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Carbohydrate Polymers 69 (2007) 774–783
Carbohydrate Polymers
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pH-sensitive cationic guar gum/poly (acrylic acid) polyelectrolyte hydrogels: Swelling and in vitro drug release

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Received 10 October 2006; received in revised form 25 January 2007; accepted 14 February 2007
Available online 21 February 2007

Abstract

Novel polyelectrolyte hydrogels (coded as GA) based on cationic guar gum (CGG) and acrylic acid monomer by photoinitiated free-radical polymerization were synthesized with various feed compositions. Fourier transform infrared spectra (FTIR), scanning electron microscopy (SEM), and differential scanning calorimetry (DSC) confirmed that the formation of the polyelectrolyte hydrogels was attributed to the strong electrostatic interaction between cationic groups in CGG and anionic groups in poly (acrylic acid) (PAA). Swelling experiments provided important information on drug diffusion properties, which indicated the GA hydrogels were highly sensitive to pH environments. Potential applications of the hydrogels matrices in controlled drug delivery were also examined. The ketoprofen-loaded CGG/PAA matrices were prepared by hydrogels and directly compressed tablets, respectively. Release behavior of ketoprofen relied on the preparative methods of matrices, ratios of CGG/AA and pH environments. The release mechanism was studied by fitting experimental data to a model equation and calculating the corresponding parameters. The result showed that the kinetics of drug release from the hydrogels in pH 7.4 buffer solution was mainly non-Fickian diffusion. However, for tablets, the drug release in pH 7.4 buffer solution was mainly affected by polymer erosion. The pH of the dissolution medium appeared to have a strong effect on the drug transport mechanism. At more basic pH values, Case II transport was observed, indicating a drug release mechanism highly influenced by macromolecular chain relaxation. The ketoprofen release is also tested in the conditions chosen to simulate gastrointestinal tract conditions. The results implied that the GA hydrogels can be exploited as potential carriers for colon-specific drug delivery.

Keywords: Cationic guar gum; Poly (acrylic acid); Hydrogels; Swelling; Controlled release

1. Introduction

In recent years, considerable attention has been focused on hydrogels that are able to alter their volume and properties in response to environmental stimuli such as pH, temperature, ionic strength, and electric field. It is well understood that, for pH-sensitive hydrogels, the difference in concentration of mobile ions in the hydrogels interior relative to external solution drives the volume change, and it has been demonstrated that theoretical predictions using Donnan theory are consistent with experimental results (Khare & Peppas, 1995). As a result, changes in the hydrogen ion concentration in the surrounding fluid can bring about an abrupt change in the swelling ratios of the hydrogels. It is well-known PAA is a typical pH-responsive polyelectrolyte, which have widely been used in the area of site-specific drug delivery to specific regions of the gastrointestinal tract (Ramakissoon-Ganorkar, Liu, Baudys, & Kim, 1999; Sinha & Kumria, 2001). However, high water solubility has limited their use as a drug carrier to a certain extent; because of dissolution before the drug can be delivered (Needleman & Smales, 1995).

In order to overcome the above drawback, PAA is usually crosslinked with organic cross-linkers to form interpenetrating networks (IPNs) and copolymers. However, the conventional chemically cross-linked hydrogels have many limitations in morphology and properties, e.g., morphological inhomogeneity, mechanical weakness, limited

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doi:10.1016/j.carbpol.2007.02.016

swelling at equilibrium, and slow response to stimuli (Siegel, Falamarzian, Firestone, & Moxley, 1988). It is well understood that PAA has carboxylic acid groups which could develop different intermolecular interaction like electrostatic interaction, hydrogen bonds, and dipole-ion with other polymers. Many investigations have shown that there are strong interactions between PAA and ionic natural polysaccharides in aqueous solutions. There is a great potential for utilizing these interactions in pharmaceutical preparations, particularly in drug delivery systems. The use of chitosan/PAA polyelectrolyte hydrogels as controlled drug release formulations has attracted much attention, as this process is simple, feasible, and usually performed under mild conditions (De la Torre, Enobakhare, Torrado, & Torrado, 2003; Shim & Nho, 2003).

The utilization of natural polysaccharides in drug delivery continues to be a subject of intense investigation because of their biodegradability and biocompatibility. Guar gum, a high-molecular weight water-soluble non-ionic natural polysaccharide isolated from the seed endosperm of the guar plant, is one of the promising materials for biodegradable plastics because it is a versatile biopolymer with immense potential and low price (Cheng, Brown, & Prud'homme, 2002). It has been suggested as a vehicle for oral controlled release purposes and for colon targeting (Wong, Larabee, Clifford, Tremblay, & Friend, 1997). From a biomedical perspective, the preparation of hydrogels of cationic polysaccharides may allow the combination of the high affinity for the negatively charged groups of the components of skin and mucose, which increases in the residence time on these substrates (Brode, Goddard, Harris, & Salensky, 1991). Compared with the naturally ionic polysaccharides such as chitosan, cationic polysaccharides through chemical modification have characteristics. In the case of cationic polysaccharides, the ionization degree is almost independent of pH owing to the presence of quaternary ammonium substituents. These substituents together with the simultaneous presence of a considerable number of hydroxyl groups in their structure as well as some relatively hydrophobic regions, may allow the establishment of different types of interactions with both non-ionic and ionic drugs. So, in this work, novel polyelectrolyte hydrogels based on CGG and PAA were designed to take advantage of the biodegradability and biocompatibility of guar gum combined with mucosal adhesion of PAA. The swelling behaviors of CGG/PAA hydrogels were controlled through changing different feed compositions and pH environments. To evaluate drug controlled release performances of hydrogels, release of the model drug ketoprofen from the GA hydrogels in phosphate buffer was studied. Compare with the CGG/PAA hydrogels, the drug release behavior from directly compressed tablets was discussed. The release mechanism was also studied by fitting experimental data to model equations and calculating the corresponding parameters.

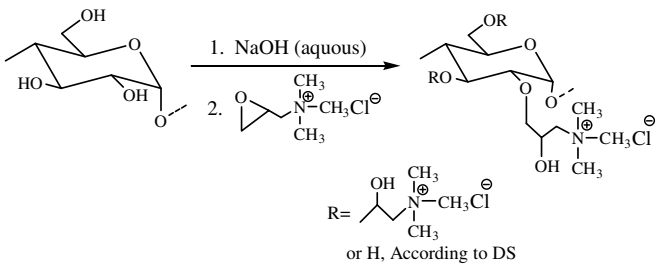
2. Experimental

2.1. Materials

Guar gum was kindly supplied by Wuhan Tianyuan Biology Co., China. The weight-average molecular weight (M_w) was 3.5×10^5, while the ratio of mannose to galactose was 1.8:1 according to the manufacturer's specification. The method of preparation and purification is followed as described earlier (Liu & Xiao, 2004). 3-Chloro-2-hydroxypropyltrimethylammonium chloride (CHPTAC) was purchased from commercial (Guofeng fine chemical Co. Ltd., Shandong, China) and applied as etherifying reagents. 2,2-Dimethoxy-2-phenyl-acetophenone (DMPAP) as a photoinitiator was purchased from Aldrich Chemical Co. and was used without any further purification. Acrylic acid (AA, purchased from Shanghai Chemical Group, China) were purified by vacuum distillation. Other reagents were used without further purification.

2.2. Synthesis of CGG

The quaternization of GG using CHPTAC as etherifying agent under the catalytic action of NaOH undergo several reaction steps. The reaction process is represented in Scheme 1. CGG was prepared using a slightly improved method by Haack, Heinze, Oelmeyer, and Kulicke (2002). Two grams of GG was dissolved in 100 ml of distilled water to prepare 2 wt% concentration solution, and then 10 ml 50 wt% aqueous NaOH was poured into the mixture. After being stirred vigorously at room temperature for 2 h, 20 ml 50 wt% CHPTAC aqueous solution was dropped into the alkali-GG solution through a dropping funnel. After continuous stirring was for 12 h at 50 °C, the solution was then neutralized with 10 wt% hydrochloric acid. The reaction product CGG was precipitated with ethanol, and then washed twice with 75% ethanol. The crude product was dispersed in distilled water again, and was purified by dialysis through a 10,000–8000 molecular weight cut-off dialysis tubing until free of chloride ions. The dialyzed product was freeze-dried and white powders were obtained. The dried samples were stored in vacuum desiccators over P_2O_5 for further analysis. Nitrogen contents of the products (N wt%) was measured



Scheme 1. Reaction scheme for the quaternization of guar gum with CHPTAC.

by elemental analyzer (EA, Heraeus Co., Germany). The degree of substitution (expressed as DS_N which is defined as the number of hydroxyl (OH) groups substituted per sugar unit of guar gum) was determined from the nitrogen contents and calculated according to the following equations:

$$DS_N = \frac{162.2 \times \text{N wt\%}}{1401 - 151.6 \times \text{N wt\%}} \quad (1)$$

The DS_N value of CGG was found to be 0.35. FTIR spectra of the GG and CGG samples are shown in Fig. 1. The peak at 1649 cm^{-1} is due to the in-plane deformation of the water molecule which is the strongly bound water of crystallization and only involved in water–polymer interactions (Daniliuc & David, 1996). Compared with GG, the band at 1479 cm^{-1} is attributed to the methyl groups of ammonium (Loubaki, Ourevitch, & Sicsic, 1991), which indicates CGG have been synthesized successfully. The weight-average molecular weight (M_w) of CGG was determined from the Debye plots by using a multi-angle laser photometer equipped with a He–Ne laser ($\lambda = 633$ nm; DAWN-DSP, Wyatt Technology Co., USA). Astra software was utilized for data acquisition and analysis. The M_w of CGG was determined to 2.32×10^5 and its polydispersity (M_w/M_n) was 1.30.

2.3. Preparation of the hydrogels

One grams of CGG samples dissolved in 50 ml of aqueous acrylic acid monomer was well mixed to form a homogeneous solution. The amount of acrylic acid monomer is varied according to Table 1. Then, 0.2 wt% DMPAP as a photoinitiator was added to the CGG/acrylic acid solution. These solution mixtures were poured onto a circular glass mold and placed in a quartz reaction vessel under N_2 atmosphere. UV irradiation was conducted using a 450 W UV lamp (Ace Glass Co.) for 40 min at a distance of 10 cm and at room temperature until gelation occurred. Then the CGG/PAA polyelectrolyte hydrogels (coded as GA) were cut into discs of 10 mm diameter and immersed in distilled water at room temperature for 7 days to remove the unreacted monomers. Then the hydrogels were dried under vacuum at 40 °C to constant weight, and stored in desiccators for further use.

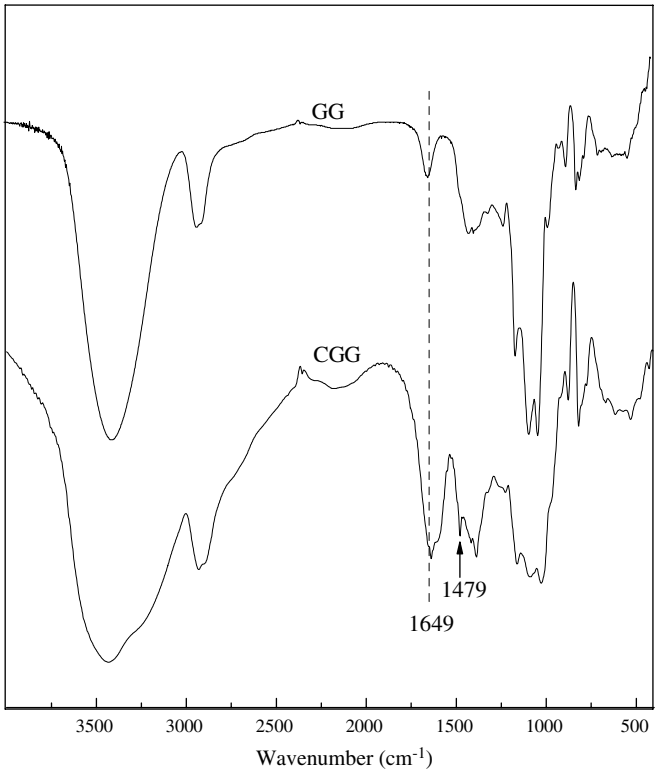


Fig. 1. FTIR spectra of the GG and CGG samples.

Table 1
Compositions and characters of the GA hydrogels

Samples	CGG (g)	AA (g)	CGG/AA (%)	ρ (g/ml^3)
GA1	1	2	50.0	1.432
GA2	1	4	25.0	1.414
GA3	1	6	16.7	1.425
GA4	1	8	12.5	1.431
GA5	1	10	10.0	1.429

2.4. Characterizations

FTIR spectra of the hydrogels were taken with KBr plate on a Nicolet 170SX FTIR spectrometer in a wave number range of 4000–400 cm^{-1}. The hydrogels were ground to a powder, and then mixed with potassium bromide.

SEM was performed on freeze-dried hydrogels (freeze-dried to maintain the porous structure without any collapse) to obtain information on the pore structure of hydrogels. Then they were plunged in liquid nitrogen and the vitrified samples were cut with a cold knife. The samples were mounted on the base plate and coated with gold. The morphology was investigated using a Hitachi (Tokyo, Japan) S-570 Scanning Electron Microscope.

DSC thermograms over the temperature range 10–200 °C were determined using a differential scanning calorimeter (TA2920, USA). Each sample conditioned at 52% RH was subjected to the heating/cooling cycle between 10 and 200 °C with a scanning rate 10 °C/min to obtain reproducible glass temperature (T_g) values. For a polymer, T_g was taken at the half-variation in heat capacity occurring at the glass–rubber transition.

2.5. Swelling studies

Swelling experiments were conducted in buffer solutions of desired pH (2.2–10.0) at 37 °C (Chen, Liu, & Zhuo, 2005). The weighed mass of dry gels was dipped in the swelling medium. At predetermined time intervals the gels were removed from the swelling medium, blotted with filter paper to remove excess water from the hydrogels surface,

and the weight of the swollen hydrogels was weighed. The swelling ratio (S) was calculated according to:

$$S_t = \frac{W_t - W_d}{W_d} \quad (2)$$

$$S_e = \frac{W_s - W_d}{W_d} \quad (3)$$

where W_d is the initial weight of the dry gels, W_t and W_s are the weight at any time t and equilibrium weight during water sorption, respectively.

2.6. Drug loading

In order to incorporate a model drug into the system, the hydrogel synthesis was performed in the presence of the drug. This is a common method for drug immobilization in hydrogels (Ward & Peppas, 2001). In this technique, the drug was added to the monomer solution, with CGG, AA and initiator. Upon polymerization, a network was formed and the drug gets trapped inside the polymer structure. The diffusion of the drug out of the systems occurs when the hydrogel was placed in an environment that allowed the hydrogel to swell and the mesh size to increase. In this work, a model drug, ketoprofen, was dissolved in the monomer mixture at a concentration of 5 wt%.

2.7. In vitro release studies

To study the release profiles for the ketoprofen-loaded hydrogels, dried test samples were immersed in a solution with different pH value, simulating gastrointestinal tract conditions (Patel & Amiji, 1996). At scheduled time intervals, 5 ml solution was withdrawn and equal volume of the same dissolution medium was added back to maintain a constant volume. The amount of ketoprofen released from the matrix was determined by UV-visible spectrophotometer measurements at 261 nm (Shimadzu UV-160A, Japan) and calculated from a previously calibrated standard curve. The drug release percent was determined using Eq. (4):

$$\text{Drug release } (\%) = \frac{M_t}{M_\infty} \times 100\% \quad (4)$$

where M_∞ and M_t represent the initial amount of drug loaded and the cumulative amount of drug released at time t. The results are the mean of three determinations.

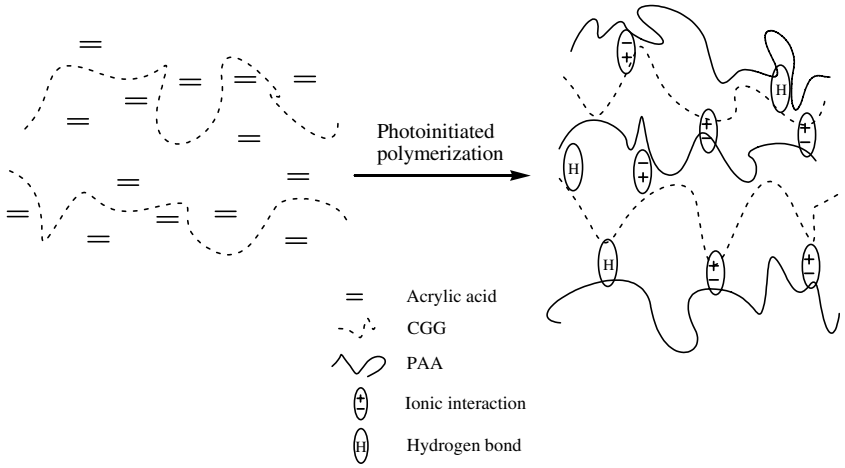
3. Results and discussion

3.1. Structures and miscibility of the hydrogels

Scheme 2 shows the ionic interactions occurring on the two polyelectrolytes, which include (i) ionic cross-links between cationic groups ($-N^+(CH_3)_3$) of CGG and carboxylate ion ($-COO^-$) of PAA, (ii) maybe hydrogen bonds existed in the CGG/PAA hydrogels. These ionic interactions are confirmed from FTIR analyses. All the three bonds exhibit affinity toward water, thereby enabling hydration of the polymer matrix, which is essential for proton mobility. The ionic bond between $N(CH_3)_3^+$ and COO^- is the strongest one formed, which induces crosslink and prevents dissolution and excessive swelling of the polymer matrix in the presence of water.

3.1.1. FTIR analyses of the hydrogels

Intermolecular interactions affect the vibration of groups on polymer segments, this information can be obtained by FTIR analysis. Fig. 2 presents the FTIR spectra of CGG/PAA hydrogels with various ratios. The pure PAA spectrum shows very broad bands between 3600 and 2500 cm^{-1}. The O–H stretching vibration of the carboxylic groups occurs between 3600 and 3300 cm^{-1}. The sharpest and the strongest band of PAA spectrum is 1715 cm^{-1}, it corresponds to carbonyl stretching vibration. In contrast with the PAA sample, a significant new peak appears at 1560 cm^{-1} in the spectra of all GA samples, which can be assigned as asymmetric deformation of



Scheme 2. Formation of polyelectrolyte hydrogels with ionic interactions and hydrogen bonds.

COO^-. These results indicate that the carboxylic groups of PAA are dissociated into COO^-, which complexes with cationic groups of CGG through electrostatic interaction to form the polyelectrolyte complexes during the polymerization procedure. Furthermore, the intensity of COO^- vibration decreases slightly with a decrease of the CGG content in the hydrogels.

3.1.2. SEM analyses of the hydrogels

The morphology of freeze-dried GA hydrogels prepared at different feed compositions is shown in Fig. 3. A porous honeycomb-like structure is clearly shown for the GA hydrogels, which seems to indicate a high accessibility of water to the amorphous regions of the hydrogels. For the GA1 sample, the structure is less homogeneous with some non-porous regions. When PAA content increases, porosity increases as shown for the GA3 sample. The average pore diameter for this sample is about 7 μm estimated from the micrographs. With a further increase of PAA content, the average pore diameter of the hydrogel expands to 12 μm in GA5, which suggests good swelling properties in water or buffer media.

3.1.3. DSC analyses of the hydrogels

The measurement of the glass transition temperature (T_g) of a polymer membrane or hydrogel is often used as a criterion to determine its miscibility. The miscible polymer membrane or hydrogel would exhibit a single transition between T_g of the two components. With increasing immiscibility there is a broadening of the transition, whereas an incompatible system would be marked by separate transitions of the polymer components in the membrane or hydrogel (Biliaderis, Lazaridou, & Arvanitoyannis, 1999). In order to demonstrate that the presence of a single transition in the hydrogels is the result of interactions between the two polymers, thermal analysis was performed on CGG/PAA (1:2) mixtures prepared putting together hydrogels of pure CGG and pure PAA. The typical second scan thermgrams corresponding to this sample is reported in Fig. 4, together with those corresponding to PAA, GA1, and CGG samples. The curve corresponding to pure PAA shows a single slope change corresponding to the glass transition at 123 °C. This value corresponds to that reported in the literature (Maurer, Eustace, & Ratcliffet, 1987). Similarly, the curve corresponding to pure CGG shows a single thermal phenomenon, corresponding to the glass transition, which occurs at 102 °C. Due to substantial differences in chemical structure of PAA compared to CGG and relatively large divergence in T_g (>20 °C) make it possible to detect individual transition of two polymers by DSC (Bikiaris, Prinos, Botev, Betchev, & Panayiotou, 2004). In the case of the hydrogels, the single T_g (118 °C) for GA1 sample suggests that the hydrogels has good miscibility. In addition, no endothermic peaks appear in the scans, indicating that crystalline regions do not exist in our samples. In this case of the Mixtures, the curve shows two separate transitions, 105 and 124 °C, corresponding to the glass transitions of the pure constituents.

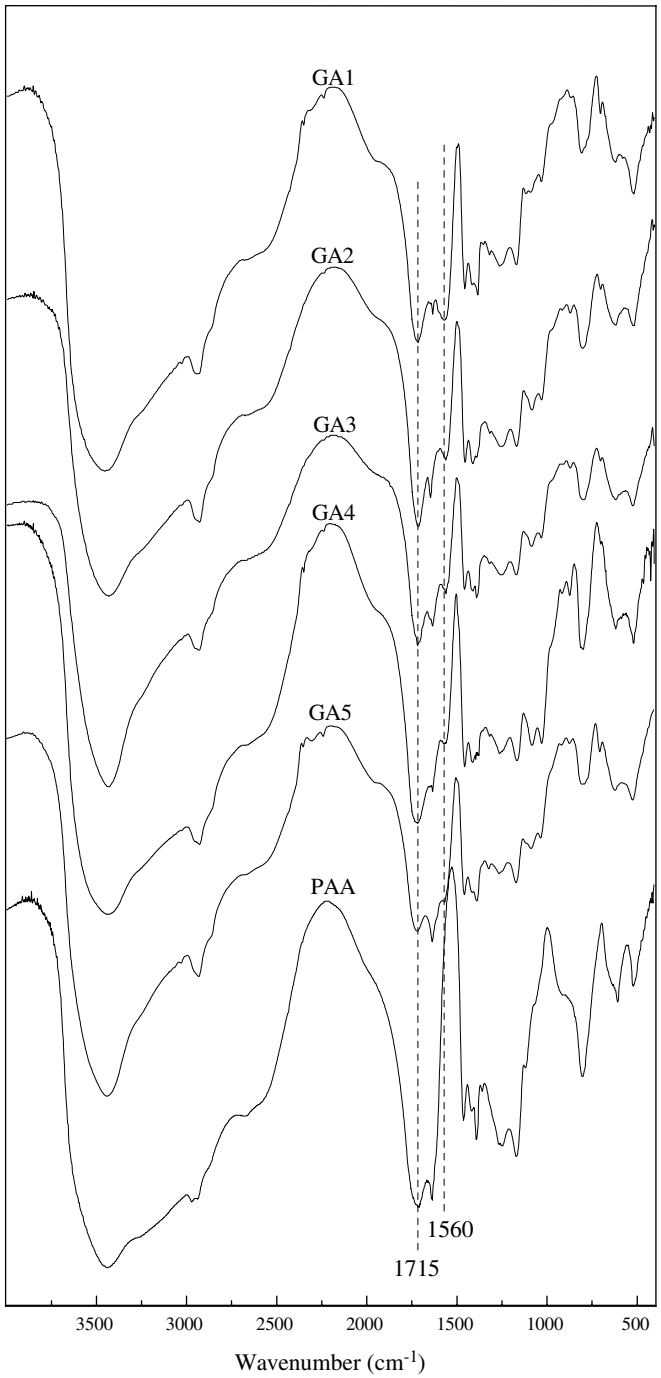
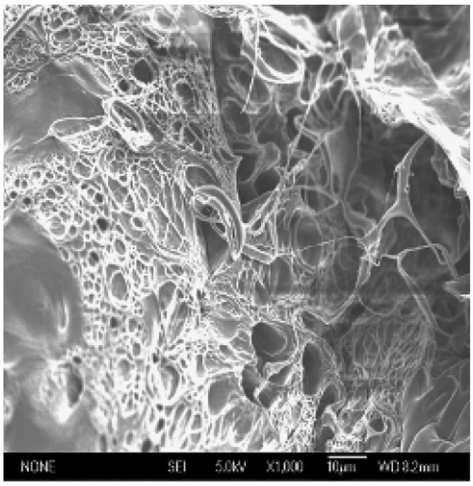


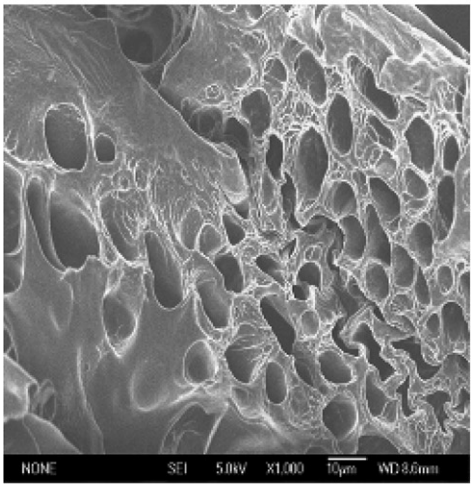
Fig. 2. FTIR spectra of the PAA and GA hydrogels.

3.2. Swelling properties of the hydrogels

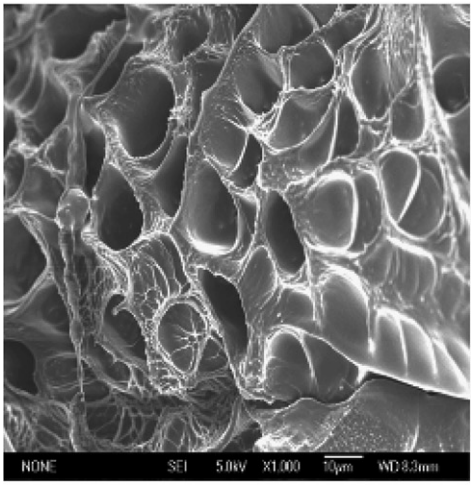
The swelling characteristics of hydrogels have a significant influence on the diffusion behavior of small molecules through the hydrogels. It is well known that the swelling ratio has a relation to ionic osmotic pressure, cross-linking density, and the affinity of the hydrogels



GA1



GA3



GA5

Fig. 3. SEM images of cross-sections of the GA hydrogels.

for water from the above equation. According to the Eq. (5) (Flory, 1953), the volume swelling ratio $Q^{5/3}$ should increase as the square of concentration of the fixed charge and as the reciprocal of I, and decrease as the cross-linking density.

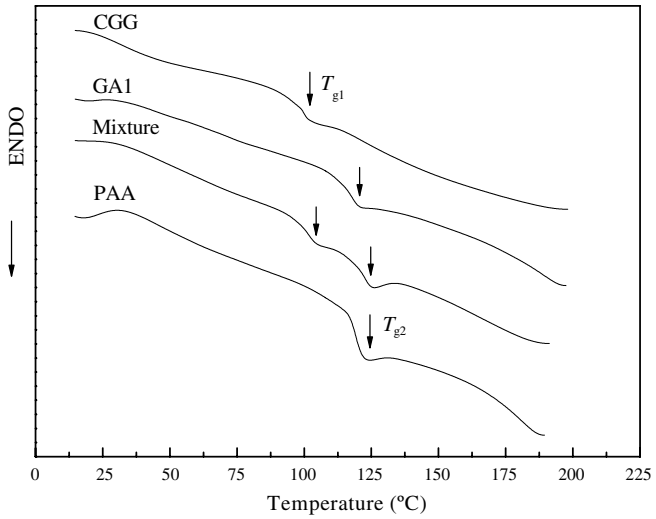


Fig. 4. DSC thermogram of PAA, GA1, mixture and CGG samples.

$$Q^{5/3} = \left[\left(\frac{i}{2V_u I^{1/2}}\right)^{1/2} + \frac{(1/2-\chi)}{V_1}\right] \Big/ v_e/V_0 \qquad (5)$$

where Q is the volume swelling ratio, i/V_u is the concentration of the fixed charges referred to the unswollen polymer, I is ionic strength in the external solution, χ is the interaction parameter between polymer and solvent, V_1 is the molar volume of the liquid and v_e/V_0 is the cross-linking density of the hydrogels.

3.2.1. Effect of compositions on the swelling properties of the hydrogels

The effect of composition on percent swelling ratios in the GA hydrogels at a temperature of 37 °C and pH 7.4 is illustrated in Fig. 5. Compared with CGG, PAA is a hydrophilic anion polymer and has much higher swelling rations. With an increase of PAA content, the equilibrium

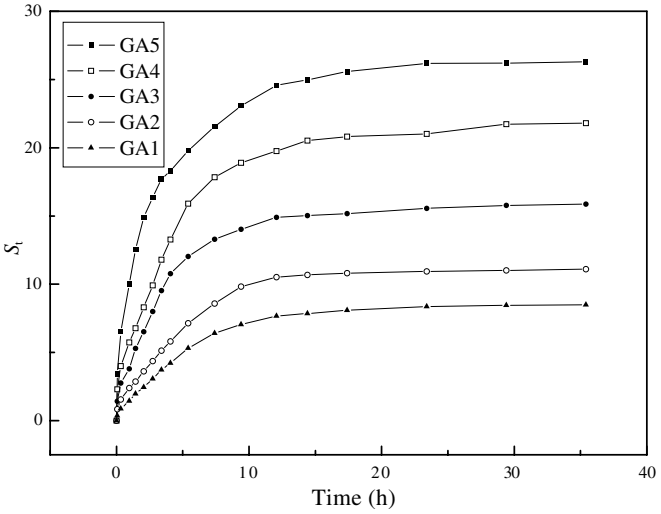


Fig. 5. The influence of different compositions on the swelling behaviors of the GA hydrogels in buffer solution of pH 7.4 at 37 °C.

swelling ratios of the hydrogels increases from 8.4 to 26.3 wt%. The more the PAA content in the hydrogels, the larger the affinity of the hydrogels to water and the higher the swelling ratio of the hydrogels.

3.2.2. Effect of pH environments on the swelling properties of the hydrogels

Environmental pH value has a large effect on the swelling behavior of the GA hydrogels. The influence of pH values of the buffer solution on the equilibrium swelling behavior of hydrogels at 37 °C is shown in Fig. 6. The swelling ratios at various pH environments depend upon the available free volume of the expanded polymer matrix, polymer chain relaxation, and availability of ionizable functional groups such as –COOH able to form hydrogen bonds with water. First, a gradual increase in swelling ratios from pH 2.2 to 7.0, then a sharp gel-phase transition is observed from pH 7.0 to 9.0. Because the pK_a of carboxylic acid containing in the polymer is about 4.5, and carboxyl groups of hydrogels tends to dissociate at a pH > 4.5, the osmotic pressure inside the hydrogels increases. In the range of pH 7.0–9.0, the system has a basic pH and the concentration of basic cations in the outer solution also increases. As a consequence, the mobile ions concentration increases more rapidly than in the outer solution. Thus, a sharp transition was observed in this pH range (Ricka & Toyoichi, 1984). The decrease in swelling above pH 9.0 can be explained in that a complete dissociation of acidic groups and further increases in the amount of mobile ions leads to a decrease in osmotic pressure.

To evaluate the reswelling ability and the pH-senstivity of the hydrogels, the equilibrium reswelling behavior of the GA4 sample is illustrated in Fig. 7. The samples were put in pH 5.0 buffer solution, and then transferred to a pH 7.4 buffer solution, for four cycles. The S_e values almost remained unchanged in pH 5.0 buffer solution or pH 7.4 buffer solution again. The results show that the GA hydrogels have good reswelling ability and maintain the high sensitivity to pH.

3.3. In vitro drug release of ketoprofen from the hydrogels

In order to study ketoprofen transport mechanism from the different molecularly designed GA hydrogels, the data was modeled by the Ritger–Peppas equation at $M_t/M_\infty < 0.6$ (Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n \tag{6}$$

Where M_t/M_∞ is the fractional drug release, k is a kinetic constant, and n is the diffusional exponent that can be related to the drug transport mechanism. For a thin hydrogel, when $n = 0.5$, the drug release mechanism is Fickian diffusion. When $n = 1$, Case II transport occurs, leading to zero-order release. When the value of n is between 0.5 and 1, anomalous transport is observed.

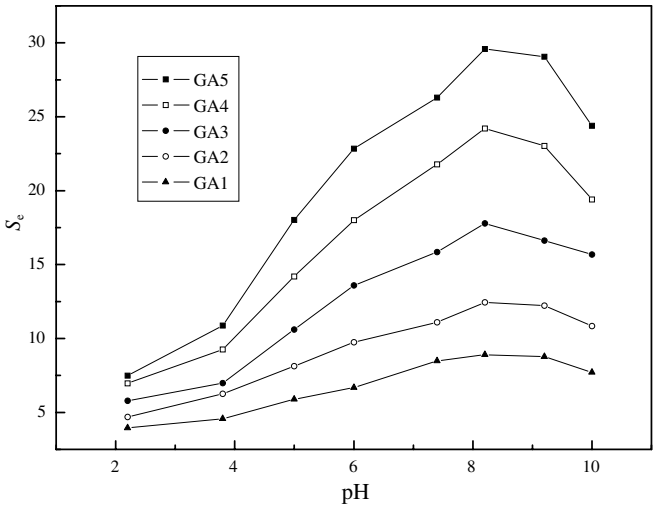


Fig. 6. The influence of pH values of buffer solution on the equilibrium swelling behaviors of the GA hydrogels at 37 °C.

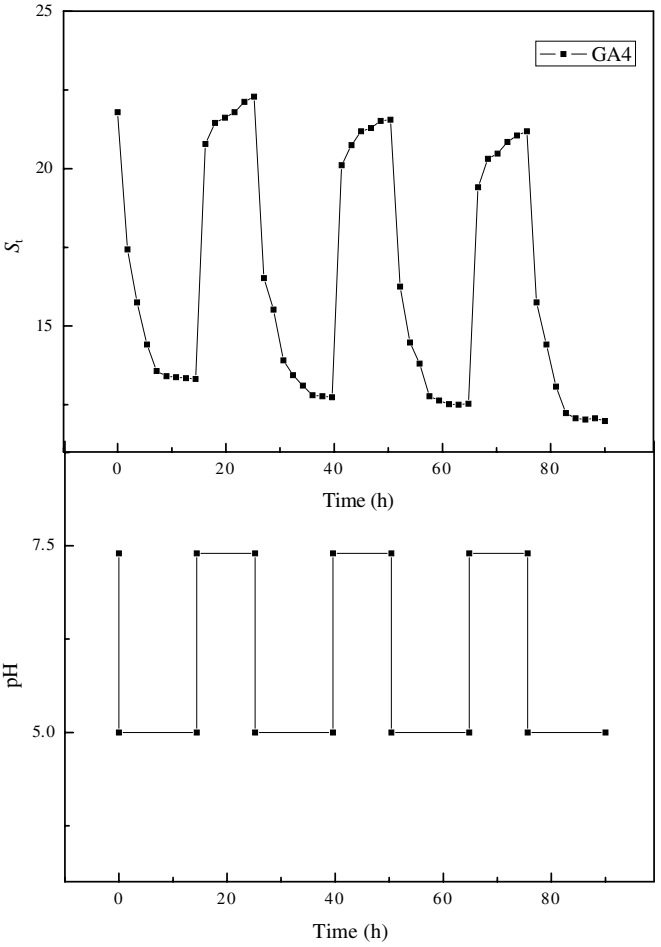


Fig. 7. Equilibrium reswelling behaviors of the GA4. Sample was transferred from pH 7.4 buffer solution to pH 5.0 buffer solution for four cycles at 37 °C.

3.3.1. Effect of compositions on the release of ketoprofen

The release kinetics of ketoprofen from the GA hydrogels in phosphate buffer solution of pH 7.4 at 37 °C is

shown in Fig. 8, and the corresponding drug release kinetic date obtained from fitting drug release experimental data to the Ritger–Peppas equation listed in Table 2. In the GA hydrogels, it is found that the ratios of CGG/AA in the hydrogels can affect the drug release rate significantly. The highest ratio of CGG/AA, GA1 shows only 80.2% drug release in 9.6 h. The results can be attributed complex formation in the hydrogels through the ionic crosslinks between $-N^{+}(CH_3)_3$ and $-COO^{-}$. With a high content of CGG, there are more entanglements between CGG and PAA during formation as a result of the polymerization process, which would retard ketoprofen diffusion from the complex. When the ratios of CGG/AA decrease, the swelling ratios increase in the hydrogels, which increase the released amount of ketoprofen. It is observed that GA5 releases 99.8% ketoprofen than others hydrogels (90.4% in GA2, 95.9% in GA3, 98.3.1% in GA4). So, the swelling is the important rate-determining steps in the controlled release processes in our release systems (Langer & Peppas, 1983). The release kinetic data are well fitted to the Ritger–Peppas equation (Eq. 6). The n value is 0.53 for the GA1 hydrogels suggesting that diffusion plays an important role in release. When the ratios of CGG/AA decrease further, an increase in the n value from 0.56 to 0.78 is seen. The higher values in n suggest ketoprofen release follows a non-Fickian mechanism, where the drug release is controlled by diffusion and relaxation of hydrogels. When the highest content of PAA is reached, the n value is 0.83, which indicates the drug release is mainly controlled by relaxation of hydrogels.

To emphasize the effect of a strong interaction between CGG and PAA molecules in the hydrogels on drug release mechanism, compare with the GA hydrogels, the drug release behavior from directly compressed tablets is also discussed. The release kinetics of ketoprofen from GAt tablets in phosphate buffer solution of pH 7.4 at 37 °C is illustrated in Fig. 9, and the corresponding drug release kinetic data obtained from fitting drug release experimental data to Ritger–Peppas equation are listed in Table 3. The lower ratios of CGG/AA in the tablets result in higher drug release compared with the tablets containing high CGG content. For instance, the drug release from GAt5, GA4 and Gat3 is rapid with almost 100% release within 2–4 h. In contrast, the release from the tablet GAt2 and GAt1 is significantly slower with only 84.6% and 73.3% release at the same time. This may be due to different property of CGG and PAA material. CGG has a high viscosity and displayed a high degree of swelling due to water uptake as well as a small degree of erosion, while PAA has a low viscosity and is highly soluble and as a result shows easy erosion. So, the release rate increases with an increase of the amount of PAA in tablets as a consequence of the more rapid hydration, swelling and dissolution of the low viscosity PAA than CGG. In a tablet formulation, release date is in good accord with the Ritger–Peppas equation (Eq. 6). In all tablets, the n value is between 0.90 and 0.95. These results indicate that the polymer erosion is a dominating factor in release process of the tablet made by mixing and compression. Drug release kinetics is non-Fickian. Visual observation confirms this thesis, during the drug release test, the size of the tablet was reduced continuously.

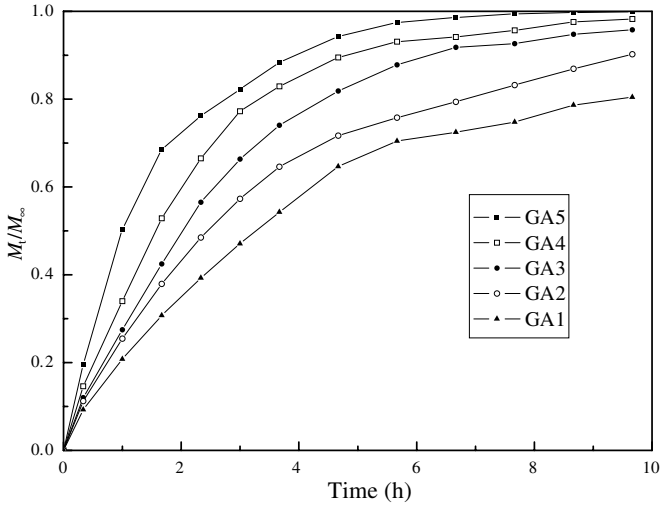


Fig. 8. Release kinetics of ketoprofen from the GA hydrogels in phosphate buffer solution of pH 7.4 at 37 °C ($n = 3$).

Table 2
Drug release kinetic data for GA hydrogels obtained from fitting drug release experimental data to Ritger–Peppas equation

Samples	k	n	r^2	Transport mechanism
GA1	0.2540	0.53	0.9512	Diffusion controlled
GA2	0.3116	0.56	0.9617	Diffusion and relaxation controlled
GA3	0.2934	0.65	0.9845	Diffusion and relaxation controlled
GA4	0.3549	0.78	0.9718	Diffusion and relaxation controlled
GA5	0.3888	0.83	0.9801	Relaxation controlled

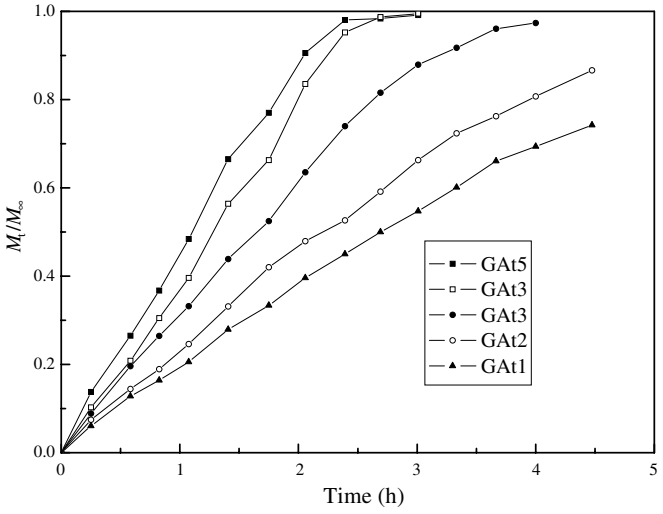


Fig. 9. Release kinetics of ketoprofen from the GAt tablets in phosphate buffer solution of pH 7.4 at 37 °C ($n = 3$).

Table 3
Drug release kinetic data for GAt tables obtained from fitting drug release experimental data to Ritger–Peppas equation

Samples	k	n	r^2	Transport mechanism
GAt1	0.2518	0.91	0.9994	Erosion controlled
GAt2	0.2402	0.90	0.9903	Erosion controlled
GAt3	0.3200	0.91	0.9806	Erosion controlled
GAt4	0.2725	0.94	0.9911	Erosion controlled
GAt5	0.3281	0.95	0.9945	Erosion controlled

3.3.2. Effect of pH environments on the release of ketoprofen

Fig. 10 shows the release kinetics of ketoprofen from the GA4 hydrogel at different pH environments at 37 °C, and the corresponding drug release kinetic data obtained from fitting the drug release experimental data to the Ritger–Peppas equation are listed in Table 4. In all the samples drug release increases, as the pH of the medium is increased from 2.2 to 8.2. This is consistent with the percentage swelling which shows that water uptake by the polymer increases with increasing pH of the medium. This observation is reiterated when the exponent n from Eq. (6) is calculated. We obtain a value of $n = 0.61$–0.72 from pH 2.2 to 6.8, which indicates that both Fickian diffusion and polymer chain relaxation influences drug release. In drug release experiments perform at pH 7.4, we obtained a value of $n = 0.78$. This indicates that the polymer chain relaxation has a much larger influence on the drug transport mechanism than Fickian diffusion. When the drug-loaded hydrogel is put in pH 8.2 environments, the value of $n = 0.85$ indicates the release is mainly by relaxation of hydrogels. From the above analyses, we can see that pH has an important effect on the drug transport mechanism. These observations are related to the anionic characteristics of the PAA polymer networks. An increase in the pH of the release medium results in the ionization of the carboxylic groups in the acrylate structure and the consequent repulsion between polymer chains. Then extensive ionization of the functional groups at pH 7 significantly influences the polymer chain relaxation and consequently, the drug transport mechanism.

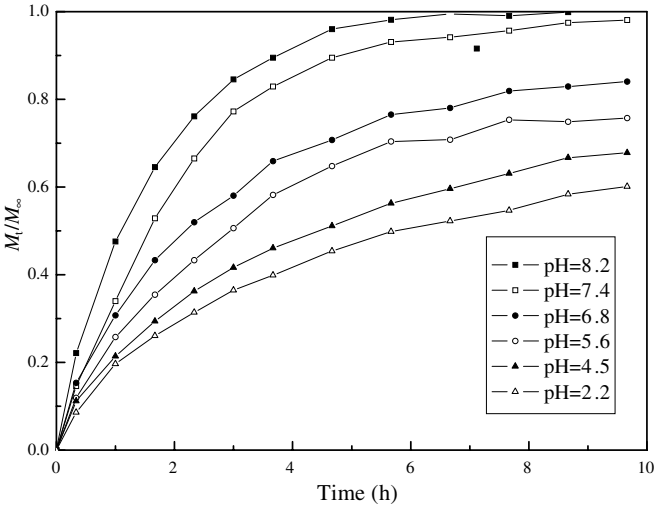


Fig. 10. Release kinetics of ketoprofen from the GA4 sample at different pH environments at 37 °C ($n = 3$).

Table 4
Drug release kinetic data for GA hydrogels obtained from fitting drug release experimental data to Ritger–Peppas equation at different pH environments

pH	k	n	r^2	Transport mechanism
2.2	0.2297	0.61	0.9904	Diffusion and relaxation controlled
4.0	0.2124	0.64	0.9812	Diffusion and relaxation controlled
5.2	0.2541	0.69	0.9693	Diffusion and relaxation controlled
6.8	0.3106	0.72	0.9849	Diffusion and relaxation controlled
7.4	0.3049	0.78	0.9718	Diffusion and relaxation controlled
8.2	0.3137	0.85	0.9882	Relaxation controlled

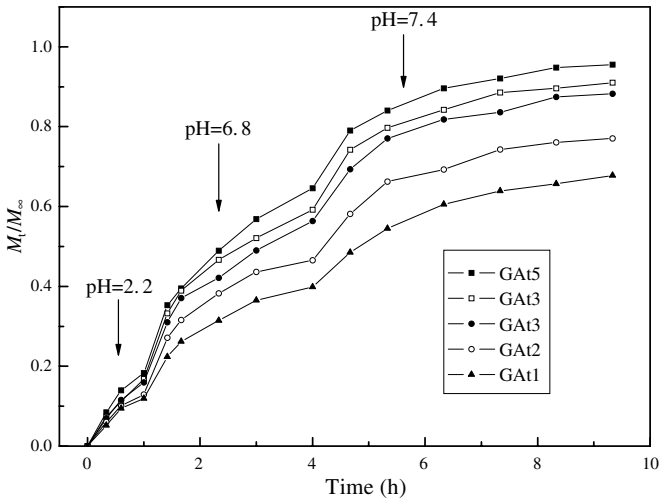


Fig. 11. In vitro release profile of ketoprofen-loaded hydrogels in different pH values at 37 °C under different conditions: 0–1 h, pH 2.2; 1–4 h, pH 6.8; 4–10 h, pH 7.4 ($n = 3$).

The ketoprofen release is also tested in the conditions chosen to simulate the pH and time interval likely to be encountered during transit from stomach to colon (Gupta, Beckert, & Price, 2001). First, the ketoprofen-loaded dry hydrogels are put in pH 2.2 buffer solution for 1 h, then in pH 6.8 buffer solution for 3 h, finally in pH 7.4 buffer solution for 8 h. The release kinetics of ketoprofen from the GA hydrogels at varied pH environments is provided in Fig. 11. From Fig. 11, we can see that there is a little release and there is no difference in the first 1 h. The small release (18.1% of release amount) is observed at the initial stage and the reason is as same as mentioned above. When the GA hydrogels are put in pH 6.8, the ketoprofen release increased evidently and there are remarkable differences between the different compositions. The accumulative release percent is much higher in GA5 (64.8%) than that in GA1 (40.4%) after 4 h, which is contributed to the higher swelling ratio in the GA5 hydrogel. When these hydrogels are put in the pH 7.4 buffer solution, the GA5 hydrogel continues to keep the highest accumulative release percent (95.7%) than other hydrogels. The in vitro release profile of model drug implies that the GA hydrogels can be exploited as potential carriers for colon-specific drug delivery.

4. Conclusion

In order to design the potential controlled-release dosage forms, CGG/PAA polyelectrolyte hydrogels was prepared through free radical solution polymerization. The GA hydrogels were well characterized through FTIR and SEM. The results indicated that the strong electrostatic interaction existed in the hydrogels, which resulted in the formation of the polyelectrolyte complexes. In the DSC analyses, the single T_g in the GA1 sample suggested that the two polymers in the hydrogel have good miscibility. The swelling ratios were studied as a function of PAA content and pH. The result indicated the GA hydrogels was highly sensitive to the pH environment.

Potential applications of the hydrogels matrices in controlled drug delivery were also examined. The ketoprofen-loaded CGG/PAA matrices were prepared as hydrogels and directly compressed tablets. The release mechanism was studied by fitting experimental data to model equations and calculating the corresponding parameters. The compositions of the hydrogel had an important effect on ketoprofen release. The increase of PAA content conduced to the rapid release of ketoprofen from the GA hydrogels. It is found that an increase of n value from 0.53 to 0.83, which indicated the ketoprofen release followed non-Fickian mechanism. Furthermore, for tablets, the n value is between 0.90 and 0.95. These results indicate that the polymer erosion is a dominating factor in release process of the tablet prepared by compression.

The pH of the dissolution medium appeared to have a strong effect on the drug transport mechanism. An increase in n from 0.61 to 0.85 with change in pH. At more basic pH values, Case II transport was observed, indicating a drug release mechanism highly influenced by macromolecular chain relaxation. The ketoprofen release is also tested under the conditions chosen to simulate the pH and time interval likely to be encountered during transit from stomach to colon. The results implied that the GA hydrogels can be exploited as potential carriers for colon-specific drug delivery.

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