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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.