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ORIGINAL ARTICLE

Development and *in vivo* evaluation of gastroretentive delivery systems for cefuroxime axetil

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Radiographic studies

Abstract The purpose of this investigation was to design and develop gastroretentive dosage form for cefuroxime axetil using floating tablet approach with various grades of hydroxypropyl methyl cellulose. Cefuroxime axetil is known to have low bioavailability, short half-life and is absorbed -largely from upper GIT. Sodium bicarbonate was used in the dosage form as a source of carbon-di-oxide to maintain buoyancy. *In vitro* dissolution study results indicated non-Fickian diffusion controlled drug release mechanism and was best fitted into Korsmeyer–Peppas equation. *In vivo* radiographic studies conducted in five healthy human volunteers for optimized formulation indicated over 6 h retention of tablet in the stomach region. Reproducible physical parameters indicated that the current formulation could be easily scaled-up.

1. Introduction

Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs that are preferentially absorbed from upper GIT.

Reported methods for the design of gastroretentive systems include mucoadhesion (Arora et al., 2005; Sheth and Tossounian, 1978), floatation, sedimentation (Ponchel and Irache, 1998; Akiyama and Nagahara, 1999; Deshpande et al., 1997), expansion (Davis et al., 1986) and modified shape systems (Urguhart and Theeuwes, 1994). Single and multiple system approaches have also been reported in the literature (Fix et al., 1993).

Floating drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. A gastric floating drug delivery system (GFDDS) (Moes, 1993; Deshpande et al., 1997; Baumgartner et al., 2000; Singh and Kim, 2000; Li et al., 2003) can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and stomach. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug.

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Table 1 Formulation composition of gastroretentive tablets of cefuroxime axetil.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefuroxime axetil (CA)	300	300	300	300	300	300	300	300	300
HPMC (K4M)	70	80	90	–	–	–	–	–	–
HPMC (K15M)	–	–	–	40	50	60	–	–	–
HPMC (K100M)	–	–	–	–	–	–	40	50	60
Lactose monohydrate	55	45	35	85	75	65	85	75	65
Sodium bicarbonate	60	60	60	60	60	60	60	60	60
Magnesium stearate	9.7	9.7	9.7	9.7	9.7	9.7	9.7	9.7	9.7
Talc	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Total weight (mg)	499.5	499.5	499.5	499.5	499.5	499.5	499.5	499.5	499.5

Cefuroxime axetil (CA) is 1-acetoxyethyl ester of a β-lactamase-stable cephalosporin, cefuroxime with a broad spectrum of activity against Gram-positive and Gram-negative microorganisms (McEvoy, 2003). After oral administration CA is absorbed and rapidly hydrolyzed by esterases to produce cefuroxime. The 1-acetoxyethylester group at 4th position of CA ensures lipophilicity and promotes the absorption of cefuroxime but at the same time compromises on solubility and hence, the prodrug shows poor and variable oral bioavailability (Perry and Brogden, 1996). CA exists in crystalline as well as amorphous forms; of these, latter exhibits higher bioavailability owing to improved solubility. The bioavailability of CA is variable and limited to 30% in fasted and 50% in fed state in humans (Crisp and Clayton, 1985; Crisp et al., 1989).

A look into the existing literature unveils few approaches for the enhancement of solubility and bioavailability for CA. Some important ones being, formulation of bi-layered floating drug delivery systems (Dhumal et al., 2006), floating delivery systems (Patel and Patel, 2006), amorphous nanoparticles (Dhumal et al., 2008) and solid dispersions (Dhumal et al., 2009).

As previously reported, CA is known to have good absorption from upper parts of GIT. Thus, retaining CA in this region for longer time would be beneficial in improving its bioavailability.

In the present work, floating delivery system approach was used in developing hydroxypropyl methyl cellulose (HPMC) based dosage form. Various grades of HPMC (K4M, K15M, K100M) were tested for their usefulness in formulating GFDDS of CA.

2. Experimental

2.1. Materials

Cefuroxime axetil was generously gifted by Orchid Healthcare Pvt. Ltd., India, HPMC (K4M, K15M and K100M) were purchased from Sigma Aldrich. Sodium bicarbonate, magnesium stearate, lactose and talc were purchased from S.D. Fine Chemical Pvt. Ltd., India. All other chemicals used were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Drug–excipient compatibility

The infrared spectra of pure drug (CA), binary mixture of drug and each excipient (1:1), optimized formulations and placebo were recorded between 600 and 4000 cm^{-1} by FT-IR spectrometer using KBr pellet technique.

2.2.2. Preparation of tablets

The tablet excipients were chosen after comprehensive drug–excipient interaction studies. All the tablets were prepared by direct compression method. Formulations were prepared by varying drug to polymer ratio and keeping other ingredients in required quantities to make the final weight of 499.5 mg per tablet. Briefly, preparation of tablets involved, passing all the ingredients except magnesium stearate and talc through sieve #40 and mixing the blend in an octagonal blender for 10 min. Magnesium stearate and talc were then passed through sieve #60 and were used to lubricate the blend. The lubrication was done for 5 min. The lubricated blend was compressed into tablets using 12 mm flat faced punches. The detailed composition of formulations is presented in Table 1.

2.2.3. Evaluation of tablets

The prepared tablets were evaluated for parameters like hardness (Monsanto hardness tester), friability, weight variation, thickness, water uptake, *in vitro* drug release, *in vitro* floating lag time and total buoyancy time, *in vivo* buoyancy studies in healthy human volunteers.

2.2.4. Water uptake study

The swelling behavior of dosage form can be measured by studying its dimensional changes, weight gain or water uptake ability (Mohammed and Khedr, 2003). The water uptake study of the dosage form was conducted by using Type II USP dissolution apparatus in 900 ml of distilled water which was maintained at 37 ± 0.5 °C and rotated at 50 rpm. At selected intervals, the tablet was withdrawn and weighed. Percentage swelling of the tablet was expressed as percentage water uptake (%WU) calculated from following equation (Chanvanpatil et al., 2006):

$$\%\mathrm{WU} = \frac{(W_t - W_0)}{W_0} \times 100 \quad (1)$$

where 'W_t' is the weight of the swollen tablet and 'W_0' is the initial weight of the tablet.

2.2.5. In vitro buoyancy study

The *in vitro* buoyancy was determined by measuring floating lag times and duration of buoyancy according to the method described by Rosa et al. (1994). The tablets were placed in a 100 ml beaker containing 100 ml 0.1 N HCl. The time required

for the tablet to rise to the surface and float was taken as the floating lag time. The time for which tablets kept floating was termed as 'buoyancy time' of the tablets which was determined for all the formulations.

2.2.6. In vitro release studies

The release of CA was studied using USP Type II dissolution apparatus using 900 ml 0.1 N HCl as dissolution media maintained at 37 ± 0.5 °C with rotation speed of 50 rpm. Aliquots of 5 ml were collected at pre-determined time intervals and were replenished with equivalent volume of fresh medium. The samples were filtered through a 0.45 μm filter and diluted to a suitable concentration with 0.1 N HCl. They were analyzed by using UV–Visible double beam spectrophotometer at 278 nm (Elico SL 164, India). The results were expressed as mean ± S.D. (n = 3).

2.2.7. Drug release kinetics

The drug release kinetics was studied by plotting the data obtained from the *in vitro* drug release in various kinetic models like zero order, first order, Higuchi, and Hixson–Crowell model. To establish the mechanism involved in drug release from the tablets, data of percentage drug release versus log time were plotted according to Korsmeyer–Peppas equation (Eq. (2)). The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight line.

$$M_T/M_\infty = Kt^n \tag{2}$$

where M_t/M_∞ is the fractional solute release, 't' is the release time and K is a constant characteristic of the drug/polymer system. If the exponent n = 0.45, then the drug release follows the Fickian diffusion and if $0.45 < n < 0.85$ then it is said to be non-Fickian or anomalous release.

2.2.8. In vivo radiographic studies

For *in vivo* studies ethical committee clearance was obtained from the local body to conduct trials on human volunteers. Signed legal consent forms in native language or in English were obtained from all the volunteers (n = 5). Placebo tablets loaded with 300 mg barium sulfate (radio opaque agent) were initially prepared; the *in vitro* buoyancy study of these tablets

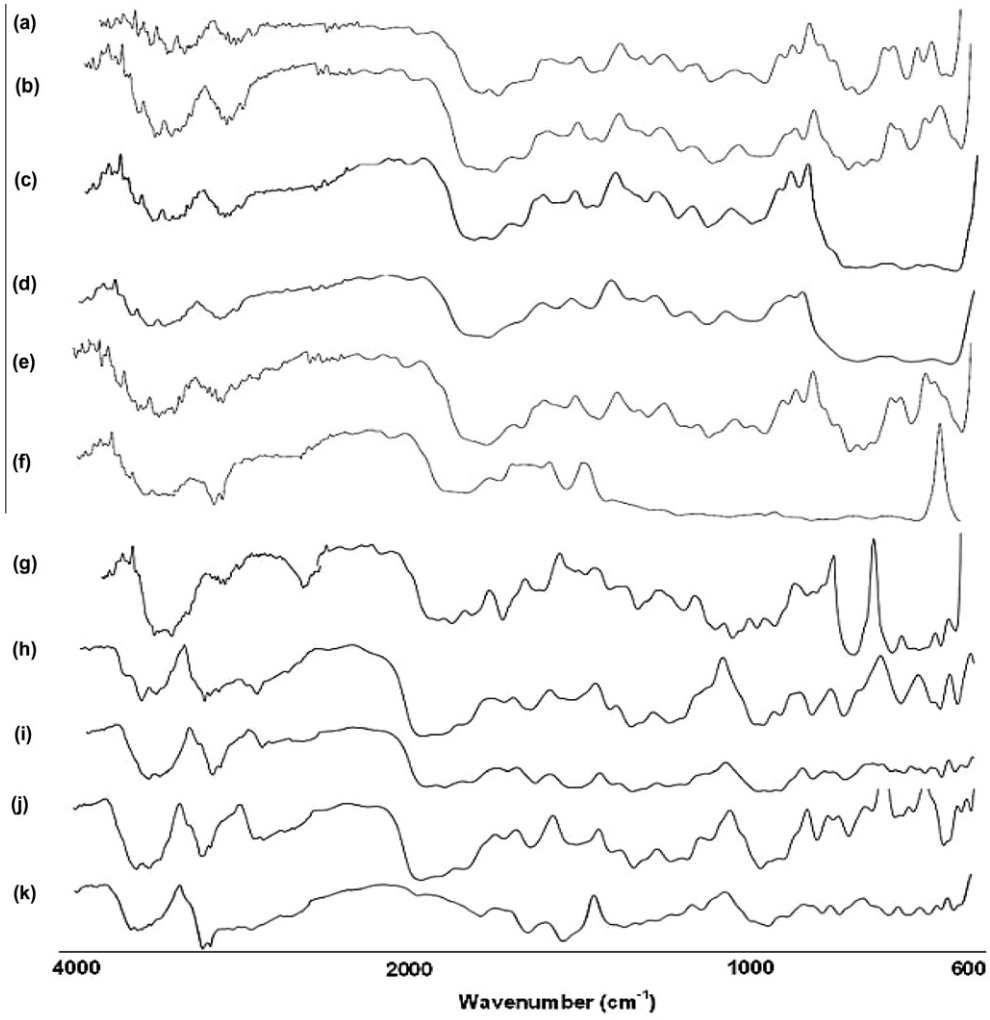

Figure 1 FT-IR spectra of drug and excipients. I. Pure drug: (a) cefuroxime axetil (CA) pure drug. II. Binary mixtures of CA with various excipients: (b) HPMC K4M, (c) HPMC K15M, (d) HPMC K100, (e) lactose, (f) magnesium stearate, (g) talc and (h) sodium bicarbonate. III. Optimized formulations: (i) optimized formulation (F2), (j) optimized formulation (F5) and (k) placebo.

Table 2 Physical parameters of gastroretentive tablets of cefuroxime axetil.

Formula	Wt. variation (mg) ± SD*	Hardness (kg/cm^2)	Diameter (mm) ± SD*	Thickness (mm) ± SD*	Friability (%)	Drug content (%) ± SD*	Floating lag time (min)	Buoyancy time (h)	Drug release (t_{12}) (%) ± SD^
F1	505 ± 8.30	7.5	12 ± 0.02	4.54 ± 0.02	0.34	98.91 ± 2.80	2.03	> 12	99.56 ± 0.55
F2	**515 ± 3.80**	**8.0**	**12 ± 0.02**	**4.61 ± 0.02**	**0.45**	**98.46 ± 3.20**	**2.08**	**> 12**	**97.97 ± 1.85**
F3	501 ± 4.90	7.2	12 ± 0.02	4.36 ± 0.02	0.25	97.41 ± 2.10	2.20	> 12	80.05 ± 3.31
F4	510 ± 5.30	7.0	12 ± 0.02	4.64 ± 0.02	0.39	96.54 ± 2.60	2.13	> 12	99.96 ± 1.82
F5	**505 ± 2.30**	**6.0**	**12 ± 0.02**	**4.64 ± 0.02**	**0.48**	**96.33 ± 2.50**	**2.26**	**> 12**	**97.98 ± 1.24**
F6	503 ± 5.40	7.2	12 ± 0.02	4.52 ± 0.02	0.45	96.54 ± 1.80	2.43	> 12	89.20 ± 1.18
F7	502 ± 3.20	7.4	12 ± 0.02	4.79 ± 0.02	0.27	96.33 ± 2.30	2.53	> 12	70.98 ± 1.46
F8	508 ± 8.20	7.0	12 ± 0.02	4.21 ± 0.02	0.55	97.41 ± 2.10	2.76	> 12	66.65 ± 1.77
F9	507 ± 4.30	7.4	12 ± 0.02	4.44 ± 0.02	0.38	95.41 ± 1.80	2.91	> 12	58.53 ± 2.66

The bold font indicates that F2 and F5 are optimized formulations form the lot.
* SD = standard deviation ($n = 3$).
^ t_{12} – %Drug release at 12 h.

showed significant increase in lag time which was attributed to high molecular weight of barium sulfate. Hence, it was excogitated to replace half of the barium sulfate (150 mg) with CA. Tablets with 150 mg barium sulfate and 150 mg CA were chosen for *in vivo* radiographic studies.

For this study, human subjects were fasted overnight and were only allowed free access to water *ad libitum*. They were orally administered one tablet each with 250 ml of water. Radio graphs were obtained using X-ray equipment after time intervals of 0.5, 1.5, 4 and 6 h. During the period of study, volunteers were allowed free access to only water. (Machida et al., 1989; Iannucelli et al., 1998).

3. Results and discussion

3.1. FT-IR studies for drug–excipient compatibility

The IR spectra of CA showed the characteristic absorption peaks at 1661, 1787, 1733 cm^{-1} indicating the presence of carbonyl C═O stretching. Strong absorption band at 3484 cm^{-1} represented primary amine N–H stretching and characteristic band at 1212 cm^{-1} represented C═H stretching. The IR spectra of physical mixture also showed the above mentioned bands of CA of respective functional groups. From the data, it was concluded that there was no interaction with the excipients used in the formulation. The FT-IR spectra of CA, binary mixture (1:1) of CA with each excipient, optimized formulations and placebo are shown in Fig. 1.

3.2. Physical properties of the compressed floating tablet systems

The floating tablets of cefuroxime axetil were prepared by direct compression technique using HPMC (K4M, K15M, and K100M), lactose, sodium bicarbonate, along with magnesium stearate and talc. The results of the physical characteristics of floating tablets are shown in Table 2. The physical evaluation of the tablets revealed uniform thickness and weight for all the tablets (evident from low% RSD values). The hardness values between 6 and 8 kg/cm^2 and low friability values (below 0.45%) across all formulations indicated that the tablets had sufficient mechanical strength. The drug content uniformity studies revealed that drug content between 96.33 ± 2.3% and 98.91 ± 2.8% is acceptable.

3.3. Water uptake studies

Swelling of tablets is a direct indication of amount of water uptake by the tablets. Water uptake studies showed that formulation with high percentage of HPMC imbibed more water and were swollen to greater extent than formulation with low percentage of HPMC.

The percentage swelling obtained from the water uptake studies of all the formulations is shown in Fig. 2. The formulations with HPMC K4M, HPMC K15M and K100M showed significant swelling and good tablet integrity. The change in sodium bicarbonate concentration has not shown any effect on swelling of the tablet. The formulations with HPMC K100M showed higher swelling compared to formulations with K4M, K15M. The swelling index of the tablets increases with an increase in the polymer viscosity grades.

3.4. In vitro lag time measurement

From the lag time measurement study, it was evident that for all the formulations, the lag time was between 2 and 3 min. This concords with the earlier reported work (Patel and Patel, 2006) where the average lag time was below 3 min. The bilayered tablet approach for CA, as reported by Dhumal et al., 2006, showed variable lag time ranging from 12 to 35 min.

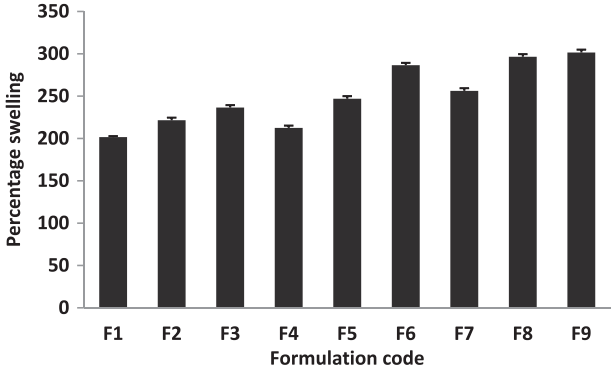

Figure 2 Percentage swelling of the different grades of HPMC formulations.

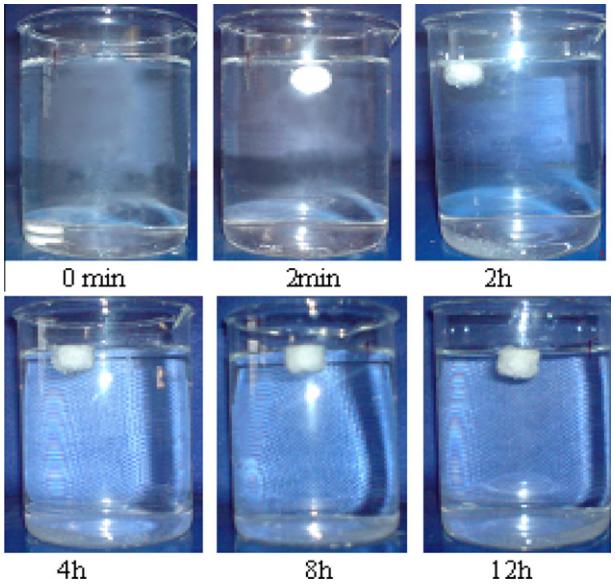

Figure 3 *In vitro* buoyancy study of optimized formulation (F2).

3.4.1. Effect of sodium bicarbonate concentration on lag time of tablets

The concentration of gas generating agent sodium bicarbonate was found to be critical factor that influenced buoyancy of tablets. Sodium bicarbonate released CO_2 gas that was trapped into the polymeric matrix of HPMC that made the tablets buoyant. Various concentrations of sodium bicarbonate ranging from 10% to 16% of tablet weight were used.

From the results, it was concluded that with the increasing concentration of sodium bicarbonate, the lag time decreased. A concentration of 12% w/w sodium bicarbonate was found to be optimal that resulted in tablets having lag time < 3 min and floating time of over 12 h. Similar conclusions were also drawn by other researchers working on floating delivery systems of CA. In both the reported works, optimum concentration of sodium bicarbonate was found to be around 10% w/w of the tablet weight (Dhumal et al., 2006; Patel and Patel, 2006) which is slightly lower than our optimal concentration.

It was interesting to note that the grade of HPMC used in the formulations has impact on lag of the tablets. With the increasing molecular weight of HPMC, the viscosities of the gel matrix around the tablet also increased which in turn increased the lag time. The lag time for HPMC K100M tablets was slightly higher compared to HPMC K4M and HPMC K15M tablets. This may be attributed to the increased density of tablets with increasing molecular weight of HPMC.

3.5. In vitro buoyancy time measurement

Buoyancy time was defined as the time period for which tablets kept floating on the surface of media before sinking completely to the bottom.

From the buoyancy studies (as indicated in Table 2 and Fig. 3), it was evident that all the formulations showed similar buoyancy times (over 12 h). Hence, the differentiating factor to choose the optimal formulation was taken as the drug release criterion in 12 h buoyancy period.

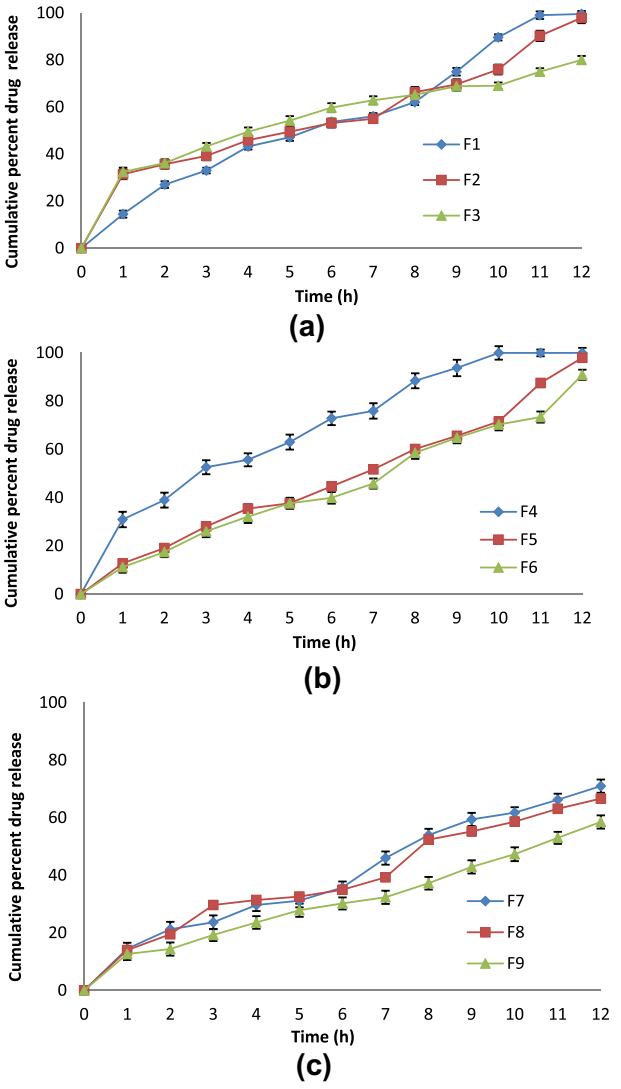

Figure 4 Drug release profiles: (a) drug release profiles of cefuroxime axetil floating tablets with HPMC K4M (F1–F3), (b) HPMC K15M (F4–F6) and (c) HPMC K100M (F7–F9).

3.6. In vitro drug release studies

A rigorous study of dissolution profile for all the formulations gave an insight into the effect of polymeric fillers and gas generating agent on release profile of the formulations.

From the release profiles, it was observed that the variation in grade of polymer and its concentrations from F1 to F9 had variable effect on drug release. These data were illustrated in Fig. 4a–c. The effects of HPMC K4M, K15M and K100M could be observed at constant sodium bicarbonate level. The presence of HPMC K4M increased the release rate and extent compared to HPMC K15M and K100M.

Similar conclusions were also drawn by earlier workers who worked in the development of floating delivery systems of CA (Dhumal et al., 2006; Patel and Patel, 2006).

Similar profiles are observed, though, to a much smaller extent (due to closeness of the formulations) in case of the optimized formulations F2, F5 (Fig. 4a and b). These findings can be explained in the light of difference in molecular weight of the two varieties of HPMC.

Table 3 Drug release kinetics of optimized formulations.

S. no.	Formulation code	Zero order	First order	Higuchi	Korsmeyer and Peppas	Peppas (*n*)	Mechanism of drug release
1	F2	0.974	0.684	0.898	0.994	0.55	Non-Fickian
2	F5	0.962	0.503	0.933	0.915	0.75	Non-Fickian

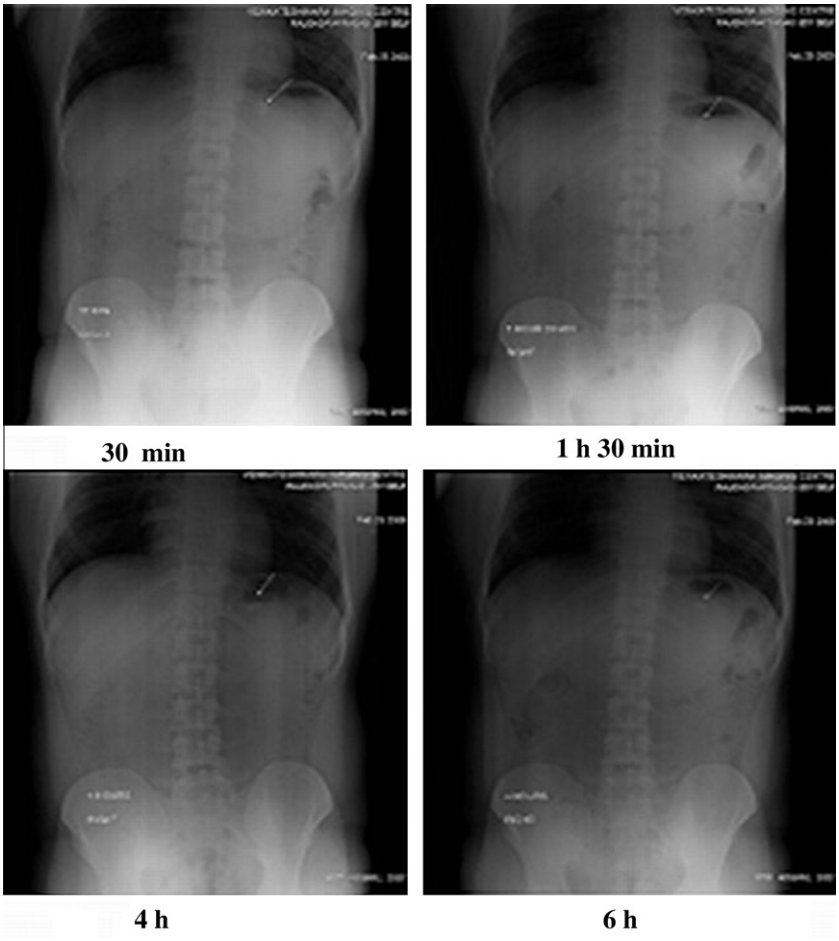

Figure 5 *In vivo* radiographic images of tablets at 0.5, 1.5, 4 and 6 h.

HPMC K15M with higher molecular weight, forms gel of higher viscosity (15,000 cps) compared to HPMC K4M (nominal viscosity 4000 cps). However, due to higher molecular weight, the polymer chains are bulkier in K15M leading to less flexibility and hence more time for polymer–solvent interaction and polymer chain relaxation. Consequently, the polymer chain unwinding is delayed in case of HPMC K15M compared to HPMC K4M, thereby leading to reduced gelling rate for the former variety.

As a result of this, the effective diffusion rate of drug through matrices containing higher percentage of HPMC K4M is more leading to higher dissolution rates from these tablets.

Formulations F2 and F5 were chosen as optimal based on their ability to sustain drug release up to 12 h period as evident from Table 2 and Fig. 4.

Though formulations F1 and F4 showed good release characteristics, more than 95% of drug was released before 12 h (at about 10 h) period which is undesirable, while, formulations F3, F6–F9 showed less than 90% drug release even after 12 h period leading to the loss of remaining drug embedded in the matrix.

By comparing three different grades of HPMC (K4M, K15M and K100M), we concluded that low-viscosity grade HPMC K4M provided better release characteristics and showed good *in vitro* buoyancy. From the results, it was also concluded that with the increase in molecular weight of HPMC, the drug release could be retarded greatly.

3.7. Drug release kinetics

The mechanism of release for the above formulations was determined by finding the R^2 value for each kinetic model viz. zero-order, first-order, Higuchi, and Korsmeyer–Peppas corresponding to the release data of each formulation. For most of the formulations the R^2 value of Korsmeyer–Peppas and zero-order model is very near to one than the R^2 values of other kinetic models. Thus, it can be said that the drug release follows Korsmeyer–Peppas and zero-order model mechanism.

The '*n*' values of Korsmeyer–Peppas model for the best formulations were in the range of 0.45–0.85. Therefore, the most probable mechanism of release was non-Fickian diffusion or anomalous diffusion. All the values are shown in Table 3.

3.8. In vivo radiographic studies

In vivo studies were conducted on healthy human volunteers to find the gastric residence time of the tablet. The studies were based on X-ray radiography. Both the optimized formulations (F2 and F5) were selected for the study. However, during the course of study, formulation F5 could not remain buoyant after 4 h period (data not shown). Hence, the study was continued with volunteers ingested with formulation F2 up to 6 h. The position of tablet at the end of various time intervals (indicated by tiny arrows) in Fig. 5 showed that the selected formulation (F2) was retained in the upper part of GIT for well over 6 h.

Statistical treatment of the data for formulation F2 did not show any significant difference ($p < 0.05$) between the volunteers ($n = 5$).

4. Conclusion

From the data obtained, it can be concluded that hydrodynamically balanced tablet of cephalosporin antibacterial drug CA can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. The derivatives of swellable polymer HPMC showed better control over the drug release. Formulated tablets gave satisfactory results for various physicochemical evaluations for tablets like tablet dimensions, hardness, weight variation, floating lag time, total floating time, content uniformity and *in vitro* drug release. Formulations F2 and F5 gave better sustained drug release in comparison to other formulations. These formulations best fitted to Korsmeyer–Peppas model and zero-order kinetics. *In vivo* radiographic studies indicated that tablets remained in the stomach for about 6 h (for formulation F2), which indicates the increase in the gastric residence time due to floating and swelling principle.

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