Biodegradable Blend Films Based on Two Polysaccharide Derivatives and Their Use as Ibuprofen-Releasing Matrices

Ju-Zhen Yi, Li-Ming Zhang

School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, People's Republic of China

Received 28 February 2006; accepted 27 March 2006
DOI 10.1002/app.24566
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Differential scanning calorimetry (DSC), FTIR, X-ray diffraction (XRD), and viscosity methods were used to examine the miscibility, interaction, and degradability of cationic guar gum (GG) and sodium carboxymethylcellulose (NaCMC) in their blend films. The experiment results prove that there exist electrostatic interactions and hydrogen bonding between GG and NaCMC. Blend films degrade quicker than pure GG or NaCMC film. Furthermore, the degradation rate of blend films is related to the interactions between GG and NaCMC. Based on the research of blend films as the drug carriers for Ibuprofen, it is found that the blend composition, initial drug concentration, and pH value affect the drug release and the GG/NaCMC blend films have good sustained release performance. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 103: 3553–3559, 2007

Key words: cationic guar gum; sodium carboxymethylcellulose; blend film; drug delivery

INTRODUCTION

Blending concepts have been used for a long time in drug delivery.[1–5] Park et al.[1] achieved the controlled release of bovine serum albumin from the blends composed of poly(lactic acid) (PLA) and poly(ethylene oxide-*co*-propylene oxide-*co*-ethylene oxide). The authors explained their results in terms of the entanglement of the triblock copolymer surfactant with the PLA amorphous phase. Cascone et al.[2] studied the blends composed of poly(vinyl alcohol) and collagen. The authors found that the release rate and quantity of growth hormone were significantly dependent on the collagen content of the polymers. However, in some systems, complicated results were observed by changing the experimental conditions. For example, Lecomte et al.[3] reported that the drug release rate in the blends composed of ethylcellulose and poly(methacrylic acid-*co*-ethyl acrylate) uniformly changed with blend composition in acidic dissolution solutions. However, the same blends, when tested at pH 7.4, provided a bimodal release pattern in which the drug was released at either a higher rate or a lower rate. Complicated release has been reported in other papers.[4,5] Obviously, more studies are needed to fully understand the relationships between the interactions, miscibility, and controlled release behavior of polymer blends.

As biodegradable and environmentally benign materials, polysaccharides and their derivatives have been extensively used in medical and pharmaceutical areas.[6–8] By adjusting the interactions between the composition polysaccharides in blends, the degradability and their drug release behavior can be modulated. Cellulose and guar gum derivatives present a glucosidic backbone that may establish hydrophobic interactions, while the presence of hydrophilic or charged groups in their substituents provides the polymer with hydrogen bonding capacity and high affinity for oppositely charged molecules. Additionally, the high bioadhesive capacity[9] and low toxicity[10] of hydrophilic cationic or anionic polysaccharides make them particularly useful for drug delivery systems able to combine long residence time at the application sites with adequate mechanical properties.

The aim of this work is to investigate the miscibility and interaction of biodegradable cationic guar gum (GG) and sodium carboxymethylcellulose (NaCMC) in their blend films, and further explore the use of these polysaccharide blend films as the release matrices for a model drug, Ibuprofen. This study is expected to provide further understanding of the relationships between the interactions, miscibility, and controlled release behavior of polymer blends. In particular, the effects of blend composition, initial drug concentration, and pH of the external medium on the drug release from the blend films are investigated. So

Correspondence to: J.-Z. Yi (cesyjz@mail.sysu.edu.cn).

Journal of Applied Polymer Science, Vol. 103, 3553–3559 (2007)

far there is no report of GG and NaCMC blend films used as drug release matrix.

EXPERIMENTAL

Materials

The used GG is a commercial product with the trade name of Ecopol 14-S, which was provided kindly by China Agent Office of Economy Polymers and Chemicals Company of USA. Its quaternary ammonium group content was determined to be 6.6×10^{-4} mol/L, which was obtained from nitrogen elemental analyses by using an Elementar Vario EL elemental analyzer. The used NaCMC was purchased from Hoechst, Germany; it has an average degree of substitution of 0.8 and a weight-average molecular weight of 5.0×10^5 g/mol. Ibuprofen was purchased from Tianjin SmithKline and French Laboratories Ltd, China. The chemical structure of GG, NACMC, and Ibuprofen are shown in Figure 1. All other chemicals and solvents were of analytical grade and used without further purification.

Preparation of blend films and drug-loaded blend films

The blend solutions of GG and NaCMC were prepared by mixing various volume ratios of 0.25 wt % GG solution and 0.25 wt % NaCMC solution. The blend solution was stirred for 12 h and cast onto the clean dry Petri dishes allowed to dry at ambient temperature for 72 h and then put in vacuum oven at 40°C for 72 h. The thickness of films was kept between 25 and 30 μm (measured by vernier caliper model CT 200–312).

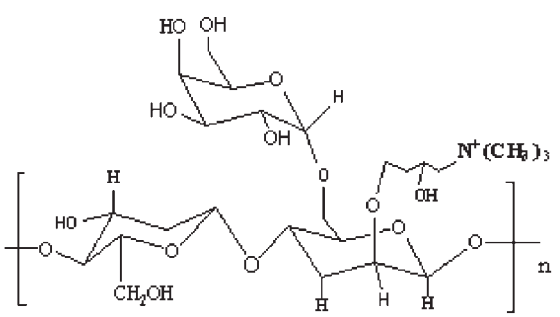
The model drug (ibuprofen) was added into the solutions of GG, NaCMC, and their blend solutions to achieve a concentration of 0.5 wt %. Drug-loaded CG_3(GG/NaCMC = 1/1) with 1 and 2% initial drug concentration are also prepared to explore the effects of different drug concentration on drug release. The blend solution containing the model drug was stirred for 12 h and left overnight to get rid of air bubbles before casting onto clean dry Petri dishes to dry at ambient temperature. The films were allowed to dry as same as GG/NaCMC blends. The thickness of films was kept between 25 and 30 μm.

Differential scanning calorimetry (DSC)

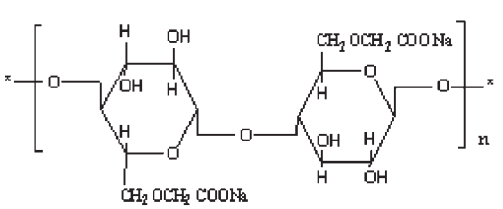
The glass transition temperature (T_g) values of various blend films were measured with a TA Instruments 2910 differential scanning calorimeter using a heating rate of 20°C/min under nitrogen atmosphere. Each sample was subjected to several heating/cooling cycles to obtain reproducible T_g values. The initial onset of the change of slope in the DSC curve is taken to be the T_g.

Fourier transform infrared spectroscopic characterization

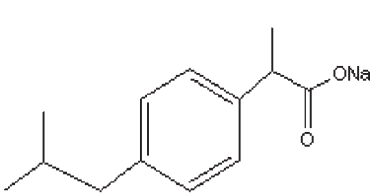
FTIR spectra were acquired using a Nicolet 210 FTIR spectrophotometer. Samples were prepared by grind-



GG



NaCMC



Ibuprofen

Figure 1 Molecular structure of GG, NaCMC, and Ibuprofen.

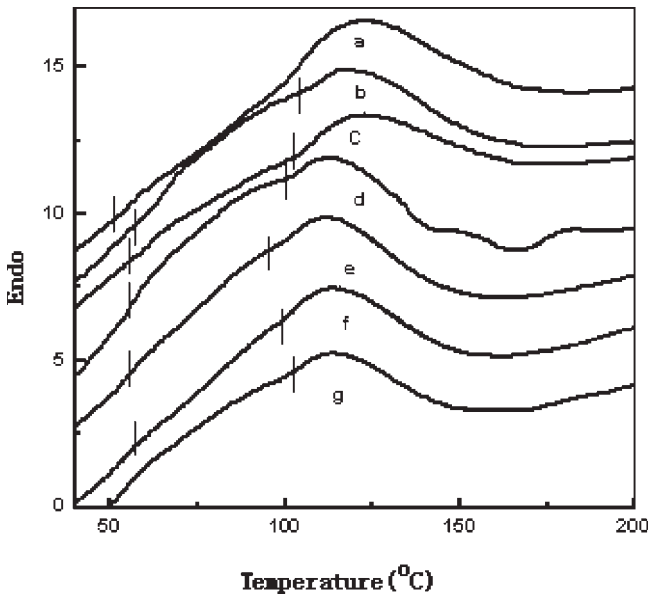


Figure 2 DSC curves of NaCMC/GG blend films containing (a) 0, (b) 10, (c) 30, (d) 50, (e) 70, (f) 90, (g) 100 wt % GG.

ing the blend films with KBr and compressing the mixture to form disks. The disks were stored in a desiccator to avoid moisture absorption. Sixteen scans were signal-averaged at a resolution of 4 cm^{-1}.

X-ray study

The crystalline forms of the blend films were determined by a C/Max-IIIA diffractometer, which has an X-ray generator of 3 kW and Cu Kα radiation. The samples were scanned at 2°/min under the diffraction angle 2θ in the range of 5–50°.

Degradation of GG/NaCMC blend films

The degradation study of the GG/NaCMC blend films were conducted *in vitro* by incubating the cylindrical blend films (diameter 7 mm) in phosphate buffered saline (PBS) solution within a test tube with same weight, respectively. The test tubes were kept at a 37°C. At predetermined time intervals, the blend film solution was taken out and the viscosity was measured. The biodegradation rate was expressed as the relative viscosity of blend solution to pure PBS solution.

Drug release study

Pieces of the cylindrical blend films were immersed in 10 mL water of pH 1.2 (HCl aq.) or pH 7.4 (PBS) and kept at 37°C. The amount of ibuprofen released was measured spectrophotometrically ($\lambda = 272$ nm) in periodically taken samples and again placed in the same vessel so that the liquid volume was kept constant.

RESULTS AND DISCUSSIONS

Miscibility and interaction of GG/NaCMC blend films

All the H_2O-cast GG/NaCMC blends are transparent, indicating miscibility optically. Figure 2 and Table I show the DSC results of GG, NaCMC, and their five blends. As shown in Table I, GG had a T_g at 55.8°C and NaCMC had a T_g at 103.7°C. All five blends had two T_g values, one at 60°C and the other at 104°C or slightly below or above. Such phenomena are very common for polymer blends. It indicated that they could not form a homogeneous phase, instead, they were partially miscible and formed two distinct phases, one is a GG-rich and the other one is a NaCMC-rich phase. Therefore, there were two new T_g values. It is noting that the two T_g values corresponding to two phases in CG_1 and CG_2 blend films are higher than those in other three polymer blends, indicating that the interactions in CG_1 and CG_2 are stronger than those in CG_3, CG_4, and CG_5.

Figure 3 shows the FTIR spectra of GG, NaCMC, and their blend films. The hydroxyl band of pure NaCMC and pure GG consists of a broad band centered at 3460 cm^{-1} and 3410 cm^{-1}, respectively, attributed to a wide distribution of hydrogen-bonded hydroxyl groups. The center of the broad hydroxyl band of the blend films shifts to a lower frequency (3400 cm^{-1}), showing the existence of the intermolecular hydrogen-bonding interactions between NaCMC and GG. NaCMC has two strong carboxyl stretching absorption bands at 1620 cm^{-1} and 1420 cm^{-1}. It is noted that the asymmetric vibration carboxyl band at 1620 cm^{-1} shows a low-frequency shift and symmetric vibration carboxyl band at 1420 cm^{-1} becomes broader in blends, indicating the involvement of carboxyl groups in interaction with GG. Both GG and NaCMC have a C—O—C band near 1110 cm^{-1}, which is overlapped with *N*—C band of $N(CH_3)_3$ group in GG. Upon mixing, a gross spectra change occurs, in which split peaks in NaCMC and GG are split further or melt in blends. Commonly the ionic interaction between polymers will exhibit such spectra change,[11,12] so the spectra change near 1110 cm^{-1} is due to the ionic interaction between GG and NaCMC.

TABLE I
Characterization of GG/NaCMC Blend Films

Films	wt %[a]	T_g(°C)	
NaCMC	0	55.8	
CG_1	90	66.4	109.9
CG_2	70	62.4	106.7
CG_3	50	57.4	104
CG_4	30	54.6	101.6
CG_5	10	54.3	102
GG	0	103.7	

[a] weight fraction of GG.

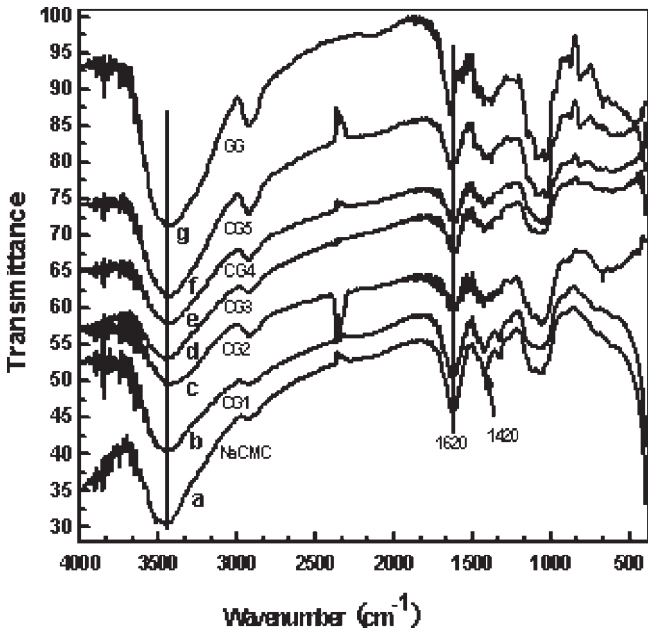


Figure 3 FTIR spectra of NaCMC/GG blend films containing (a) 0, (b) 10, (c) 30, (d) 50, (e) 70, (f) 90, (g) 100 wt % GG.

On the whole, the above results confirm that there exist the ionic interaction and hydrogen bonding between GG and NaCMC.

Figure 4 shows the pH values of GG, NaCMC and their blend solutions. All the blend solutions show a higher pH value than pure GG or NaCMC solution, indicating the existence of the interactions between GG and NaCMC.

Crystallinity and degradability of blend films

Figure 5 shows the X-ray diffraction patterns of GG, NaCMC, and their blend films. As shown in Figure 5, Pure GG has two diffraction peaks at $2\theta = 22.0^\circ$ and 19.0°, and pure NaCMC has two diffraction peaks at $2\theta = 22.2^\circ$ and 19.3°. Upon mixing, the peak intensity of blend films at about 22° becomes weaker, and the shoulder peak at about 19° also weakens or even disappears, so the crystallinity of blend films are in the order of $CG_1 < CG_2 < CG_4 < CG_5 < CG_3$, indicating that the interactions between GG and NaCMC in CG_1 and CG_2 are stronger than those in CG_3, CG_4, and CG_5. This conclusion is in agreement with DSC results, in which both CG_1 and CG_2 have higher T_g value than do other three blend films, so it is generalized that the interactions between GG and NaCMC make the blend films partially miscible and decrease the crystallinity.

Figure 6 shows the degradation of GG, NaCMC, and their blend films. The biodegradation rate was expressed as the relative viscosity of blend solution to pure PBS solution. As shown in Figure 6, pure GG or pure NaCMC degrades slowly, which is still in the process of degradation after 36 days. However, CG_1 and CG_2 degrade faster, which degrade completely during 15 days or so. CG_3, CG_4, and CG_5 show the fastest degradation rate, which degrade completely after 5 days. The results suggest that the degradation rate of blend films is related to the interactions between GG and NaCMC. The stronger the interactions between GG and NaCMC are, the more compact the blend film is, and the slower degradation rate the blend film has.

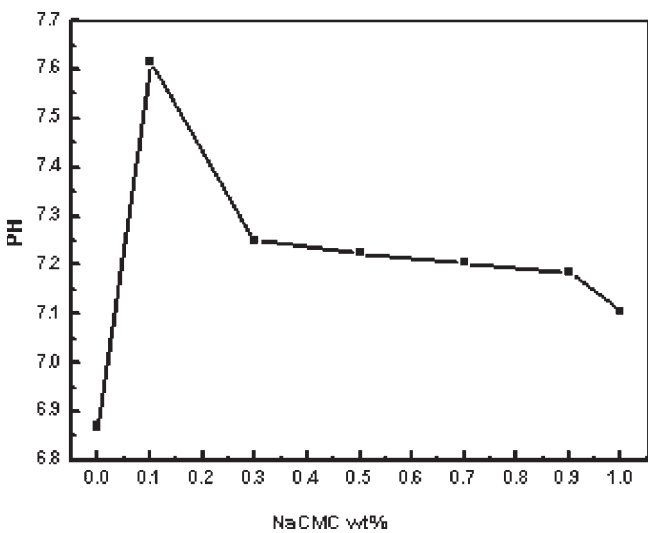


Figure 4 pH values of GG, NaCMC, and their blend solutions.

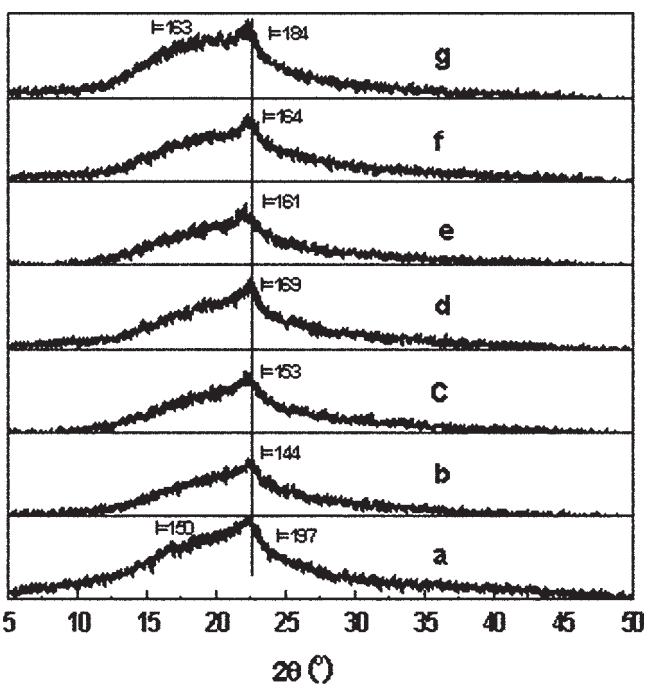


Figure 5 X-ray diffraction of NaCMC/GG blend films containing (a) 0, (b) 10, (c) 30, (d) 50, (e) 70, (f) 90, (g) 100 wt % GG.

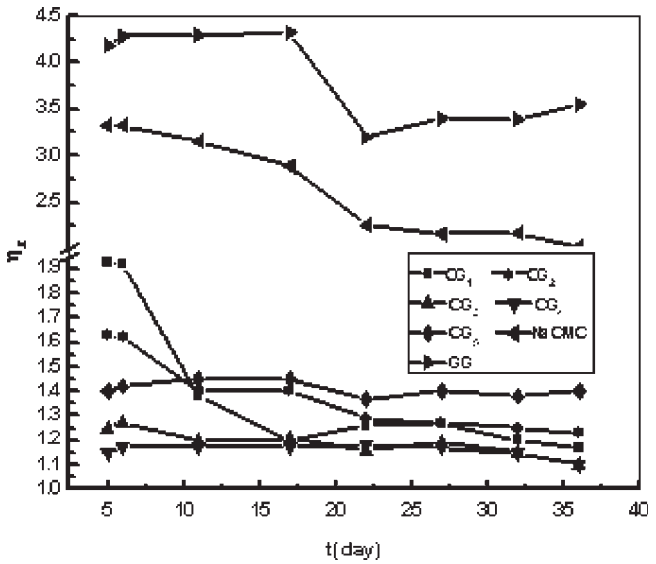


Figure 6 Degradation profile of GG, NaCMC, and their blend films.

Interactions between blend films and drug-loaded blend films

Figure 7 shows the FTIR spectra of CG_1 blend and its 0.5 wt % drug-loaded blend. The characteristic bands of ibuprofen (benzene ring at 2960 cm^{-1}; ionized carboxylic groups at 1620 and 1420 cm^{-1}) are clearly visible, but the bands corresponding to the carboxylic groups of ibuprofen are moved to lower wave numbers (1600 cm^{-1}), suggesting that there are ionic interactions between the drug and the polymer blend films. It is noted that the band of carboxylic acid dimer at 1720 cm^{-1} is very strong, indicating that the self-association of ibuprofen is not completely broken after blending.

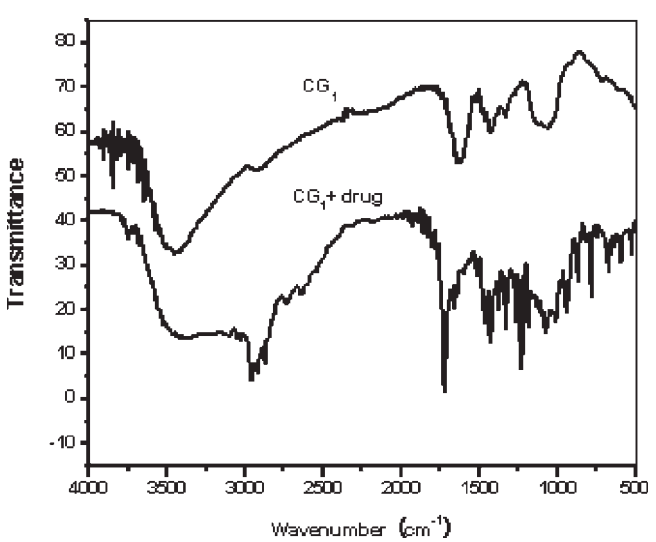


Figure 7 FTIR spectra of CG_1 blend and its drug-loaded blend films.

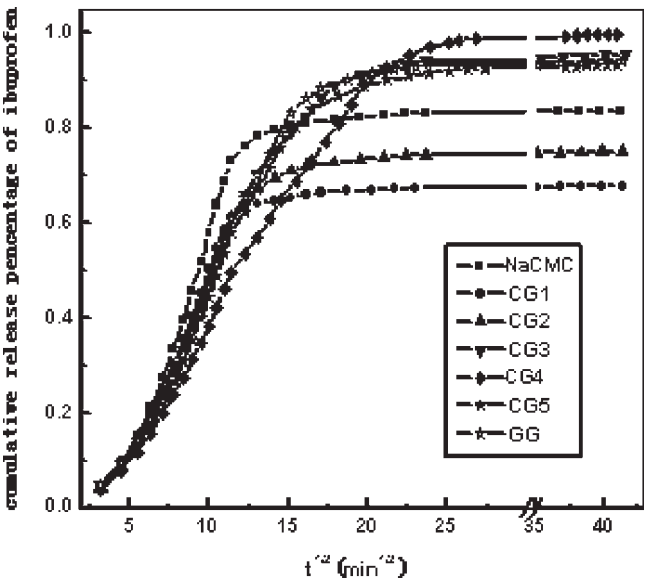


Figure 8 Release profile of ibuprofen among drug-loaded GG, NaCMC and their blend films under pH 7.4 and 37°C.

The release data were simulated using Higuchi[13–14] theory [eq. (1)], which investigated whether the ibuprofen cumulative release percentage from blends were proportional to the square time during the initial stage.

$$Q_t = kt^{1/2} \tag{1}$$

Where Q_t is the ibuprofen cumulative release percentage and t is the time. Furthermore, Peppas[15,16] equation [eq. (2)] was used to study the release mechanism.

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

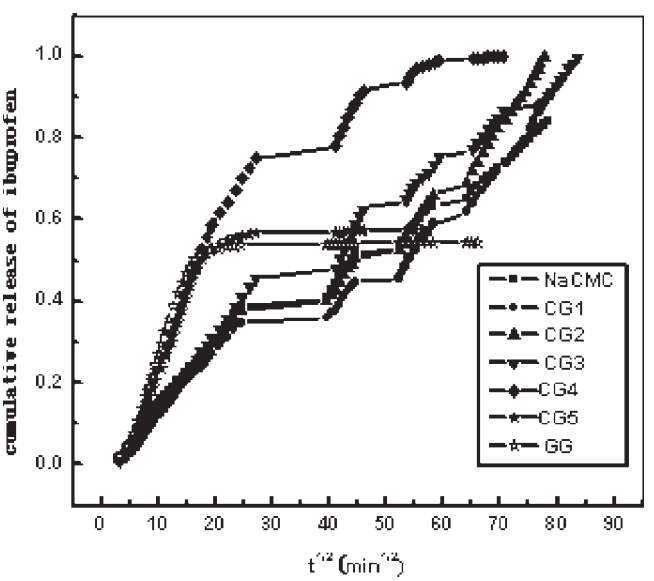


Figure 9 Release profile of ibuprofen among drug-loaded GG, NaCMC, and their blend films under pH 1.2 and 37°C.

TABLE II
Release Data of Drug-Loaded GG, NaCMC, and Their Blend Films

	PBS medium (pH 7.4)		HCl medium (pH 1.2)	
Drug-loaded films	K ($\times 10^3$ L/min)	n	K ($\times 10^3$ L/min)	n
NaCMC+0.5% drug	3.0	1.13	2.9	0.90
CG_1+0.5% drug	4.4	1.03	4.2	0.77
CG_2+0.5% drug	3.0	1.13	1.9	0.95
CG_3+0.5% drug	5.0	0.99	0.8	1.11
CG_4+0.5% drug	3.0	1.13	0.8	1.29
CG_5+0.5% drug	2.0	0.63	2.4	0.94
GG+0.5% drug	5.0	0.97	2.6	0.99
CG_3+1% drug	2.0	0.63	0.2	1.37
CG3+2% drug	2.0	0.63	0.7	1.2

Where M_t/M_∞ is drug cumulative release percentage and t is the time. K is a constant, which characterizes the release rate and n is release feature parameter indicating the type of drug release mechanism. If n approaches to 0.45 the release mechanism can be Fickian diffusion. If n approaches to 0.89 the release mechanism can be zero order and on the other hand if $0.45 < n < 0.89$ non-Fickian transport (a synergistic effect of drug diffusion and matrices erosion) could be obtained.

Effect of pH on drug release

Since the solubility of ibuprofen changes in different pH medium, the effect of pH on drug release from blend films was investigated and the results are shown in Figures 8 and 9. It is clearly seen that the release profiles of ibuprofen from the blend films in PBS (pH = 7.4) and in HCl (pH = 1.2) are completely different. During the first 2 h ibuprofen was released at pH 7.4 in a constant manner, which subsequently reached a plateau, while ibuprofen was released nearly in a constant manner at pH 1.2 during 4 days. It is also known that the release of ibuprofen at pH 7.4 is faster than that at pH 1.2. These phenomena are explained in two aspects: the first is that the solubility of ibuprofen in basic medium is larger than that in acidic medium; the other is that the interactions between the drug and the blend film at pH 1.2 are stronger than those at pH 7.4. Rosalia et al.[7] studied the interactions of ibuprofen with polysaccharides and drew the conclusions that at acidic pH drug-polymer affinity was maintained, preventing drug release and at pH 8 the interactions were broken and the release process was sustained.

Nearly 80% drug release data are in agreement with Higuchi[13,14] theory in PBS and in HCl. Most of release parameter n in Peppas equation are more than 0.89 (Table II), indicating the zero-order release kinetic, so the drug release occurs by an erosion process of matrices in this system.

Effect of blend composition on drug release

The effect of blend composition on the drug release is also shown in Figures 8 and 9. It is found that the drug release profile and release rate in different pH medium are not much affected by the blend composition, while the amounts of drug release with different composition are a little different. It is worth noting that CG_1 and CG_2 blends only release 70 and 50% drug at pH 7.4 and pH 1.2, respectively, while other blend films release about 100% drug. This could be explained by the stronger interactions between GG and NaCMC in CG_1 and CG_2 blend films, which prevent drug release from blend matrices.

Effect of initial drug concentration on drug release

Ibuprofen is an amphipathic substance, which can easily penetrate and diffuse from matrix to the medium outside. The effect of initial drug concentration on the drug release was shown in Figures 10 and 11,

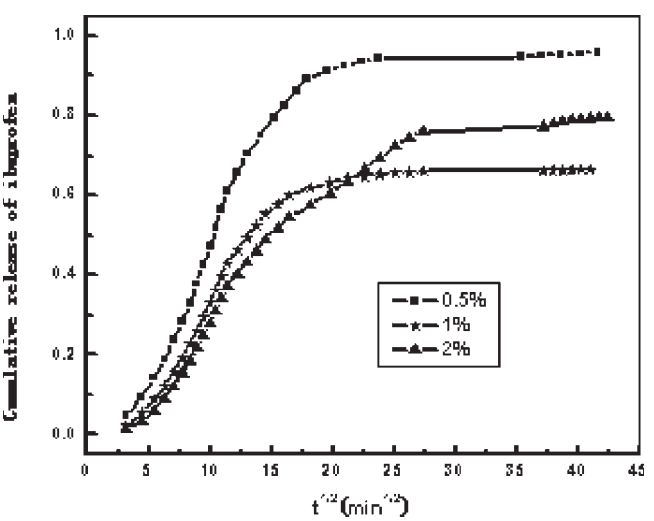


Figure 10 Release profile of Ibuprofen among drug-loaded CG_3 (the weight ratio of the blend was 1 : 1) with 0.5%, 1%, 2% initial drug concentration under pH 7.4 and 37°C.

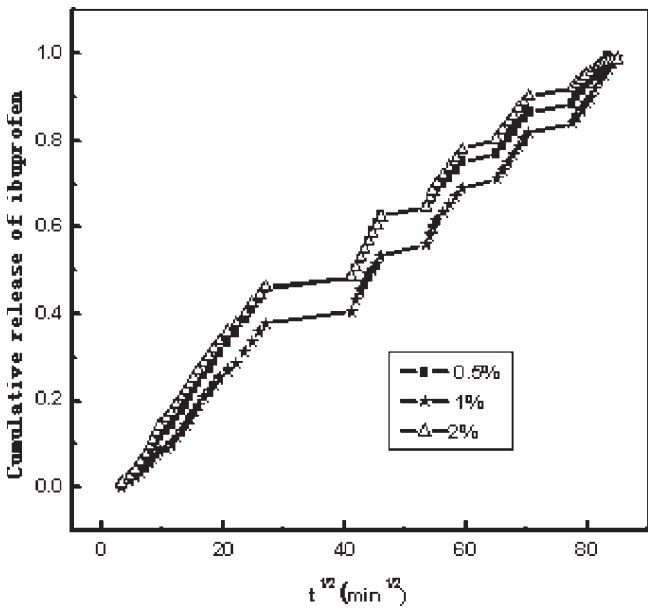


Figure 11 Release profile of Ibuprofen among drug-loaded CG_3 (the weight ratio of the blend was 1 : 1) with 0.5%, 1%, 2% initial drug concentration under pH 1.2 and 37°C.

in which CG_3 with different drug concentrations was taken out as an example. It is found that the drug release profile at pH 7.4 or at pH 1.2 is not affected by the initial drug concentration. In basic PBS (pH 7.4) medium, the release rate of ibuprofen decreases with the increasing of drug concentration, and amounts of drug release are not regularly changed with drug concentration. In acidic (pH 1.2) medium, neither drug release rate nor amounts of drug released is regularly changed with drug concentration. Based on the results of the pH effect, different drug solubility in basic and in acidic medium could be the main reason for such phenomena.

Nearly 80% drug release data are in agreement with Higuchi theory in PBS and in HCl. Most values of release parameter *n* in Peppas equation are more than 0.89 (Table II), indicating the zero-order release kinetic. It is mentioned that CG_3 with 1 and 2% initial drug concentration has the same *n* value which is between 0.63 and 0.89, indicating a synergistic effect of drug diffusion and matrices erosion coexist.

CONCLUSIONS

DSC, FTIR, XRD, and viscosity methods were used to examine the miscibility and interactions of GG and NaCMC in their blend films. The experiment results prove that the blend films are partially miscible and there exists the electrostatic interactions and hydrogen bonding between GG and NaCMC. Blend films degrade quicker than pure cationic GG or NaCMC film. Furthermore, the degradation rate of blend films is related to the interactions between GG and NaCMC. Based on the research of blend films as the drug carriers for Ibuprofen and their *in vitro* release in PBS and in HCl, it is found that pH value affect the drug release heavily, while the blend composition and initial drug concentration have little effect on the drug release. GG/NaCMC blend films have good sustained release performance for ibuprofen in HCl due to its good solubility and interactions between blend films and drug. Nearly 80% drug release data are in agreement with Higuchi theory in PBS and in HCl. Most values of release parameter *n* calculated using Peppas equation are more than 0.89, indicating the zero-order release kinetic rule.

References

1. Park, T.; Cohen, S.; Langer, R. Macromolecules 1992, 6, 116.
2. Cascone, M.; Sim, B.; Downes, S. Biomaterials 1995, 16, 569.
3. Lecomte, F.; Siepmann, J.; Walther, M.; Macrae, R.; Bodmerier, R. J Contr Release 2003, 89, 457.
4. Mi, F.; Lin, Y.; Shyu, S.; Tsai, Y. Biomaterials 2003, 24, 5023.
5. Mi, F.; Lin, Y.; Shyu, S.; Tsai, Y. Biomaterials 2002, 23, 3257.
6. Whateley, T. L. Macroencapsulation of Drugs; Harwood Academic Publishers: Amsterdam, 1992.
7. Rosalia, R.; Carmen, A. L.; Angel, C. Eur J Pharm Sci 2003, 20, 29.
8. Qiu, X. P.; Leporatti, S.; Donath, E.; Mohwald, H. Langmuir 2001, 17, 5375.
9. Gruber, J.; Kreeger, R. In Polymeric Materials Encyclopedia; Salamone, J. C., Ed.; CRC: New York, 1996; Vol. 2, p 1113.
10. Anon. J Am Coll Toxicol 1988, 7, 335.
11. Tannenbaum, R.; Rutkowska, M.; Eisenberg, A. J Polym Sci Part B: Polym Phys 1987, 25, 663.
12. Weiss, R. A.; Beretta, C.; Sasongko, S.; Garton, A. J Appl Polym Sci 1990, 41, 91.
13. Higuchi, T. J Pharm Sci 1963, 52, 115.
14. Higuchi, W. I. J Pharm Sci 1962, 51, 802.
15. Sinclair, G. W.; Peppas, N. A. J Membr Sci 1984, 17, 329.
16. Peppas, N. A.; Ritger, P. L. J Contr Release 1987, 5, 37.