AAPS PharmSciTech, Vol. 12, No. 1, March 2011 (© 2011)
DOI: 10.1208/s12249-011-9595-0

Research Article

Prolonged Intragastric Drug Delivery Mediated by Eudragit® E-Carrageenan Polyelectrolyte Matrix Tablets

Ahmad Bani-Jaber,[1,2] Leena Al-Aani,[1] Hatim Alkhatib,[1] and Bashar Al-Khalidi[1]

Received 2 May 2010; accepted 19 January 2011; published online 8 February 2011

Abstract. Interpolyelectrolyte (IPE) complexation between carrageenan (CG) and Eudragit E (EE) was studied in 0.1 M HCl and was used to develop floating matrix tablets aimed to prolong gastric-residence time and sustain delivery of the loaded drug. The optimum EE/CG IPE complexation weight ratio (0.6) was determined in 0.1 M HCl using apparent viscosity measurements. The IPE complex was characterized by Fourier transform infrared spectroscopy and differential scanning calorimetry. Metronidazole matrix tablets were prepared by direct compression using EE, CG, or hybrid EE/CG with ratio optimal for IPE complexation. Corresponding effervescent tablets were prepared by including Na bicarbonate as an effervescent agent. Tablets were evaluated for *in vitro* buoyancy and drug release in 0.1 M HCl. Both CG and EE–CG effervescent matrices (1:2 drug to polymer weight ratio, 60 mg Na bicarbonate) achieved fast and prolonged floating with floating lag times less than 30 s and floating duration of more than 10 h. The corresponding EE effervescent matrices showed delayed floating and rapid drug release, and completely dissolved after 3 h of dissolution. CG matrices showed an initial burst drug release (48.3±5.0% at 1 h) followed by slow drug release over 8 h. EE–CG matrices exhibited sustained drug release in almost zero-order manner for 10 h (68.2±6.6%). The dissolution data of these matrices were fitted to different dissolution models. It was found that drug release followed zero-order kinetics and was controlled by the superposition of the diffusion and erosion.

KEY WORDS: Eudragit E; carrageenan; gastric retention; polyelectrolyte complexation.

INTRODUCTION

Intragastric floating systems have been used pharmaceutically to deliver active compounds for sustained release and targeting. Amoxicillin and metronidazole, which are effective in treating *Helicobacter pylori* under *in vitro* conditions, score poorly when used to treat infections *in vivo*. The failure of these antibiotics has been attributed to sub-effective bactericidal concentrations at the site following oral administration (1). The prolongation of the local availability of the antibacterial agents showed positive effects of increasing the effectiveness of *H. pylori* treatment. This will ensure a high drug concentration in the gastric mucosa (2). A matrix tablet along with gastroretentive delivery strategies have been proposed to achieve this goal (3). Several approaches are used to prolong gastric-retention time including polymeric bioadhesive systems (4), swelling and expanding systems (5,6), and floating drug delivery systems (7,8). The principle of buoyant preparation offers a simple and practical approach to achieve longer gastric-residence time for the dosage form and sustained drug release of the loaded drug (9). In addition, floating drug delivery systems may result in higher clinical safety than that in other approaches used to prolong retention time (10). To achieve intragastric floating systems, low-density additives (*e.g.* fatty acids and fatty alcohols) and gas-generating agents (effervescent type) are used (11). The effervescent type consists of polymeric matrix containing effervescent components, such as Na bicarbonate. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidic pH of the stomach and is then entrapped in a gelling hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy (12).

Polymethacrylates are synthetic cationic or anionic polymers of dimethyl-aminoethylmethacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Such polymers are used in pharmaceutical formulations as film coating-agents, binders, direct-compression excipients, and gel bases (13). Eudragit E (EE), a cationic polymer prepared by copolymerization of butyl methacrylate, 2-dimethylaminoethylmethacrylate, and methyl methacrylate with mole ratio of 1:2:1, is used as a film former in pharmaceutical coating (14). EE is usually dissolve in organic solvent during usage, however, it is soluble in gastric fluid below pH 5.0 (14).

Carrageenans (CG) have hydrocolloidal properties and have been used in controlled drug-release technology. They are natural polysaccharides extracted from algae of the class of Rhodophyceae. CG consists of the sulfate esters of galactose and 3, 6-anhydrogalactose copolymers (15).

Interpolyelectrolyte (IPE) complexation between EE and CG was previously reported and the corresponding IPE complex was synthesized by reacting the two polymers in

[1] Faculty of Pharmacy, University of Jordan, Amman, Jordan.
[2] To whom correspondence should be addressed. (e-mail: abjaber@ju.edu.jo)

solutions (16). The product IPE complex was isolated and then freeze-dried for 3 days, before utilized as a matrix for controlled drug release. As an alternative for this lengthy process, we propose *in situ* EE–CG IPE complexation in an acidic medium simulating the gastric fluid. Our proposal is dependent on the fact that the sulfate groups in CG are strongly acidic, which allows for polymer ionization and interaction with the cationic EE even at low pH values.

Our work aimed to utilize IPE complexation between EE and CG in designing effervescent EE–CG hybrid matrix as gastric-buoyant system with controlled drug release. The matrix was made as tablet by direct compression as a low-costly and fast manufacturing method. The main objectives of this study were to (1) study EE–CG complexation in 0.1 M HCl, (2) find out the optimum EE/CG weight ratio of the complexation, (3) evaluate the effect of Na bicarbonate as an effervescent agent on gastric buoyancy of tablets having metronidazole as a model drug, and EE–CG, CG and EE as different matrix formers, (4) study drug dissolution in 0.1 M HCl from the buoyant tablets, and (5) compare the buoyant behavior and drug- release performance between the different matrices.

MATERIALS AND METHODS

Materials

EE PO (molecular weight (mol. wt.) 15 kD) was generously donated by RÖhm Pharma GmbH, Darmstadt, Germany. Multiple type food grade CG with mol. wt. 400–600 kD was supplied by BDH Chemicals, Poole, England. Metronidazole was a gift from The Jordanian Pharmaceutical Co., Naur, Jordan. For all experiments, distilled water was used and all other chemicals were of analytical grade.

Methods

Viscosity Measurements

CG and EE solutions (1% in 0.1 M HCl) were mixed at different EE/CG weight ratios in the range of 0.2–0.8. The mixtures were placed on a shaker operating at a speed of 4.5 L/min for 1 h, and then centrifuged for 10 min. Supernatants were collected and viscosity was measured at shear rate of 160 L/s using Haake Viscometer 550 (Germany). Each measurement was repeated thrice.

Swelling Studies

Flat-face tablets (10 mm diameter) of 100% CG, 100% EE, or physical mixtures of EE and CG at different EE/CG weight ratios in the range of 0.3–2 were prepared by direct compression in a hydraulic tablet press at tablet weight of 200 mg and compression force of 50 kN. The tablets were initially weighed (W_i) and then soaked in 900 ml 0.1 M HCl using USP Type II dissolution apparatus at 37.0±0.1°C and paddle speed of 100 rpm. At suitable time intervals, stirring was stopped to allow for the removal of tablets by a spatula. The removed tablets were rolled on a filter paper to remove any liquid on the surface and then weighed to give the wet weight (W_w). Swelling ratio was calculated as $(W_w - W_i)/W_i$. The experiment was repeated at room temperature.

IPE Complexation and Drug-Polymer Interaction

IPE complexation was attempted by combining acidic solutions (1% in 0.1 M HCl) of EE (30 ml) and CG (50 ml) in a beaker and the beaker was then placed on a shaker at room temperature. After 24 h, a precipitate was obtained and collected by centrifugation. The precipitate was washed twice with distilled water and then once with absolute ethanol to remove any free polymers before it was left to dry at room temperature under vacuum for 2 days. The dry precipitate was ground into powder using a mortar and pestle and then stored in tightly closed glass-bottles for further studies. Drug-polymer interaction was studied by kneading physical mixtures of metronidazole (1 g) and each polymer (2 g) using 0.1 M HCl with subsequent drying in an oven at 37°C and grinding into powders. The IPE complex powder was compared to CG, EE, and physical-mixture of the polymers, using Fourier transform infrared (FT-IR) spectroscopy according to the KBr disk method using Shimadzu FT-IR spectrometer (Japan). The powders were further analyzed using differential scanning calorimetry (DSC; Mettler–Toledo DSC823e, Switzerland) under dry nitrogen atmosphere (80 ml/min) from ambient temperature to 300°C at heating rate of 10°C/min. The kneaded drug-polymer powders were run for this DSC analysis, in comparison to pure metronidazole and untreated drug-polymer physical mixtures.

Tablet Preparation

Polymeric matrices, 100% CG, 100% EE, and hybrid EE–CG with CG/EE weight ratio that was optimal for IPE complexation, were used to prepare metronidazole tablets by direct compression. Briefly, metronidazole was mixed with the polymer(s) in a mortar and pestle at 1:2 (drug/polymer) weight ratio. The mixture was directly compressed into 300-mg tablets in 10 mm die using a manual hydraulic press at 50 kN. Tablets were found acceptable for weight variation (±5%) and friability (<1%) and their hardness was higher than 40 N (Table I). Corresponding effervescent tablets were also prepared by adding Na bicarbonate to the formulas at levels of 20, 40, and 60 mg per tablet.

Table I. Some Physical Properties of Metronidazole Tablets with Different Matrix Formers

Matrix former	Weight (mg)±SD	Hardness (N)±SD	Friability %
EE	296.8±3.6	172.0±6.6	0.011
CG	297.6±3.3	47.8±3.4	0.204
EE–CG (noneffervescent)	297.0±7.3	78.1±2.3	0.002
EE–CG (effervescent)	358.6±5.1	57.7±4.0	0.002

In Vitro buoyancy

Floating behavior was studied as described previously (17). Glass beakers containing 100 ml 0.1 M HCl were placed in a water bath shaker at 37°C. The tablets were added separately into these beakers and observed for floating over 10 h. The time required for the tablets to rise to the surface and float was determined as floating lag-time (T lag) and floated tablets were then followed for the duration of floating (floating time).

Swelling Profile of EE–CG Floating Tablets

EE–CG tablets with the best floating parameters were subjected to swelling studies according to the procedure of the *in vitro* buoyancy, however, the tablets were measured for the swelling percent every hour for 10 h. The tablets were also measured for thickness and diameter before soaking (0 h) and at the end of the experiment (10 h).

Dissolution Studies

The dissolution studies were performed in triplicate using USP type II (paddle method) dissolution apparatus (Vankel dissolution tester, USA). Tablets were placed in 0.1 M HCl dissolution medium and then stirred at a rate of 100 rpm and temperature of 37±0.1°C. Samples (10 ml) were drawn at predetermined time intervals and assayed for drug content using UV spectrophotometery at 280 nm (18). To keep constant volume of dissolution medium, equal volumes were used to replace drawn samples.

RESULTS AND DISCUSSIONS

Viscosity Measurements

Figure 1 shows how the supernatant viscosity changed when EE/CG weight ratio varied. The viscosity progressively decreased with the increase in ratio until reaching a minimum at ratio of 0.6, beyond which the viscosity started to increase. Minimum viscosity is the result of optimum reaction between the polymers leading to greatest utilization of the free polymer molecules towards the formation of insoluble complex and leaving a supernatant with the least amount of dissolved polymer (free polymers).

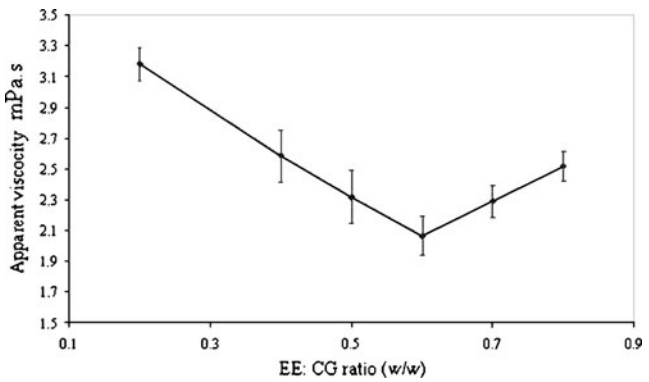

Fig. 1. Apparent viscosity values of supernatants from EE–CG systems as a function of EE/CG weight ratio

Swelling Studies

Figure 2, A shows the swelling behavior of EE–CG tablets in 0.1 M HCl at 37°C as a function of EE/CG weight ratios. At high weight ratio of 4, tablet weight increased by approximately 1.8 fold as a result of swelling after 2 h of exposure to the acidic medium. At this ratio, which is much higher than the optimum ratio for EE–CG complexation (0.6) determined by the viscosity measurements, swelling is likely attributed to excess EE with minimal formation of IPE complex. The free amino groups of EE are completely protonated at this pH, consequently, the electrostatic repulsions, the solvation of the ionic groups, and the osmotic contribution are maximal, thus resulting in the high degree of swelling. With decreasing EE/CG weight ratio from 4 to 0.6, swelling ratio progressively increased until reaching the highest (3.97) at weight ratio of 0.6. However, further decrease in weight ratio to 0.4 and then to 0.3 resulted in lower swelling ratios as 3.78 and 3.70, respectively. This trend in the swelling behavior is consistent with the viscosity measurement results. As the system is closer to the optimum IPE complexation ratio, lesser fractions of free polymers and higher fraction of IPE complex are in the soaked tablets. Since both polymers are already in the ionized state, the fact that the formed complex is polyelectrolyte in nature explains the highest swelling obtained at EE/CG weight ratio of 0.6. Similar trend in swelling was obtained at room temperature (Fig. 2b).

IPE Complexation and Drug-Polymer Interaction

FT-IR spectra of CG and EE are shown in Fig. 3. The spectrum of CG showed various distinct peaks: very broad band spreading from 3,100 to 3,800 cm^{-1} (strong; s) due to poly hydroxyl $(-OH)_n$ group; 2,923 cm^{-1} (s), and 2,849 cm^{-1} due to C-H stretch; 1,435 cm^{-1} (s) and 1,377 cm^{-1} (s) due to C-H deformation; 1,248 cm^{-1} (s) due to S=O stretch of sulfate ester salt; 1,031 cm^{-1} due to C-O stretch of cyclic ethers; 931 cm^{-1} (s) due to C-O stretch of poly hydroxyl groups attached to carbons (19). The spectrum of EE showed the characteristic bands of the ester groups at 1,149, 1,242 and 1,271 cm^{-1}, as well as the C=O ester vibration at 1,730 cm^{-1}. In addition, CH_X vibrations can be discerned at 1,390, 1,459, and 2,957 cm^{-1}, and the bands at 2,772 and 2,823 cm^{-1} can be assigned to the dimethylamino groups. The spectrum of the physical mixture (Fig. 4a) showed the absorptions bands corresponding to the dimethylamino groups of EE (at 2,772 and 2,825 cm^{-1}). These two bands were absent in the spectrum of EE–CG IPE complex (Fig. 4b). This disappearance suggested that the dimethylamino groups of EE were involved in electrostatic interaction with the sulfate groups of CG. The absorption band corresponding to S=O stretch of sulfate ester salt shown for CG powder at 1,248 cm^{-1} was missing in the spectrum of the physical mixture. This is likely because EE powder showed overlapped peaks at 1,242 and 1,271 cm^{-1}, which were shown in the spectrum of the physical mixture, and these peaks likely concealed the S=O stretch band of CG (at 1,248 cm^{-1}) because of the relatively lower intensity of the later band. Interestingly, the bands of EE at 1,242 and 1,271 cm^{-1}, shown for EE and the physical mixture, were not shown as overlapped peaks in the

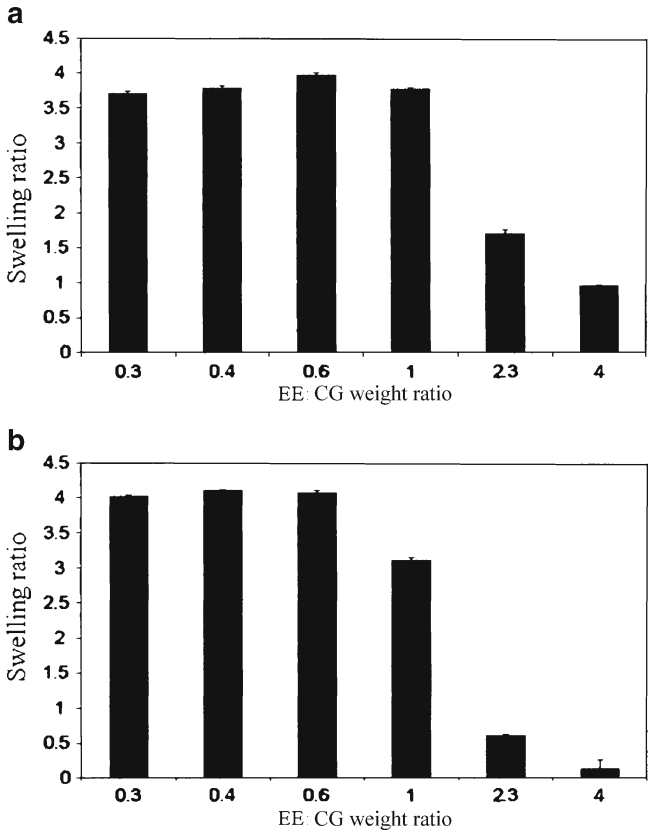

Fig. 2. Swelling ratios of EE–CG tablets made at different EE/CG ratios (*w*/*w*) after soaking in 0.1 M HCl for 2 h

spectrum of EE–CG IPE complex, instead new broad peak was shown for the complex at 1,266 cm^{-1}. This new band was different from S=O stretch of CG (at 1,248 cm^{-1}) by 18 cm^{-1}, and was more intense. Accordingly, it could be hypothesized that complexation of CG with EE occurs by electrostatic interaction between sulfate groups of CG and dimethylamino groups of EE resulted in shifting the S=O stretch of sulfate ester group of CG to higher wave number with higher intensity of the corresponding band.

DSC thermograms of EE, CG, IPE complex of EE–CG, and EE–CG physical mixture are reported in Fig. 5. The thermograms were recorded for samples heated from 25 to 100°C as preheating stage to remove free moisture. The heated samples were cooled down to 25°C, and then reheated from 25 to 300°C as a rerun. The thermogram of EE showed an endothermic peak during preheating at 60.8°C. After cooling and during the rerun, this endothermic peak did not show up and endothermic heat absorption was shown with an onset temperature of 237°C. The endothermic peak at 60.8°C was due to the glass transition temperature of EE (14). The disappearance of this peak during the rerun was attributed to the ordered crystallization of EE during preheating to form crystalline methacrylic polymer rather than glassy one (14). The endothermic heat absorption started at 337°C was attributed to the loss of water by condensation that resulted in the anhydride formation of EE (14). During preheating, CG showed broad endothermic peak which appeared again but relatively at lower magnitude during the rerun. This behavior indicated loss of moisture and/or conformational changes of the polymer. During rerun, CG showed two distinctive peaks as endothermic heat absorption at approximately 150°C and exothermic heat absorption at approximately 200°C, which were assigned as melting and thermal degradation peaks, respectively. During preheating, EE–CG physical mixture showed two peaks: broad endothermic peak also shown for CG and the other one matched the glass transition peak of EE. On the other hand, EE–CG IPE complex did not show the glass transition peak shown for EE during preheating. This disappearance could be due to the fact that the complex has homogenic structure and actually does not include microdomains of free EE macromolecules (20). Indeed, more heating is required before the complex gains the desired mobility to enter the glass transition region, thus confirming the existence of strong electrostatic interaction between the polymer chains (20). During rerun, the physical mixture showed the melting and thermal degradation peaks of CG. However, these peaks did not appear in the thermogram of the IPE complex, and instead broad exothermic peak appeared between 160 and 270°C in this thermogram. These thermal behaviors go in line with the explanation adopted for the disappearance glass transition of the complexed EE during preheating. Very likely, the homogenic structure of the complex with strong electrostatic interaction between the polymer chains changed the thermal behavior of CG.

There was no significant interaction between metronidazole and EE as the thermograms of the drug and kneaded drug-EE physical mixture by 0.1 M HCl showed melting endotherms of similar temperatures (Fig. 6). In addition, the thermogram of the kneaded mixture was not significantly different from that of the untreated physical mixture. Similar results were obtained for CG.

In Vitro Buoyancy

Noneffervescent tablets made of free EE, free CG, or hybrid EE–CG as polymeric matrix showed no floatation in 0.1 M HCl. The corresponding effervescent tablets showed variable floating parameters. Effervescent EE–CG matrices showed average T lag values (n=3) of 180.0±30.0, 80.0±17.3, and 6.3±2.5 s at Na bicarbonate levels of 20, 40, and 60 mg, respectively, with floating times greater than 10 h. Since for the 60 mg Na bicarbonate level T lag was much less than for the other levels, EE–CG tablets with 60 mg Na bicarbonate were selected for the dissolution studies. Fast floating was observed for effervescent tablets made of CG (60 mg Na bicarbonate) with T lag of 10.7±5.1 s (n=3) and floating times of more than 10 h. However, the corresponding EE matrices showed much longer T lag (135±13.2 min) and dissolved after 3 h of the acidic soaking.

Swelling Profile of EE–CG Floating Tablets

The swelling profile of EE–CG floating tablets is shown in Fig. 7. The profile can be divided into three distinct phases. Rapid swelling phase (0–2 h) during which the swelling rate was the highest followed by a slower swelling phase between 2 and 7 h. After 7 h, a plateau phase was reached with insignificant swelling. The swelling rates were calculated by linear regression (n=3) and were found to be 80.1±7.2%.h^{-1}

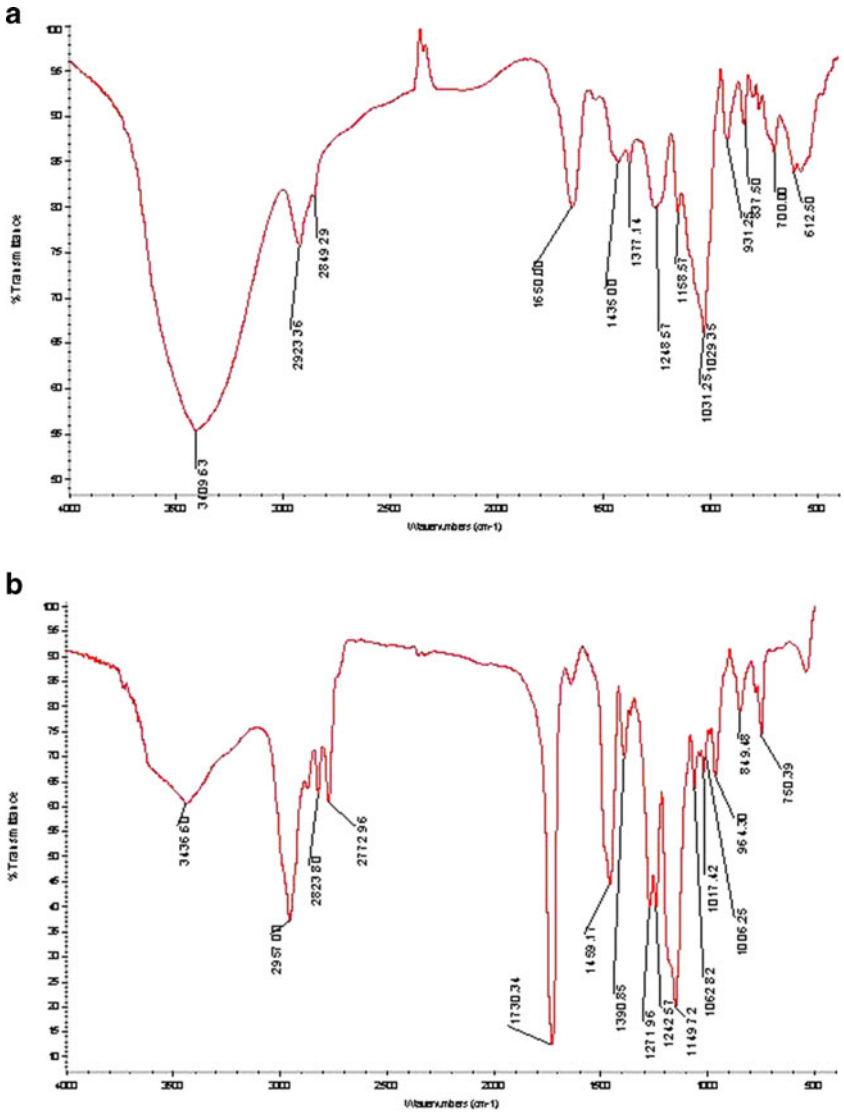

Fig. 3. FT-IR spectra of CG **a** and EE **b**

(r^2=0.997±0.002) and 27.6±1.7%.h^{-1} (r^2=0.974±0.006) for 0–2 h and 2–7 h, respectively. These results were likely due to rapid IPE complexation and gel formation at the tablet surface during early times of soaking and this gel formation slowed further solvent penetration inside the tablets resulting in slower swelling afterwards. When the tablets were completely wetted and IPEC was maximized, the plateau was reached. Based on the dimensions of the cylindrical tablets (thickness of 16.33±0.94 mm and diameter of 7.0±0.0 mm) after 10 h of soaking and the corresponding initial dimensions before swelling, the percent volume increase of the tablets as a result of swelling was calculated and was found to be 668.5±86.2% (n=3).

Drug-Release Studies

The dissolution profiles of various effervescent tablets are presented in Fig. 8. Metronidazole release in 0.1 M HCl from the effervescent EE matrices with drug/polymer weight ratio of 1:2 was rapid, since the average drug release was 77% at 1 h and complete drug release was achieved at 3 h. This could be attributed to the high solubility of free EE and the drug in the acidic medium. Drug release from the corresponding free CG matrices was relatively slower and extended for 8 h. However, initial burst drug release from these matrices was apparent with average drug release of 48% at 1 h. This burst effect was prevented when combination of the polymers at EE/CG weight ratio of 0.6 was used as a matrix former (1:2 drug to polymer weight ratio) as the hybrid matrices released an average value of less than 9% at 1 h. In addition, these matrices maintained the slow drug release in almost zero-order manner for 10 h (68.2±6.6%). This slower release performance could be attributed to the IPE complexation between CG and EE upon tablet hydration in the acidic medium leading to the formation of insoluble IPE complex (gel-like layer), and consequently slower solvent penetration into the matrices and more controlled drug diffusion were achieved. It is worth mentioning that the presence of strongly acidic sulfate groups in CG molecule allows a certain degree of polymer ionization to be maintained at low pH (21) and the amino groups of the polycationic nature of EE are mostly protonated in 0.1 M

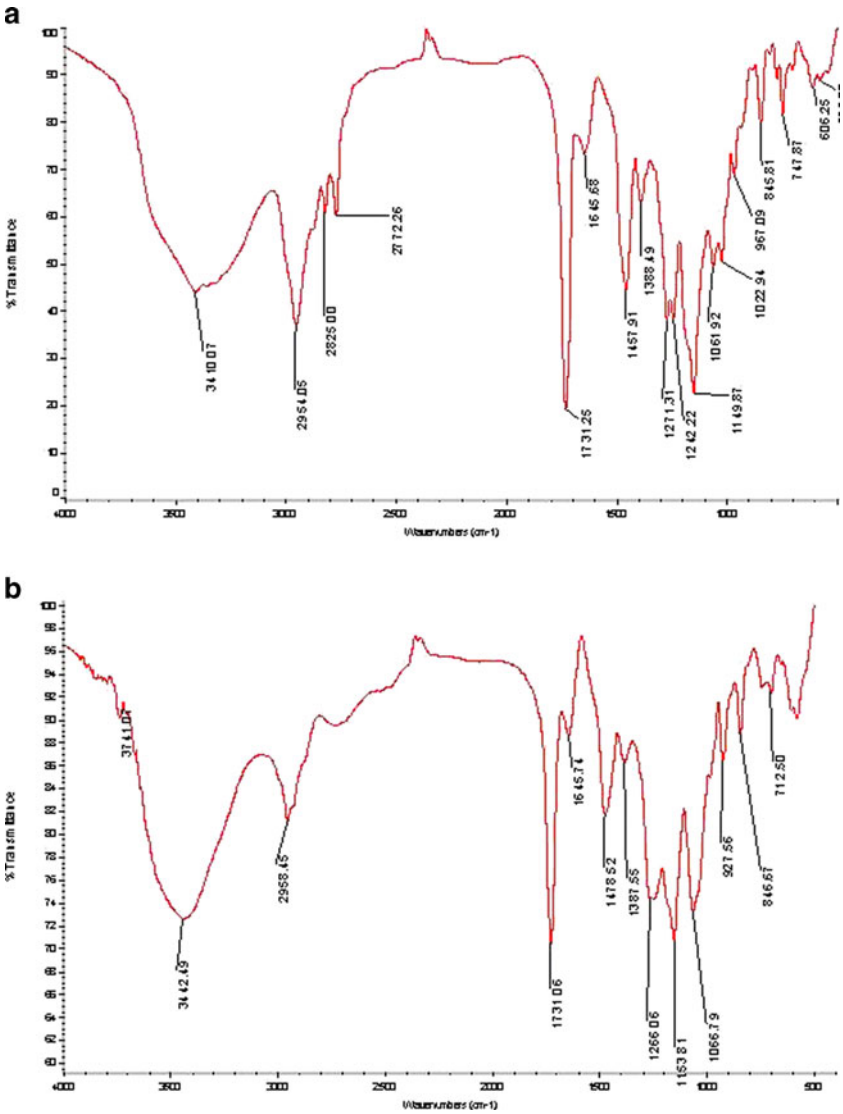

Fig. 4. FT-IR spectra of CG–EE physical mixture **a** and CG–EE IPE complex **b**

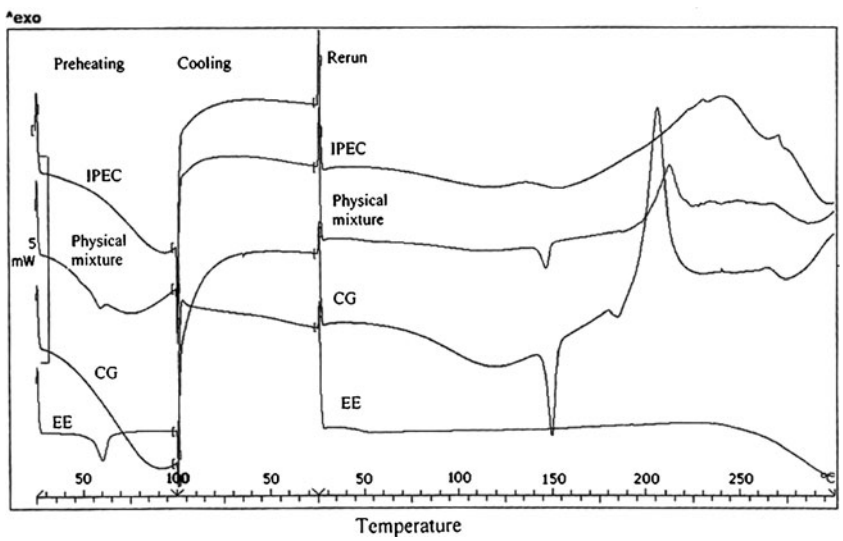

Fig. 5. DCS thermograms of CG, EE, EE–CG physical mixture and EE–CG IPE complex

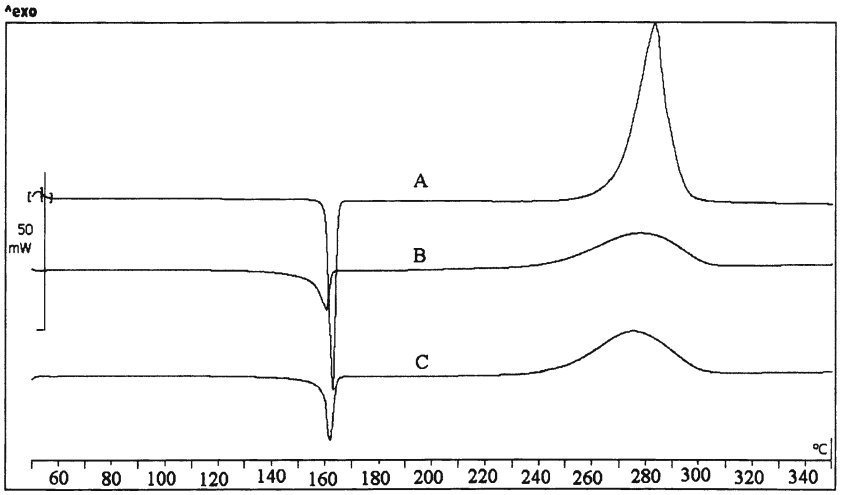

Fig. 6. DCS thermograms of metronidazole **a** and metronidazole–EE physical mixtures: kneaded using 0.1 M HCl **b**, and untreated **c**

HCl (pH 1.2). Accordingly, both polymers will be sufficiently ionized for electrostatic interaction, and consequently complex formation in 0.1 M HCl. Decreasing the drug to polymer weight ratio in the hybrid matrices from 1:2 to 1:1, resulted in faster drug release, which could be attributed to less complex formation between the polymers resulting in thus less control of solvent penetration and drug diffusion.

The dissolution data of EE–CG matrices were fitted into different models: the zero-order, first-order, Higuchi's square root of time, and Hixson–Crowell's cube root of time. The goodness of fit was evaluated by r^2 (correlation coefficient) values. At 1:2 drug/polymer weight ratio, the best fit with highest r^2 coefficient was shown by zero-order (r^2=0.992±0.004), followed by Hixon–Crowell (r^2=0.983±0.005) and then first-order (r^2=0.949±0.012). The data poorly fitted to the Higuchi-model (r^2=0.806±0.071). At 1:1 drug/polymer weight ratio, the data best fitted the first-order model (r^2=0.978±0.015). To determine the release mechanism of drug from the EE–CG matrices, the drug dissolution data were fitted to Korsmeyer–Peppas' power law equation (22,23),

$$Q_t/Q_\infty = Kt^n$$

where Q_t is the amount of drug dissolved at time t, Q_∞ is the amount of drug dissolved at ∞ time (the drug loaded in the formulation), Q_t/Q_∞ is the fractional release of the drug at time t, K is a constant incorporating structural and geometric characteristic of dosage form, n is the release (diffusional) exponent that depends on the release mechanism and the shape of the matrix tested and t is release time. For the tablets, when $n<0.45$, the drug release is controlled by diffusion and when $n>0.98$, the drug release is controlled by the matrix erosion. Values of n between 0.45 and 0.98 indicate a superposition of both phenomena. The fitting was performed for $Mt/M_\infty \leq 0.7$. The mean n values obtained at 1:1 and 1:2 drug/polymer weight ratios were 0.707±0.055 (r^2=0.927±0.016) and 0.897±0.026 (r^2=0.989±0.010), respectively, which suggested that drug release was controlled by the superposition of the diffusion and erosion.

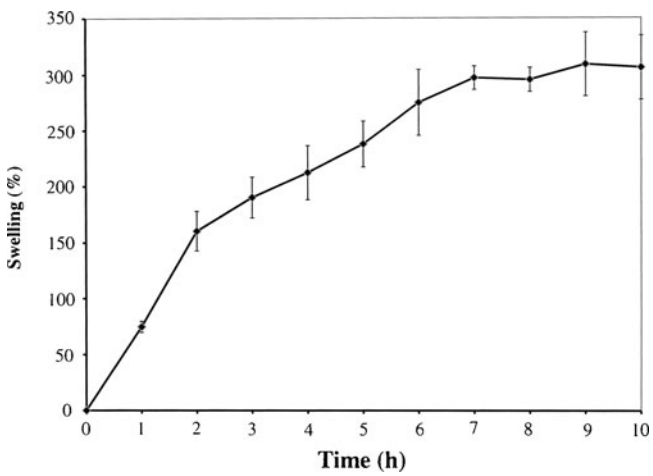

Fig. 7. Swelling profile of floating EE–CG matrices

CONCLUSIONS

IPE complexation between EE and CG was achieved in 0.1 M HCl at an optimal EE/CG weight ratio of 0.6. Supported by FT-IR and DSC analysis results, IPE complexation was explained by electrostatic interactions between the

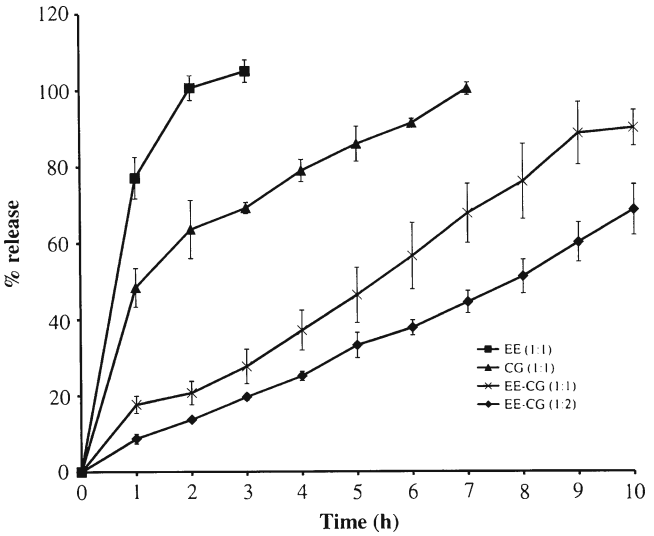

Fig. 8. Metronidazole release from different effervescent matrices. Drug/polymer weight ratio is given in *parenthesis*

sulfate groups of CG and amino groups of EE. IPE complexation between EE and CG offered an ideal milieu for novel effervescent floating tablet formulation with prolonged drug release.

REFERENCES

1. Risbud MV, Hardikar AA, Bhat SV, Bhonde RR. pH-sensitive freeze-dried chitosan-polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery. J Control Release. 2000;68:23–30.
2. Burton S, Washington N, Steele RJ, Musson R, Feely L. Intragastric distribution of ion-exchange resins: a drug delivery system for the topical treatment of the gastric mucosa. J Pharm Pharmacol. 1995;47:901–6.
3. Wu Y, Fassihi R. Stability of metronidazole, tetracycline hcl and famotidine alone and in combination. Int J Pharm. 2005;290:1–13.
4. Santus G, Lazzarini C, Bottoni G, Sandefer EP, Page RC, Doll WJ, *et al*. An *in vitro-in vivo* investigation of oral bioadhesive controlled release furosemide formulations. Eur J Pharm Biopharm. 1997;44:39–52.
5. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm. 1996;22:531–9.
6. Deshpande AA, Shah NH, Rhodes CT, Malick AW. Development of a novel controlled-release system for gastric retention. Pharm Res. 1997;14:815–9.
7. Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994;83:239–45.
8. Whitehead L, Fell JT, Collett JH, Sharma HL, Smith AM. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. J Control Release. 1998;55:3–12.
9. Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR. Development and *in vitro* evaluation of an oral floating matrix tablet formulation of diltiazem hydrochloride. AAPS PharmSciTech. 2007;8:E73.
10. Li S, Lin S, Chien YW, Daggy BP, Mirchandani HL. Statistical optimization of gastric floating system for oral controlled delivery of calcium. AAPS PharmSciTech. 2001;2:E1.
11. Xu G, Groves MJ. Effect of FITC-dextran molecular weight on its release from floating cetyl alcohol and HPMC tablets. J Pharm Pharmacol. 2001;53:49–56.
12. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63:235–59.
13. Shan-Yang L, Hui-Ling Y. Microscopic Fourier transform infrared/differential scanning calorimetry system used to study the different thermal behaviors of polymethacrylate copolymers of Eudragits RS, RL, E 30D, or E. J Appl Polym Sci. 2000;78:8298–35.
14. Shan-Yang L, Hui-Ling Y, Mei-Jane L. Formation of six-membered cyclic anhydrides by thermally induced intramolecular ester condensation in Eudragit E Film. Polymer. 1999;40:3589–93.
15. Picker K. The use of carrageenan in mixture with microcrystalline cellulose and its functionality for making tablets. Eur J Pharm Biopharm. 1999;48:27–36.
16. Prado HJ, Matulewicz MC, Bonelli P, Cukierman AL. Basic butylated methacrylate copolymer/kappa-carrageenan interpolyelectrolyte complex: preparation, characterization and drug release behaviour. Eur J Pharm Biopharm. 2008;70:171–8.
17. Jaimini M, Rana AC, Tanwar YS. Formulation and evaluation of famotidine floating tablets. Curr Drug Deliv. 2007;4:51–5.
18. Bakre LG, Jaiyeoba KT. Effects of drying methods on the physicochemical and compressional characteristics of okra powder and the release properties of its metronidazole tablet formulation. Arch Pharm Res. 2009;32:259–67.
19. Sankalia MG, Mashru RC, Sankalia JM, Sutariya VB. Stability improvement of alpha-amylase entrapped in kappa-carrageenan beads: physicochemical characterization and optimization using composite index. Int J Pharm. 2006;312:1–14.
20. Moustafine R, Zaharov I, Kemenova V. Physicochemical Characterization and Drug Release Properties of Eudragit E PO/Eudragit L 100-55 Inter Polyelectrolyte Complexes. Eur J Pharm Biopharm. 2006;63:26–36.
21. Bonferoni M, Rossi S, Ferrari F, Bettinetti G, Caramella C. Characterization of a diltiazem-λ-carrageenan complex. Int J Pharm. 2000;200:207–16.
22. Korsmeyer R, Gurny R, Doelker E, Buri P, Peppas N. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15:25–35.
23. Peppas N. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985;60:110–1.