A biodegradable, non-thrombogenic elastomeric poly(ester urethane)urea with paclitaxel release as a drug eluting stent coating

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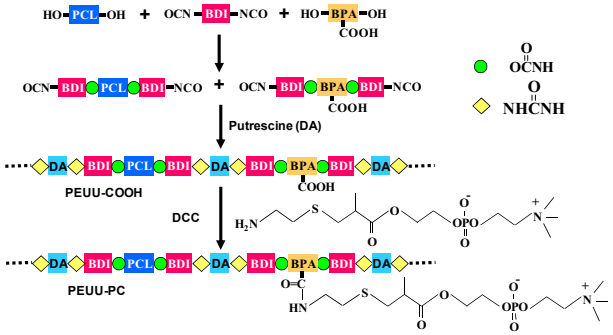
Statement of Purpose: Drug eluting stents dramatically gained market share due to their reduced restenosis rates relative to uncoated stents, yet they are associated with late stent thrombosis where thrombotic complications appear much later than the normal early risk period. The coated stents have a tendency to not endothelialize while presenting a relatively thrombogenic surface to the blood. To address this problem, a biodegradable non-thrombogenic polymer with anti-proliferative drug release capacity might be employed as a stent coating. Our objective here was to synthesize a new biodegradable elastomeric poly(ester urethane)urea (PEUU) incorporating 2-methacryloyloxyethyl phosphorylcholine (MPC) (PEUU-PC). The synthesized polymer was characterized in terms of its thermal and mechanical properties, blood biocompatibility, as well as its ability to serve as a reservoir for the controlled release of a model anti-proliferative drug, paclitaxel.

Methods: PEUU-PC was synthesized using a 2-step synthesis. First, PEUU containing carboxyl groups (PEUU-COOH) was synthesized from a soft segment blend of polycaprolactone diol (PCL, Mn=2000) and 2,2-bis(hydroxymethyl)propionic acid (BPA), a hard segment of 1,4-diisocyanatobutane (BDI) with putrescine (DA) as a chain extender (**Scheme 1**). The PCL/BPA molar ratio was 70/30 and the (PCL+BPA):BDI:DA molar ratio was 1:2:1. PEUU without BPA was served as a control [**1**]. PEUU-COOH was reacted with an excess of amine-modified MPC (which was synthesized from MPC and cysteamine in methanol under UV irradiation) using a condenser dicyclohexylcarbodiimide (DCC) to obtain the final product, PEUU-PC (**Scheme 1**). Films were cast from hexafluoroisopropanol (HFIP) solutions.



Scheme 1. Synthesis of PEUU-PC.

Polymer chemical structures were confirmed with ^{1}H-NMR and surface composition was assessed by X-ray photoelectron microscopy (XPS). Thermal properties were determined with DSC at a heating rate of 20°C/min. Tensile testing was completed according to ASTM D638-98. Surface thrombotic deposition was observed with scanning electron microscopy (SEM) and platelet number was quantified by a lactate dehydrogenase (LDH) assay after 2 h ovine blood contact. Furthermore, 5 wt% drug-loaded films were cast from polyurethane/paclitaxel HFIP solutions. Release profiles were determined in a 10% ethanol/PBS solution at 37°C by UV absorbance at 230 nm. Cellular proliferation inhibition was assessed by culturing smooth muscle cells (SMC) with the drug-loading films, followed by mitochondrial assay and live/dead staining.

Results: PEUU-PC chemical structure was verified by the appearance of δ=3.1-3.2 ppm (-N$(CH_3)_3$) with ^{1}H-NMR, while this peak did not appear with PEUU and PEUU-COOH. Compared to the XPS of PEUU and PEUU-COOH surfaces, PEUU-PC surfaces showed the appearance of phosphorus, increased nitrogen and reduced oxygen further confirming successful PC grafting. PEUU-COOH and PEUU-PC had decreased water contact angles of 70±2° and 53±2° respectively relative to PEUU (80±2°). Glass transition temperatures for all polyurethanes were lower than -50°C, while melting temperatures ranged from 34 to 40°C. Tensile strengths of PEUU-COOH (22±2 MPa) and PEUU-PC (22±5 MPa) were significantly lower than for PEUU (34 ± 3 MPa), but the breaking strain of PEUU-PC (1250±221%) was higher than for PEUU-COOH (649±47%) and PEUU (660±85%). Ovine blood contact resulted in significantly lower platelet deposition on PEUU-PC surfaces than on PEUU or PEUU-COOH. All paclitaxel loaded polyurethanes released paclitaxel that was bioactive over at least a 1 wk period, inhibiting SMC growth (longer term release data under evaluation).

Conclusions: A biodegradable elastomeric poly(ester urethane)urea was synthesized that incorporated non-thrombogenic pendant groups and possessed attractive mechanical properties for coating applications. The new polymer exhibited markedly reduced platelet deposition as well as the capacity for paclitaxel controlled release. This biomaterial may find application as a drug-eluting coating for metallic vascular stents or as a scaffold for vascular tissue engineering applications where minimal acute thrombogenicity is required.

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References:

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