Published in final edited form as:

Chem Commun (Camb). 2012 May 18; 48(40): 4833–4835. doi:10.1039/c2cc31188g.

Biodegradable, multi-layered coatings for controlled release of small molecules†

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Abstract

Incorporation of orthogonal functional groups into biodegradable polymers permits the fabrication of multi-layered thin films with improved adhesion and tunable degradation profiles. The bi-layer structure also allows for accurate control over small molecule release.

The design of biocompatible polymers and materials with multiple functional groups is a true challenge for synthetic chemists.¹ These materials have to fulfil numerous criteria: they should possess multiple functions for attachment of biomolecules, control of surface properties, *etc.* while at the same time meeting strict performance requirements for biocompatibility, biodegradation, adhesion, flexibility and more.² To address these needs, polymers such as poly(lactic acid) (PLA), polycaprolactone (PCL) and poly(glycolic acid) (PGA) and their copolymers have been widely used as coatings for implantable devices, drug delivery and diagnostic systems.³ These polyesters undergo hydrolysis *in vivo* and *in vitro* over a period of weeks to years, and their degradation products have been shown to be non-toxic. However, one of the major challenges encountered with drug delivery from these polyester systems is fast initial release of the payload from the polymer matrix (burst release), followed by slow degradation of the residual material.⁴ Furthermore, when polyesters are used as coatings for implantable devices, in many cases poor adhesion of the polymer to the surface of the device leads to delamination of the coating from the surface.^{5,6} In order to circumvent these problems, this manuscript describes a novel approach to functionalized and adhesive coatings based on a bi-layer system with tunable polymer degradation and small molecule release profiles.

†Electronic supplementary information (ESI) available: See DOI: 10.1039/c2cc31188g

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The fundamental design principle is the introduction of a crosslinkable and degradable polyester sub-layer, which serves multiple purposes: as a reservoir for the molecules to be released, to provide adhesion to the substrate and through orthogonal covalent coupling to the surface layer and improved mechanical stability. By adding a surface layer to this sub-layer, control over surface chemistry, permeability, release and degradation of the underlying polyester layer through varying the crosslinking density and hydrophilicity of the surface layer can be achieved. A schematic representation of the bi-layer strategy is shown in Scheme 1 with the inner, PLA layer being protected by an outer biodegradable thiol-ene based layer, resulting in accurate control over the release rate of the cargo molecules from the underlying layer. It should also be appreciated that both layers could act as individual and independent reservoirs for small molecules resulting in the controlled release of different and potentially incompatible, active agents.

To demonstrate the utility and potential of this concept, PLA functionalized with two orthogonal functional groups (epoxides and alkenes) was selected as the underlying layer. The epoxides are employed for covalent attachment of the polymer to the surface leading to improved adhesion while also allowing for secondary crosslinking. The incorporation of the orthogonal alkene groups allows these units to persist during coating/crosslinking of this initial layer and then to undergo reaction with an overlying thiol-ene coating containing ene-functionalized poly- β -aminoester⁷ and a multifunctional thiol. It is envisaged that covalent crosslinking of both layers and covalent reinforcement of the interface will lead to improved mechanical stability of the overall bi-layer structure.

Initially, a facile approach to the synthesis of orthogonally functionalized PLA was developed based on the alkene substituted, cyclic carbonate building block, **1**.⁸ Ring opening polymerization of **1** and D,L-lactide was carried out using benzyl alcohol as an initiator and stannous octanoate as a catalyst (Scheme 2A) to give alkene-functionalized polymers, **2** and **3**, with molecular weights of 27 kDa (PDI = 1.6) and 35 kDa (PDI = 1.5) respectively and comparable degrees of alkene functionality – 11 mol% for **2** and 12 mol% for **3**.

The rich chemistry associated with the alkenes units then allows modular introduction of the epoxy units into the polymer backbone *via* epoxidation of the double bonds using *m*-chloroperbenzoic acid (*m*CPBA). This reaction can be controlled by either reaction time or temperature and permits the level of epoxide groups to be essentially titrated. For example, room temperature reaction of **2** with *m*CPBA for 12 h yields **4** having 6 mol% of epoxides and 5 mol% of alkenes, while room temperature reaction of **3** with *m*CPBA for 18 h gives **5** having 8 mol% of the epoxide groups and 4 mol% of alkenes. (Scheme 2B).

In order to test the adhesion strength parameters of the polymers to metal oxide surfaces, silicon wafers were used as model substrates. The wafers were treated with oxygen plasma in order to expose free hydroxyl groups on the surface, followed by spin coating of polymers **4** and **5**. For comparison, commercially available non-functional PLA was also tested as a control material. Adhesion tests were performed 50 times for each sample at different locations under ambient temperature and humidity (see ESI[†]). The average adhesion force for the modified samples closely mirrors the modification level for the polymer backbone

with the control (unmodified) polymer showing no adhesion to the surface, while both epoxide-functionalized polymers showed good adhesion, with the adhesion force for the polymer **5** (8 mol% epoxide, 1.53 mN) being greater than that for **4** (6 mol% epoxide, 1.14 mN).

One of the challenges in manufacturing a well-defined bi-layer system is determining the optimal processing conditions for fabrication of each layer while also ensuring covalent attachment between the polymer layers. Having demonstrated that the incorporation of epoxy groups leads to improved adhesion of the PLA layer to the substrate, the epoxy groups remaining after reaction with the inorganic surface⁹ offer the possibility for further chemical modification. In this study they were utilized for crosslinking of the PLA-based coating through cationic ring opening polymerization initiated by a thermal acid generator. In this step, a hexafluoroisopropanol solution containing polymer **4**, rhodamine B as a model small molecule for release and 4,5-dimethoxy-2-nitrobenzyl 2,4,6-trimethylbenzenesulfonate as thermal acid generator¹² was spin coated on silicon wafers. Crosslinking of this sub-layer was achieved by curing the film at 135 °C for 1 h, followed by removal of the excess dye by washing with ethyl acetate.

The role of the second coating is to act as a protecting layer on top of dye/drug loaded PLA-based coating and tune the release rate. The design of this coating is based on thiol-ene chemistry,¹⁰ with commercially available pentaerythritol tetrakis-(3-mercaptopropionate) (PTMP) and the ene-functionalized poly- β -aminoesters,⁷ **6** and **7**, being chosen as biodegradable starting materials (Scheme 3A). The choice of the diacrylate monomers for the preparation of poly- β -aminoesters allows control over hydrophobicity of the polymers: for example, synthesis of the hydrophobic poly- β -aminoester, **6** is based on 1,6-hexane diacrylate, while the hydrophilic poly- β -aminoester **7** was prepared from tetra(ethylene glycol) diacrylate (Scheme 3B).

In order to introduce the second polymer coating, an ethyl acetate solution of ene-functional poly- β -aminoester **6**, PTMP and catalytic amount of radical initiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA), was spin coated on top of the PLA-based layer. The curing of the second coating was conducted by exposure to UV-radiation at 365 nm for 2 min. The presence of allyl groups on both **6** as well as the PLA underlayer permits both rapid photocrosslinking of the poly- β -aminoester containing top-coat as well as the covalent coupling of the interface between layers. An enabling feature of this strategy is the orthogonal crosslinking of each polymer layer with the mild thermal acid/photochemical conditions allowing a variety of materials to be employed.^{7,11}

Scanning electron microscopy (SEM) was used to visualize the formation of a well-defined bi-layer with a sharp interface and controlled thicknesses for each layer. In this representative example, the thickness for the dye loaded PLA-based monolayer is 6.5 microns and the thickness for the thiol-ene based coating is 2.9 microns (Fig. 1). It is important to note that this strategy allows various thicknesses to be achieved and in each case, extensive solvent treatment and degradation studies did not reveal any delamination at the bi-layer interface.

[†]Electronic supplementary information (ESI) available: See DOI: 10.1039/c2cc31188g

One of the prime motivations for developing this orthogonal bi-layer strategy is modulating the release of small molecules from the underlying PLA layer through changes in the nature of the thiol-ene top-coat. To initially demonstrate this feature, rhodamine B release from a PLA layer with a top layer of either **6** or **7** and PTMP was studied and compared to the release from the unprotected monolayer. The release was tested in phosphate-buffered saline (PBS, pH 7.4) at 37 °C, mimicking physiological conditions. Fig. 2 shows cumulative release of rhodamine B over time. As expected, a single coating of polymer **4** showed burst release of the dye, having lost almost 50% of its content in ~3 days. When a hydrophilic poly- β -aminoester **7** was used for the fabrication of the top coating, no burst release was observed and a linear profile was achieved with about 50% of the dye being released after 8 days. In direct contrast, the use of a hydrophobic poly- β -aminoester protecting layer, which is more resistant to water penetration, allowed a much lower, though still linear, rate of release to be achieved with only ~30% of the dye released at 20 days. These tunable, linear release profiles are highly desired for drug-loaded polymer systems,¹³ and demonstrate that the use of a top-coat as a variable, protecting layer allows tuning small molecule release from a degradable polyester sub-layer.

In conclusion, we have developed a novel bi-layer system based on functional and biocompatible polyesters that offers significant potential as a general coating strategy for biomedical and controlled release applications with improved adhesion, mechanical properties and tunable, linear release profiles. The robust nature of the functional groups employed in this bi-layer strategy also allows a wide variety of polymer backbones to be utilized in order to further modify polymer degradation and cargo release rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project has been funded in part by the National Heart, Lung, and Blood Institute, National Institutes of Health, under Contract No. HHSN268201000046C (EA, PA and RJA). This work was also supported by the National Science Foundation (MRSEC Program DMR-1121053 (MRLUCSB)– LMC and Chemistry Program CHE-0957492–NG). ED gratefully acknowledges the Institut Universitaire de France (IUF) and NP support from a Pfund grant through the Louisiana Board of Regents.

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Fig. 1.
Side-view SEM image of monolayer (A) and bi-layer (B).

Fig. 2. Accumulative release of rhodamine B from PLA-based monolayer (red squares), bi-layer system with hydrophilic top coating (black circles) and bi-layer system with hydrophobic top coating (blue triangles).

Scheme 1.

Schematic representation of the bi-layer platform based on dual-functionalized PLA coating and ene-functionalized thiol-ene coating.

Scheme 2.

Synthesis of ene-functionalized PLA-based copolymers **2** and **3**, followed by partial epoxidation of the double bonds to produce dual-functionalized polymers **4** and **5**.

Scheme 3.

Chemical structures of the thiol and alkene crosslinkers and radical initiator employed for the thiol-ene based coating (A). Synthesis of the ene-functionalized poly- β -aminoesters **6** and **7** (B).