International Journal of Pharmaceutics 419 (2011) 77–84

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Effects of amphiphilic PCL–PEG–PCL copolymer addition on 5-fluorouracil release from biodegradable PCL films for stent application

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ARTICLE INFO

Article history:
Received 26 April 2011
Received in revised form 14 June 2011
Accepted 14 July 2011
Available online 23 July 2011

Keywords:
Film
5-Fluorouracil
PCL–PEG–PCL
Poly(ε-caprolactone)
In vitro drug release

ABSTRACT

Biodegradable film-based stents emerged as a promising medical platform for drug delivery to resolve stenosis encountered in physiological conduits (e.g. blood vessels, biliary and urethral tracts). Drug release kinetics significantly affects the pharmacological effects of a stent, thus it is desirable for a stent to possess highly adjustable drug release kinetics. In this study, a series of amphiphilic poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL–PEG–PCL) copolymers were used as additives to adjust 5-fluorouracil (5-FU) release from PCL films. The effects of the copolymer addition on drug release behavior, drug permeability, crystalline states, and surface and internal morphologies of the films were investigated. It was found that, the addition of PCL–PEG–PCL could accelerate 5-FU release. The release rate of 5-FU increased with increasing content of PCL–PEG–PCL in the film, but it decreased with the ratio of PCL blocks in the PCL–PEG–PCL copolymer. The diffusion test results showed that 5-FU diffused through the film containing PCL–PEG–PCL faster than it permeated through the pure PCL film, indicating that the addition of PCL–PEG–PCL can improve the permeability of 5-FU in PCL film. The addition of PCL–PEG–PCL copolymer showed high drug-release-regulating ability in the 5-FU-loaded PCL films.

1. Introduction

Drug-eluting stents (DES) are widely used to support strictured or occluded physiological tubular structures such as blood vessels, biliary tract, and esophagus (Guo et al., 2007; Neyt et al., 2009). Although the current metallic DES have more advantages such as good deliverability, less invasiveness, effectiveness in reducing restenosis (Hogg et al., 2007; Watt et al., 2007), they still face critical challenges including restenosis, late thrombosis and inflammation (Moreno, 2005) due to their permanent presence. In order to overcome these limitations, biodegradable polymeric stents emerged as a promising alternative to metallic stents. Biodegradable stents is a new generation of stents, with the particular virtue of being easily eliminated by human body (Soares et al., 2010). In addition, biodegradable polymeric stents have good biocompatibility and can be readily loaded with drugs in the polymer bulk. The most widely used biodegradable polymers are PLA, PGA, PLGA, PCL and their copolymers (Yuki et al., 2010).

Previous studies indicated that addition of a second water-soluble additive into the biodegradable polymeric films can alter drug release rate and the degradation speed of the matrix (Rohera and Parikh, 2002; Siepmann et al., 2008; Tang et al., 2000). Amphiphilic polymers represent a new type of materials, which have been extensively used for biological and pharmaceutical applications (Patrickios and Georgiou, 2003). Thanks to the unique molecular structures characterized by concurrent presence of hydrophilic blocks (A) and hydrophobic blocks (B), amphiphilic polymers (e.g. AB diblock, ABA or BAB triblock) can self-assemble into nanoscale micelles which have been widely investigated for drug delivery (Adams et al., 2003; Mao and Gan, 2009). Poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL) have been widely used in biomedical and pharmaceutical applications (Chen et al., 2008; Richter et al., 2010), and poly(ε-caprolactone)-polyethylene glycol-poly(ε-caprolactone) (PCL–PEG–PCL) copolymers have been extensively studied for developing drug delivery systems, for example, drug-loaded hydrogel and nanoparticles (An et al., 2001; Gong et al., 2009; Gou et al., 2010; Huang et al., 2004).

Based on their amphiphilic attribute, we speculated that the hydrophilic and hydrophobic blocks of PCL–PEG–PCL copolymer may have different interactions with the drug or PCL molecules in the drug-loaded PCL matrix. Consequently, the mixture of amphiphilic PCL–PEG–PCL copolymers into the drug-loaded polymer matrix may alter the film physiochemical properties which manipulate the release of drug, providing an opportunity to optimize the drug release behavior. With this motivation, we designed a series of PCL films and mixed different contents of PCL–PEG–PCL copolymers into the films. 5-Fluorouracil (5-FU), a water-soluble antimetabolite drug which is widely used in the

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doi:10.1016/j.ijpharm.2011.07.020

treatment of a range of cancers, including pancreatic (Regine et al., 2006), breast (Coudert et al., 2006), and colon (Zhao et al., 2008) cancers, was used as the model drug and incorporated into the films. A variety of film properties, including the drug release behaviors, drug permeability, crystalline states, surface and internal morphologies, were examined to verify the effects of copolymers.

2. Materials and methods

2.1. Materials

PCL 80K (Mw = 80,000) was obtained from Shenzhen Bright China Industrial Co., Ltd. (Shenzhen, China). Polyethylene glycol (PEG, Mw = 20,000) was obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). 5-Fluorouracil was purchased from Nantong Jinghua Pharmaceutical Co., Ltd. (Nantong City, China) and micronized by a planetary ball-mill (Pulverisette 6, Fritsch, Germany) at a rotating speed of 250 rpm for 2 h. The size of 5-FU particles was in a range of 8–40 μm, determined by a laser granulometer (Analysette 22 Compact, Fritsch, Germany). All other chemicals were of analytical grade and used without further purification.

2.2. Preparations of amphiphilic copolymers and films

The amphiphilic PCL–PEG–PCL copolymers were synthesized by the solution polymerization of CL in the presence of PEG with stannous octoate as catalyst, according to a previous method (Zhang et al., 2007).

The films were prepared with a previous method (Lei et al., 2010). In brief, either PCL 80K only or mixtures of PCL 80K and PCL–PEG–PCL or PEG were added into the chamber of a HAAKE Rheocord System (Polylab OS, Thermo, America) and heated until they were completely melted. Then 5-FU particles were fed into the chamber and blended with molten PCL 80K at 70 °C with a rotating speed of 45 rpm for about 40 min. The resulting blends were further hot-pressed into films in a drying oven (DHG-9145A, Shanghai Yiheng Instrument, China) at approximately 100 °C for 5 min and then cooled to room temperature. The obtained films with a predetermined thickness were the drug-loaded films. The drug-free films were prepared in the same way but without the addition of drug.

2.3. Characterizations

2.3.1. ^1H NMR of the amphiphilic copolymers

A 400-MHz NMR spectrometer (Mercury) was used to obtain ^1H NMR spectra of the amphiphilic copolymers. The copolymer solutions in $CDCl_3$ were prepared at a concentration of 1% (w/v), with tetramethylsilane 0.03% (v/v) as an internal standard.

2.3.2. X-ray diffraction (XRD) analysis

XRD analysis of the films and 5-FU powders was conducted by an X-ray diffractometer (D/max-2200/PC, Rigaku Corporation, Japan) equipped with a Cu Kα radiation source (40 kV, 20 mA, λ = 0.15418 nm). 5-FU powders were pressed onto the sample holder to form a thin 5-FU layer, while films were directly placed on the sample holder. The samples were measured from 5° to 45° at a rate of 10°/min.

2.3.3. Scanning electron microscopy (SEM) of the films

The morphologies of the films were analyzed by a JSM-7401F scanning electron microscopy (SEM) (JEOL, Tokyo, Japan). For imaging the internal structures of the films, the cross-section of the films were obtained by freeze-fracturing the films in liquid nitrogen. Before imaging, samples were coated with gold using an Emitech K-575 Sputter Coater. Images were obtained at an accelerating voltage of 1 kV and a current of 20 mA.

2.4. In vitro release

Prior to in vitro release test, the drug-loaded films were cut into 1 cm × 1 cm squares, and then one side of the drug-loaded film square was sealed with a thin PCL layer. Each film was placed in a polyethylene tube containing 15 mL of phosphate buffered saline (PBS, pH 7.4). The tubes were placed in a shaking water bath at 37 °C and shaken at a speed of 65 rpm. At predetermined time points, the release medium was completely withdrawn and replaced with 15 mL of fresh PBS. 5-FU concentration in release medium was quantified by a UV spectrophotometry (Spectrumlab 54, Shanghai Lengguang Technology Co.) at 266 nm.

2.5. Horizontal diffusion test

The drug-free films were cut into discs of 2 cm in diameter. Each disc was clamped between a pair of side-by-side diffusion cells with an effective diffusion area of 1 cm^2. Of the two cells, one (the donor cell) was filled with 4 mL 5-FU saturated PBS (pH 7.4) with an excess of 5-FU drug suspended in the medium, and the other (the receiver cell) was filled with 4 mL of blank PBS. The temperature of the cells was maintained at 37 °C, and the media in two cells were stirred with magnetic stirring bars at a speed of 240 rpm. At predetermined time points, medium in the receiver cell was completely withdrawn and replaced with 4 mL of fresh PBS. 5-FU concentration in the medium from the receiver cell was measured in the same way as described in Section 2.4.

3. Results and discussion

3.1. Formulation of the copolymer-containing films

3.1.1. Synthesis and characterization of the amphiphilic PCL–PEG–PCL copolymers

Fig. 1 shows the ^1H NMR spectra of the synthesized amphiphilic PCL–PEG–PCL copolymers. The sharp single peak at 3.65 ppm can be assigned to the methylene protons of the oxyethylene unit from the PEG block. Meanwhile, the other four peaks at 4.05, 2.28, 1.61, and 1.36 ppm can be attributed to the methylene protons of the oxycarboxy-1, 5-pentamethylene unit of the PCL blocks (Fig. 1). By comparing the integration area ratio of the peak at 4.05 ppm (due to the PCL block) to that of the peak at 3.65 ppm (due to the PEG block with the molecular weight of 20,000), the final molecular weights of the three amphiphilic copolymers were calculated to be 22,000; 28,000; and 60,000. The three copolymers were denoted as PCL_{1000}–$PEG_{20,000}$–PCL_{1000} (Block1), PCL_{4000}–$PEG_{20,000}$–PCL_{4000} (Block2), $PCL_{20,000}$–$PEG_{20,000}$–$PCL_{20,000}$ (Block3), respectively.

3.1.2. Film compositions

The compositions of the drug-loaded and drug-free films are listed in Table 1. In general, three types (Block1, Block2 and Block3) and various contents (10–40%) of copolymers were added in the films. Also, films (Film 5-FU 40%–PEG 5% and 5-FU 40%–PEG 15%) containing 5% or 15% of PEG (without any PCL block) were also prepared as controls to investigate the differences between PEG- and PCL–PEG–PCL-containing films. For a fixed content (20%) of Block2, Films 5-FU 10%–Block2 20%, 5-FU 20%–Block2 20%, 5-FU 30%–Block2 20% and 5-FU 40%–Block2 20% were incorporated with 10%, 20%, 30%, and 40% of drug, respectively.

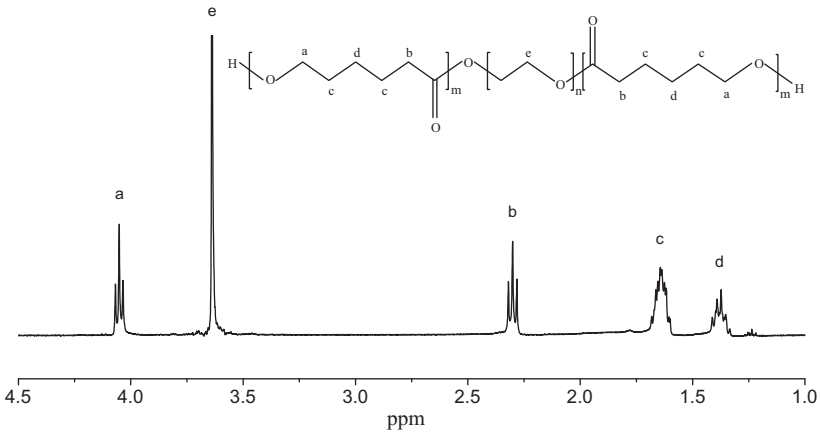

Fig. 1. ^{1}H NMR spectra of amphiphilic PCL–PEG–PCL copolymers.

3.2. Crystallinity of the compositions in the films

XRD analyses were performed to elucidate the crystalline states of the compositions in the films. 5-FU powder presented high crystallinity by its sharp and intense diffractive peaks at 29° with a series of weak peaks between 21° and 32° (Fig. 2A). These results were similar to those reported by previous studies (Yadav et al., 2010; Zhang et al., 2008). The XRD patterns of the 5-FU-loaded films also exhibited weak but typical peaks for 5-FU, indicating that the incorporated drug was still in its crystalline state. The drug-loaded films showed two characteristic peaks at 21° and 24° which were also presented by the PCL film (Fig. 2B), indicating that after the incorporation of drug PCL was still in a semi-crystalline state. Another interesting result shown in Fig. 2A was that with the increase of drug loading, the intensities of diffractive peaks for 5-FU increased but those for PCL decreased, indicating that the relative contents of 5-FU and PCL in the films could influence the crystalline states of the compositions in the films.

As shown in Fig. 2B and C, PEG exhibited two typical peaks at 19° and 23°, but the peak at 23° was difficult to distinguish from the peak of PCL at 24°. Therefore, the peak at 19° was used to evaluate the crystallinity of PEG in films. Films Block1 30%, Block2 30% and Block2 40% had weak diffractive peaks at 19°, demonstrating the crystalline state of PEG in the PCL films. The intensity of PEG peak increased with the increasing PEG block ratio in PCL–PEG–PCL copolymer and the copolymer contents in the films.

3.3. Drug release

3.3.1. Effect of PCL–PEG–PCL addition on the drug release

Amphiphilic PCL–PEG–PCL copolymer was used to regulate drug release for the films. PCL–PEG–PCL was expected to affect the drug release behavior by virtue of its special chemical structure with a hydrophilic block of PEG and two hydrophobic blocks of PCL. Three PCL–PEG–PCL copolymers were added in the films (e.g. Films 5-FU 20%–Block1 30%, 5-FU 20%–Block2 30% and 5-FU 20%–Block3 30%), and Fig. 3A displays the drug release profiles for the films. During the same release period, the cumulative amounts of drug released increased with the decreasing length of the PCL block in copolymers, indicating that the drug release can be regulated by altering the copolymer compositions. We also investigated the 5-FU release behavior of the films with different contents of Block2. Fig. 3B shows the 5-FU release curves for Films 5-FU 20%, 5-FU 20%–Block2 10%, 5-FU 20%–Block2 20%, 5-FU 20%–Block2 30% and

Table 1
Compositions of the films.

Sample	Drug-loaded films/drug-free films				
	PCL 80K (%)	PCL–PEG–PCL content (%)	PEG content (%)	Drug loading (%)	Thickness (μm)
Film Block2 40%	60	Block2 40	–	–	150
Film Block2 30%	70	Block2 30	–	–	150
Film Block2 20%	80	Block2 20	–	–	150/1000
Film Block2 10%	90	Block2 10	–	–	150/1000
Film 5-FU 20%–Block2 40%	40	Block2 40	–	20	2000
Film 5-FU 20%–Block2 30%	50	Block2 30	–	20	2000
Film 5-FU 20%–Block2 20%	60	Block2 20	–	20	2000
Film 5-FU 20%–Block2 10%	70	Block2 10	–	20	2000
Film 5-FU 10%–Block2 20%	70	Block2 20	–	10	2000
Film 5-FU 30%–Block2 20%	50	Block2 20	–	30	2000
Film 5-FU 40%–Block2 20%	40	Block2 20	–	40	2000
Film Block1 30%	70	Block1 30	–	–	150
Film 5-FU 20%–Block1 30%	50	Block1 30	–	20	2000
Film Block3 30%	70	Block3 30	–	–	150
Film 5-FU 20%–Block3 30%	50	Block3 30	–	20	2000
Film PEG 5%	95	–	5	–	150/1000
Film PEG 15%	85	–	15	–	150/1000
Film 5-FU 40%–PEG 5%	55	–	5	40	2000
Film 5-FU 40%–PEG 15%	45	–	15	40	2000
Film 5-FU 20%	80	–	–	20	2000
Film PCL	100	–	–	–	150

All the drug-loaded films were sealed on one of the two sides with a thin PCL layer 200 μm, to ensure the drug release from just one side.

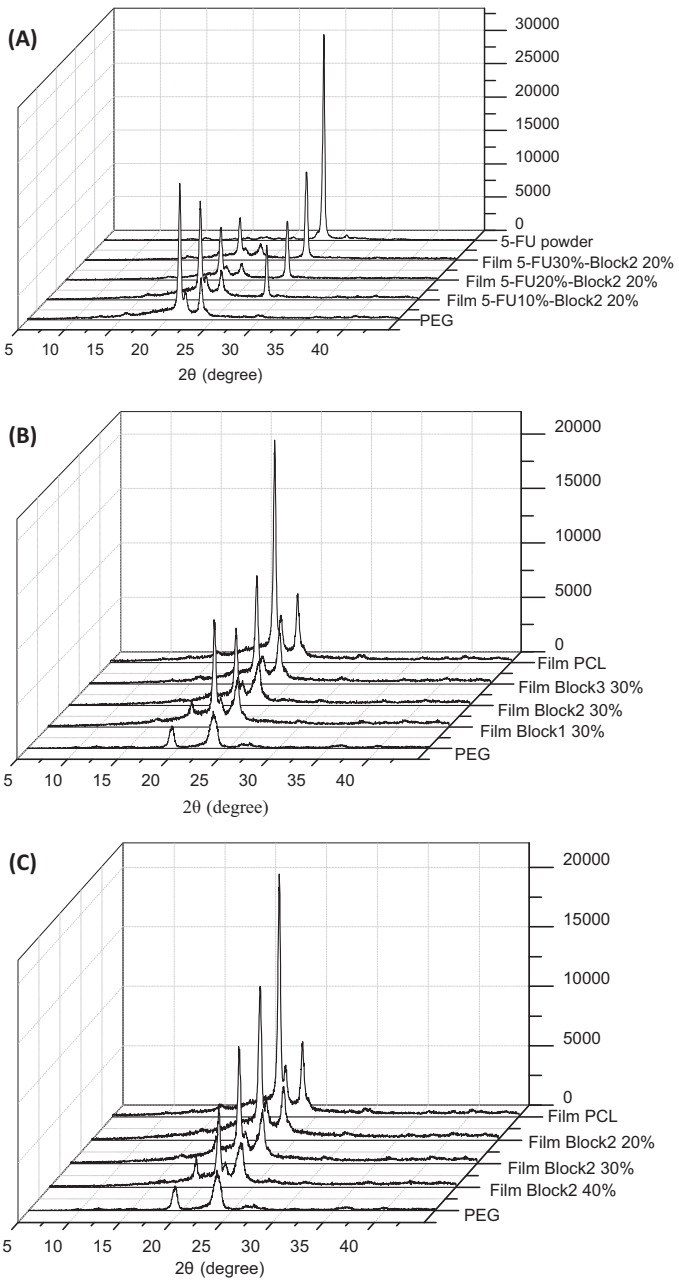

Fig. 2. XRD traces for PEG, 5-FU and all the films.

5-FU 20%–Block2 40%. The drug release rates increased with the Block2 contents (from 10% to 40%). As a comparison, Film 5-FU 20% (without any copolymers) released less than 10% of drug within 10 days (Fig. 3). It was noted that when the copolymer content reached 40%, the incorporated 5-FU could be released completely within just 16 h during which Film 5-FU 20%–Block2 40% disintegrated gradually, indicating that addition of too much copolymer in the stent film may substantially deteriorate the mechanical properties of the films.

3.3.2. *Different effects of PCL–PEG–PCL and PEG*

PEG is a hydrophilic polymer which has been widely used as additives to promote drug release from various matrix-based formulations (Cheng et al., 2010; Lei et al., 2010; Lu and Lin, 2002). In our test, both additive PEG and PCL–PEG–PCL promoted drug release, as indicated by the three release profiles of Films 5-FU 40%–Block2 20%, 5-FU 40%–PEG 5% and 5-FU 40%–PEG 15% (Fig. 4).

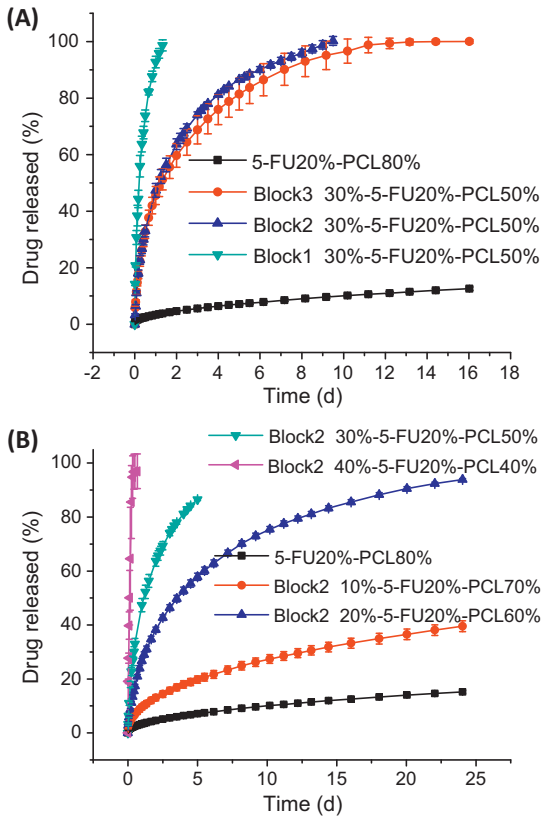

Fig. 3. (A) Drug release profiles of the 5-FU-loaded films with different amphiphilic copolymers (Block1, Block2, and Block3). (B) 5-FU release profiles for the films with and without Block2 content. (Mean ± SD, $n = 3$.)

For Film 5-FU 40%–Block2 20%, the absolute percentage of hydrophilic PEG block in the film is 14.3%, while that for Film 5-FU 40%–PEG 5% is 5%. The drug release for the former was faster than the latter, suggesting that the drug release rate increased with the increasing content of hydrophilic PEG block in film. Although the PEG percentage (14.3%) for Film 5-FU 40%–Block2 20% was very close to that for Film 5-FU 40%–PEG 15%, the drug release rate of the later was much faster than the former one, which indicated that hydrophobic PCL block in Film 5-FU 40%–Block2 20% may influence the effect of its hydrophilic PEG block. That is to say PCL–PEG–PCL may have less drug-release-promotion effect than PEG due to the presence of hydrophobic PCL block.

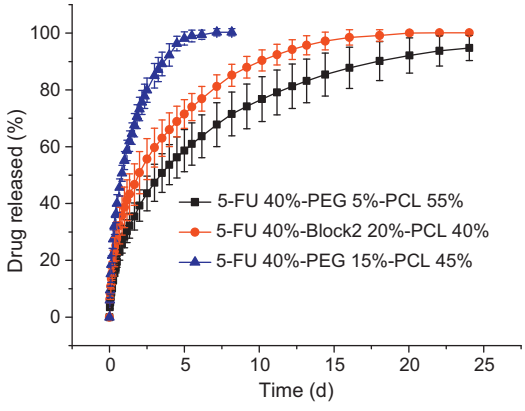

Fig. 4. Drug release profiles of the 5-FU-loaded films with the content of Block2 or PEG. (Mean ± SD, $n = 3$.)

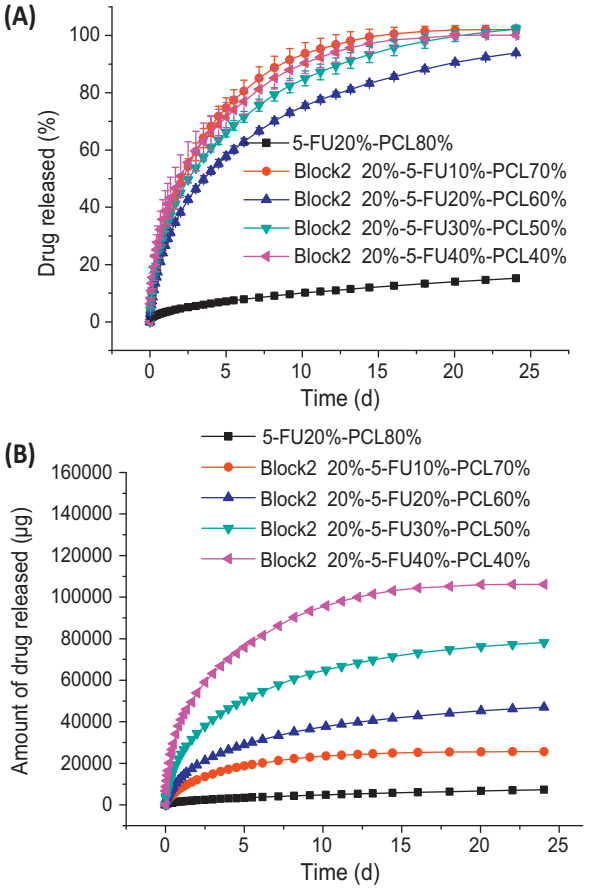

Fig. 5. (A) Drug release profiles of the films incorporated with different contents of 5-FU (10%, 20%, 30%, 40%, and 50%). (B) 5-FU release curves of the absolute amounts of drug released with different drug-loading in the films. (Mean ± SD, $n = 3$.)

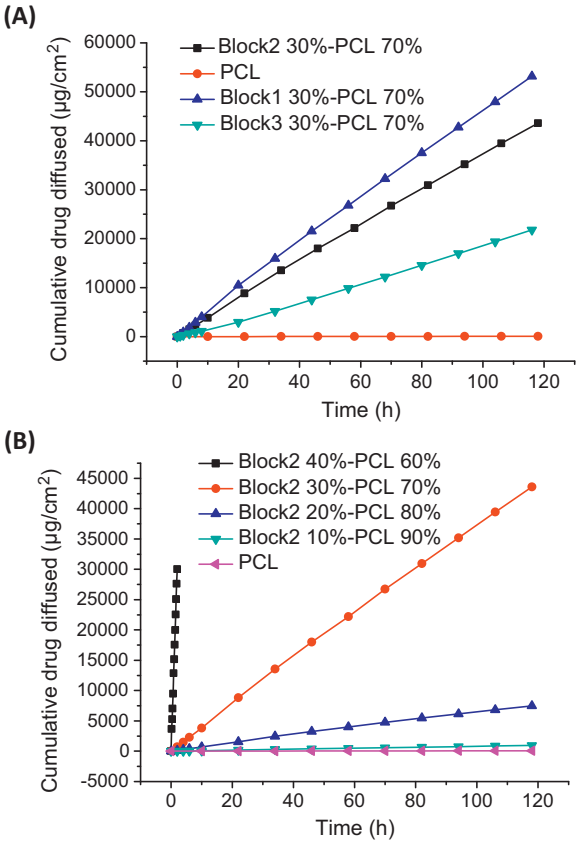

Fig. 6. (A) Cumulative 5-FU diffusion curves of the drug-free films with different amphiphilic copolymers. (B) 5-FU diffusion through the films with five contents of Block2 (0%, 10%, 20%, 30%, and 40%).

3.3.3. *Effect of drug loading on drug release study*

It has been reported in many studies that drug loading in the films had more or less effect on drug release behaviors (Jayant et al., 2011; Klose et al., 2010). Here we investigated the in vitro drug releases from films with different drug loading (10%, 20%, 30% and 40%). Fig. 5A shows an interesting result that the 5-FU loading has less effect on drug release behavior, because the films with different drug loadings had similar drug release profiles. However, it can be seen from Fig. 5B that the absolute amounts of drug released differed with the varying drug loading dose; higher 5-FU loading led to larger amount of drug released. These results suggest that it is feasible to adjust the in vivo drug concentration level by changing the initial drug loading dose in the film.

3.4. *Effect of PCL–PEG–PCL addition on film permeability to drug*

For slowly degrading PCL martix, the drug release is believed to be driven by the diffusion of drug molecules out of the matrix (Fu and Kao, 2010; Lei et al., 2011). In order to explore the effects of added PCL–PEG–PCL copolymer on drug diffusion through the films, a diffusion test was conducted to investigate the permeability of 5-FU through a variety of films by using a set of side-by-side diffusion cells. Fig. 6A displays the 5-FU diffusion curves of Films PCL, Block1 30%, Block2 30% and Block3 30%. It can be seen from Fig. 6 that the diffusion profiles for the films are linear, indicating that the diffusion rates of 5-FU through these films are relatively constant. The drug diffusion rates of 5-FU through the films depended largely on the film composition and higher diffusion rates could be obtained when copolymers with shorter PCL blocks were used. These diffusion results of such films were highly consistent with their drug release results shown in Fig. 3. Five contents of Block2 (0%, 10%, 20%, 30%, and 40%) were mixed into the PCL films (Fig. 6B), and it was found that the diffusion rates increased with copolymer contents in the films. When the block content in film reached 40% (Film Block2 40%), the cumulative amounts of drug diffused within the first 2 h was up to 30,000 μg/cm^2 due to the partial disintegration of film (Fig. 6B), which in turn explains the very fast release of 5-FU for Film 5-FU 20%–Block2 40% (Fig. 3B).

3.5. *Evolution of the surface morphologies and internal structures of films*

3.5.1. *Evolution of surface morphologies*

Figs. 7 and 8 show representative SEM images of the surface morphologies and internal structures of films. The surfaces of all the prepared films were relatively smooth before drug release test (Fig. 7A) or diffusion test (Fig. 7G). After drug release test, however, various numbers of pores emerged on the surfaces of the films due to the release of 5-FU particles located on or near the surface of the PCL films. What's more, Film 5-FU 40%–Block2 20% had far more pores on the surface than Film 5-FU 10%–Block2 20% (Fig. 7E and F) did, indicating that the number of microcavities on the surfaces increased with the initial drug loading of the films.

Although with the same 5-FU content, the surface morphologies of films with different compositions or contents of PCL–PEG–PCL copolymers are remarkably different. More pores were observed on the surface of Film 5-FU 20%–Block2 30% (with a higher copolymer content) compared to Film 5-FU 20%–Block2 10% (with a lower copolymer content) (Fig. 7B and C). Meanwhile, markedly larger

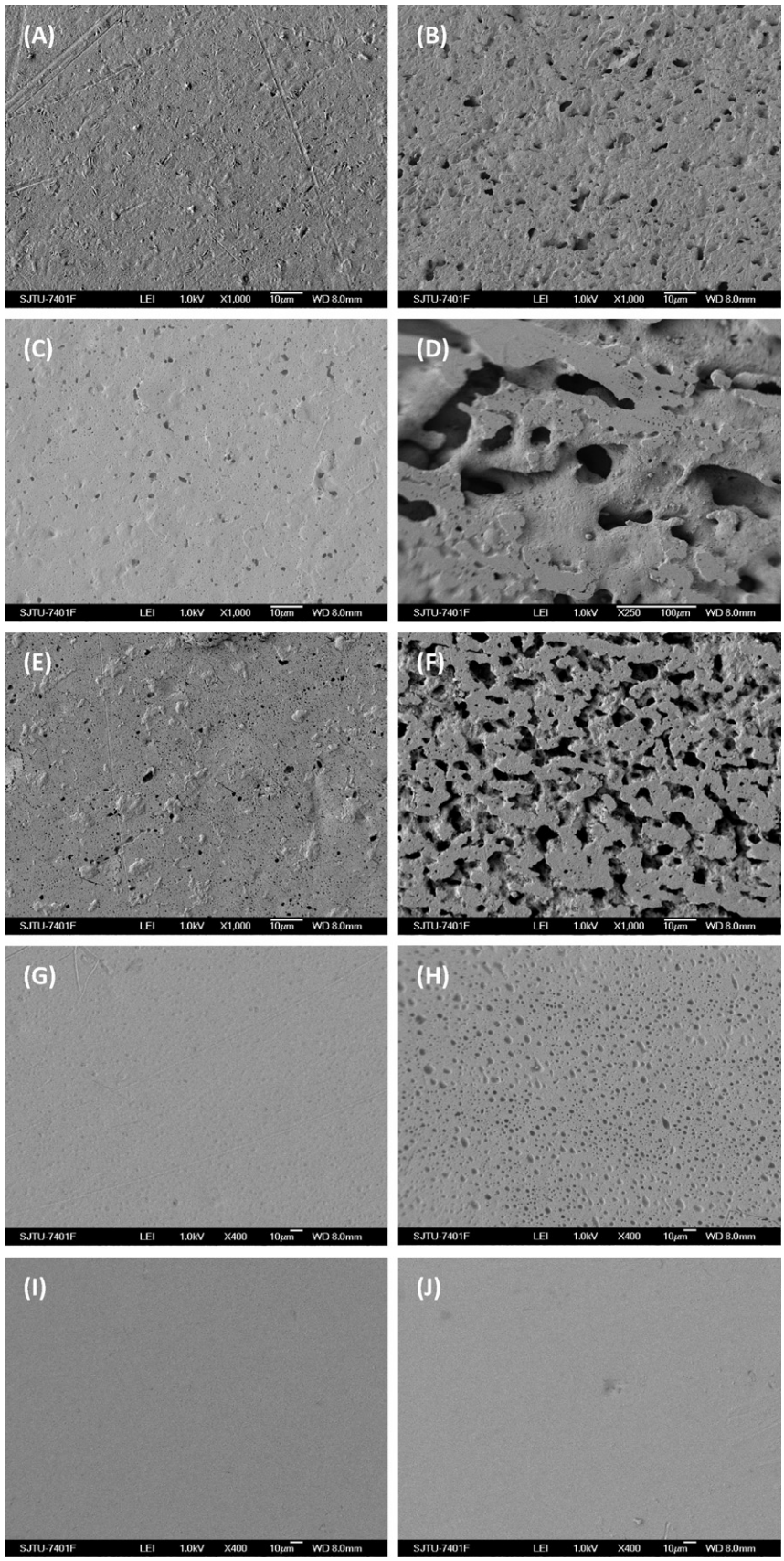

Fig. 7. Surface morphologies of the drug-loaded films before and after drug release test (A)–(F), the drug-free films before and after drug diffusion test (G)–(J): (A and B) Film 5-FU 20%–Block2 30% at 0d and 9d, respectively; (C)–(F) Films 5-FU 20%–Block2 10%, 5-FU 20%–Block1 30%, 5-FU 10%–Block2 20% and 5-FU 40%–Block2 20% at 36 d, 2 d, 24 d and 24 d, respectively; (G and H) Film 2 at 0 d and 5 d, respectively; (I and J) Films 4 and 14 at 5 d and 5 d, respectively.

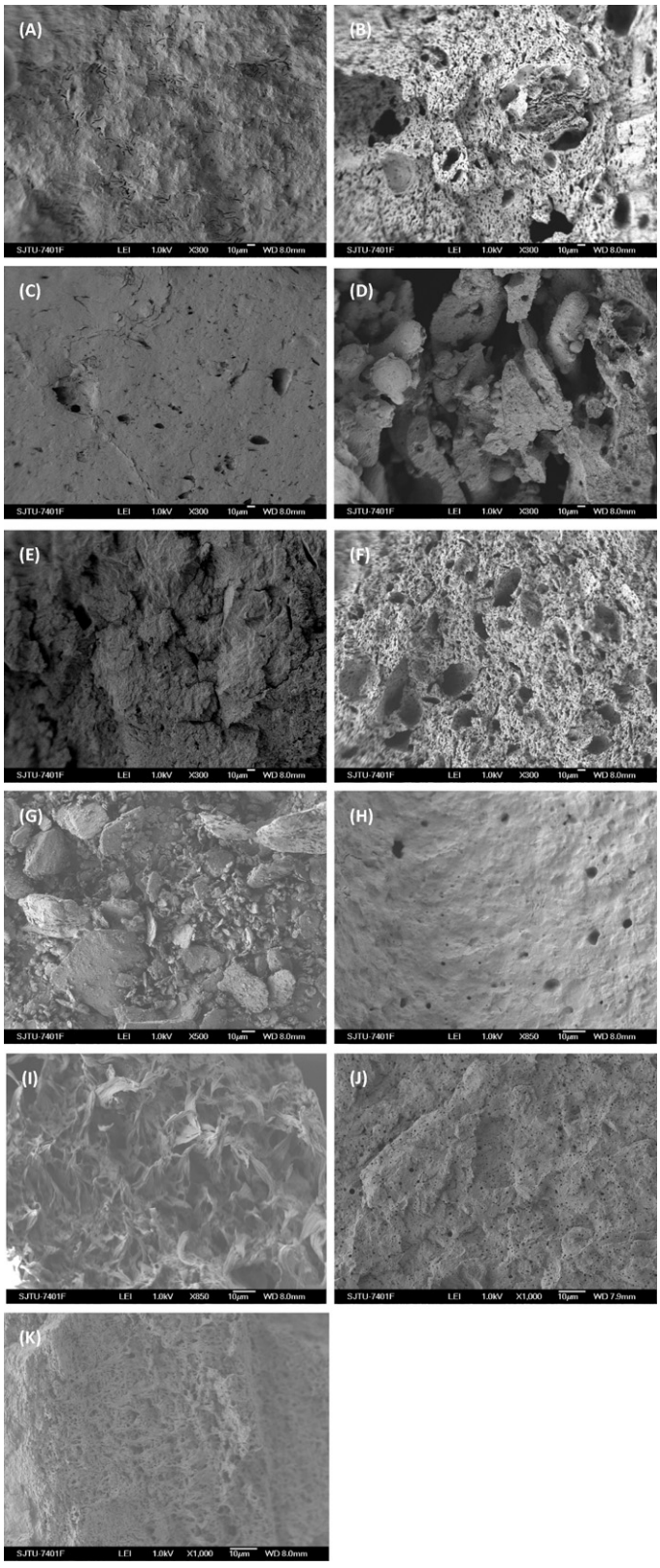

Fig. 8. Cross-section views of the drug-loaded films before and after drug release test (A)–(F), the drug-free films before and after drug diffusion test (H)–(K), 5-FU particles(G): (A and B) Film 5-FU 20%-Block2 30% at 0 d and 9 d, respectively; (C)–(F) Films 5-FU 20%–Block2 10%, 5-FU 20%–Block1 30%, 5-FU 10%–Block2 20% and 5-FU 40%–Block2 20% at 36 d, 2 d, 24 d and 24 d, respectively; (H and I) Film Block2 30% at 0 d and 5 d, respectively; (J and K) Films 4 and 14 at 5 d and 5 d, respectively.

pores appeared on the surface of Film 5-FU 20%–Block1 30% in comparison with Film 5-FU 20%–Block2 30% (Fig. 7D).

After diffusion test, the surfaces of Film Block2 10% (with a lower copolymer content) was still smooth (Fig. 7I), however, Film Block2 30% (with a higher copolymer content) presented a surface with many pores (Fig. 7H). Unlike the Film Block2 30% containing Block2, Film Block3 30% containing Block3 which had a longer PCL block did not present pores on the film surface (Fig. 7 J).

These observations indicate that the addition of PCL–PEG–PCL copolymers may lead to different morphological evolutions; the use of higher contents of copolymers and copolymers with lower PCL block ratios could produce more remarkable influences on the evolution of surface morphologies.

3.5.2. Evolution of internal structures

The cross-section of Films 5-FU 20%–Block2 30% and Block2 30% were relatively flat before drug release (Fig. 8A) and diffusion test (Fig. 8H), respectively. However, after drug release, many pores were observed (Fig. 8B–F). The sizes and shapes of the pores are very similar with those of 5-FU particles (Fig. 8G), indicating that the pores were left by the released 5-FU particles. On the other hand, the numbers of the pores in these films were different; Film 5-FU 40%–Block2 20% with higher drug loading (Fig. 8F) had more pores in the cross-section than Film 5-FU 10%–Block2 20% with lower drug loading (Fig. 8E).

The cross-sections for Films 5-FU 20%–Block2 30% (Fig. 8B) and 5-FU 20%–Block2 10% (Fig. 8C) also had great differences; more small voids appeared on the cross-section of film with a higher content of PCL–PEG–PCL (Fig. 8B). Many pores with very large sizes appeared in the cross-section of Film 5-FU 20%–Block1 30% (Fig. 8D), which could be attributed to the release of 5-FU particles and PCL–PEG–PCL. The formation of large pores explained the very fast drug release of Film 5-FU 20%–Block1 30% (Fig. 3).

Many small pores were also generated in the film cross-sections after diffusion test (Fig. 8I–K), and the number and size of the pores increased with the increasing copolymer content and decreasing length of PCL block in copolymer.

4. Conclusion

The mixing of amphiphilic PCL–PEG–PCL copolymers into PCL matrix-based films was demonstrated to be an effective strategy for regulating the drug release from PCL films. The length of hydrophobic PCL block in the PCL–PEG–PCL copolymer and the contents of copolymers in PCL films could significantly affect the release behaviors of 5-FU from the films. Compared to traditional PEG additive, PCL–PEG–PCL exerted a more flexible regulating effect on drug release due to the presence of two hydrophobic PCL blocks which may interact with the PCL matrix. The drug release rate of the film was demonstrated to be in direct relationship with the film's drug permeability which was in turn determined by the compositions and contents of PCL–PEG–PCL copolymers added in film. As a particular type of additive, amphiphilic PCL–PEG–PCL copolymer was shown to be a highly effective drug-release regulator for adjusting drug release from PCL matrix-based drug delivery system.

Acknowledgements

This work was funded by National Natural Science Foundation of China (NSFC) (Grant no. 30872554), Key Program of Shanghai Science and Technology Committee (Grant no. 10441902000) and 973 Project (Grant no. 2010CB529902). The authors would like to thank Instrumental Analysis Center of Shanghai Jiao Tong University for their technical support.

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