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D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) modified poly(L-lactide) (PLLA) films for localized delivery of paclitaxel

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Abstract

D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) was used as a novel additive to the poly(L-lactide) (PLLA) films for local drug delivery with paclitaxel as a prototype therapeutic agent. Paclitaxel-loaded PLLA/TPGS films were prepared by the solvent casting technique with dichloromethane as the solvent. Effects of TPGS component on the films' physicomechanical properties and the drug release profile were investigated. It was found by field emission scanning microscopy (FESEM) that a biphasic honeycomb surface was formed for the PLLA/TPGS films, while the PLLA film exhibited a smooth and homogeneous surface. There was no significant effect of the drug loading on the morphological structure of the PLLA/TPGS films. Differential scanning calorimetry (DSC) demonstrated that the PLLA/TPGS films was a phase-separated system. Tensile testing showed that the flexibility of the PLLA/TPGS films was much higher than that of the PLLA film. The elongation at break for the PLLA/TPGS film of 5%, 10% and 15% TPGS content was 6.8, 8.9 and 19.4 times of that for the PLLA film, respectively. *In vitro* drug release studies found that incorporation of TPGS considerably facilitated paclitaxel release.

Keywords: Anticancer drugs; Antiproliferative drugs; Biodegradable films; Biodegradable polymers; Controlled release; Localized drug delivery

1. Introduction

Paclitaxel is one of the potent antiproliferative agents for treatment of a wide range of cancers, especially ovarian and breast cancers (Wani et al., 1971; Schiff et al., 1979; Kohler and Goldspiel, 1994). In clinical, paclitaxel is formulated in the mixture of 50% Cremophor EL and 50% dehydrated alcohol (Taxol®) and given by intravenous (i.v.) infusion. Due to the serious side effects associated with Cremophor EL, alternative i.v. formulations for paclitaxel have been under intensive investigation, which include emulsions, micelles, liposomes, nanoparticles, etc. (Meerum Terwogt et al., 1997; Singla et al., 2002). Films made of natural or synthetic polymers have also gained attention for localized delivery of paclitaxel to treat cancers or prevent post-surgical adhesion (Jackson et al., 2002; Alexis et al., 2004; Dhanikula and Panchagnula, 2004; Shi and Burt, 2004; Grant et al., 2005; Ho et al., 2005; Panchagnula et al., 2006; Vodouhê et al., 2006; Schneider et al., 2007). Paclitaxel has also been formulated in the polymeric films for restenosis prevention (Jackson et al., 2004; Ranade et al., 2004; Livnat et al., 2005; Sharkawi et al., 2005; Westedt et al., 2006). Homopolymers of poly(L-lactide) (PLLA) or poly(D,L-lactide) (PDLLA) and copolymers of lactide and glycolide (PLGA) have been widely used to form films to deliver various drugs due to their good biocompatibility and biodegradability (Maze et al., 1995; Blanco et al., 1999; Gumusderelioglu and Deniz, 2000; Dorta et al., 2002a,b; Jackson et al., 2004; Gomez et al., 2004; Santoveña et al., 2004; Wang et al., 2004; Lee et al., 2005). However, films made of pure polylactide polymers, especially PLLA, feature brittleness. A suitable elasticity is essential for the integrity of drug-loaded films in handling and clinical appli-

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cations. Biocompatible additives, such as low molecular weight PEG and PLGA, have been used to enhance the film's flexibility and modulate the drug release rate (Webber et al., 1998; Jackson et al., 2004; Tan et al., 2004).

We aimed to develop a novel additive, D-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS or simply, TPGS), to form TPGS-modified PLLA films for localized delivery of paclitaxel. The focus of the current work is to investigate the effect of TPGS on the physicomechanical properties and *in vitro* drug release of the drug-loaded films. TPGS is a water-soluble derivative of natural vitamin E, which is formed by esterification of vitamin E succinate with polyethylene glycol 1000. Being an amphiphilic molecule with hydrophobic–lipophilic balance (HLB) number 13 and molecular weight 1513, TPGS can be used as an absorption enhancer, emulsifier and solubilizer, and has wide applications in food industry (Wu and Hopkins, 1999). Considering its biocompatibility, amphiphilicity and low molecular weight, TPGS could be a suitable additive for both hydrophilic and hydrophobic films. To our knowledge, TPGS is reported as the additive only for cellulosic films so far (Repka and McGinity, 2000, 2001; Bernard, 2004, 2006). In the present work, paclitaxel-loaded PLLA and PLLA/TPGS films with various levels of TPGS content (5%, 10%, and 15%) were prepared by the solvent casting technique with dichloromethane as the solvent. The morphology and thermal behavior of the films were investigated by field emission scanning electron spectroscopy (FESEM) and differential scanning calorimetry (DSC), respectively. The results showed that the PLLA films containing TPGS were a phase-separated system with a biphasic honeycomb structure. Tensile testing demonstrated that the elongation at break of the films was significantly increased from 8% for the PLLA film to 55%, 71% and 155% for the TPGS-modified PA films of the TPGS content of 5%, 10% and 15%, respectively. The *in vitro* paclitaxel release from the film was found to be accelerated by incorporating TPGS.

2. Materials and methods

2.1. Materials

Poly(L-lactide) (PLLA) (Lactel BP-0600, Mw 85,000–160,000) was purchased from Sigma. D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) was provided by Eastman Chemical Company (USA). Paclitaxel of purity 99.8% was supplied by Dabur India Ltd. (India). The solvent dichloromethane and acetonitrile of HPLC grade were from Aldrich.

2.2. Preparation of paclitaxel-loaded PLLA and PLLA/TPGS films

PLLA or PLLA/TPGS mixture (500 mg), which were made of PLLA/TPGS weight ratios 100/0, 95/5, 90/10 and 85/15, respectively, and 25 mg paclitaxel were completely dissolved in 10 ml dichloromethane. The resultant solution was poured to 7 cm × 7 cm leveled PTFE film, which was attached to a smooth glass plate by double-sided tape. The solvent was evaporated for half day at room temperature and the resultant films were vacuum dried for another 2 days to remove the solvent completely.

2.3. Morphology

The surface morphology of the paclitaxel-loaded films was observed by FESEM (JEOL, JSM-6700F). The films were coated by gold and then observed by tilting the films at 60°.

2.4. DSC

The thermal behavior of the paclitaxel-loaded PLLA and PLLA/TPGS films was investigated by DSC (DSC 822e, Mettler Toledo, Switzerland) under nitrogen atmosphere at a flow rate of 20 ml/min. Ten milligrams films were heated from 20 to 250 °C at a speed of 10 °C/min.

2.5. Tensile testing

The thickness of films was measured to be 90 ± 10 μm by a digital micrometer (Mitutoyo, Japan). 1 cm × 3 cm strips of the paclitaxel-loaded PLLA or PLLA/TPGS films were prepared for tensile test. The measurement was performed on Instron 3345 tabletop mechanical tester with a crosshead speed of 5 mm/min. The initial gauge length was 1 cm (L0). Stress was calculated as load/(thickness × width); while strain was determined as (extension/initial length) × 100%. Tensile strength was expressed as maximum load/(thickness × width).

2.6. In vitro drug release

The content of paclitaxel loaded in the film was assayed as follows: ∼7 mg (0.8 cm × 0.8 cm) strip, cut from the film, was dissolved in 1 ml dichloromethane. Upon evaporation of the solvent, the deposited drug was reconstituted in 1 ml 50% Millipore water plus 50% acetonitrile for HPLC analysis (Agilent LC 1100) by using a reverse phase ZORBAX Eclipse XDB-C18 column (250 mm × 4.6 mm i.d., pore size 5 μm) with a mobile phase containing of 50% water and 50% acetonitrile at a flow rate of 1 ml/min. The UV detection wavelength was 227 nm.

To measure the drug release *in vitro*, 0.8 cm × 0.8 cm strips cut from the films were suspended in test tubes containing 5 ml phosphate buffer solution and 0.2% (w/v) Tween 80. The tubes were placed in a water bath at 37 °C shaking at 120 rpm. At the designated intervals, the release medium containing the drug was transferred out and extracted with 1 ml dichloromethane. Fresh release medium (5 ml) was then added back to the test tubes to continue the drug release study. The extracted dichloromethane solution was allowed to evaporate completely and the residue was reconstituted in 1 ml 50% Millipore water plus 50% acetonitrile for HPLC analysis as described before. The measurement was done in triplicate.

3. Results and discussion

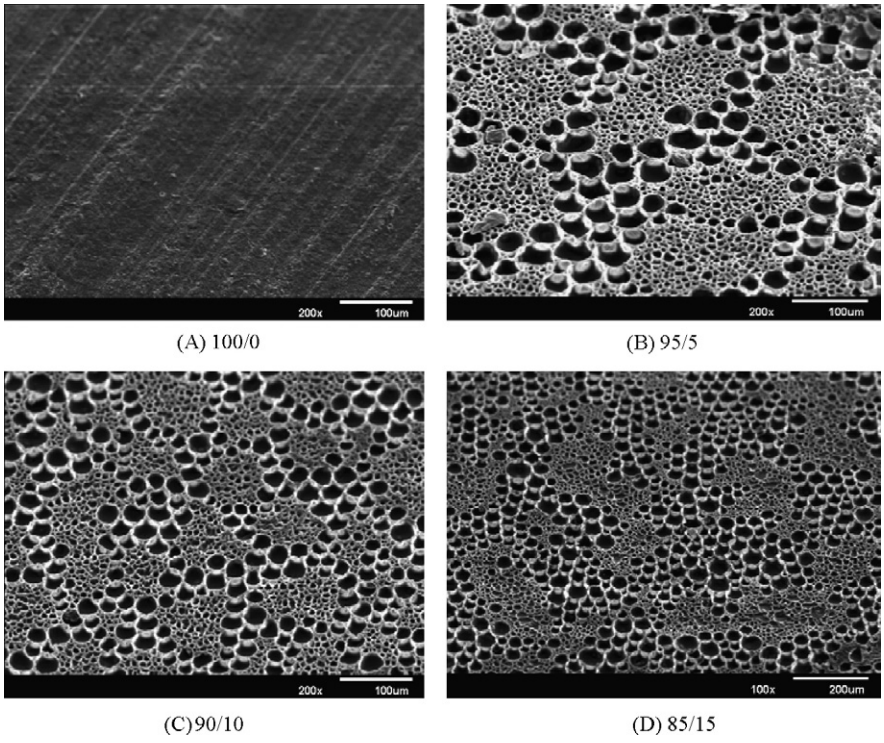
3.1. Morphology

In this research, paclitaxel-loaded PLLA and PLLA/TPGS films were prepared by the solvent casting method with dichloromethane as the solvent. Under the preparation conditions described in the last section, all the films possessed a thickness of $90 \pm 10\,\mu m$. Fig. 1 shows the FESEM images of the paclitaxel-loaded PLLA/TPGS films of PLLA:TPGS ratio 100:0, 95:5, 90:10 and 85:15, respectively. The images were made at the air-solvent interface. The surface of the PLLA film (100/0) was found smooth, homogeneous and nearly featureless. For the drug-loaded PLLA/TPGS films of 95/5, 90/10 and 85/15, however, a biphasic honeycomb surface was observed. The continuous phase was composed of the interconnected pores with the diameter of $22.28 \pm 4.76\,\mu m$ (estimated from the SEM images, $n = 10$); while the dispersed phase, which was separated by the continuous phase to many isolated regions, was composed of smaller pores, the diameter of which was $5.75 \pm 0.80\,\mu m$. With increase of TPGS content, the pores of the dispersed phase kept to be interconnected. Such a honeycomb structure indicates that the PLLA/TPGS films are a phase-separated system, which could induce the formation of a pitted surface (Walheim et al., 1997; Ton-That et al., 2000, 2002; Wang and Koberstein, 2004). The surface of PLLA/TPGS film at the solvent-substrate interface, however, was found to be homogeneous and smooth (SEM images were not shown). This could be explained by the different solubility of PLLA and TPGS in dichloromethane. Due to the lower molecular weight, TPGS had a higher solubility in dichloromethane than PLLA. With the evaporation of the solvent, PLLA would first precipitate out and deposited onto the substrate forming a homogeneous surface; on the contrary, TPGS accumulated at the air-solvent interface and formed an immiscible blending with PLLA inducing the pores formation. It is noteworthy that such a honeycomb surface is perhaps of more significance in tissue engineering, since the rough surface is beneficial for cell attachment and proliferation.

To see if the drug loading could have any significant effect of the PLLA/TPGS films, we also made the film sample of no drug loaded and conducted FESEM. We found that there were no significant effects of the drug loading on the surface morphology of the films. The texture, the phase separation feature, the shape and size of the two phases, and the pore size in the two phases all kept similar (images are thus not shown).

3.2. DSC

The DSC thermograms of the paclitaxel-loaded PLLA/TPGS films of PLLA:TPGS ratio 100:0, 95:5, 90:10 and 85:15, respectively are depicted in Fig. 2. As seen from the curves, the paclitaxel-loaded PLLA film (100/0) exhibited a glass transition (T_g) at ~52 °C, crystallization (T_c) at ~93.6 °C and melting (T_m) at ~172.6 °C consecutively. For the paclitaxel-loaded PLLA/TPGS films of 95/5, 90/10 and 85/15, there was no noticeable shift in terms of T_g compared with the PLLA film, which demonstrated that the blended films of PLLA and TPGS are phase-separated system. This result also confirms the previous FESEM observations. The crystallization temperature of PLLA, however, had a significant decrease from 93.6 °C (for PLLA/TPGS 100/0) to 81.4 °C (for PLLA/TPGS 85/15). In addition, the extent of crystallization temperature depres-



(A) 100/0 (B) 95/5

(C)90/10 (D) 85/15

Fig. 1. FESEM images of the paclitaxel-loaded PLLA/TPGS films of PLLA:TPGS ratio 100:0 (the pure PLLA film); 95:5, 90:10 and 85:15, respectively.

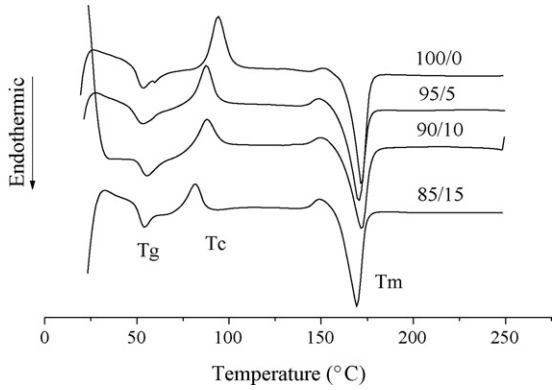


Fig. 2. DSC thermograms of the paclitaxel-loaded PLLA and PLLA/TPGS films.

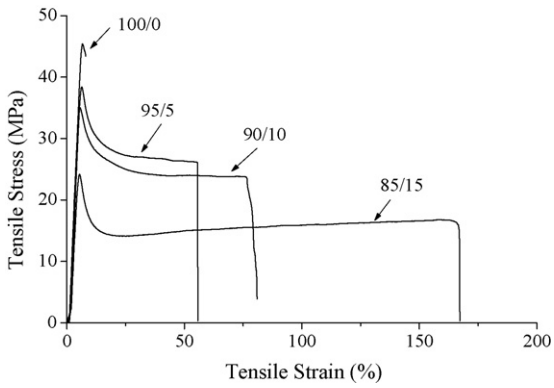


Fig. 3. Tensile stress–strain curves of the paclitaxel-loaded PLLA and PLLA/TPGS films.

sion depends on the content of TPGS, and the higher the TPGS content, the lower the crystallization temperature. Such a crystallization temperature depression indicates that the presence of TPGS enhances the mobility of PLLA chains, resulting in a faster crystallization rate. Likewise, melting temperature of the PLLA/TPGS films also exhibited a little decrease from 172.6 °C for PLLA/TPGS 100/0, i.e. the pure PLLA film, to 168.9 °C for PLLA/TPGS 85/15. A similar result was also obtained from immiscible blended system of polylactide and poly(butylene adipate-*co*-terephthalate) (PLA/PBAT) in the literature (Jiang et al., 2006). ΔH_c of the sample PLLA/TPGS 100/0, 95/5, 90/10 and 85/15 was found to be 24.7, 22.1, 25.1 and 21.4 J/g, respectively. It seems that the influence of TPGS on the final extent of recrystallization of PLLA upon heating is not as pronounced as that on the crystallization rate (indicated by T_c). ΔH_m of the PLLA/TPGS 100/0, 95/5, 90/10 and 85/15 films was 42.1, 41.8, 45.1 and 33.2 J/g, respectively. It is obvious that a small amount such as 5% and 10% of TPGS did not exhibit significant influence on the crystallization of the PLLA, while a larger amount of TPGS (15%) showed a significant negative influence causing a pronounced decrease of ΔH_m from 42.1 for PLLA/TPGS 100/0 to 33.2 J/g for the PLLA/TPGS 85/15. For the loaded paclitaxel, its pristine form generally exhibits an endothermic melting peak at around 230 °C. For the paclitaxel-loaded PLLA and PLLA/TPGS films, there was no such a peak detected, indicating that paclitaxel was molecularly or amorphously distributed in the films.

3.3. Tensile testing

Tensile testing was carried out to determine the effect of TPGS on the mechanical properties of paclitaxel-loaded PLLA film. The stress–strain curves of the paclitaxel-loaded PLLA and PLLA/TPGS films are shown in Fig. 3. For the PLLA film (100/0), the testing samples were fractured subsequently following the onset of maximum imposed load, suggesting a brittle fracture behavior. On the contrary, PLLA/TPGS films showed a large amount of plastic deformation before fracture, exhibiting a typical ductile fracture. The elongation at break and tensile strength of the films are detailed in Table 1. The elongation at break of the paclitaxel-loaded PLLA film was only 8%. For the paclitaxel-loaded PLLA/TPGS films, the elongation at break was tremendously enhanced to 55% (95/5), 71% (90/10) and 155% (85/15), which was 6.9, 8.9 and 19.4 times larger, respectively. Conversely, with the increase of the content of TPGS, the tensile strength was gradually decreased from 40.2 for the PLLA film to 35.9 MPa for the PLLA/TPGS 95/5 film, 34.1 MPa for the PLLA/TPGS 90/10 film and 22.6 MPa for the PLLA/TPGS 85/15 film. These results showed that paclitaxel-loaded PLLA/TPGS films possess much higher flexibility than paclitaxel-loaded pure PLLA film. It was reported that the drug particles may act as the plasticizer to increase the flexibility of the films (Wu and Mcginity, 1999; Siepmann et al., 2006). In our study, since the same drug content was used in the all films formulations, the flexibility enhancement for paclitaxel-loaded PLLA/TPGS films caused by the drug can thus be precluded. It was also reported that TPGS was a good plasticizer to depress the T_g of cellulosic films and thus enhance their flexibility (Repka and McGinity, 2000, 2001; Bernard, 2004, 2006). Our results, however, showed that TPGS did not decrease the T_g of PLLA film. Similar result was also found from another immiscible blending system of polylactide and poly(butylene adipate-*co*-terephthalate) (PLA/PBAT) (Jiang et al., 2006). The presence of PBAT (5–20 wt.%) lowered the cold crystallization of temperature of PLA ~ 10 °C while the glass transition temperature of PLA was not depressed. The elongation at break, however, was tremendously increased from 3.7% for PLA film to >200% for PLA/PBAT film even at 5% of PBAT. The author ascribed it to the cavities formed between the PBAT particles and the PLA matrix. Cavitation is an important energy dissipation process. The enhancement of flexibility of PLLA/TPGS films, compared with PLLA film, is presumably ascribed to the honeycomb structure of the former. The pores (cavities) on the PLLA/TPGS films' surface altered the

Table 1
Tensile strength and elongation at break of films

Sample	Tensile strength (MPa)	Elongation at break (%)
100/0	40.2 ± 1.1	8 ± 0.7
95/5	35.9 ± 2.2	55 ± 6
90/10	34.1 ± 3.5	71 ± 16
85/15	22.6 ± 0.5	155 ± 30

stress state and the applied tension was locally released, which leaded to a shear yielding and a plastic deformation was thus obtained (Jiang et al., 2006). More work on the PLLA/TPGS films with or without drug is now under investigation to understand the effects of the process parameters, such as solvent type, solvent removal rate, etc. on the physicomechanical properties of the formed PLLA/TPGS films. Also, the mechanical properties PLLA/TPGS films in wet state (incubation with phosphate buffer solution) and the detailed toughing mechanism will be studied further.

3.4. In vitro drug release

It is known that the release mechanism of the loaded drug from the polymeric films can be divided into: (1) diffusion, (2) polymer erosion and (3) combination of diffusion and polymer erosion. For PLLA, diffusion could be mainly responsible for the drug release at the first tens of days, since PLLA films was found to be hydrolytically degraded to only a minor extent in 24 weeks (Saha and Tsuji, 2006). The release profiles of paclitaxel from the PLLA and PLLA/TPGS films in 14 days were investigated and the results are shown in Fig. 4. In all cases, paclitaxel was released out in a biphasic pattern: a fast release rate in the first 5 days followed by a slow, sustainable one. The drug molecules located on or near the film surface could contribute to the initial fast release rate, while the followed slow release rate can be ascribed to the drugs inside the films, which possessed a long diffusion path to the release medium. Though paclitaxel was released in a similar extent from the PLLA film, the PLLA/TPGS 95/5 and 90/10 films in the first 3 days, the drug release from the PLLA/TPGS 85/15 film was apparently faster in the same period. In 14 days, totally 45.1% of the loaded drug was released from the PLLA/TPGS 85/15 film, while in the same period, the amount of released drug was 24.9%, 28.5% and 40.9% for the PLLA, the PLLA/TPGS 95/5 and 90/10 films, respectively. It is obvious that the TPGS facilitated the drug release from the PLLA films; and the higher TPGS content the faster paclitaxel release was resulted. Such accelerated drug release rate could be explained by the increased hydrophilicity of PLLA/TPGS films in comparison with the PLLA films; also, the honeycomb structure of PLLA/TPGS films possessed larger surface area to volume ratio compared to the smooth neat PLLA films, which increased the exposed area of the matrix to the release medium resulting in a faster release rate.

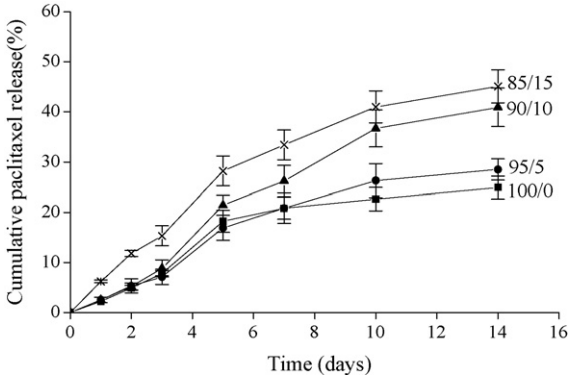


Fig. 4. *In vitro* drug release profiles of paclitaxel from the PLLA and PLLA/TPGS films.

4. Conclusions

PLLA/TPGS films were developed for potential applications for localized drug delivery. Paclitaxel was used as a prototype drug due to its excellent therapeutic effects against a wide spectrum of cancers. The paclitaxel-loaded PLLA/TPGS films of PLLA/TPGS 100/0, 95/5, 90/10, and 85/5 were prepared by the solvent casting method with dichloromethane as the solvent. FESEM imaging showed that the surface of the PLLA film, i.e. the PLLA/TPGS 100/0 film was smooth and nearly featureless in the equipment resolution scope; while other PLLA/TPGS film exhibited a biphasic honeycomb structure. The PLLA/TPGS film was found to be a phase-separated system. Tensile testing of the PLLA/TPGS films exhibited a much higher flexibility than the PLLA film. The release of paclitaxel from the PLLA films was notably accelerated by incorporating TPGS. Such a honeycomb-patterned PLLA/TPGS film could have better performance than the PLLA film as implants for localized drug delivery, which also have potential to be used as scaffold in tissue engineering to facilitate cell attachment and proliferation.

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