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Sustained release of ketoprofen from fibrous chitosan-poly(ε-caprolactone) membranes

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ABSTRACT

Chitosan-poly(ε-caprolactone) was fabricated into drug-enclosed fibrous membranes by loading with ketoprofen and using a wet-spinning method. The optimized chitosan-poly(ε-caprolactone) fibrous membranes with poly(ε-caprolactone) proportions changing from about 20 to 40 wt% showed notably enhanced tensile strength in wet state as compared to pure chitosan fibrous membranes. Some membranes loaded with an initial amount of around 8 wt% ketoprofen were capable of maintaining sustained releases of ketoprofen for a period of time longer than 50 h without significant initial burst release, and the corresponding release profiles could be effectively controlled by regulating the composition and diameters of the filaments. Kinetic analysis indicated that ketoprofen-release patterns from selected membranes were well fitted with Higuchi model and showed biphasic characteristics with different release-rate constants depending on the parameters of the membranes; and ketoprofen-releases were administrated by anomalous mechanisms involved both initial swelling and follow-up diffusion.

1. Introduction

Wound healing is a complex process involved multifarious sequences for regenerating dermal and epidermal tissues (Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004; Martin, 1997). To date, many kinds of wound dressings in the form of fibrous mats or hydrogels have been developed using different polymers (Lionelli & Lawrence, 2003; Muzzarelli & Muzzarelli, 2005). Chitosan is a naturally occurring polymer and it has been also used as an important biomaterial for wound management (Lloyd, Kennedy, Methacanon, Paterson, & Knill, 1998; Muzzarelli, 2009) due to its many enticing properties, including biocompatibility, biodegradability, hydrophilicity, nontoxicity, antimicrobial activity and hemostatic functions (Muzzarelli, 2009; Muzzarelli, Stanic, Gobbi, Tosi, & Muzzarelli, 2004). Nevertheless, chitosan usually exhibits mechanically weak features in wet state regardless of whether it is processed into membranes, fibers and gels, and thus, its applications in wound healing are limited to different extents (Wittaya-areekul & Prahsarn, 2006). To improve mechanical properties of chitosan-based fibers, we have modified chitosan by grafting mechanically strong poly(ε-caprolactone) (PCL) side chains onto chitosan backbone and processed the resultant chitosan-poly(ε-caprolactone) (CH-PCL) into fibers (Wan, Wu, Xiao, Cao, & Dalai, 2009). It is found that these CH-PCL fibers show tailorable properties with main merits of both chitosan and PCL components, including hydrophilicity, antibacterial characteristics and enhanced mechanical strength in the wet state if they have proper compositional proportions.

In recent years, many studies have suggested that wound dressings should serve not only as a protector for wounds but also as therapeutic carriers for delivering suitable drugs (Boateng, Matthews, Stevens, & Eccleston, 2008; Lim & Hudson, 2003; Maestrelli, Zerrouk, Cirri, Mennini, & Mura, 2008; Muzzarelli, 2009; Popa, Lisa, & Aelenei, 2008). To endow CH-PCL fibrous membranes with increasing functions, in the present study, a hydrophobic non-steroidal drug, ketoprofen, which has analgesic and antipyretic functions and been widely used for wound healing by being incorporated into different carriers (Bazzo, Lemos-Senna, & Pires, 2009; Braga & Oliveira, 2007; Prabaharan & Gong, 2008; Prabaharan, Grailer, Steeber, & Gong, 2008), was enclosed into CH-PCL fibrous membranes. It is expected that ketoprofen could be controllably released from these membranes over a longer period of time without significant burst-release characteristics. Some results about the

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fabrication of ketoprofen-loaded CH-PCL fibrous membranes, their tensile properties in the wet state and swelling behavior as well as in vitro ketoprofen-release profiles were thus reported.

2. Experimental

2.1. Materials

Chitosan was supplied by Fluka. To obtain highly deacetylated chitosan, the received samples were deacetylated in 50 wt% NaOH solution for 2 h at 100 °C, and the alkali treatment was repeated once. Viscosity average molecular weight and degree of deacetylation of the resultant chitosan were measured as $1.21(\pm0.19)\times10^5$ and 93.1(±1.3)%, respectively, following reported methods (Wan, Creber, Peppley, & Bui, 2003). Caprolactone and other chemicals were obtained from normal commercial channels in China and they all were of analytical grade.

2.2. Fabrication of ketoprofen-loaded fibrous membranes

CH-PCLs were synthesized using reported methods (Liu, Chen, & Fang, 2006; Liu, Wang, Shen, & Fang, 2005). Ketoprofen-loaded CH-PCL fibrous membranes were fabricated with a wet-spinning technique (Wan et al., 2009). In brief, selected CH-PCL powder with required degrees of substitution was dissolved in 0.5% aqueous acetic acid solutions to prepare 4.0 wt% CH-PCL solutions. Complete dissolution of CH-PCL powder was ensured by using a Tissuemiser Homogenizer. To each solution, a known amount of ketoprofen in ethanol was introduced and the mixture was homogenized. After removal of air bubbles, the mixture was introduced into a vessel, and then pumped through stainless steel spinnerets using a volume-metering pump at nitrogen pressure varied from 27.57 to 48.26 kPa. The selected spinnerets were mounted very close to the liquid level of the coagulation bath which was already filled with 0.5 wt% NaOH solution as coagulant. The filaments coming out of spinnerets were allowed to go through coagulant and reach a plastic dish inside the coagulation bath. The plastic dish was placed in such a way that it was able to move in the direction vertical to the liquid level, and the distance between the dish and the liquid level could be adjusted within a certain range. The resulting fibrous membranes were remained in coagulation bath for a given period of time, repeatedly washed with deionized water, dried in air first at ambient temperature and again in vacuum until constant weight was reached. A similar method was followed for preparing ketoprofen-loaded chitosan fibrous membranes and they were used as controls.

2.3. Characterization

The content of C, H, and N in CH-PCLs was measured using an elemental analysis instrument and the weight percent of PCL in CH-PCLs was calculated on the basis of elemental analysis. Average diameters of filaments were obtained using a computed image analyzer by randomly measuring diameters of 100 filaments in 712 × 484 SEM images for each fibrous membrane. Average pore-sizes of fibrous membranes were also measured with the same method.

Porosity of fibrous membranes was calculated as follows (Wan et al., 2009):

$$\text{Porosity} = \frac{V-(W/\rho)}{V}\times 100\% \quad (1)$$

where V is the volume of fibrous membrane (cm^3), W is the mass of fibrous membrane (g), ρ is the density of nonporous film (g/cm^3), and it was determined with a floating method using mixed solvents composed of carbon tetrachloride (density: 1.586 g/cm^3) and ethanol (density: 0.816 g/cm^3).

Swelling index was determined with a gravimetric method. The accurately weighed fibrous membranes were immersed in a PBS solution (pH 7.2) at 37 °C for various periods of time up to 30 h. At predetermined time intervals, selected samples were transferred into glass tubes with a sintered glass bottom and the excess of absorbed water was removed by centrifugation at 2000 rpm for 1 min. Swelling index of membranes at time t was calculated with following formula:

$$\text{Swelling index} = \left[\frac{W_t - W_d}{W_d}\right]\times 100\% \quad (2)$$

where W_t is the weight of the hydrated fibrous membranes at time t, and W_d is the weight of the dry fibrous membranes.

2.4. Measurements of mechanical parameters

Tensile parameters of fibrous membranes in the wet state were measured using an Instron universal testing machine at ambient temperature. Dry membranes were cut into rectangular strips with dimensions of 50 mm × 20 mm (average thickness of the fibrous membranes was determined using a vernier caliper) and immersed in PBS solution for 2 h prior to measurements. After removal of excess water by centrifugation at 2000 rpm for 1 min, these strips were strained to failure on employing a gauge length of 20 mm at a crosshead speed of 2 mm/min.

2.5. Determination of loading efficiency

Ketoprofen-loaded fibrous membranes were cut into very tiny strips and ground into powder using an impact mill cooled with liquid-nitrogen. Precisely weighed powder was extracted with a given amount of ethanol at 60 °C for 72 h with stirring. After centrifugation, the supernatant was assayed using a UV–vis spectrophotometry at the wavelength of 260 nm for determining the initial ketoprofen content. The supernatant from the empty fibrous membranes (without ketoprofen) was taken as a control. The loading efficiency was defined as a ratio of measured initial ketoprofen content inside fibrous membranes to the fed amount of ketoprofen during the wet-spinning processing.

2.6. In vitro release of ketoprofen

Ketoprofen-loaded fibrous membrane samples with a known weight were suspended in 30 mL of PBS solutions (pH 7.2) in glass vessels and they were shaken at 37 °C in a reciprocal shaking incubator at 100 rpm for various durations. At the predetermined time point, aliquots of solutions were withdrawn, and they were replaced by the same volume of fresh medium. The amount of ketoprofen released from fibrous membranes was spectrophotometrically determined at a wavelength of 260 nm.

Analysis of variance was performed using a commercially available statistical software (SPSS 15.0 for Windows) to examine whether significant differences existed between the measured data. $p < 0.05$ was employed to assess the statistical significance of results.

3. Results and discussion

3.1. Morphology and parameters of fibrous membranes

To leave amino groups at the C-2 sites of chitosan backbone free for the potential functions, in the present study, PCL side chains were selectively grafted onto the C-6 sites of chitosan units using

a group-protection method in which the amino groups at C-2 sites were protected beforehand using phthaloyl groups (Liu, Wang, Shen, & Fang, 2005). It was found that PCL content in CH-PCLs was markedly dependent on both the feed ratios of caprolactone to chitosan and the synthesis conditions, and the maximum weight percent of PLC in CH-PCLs could reach around 74 wt% by using present synthesis technique. However, PCL content in CH-PCLs should be well balanced because the resultant CH-PCLs would have some characteristics more similar to pure PCL if the weight ratio of PCL in CH-PCLs was too high. To take full advantage of both chitosan and PCL components, some CH-PCLs with PCL content ranging from 20 to 40 wt% were thus selected for the fabrication of fibrous membranes.

By employing selected spinnerets with various diameters and capillary lengths and changing processing conditions, different ketoprofen-loaded fibrous membranes with desirable parameters were fabricated. Fig. 1 presents two representative SEM images of the achieved fibrous membranes. It can be observed that (1) filaments in the membranes have dense bodies and relatively flat surface with small defects (see arrows in Fig. 1(A)), and these filaments are randomly accumulated together and the resultant fibrous membranes have fully interconnected pores; (2) some filaments show nonuniform characteristics along their longitudinal axis (see arrows in Fig. 1(B)); and (3) the average diameters of filaments can be effectively regulated by selected proper spinnerets, as shown in Fig. 1(A) and (B) where two kinds of spinnerets with different diameters and capillary lengths were employed.

To date, although a great variety of polymer-based wound dressings have been developed, unfortunately, there are no any standard parameters available for their morphology and structure. In the cases of fibrous wound dressings (Huang, Zhang, Kotaki, & Ramakrishna, 2003; Lim & Hudson, 2003; Lionelli & Lawrence, 2003), data in the literature of wound dressings show that the fibrous wound dressings could have quite various porosities (from 30% to 80%), different pore-sizes (from a few microns to several hundred microns) and changeable diameters of filaments (from less than 500 nm to several hundred microns). At a compromise level, in the present instance, the average porosity and average pore-size of fibrous membranes were set as around 50% and 100 μm, respectively, and the average diameters of filaments were selected between 100 and 200 μm. These basic parameters were selected in such a way that the resultant fibrous membranes have medium parameter values as compared to the reported data in the literature.

After many trials, it was reached that (1) the composition and average diameter of CH-PCL filaments acted as two crucial factors to manipulate the release profiles of ketoprofen and the mechanical properties of the fibrous membranes, and (2) the average porosity and pore-size of CH-PCL fibrous membranes imposed certain impacts on the tensile properties of the hydrated membranes but did not significant influence the release patterns of ketoprofen. To mainly evaluate the effect of composition and average diameters of CH-PCL filaments on the properties of fibrous membranes and keep other parameters with similarity, three sets of ketoprofen-loaded CH-PCL fibrous membranes were fabricated and designated as CH-PCL-*i*(*j*) (*i* = I, II, III; *j* = a, b), and meanwhile, some ketoprofen-loaded chitosan fibrous membranes with similar parameters were used for controls and named as chitosan(a) and chitosan(b), respectively. These membranes were built by selecting proper processing conditions so that they had similar average porosity and average pore-size but three sets of CH-PCL samples had different CH-PCL proportions and the samples in each set had various average diameters of CH-PCL filaments. Relevant parameters for these fibrous membranes are summarized in Table 1.

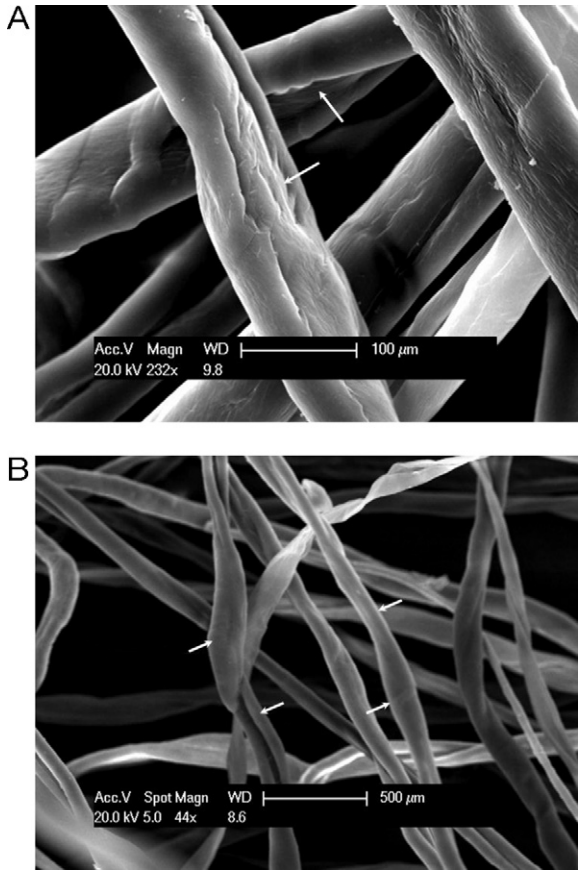

Fig. 1. SEM micrographs of fibrous membranes fabricated under various processing conditions. (A) CH-PCL-I fibrous membranes (initial ketoprofen content: 8.2 wt%); and (B) CH-PCL-III fibrous membranes (initial ketoprofen content:8.4 wt%).

Table 1
Parameters of ketoprofen-loaded fibrous membranes.[a,b]

Fibrous membranes	Average diameter of filament (μm)	Average pore size (μm)	Average porosity (%)	PCL content in CH-PCL (wt%)[c]
Chitosan(a)	97.5 ± 5.7	103.1 ± 11.4	50.3 ± 4.2	–
Chitosan(b)	202.6 ± 9.8	97.4 ± 11.7	48.9 ± 4.3	–
CH-PCL-I(a)	101.3 ± 5.2	98.3 ± 10.9	52.6 ± 5.1	21.2(±1.17)
CH-PCL-I(b)	196.4 ± 8.3	105.2 ± 11.2	54.1 ± 5.5	21.2(±1.17)
CH-PCL-II(a)	105.1 ± 4.6	104.4 ± 9.8	47.4 ± 4.7	30.9(±1.24)
CH-PCL-II(b)	205.3 ± 7.4	97.6 ± 11.5	49.2 ± 4.9	30.9(±1.24)
CH-PCL-III(a)	98.7 ± 4.3	101.3 ± 10.3	51.3 ± 4.8	41.8(±1.31)
CH-PCL-III(b)	203.8 ± 6.9	104.6 ± 9.7	53.2 ± 5.4	41.8(±1.31)

[a] Initial ketoprofen content in these membranes was 8.2 ± 0.41 wt%.
[b] Data in table were the average values (n = 6) with standard deviation for each sample.
[c] PCL content in CH-PCLs was calculated using the results obtained from elemental analysis.

3.2. Loading efficiency of ketoprofen

It was observed that the loading efficiency of ketoprofen in different fibrous membranes significantly varied with the composition and diameters of filaments as well as ketoprofen-feed-ratios. All fibrous membranes had a higher loading efficiency when the ketoprofen-feed-ratio was low, for instance, less than 5 wt%; and their loading efficiency could markedly decrease when the ketoprofen-feed-ratio was higher than 10 wt%. Under present processing conditions, the maximum initial ketoprofen loading in chitosan(a) and chitosan(b) membranes (see Table 1) can reach around 14–19 wt%, respectively; whereas the maximum initial ketoprofen loading in CH-PCL fibrous membranes varies from 24 to 38 wt%, strongly depending on the compositional proportions and diameters of CH-PCL filaments. In considering the suggested daily dose of ketoprofen in the clinic practices (Airaksinen, Venalainen, & Pietilainen, 1993; Kantor, 1986) and the structures and release characteristics of CH-PCL fibrous membranes, all membranes in this study were loaded with similar initial ketoprofen content of around 8 wt%.

3.3. Tensile properties of ketoprofen-loaded fibrous membranes

Since ketoprofen-loaded CH-PCL fibrous membranes will be possibly used in a wet environment when they serve as wound dressings, their tensile properties in wet state were therefore examined and relevant parameters obtained from tensile measurements are listed in Table 2.

Data in Table 2 show that the hydrated chitosan(a) and chitosan(b) membranes have larger breaking elongations, and their tensile strength and modulus are significantly lower than that of CH-PCL membranes. Chitosan is known to be hydrophilic. After being hydrated, the original microcrystalline domains inside the filaments would be highly destroyed due to hydration and swelling, and thus, the tensile strength and modulus of hydrated chitosan fibrous membranes would be remarkably low, accompanied by increased breaking elongation. CH-PCLs are composed of both hydrophilic chitosan component and very hydrophobic PCL component, and hence, PCL side chains in CH-PCLs could turn inward and aggregate together as close as possible while chitosan chains would stretch outward during the preparation of CH-PCL filaments because aqueous solutions were employed as solvents. By doing so, hydrophobic domains constructed by PCL side chains would possibly act as physically crosslinked sites inside the filaments and reinforce the strength and modulus of hydrated CH-PCL fibrous membranes, which is somewhat similar to the case of polylactide–chitosan gels (Qu, Wirsen, & Albertsson, 1999). In addition, it can be seen from Table 2 that tensile strength and modulus of hydrated CH-PCL fibrous membranes significantly increase ($p < 0.01$) with increasing PCL content in CH-PCLs, demonstrating that PCL component in CH-PCLs is able to predominately regulate the tensile properties of fibrous membranes, and meanwhile, the average diameters of filaments can also significantly modulate ($p < 0.05$) the strength and modulus of hydrated fibrous membranes.

Table 2
Tensile mechanical parameters of hydrated fibrous membranes.[a,b]

Fibrous membranes	Tensile strength (kPa)	Elongation at break (%)	Young's modulus (kPa)
Chitosan(a)	107.4 ± 17.9	62.7 ± 5.2	974.1 ± 71.4
Chitosan(b)	161.9 ± 21.2	59.2 ± 4.6	1175.2 ± 82.3
CH-PCL-I(a)	615.7 ± 54.8	51.4 ± 4.8	5892 ± 146.1
CH-PCL-I(b)	784.5 ± 64.7	49.5 ± 5.1	8352.3 ± 209.4
CH-PCL-II(a)	905.3 ± 81.3	47.1 ± 4.1	9121.4 ± 218.2
CH-PCL-II(b)	1141.2 ± 80.3	43.6 ± 4.3	12039.5 ± 263.8
CH-PCL-III(a)	1179.6 ± 78.1	44.3 ± 4.2	11694.6 ± 232.5
CH-PCL-III(b)	1367.3 ± 91.6	41.8 ± 4.5	14475.3 ± 241.7

[a] Data quoted were average values from four specimens for each sample.
[b] See Table 1 for other parameters.

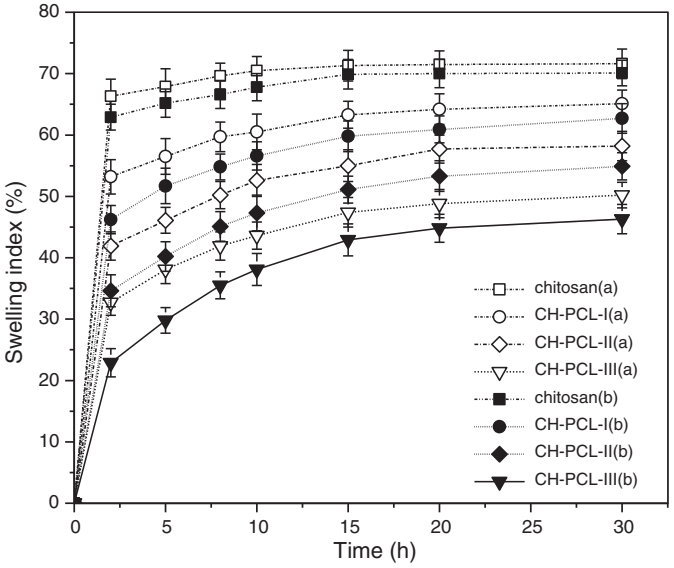

Fig. 2. Swelling behavior of different fibrous membranes (immersion in PBS solutions, pH 7.2, 37 °C; average diameters of filaments: around 100 μm (open symbols) and 200 μm (filled symbols); see Table 1 for other parameters).

3.4. Swelling behavior of fibrous membranes

In principle, swelling properties of polymer vehicles can exert a strong impact on their drug-release behavior (Yu & Mao, 2008), swelling indexes of all fibrous membranes were therefore measured and the relevant data are plotted in Fig. 2. It can be observed from Fig. 2 that (1) swelling index of chitosan fibrous membranes is much higher than that of CH-PCL fibrous membranes, and swelling index of CH-PCL fibrous membranes gradually decreases as PCL content increases; and (2) chitosan fibrous membranes swell very rapidly in a short period of time and reach their swelling equilibrium within about 10 h; and on the other hand, CH-PCL fibrous membranes exhibit a two-stage swelling characteristic, namely, they swell relatively fast in the first stage and progressively reach a swelling equilibrium around 20 h, strongly depending on PCL content in CH-PCLs. The large swelling index and high swelling rate of chitosan fibrous membranes can be ascribed to their highly hydrophilic properties and quick failure of hydrogen-bond interactions. With respect to CH-PCL fibrous membranes, since CH-PCL filaments contain many hydrophobic domains built by PCL side chains, these domains will prevent water from penetrating into the filaments and result in lower swelling rates and smaller swelling indexes. Results shown in Fig. 2 suggest that the composition of CH-PCL filaments governs the swelling behavior of the membranes, and average diameters of filaments can impose a measurable effect on the swelling index of CH-PCL fibrous membranes.

3.5. In vitro drug release studies

3.5.1. Release profiles of ketoprofen

The release profiles of ketoprofen from different fibrous membranes as a function of time are shown in Fig. 3. The plots in Fig. 3 illustrate that the drug release rate of chitosan(a) membranes is quite high in the initial stage, around 65% drug is released in less than 2 h, and most of ketoprofen is released within 5 h. On the other hand, CH-PCL membranes show a faster release within the

Table 3
Estimated kinetic parameters of different fibrous membranes.

Sample	Ritger and Peppas model[a]			Higuchi model[b]			
	$k(\%/h^n)$	n	r^2	$k_1(\%/h^{0.5})$	r^2	$k_2(\%/h^{0.5})$	r^2
Chitosan(a)	35.2	0.81	0.9829	59.6	0.9875	–	–
Chitosan(b)	31.6	0.76	0.9817	45.8	0.9836	–	–
CH-PCL-I(a)	26.5	0.57	0.9839	21.1	0.9802	–	–
CH-PCL-I(b)	22.4	0.55	0.9821	17.8	0.9985	8.5	0.9969
CH-PCL-II(a)	18.1	0.53	0.9842	14.3	0.9969	6.6	0.9957
CH-PCL-II(b)	15.1	0.54	0.9896	12.9	0.9907	5.9	0.9984
CH-PCL-III(a)	11.5	0.53	0.9823	12.6	0.9961	5.6	0.9992
CH-PCL-III(b)	7.4	0.54	0.9814	10.9	0.9953	5.1	0.9976

[a] Kinetic constants (k), diffusional exponents (n), and correlation coefficients (r^2) were calculated by linear regression based on plots of log (M_t/M) vs. log t in Fig. 3.
[b] Kinetic constants (k_1 and k_2) and correlation coefficients (r^2) were calculated using Fig. 4; and they corresponded to the early and later stage of release, respectively; "–" denotes that there were no significant changes in kinetic constants and k_2 was not calculated.

first 2 h, and after that, they exhibit a gradually slow and steady release. Release rates and equilibrium releases for different CH-PCL membranes are strongly dependent on the composition of CH-PCL filaments. It is observed from Fig. 3 that chitosan(b) membranes exhibit a release profile very similar to that of chitosan(a) membranes, and ketoprofen-release patterns of CH-PCL membranes consisted of thicker filaments show a slowdown characteristic as compared to the corresponding ones composed of thinner filaments.

Fig. 2 indicates that chitosan fibrous membranes swelled very fast in the aqueous medium. Ketoprofen molecules could be therefore easily detached from chitosan filaments due to the poor interactions between hydrophobic ketoprofen molecules and hydrophilic chitosan chains, which would lead to burst release of ketoprofen. In the cases of CH-PCL fibrous membranes, the relatively faster release of ketoprofen at early stage is possibly due to the detachment of ketoprofen molecules residing inside the superficial layer near the surface of CH-PCL filaments (Yu, Li, Yuan, Dai & Liu, 2006); and the followed slowdown release of ketoprofen could be ascribed to the effect of PCL component in CH-PCL filaments.

In principle, amphiphatic polymers can gather together to form aggregates with hydrophobic cores when exposing to aqueous media (Muzzarelli & Muzzarelli, 2005). Since CH-PCL is an amphiphatic polymer and CH-PCL filaments were prepared using aqueous solvents many hydrophobic domains containing hydrophobic ketoprofen molecules could form and reside inside CH-PCL filaments during the fabrications of CH-PCL fibrous membranes. The size and number of ketoprofen-contained hydrophobic domains should be strongly dependent on the composition of CH-PCL filaments because of interactions between ketoprofen molecules and hydrophobic PCL side chains. These hydrophobic domains would create a certain kind of barrier which will limit the access of water and obstruct dissolution of ketoprofen from CH-PCL fibrous membranes, resulting in slower releases of ketoprofen in the late stage. The CH-PCL filaments containing a higher amount of PCL component should have more hydrophobic domains than that containing lower PCL content and as a result, ketoprofen-release rates would decrease with increasing PCL content, as indicated in Fig. 3.

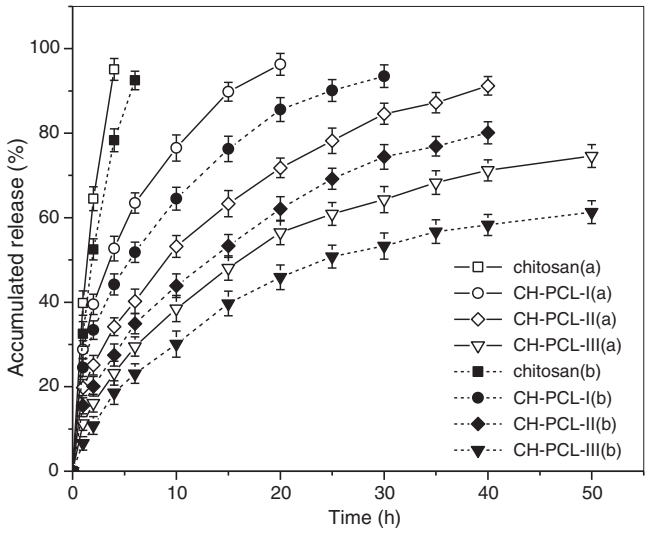

Fig. 3. Release profiles of ketoprofen from fibrous membranes (average diameters of filaments: around 100 μm (open symbols) and 200 μm (filled symbols); see Table 1 for other parameters).

The plots in Fig. 3 reveal that the average diameter of CH-PCL filaments can also significantly ($p < 0.05$) influence the ketoprofen-release patterns even though the releases of ketoprofen from chitosan fibrous membranes are not sensitive to the average diameter of chitosan filaments. This is understandable in considering following facts: (1) both chitosan(a) and chitosan(b) fibrous membranes swell so significant that the effect of the diameter of filaments on their release behavior could become negligible; and (2) enclosed ketoprofen in thicker filaments would go through longer pathways to diffuse into the medium, and meanwhile, it would be difficult for water to penetrate into the hydrophilic domains inside thicker filaments, both factors can result in delayed releases of ketoprofen. These results suggest that the average diameter of filaments can also act as an important variable to control the release profiles of ketoprofen from CH-PCL fibrous membranes.

On the basis of above observations, it can be reached that chitosan fibrous membranes are unsuitable for the sustained release of ketoprofen whereas some CH-PCL fibrous membranes have the potential to serve as desirable carriers for locally delivering ketoprofen in a sustained and controllable manner.

3.5.2. Kinetics of release

Many different drugs, proteins and peptides have been systematically or locally delivered by using various polymer vehicles so far. Although the diversity and complexity of different drug release systems several empirical models have been established to quantitatively describe kinetics of drug release (Kumar et al., 2004; Yu & Mao, 2008). In the case of swellable polymer matrices, the kinetic behavior of drug release can be effectively estimated using following empirical equation:

$$\frac{M_t}{M} = kt^n \quad \text{or} \quad \log\left(\frac{M_t}{M}\right) = \log k + n \log t \left(\frac{M_t}{M} < 0.6\right) \tag{3}$$

where M_t/M is the amount of released drug (%) at time t (h), k ($\%/h^n$) is a constant incorporating structural and geometric characteristics of the drug-loaded devices, and n is the release exponent, indicative of the mechanism of drug release.

Based on the linear regression method, n and k were calculated from the plots of log (M_t/M) versus log t, and relevant parameters for different fibrous membranes are summarized in Table 3. It is observed that k-values of chitosan fibrous membranes are higher than 30 $(\%/h^n)$ while k-values of CH-PCL fibrous membranes decrease as the PCL content in CH-PCLs increases. The average diameter of CH-PCL filaments also exerts measurable impacts on k-values of the membranes. Comparing samples in Table 3 with corresponding ones shown in Fig. 3, it can be reached that fibrous membranes having a faster release rate would have a larger k-value. These results are in basic agreement with some published reports in which the release systems are involved in swellable polymer matrices (Peng, Zhang, & Kennedy, 2006).

In the cases of drug-loaded slab or film systems, several specific values for n in Eq. (3) have distinct meanings for the mechanism of drug release. $n = 0.5$, drug-release follows a diffusion-controlled mechanism which is commonly regarded as Higuchi model; and $n = 1.0$, the rate of drug-release would be independent of time and this case is usually known as case-II transport or zero-order release kinetics. Values of n located between 0.5 and 1.0 can be regarded as an indicator for the superposition of two apparently independent mechanisms of drug transport (anomalous transport), a Fickian diffusion and a case-II transport. However, for a cylinder system (for example, fibers), the threshold of n-value distinguishing between Fickian and non-Fickian diffusion mechanism has been slightly modified from 0.5 to 0.45 and n-values between 0.45 and 0.89 can be considered as anomalous transport.

In the present instance, Table 3 indicates that n-values of chitosan fibrous membranes are larger than 0.75 with correlation coefficients higher than 0.98, revealing that the release of ketoprofen from chitosan fibrous membranes was predominately mediated by a swelling-controlled mechanism. It can be seen that all CH-PCL fibrous membranes have their n-values close to 0.5 or slightly higher. In considering the amphiphatic properties of CH-PCLs and n-values of CH-PCL fibrous membranes, it could be deduced that the release of ketoprofen from CH-PCL fibrous membranes possibly followed an anomalous mechanism involved both swelling and diffusion, which is somewhat similar to the case of ketoprofen-release from amphiphatic carboxymethyl chitosan-g-phosphatidylethanolamine beads described elsewhere (Prabaharan, Reis, & Mano, 2007).

Since n-values of CH-PCL fibrous membranes are close to 0.5 the release profiles of the membranes should be better to fit Higuchi model and thus more details about the ketoprofen release could be visualized. Data shown in Fig. 3 are thus plotted as fractional ketoprofen release versus square root of time and represented in Fig. 4. It is observed that (1) release behavior of ketoprofen from CH-PCL fibrous membranes can be well described by Higuchi model with correlation coefficients higher than 0.99; and the corresponding ketoprofen-release profiles exhibit biphasic characteristics. Of the two phases, the initially faster release phase lasts for various periods of time between 16 and 30 h, depending on PCL content in CH-PCLs, and the terminal release phase is significantly slowed down. The initial (k_1) and the terminal (k_2) release rate constants for each plot were calculated and they are also listed in Table 3. Fig. 2 shows that CH-PCL fibrous membranes reach their swelling equilibrium at around 20 h, and the turning-points in ketoprofen-release patterns in Fig. 4 change between about 16 and 30 h, potentially meaning that the initially faster release phase can be ascribed to a combination of ketoprofen release from surface and superficial layers of CH-PCL filaments, predominately controlling by a swelling mechanism; and the terminal release phase is due to the release of entrapped ketoprofen inside the hydrophobic domains of CH-PCL filaments, mainly governing by a diffusion-regulated mechanism.

Based on above examinations, it can be reached that some ketoprofen-loaded CH-PCL fibrous membranes are able to maintain required strength in wet state and their release behavior can be effectively controlled by the composition and diameters CH-PCL filaments, respectively, suggesting their potential applications in wound dressings with some therapeutic functions.

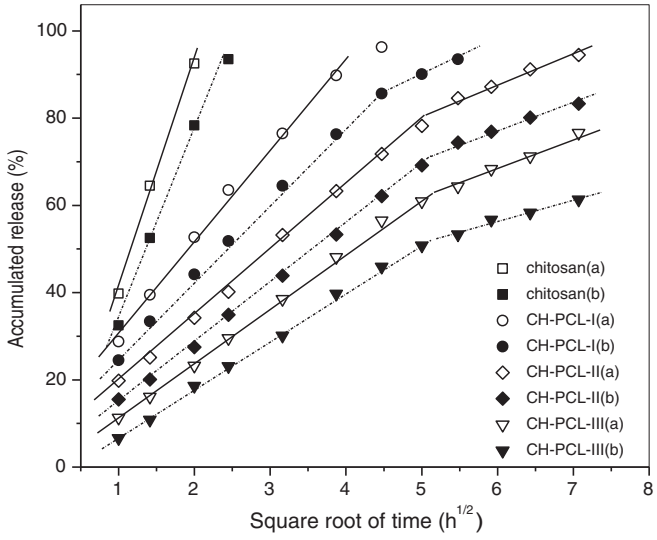

Fig. 4. Fractional ketoprofen release from different membranes versus square root of time (average diameters of filaments: around 100 μm (open symbols) and 200 μm (filled symbols); see Table 1 for other parameters).

4. Conclusions

The present technique was confirmed to be successful for sustained delivery of ketoprofen using chitosan-poly(ε-caprolactone) fibrous membranes as carriers. Some ketoprofen-loaded membranes built with selected chitosan-poly(ε-caprolactone) filaments could show significantly higher tensile strength in wet state as compared pure chitosan fibrous membranes, indicating they would be useful for the applications where basic mechanical strength in the wet state is required. The ketoprofen-loading efficiency for these membranes was distinctly dependent on the composition and average diameters of filaments as well as the ketoprofen-feed-ratios. The composition of the filaments governed swelling behaviors of the membranes while the average diameters of the filaments could impose a slight impact on the swelling of membranes. Release results showed that chitosan fibrous membranes were unsuitable for the sustained release of ketoprofen whereas chitosan-poly(ε-caprolactone) membranes had the potential to serve as desirable carriers for delivering ketoprofen in a sustained and controllable manner. Release patterns of chitosan-poly(ε-caprolactone) membranes basically followed Higuchi model with a biphasic characteristic, and the initially faster release phase could be controlled by a swelling mechanism while the terminally slower release phase was mainly governed by a diffusion-regulated mechanism.

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