hydrochloric acid and barium sulfate (extra pure quality for X-ray diagnosis) were obtained from E. Merck (Darmstadt, Germany). Silicified microcrystalline cellulose (Prosolv® 90) was procured from JRS Pharma (Rosenberg, Germany). Magnesium stearate was purchased from CG Chemikalien (Laatzen, Germany). Sodium bicarbonate and calcium carbonate were obtained from El-Nasr Pharmaceutical Chemicals Co. (Abu Zaabal, Egypt).

2.2. Preparation of Cipro HCl floating tablets

Tablets containing 291 mg Cipro HCl (equivalent to 250 mg ciprofloxacin) were prepared, according to the design depicted in Table 1, by direct compression. The respective powders, namely Cipro HCl, release-retarding polymer(s) (HPMC K15M and/or sodium alginate), a gas-forming agent ($NaHCO_3$ or $CaCO_3$) were passed through sieve no. 20, separately. Mixing of powders was carried out using a pestle and mortar for 10 min. Prosolv® 90 and magnesium stearate were then added to the mixed powders. Mixing was continued for another 3 min. Finally, 700 mg of each mixture were weighed and fed manually into the die of a single punch tabletting machine (Royal artist, Bombay, India), equipped with flat-faced punches (11.0 mm), to produce the desired tablets. The hardness of the tablets was adjusted at 5 kg/cm^2 using a Monsanto hardness tester (Monsanto Chemical, St. Louis, MO).

2.3. In vitro evaluation of the prepared tablets

2.3.1. Tablet weight variation

Twenty tablets were randomly selected and accurately weighed. Results are expressed as mean values ± SD.

2.3.2. Tablet thickness

A vernier caliper (For-bro Engineers, Mumbai, India) was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values ± SD.

2.3.3. Drug content uniformity

Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (700 mg) was extracted in 100 mL of 0.1N HCl. The solution was filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined by UV spectroscopy (1601-PC Double beam spectrometer, Shimadzu, Kyoto, Japan) at a wavelength of 278 nm after a suitable dilution with 0.1 N HCl.

2.3.4. Tablet friability

According to the BP specifications [21], 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus (FAB-2, Logan Instruments Corp., NJ, USA). The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated.

2.3.5. Tablet swelling ability

The swelling behaviour of the tablets was determined, in triplicate, according to the method described by Dorozynski et al. [22]. Briefly, a tablet was weighed (W1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 °C. At regular time intervals, the tablet were removed and the excess surface liquid was carefully removed by a filter paper [23]. The swollen tablet was then reweighed (W2). The swelling index (SI) was calculated using the formula (1);

$$SI = (W2 - W1)/W1 \quad (1)$$

2.3.6. Tablet floating behaviour

The floating behaviour of the tablets was visually determined, in triplicate, according to the floating lag time method described by Rosa et al. [24]. Briefly, a tablet was placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 °C. The floating lag time "the time between tablet introduction and its buoyancy" and total floating duration "the time during which tablet remains buoyant" were recorded.

2.3.7. Tablet adhesion retention period

The adhesion retention period of the tablets was evaluated, in triplicate, in comparison with the commercially available Ciprobay® 250 mg tablets [manufactured by Alkan Pharma (6th of October city, Egypt) under license of Bayer (Leverkusen, Germany)] by an *in vitro* method reported by Nakamura et al. [25] for measuring the nasal mucoadhesion of some water-soluble polymers. Briefly, an agar plate (1%, w/w) was prepared in 0.1 N HCl (pH 1.2). A side of the tablet was wetted with 50 μL of 0.1 N HCl and attached to the center of agar plate by applying a light force with a fingertip for 20 s [26]. Five minutes later, the agar plate was attached to a USP disintegration test apparatus (DST-3, Logan Instruments Corp., NJ, USA) and moved up and down in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C (Fig. 1). The adhering tablet on the plate was immersed

Table 1
The composition, in milligrams, of the investigated Cipro HCl floating tablets.

Formula code	Drug	HPMC K15M	Na alginate	Sodium bicarbonate	Calcium carbonate	Prosolv® 90	Mg stearate
F1	291	–	200	70	–	125	14
F2	291	50	150	70	–	125	14
F3	291	100	100	70	–	125	14
F4	291	150	50	70	–	125	14
F5	291	200	–	70	–	125	14
F6	291	150	50	105	–	90	14
F7	291	150	50	140	–	55	14
F8	291	150	50	–	70	125	14
F9	291	150	50	–	105	90	14
F10	291	150	50	–	140	55	14

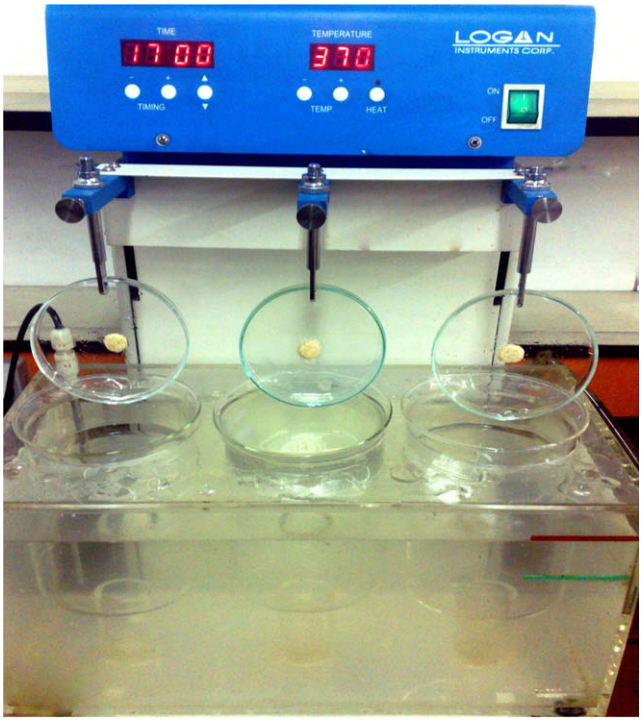

Fig. 1. A photograph taken during the *in vitro* adhesion study of formula (F1) in a USP disintegration test apparatus. (For interpretation of colours in this figure, the reader is referred to the web version of this paper.)

into the solution at the lowest point and got out of the solution at the highest point. The retention period of the tablet on the plate was noted visually.

2.3.8. Drug release studies

Drug release studies of the prepared floating tablets as well as the commercially available Ciprobay® 250 mg tablets were performed, in triplicate, in a USP Dissolution Tester Apparatus, type-II (Paddle method) (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ, USA) at 37 ± 0.5 °C. The paddles rotated at a speed of 100 rpm. The tablets were placed into 900 mL of 0.1 N HCl solution (pH 1.2). Aliquots of 5 mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a cellulose acetate membrane (0.45 μm). The drug content was determined spectrophotometrically at a wavelength of 278 nm, as mentioned before. At each time of withdrawal, 5 mL of fresh medium was replaced into the dissolution flask.

2.3.9. Statistical analysis of drug release profiles

The resulting data were analyzed by using the software SPSS 14.0 (SPSS Inc., Chicago, USA) applying one way ANOVA. Post hoc multiple comparisons were carried out using the least square difference (LSD) test. Differences between formulations were considered to be significant at $p < 0.05$.

2.3.10. Kinetic modeling of drug release profiles

The dissolution profiles of all formulae in 0.1 N HCl were fitted to zero-order, first-order, Higuchi [27] and Korsmeyer–Peppas kinetic models [28]. The model with the highest correlation coefficient was considered to be the best fitting one.

2.3.11. Physical stability studies

Physical stability studies were conducted according to International Conference on Harmonization (ICH) guidelines [29]. The best formulae, F7 and F10, were enclosed in polyethylene bottles and loaded in a desiccator containing a saturated solution of sodium chloride (75% RH) [30]. The desiccator was kept in an oven at 40 °C for 3 months [23]. At specified time intervals, the tablets were examined for any statistical difference in their hardness values, matrix integrity, adhesion retention periods and floating characteristics using a paired Student's *t*-test. Differences were considered to be significant at $p < 0.05$.

2.4. In vivo studies in healthy volunteers

Six healthy male volunteers participated in the studies after giving informed written consent. The subjects ranged in age from 20 to 30 years (mean 26 year), in height from 165 to 180 cm (mean 172 cm) and in weight from 70 to 80 kg (mean 74 kg). The studies were approved by the Cairo University Protection of Human Subjects Committee and the protocol complies with the declarations of Helsinki and Tokyo for humans.

An expert radiologist and physician supervised the studies. Health status of the volunteers was confirmed by complete medical history, physical examination and complete hematological and biochemical laboratory analyses. The subjects were instructed to take no medicines for 1 week prior to and during the course of the study.

2.4.1. Abdominal X-ray imaging

To make the best achieved formula (F10) X-ray opaque, 100 mg of the drug was replaced with barium sulfate and all other ingredients were kept constant. This amount was determined experimentally to allow X-ray visibility but not to hinder tablet buoyancy.

After overnight fasting, the volunteers were fed with a low calorie food. Half an hour later, a barium sulfate-labeled tablet was given to every subject with 200 mL of water. At different time intervals (0, 1.5, 3, 4.5 and 6 h post-administration of tablets), the volunteers were exposed to abdominal X-ray imaging (Genesis 50, Josef Betschart AG, Brunnen, Switzerland) in a standing position. A radiograph was made just before the administration of the tablet, at zero time, to ensure the absence of radio-opaque material in the stomach. The distance between the source of X-rays and the subject was kept constant for all images. Thus, the observation of the floating tablet movements could be easily noticed [23]. The mean gastric retention period was estimated.

3. Results and discussion

3.1. Physicochemical characteristics of tablets

Controlled-release Cipro HCl effervescent floating tablets were developed using release-retarding gel-forming polymer(s) like HPMC K15M and/or Na alginate and a gas-forming agent like $NaHCO_3$ or $CaCO_3$.

The incorporation of silicified microcrystalline cellulose "Prosolv® 90" in the designed systems was suggested to impart superior flow and enhance powder compaction in direct compression. Moreover, it was proved [31] that microcrystalline cellulose is capable of swelling in contact with aqueous fluids as simulated gastric fluid leading to an increase in the water uptake capacity, porosity of the matrix and consequently would enhance floating abilities.

In a previous work, Gambhire et al. [32] studied the influence of the tablet hardness on: (i) the floating lag time and (ii) the release of diltiazem hydrochloride and concluded that tablet hardness had no (or little) effect on the drug release profile but was a determining factor with regard to buoyancy of the tablets. Increasing the hardness (>5–6 kg/cm^2) would possibly lead to prolongation of the floating lag time by affecting the rate of the tablet penetration by the dissolution medium. Based on these conclusions, the

Table 2
Physicochemical properties of the prepared Cipro HCl floating tablets.

Formula code	Tablet thickness (mm)	Tablet weight (mg)	Drug content (%)	Tablet friability (%)	Floating lag time (s)	Total floating duration (h)	Adhesion retention period (min)
F1	3.97 ± 0.05	698.19 ± 2.94	99.33 ± 0.92	0.54 ± 0.10	14.50 ± 1.50	8	58.75 ± 2.50
F2	3.92 ± 0.10	691.18 ± 3.77	97.20 ± 0.34	0.41 ± 0.08	31.25 ± 2.50	10	66.50 ± 3.00
F3	4.03 ± 0.05	708.33 ± 1.50	102.19 ± 0.55	0.34 ± 0.12	73.00 ± 4.75	>12	73.50 ± 4.50
F4	3.95 ± 0.05	698.30 ± 3.30	99.60 ± 1.39	0.26 ± 0.10	100.75 ± 6.25	>12	81.00 ± 4.25
F5	3.93 ± 0.10	694.13 ± 3.10	99.21 ± 1.07	0.16 ± 0.04	164.75 ± 13.50	>12	93.50 ± 5.00
F6	4.12 ± 0.06	703.16 ± 2.33	98.14 ± 1.69	0.31 ± 0.07	52.50 ± 4.25	>12	75.50 ± 4.50
F7	4.05 ± 0.05	705.18 ± 3.11	101.50 ± 1.81	0.21 ± 0.05	8.25 ± 1.25	>12	66.25 ± 4.00
F8	3.98 ± 0.05	697.04 ± 2.56	101.34 ± 0.65	0.28 ± 0.08	116.50 ± 4.75	>12	84.50 ± 3.50
F9	4.06 ± 0.05	706.39 ± 1.14	102.11 ± 0.92	0.38 ± 0.15	72.50 ± 2.00	>12	80.75 ± 3.25
F10	4.01 ± 0.05	698.43 ± 2.70	99.34 ± 0.37	0.31 ± 0.14	16.00 ± 1.50	>12	74.00 ± 3.00

hardness of the floating tablets was adjusted, in the current work, to 5 kg/cm^2.

The physicochemical properties of the tablets are summarized in Table 2. The thickness of all tablet batches ranged from 3.92 ± 0.10 to 4.12 ± 0.06 mm. All the tablet formulae showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ranged from 691.18 to 708.33 mg. All the prepared formulae meet the USP 27 [33] requirements for weight variation tolerance; CV% was less than 2%. Drug uniformity results were found to be good among different batches; the percentage of drug content ranged from 97.20% to 102.11%. The percentage friability for all formulae was less than 1%, indicating good mechanical resistance.

3.2. Swelling indices

The hydration ability of the formula is important because it influences: (i) tablet buoyancy, (ii) adhesion ability of swellable polymers as HPMC K15M and/or Na alginate in contact with the test fluid and (iii) drug release kinetics.

It could be concluded that the test medium uptake of the prepared matrices depends on the type of polymer (Fig. 2). Formula F1 showed the highest swelling indices throughout the study period. This may be related to the high affinity of Na alginate-containing matrices to the test medium. The maximum swelling index of this formula (4.1 ± 0.3) was achieved after 6 h. On the other hand, significant reductions ($p < 0.05$) in the swelling indices were observed with the formulae F2–F4 containing higher HPMC K15M/Na alginate ratios. The maximum swelling indices of these formulae (3.2 ± 0.25, 2.9 ± 0.17 and 2.7 ± 0.13) were achieved after 6, 9 and 9 h, respectively. Throughout the study period, a gradual increase in the swelling indices was achieved with formula F5. This could be related to the lower affinity of HPMC K15M-containing matrices to the test medium.

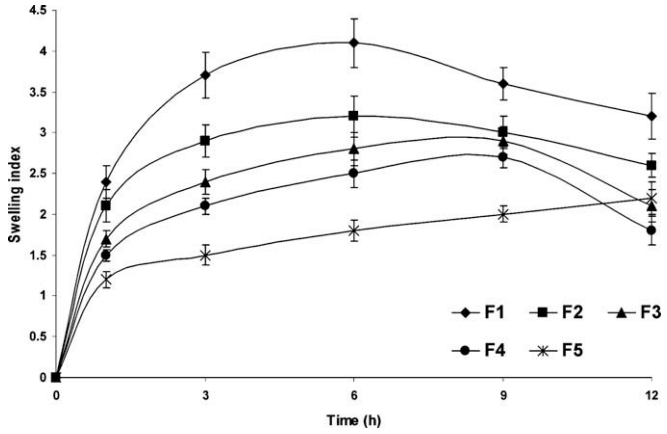

Fig. 2. The influence of HPMC K15M/Na alginate ratio on the swelling indices of Cipro HCl floating tablets (mean ± SD, $n = 3$).

As reported by Bertram and Bodmeier [34], the ability of hydrogels to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. Peppas and Khare [35] suggested that the swelling equilibrium (maximum swelling index) is reached when the osmotic forces of the functional groups are balanced by the restrictive forces of the higher ordering of the polymer chains.

Swelling and erosion mechanisms of HPMC matrices have been reported by Viridéna et al. [36]. It was assumed that swelling behaviour of these hydrophilic tablets starts with water diffusion into the glassy HPMC material where the water plasticizes the polymer and reduces its glass transition temperature, T_g. When T_g has decreased to ambient temperature, a transformation from a glassy state to a rubbery state occurs. As the water continues to enter the tablet, a highly concentrated polymer solution is formed, denoted as a gel layer. The solvent continues to penetrate the tablet, and the gel layer and the dimensions of the swollen tablet increase, a process normally referred to as the swelling process. In a parallel line, Ju et al. [37] suggested that a polymer concentration gradient is formed in the tablet, starting at a high concentration in the more or less dry core and declining through the gel layer towards the gel layer surface. At the surface of the gel layer, denoted as the erosion front, the polymer concentration is assumed to correspond to the critical polymer concentration, c_{crit} at which the polymer chains can withstand the shear forces surrounding the gel. At concentrations below c_{crit}, the polymer chains detach and release from the matrix as a result of too high shear forces.

3.3. Floating lag time and duration

The investigated gastric floating systems employed $NaHCO_3$ or $CaCO_3$ as a gas-forming agent dispersed in a hydrogel matrix (HPMC K15M and/or Na alginate). The *in vitro* testing revealed the ability of most formulae to maintain buoyant more than 12 h (Table 2 and Fig. 3). This suggests that the gel layers, formed by the investigated polymers, enabled efficient entrapment of the generated gas bubbles. The possible increase in tablet porosity made it float on the test medium (0.1 N HCl) for this extended period of time.

These matrices are fabricated so that upon arrival in the stomach, carbon dioxide gas is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. A decrease in specific gravity causes the dosage form to float on the chyme [14]. The extended residence time of drug in stomach could cause increased absorption due to the fact that the duodenum was the main absorption site for Cipro HCl [19].

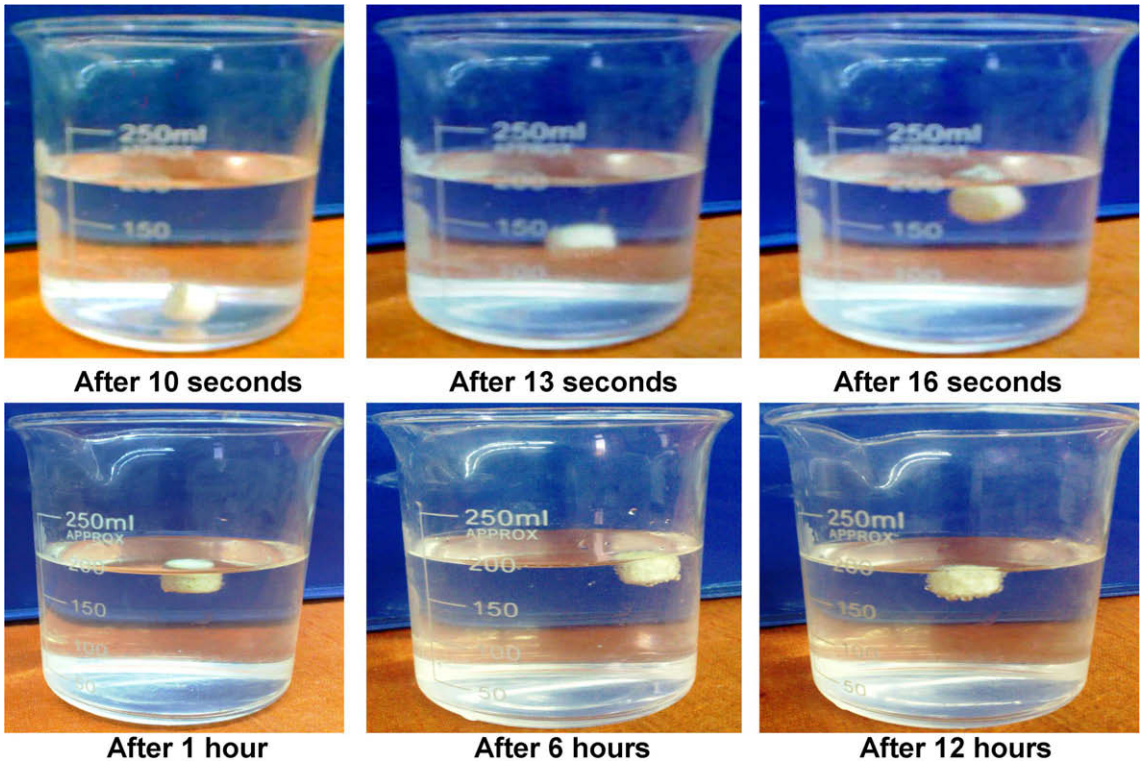

Fig. 3. Photographs taken during *in vitro* buoyancy study of formula F10 in 200 mL 0.1 N HCl at different time intervals. (For interpretation to colours in this figure, the reader is referred to the web version of this paper.)

One of the factors influencing the behaviour of the effervescent systems is their floating lag time. As shown in Table 2, the HPMC K15M/sodium alginate ratio has a marked effect on the floating lag time of the formulae (F1–F5) prepared with a constant $NaHCO_3$ ratio; 10%, w/w. The lag time of formula F1, containing Na alginate alone, was 14.50 s only. This time was statistically shorter ($p < 0.05$) than that obtained with other formulae containing increasing concentrations of HPMC K15M (formulae F2–F5). This could be explained with regard to the rate of the test medium penetration into these matrices and consequently the time required for gel formation.

The formulae containing higher $NaHCO_3$ ratios – 15%, w/w (formula F6) and 20%, w/w (formula F7) – had significantly shorter ($p < 0.05$) buoyancy lag times (52.50 and 8.25 s, respectively) than that of formula F4 (100.75 s). Similar behaviour was observed with those formulae utilizing $CaCO_3$ as a gas-forming agent. The formulae containing higher $CaCO_3$ ratios (F9 and F10) had significantly shorter ($p < 0.05$) floating lag times (72.50 and 16.00 s, respectively) than that of formula F8 (116.50 s). Similar observations were noted by Gambhire et al. [32] who concluded that as the percentage of $NaHCO_3$ increases, the floating lag time decreases. This phenomenon might be due to the generation of larger amounts of effervescence with higher $NaHCO_3$ percentages. This would lead to an increase in the rate of pore formation and consequently rapid hydration of the tablets' matrices. It is worth to note that $NaHCO_3$-containing formulae (F4, F6 and F7) have shorter floating lag times than the corresponding formulae prepared with $CaCO_3$ (F8–F10). This may be due to the lower efficiency of the latter as a gas-forming agent [38].

3.4. Adhesion retention periods

Like mucin covering the mucus membranes, agar gels contain large numbers of negatively charged carboxyl and sulfate groups; therefore, they have a high negative charge. The adhesion retention period of Ciprobay® 250 mg tablets was 12.50 ± 1.5 min only. The adhesion retention periods of the prepared formulae are shown in Table 2.

A relatively short adhesion retention period (58.75 ± 2.50 min) was obtained with formula F1. This may be due to the lower ability of the negatively charged Na alginate to interact with agar either electrostatically or by entanglements because of the low solution viscosity of the former; 230 cP (2% w/v solution at 25 °C). However, the availability of hydrogen bonding sites and the presence of an open expanded conformation could provide a possible mechanism of interaction [37]. The incorporation of HPMC K15M in increasing ratios, to sodium alginate matrices, caused significant increments ($p < 0.05$) in the adhesion retention periods of the formulae F2–F4 (66.5 ± 3.00, 73.50 ± 4.50 and 81.00 ± 4.25 min, respectively).

The longest adhesion retention period (93.50 ± 5.00 min) was obtained with formula F5. HPMC K15M is a neutral polymer unable to interact electrostatically with agar. However, it may do so by entanglements due to its high molecular weight. Indeed, the high viscosity of the HPMC K15M, 15,000 cP, would possibly retard the removal of the hydrated matrix [34].

It is clear that the higher gas-forming agent ratio, the shorter adhesion retention time. This behaviour was observed with $NaHCO_3$-containing formulae (F4, F6 and F7) as well as $CaCO_3$-containing ones (F8–F10).

Post hoc multiple comparisons using LSD test revealed that the former formulae have significantly ($p < 0.05$) shorter adhesion retention periods than the corresponding latter ones. This could be explained with regard to the their higher rate of the test medium penetration.

3.5. Drug release studies

A rapid drug release rate was achieved following the dissolution of Ciprobay® 250 mg tablets in 0.1 N HCl. Indeed, 99.56% of the drug was released within 15 min. Depending on the type and con-

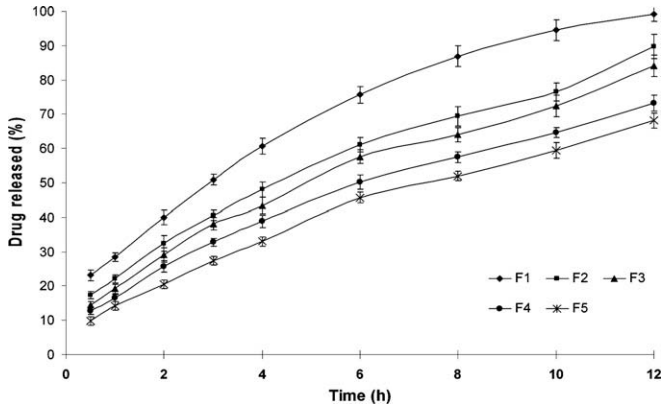

Fig. 4. The influence of HPMC K15M/Na alginate ratio on the release of Cipro HCl from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C (mean ± SD, $n = 3$).

centration of the investigated polymer(s) in the current study, variable drug release profiles were successfully tailored. The influence of HPMC K15M/Na alginate ratio on the release of Cipro HCl from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C was shown in Fig. 4. It is clear that all formulae succeeded in controlling the rate of drug release for 12 h. However, the drug release rate was dependent on the type and concentration of the investigated polymer(s). The $t_{50\%}$ of formula F1, containing Na alginate was 2.91 ± 0.25 h. Under identical experimental conditions, the drug diffusivity in HPMC K15M matrix, formula F5, was much lower. Indeed, formula F5 showed a significantly ($p < 0.05$) lower drug release rate ($t_{50\%}$ = 7.32 ± 0.24 h). The degree of retardation of the drug release rate from other formulae (F2–F4) was a function of HPMC K15M/Na alginate ratio ($t_{50\%}$ = 4.21 ± 0.31, 4.86 ± 0.27 and 6.12 ± 0.41 h, respectively). The higher viscosity of HPMC K15M would promote the formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rate. In a parallel line, Siepmann and Peppas [39] suggested that the drug release from HPMC matrices is sequentially governed as follows: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. (ii) Due to the imbibition of water, HPMC swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system. (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients. (iv) With increasing water content, the diffusion coefficient of the drug increases substantially.

It is worth to note that, a burst effect was observed with all formulations. This could be due to the fact that the gel layer, which controls the drug release rate, needs some time to become effective. The rapid drug dissolution from the surface of the tablets could be another possible explanation. Interestingly, this effect was less predominant with those formulae containing higher HPMC K15M ratios; F2–F5. Kulkarni and Bhatia [40] suggested that the resulting gel-like networks surrounding these matrices, upon contact with aqueous media, would produce strong surface barriers that would effectively reduce the burst drug release.

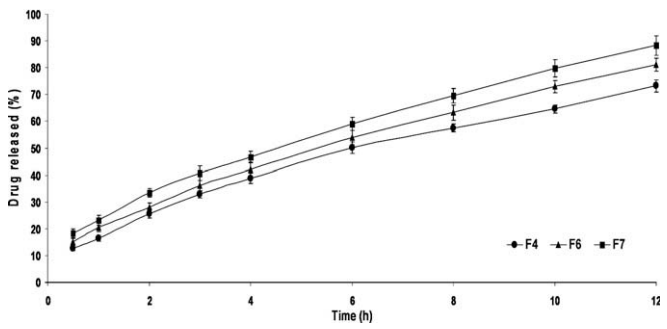

Fig. 5. The influence of sodium bicarbonate ratio on the release of Cipro HCl from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C (mean ± SD, $n = 3$).

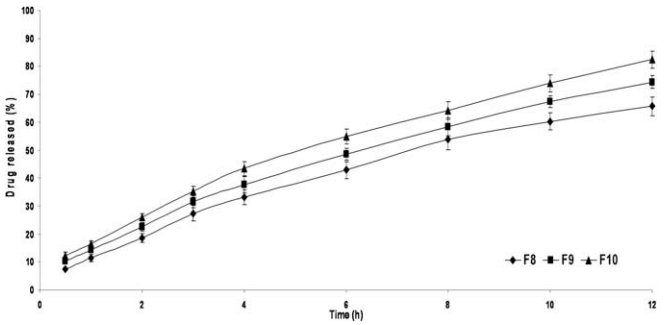

Fig. 6. The influence of calcium carbonate ratio on the release of Cipro HCl from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C (mean ± SD, $n = 3$).

Taking into consideration the goal of the work of achieving a compromise between excellent floating behaviour (very short floating lag time and prolonged floating duration), extended adhesion period and sustained drug release characteristics, formula F4 was chosen for further studies.

The influence of the gas-forming agent type ($NaHCO_3$ or $CaCO_3$) and concentration (10%, 15% and 20%, w/w) on the release of the drug from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5 °C was shown in Figs. 5 and 6, respectively. An inverse relationship was observed between the investigated concentration of the gas-forming agent and the drug release rate; formulae (F7 and F10) containing the highest gas-forming agent concentrations showed the highest drug release rates ($t_{50\%}$ = 4.18 ± 0.24 and 5.10 ± 0.32 h, respectively). The elevation of the gas-forming agent concentration to 20% (w/w) would generate larger amounts of effervescence leading to an increase in the rate of pore formation, rapid hydration of the tablets' matrices and consequently a faster drug release rate. In order to explain the more retarded drug release rates of $CaCO_3$-containing formulae over the corresponding $NaHCO_3$-containing ones, Choi et al. [38] suggested that since $CaCO_3$ is water soluble in acidic media, then it will react with the acid to produce the effervescence. Meanwhile, the ionized Ca^{2+} ions will promote internal gelation by cross-linking with the alginate carboxyl groups. This would produce a more prolonged drug release rate. Based on the above, the formulae F7 and F10 were chosen for further studies.

The drug release from the polymeric systems is mostly by diffusion and is best described by Fickian diffusion. But in case of the formulae containing swelling polymers, as HPMC K15M and/or Na alginate, other processes take place, like relaxation of polymer chains, imbibition of water causing polymers swelling and considerable volume expansion [41,42]. Korsmeyer and Peppas equation [28] 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. 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). The values of n with the corresponding correlation coefficients for all the formulae is shown in Table 3. It is clear that all formulae have n values between 0.45 and 0.89, indicating anomalous transport. The relative complexity of the prepared formulae may indicate that the drug release is controlled by more than one process; a coupling of diffusion and erosion.

Table 3
Mathematical modeling and release kinetics of Cipro HCl from the prepared floating tablets.

Formula code	Zero-order plots	First-order plots	Higuchi's plots	Korsmeyer–Peppas plots		
	Correlation coefficient (R^2)	Correlation coefficient (R^2)	Correlation coefficient (R^2)	Correlation coefficient (R^2)	Diffusional exponent (n)	Order of release
F1	0.979	0.871	0.991	0.992	0.490	Non-Fickian
F2	0.977	0.953	0.994	0.995	0.525	Non-Fickian
F3	0.975	0.977	0.994	0.996	0.561	Non-Fickian
F4	0.976	0.994	0.995	0.996	0.565	Non-Fickian
F5	0.983	0.996	0.993	0.997	0.619	Non-Fickian
F6	0.986	0.990	0.993	0.995	0.535	Non-Fickian
F7	0.985	0.976	0.992	0.994	0.505	Non-Fickian
F8	0.973	0.995	0.996	0.997	0.711	Non-Fickian
F9	0.980	0.995	0.996	0.997	0.640	Non-Fickian
F10	0.976	0.992	0.995	0.996	0.623	Non-Fickian

3.6. Physical stability studies

Statistical analysis of the results, before and after conducting the stability studies for 3 months, was carried out using paired Student's *t*-test. No significant difference ($p > 0.05$) was observed in the tablet hardness or adhesion retention periods. Similarly, there was very little/or no effect on the total floating duration or matrix integrity of the tablets.

The significant increase ($p < 0.05$) in the floating lag time of formula F7, from 8.25 ± 1.25 s, when freshly prepared, to 53.00 ± 3.5 s, after storage for 3 months at 40 °C under 75% RH, could indicate the possibility of reaction of $NaHCO_3$ with moisture under the investigated conditions. Kuu et al. [43] studied the effect of relative humidity and temperature on the moisture sorption and stability of $NaHCO_3$ powder and concluded that at 25 °C, the powder is stable below 76% RH. However, at 40 °C, the powder is less stable and started to degrade at 75% RH. It seems that the increase in temperature would result in an increase in the rate of moisture uptake and the amount of the adsorbed moisture at equilibrium. On the other hand, the difference between the floating lag time of formula F10 when freshly prepared (16.00 ± 1.50 s) and that obtained after storage for 3 months at 40 °C under 75% RH (17.50 ± 1.50 s) was not statistically significant ($p > 0.05$). This may be related to the stability of $CaCO_3$ under various storage conditions [44]. Based on the above, formula F10 was chosen for further *in vivo* studies.

3.7. The mean gastric retention period

The *in vitro* buoyancy lag time of the barium sulfate-loaded tablet was 78.50 ± 2.5 s. The increase in the lag time, compared to the original formula F10 (16.00 ± 1.50 s), was expected because barium sulfate, as reported by its manufacturer, has a high relative density (4.5 g/cm^3). Fig. 7 shows the radiographic images taken at different periods post-administration of the barium sulfate-loaded tablet in one volunteer. It is clear that the tablet appears more or less at the same position in the stomach for the first 3 h. This could be related to its adhesive nature. Later on, the tablet slightly moved downwards, yet, remained within the stomach till the end of 6 h. The mean gastric retention period was 5.50 ± 0.77 h.

4. Conclusions

Promising controlled-release floating tablets of Cipro HCl were successfully formulated by effervescent technique. Tablets containing HPMC K15M (21.42%, w/w), Na alginate (7.14%, w/w) and $NaHCO_3$ (20%, w/w) (formula F7) or $CaCO_3$ (20%, w/w) (formula F10) showed satisfactory results with respect to floating lag time, total floating duration, swelling ability, adhesion retention period and sustained drug release rates. Formula F10 showed better physical stability when stored at 40 °C under 75% RH for 3 months. The mean gastric retention period of formula F10, loaded with barium sulfate, in six healthy human volunteers was 5.50 ± 0.77 h.

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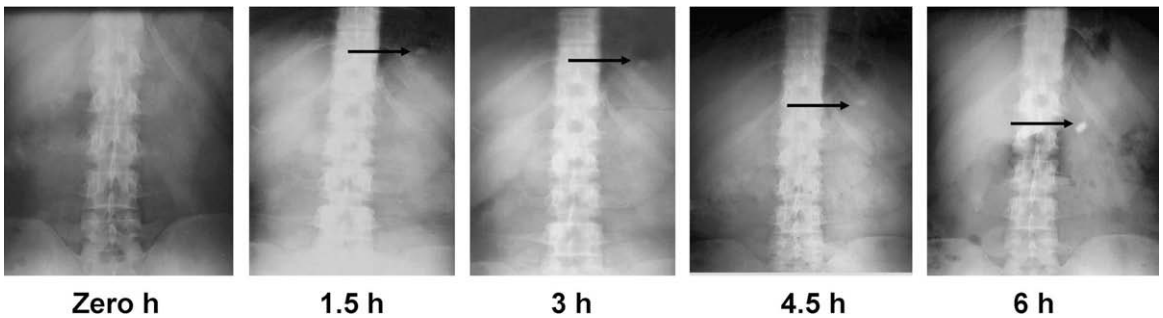

Fig. 7. Radiographic images showing the presence of a BaSO4-loaded floating tablet in the stomach at different time periods (the location of the tablet is indicated with an arrow).

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