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Evaluation of two polymeric blends (EVA/PLA and EVA/PEG) as coating film materials for paclitaxel-eluting stent application

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Abstract The ethylene vinyl acetate copolymer (EVA)/Poly (lactic acid) (PLA) blend and EVA/Poly (ethylene glycol) (PEG) blend were applied as the drug carrier materials for a bi-layer drug-loaded stent coating film, which consisted of a paclitaxel (PTX)-loaded layer and a drug-free EVA layer. The changes of weight and appearance of the drug-free polymeric blend films with increasing time were examined by X-ray diffraction analysis (XRD), gel permeation chromatography (GPC) tests and scanning electronic microscopy (SEM), and the results showed the degradation of PLA and the leaching of PEG from the films. The effects of PLA, PEG and drug contents on in vitro drug release were investigated, and the results demonstrated that the addition of PLA promoted the drug release while the addition of PEG almost did not. Franz cells diffusion test results indicated that the bi-layer structure successfully endowed the stent coating with the release of drug in a unidirectional fashion. The release profiles of films incorporated PTX and the mechanical performance of the film could be customized by readily adjusting the contents of the blend components. Therefore, the polymeric blends could be useful drug carrier materials for drug-loaded stent coating capable of releasing drug in a highly tunable manner.

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1 Introduction

Stents have been widely used in treating the occlusion or stenosis of physiological tubular structures, such as esophagus, bile duct, prostate, urethral duct and blood vessel [1]. Because they could provide support or expanding the lumen and don't need open lumen with surgery, the patient's quality of life has been greatly improved. However, restenosis occurs frequently when stents are applied in benign or malignant stricture, many efforts, including coating the stents with biodegradable or bio-inert polymers and chemically modifying the surface [2, 3], have been made to improve the biocompatibility or to alleviate pathologic reactions of metallic stents.

More recently, drug-eluting stent (DES) was introduced to reduce incidences such as in-stent restenosis and complications. It was reported that the DES loading with the anti-proliferative compounds PTX and rapamycin has reduced the restenosis rate from 20–30% to 1–3% at 1 year in interventional cardiology [4]. Drug-loaded polymer-based coatings are commonly adopted as the drug reservoirs for DES to release drug in a period of several weeks or months. Many polymer-coated stents with antiproliferative drugs have been developed [5], and they can inhibit thrombus formation, inflammation or cellular proliferation relying on the drug released from the coatings [6]. Some of them have became commercially available, such as Cypher^{TM} and Taxus^{TM} [7].

PTX, a natural or semisynthetic alkaloid against a wide variety of tumors especially the ovarian and breast tumors [8], was used as the model drug and incorporated in the

tested films. PTX has anti-inflammatory, anti-angiogenic, and anti-proliferative abilities [9, 10], and it can attenuate stent-induced intimal thickening of lumen markedly [11]. Moreover, some studies have also demonstrated that PTX can prevent the formation of postsurgical adhesion which is a common and serious surgical problem [12].

EVA copolymer is a heat-processable, flexible and inexpensive material. Due to its safety and biocompatibility, EVA has been used as a biomaterial for artificial heart application and for delivering drug to treat thrombosis diseases for an extended period of time [13]. In addition, EVA has also been used as a drug carrier material for biomedical implant, stent and other drug delivery devices for treating oral infections [14–17].

Generally, the coating materials of DES are mainly non-degradable or biodegradable polymers, such as EVA, PLGA and PCL. However, few studies have reported the application of various polymeric blends as the coating material. In this study, we employed the PLA/EVA blend and PEG/EVA blend as coating film materials and designed a unique type of stent coating film (stent-covering membrane) which consisted of a drug-loaded layer and a drug-free EVA-alone backing layer. This stent coating contacts the tissue wall by its drug-loaded layer side, with the drug-free EVA-alone layer side facing the stent lumen. To ensure the consistency in geometry of the coating film with the stents, the coating film can be on-site formed on the metallic stent by repeatable dip-dry method; alternatively, the metallic stent can be wrapped with the coating film with a custom-made dimension. In the present work, the influences of additives PLA and PEG on the mechanical properties, dynamic evolution of film appearance, and drug release profiles were presented. The relationship between blend component contents as well as drug loading dose and the performance of the coating films was also discussed with respects of the mechanical properties, crystallites and drug release behaviors.

2 Materials and methods

2.1 Materials

EVA copolymer with vinyl acetate content of 42% (w/w) and melt index of 1 g/min was purchased from Shanghai Research Institute of Chemical Industry (China). PEG with a molecular weight of 6000 g/mol was obtained from Chinese Medicine Group (Shanghai, China). PLA (M_w = 121.5 kDa, polydispersity = 1.197) was from Nature Works LLC, USA. PTX (PTX) was obtained from Xi'an Haoxuan Biological Technology Co., Ltd (Xi'an, China). All other reagents were analytical grade and used as received.

2.2 Preparation of coating film

Two kinds of films were prepared in this work: a single-layer drug-free coating films and a bi-layer drug-loaded coating films. The bi-layer films contained an EVA-alone backing layer and a drug-loaded layer based on the polymer blends. A solution-cast method was used for the preparation of the coating films. For preparation of the bi-layer film, 1.5 g of EVA copolymer beads was well dissolved in dichloromethane, and then the solution was poured onto a glass Petri dish, dried for 5 h in a ventilation cabinet at room temperature. After the formation of an EVA film in the glass Petri dish, the formulation solution for the drug-loaded layer consisting of EVA, PTX and PLA or PEG was directly poured onto the formed EVA film in the glass Petri dish, dried for 24 h in a ventilation cabinet at room temperature to evaporate the solvent. After that, the bi-layer films were removed from the dish and dried at 25°C under vacuum for 48 h till constant weight. The preparation methods of the single-layer drug-free coating films were similar with those of the bi-layer films only without the preparation of the second layer. The compositions of all the films were listed in Table 1.

2.3 Determination of drug content uniformity

Several samples (1 cm × 1 cm) were randomly cut from a film, and then accurately weighed. Then each sample was cut into small pieces and transferred to a 10 ml volumetric flask containing 8 ml of methanol, and extracted at 37°C for 4 h. Subsequently, the extraction solution was sonicated for 10 min. After cooling down, the flask was brought up to the mark with methanol and then mixed well. PTX concentration in the obtained solution was analyzed by HPLC, and the real drug contents in the films were then calculated. The drug uniformities of the films were evaluated by the standard deviation (SD) values of the drug contents in the randomly cut square samples from the film.

2.4 Weight loss test

The single-layer drug-free coating films (Film11–17 in Table 1) were accurately weighed to determine the initial mass of the films, W_0. Then each sample was placed in a 50 ml tube containing 50 ml distilled water. The tubes were put in an orbital shaker bath at 37°C with a shaking speed of 75 rpm. The phosphate buffer solution was not used in the test because the salt in the PBS was difficult to wash away thoroughly, which could affect the accurate weight measurement of the films. At predetermined time intervals, the samples were withdrawn from the tubes, washed with distilled water gently, wiped with filter paper and dried at 25°C under vacuum for 48 h. Then the dry

Table 1 Compositions of the coating films

	Samples	Drug layer			Backing layer
		Drug loading (%)	Polymer content (%)	Polymer composition	
PTX-loaded films[a]	Film 1	10	90	30% PLA + 70% EVA	100% EVA
	Film 2	20	80	30% PLA + 70% EVA	100% EVA
	Film 3	30	70	30% PLA + 70% EVA	100% EVA
	Film 4	20	80	50% PLA + 50% EVA	100% EVA
	Film 5	10	90	10% PEG + 90% EVA	100% EVA
	Film 6	20	80	10% PEG + 90% EVA	100% EVA
	Film 7	30	70	10% PEG + 90% EVA	100% EVA
	Film 8	20	80	5% PEG + 95% EVA	100% EVA
	Film 9	20	80	15% PEG + 85% EVA	100% EVA
	Film 10	20	80	100%EVA	100% EVA
Drug-free films[b]	Film 11	–	100	10% PLA + 90% EVA	–
	Film 12	–	100	30% PLA + 70% EVA	–
	Film 13	–	100	50% PLA + 50% EVA	–
	Film 14	–	100	5% PEG + 95% EVA	–
	Film 15	–	100	10% PEG + 90% EVA	–
	Film 16	–	100	15% PEG + 85% EVA	–
	Film 17	–	100	100% EVA	–

[a] PTX-loaded film is the bi-layer drug-loaded coating film

[b] Drug-free film is the single-layer drug-free coating film

mass, W_1, of each film were measured immediately. The degree of weight loss (wt%) was calculated using the following equation: Weight loss (wt%) $= [(W_0 - W_1)/W_0] \times 100\%$.

2.5 X-ray diffraction analysis (XRD)

X-ray diffraction (XRD) patterns of the samples were obtained using an X-ray diffractometer (D/max 2200, Rigaku, Japan) equipped with a Cu-Kα radiation source (40 kV, 20 mA). The samples (1.5 cm × 1.5 cm) were cut from the coating films and placed in a steel holder and scanned at the rate of 5°/min over a 2θ range of 2.5–40°.

2.6 Scanning electron microscopy (SEM)

The coating films were imaged by a JSM-7401F scanning electron microscopy (SEM) (JEOL, Tokyo, Japan). Prior to imaging, all the samples were placed on a metal sample holder and sputter coated (Emitech K-575 Sputter Coater) with a gold–palladium target for 30 s at 20 mA. Images were obtained at 5 kV accelerating voltage and 20 mA current.

2.7 Gel permeation chromatography (GPC)

About 8 mg of sample was well dissolved in tetrahydrofuran and filtered through 0.45 μm Nylon filters before analysis. The GPC analyses were performed at 40°C using a Waters HPLC system equipped with a model 1525 binary HPLC pump, a model 2414 refractive index detector, and a series of Styragel columns (HR3 and HR4). Tetrahydrofuran was used as the eluent at a flow rate of 1.0 ml/min. The GPC system was calibrated with polystyrene standards.

2.8 In vitro drug release

The bi-layer drug-loaded coating films (Film1–10 in Table 1) were cut into discs with a diameter of 1 cm. Each disc was placed in a 15 ml tube containing 15 ml phosphate buffer solution (PBS, pH 7.4) with 1% v/v tween80 to keep sink conditions. And then the tubes were put in an orbital shaker bath at the temperature of 37 ± 0.5°C and shaken at the rate of 75 rpm. At predetermined time intervals, the release medium was completely withdrawn and replaced by an equal volume of fresh PBS medium. The collected release medium was subjected to HPLC for drug concentration determination.

2.9 Franz cells diffusion

Permeations of PTX through EVA backing layer and from the drug-loaded layer was examined by using the Franz diffusion cells which provided an effective diffusion area of 1.77 cm^2. The coating was clamped between the cell cap and receptor compartment, with either the backing layer or the drug-loaded layer facing the receptor compartment

respectively. The cell was maintained at 37°C in a water bath and stirred constantly at 250 rpm. At predetermined time points, the whole solution in the receptor compartment was withdrawn and replaced with fresh PBS solution and then analyzed by HPLC.

2.10 High-performance liquid chromatography (HPLC)

The amount of PTX was analyzed by an HPLC system equipped with a variable wavelength UV–vis detector (SPD-10ADvp, Shimadzu, Japan). A pump (model LC-10AD, Shimadzu, Japan) was used at a constant flow rate of 1.0 ml/min. A C-18 reversed-phase column (4.6 mm × 250 mm, 5 μm, Dikma Technologies, Beijing, China) was used for the analysis. The mobile phase was a mixture of methanol and ultra filtrated water (75/25, v/v). The wavelength was set at 227 nm and column temperature at 30°C. The linear range for the quantification of PTX was 1–100 μg/ml ($R^2 = 0.9996$).

2.11 Measurement of mechanical properties

The tensile properties of the coating films were measured using a universal electromechanical tester (Instron 4465, Instron Corp., USA) at 20°C. The films were cut into sample strips, about 50 mm long, and 4 mm wide at the center, and thickness of each sample was measured with an electronic micrometer. The unidirectional tension speed was 50 mm/min. Three repetitions for each sample were performed in the test. The tensile strength, elastic modulus and elongation of the films were recorded.

3 Results and discussion

3.1 Characterization of the coating films based on PLA/EVA blends and PEG/EVA blends

3.1.1 The appearances and microstructures of the coating films

The compositions of the coating films are listed in Table 1. Generally, all the PTX-loaded films were bi-layer films with a backing layer, while the sing-layer drug-free films without. The thicknesses of the single-layer drug-free coating films (Film 11–17) and the bi-layer drug-loaded films (Film 1–10) were approximately 250 and 450 μm, respectively.

The surface appearances of all the films are shown in Fig. 1. In general, the surfaces of the films were smooth and flat by visual observation. At a high magnification by SEM, it could be seen that some additional flakes (Fig. 1f) were dispersed on the surface of Film 10 loaded with drug compared with Film 17 without drug (Fig. 1c), and the flakes disappeared after incubation in release medium for 63 days (Fig. 1j). This suggested that the flakes were probably the PTX located on the film surface and that for EVA-based film, PTX could not be well trapped in the film matrix during preparation. However, no PTX flakes in Films 4 and 7 based on EVA/PLA blend and EVA/PEG blend, respectively, were observed (Fig. 1d, e, respectively), indicating that PTX was well entrapped in the films based on blends. The drug-loaded and drug-free films based on EVA/PLA blend and EVA/PEG blend presented different surface morphologies (Fig. 1a, b, d, e), and there existed many regular structure units. This could be due to the different compatibilities of the corresponding film components, i.e., EVA, PLA, PEG and PTX.

3.1.2 The physical states of the components in the tested coatings film

The XRD patterns of EVA, PLA, PEG, PTX and the films with various compositions are shown in Fig. 2. EVA did not show any obvious diffraction peaks, confirming its amorphous nature [18, 19]. The PLA also did not display any XRD diffraction peaks, suggesting the amorphous state of PDLLA used [20]. PEG displayed two distinct peaks at 19.24 and 23.42° [21], and these peaks became weak in the film based on EVA/PEG blend. The result implies that most of the PEG in the EVA matrix presented in an amorphous form. Besides, from the SEM image (Fig. 1b), it can be seen that some incompatible PEG was on the surface of the film based on EVA/PEG blend. This in turn suggested the existence of crystalline PEG, which is consistent with the weak XRD peaks for PEG. PTX powers are crystalline and exhibits several intense peaks at 5.6, 9.9 and 12.7°, as also reported by Cavalcanti et al. [22]. However, there were not any PTX peaks in PTX-loaded films based on EVA/PLA blends and EVA/PEG blends, whereas weak PTX peaks appeared in the film based on EVA alone. Therefore, it was indicated that the drug was dispersed at molecular level or dispersed in an amorphous state and that some PTX crystals existed on the surface of the PTX-loaded film based on EVA alone. These results were consistent with the SEM observations as discussed above.

3.1.3 Drug content uniformity

The content uniformity of PTX in the PTX-loaded films was determined with the method reported by the paper [23] to verify the drug loading performance of the coating films based on the blends. The drug uniformity of a film was denoted by the standard deviation (SD) values for the determined drug contents of ten randomly cut square

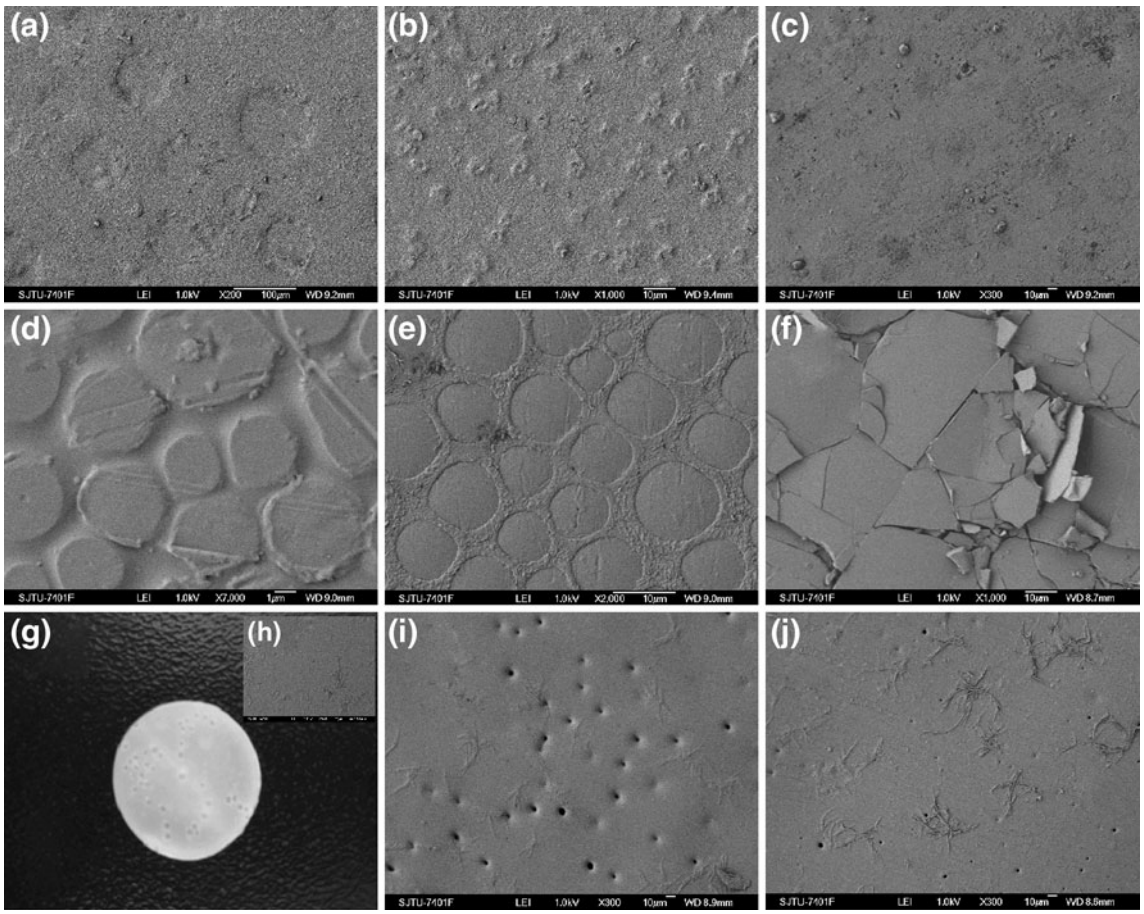

Fig. 1 SEM images: the surfaces of Films 13, 15, 17, 4, 7 and 10, respectively (**a–f**, respectively), and the surfaces of Films 4, 7 and 10 after incubation in the release medium for 63 days, respectively (**h**, **i**, **j**, respectively); macroscopic image of Film 4 after incubation in the release medium for 63 days (**g**)

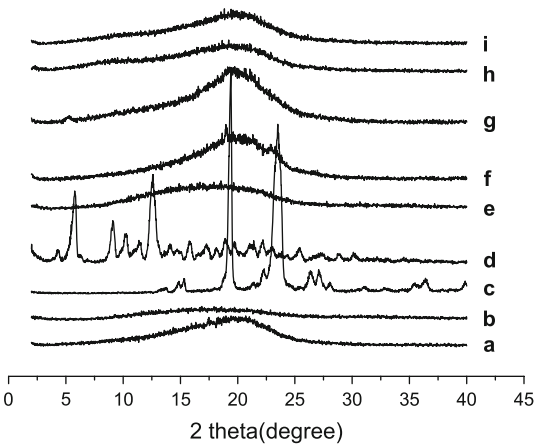

Fig. 2 X-ray diffraction patterns of pure EVA (**a**), pure PLA (**b**), pure PEG (**c**), pure PTX (**d**) and Films 13, 16, 10, 4 and 9, respectively (**e**, **f**, **g**, **h**, **i**)

samples (1.5 cm × 1.5 cm) from the film. A smaller SD value indicates a better drug uniformity. The results manifested that the determined drug contents were close to the predefined drug content values and the calculated SD values were all less than 3.0%, suggesting that PTX is dispersed homogeneously throughout the films. It demonstrated that the preparation methods for the films were stable and reliable, and that the blends could be used to generate a homogeneous drug/polymer matrix system.

3.1.4 Mechanical properties of stent coatings

As listed in Table 2, the results of the tensile test gave an indication of the strength and elasticity or flexibility of the coating films, reflected by the mechanical parameters of maximum tensile strength, maximum elongation and elastic modulus. EVA is an elastic, flexible and tear-resistant material. After being blended with PLA or PEG, the mechanical properties of the formed EVA/PLA and EVA/PEG blends were in some degree different with those for EVA alone, depending on the film compositions. The maximum tensile strength and maximum elongation decreased with the increase of the PLA content whereas the tensile modulus showed a remarkable increase. The film

Table 2 Tensile test results for films with various compositions and drug loadings

	Sample	Maximum tensile strength (MPa)	Maximum elongation (%)	Elastic modulus (MPa)
Drug-free film	Film 11	13.00 ± 2.61	832.22 ± 66.98	284.85 ± 20.56
	Film 12	10.08 ± 1.74	727.77 ± 46.86	1073.65 ± 39.53
	Film 13	6.56 ± 2.82	582.22 ± 56.79	1932.19 ± 82.37
	Film 14	19.77 ± 1.05	840.00 ± 52.38	1.70 ± 0.12
	Film 15	17.23 ± 0.45	886.66 ± 2.01	2.31 ± 0.68
	Film 16	14.86 ± 1.44	855.56 ± 45.50	2.33 ± 0.29
	Film 17	20.07 ± 1.20	860.22 ± 9.42	1.55 ± 0.56
PTX-loaded film	Film 5	16.77 ± 0.55	836.66 ± 18.46	2.84 ± 0.069
	Film 6	15.43 ± 0.61	820.01 ± 10.02	4.55 ± 0.50
	Film 7	13.33 ± 0.40	681.11 ± 17.10	7.67 ± 1.42

with a high content of PLA (50%) was much less flexible. However, the addition of PEG did not change the mechanical properties of EVA very much with respect of maximum elongation, maximum tensile strength and elastic modulus. This may be attributed to the low contents of additive PEG.

For the PTX-loaded films, drug particles in the film had impact on the mechanical properties. It can be seen from Table 2 that the increase of drug content in the films led to the decrease of maximum tensile strength and maximum elongation and the increase of the elastic modulus. These obtained mechanical parameter values of the coatings are comparable to those of the 5-fluorouracil-loaded EVA coatings reported by a previous paper [15], which demonstrated that even the EVA coating with a very high drug loading of 60% could keep intact without cracking or peeling off from the stent after bound and deployed many times. Therefore, it was justifiable to conclude that the films were flexible and stable enough for stent deployment.

3.2 Evolution of the films based on EVA/PLA or EVA/PEG blend in water

3.2.1 The weight changes of the films based on blends

The weight change curves of single-layer drug-free coating films (Film 11–17) based on various blends were shown in Fig. 3. As presented in Fig. 3, the weight losses of both films based on EVA/PLA blends and EVA/PEG blends increased with time. The weight losses of the films exhibited significant PLA or PEG content-dependence, as the weight loss of films increased with the increasing PLA or PEG contents. For the films based on EVA/PLA blends, larger weight loss happened in the first 4 days and then the weight decreased slowly. With a low PLA content, Film 11 underwent no evident weight loss; while Film 13, with a high PLA content, underwent a weight loss of up to 7%

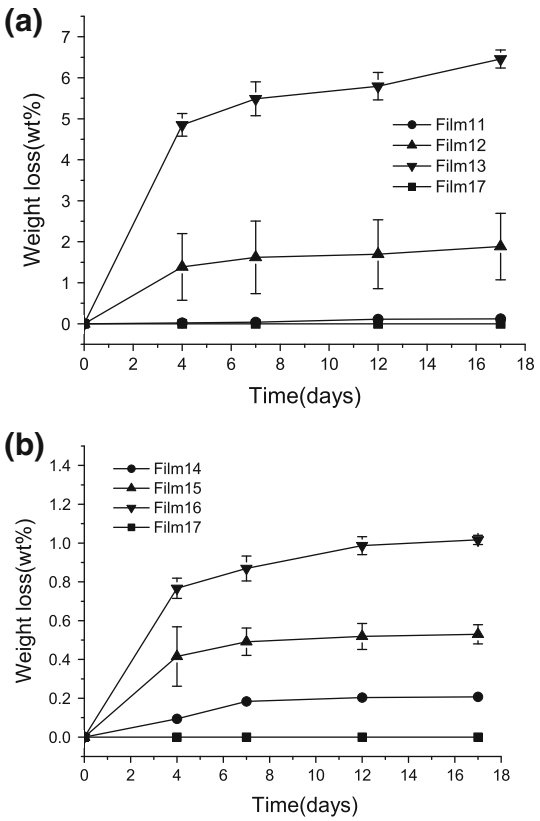

Fig. 3 In vitro weight loss profiles of drug-free coating films with various PLA contents (0, 10, 30, and 50%) (**a**) and various PEG contents(0, 5, 10 and 15%) (**b**)

during the investigation period. It should be noted that Film 17 (based on EVA alone) underwent nearly no weight loss during the investigation period. It was speculated that the weight loss was attributed to the degradation and leach of the PLA blended in the films.

As shown in Fig. 3b, Films 14–16 (based on EVA/PEG blends) almost underwent no weight changes after the rapid weight decrease during the beginning stage. It indicated

that it was difficult for the internal PEG to leach out from the films after the initial quick leach of superficial PEG on the surface of the films. In comparison with the weight losses for Films 11–13 based on EVA/PLA blends, Films 14–16 underwent smaller weight loss. This may be due to the lower contents of PEG compared with higher contents of PLA in the films. A smaller percentage of additives (PLA or PEG) could be better entrapped by the larger percentage of EVA.

3.2.2 *The appearance changes of the films*

The appearances of the single-layer drug-free films before and after immersion in distilled water were recorded by digital camera and are shown in Fig. 4. The surfaces of all the films before immersion in water were smooth and relatively transparent (Fig. 4a, c, e). But after immersion in water for 25 days, the surfaces of the films displayed different morphologies. For Film 11 (based on EVA/PLA blends, with a low PLA content of 10%), as shown in Fig. 4b, there appeared many small bubbles in the films after immersion in water. The bubbles in the films may be the voids generated by the degradation and shrinking of the PLA phase in the EVA matrix. As a contrast, for Film 13 with a high PLA content of 50%, there appeared many small open holes on the surface of the film (Fig. 4d). These holes should be attributed to the degradation and erosion of PLA in the films. However, for Film 15 based on PEG/EVA blend, there did not appear any bubbles or holes like those for Films 11 and 13 on the surface after immersion in distilled water for 25 days (Fig. 4f). It was speculated that PEG and EVA were relatively compatible in the films and the leach of PEG occurred at molecular or microscopic level, thus no macroscopic bubbles or holes could be observed.

3.2.3 *The crystallinity changes of the films*

The XRD spectra of Film 13 based on EVA/PLA blend before and after immersion in distilled water for 25 days are displayed in Fig. 5. After immersion in distilled water for 25 days the crystallinity of the film was enhanced evidently, compared with that of the film before immersion. This can be explained by the findings by Miyajima

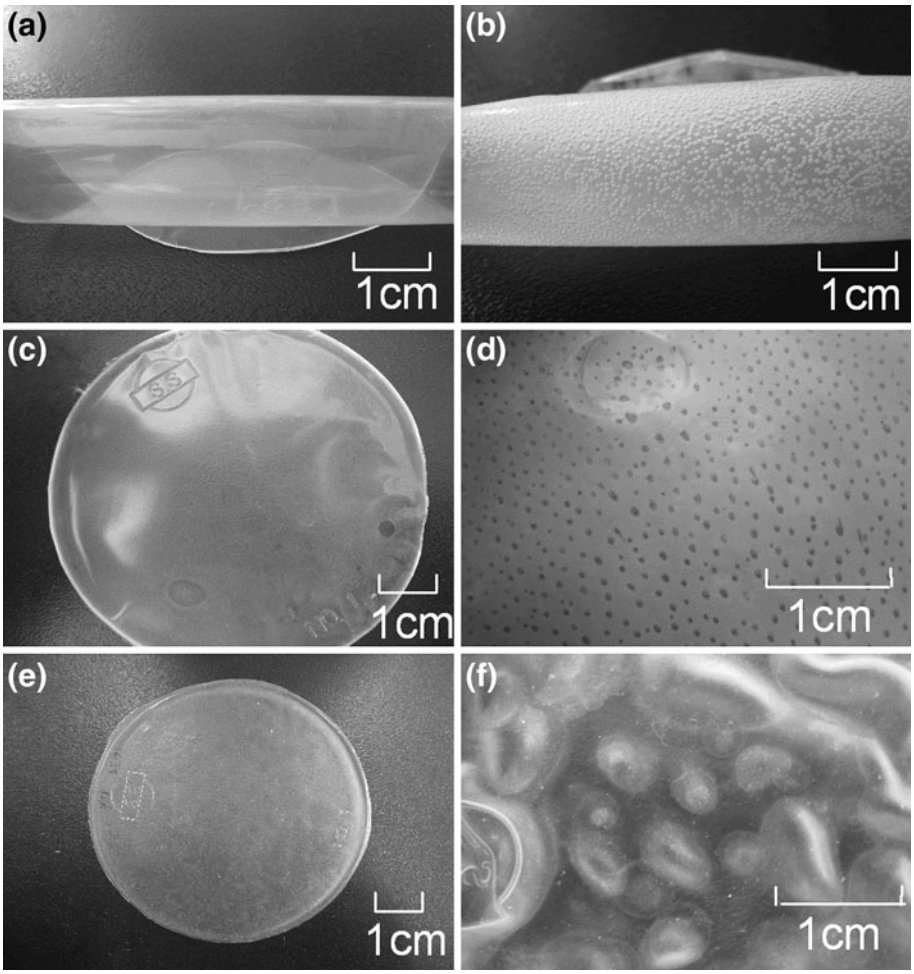

Fig. 4 Macroscopic images of the surfaces of Films 11, 13 and 15 before (**a**, **c**, **e**, respectively) and after (**b**, **d**, **f**, respectively) the immersion in distilled water for 25 days

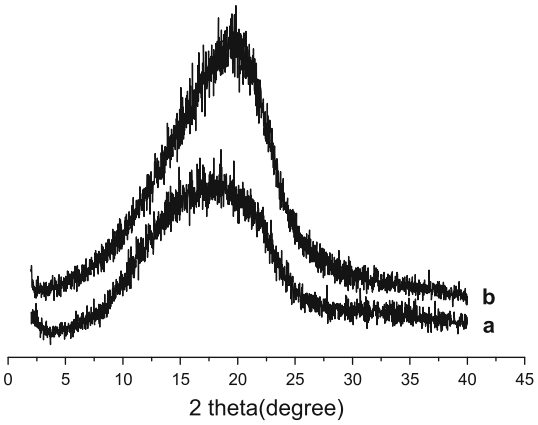

Fig. 5 XRD patterns of Film 13 before (**a**) and after (**b**) immersion in distilled water for 25 days

et al. [24] and Park et al. [25] that the degradation of amorphous PLA could increase the crystallinity due to the production of PLA with lower molecular weight and shorter chains which was more mobile and more susceptible to crystallize than longer ones. The results also confirm that the PLA in the films underwent degradation during the immersion.

However, the crystallinities of films based on PEG/EVA blends showed no significant changes after immersion in distilled water for 25 days, except that an above-mentioned weak peak in Fig. 2f, which was contributed by the PEG on the surface of the film, disappeared.

3.2.4 The retention of PEG in the film

GPC results showed that EVA and PEG exhibited different peaks in the GPC spectra due to their different molecular weights, as showed in Fig. 6a, b, respectively. Thus the corresponding two peaks appeared in the GPC spectrum (Fig. 6c) for Film 16 based on EVA/PEG blend could be used to indicate the existence of EVA and PEG, respectively. After immersion in water for 25 days, the two peaks for EVA and PEG still existed in the GPC spectrum (Fig. 6d). Therefore, this result indicated that PEG still existed in the film even after immersion in water for 25 days. In other words, it was hard for the PEG to leach from the film, which is consistent with of the above weight change test results and appearance changes of the films based on EVA/PEG blends.

3.3 Evaluation of in vitro release performance

3.3.1 Unidirectional drug release of the double-layer coating films

In practical application, the drug loaded in a stent coating is expected to be delivered to the diseased tissue wall, thus it is necessary to block the undesirable release towards the lumen of the stent. In this study, a double-layer structure design of the stent coating film, i.e., a combination of a drug-loaded layer and a drug-free bank layer, was employed to achieve a unidirectional drug release pattern. To check if this double-layer film realized a unidirectional drug release, drug release from the two sides of the film were examined using Franz cells. From Fig. 7, it can be seen that the cumulative amount of PTX released through the drug-free bank layer of the double-layer stent coating is more than 50 times lower than that released from the drug-loaded layer side. The cumulative amount of PTX released through the drug-free bank layer at 11 days is just about 20 μg, which is very small. Thus, it can be considered that

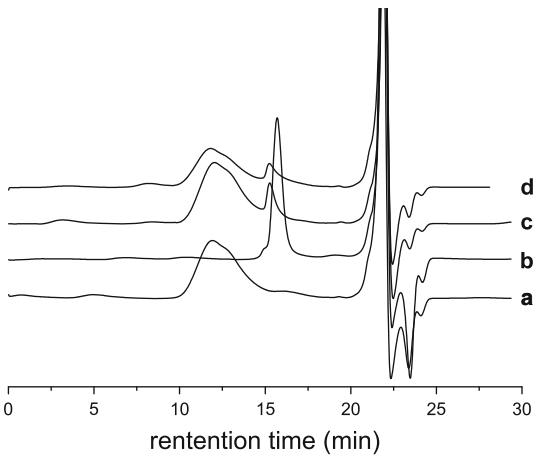

Fig. 6 GPC spectra of pure EVA (**a**), pure PEG 6000 (**b**), and Film 16 before and after immersion in water for 25 days, respectively (**c**, **d**, respectively)

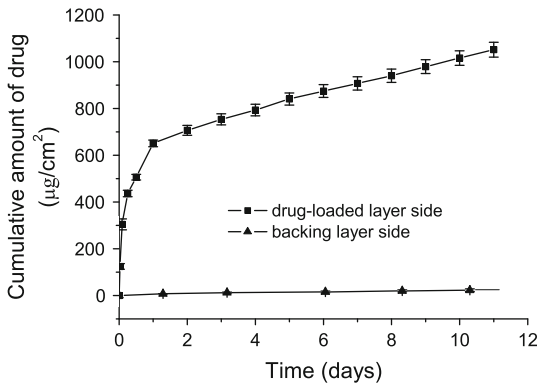

Fig. 7 PTX releases from the two sides of a double-layer coating film (Film 7) with a drug-loaded layer (with drug loading of 20% and thickness of 200 μm) and a drug-free bank layer (with thickness of 250 μm)

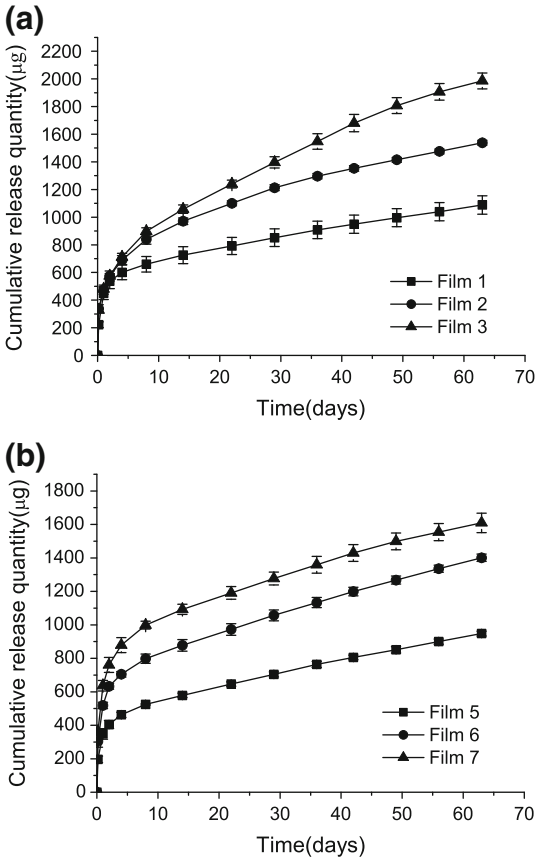

Fig. 8 Effects of drug loadings (10, 20 and 30%) on drug release from the PTX-loaded films with the same PLA content of 30% (**a**) and the PTX-loaded films with the same PEG content of 10% (**b**)

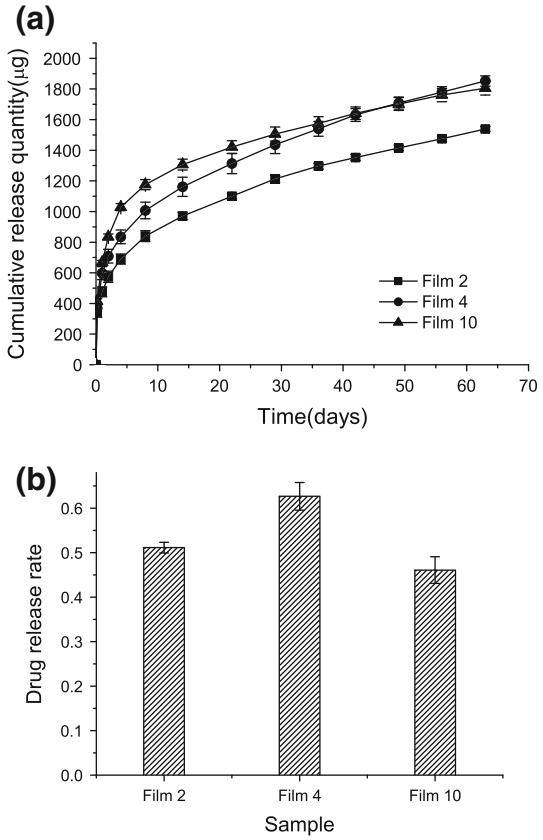

Fig. 9 (**a**) Effect of PLA contents (0, 30 and 50%) on drug release from the PTX-loaded films with the same drug loading of 20%; (**b**) drug release rates for films with different PLA contents (0, 30 and 50%) during 8–63 days

the drug delivery of the stent coating was in a unidirectional fashion.

3.3.2 Effects of drug loading

The release profiles of the films with various loadings of PTX are shown in Fig. 8. Three different drug loadings (10, 20 and 30%) were investigated for the films with a fixed content of PLA (30%) or PEG (10%). Fig. 8 shows that the cumulative amounts of PTX released from the films with higher drug loadings were always larger. A higher drug loading (or drug percentage) indicated a lower content of polymer matrix in the film, which diminished the retarding effect of polymer matrix and thus facilitated the drug release. This phenomenon has also been observed in other drug release studies [26]. In addition, the amounts of PTX released from the films based on EVA/PLA blends were larger than those from the films based on EVA/PEG. This could be attributed to the degradation of the PLA in the films based on EVA/PLA blends which promoted drug release as well as the comparatively higher contents of PLA than the lower contents of PEG in the films based on EVA/PEG blends.

3.3.3 Effects of the PLA content on drug release

The effects of different contents (0, 30 and 50%) of PLA in the films on PTX release from the films based on EVA/PLA blends with a constant drug loading of 20% are shown in Fig. 9. The PTX was released fast from all the films during the first 1 week. But during the later stage, the drug release slowed down and retained a constant rate. In the later stage, drug release from Films 4 and 2 based on EVA/PLA blends were faster than those from Film 10 without PLA, and the drug release rate increased with the increasing content of PLA. The drug release rate for Film 4 containing 50% of PLA was the highest and that for Film 10 without PLA was the lowest. The main reason was that the degradation and leach of PLA in the films left many voids (as shown in Fig. 1g, h) which facilitated the diffusion of drug out of the film. Although Films 2 and 4 released drug faster than Film 10 during the later stage, Film 10 release more drug in the early stage. The more drug released from Film 10 could be ascribed to the PTX flakes on the surface of Film 10, as revealed by its SEM image (Fig. 1f).

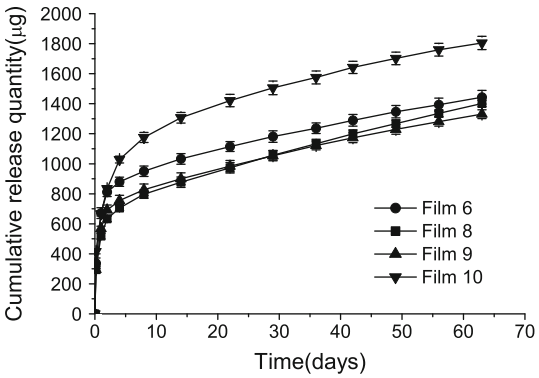

Fig. 10 Effect of PEG contents (0, 5, 10 and 15%) on drug release from the PTX-loaded films with the drug loading of 20%

3.3.4 Effects of the PEG content on drug release

It was originally expected that the leach of PEG from the films based on EVA/PEG blends would cause pores or spaces in the films and resultantly promote the PTX release. For example, it was reported that the addition of PEG to the poly (epsilon-caprolactone) matrix could promote drug release from the matrix [1]. However, the drug release rates from these films were slower than that from the Film 10 based on EVA alone. This is due to the fact that the PEG was difficult to leach from the films, thus not able to generate any pores or channels, as demonstrated by the above GPC and weight loss test results. In the other respect, the addition of PEG improve the compatibility of EVA and PTX, thus no PTX flakes appeared on the surface of the film based on EVA/PEG blends (as shown in Fig. 1e). This in turn explained the less release of drug for Films 6, 8 and 9 (based on EVA/PEG blends) compared with Film 10.

3.3.5 Release behaviors of PTX from the stent coating films

As displayed in Figs. 8, 9 and 10, all the release profiles were characterized by an initial quick release phase followed by a plateau stage with a slow and constant release rate. Therefore, the release profile can be divided into two stages: the early-stage (1–14 days) and the later-stage (14–63 days). All the drug release data for the two stages were fitted by the zero-order model and the correlation coefficients obtained were listed in Table 3. All the obtained correlation coefficients for the release data in the later-stage were above 0.990, which indicated that the drug release in the later stage fitted the zero-order kinetics well. Meanwhile, the obtained correlation coefficients for the release data in the early-stage were generally below 0.990 but above 0.900, suggesting that drug release in the early-stage followed a time-dependent kinetics.

Table 3 Fitting results of the drug release data by zero-order model

Sample	Parameters for the zero-order model ($M_t/M_\infty = kt$)[a]			
	Early-stage (1–14 days)		Later stage (14–63 days)	
	k	r	k	r
Film1	18.78	0.911	7.35	0.998
Film2	36.35	0.960	10.31	0.992
Film3	43.29	0.969	19.34	0.993
Film4	41.43	0.964	13.97	0.991
Film5	16.45	0.936	7.49	0.998
Film6	24.71	0.917	10.67	0.999
Film7	32.17	0.917	10.67	0.996
Film8	23.63	0.882	8.33	0.997
Film9	22.03	0.900	8.78	0.997
Film10	45.01	0.907	10.10	0.992

[a] M_t/M_∞ fractional drug release, t the release time, k a constant of the drug/polymer system, r correlation coefficient

4 Conclusions

The EVA/PLA blend and EVA/PEG blend were successfully applied as the drug carrier material for a PTX-loaded stent coating film. In addition to the good mechanical properties, the blends also have shown good drug loading performance. In the multi-component systems based on the blends, the mechanical properties and drug release behaviors can be regulated by changing the contents of the components in the films. The coating films with multiple components possess many advantages, for instance, the blends can alleviate the early quick release for film based on EVA alone. Besides, the selection of different additives could have distinct effects, e.g., the addition of PLA can promote the drug release while that of PEG slow down the drug release. By virtue of the high adjustability of release profiles and mechanical performance via readily adjusting the contents of the blend components, the blends could be useful drug carrier materials for developing drug-loaded stent coating with improved clinical performance by releasing drug in a highly tunable manner.

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