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Modulating drug release from poly(lactic-co-glycolic acid) thin films through terminal end-groups and molecular weight

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ABSTRACT

Biodegradable PLGA is commonly employed for controlled drug release on the order of weeks to months. Hydrophobic drugs distribute homogeneously in PLGA, but their strong hydrophobic interaction typically results in narrow release profiles. In this study, three molecular weights (MW) and two different terminal end-groups of biodegradable PLGA were applied to broaden the range of drug release and vary the mechanical properties without the use of additives. Films knife-casted from PLGA polymers with terminal carboxylic acid end-groups were found to 1) absorb more water, 2) have higher rates of polymer mass loss, 3) increased hydrophobic drug release as compared to films knife casted from similar MW PLGA polymers with terminal ester end-groups. The highest drug release rates were obtained from low MW PLGA that had the densest surface concentration of terminal acid groups. An intermediate drug release profile was obtained with a blend of high and low MW PLGA. The various PLGA polymers (differing in MW, terminal groups, and combinations thereof) described herein could give rise to PLGA\PLGA blends that would allow independent tuning of drug release and mechanical properties without the inclusion of non-degradable additives with respect to hydrophobic, small molecule drugs.

1. Introduction

Resorbable polymers have been commonly chosen as materials for drug delivery and medical device implants [1,2]. Polyesters such as poly(lactic-*co*-glycolic acid) (PLGA), are a class of biodegradable polymers commonly employed in drug delivery systems. They have been widely used in the development of biodegradable nanoparticles, microparticles, scaffolds, films and bulk implants, giving a wide range of drug delivering capabilities [3–7]. Biodegradable polymers such as PLGA are commonly used as drug delivery carriers due to many favorable characteristics such as biocompatibility, biodegradability, and desirable mechanical properties [8–11]. In recent decades, PLGA has been widely studied for localized drug delivery in treating periodontal diseases [12,13], glaucoma [14,15], cancer [16,17], coating on metallic stents [18,19], and even as fully biodegradable stents [20,21]. Different strategies have been investigated to adjust drug release and degradation profiles to cater to various biomedical applications. For example, the frequency of drug administration in a certain therapy can be reduced by the use of suitable carriers that can modulate the release of drugs over a required period of time. Such systems are beneficial for patient compliance and therapeutic regimens that require frequent injections, long term application, or both.

Anti-proliferative drugs such as paclitaxel are often loaded into PLGA carrier systems for sustained drug therapies [1,20–25]. Due to the strong interaction between paclitaxel and PLGA, such a drug delivery system is often limited to a narrow range of drug therapy. The hydrophobic nature and poor aqueous solubility of paclitaxel (~0.5 μg/mL) also influence the drug release characteristics [26,27]. Additives such as leachants or porogens are commonly used to enhance drug release by increasing water infiltration [5,7,26,28–32]. However, the effects are usually short lived and may negatively affect the mechanical properties. Therefore, one of the aims of this study is to exploit the different molecular weights (MW) and terminal end-groups of commercially available PLGA to widen the range of drug release profiles without the use of hydrophilic or non-degradable additives such as salt particles, polyethylene glycol, etc.

In this study, PLGA films were synthesized of three MW PLGAs with terminal ester, terminal acid end-groups, or combination thereof, to modulate the release of hydrophobic paclitaxel. An initial high-throughput screening method using fluorescein

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diacetate (FDAc) provided a quick indication of the release characteristics from these PLGA polymer films [33]. The release of paclitaxel was then monitored in tandem with the degradation of these PLGA films. A blend that gave the lowest and highest release was subsequently assessed for their combined release characteristics. Our subsequent investigations (manuscript in preparation) will focus on high-throughput gradient films that display tuning of drug delivery by exploiting the five PLGA variants characterized herein.

2. Materials & methods

2.1. Materials

Poly(DL-lactide-co-glycolide) (PLGA 53/47) with inherent viscosity (i.v.) 1.03, 0.4, 0.4A, 0.2, 0.2A dL/g (abbreviated P103E, P04E, P04A, P02E, P02A) were purchased from Purac, (The Netherlands). Dichloromethane (DCM) was purchased from Tedia (USA). Paclitaxel (PCTX) was purchased from Yunnan Hande Bio-Tech, China (>99%). Fluorescein diacetate (FDAc) was purchased from Tokyo Kasei Kogyo Co., Ltd Japan. All other polar solvents used were of high performance liquid chromatography (HPLC) grade and purchased from Sigma–Aldrich, Singapore. All chemicals and materials were used as received.

2.2. Methods

2.2.1. Film preparation

The respective polymer solutions of P103E, P04E, P04A, P02E, P02A (15% *w*/*v*) were prepared with 10% *w*/*w* PCTX or FDAc in DCM. A typical film formulation consisted of 150 mg of PCTX or FDAc and 1500 mg of PLGA in 10 mL of DCM. Film applicator height was fixed at 500 μm and the polymer solution was casted onto polyethylene terephthalate (PET) sheets at 50 mm/s, under room temperature and pressure in a fume hood. The use of PET layer serves to provide mechanical support to the fast-degrading films. The casted films were left to dry in a solvent saturated atmosphere before transferring to vacuum oven for further drying at RT for 5 days.

2.2.2. Surface hydrophobicity

Films were cut into rectangular strips (3 cm × 1 cm) and their surface properties analyzed by contact angle and wetting tension using a static sessile drop technique on a contact angle goniometer. The static measurements were carried out at room temperature at five locations, with distilled H_2O being pumped out at a rate of 5 μL/s. A still image was captured for analysis after allowing the droplet to relax for 10 s and analyzed with FTA32 software, version 2.0 build 276.2.

2.2.3. In-vitro paclitaxel/FDAc release study (as previously described and cite)

The *in-vitro* release of paclitaxel (PCTX) was conducted in 2 mL of PBS spiked with 2% Tween 80 in release buffer (pH 7.4) at 37 °C, using 1 cm × 1 cm cut-outs, in triplicate. At predetermined time points, 1 mL of buffer was withdrawn and filtered through a 0.2 μm cellulose syringe filter directly into HPLC vials and immediately capped. The remaining 1 mL is discarded and replaced with 2 mL of fresh buffer. PCTX was quantified with an Agilent Series 1100 HPLC (Santa Clara, CA, USA) equipped with UV/Vis detector. Acetonitrile/water 70/30 (% *v*/*v*) served as the mobile phase, eluting the PCTX peak approximately at 2 min with a flow rate 1.0 mL/min through Poroshell 120 EC-C18 column of pore size 2.8 μm (Agilent Technologies) with UV/Vis detector of HPLC recorded at 227 nm. A total dissolution quantification of the 1 cm × 1 cm samples was conducted by dissolving the films in acetone, in triplicate.

The *in-vitro* release of FDAc was monitored by Fluorescence Microplate Reader (Tecan, Seestrasse, Männedorf, Switzerland). Sodium hydroxide (100 mM, 180 μL) was first added into the wells of the 96-well Greiner black plate. Subsequently 20 μL of aliquot was pipetted into the wells of the microarray plate. The fluorescence units were recorded and its concentration calculated from standard curves set up at various gain settings.

2.2.4. In-vitro degradation and mass loss study

1 cm × 1 cm film samples were initially weighed (W_o) prior to incubation in PBS maintained at 37 °C, in triplicate. At predetermined time points, the films were rinsed with deionized water and the excess blotted off before measuring the wet weight (W_{wet}). The samples were then dried thoroughly in a vacuum oven for at least a week before measuring the dry weight (W_{dry}) gravimetrically. These samples were then dissolved in 1 mL of chloroform for at least an hour, vortexed and filtered through 0.2 μm cellulose filters into HPLC vials and immediately capped. GPC (Agilent series 1100 Santa Clara, USA) was used to monitor the MW change in the films as degradation proceeds. At each time point, each dried sample was dissolved in 1 mL chloroform, filtered and injected into GPC that was fixed with PLgel 5 μm column maintained at 35 °C and coupled to a refractive index detector. The flow rate was set at 1 mL/min and the mobile phase was chloroform. The calibration was done prior to sample analysis using a series of standard polystyrene of known molecular weight.

Water absorption and mass loss were calculated using the equations as follows:

$$\text{Water absorption } (\%) = \frac{W_{wet} - W_{dry}}{W_{dry}} \times 100\%$$

$$\text{Weight loss } (\%) = \frac{W_o - W_{dry}}{W_o} \times 100\%$$

2.2.5. Mechanical properties

To assess the mechanical properties of these films, they had to be separately casted onto a Teflon-coated base instead of PET. These films were dried similarly as described earlier. Each 8 cm × 1 cm rectangular film was clamped to the water grip setup designed to mount onto the Instron Tensile Tester, Model 5567. The samples were subjected to tensile stress at rate of 5 mm/min in PBS medium maintained at 37 °C via a circulator to mimic physiological conditions. The data was plotted and analyzed with Bluehill software version 3.00. The Young's modulus (E), yield strength (σ_{ys}), tensile stress at break (σ_b) and elongation-to-break (ε_b), in MPa, were recorded and calculated, in triplicate. No isotropic effects on the mechanical properties were investigated.

2.2.6. Thermal analysis

The thermal properties of pure polymers and films were characterized by differential scanning calorimetry (Q500 DSC, TA Instruments). Film samples were sealed in crimped aluminum pans with lids before purging with purified nitrogen gas in the chamber to avoid oxidative degradation. Empty crimped aluminum pan was used as a reference. Both reference and sample pans were heated and cooled at a rate of 10 °C/min. The change in glass transition temperature (T_g) from the second DSC thermogram was plotted as a function of degradation time.

2.2.7. Film surface and film cross-section topography

Film surfaces and cross-sections were coated with platinum for 50 s under a chamber pressure of less than 5 Pa at 20 mA (JEOL JFC-1600 Auto Fine Coater, Japan). Secondary electron images of