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Research Article

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Release Mechanisms Behind Polysaccharides-Based Famotidine Controlled Release Matrix Tablets

Enas M. Elmowafy,[1] Gehanne A. S. Awad,[1] Samar Mansour,[1,2] and Abd El-Hamid A. El-Shamy[1]

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Abstract. Polysaccharides, which have been explored to possess gelling properties and a wide margin of safety, were used to formulate single-unit floating matrix tablets by a direct compression technique. This work has the aim to allow continuous slow release of famotidine above its site of absorption. The floating approach was achieved by the use of the low density polypropylene foam powder. Polysaccharides (κ-carrageenan, gellan gum, xyloglucan, and pectin) and blends of polysaccharides (κ-carrageenan and gellan gum) and cellulose ethers (hydroxypropylmethyl cellulose, hydroxypropylcellulose, sodium carboxymethyl cellulose) were tried to modulate the release characteristics. The prepared floating tablets were evaluated for their floating behavior, matrix integrity, swelling studies, *in vitro* drug release studies, and kinetic analysis of the release data. The differential scanning calorimetry and Fourier transform infrared spectroscopy studies revealed that changing the polymer matrix system by formulation of polymers blends resulted in formation of molecular interactions which may have implications on drug release characteristics. This was obvious from the retardation in drug release and change in its mechanistics.

KEY WORDS cellulose ethers; famotidine; floating tablets; polypropylene foam powder; polysaccharides.

INTRODUCTION

Natural polysaccharides such as carrageenan, gellan gum, pectin, and xyloglucan have lately received attention due to their gelling and viscosity building properties as well as their proven safety. Carrageenans are naturally occurring high molecular weight polysaccharides extracted from seaweeds. They consist of the sulfate esters of galactose and 3,6 anhydrogalactose joined by alternating α-1,3 and β-1,4 glycosidic linkages (1). They are present in three different types: the highly sulfated λ carrageenan, which does not gel, and both κ and ι-carrageenan, which are able to generate gels with different characteristics (2). Gellan gum is an exocellular polysaccharide secreted by *Pseudomonas elodea*, with a tetrasaccharide-repeating unit of one α-L-rhamnose, one β-D-glucuronic acid, and two β-D-glucose residues (3). Xyloglucan is a cell wall heavily substituted polysaccharide consisted of (1–4)-β-D-glucan backbone that is partially substituted at the *O*-6 position of its glucopyranosyl residues with α-D-xylopyranose (4). Pectins are hydrophilic polysaccharides derived from plant cell walls. They contain linear chains of (1→4) linked α-D-galacturonic acid residues, some of which are naturally presented as methyl esters. The degree of esterification (DE), which is expressed as a percentage of the esterified carboxyl groups, is an important mean to classify pectins. High methoxy pectin (with DE >50%) requires a relatively high concentration of soluble solids and a low pH for gel formation, whereas low methoxy (LM) pectin (with DE <50%) forms rigid gels by the action of calcium or multivalent cations (5).

Various studies have used carrageenan and pectin in controlled release tablet technology (6,7). Gellan gum has found many applications for ophthalmic drug delivery (8), oral *in situ* gelling sustained formulations (3), sustained delivery beads (9), and for the new intragastric floating *in situ* gelling system (10). Xyloglucan was used rectally as gels (11), intraperitoneally (12) and orally as *in situ* gelling formulations (13). Blends of polysaccharides and cellulose ethers can be used to modulate drug release profiles not achievable by the use of either type of polymers. Studies correlating the polymer–polymer interactions and their implication on drug release and drug release kinetics have not been reported to our knowledge.

Famotidine is a potent histamine H_2-receptor antagonist used to treat peptic ulceration, reflux esophagitis, Zollinger–Ellison syndrome, and other conditions where reduction of gastric acid is beneficial (14). It is not absorbed uniformly throughout the gastrointestinal tract (GIT) but mainly at a specific absorption site (15) leading to incomplete and variable absorption (16). So, a dosage form that achieves gastric retention would be presented at the absorption site over a prolonged period improving its bioavailability and reducing

[1] Department of Pharmaceutics, Faculty of Pharmacy, Ain Shams University, Monazamet El Wehda El Afrikia St., El Abbassia, Cairo, Egypt.
[2] To whom correspondence should be addressed. (e-mail: samar_holayel@yahoo.com)

its wastage (17). Moreover, being a weak base, famotidine with a pKa of 7.06 (BP, 1998) has pH dependant solubility and its gastric retention would allow adequate time for its dissolution, the rate-limiting step in drug absorption (17).

Different famotidine gastroretentive systems were lately formulated including gastroretentive controlled release microspheres (18), mucoadhesive granules compressed to tablets (19), floating osmotic device (15), and recently floating tablets based on effervescent mechanism (20). Although multiple unit dosage forms distribute uniformly along the GIT resulting in longer lasting effects and reduced intersubject variability, single unit tablets still have the advantages of ease of production, cost effectiveness, and lack of using hazardous organic solvents in some production techniques of multiple units.

In the current work, polysaccharides-based famotidine floating matrix tablets were prepared, using the previously mentioned polysaccharides, alone or in combination with cellulose ethers, to optimize matrix integrity and modulate drug release characteristics. Polypropylene foam powder was incorporated into tablets to ensure instantaneous floatation with no lag time (21), preventing premature evacuation through the pyloric sphincter, an inevitable event observed with gas-generating systems (22). Investigation of the release mechanistics, as well as thermal behavior and molecular interaction of different polymer blends, were done to elucidate the degree of interaction between different blends which could govern the physical and mechanical properties of the formulated tablets.

MATERIALS AND METHODS

Materials

Famotidine was kindly supplied by Memphis, Cairo, Egypt. Polypropylene foam powder (Accurel MP 1000) was purchased from Membrana, Obernberg, Germany. Hydroxypropylmethyl cellulose (HPMC E_4; 3,500–5,600 cp) and hydroxypropylcellulose (HPC) MF (4,000–6,500 cp) were gifted by EIPICO, Cairo, Egypt. κ-Carrageenan and gellan gums were purchased from Sigma, USA. Xyloglucan was purchased from Carbomer industry, USA. Pectin LM 104 was obtained as gift sample from CP Kelco, Denmark. High Na carboxymethyl cellulose (H CMC; 3,000,000 cp) was purchased from Luna pharmaceuticals, Cairo, Egypt. Medium Na CMC (M CMC; 1,500–2,500 cp) was gifted by Memphis, Cairo, Egypt. Magnesium stearate (Mg. St.) was obtained from Win Lab Chemicals, Leicestershire, UK.

Tablet Formulations

Famotidine floating tablets of composition shown in Table I were prepared by direct compression. The respective powders (11.4% "40 mg" famotidine, 25% "87.5 mg" foam powder as a floating aid, and 62.5% "219 mg" single or polymers blends) were mixed thoroughly then Mg. St. was added in 1% *w/w* "3.5 mg". The mix was then fed manually into a die, with 12.84 mm internal diameter, of a single-punch tablet compression machine (Karishma Pharma Machines 400007, Mumbai, India) to produce 350 mg tablets, using 12-mm-diameter flat-faced punch at compression force ranging between 3.3 and 4.6 kN.

Floating Behavior and Matrix Integrity Studies

The *in vitro* floating behavior of the tablets was studied by placing them in 50 mL 0.1 N HCl at 37°C (23). Floating lag time (time required for the tablet to float on surface) and floating duration were determined by visual observation. The relative matrix integrity was inspected visually as well.

Density Measurements

The apparent densities of the tablets were calculated from their volumes and masses (21). The volume (V) of the

Table I. Composition of the Prepared Famotidine Floating Matrix Tablets

	Composition[a] (% *w/w*)							
Formulation no.	κ-Carrageenan	Gellan gum	Xyloglucan	Pectin	HPMC E_4	HPC	H CMC	M CMC
F1	62.5	–	–	–	–	–	–	–
F2	–	62.5	–	–	–	–	–	–
F3	–	–	62.5	–	–	–	–	–
F4	–	–	–	62.5	–	–	–	–
F5	31.25	–	–	–	31.25	–	–	–
F6	31.25	–	–	–	–	31.25	–	–
F7	31.25	–	–	–	–	–	31.25	–
F8	41.66	–	–	–	–	–	20.83	–
F9	31.25	–	–	–	–	–	–	31.25
F10	–	31.25	–	–	31.25	–	–	–
F11	–	41.66	–	–	20.83	–	–	–
F12	–	31.25	–	–	–	31.25	–	–
F13	–	31.25	–	–	–	–	31.25	–
F14	–	41.66	–	–	–	–	20.83	–
F15	–	31.25	–	–	–	–	–	31.25

[a] All formulae contained 11.4% famotidine (40 mg), 25% foam powder (87.5 mg), and 1% Mg. St. (3.5 mg)

tablets was calculated using the following equation for a cylinder:

$$V = \pi r^2 h \quad (1)$$

where:

V volume of the tablet
r radius of the tablet
h height of the tablet (determined by a Vernier calliper)

The results are average of three determinations.

In Vitro Drug Release Studies

The release of famotidine from the tablets was studied using US Pharmacopeia dissolution apparatus I (Pharma Test, Hainburg, Germany) at 37±0.5°C and 50 rpm. The dissolution medium was 900 mL 0.1 N HCl (pH 1.2). Samples of 5 mL were withdrawn, replenished with fresh medium at predetermined time intervals for 6 h, and analyzed using UV spectrophotometer (Shimadzu UV visible 1601 PC, Kyoto, Japan) at 265 nm.

Swelling Studies

Each tablet was initially weighed (W_1) then placed in 50 mL 0.1 N HCl (pH 1.2) at 37±0.5°C in shaking water bath (Kotterman, Hanigsen, Germany). At different time intervals (0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 h), each tablet was removed from the medium, dried between two filter papers, to remove surface water, and reweighed (W_2) as soon as possible. The percent water uptake was determined using the following equation:

$$\%\ \text{water uptake} = \frac{(W_2 - W_1)}{W_1} \times 100 \quad (2)$$

Kinetic Analysis of The Release Data

The kinetics of famotidine release from the various matrices were analyzed using the exponential Peppas equation.

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where:

M_t/M_∞ the fraction of drug released at time t.
k a constant incorporating the structural and geometric characteristics of the drug/polymer system.
n the release exponent indicative of the drug release mechanism.

The values of n and k were determined from the slope and intercept of the plot of (M_t/M_∞) as a function of time, on a logarithmic scale, according to Eq. 3. n values=0.45 for Fickian (case I) release, $0.45>n<0.89$ for non-Fickian (anomalous) release, $n=0.89$ for case II (zero order) coupling drug diffusion and polymer relaxation (24), and $n>0.89$ for super case II which is generally related to the dissolution of the polymeric matrix due to the relaxation of the polymer chain.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermograms of carrageenan and gellan gum and their blend with cellulose ethers were recorded using a differential scanning calorimeter (DSC-50; Shimadzu-Japan; connected with thermal analyzer TA-501). Each sample (10 mg) was placed in aluminum pan and heated at a rate of 10°C/min, with indium in the reference pan in an atmosphere of nitrogen to a temperature of 400°C.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) spectra of carrageenan, gellan gum, HPMC E_4, H CMC, and HPC and their blends were recorded with a FTIR spectrophotometer (Nicolet 6700 FTIR; Thermal Scientific; Class 1 laser product; USA) using KBr disc method. Each sample was gently triturated with KBr powder in a weight ratio of 1:100 and then pressed using a hydrostatic press at a pressure of 10 tons for 5 min. The disc was then placed in the sample holder and scanned from 4,000 to 400 cm^{-1}. All spectra were recorded at ambient temperature under vacuum to remove air humidity contribution at a resolution of 4 cm^{-1} and 16 times scanning for each measurement to obtain an adequate signal-to-noise ratio. Flat baselines were obtained after baseline correction to correct spectra that have sloping or curved baselines and a 15-point smoothing was chosen. Finally, the spectra were all normalized by dividing all the absorbances in a spectrum by the largest absorbance in each one.

RESULTS AND DISCUSSION

Floating Behavior and Matrix Integrity Studies

A preliminary study proved that tablets could float immediately on 0.1 N HCl with the use of 25% *w/w* of polypropylene foam powder. Table II shows that all formulations densities were less than 1 gm/cm^3, ranging between 0.746 to 0.989 gm/cm^3. Extended floating durations for 6 h were achieved due to air entrapment within the foam powder particles which was slowly removed from the system upon contact with the release medium (21).

Regarding the matrix integrity from Table II, it is obvious that among the tested single polysaccharides, only xyloglucan and pectin containing tablets (F3 and F4, respectively) maintained their physical integrity for 6 h. The respective early, partial, and complete disintegration seen with carrageenan (F1) and gellan gum tablets (F2) could be due to the ionization of these polysaccharides in 0.1 N HCl. Consequently, electrostatic repulsions, solvation of the ionic groups, and osmotic contribution were at maximum, contributing to extensive swelling accompanied by tablet disintegration (25).

Combinations of carrageenan and gellan gum with HPMC E_4 and H CMC (31.25%; F5, F7, F10, and F13) yielded nondisintegrating tablets. Decreasing the percent of

Table II. Matrix Integrity, Density Measurements, and % Swelling of the Prepared Famotidine Floating Matrix Tablets

Formulation no.	Matrix integrity	Density (gm/cm^3)	% Swelling (mean ± SD)	
			After 1/2 h	After 6 h
F1	PD	0.972±0.009	NA	NA
F2	CD	0.774±0.006	NA	NA
F3	ND	0.989±0.011	66.40±3.70	87.32[a]±0.96
F4	ND	0.967±0.035	42.22±1.34	75.51±2.69
F5	ND	0.746±0.003	140.50±5.06	171.57±2.73
F6	PD	0.978±0.003	NA	NA
F7	ND	0.939±0.019	75.10±3.87	150.35±6.06
F8	ND	0.866±0.009	89.02±0.09	182.63[a]±0.13
F9	PD	0.978±0.020	NA	NA
F10	ND	0.819±0.061	56.41±2.60	143.94±3.21
F11	ND	0.896±0.002	53.17±3.57	115.89±2.65
F12	PD	0.885±0.039	NA	NA
F13	ND	0.886±0.005	56.48±2.17	200.82[b]±0.27
F14	PD	0.905±0.009	NA	NA
F15	CD	0.900±0.006	NA	NA

ND nondisintegration, *NA* not applicable, *PD* partial disintegration with loss of tablet shape, *CD* complete disintegration
[a] Maximum measurement after 5 h, after then erosion started
[b] Maximum measurement after 3 h, after then erosion started

H CMC in combination with gellan gum (F14) or blending M CMC with carrageenan (F9) gave partially disintegrating tablets. When gellan gum was combined with M CMC (F15), complete tablet disintegration occurred. Although both HPMC E_4 and HPC had similar viscosity values (3,500–5,600 and 4,000–6,500 cp, respectively), yet HPC containing tablets (F6 and F12) disintegrated partially, while HPMC E_4 containing tablets (F5 and F10) were nondisintegrating ones. The methyl groups in HPMC E_4 enabled it to have an easier interaction with water with a better hydration extent (26) added to the low viscosity gel layer of HPC unable to resist the erosion (27).

It is to be noted that the human pyloric sphincter diameter is 12±7 mm (28). It is accepted that a diameter >15 mm is satisfactory for gastric retention (22). Formulae F9 and F14 with initial respective diameters of 12.21±0.03 and 12.18±0.04 mm swelled and split into two big gelatinous masses with respective diameters of 20.04±0.08 and 15.18±0.60 mm. These masses sank to the bottom of the beaker after 1 h (Fig. 1) and 2.5 h, respectively. Accordingly, these gelatinous masses would not be able to pass through the pylorus and can form plug-type gastroretentive systems (29).

In Vitro Drug Release Studies

Drug dissolution increased when reducing the amount of foam powder from 87.5 to 0 mg (control) as shown in Fig. 2. At higher foam powder content, 74.7% of the drug was dissolved after 30 min and remained constant for 6 h. This might be due to the dissolution of the adsorbed drug on surface, then the hydrophobic polypropylene powder was the only exposed surface for the dissolution medium. This was explained by the presence of multiple mechanisms causing mass transfer and large tortuosity values depending on pore network leading to retardation in drug release (30).

Tablets containing gellan gum (F2) and carrageenan (F1) released their whole famotidine content in 30 and 240 min, respectively (Fig. 2). On the contrary, xyloglucan and pectin containing tablets, F3 and F4, showed slower drug release with respective T_{6h} of 85.01% and 71.15%. However, higher initial burst effect (in the first 30 min) was noticed with these polymers with respective values (27.54% and 20.59% *versus* 8.21% of carrageenan). The acidic nature of the sulfate groups of carrageenan, acquired at low pH, hindered the early release of the cationic famotidine.

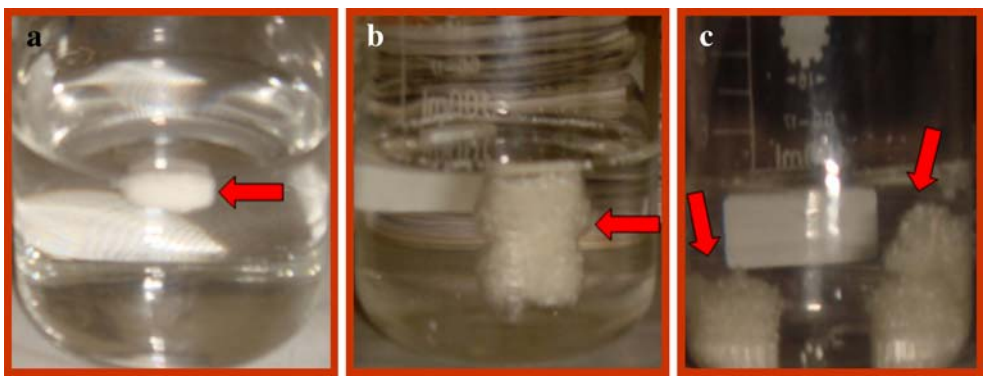


Fig. 1. Floating behavior and dimensional changes occurred in F9 after 1 h of immersion in 0.1 N HCl. **a** At zero time. **b** At 30 min. **c** After 1 h

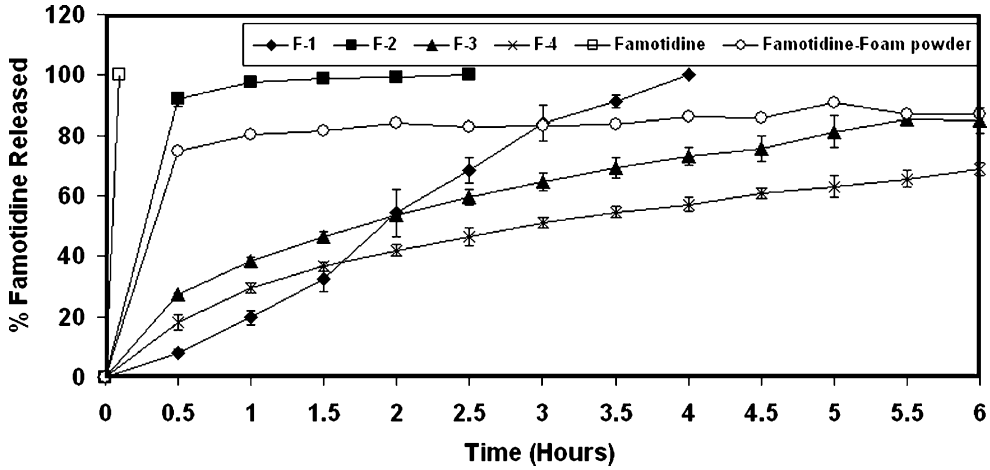


Fig. 2. Release profiles of famotidine, famotidine-foam powder physical mixture, and floating tablets (F1 to F4) in 0.1 N HCl at 37°C

Blending carrageenan with either HPC (F6) or M CMC (F9) gave respective T_{6h} of 62.43% and 84% (Fig. 3). On the other hand, mixing carrageenan with HPMC E_4 (F5) and H CMC (F7) resulted in releasing 22.33% and 33.89% of drug, respectively. Attempt to improve famotidine release by decreasing the H CMC content (F8) yielded insignificant increase in drug release (39%; $P>0.05$). Decreasing the HPMC E_4 content led to further decrease in famotidine release (data not shown).

Combinations of gellan gum with HPC (F12) and M CMC (F15) resulted in drug release > 90% after 6 and 2 h, respectively, while blending gellan gum with HPMC E_4 (F10) and H CMC (F13) yielded T_{6h} of 48.71% and 65% as shown in Fig. 4. Decreasing H CMC content (F14) enhanced drug release significantly where 100% of drug was released after 2.5 h.

The above results showed that although some cellulose ethers had same physical properties (e.g., viscosity), yet when present with different polysaccharides gave dissimilar tablet properties. Hence, a possible polymer–polymer interaction at a molecular level might be at the base of these characteristics.

Swelling Studies

According to the magnitude of swelling percentage after 6 h, noneroding famotidine tablets can be arranged in a descending order as follows: F5>F7>F10>F11>F4 with respective values, 171.57>150.35>143.94>115.89>75.51% with the lowest swelling percentage noticed with LM pectin containing tablets (F4) (Table II). The relatively low swelling ability of pectin containing tablets (F4) might be attributed to its acidic nature which reduced its solubility, hence, its swelling, in 0.1 N HCl (31). Xyloglucan containing tablets (F3) exhibited also low % swelling amounting to 87.32% after 5 h followed by erosion.

For polysaccharides–cellulose ethers blends, carrageenan-based matrices blends (F5, F7, and F8) showed higher swelling capacity in the first 30 min as compared to gellan

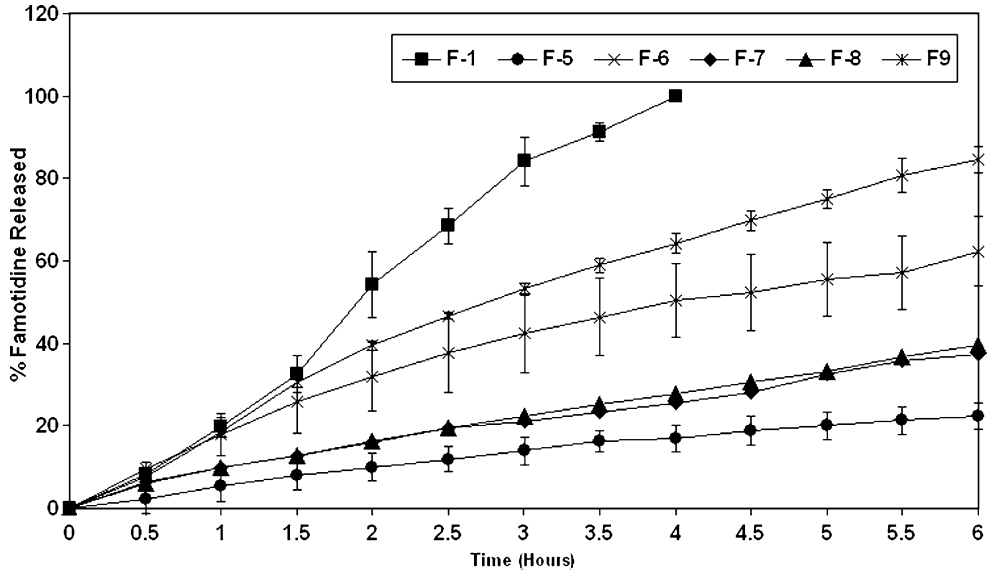


Fig. 3. Release profiles of floating tablets (F1 and F5–F9) containing pure κ-carrageenan and its blends with cellulose ethers in 0.1 N HCl at 37°C

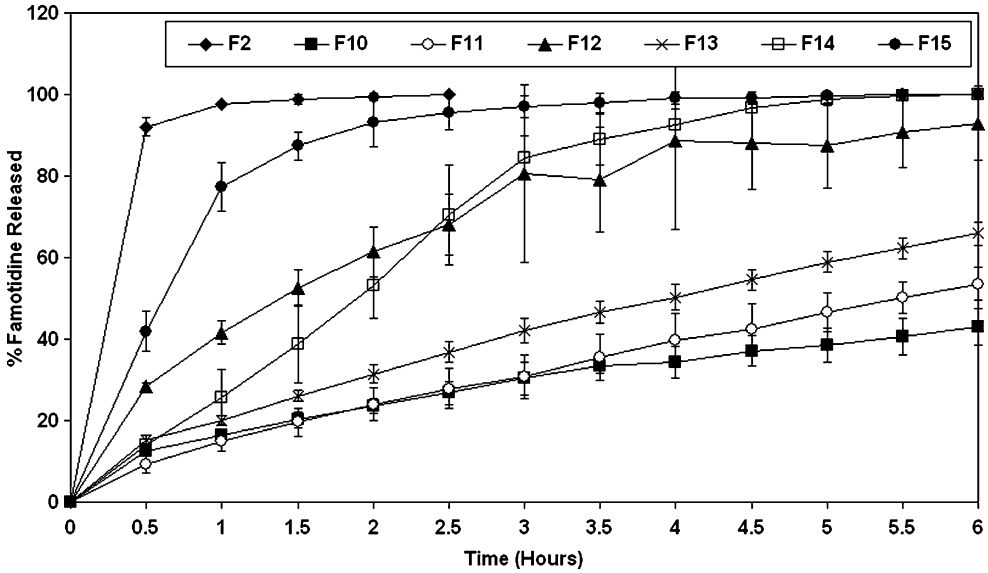


Fig. 4. Release profiles of floating tablets (F2 and F10–F15) containing pure gellan gum and its blends with cellulose ethers in 0.1 N HCl at 37°C

gum-based matrices blends (F10, F11, and F13) as shown in Table II. It has been reported that carrageenan binds water extensively because of the high mobility of water molecules between polymer chains wherein sulfate groups get hydrated (2). In addition, it was found recently that gellan gum formed denser polymer matrix hindering passage of water molecules through (32).

Moreover, in carrageenan-based matrices, HPMC containing matrices (F5) showed a significantly higher swelling capacity than H CMC containing ones (F7and F8). This might be attributed to the higher swelling rate of HPMC containing tablets (slope=10.804) than H CMC ones (slope=7.157) as found experimentally in our lab. Increasing carrageenan content led to higher swelling rate (slope=8.778) as observed with F8.

On the contrary, blending HPMC E_4 and H CMC with gellan gum (F10, F11, and F13) gave matrices with similar swelling capacities. The denser matrix formed by gellan gum hindered the water passage whatever the cellulose ether used. The effect of gellan gum was also noticed in F11 where its higher content decreased matrix swelling rate (slope=4.696 as compared to slope=6.307 in case of F10). Finally, F13 showed an exceptionally high swelling rate with a slope of 18.185 and tablet erosion started after 3 h.

An inverse correlation was found between swelling behavior of the nondisintegrating noneroding matrices and famotidine release. This relationship was not seen with erodible matrices (F8 and F13) where the increase of swelling rate with respective values 8.778 and 18.185 was accompanied by faster drug release. Reaching maximum swelling would have stretched the gel network such that the bonds responsible for gel structure were broken thereby initiating polymer erosion (33).

Kinetic Analysis of the Release Data

The Peppas power law model gave a good fit to all dissolution profiles of all tablets as shown by the R^2 values

Table III. Values of Release Exponent *n, k*, and R^2 of the Prepared Famotidine Floating Matrix Tablets

Formulation no.	*n* (mean ± SD)	*k* (mean ± SD)	R^2	Release mechanism
F1	1.3345±0.130	20.216±1.783	0.9967	Super case II
F2	NA	NA	NA	NA
F3	0.4783±0.445	40.068±3.003	1	Non-Fickian
F4	0.4901±0.026	27.995±4.575	0.9954	Non-Fickian
F5	0.8741±0.414	5.973±3.658	0.9867	Non-Fickian
F6	0.7343±0.039	17.813±4.385	0.9854	Non-Fickian
F7	0.7109±0.043	9.285±1.165	0.9956	Non-Fickian
F8	0.7641±0.047	9.731±0.839	0.9989	Non-Fickian
F9	0.9812±0.064	17.820±1.222	0.9794	Super case II
F10	0.5107±0.036	17.022±2.603	0.9956	Non-Fickian
F11	0.7032±0.056	14.853±2.890	0.9987	Non-Fickian
F12	0.5509±0.077	41.610±2.624	0.9993	Non-Fickian
F13	0.6081±0.021	21.367±0.560	0.9901	Non-Fickian
F14	0.9900±0.031	26.845±4.699	0.9947	Super case II
F15	NA	NA	NA	NA

NA not applicable

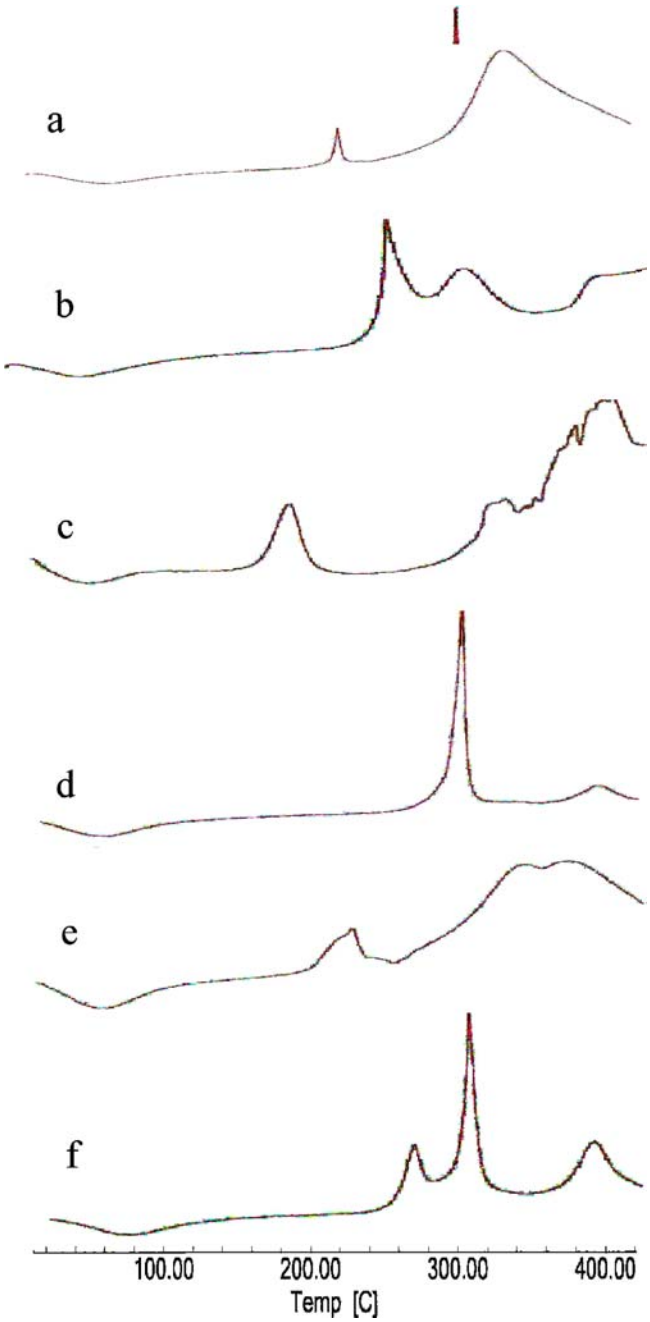


Fig. 5. DSC thermograms of **a** κ-carrageenan, **b** gellan gum, **c** HPC, **d** H CMC, **e** κ-carrageenan–HPC blend, and **f** gellan gum–H CMC blend

($0.97<R^2<1$; Table III) except for F2 and F15. The *n* value of xyloglucan and pectin containing formulae (F3 and F4) with limited swelling ability were found to be the lowest and nearer to diffusion mechanism (0.4783 and 0.4901, respectively). On the other hand, the highest *n* value of 1.3345 indicating a super case II release mechanism was noticed with F1 containing carrageenan.

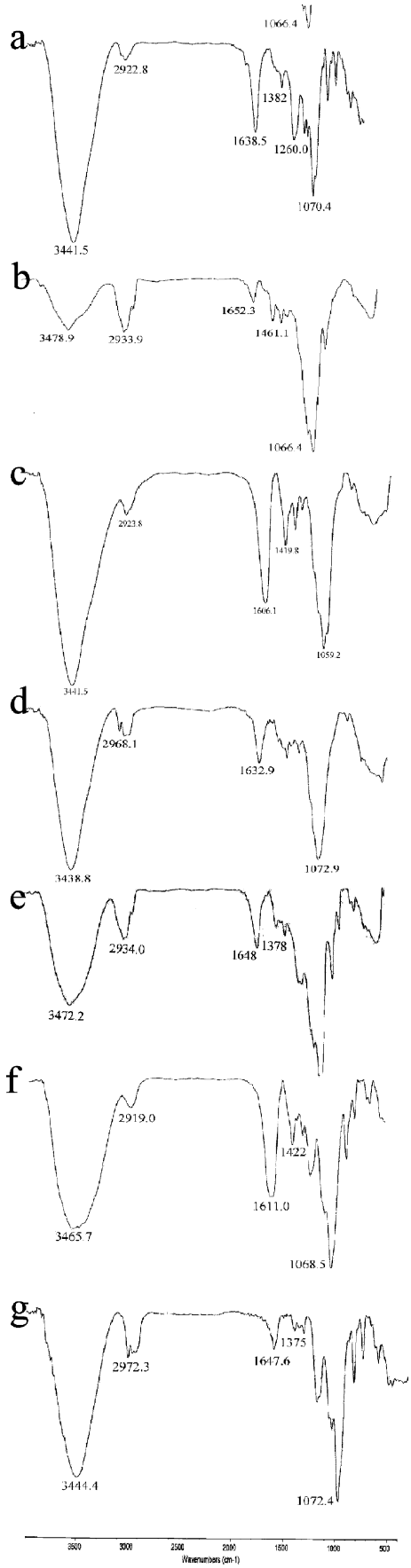
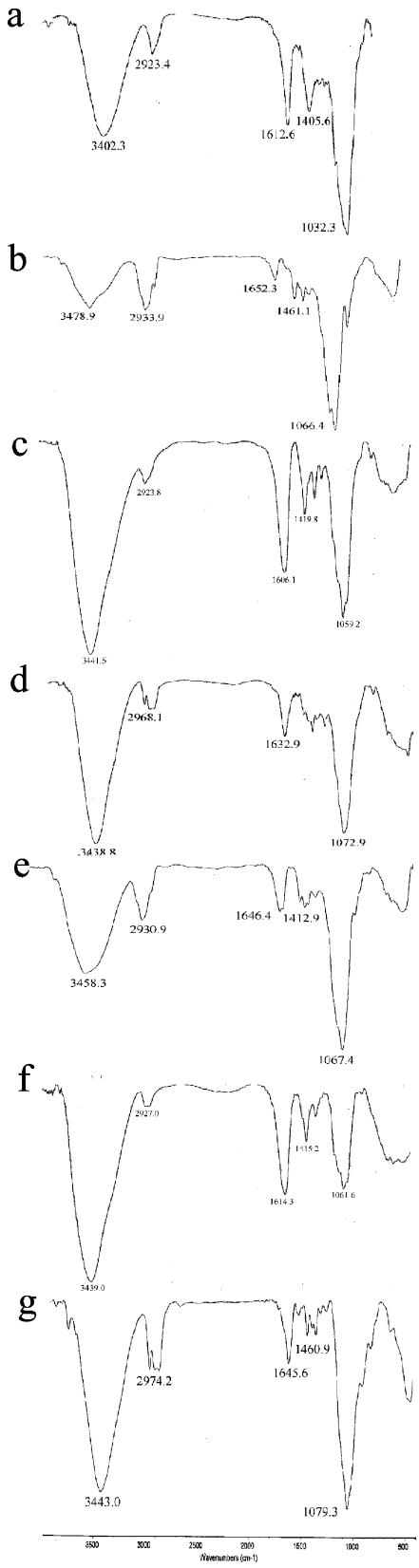


Fig. 6. FTIR spectra of **a** κ-carrageenan, **b** HPMC, **c** H CMC, **d** HPC, **e** κ-carrageenan–HPMC blend, **f** κ-carrageenan–H CMC blend, and **g** κ-carrageenan–HPC blend



◀ **Fig. 7.** FTIR spectra of **a** gellan gum, **b** HPMC, **c** H CMC, **d** HPC, **e** gellan–HPMC blend, **f** gellan–H CMC blend, and **g** gellan–HPC blend

Mixing carrageenan with the highly viscous cellulose ethers (F5–F8) decreased the *n* value (Table III) changing release kinetics to a non-Fickian release mechanism (nearer to erosion limit). Meanwhile, the addition of the less viscous M CMC (F9) to the same polymer had no effect on release mechanistics.

Blending gellan gum with highly viscous cellulose ethers (F10, F12, and F13) resulted in non-Fickian release mechanism showing *n* value nearer to the diffusion mechanism. Increasing its content with HPMC E_4 (F11) did not change release mechanism while increasing its amount with H CMC (F14) shifted the mechanism of release towards a super case II type. For elucidation of the reason behind different release mechanisms occurring with carrageenan and gellan gum blends, DSC and FTIR spectroscopy studies were performed on the different formulae.

Differential Scanning Calorimetry

Gellan gum–H CMC blend thermogram shows simple superpositions of those obtained for each component separately, except for minor upward shift in the exothermic peaks of both polymers as shown in Fig. 5. This might be attributed to change in the purity of the individual components (because of dilution effect) and/or interaction between both polymers.

On the other hand, blending HPC with κ-carrageenan led to disappearance of its exothermic peak at 186°C and an upward shift in the other two exothermic peaks. This might indicate possible soild–solid interaction between the two components.

Moreover, the single Tg observed in the DSC curve of the blends was suggestive of their miscibility which might lead to an intermolecular interaction. Furthermore, DSC thermograms shows that κ-carrageenan had a higher Tg (66°C) than gellan gum (48°C) indicating higher inherent mechanical strength of the first polysaccharide. Accordingly, gellan gum containing matrices disintegrated completely in 0.1 N HCl whereas carrageenan containing matrices disintegrated only partially (Table II).

Fourier Transform Infrared Spectroscopy

Molecular interactions between both κ-carrageenan and gellan gum and cellulose ethers could occur due to the presence of polyhydroxy groups in the cellulose backbone which can form intermolecular hydrogen bonding with hydroxyl groups of κ-carrageenan and gellan gum as well as the carboxyl groups of the latter polysaccharide. FTIR could be a good confirmatory tool in this respect.

Figure 6a showed that FTIR spectrum of κ-carrageenan revealed the principal peaks around 3,441.5, 1,382, 1,070.4 cm^{-1} corresponding to the stretching of OH, SO_4^-, and C–O–C groups, respectively. This was similar to that previously reported (34). Blending κ-carrageenan with HPMC, H CMC, and HPC (Fig. 6b–g) caused band broadening and an obvious shift to higher wave number of

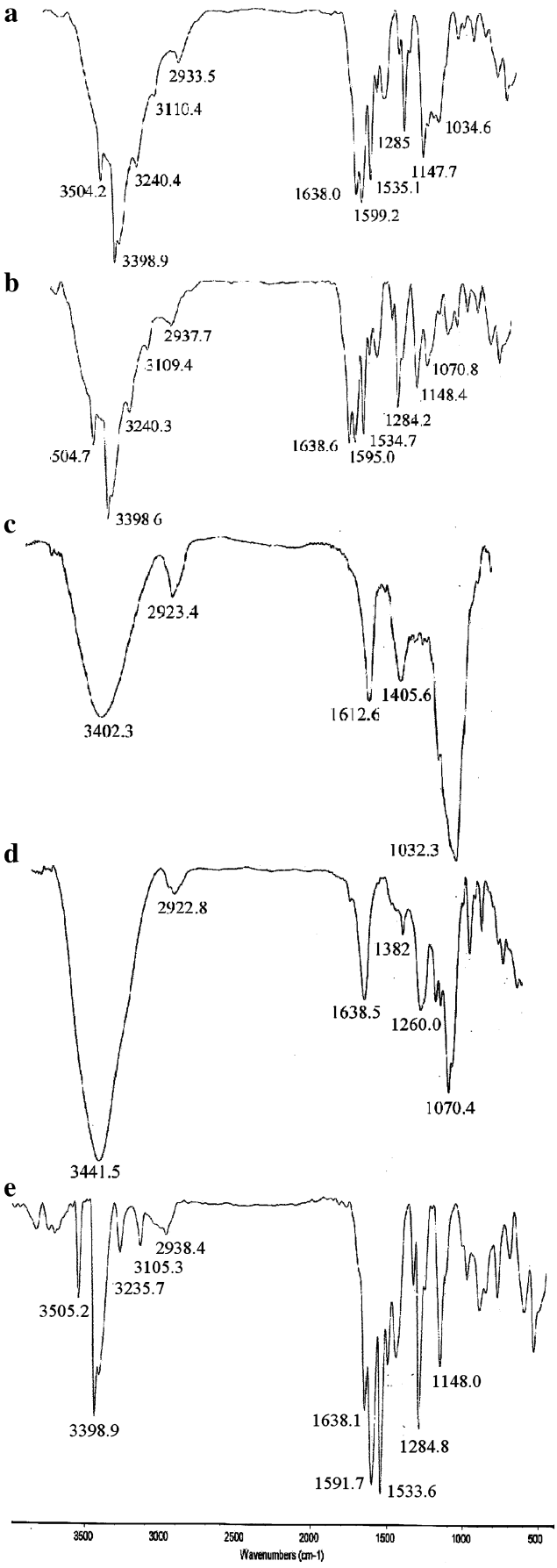


Fig. 8. FTIR spectra of **a** famotidine, **b** κ-carrageenan, **c** gellan gum, **d** famotidine–κ-carrageenan blend, and **e** famotidine–gellan blend

OH stretching peaks of the polysaccharide. The observed shift in OH stretching peaks was the lowest in κ-carrageenan—HPC blend (+3 cm^{-1})—as compared to κ-carrageenan—H CMC (+21 cm^{-1})—and κ-carrageenan—HPMC (+28 cm^{-1}). This could suggest that the extent of interaction between κ-carrageenan and different cellulose ethers went in the same direction. It was postulated that the smaller the value of the OH stretching peaks shift, the weaker the nature of the intermolecular hydrogen bonding interaction (35).

On the other hand, gellan gum spectra revealed absorption bands at 3,402.3 (O–H stretching peak), 1,612.6 (asymmetric COO– stretching), 1,405.6 (symmetric COO– stretching), and 1,032.3 (C–O stretching; Fig. 7a). These assignments are similar to that recently reported (36). The addition of cellulose ethers to gellan gum (Fig. 7b–g) also shifted O–H stretching peak to a higher wave number. The lowest shift was seen in gellan gum—H CMC blend (+37 cm^{-1})—in comparison with gellan gum—HPC (+41 cm^{-1})—and gellan gum—HPMC (+56 cm^{-1}). It is to be noted that HPMC had the highest shift indicating the strongest interaction with the two polymers. Moreover, the symmetric peaks of COO– group and C–O stretching peak in gellan gum—H CMC blend—were also shifted to higher wave number. This predicts the formation of ionic bonding between the carboxyl groups of gellan gum and sodium ions of H CMC in addition to a partial covalent bonding between oxygen atoms of ether groups and sodium ions.

So, according to FTIR studies, the retardation of drug release and changes in release mechanisms upon blending of the polysaccharides and cellulose ethers can be attributed to the possible formation of intermolecular hydrogen bonding between the blend components with subsequent synergistic increase in viscosity. Furthermore, the cross-linked matrix blends will have different degrees of interaction leading to different network with dissimilar viscosities. This will participate in different drug release mechanisms and profiles.

In carrageenan famotidine mixture FTIR spectra (Fig. 8), a shift in amino groups peaks of famotidine (3,235 and 3,105) to a higher wave number and a shift to lower wave number of 3,441 OH peak of carrageenan were seen suggesting hydrogen bond formation between NH_2 groups of famotidine and OH groups of carrageenan. The 1,375 peak of sulfate groups of carrageenan disappeared, indicating the formation of an ionic bonding between NH_2 groups of famotidine and SO_4^- groups of carrageenan. A strong reduction in the intensity of the absorption band of SO_4^- groups of carrageenan was previously reported to be an indication of a strong interaction between the negatively charged carrageenan and the positively charged chitosan (37). In spite of the strong interaction confirmed by the absence of the SO_4^- groups peak of carrageenan, the observed slight shifts occurring in the amino groups peaks of famotidine might be due to the presence of the drug in its folded B polymorphic form (38) with subsequent decrease in some available amino groups for association with the studied polymer.

On the other hand, mixing famotidine with gellan gum resulted also in a slight shift in the wave number of its amino group and shift to lower wave number of 3,402 OH peak in addition to disappearance of 1,612 and 1,405 peaks of COO–

groups of gellan gum indicating H– bond formation between NH_2 of famotidine and OH and COO groups of gellan gum.

Accordingly, famotidine had an ionic and H– bonding with carrageenan and only H– bonding with gellan gum. This might be at the base of the difference in drug early release with both polymers (8% and 100% after 30 min, respectively).

CONCLUSION

The density of floating tablets did not change by blending the polymers together. However, the matrix integrity, swelling, *in vitro* drug release studies, and kinetics of release data were shown to depend on the type and composition of the polysaccharides or blends with cellulose ethers. Formulae containing either carrageenan with M CMC (1:1) or high content of gellan gum with H CMC (2:1) underwent partial disintegration into two big gelatinous masses with a size easily retained in the stomach. Meanwhile, these two formulations in addition to xyloglucan containing tablets were able to sustain drug release over 6 h.

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