Characteristics of Konjac Glucomannan and Poly(acrylic acid) Blend Films for Controlled Drug Release

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Received 2 May 2005; accepted 16 September 2005
DOI 10.1002/app.23634
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Novel polymer blend films composed of konjac glucomannan (KGM) and poly(acrylic acid) (PAA) were prepared by mixing the aqueous solution of both samples at a different weight ratio. Their structure and properties were studied by attenuated total reflection infrared spectroscopy (ATR-IR), wide angle X-ray diffraction (WAXD), thermo gravimetric analysis (TGA), scanning electron microscopy (SEM), tensile strength test, and equilibrium swelling test. The structure analysis indicated that there is a strong interaction between KGM and PAA, which result in a uniform structure and complete miscibility between the components. Potential applications of the polymer composed matrices in controlled drug delivery were also examined. The drug-loaded KGM/PAA composed matrices were prepared by coated films and directly compressed tablets, respectively. The release mechanism of a model drug, ketoprofen, from two matrices in phosphate buffer solution (pH = 7.4) was studied. Release behavior of ketoprofen rely on preparation methods of matrices and the ratio of KGM to PAA in matrices. The result showed that the drug release from the coated films is Fickian diffusion mechanism. However, for tablets, the drug release is a non-Fickian kinetics process. Various delivery parameters have been calculated and the results are discussed. J Appl Polym Sci 100: 1561–1570, 2006

Key words: polysaccharides; miscibility; drug delivery systems

INTRODUCTION

Drugs for the treatment of a lot of diseases must be administered so as to maintain a therapeutic blood level, which is stable for a long time. For this purpose, controlled drug release matrix systems for oral administration have already been developed using various techniques and additives. Natural polymers are playing an important role in drug controlled release systems due to their biocompatibility, biodegradation, and nontoxicity on administration.[1] The widely used natural polymers for sustaining the drug delivery are chitosan,[2] alginate,[3] cellulose derivatives,[4] guar gum,[5,6] and so forth. However, a few reports appear in the literature on the use of konjac glucomannan (KGM), as a carrier, for oral controlled delivery of drugs.

KGM is a high-molecular weight, water-soluble, nonionic, natural polysaccharide isolated from the tubers of the amorphophallus konjac plants and the main crop in mountainous areas of China. It not only has long been used as a health food in China, but also has wide applications in the food industry[7,8] as a thickening agent and in biochemistry.[9,10] Moreover, characters of low cost, excellent film-forming ability and good biocompatibility, biodegradability, and hydrophilicity entitle KGM to be a novel polymer material applied in the fields of coating, food preservative,[11] and enzyme entrapment.[12] In recent years, by modifying with physicochemical methods, KGM shows promise in controlled release systems and serves as biomedical materials.[12–15]

Except for the natural polysaccharide mentioned earlier, several synthetic polymers including poly(acrylic acid) (PAA), poly(vinyl alcohol), and polymethacrylate have been described as bioadhesive polymers and used in controlled release systems.[16–18] Of these, PAA exhibits strongest mucosal adhesion and wide applications as biomedical material. However, its high water solubility limits their use as a drug carrier to a certain extent, because it might be dissolved before the drug is delivered across the membrane.[19] PAA has carboxylic acid groups that could develop different intermolecular interaction like hydrogen bonds, ion–ion, and dipole–ion with other polymers. Many investigations have been approved that PAA with nonionic natural polysaccharide in aqueous solutions usually results in the formation of strong interactions. There is a great potential in utilizing these strong interactions in many pharmaceutical preparations, particularly, in control release drug delivery systems.[20]

In this work, a series of blend films was designed to take advantage of the biocompatibility and nontoxic-

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ity of KGM combined with mucosal adhesion of PAA. Morphology, mechanical characteristics, thermal characteristics, and swelling behavior of the blend films were evaluated. In addition, the blend films can be prepared in aqueous medium under lower temperature and were detected insoluble in water after stored in desiccator for 5 weeks without chemical or physical crosslinking treatment. So, the blend films have potential application in bioactive macromolecules control release systems, because the activity of bioactive macromolecules can be maintained during the coating of the films. To evaluate drug controlled release performances of films, release of model drug ketoprofen from the blend films in phosphate buffer was studied. Compared with coated films, the drug release behavior from directly compressed tablets is also discussed. The effect of preparation methods of matrices and the ratio of KGM to PAA in matrices on release mechanism was investigated.

EXPERIMENTAL

Materials

PAA was synthesized by free-radical polymerization in dioxane using azoisobutyronitrile as initiator at 60°C under N_2 atmosphere. The reaction time was 24 h. The synthesized polymer was precipitated by chloroform for three times and was dried in a vacuum desiccator at 30°C.

Konjac glucomannan (KGM) was purchased from Huaxianzi Konjac Corp., ShiYan, China. The content of glucomannan is above 95%. The viscosity is 10 Pa S in 1 wt % concentration. Konjac glucomannan was used without further purification. Other chemicals were of reagent grade.

Preparation of the blend films

Desired quantities of KGM and PAA were dissolved in water to obtain the transparent solution with the concentration of 1 wt % and 3 wt %, respectively. Then, two kinds of aqueous solutions were mixed. The weight ratios of two pure components KGM/PAA are 100/0, 90/10, 70/30, 50/50, 30/70, 10/90, and 0/100, respectively, The resulting solutions were stirred energetically at room temperature for 2 h and degassed, and then were spread over a glass plate and water was allowed to evaporate at room temperature for 3 days. The films of different ratios mentioned earlier were coded as KGM, kp9, kp7, kp5, kp3, kp1, and PAA. All film samples were stored in a desiccator at room temperature for 5 weeks before being used.

FTIR spectroscopy

IR spectra of the films were recorded with a Nicolet (USA) 170SX Fourier transform infrared (FTIR) spectrometer for investigation of intermolecular interaction. Spectra were signal averaged over 64 scans, with a resolution of 4 cm^{-1} at room temperature.

Microscopic studies

The micrographs of the films were taken with a scanning electron micrograph (S-570, Hitachi, Japan) to study the morphology of films. All films cross sections were observed and photographed after sputter-coating with gold.

X-ray diffraction

Wide-angle X-ray diffraction of the films was analyzed using a Shimadzu XRD-6000 (Japan) diffractometer equipped with a Cu Kα target at 40 kV and 30 mA with a scan rate of 4°/min. The diffraction angle was ranging from $2\theta = 8°$ to $2\theta = 45°$.

Thermal analyses

Thermal gravimetric analysis was conducted with Netzsch STA 449C instrument (Germany) under a nitrogen atmosphere with a flow capacity of 30 mL/min. The scan was carried out at a heating rate of 10°C/min from 0 to 500°C. The sample weight was about 8–10 mg and analyzed using a-Al_2O_3 crucible.

Mechanical characterization

Tensile strength and elongation at break of the films were measured on a versatile electron tensile tester (CMT-6503, Shenzhen SANS Test Machine, China) with a tensile rate of 5 mm/min. The size of the film strips was 70 mm length, 10 mm width, with 40 mm distance between the two clamps. Three parallel measurements were carried out for every sample and the mean value was obtained.

Swelling study

The swelling ratio of the empty blend films was studied. The experiment process was performed as follows: 0.1 g blend films were immersed in glass bottles and incubated on a shaking water-bath at 37°C for 24 h to reach swelling equilibrium. The dissolution medium was 200 mL phosphate buffer solution (pH = 7.4). The swollen films were taken out and weighed after the excess of water lying on the surfaces was absorbed with a filter paper. The swelling ratio of the blend films was calculated by the following:

$$Swelling\ ratio = W_s/W_d$$

where W_s is the weight of the swollen films and W_d is the initial weight of the dry films.

TABLE I
Physical Property of Tablets

Tablet code	KGM/PAA ratio	Tablet density (g/cm^2)
KGMt	10/0	1.471
kpt9	9/1	1.429
kpt7	7/3	1.403
kpt5	5/5	1.377
kpt3	3/7	1.362
kpt1	1/9	1.350
PAAt	0/10	1.270

Drug loading

The films loaded with ketoprofen were prepared by the mixture of aqueous solutions with PAA, KGM and ketoprofen power, followed by drying in oven at 30°C, and the amount of drug loaded is 2% (w/w). The blend films weight was 250 mg and stored in desiccator at room temperature for 5 weeks before being used. The thickness of films is not measured due to roughness surfaces.

Tablets were prepared by direct compression of the power mixture of drug, KGM, and PAA using IR tabletting machine. The pressure is 500 kg/cm^2 and applied for 5 min of dwell time. The tablet weight was 400 mg and diameter of tablet is 12.5 mm, each tablet contains 2% (w/w) of the drug ketoprofen. Some physical properties of tablets are given in Table I. For good compatibility of KGM power, KGM is first dissolved in water and then precipitated by acetone for three times.

In vitro release studies

To understand the release kinetics of matrix, *in vitro* drug release from tablet and blend films was carried out under the same conditions described in swelling studies. 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 results are the mean of two determinations.

RESULTS AND DISCUSSION

FTIR spectroscopy

Intermolecular interactions affect the vibration of groups on polymer segments, this information can be obtained by FTIR analysis.

Figure 1 presents the FTIR spectra of films in the range of 4000–700 cm^{-1}. The pure PAA spectrum shows a very broad band between 3600 and 2500 cm^{-1}. The O—H stretching vibration of the carboxylic groups occurs between 3600 and 3300 cm^{-1}.[21,22] A sharp peak at 2926 cm^{-1} is related to the stretching

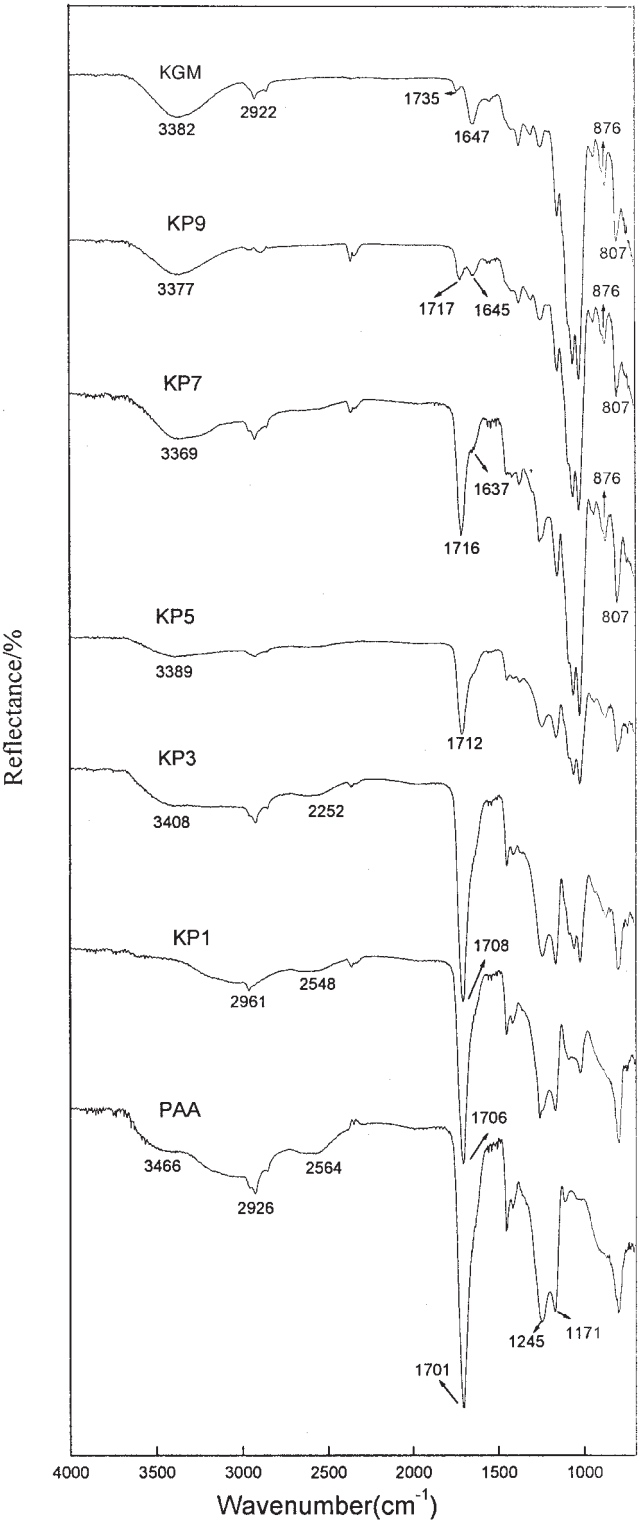

Figure 1 IR spectra of the pure and blend films in the range 4000–700 cm^{-1}.

vibrations of the —CH_2— polymer chain. The satellite bands centered at 2564 cm^{-1} is secondary absorption of the O—H stretching in PAA. The sharpest and the strongest band of pure PAA spectrum is 1701 cm^{-1}, it corresponds to carbonyl stretching vibration in intermolecular dimer.[23]

From the IR spectra of KGM, we can see that the stretching vibration modes of O—H groups from KGM is a broad band and occur at about 3382 cm^{-1}, the stretching peaks of —CH_2— are related to 2922 cm^{-1}, the peak at 1735 cm^{-1} is assigned to the C═O groups in pure KGM, the peak at 1647 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,[24,25] we also regard it as the stretching of intramolecular hydrogen bond of KGM.[11] The characteristic absorption peak of the mannose in the KGM appeared at 807 and 876 cm^{-1}.[26]

Comparing the KGM-PAA blends spectrum with that of pure KGM, it is clear that the absorption peak at 1647 cm^{-1} in pure KGM coupled and shifted to around 1645 cm^{-1} (kp9) and 1637 cm^{-1} (kp7), and indicating that the new hydrogen bonds between KGM and PAA molecules in the blend films occurred. At the same time, the peak at 1735 cm^{-1}, because of the carbonyl groups in pure KGM, has disappeared in blend films, suggesting the carbonyl groups in pure KGM were affected by the intermolecular interaction, namely, it attached to the formation of new hydrogen bonds.

The stretching vibration of —C═O in the blend films, when compared with that of pure PAA at 1701 cm^{-1}, was weakened and gradually shifted to higher wave number with increasing KGM content. The peaks corresponding to the stretching vibration of —C═O in the films kp1, kp3, kp5, kp7, and kp9 appear at 1706, 1708, 1712, 1716, and 1717 cm^{-1}, respectively. This indicates the decrease in the intermolecular cyclic dimer of PAA, and hydrogen bonds interactions that form acid cyclic dimer are progressively replaced by hydrogen bonds interactions between KGM and PAA molecular. After KGM blending with PAA, the O—H band at 3382 cm^{-1} in pure KGM is gradually weakened, broadened, and screened by O—H stretching vibration of the carboxylic groups in PAA with the increase of PAA content, meaning the interrupting of intramolecular and intermolecular hydrogen bonds of KGM. As regards to broad band at about 3400 cm^{-1} in blend films such as kp5 and kp3 may display a distribution of free O—H groups of PAA and KGM. But it is difficult to discern the contribution of O—H groups of PAA from O—H groups of KGM.

Microscopic studies

Pure and blend films were all transparent and smooth surface to the naked eyes. The scanning electron micrographs of the cross section of all samples are shown in Figure 2. All of the blends showed smooth surface (without show) and dense structures without pores or cracks, which indicate the good miscibility between the two polymers. The scanning electron microscopy (SEM) photographs of cross section of the investigated samples exhibited different structures. It can be seen that pure PAA have much smoother and more homogeneous structure than pure KGM, which exhibited a much rougher cross section. However, with an increasing amount of the KGM in the blends, the cross section of the blend films changed from smooth to rough. The probable cause is that when KGM content in blend films was higher than 50%, KGM formed a continuous phase and PAA a dispersed phase, morphology of the film incline to the pure KGM. The blends with high KGM content should possess relatively rough cross section. For example, kp9 has more similar rough cross section to KGM than other blend films. Even so, the SEM image of the blend films does not show any evidence of phase separation. The homogeneous structure of films is observed, which indicates high compatibility and miscibility between PAA and KGM in entire ratio range, and good mechanical properties would be expected.

X-ray diffraction

In Figure 3, Wide angle X-ray diffraction patterns (WAXD) of KGM, PAA, and the blends are shown. KGM exhibited a typical broad peak that appeared at $2\theta = 21°$ and several small and weak crystalline peaks at 14.8, 24.3, and 30.2°, which were assigned to a few Mannan II crystals of KGM glucomannan.[27] As for PAA, they do not show any characteristic crystalline peak, indicating that PAA is amorphous. If KGM and PAA have low compatibility, each polymer would have its own crystal region in the blend films; however, with the increase of PAA, it is obvious that several small and weak crystalline peaks of KGM becomes gradually lowered and disappear in kp3 and kp1. It is possible that the addition of PAA may suppress crystallization of KGM. According to the report of Hendrixson and Millane,[28] the crystal structure of Mannan II is stabilized by both intermolecular and intramolecular hydrogen bonds. The aforementioned results indicated that there are strong hydrogen bond interactions between PAA and KGM molecular in the blends, which break the intermolecular and intramolecular hydrogen bonds of KGM, and then lead to lower crystallinity in the blends with higher PAA content as well as appearance of amorphous structure in kp3 and kp1.

Thermal analysis

Thermal stability analysis of polymer material is helpful in the selection of materials with the best properties for specific used.

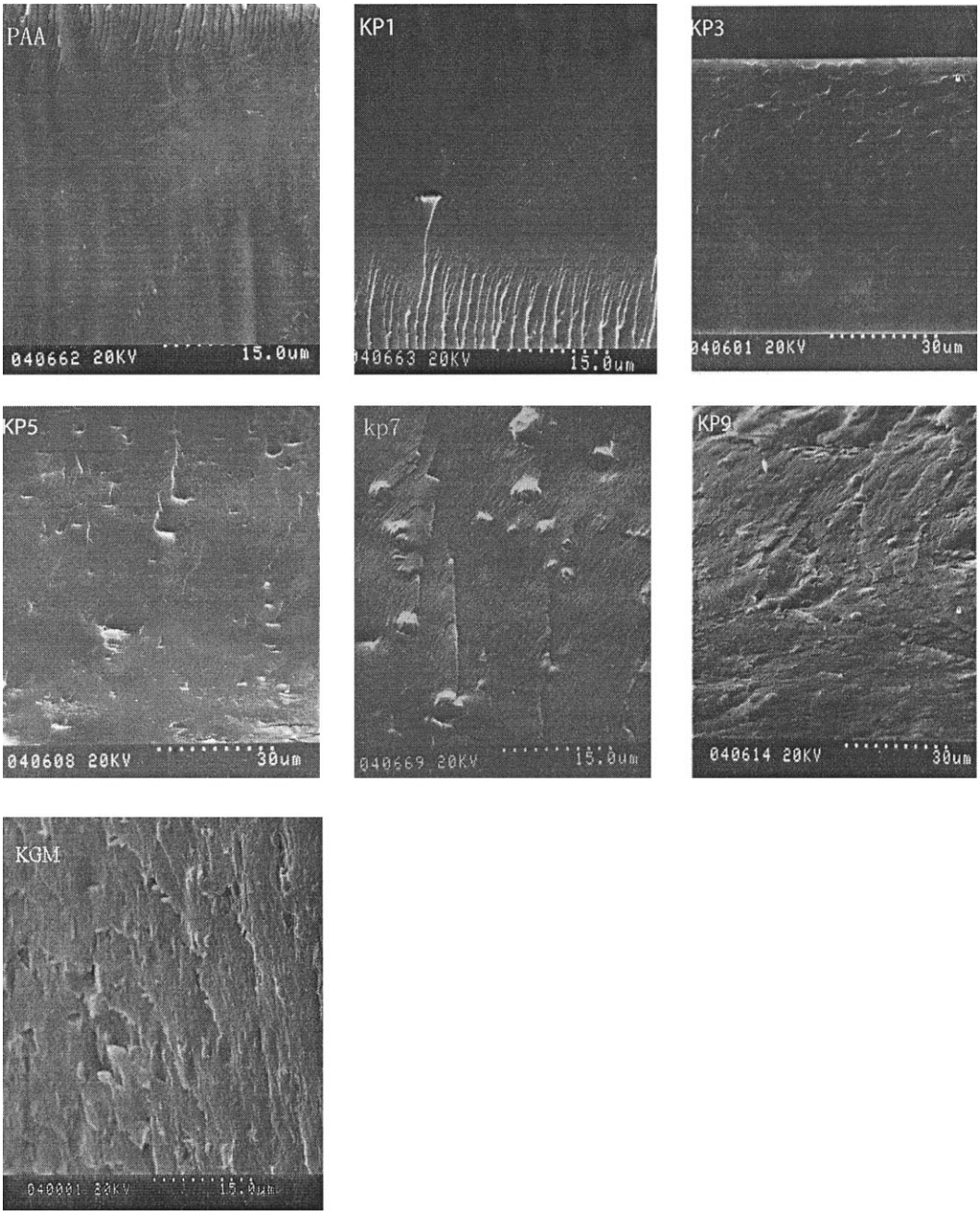

Figure 2 SEM photographs of the cross section of pure and blend films.

The thermo gravimetric analysis (TGA) curves of all samples are shown in Figure 4. Pure KGM shows a one stage degradation process within the range of 250–331°C, characterized by a weight loss of about 87%. It may be attributed to the loss of hydroxyl group of KGM as water molecules and disintegration of macromolecule chains of KGM, according to Soppirnath and Aminabhavi.[29] Pure PAA shows a three-step mechanism for thermal degradation. The first stage, which is a consequence of anhydride formation with loss of water, occurs at ~200°C. The second stage occurs in the range of 240–300°C and caused by anhydride decomposition with loss of CO_2. The third step weight loss is related to the full degradation of the macromolecule and occurs within the range of 350–460°C. The results in this work are somewhat similar to the previous reports.[30–32]

The relative thermal stability of samples was evaluated by comparing residual weight percent at 500°C. The TGA results are summarized in Table II. It is clear in Figure 4 and Table II that pure PAA and KGM show a residual mass percent of 17% and 13% at 500°C, respectively. The residual weight percent of all blend films at 500°C is higher than that of pure PAA or

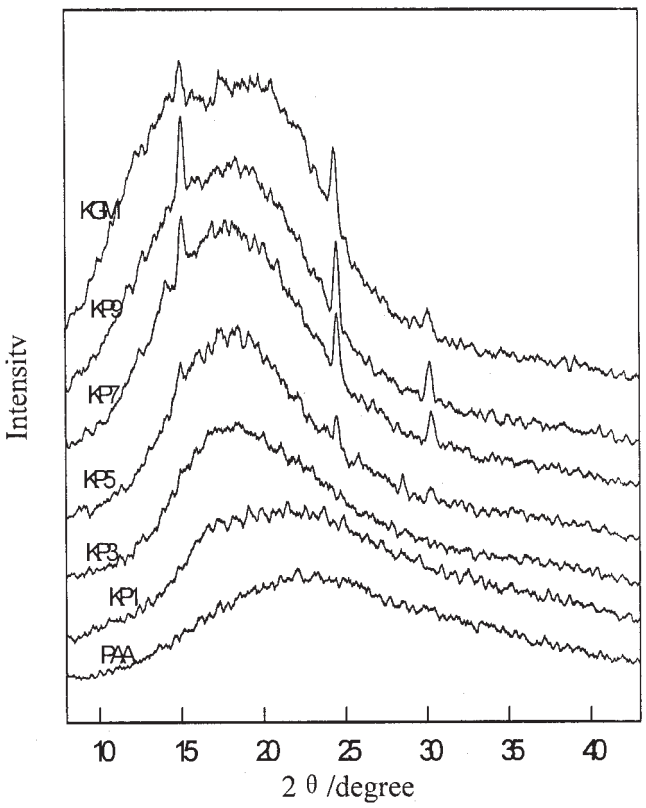

Figure 3 X-ray diffraction patterns of the pure and blend films.

KGM, which indicated the presence of strong interactions between the carboxylic groups of PAA and the hydroxyl groups of KGM. If the two components in blends have no intermolecular interaction, namely, degrade independently, then one would have expected residual weight percent based on the additivity rule. The residual weight percent of blend films

TABLE II
Results of Thermo Gravimetric Analysis of Pure and Blend Films

Film code	% residual weight at 500°C
KGM	13
kp9	33.4
kp7	33.6
kp5	33.8
kp3	28.9
kp1	23
PAA	17

should occur in the range 17% and 13%. However, the observed values were higher than the expected values, which indicate the blends are stable than the pure component since an extra energy is required to cause the blends more weight loss. These results of the TG analysis are in agreement with results of IR, SEM, and X-ray analysis.

To emphasize the differences among the thermal stability of sample films, the influence of temperature on loss of mass by sample films are shown in Figure 5. When the weight-loss value is 10%, the temperature of blend films with high KGM content is higher than that of blend films with low KGM content. This indicates that increasing the KGM content enhanced the primal decomposition temperature of blends. However, when the weight-loss value is above 10%, the kp5 has highest decomposition temperature than other blend films. At the same time, the decomposition temperature of kp7 and kp3 was prominently improved compared with that of pure PAA and KGM. It suggested that the blend of KGM and PAA dose contribute to thermal stability of material, which indicates again the

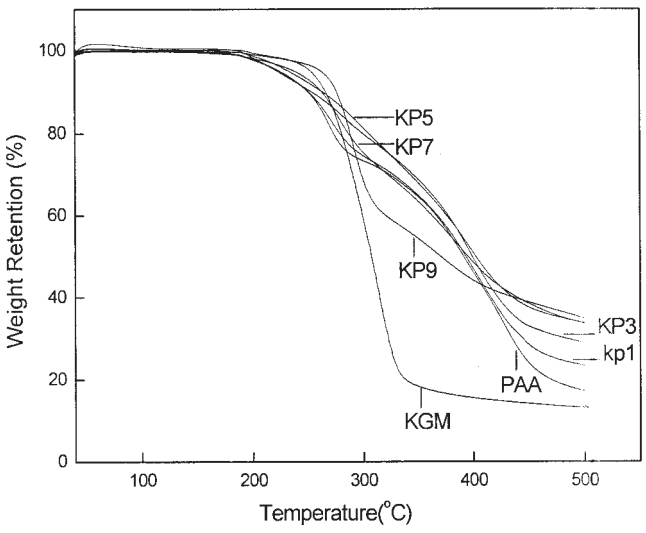

Figure 4 TGA curves of the pure and blend films.

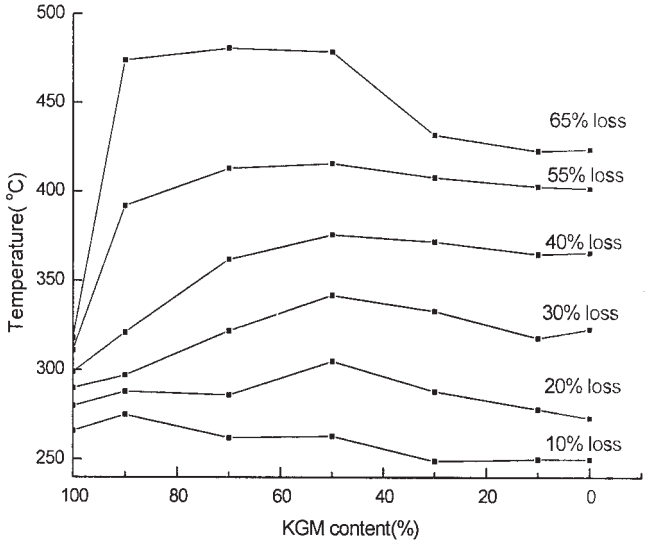

Figure 5 Influence of temperature on the loss mass by pure and blend films.

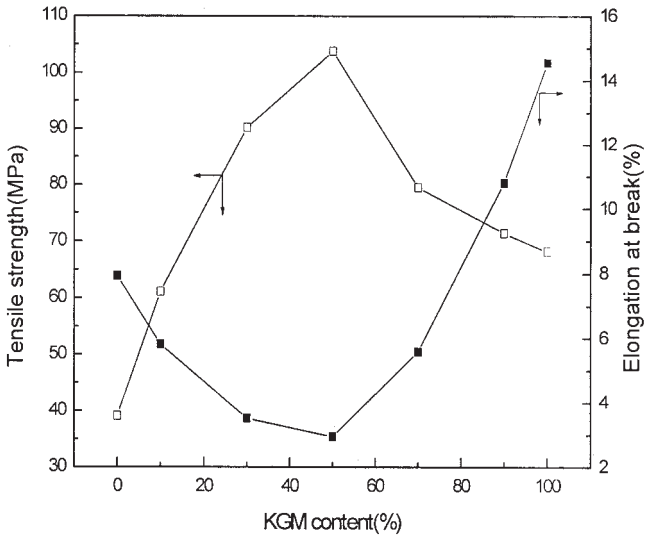

Figure 6 The mechanical properties of the films as a function of the KGM content.

presence of strong interactions between PAA and KGM. These strong interactions would hinder the formation of anhydride and later decarboxylation of PAA as well as inhibit disintegration of macromolecule side chains and main chain of KGM.

From the above analysis, it can be seen that kp5 has more stable thermal properties than other blend films. This phenomenon can explain that the molar ratio of —COOH groups of PAA and the —OH groups of KGM is more approximate to 1 than other blend films, and there are more hydrogen bond interactions points than in other blend films.

Mechanical characterization

It is known that the interaction between polymers should influence the mechanical properties of the blend polymer. The tensile strength and elongation at break of PAA, KGM, and their blend films are shown in Figure 6. The tensile strength of pure KGM and PAA were 68 MPa and 39 MPa, respectively. With the increase in PAA content, the tensile strength gradually enhances from about 71 MPa for kp9 to a maximum of about 103 MPa for kp5. On further increase of PAA content, the tensile strength shows a decline to about 61 MPa for kp1. This result suggests that compatibility between KGM and PAA. When PAA is mixed with KGM, some of each molecular hydrogen bonds interaction of PAA and KGM would break. The stronger intermolecular hydrogen bond interactions would be established. There is more hydrogen bond interactions points in kp5 than those in other blend films, and so kp5 holds higher tensile strength than other blend films. These mechanical properties agree with the thermal characteristics discussed earlier.

The elongation curve of the films expresses a tendency opposite to the tensile strength curve. PAA-KGM blend films exhibited decreased elongation at break compared with average values of PAA and KGM, and reached the minimum of 2.95% for kp5, which indicate the fall of the toughness of the films by mixing PAA with KGM. It may be that the new H-bond interaction between KGM and PAA is very strong, which impaired the partial intramolecular hydrogen bond interaction of two pure components and restricted sliding or the stretch of molecular chains in the blends and led to lower elongation at break.

Swelling study

The swelling ratio of blend films is shown in Table III. It showed deposited treatment of blend films at room temperature for 5 weeks dose that leads to the formation of insoluble materials but able to swell in water. However, after employed deposited treatment at room temperature for 5 weeks, two pure component PAA and KGM films are still soluble in water. In addition, with increase in the content of PAA, the swelling ratio of the blend films reduces and reaches a minimum of 3.10 for kp5, continue increasing the content of PAA, the swelling ratio of the blends presents ascendable trend and reaches to 17.89 for kp9. This observation can be explained on the following premises: First, hydrogen bond interactions between PAA and KGM are stronger than interactions of water–PAA or water–KGM. In this way, water could not effectively impair the interaction between PAA and KGM and dissolve blend films. Second, when blend films were treated by deposited treatment for long time, it is possible that PAA binds its carboxyl groups onto the KGM chain through some chemical reactions like esterification or formation of ether bonds[33] and leads to the formation of crosslinking network in blend films. In this way, the number of hydrophilic groups (—COOH and —OH) of the blends decline and attribute to ester formation and reach a minimum in kp5. All of these restrict the diffusion and penetration of the water molecules into the crosslinking network of the blend films. kp5 possess minimum swelling

TABLE III
The Swelling Ratio of Blend Films (Deposited Treatment at Room Temperature for 5 weeks)

The blend film code	Swelling ratio
kpl	4.28
kp3	3.39
kp5	3.1
kp7	4.22
kp9	17.89

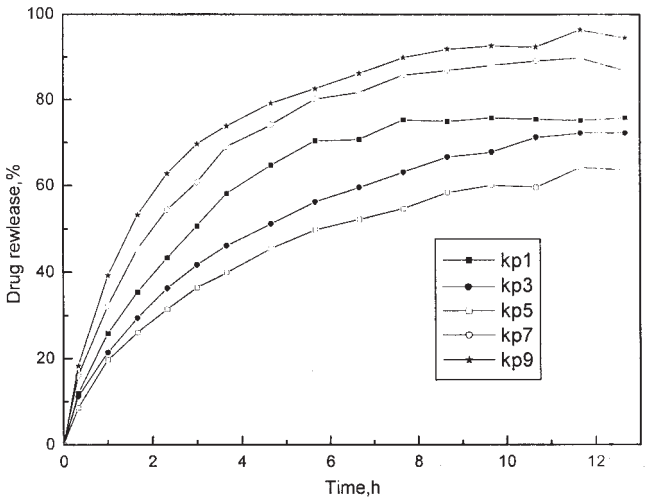

Figure 7 Release kinetics of ketoprofen from KGM-PAA blend films.

ratio, which coincide with the thermal and mechanical characterization discussed earlier.

However, FTIR spectral analysis of the insoluble films is difficult to reveal the appearance of new ester or ether band, and this phenomenon is similar to Khutoryanskiy report.[34] It is probably that the ester formation during the crosslinking reaction of PAA-KGM blends occurs only to a minor extent. So, it is possible that insoluble films would be made without chemical or physical crosslinking procedures, which has potential application in biomedicine field.

In vitro release study

To emphasize effect of strong interaction between KGM and PAA molecular in blend films on drug release mechanism, compared with blend films, the drug release behavior from directly compressed tablets is also discussed. The plot of cumulative drug release versus time for KGM-PAA insoluble blend films and mixing tablets are shown in Figures 7 and 8, respectively. The relationship between the drug release of insoluble blend films and the time is an approximate parabolic curve, while the relationship between the drug release of mixing tablets and the time is nearly linear.

In KGM-PAA blend films, it is found that the ratio of KGM to PAA can affect significantly the drug release rate. Kp9 hold highest ratio of KGM to PAA, and showed most rapid drug release rate than other blend films. Moreover, the drug release rates reduce with decrease of the ratio of KGM to PAA and reach to minimum for kp5, and then ascend. This may be explained through the fact that swelling is the most important rate-determining steps in controlled release processes.[35] From previous analysis and Table III, it can be concluded that kp5 has lowest swelling ratio, which contributes to slowest drug release of kp5. From Table III, we also see that kp1 provides a slower and more prolonged drug release than kp7, although the former hold higher swelling ratio than that of the latter. This may be due to the information that drug release from hydrophilic matrices is a complex interaction between swelling, diffusion, and erosion.

In KGM-PAA mixing tablets, much release variation is observed by varying the ratio of KGM to PAA. The high ratio of KGM to PAA in tablets results in slower drug release compared with the tablets containing low KGM to PAA ratio. For instance, the drug release from PAAt and kpt1 was rapid with almost 100% release within 2–4 h. In contrast, the release from the tablet KGMt and kpt9 was significantly slower with only 69 and 80% release with 8-h period of measurement. It may be due to different property of KGM and PAA material. KGM has high viscosity and displayed a high degree of swelling because of water uptake as well as a small degree of erosion nature polymer, while PAA has low viscosity and high water-solubility as well as easy to eroding polymer. So, the release rate increased with 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 KGM.

To precisely understand the release mechanism, the drug released from the blend films and mixing tablets was fitted to following equations proposed by Riteger and Peppas[36] (eq. (1)), Kopcha et al.[37] (eq. (2)) and Higuchi[38] (eq. (3)).

$$M_t/M_\infty = kt^n \tag{1}$$

$$M_t/M_\infty = At^{1/2} + Bt \tag{2}$$

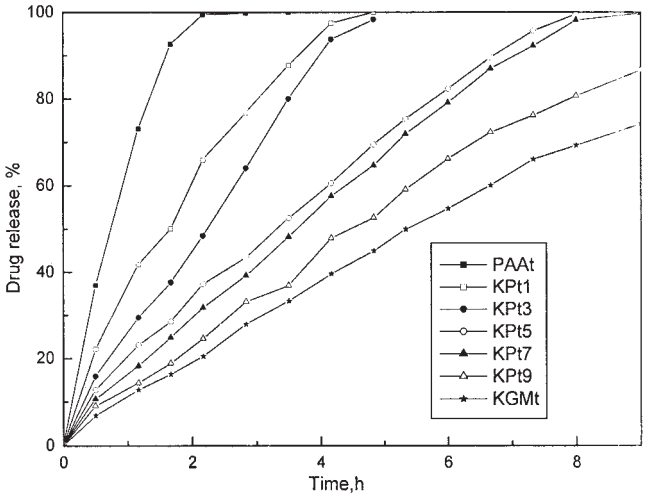

Figure 8 Release kinetics of ketoprofen from KGM-PAA tablets.

TABLE IV
Comparison of Drug Release Kinetic Date from KGM/PAA Blend Films and Mixing Tablets Derived Using Various Modeling Equation

Formulation code	Equation								
	Riteger			Kopcha			Iliguchi		
	k	*n*	*r*	*A*	*B*	*r*	*a*	*b*	*r*
KGMt	0.1131	0.8723	0.9971	0.0885	0.0601	0.9968	0.3163	0.2257	0.9819
kpt9	0.1345	0.8658	0.9939	0.1085	0.0691	0.9934	0.3704	0.2620	0.9791
kpt7	0.1648	0.8673	0.9983	0.0953	0.0945	0.9981	0.4352	0.2893	0.9840
kpt5	0.1961	0.7981	0.9988	0.1153	0.0897	0.9990	0.4333	0.2483	0.9873
kpt3	0.2437	0.9387	0.9955	0.0813	0.1749	0.9914	0.5959	0.3352	0.9745
kpt1	0.3719	0.6842	0.9956	0.4417	0.0448	0.9961	0.5733	0.1994	0.9950
PAAt	0.6360	0.6346	0.9723	1.8680	−0.4749	0.9964	0.8445	0.2052	0.9806
kp9	0.4242	0.3815	0.9610	0.6354	−0.0932	0.9969	0.2351	0.2119	0.8992
kp7	0.3860	0.3753	0.9517	0.6310	−0.0916	0.9967	0.2374	0.1518	0.9036
kp5	0.2426	0.4613	0.9892	0.3564	0.0341	0.9981	0.2098	0.0321	0.9801
kp3	0.2131	0.4589	0.9856	0.3199	−0.0317	0.9977	0.1839	0.0272	0.9777
kp1	0.2976	0.4492	0.9596	0.5744	−0.0838	0.9909	0.2144	0.0997	0.8962

$$M_t/M_\infty = at^{1/2} + b \quad (3)$$

In the above equations, M_t/M_∞ is the fraction of drug released at time t, k is a constant related to the properties of the drug delivery system, and n is the diffusion exponent, which characterizes the drug release mechanism. The values of n are >0.5, indicating that the release in these systems is non-Fickian. The values of n are <0.5, indicating that the drug release in the systems follows the Fickian diffusion; while a, b are constants; A, B are diffusion and erosion terms, respectively. When $A > B$, the diffusion factor prevails in release system, while $A < B$, erosion predominates. If $A = B$, then the release mechanism includes both diffusion and erosion equally.[5] Values of the various parameters are shown in Table IV.

When the KGM-PAA blend films were subjected to *in vitro* drug release studies, there was a slow drug release. Release date fitted to Riteger equations (eq. (1)) with correlation coefficient r value of 0.959–0.989. The n value was between 0.375 and 0.461. It suggested that diffusion play an important role in release, and kinetic evaluation showed that it is Fickian process. In addition, release date is in good accord with the Kopcha equations (eq. (2)) with correlation coefficient r value of 0.991–0.998. Moreover, in all cases, value of A is greater than B value, which again maintains dominant role of diffusion release mechanism in blend films matrix.

In tablets formulation, release date is in good accord with the Riteger (eq. (1)) and Kopcha (eq. (2)) with correlation coefficient r value of 0.972–0.998 and 0.991–0.999. In all tablets, the n value was between 0.634 and 0.938. These results indicate that the polymer erosion is a dominating factor in release process of the tablet made by mixing compress method. Drug release is expressed by non-Fickian mechanism. Visual observation confirms this thesis, during the drug release test, the size of the tablet was reduced continuously in high PAA content tablet PAAt and kpt1. However, by comparing the value of A and B, we also see that diffusion coefficient A is greater than erosion coefficient B in all cases except for kp3. These results can be explained as follows: A part of drug release via PAA erosion, while a part drug might have diffused from the hydrated layer of KGM in tablets, and then there are part drug deliver with the dissolving hydrated layer. It is because that drug release from mixing tablets depends on high water-solubility of PAA and high water uptake capacity of KGM, which dissolves slowly in water.

To understand in detail the release controlled factor in tablets, when cumulative release percentage is less than 70%, release date was be fitted to eq. (2) (Table V). Value of B is greater than that of A, which supports the dominant role of erosion release mechanism in mixing tablets. Clearly, because of strong intermolecular interaction in blend films, drug release mechanism of blend films differs from drug release mechanism of mixing tablet.

TABLE V
Release Coefficients Derived Using Kopcha Equation for Mixing Tablets

Formulation code	*A*	*B*	*r*
KGMt	0.0435	0.0740	0.9985
kpt9	−0.0469	0.1189	0.9975
kpt7	0.0205	0.1335	0.9995
kpt5	0.0649	0.1069	0.9985
kpt3	0.1546	0.2675	0.9979
kpt1	0.0725	0.2214	0.9893
PAAt	—	—	—

CONCLUSIONS

A series of blend films based on KGM and PAA were prepared by casting techniques. Swelling properties, morphology, mechanical characteristics, and thermal characteristics were investigated. The results showed that the films obtained were characterized by an uniform structure and complete miscibility between the components, 1:1 weight ratio of KGM to PAA contribute to production of films of high mechanical strength. The KGM-PAA drug release matrices were prepared by coated films and directly compressed tablets, respectively. The results show that the release rate of drug from two kinds of matrices can be controlled by weight ratio of KGM to PAA. Release date were fitted to Riteger, Kopcha, and Higuchi equations, various parameters were obtained and suggested that the predominance of diffusion on drug release from blend films, while in mixing tablets, both diffusion and erosion play an important role. It can be concluded that KGM-PAA matrices are a suitable carrier for drug delivery systems. *In vivo* delivery is required to further investigate.

References

1. Takka, S.; Acarturk, F. J Microcapsul 1999, 16, 275.
2. Miyazaki, S.; Nakayama, A.; Oda, M.; Takada, M.; Attwood, D. Int J Pharm 1995, 118, 257.
3. Shu, X. Z.; Zhu, K. J. Eur J Pharm Biopharm 2002, 53, 193.
4. Liesiene, J.; Matulioniene, J. React Funct Polym 2004, 59, 185.
5. Toti, U. S.; Aminabhavi, T. M. J Contr Release 2004, 95, 567.
6. Al-Saidan, S. M.; Krishnaiah, Y. S. R.; Satyanarayana, V.; Bhaskar, P.; Karthikeyan, R. S. Eur J Pharm Biopharm 2004, 58, 697.
7. Shen, Y.; Yang, X. Food Sci (Chin) 1995, 16, 14.
8. Pan, X. Food Sci (Chin) 1995, 16, 71.
9. Izumi, T.; Yamaguchi, M.; Yoneda, K.; Isobe, T.; Okuyama, T.; Shinoda, T. J Chromatogr A 1993, 41, 625.
10. Zhang, K.; Sun, J.; He, B. Ion Exchange Adsorp (Chin) 1998, 14, 204.
11. Xiao, C.; Gao, S.; Wang, H.; Zhang, L. J Appl Polym Sci 2000, 77, 617.
12. Perols, C.; Piffaut, B.; Scher, J.; Ramet, J. P.; Poncelet, D. Enzyme Microb Technol 1997, 20, 57.
13. Du, J.; Sun, R.; Zhang, S. et al. Macromol Rapid Commun 2004, 25, 954.
14. Wang, K.; He, Z. Int J Pharm 2002, 244, 117.
15. Liu, Z.; Hu, H.; Zhuo, R. J Polym Sci Part A: Polym Chem 2004, 42, 4370.
16. Ahn, J. S.; Choi, H. K. et al. Biomaterials 2002, 23, 1411.
17. Smart, J. D.; Kellaway, I. W.; Worthington, H. E. C. J Pharm Pharmacol 1984, 36, 295.
18. Siegel, R. A.; Falamarzian, M.; Firestone, B. A.; Moxley, B. C. J Contr Release 1988, 81, 79.
19. Needleman, I. G.; Smales, F. C. Biomaterials 1995, 16, 617.
20. Anlar, S.; Capan, Y.; Guven, O.; Gogus, A.; Dalkara, T.; Hincal, A. A. Pharm Res 1994, 11, 231.
21. Hu, H.; Saniger, J. M.; Banuelos, J. G. Thin Solid Films 1999, 374, 241.
22. Coleman, M. M.; Yang, X. M.; Painter, P. C. Macromolecules 1992, 25, 4414.
23. Lee, J. Y.; Painter, P. C.; Coleman, M. M. Macromolecules 1988, 21, 346.
24. Daniliuc, L.; David, C. Polymer 1996, 37, 5219.
25. Zhang, H.; Yoshimura, M.; Nishinari, K.; Williams, M. A. K.; Foster, T. J.; Norton, I. T. Biopolymers 2001, 59, 38.
26. Jia, C.; Chen, S.; Mo, W.; Meng, Y.; Yang, L. Chin Biochem J 1988, 4, 407.
27. Hu, M. Res Dev Nature Product (Chin) 1990, 2, 2.
28. Hendrixson, T. L.; Millane, R. P. Polym Preprint 1992, 33, 329.
29. Soppirnath, K. S.; Aminabhavi, T. M. Eur J Pharm Biopharm 2002, 53, 87.
30. Khutoryanskiy, V. V.; Cascone, M. G.; Lazzeri, L.; Barbani, N.; Nurkeeva, Z. S.; Mun, G. A.; Dubolazov, A. V. Polym Int 2004, 53, 307.
31. Garay, M. T.; Llamas, M. C.; Lglesias, E. Polymer 1997, 38, 5091.
32. Maurer, J. J.; Eustace, D. J.; Ratcliffe, C. T. Macromolecules 1987, 20, 196.
33. Nurkeeva, Z. S.; Mun, G. A.; Khutoryanskiy, V. V.; Bitekenova, A. B.; Dzhusupbekova, A. B.; Park, K. J Appl Polym Sci 2003, 90, 137.
34. Khutoryanskiy, V. V.; Cascone, M. G.; Lazzeri, L.; Nurkeeva, Z. S.; Mun, G. A.; Mangazbaeva, R. A. Polym Int 2003, 52, 62.
35. Langer, R.; Peppas, N. A. Rev Macromol Chem Phys 1983, C23, 61.
36. Ritger, P. L.; Peppas, N. A. J Contr Release 1987, 5, 37.
37. Kopcha, M.; Lordi, N.; Tojo, K. J. J Pharm Pharmacol 1991, 43, 382.
38. Higuchi, T. J Pharm Sci 1963, 52, 1145.