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Special Issue: Bioactive Surface Functionalization

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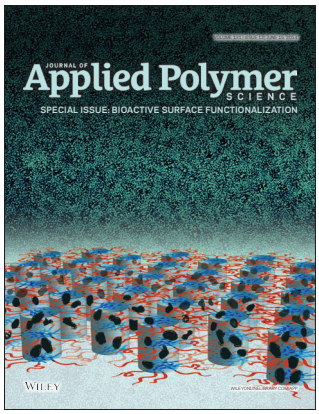

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Journal of Applied Polymer Science

REVIEW

Surface Modifying Oligomers Used to Functionalize Polymeric Surfaces: Consideration of Blood Contact Applications

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ABSTRACT: The surface modification of existing polymeric biomaterials represents a key strategy for improving the hemocompatibility in long- and short-term biomedical materials without altering their bulk properties. Several techniques have been widely explored to generate surfaces that can prevent the activation of the coagulation system and lead to subsequent clot formation on the surfaces of polymeric blood contacting devices. In particular, strategies whereby the base polymer is blended with surface additives (SMAs) and surface modifying macromolecules (SMMs) are now recognized as practical and effective methods to improve surface polymeric materials. This review highlights the more recent advances in the synthesis of such additives and their blending with base polymers, with a specific focus on SMAs and SMMs with a molecular weight in the oligomeric range ($<M_n$ ~12 kDa). The surface characterization of these modified materials is discussed in terms of water contact angle, X-ray photoelectron microscopy, atomic force microscopy, and the blood compatibility behavior, with specific attention to coagulation proteins and platelet adhesion. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40328.

KEYWORDS: surfaces, blood/polymer interfaces; additives; polymer blends; proteins; adsorption

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INTRODUCTION

The biomaterials device market has increased over the last decade and it is anticipated that their proliferation into the health care field will reach over $100 billion by 2016 with projected growth of 8–20% annually over the next 10 years.[1] Among the various types of synthetic polymeric biomaterials used in devices, the list includes polymers such as polysulfone (PSf), poly (methyl methacrylate) (PMMA), polyurethanes (PU), polydimethylsiloxane (PDMS), polyhexamethylene oxide, polytetrafluoroethylene (PTFE), polyvinyl alcohol (PVA), polypropylene (PP), poly(ethylene terephthalate) (PET), poly(glycolic acid), and poly(L-lactic acid) (PLLA). These latter materials are all widely applied in blood-contacting devices (e.g., vascular grafts, hemodialysis membranes, catheters, heart valves, intravascular stents) for interventional therapy related to various cardiovascular diseases. Although there has been more than 50 years of historical use for synthetic polymers in the cardiovascular field, many of the same limitations still persist: haemolysis, thrombosis, thromboembolic complications, anticoagulation-related haemorrhage, immune responses, infection, and tissue overgrowth.[2,3]

To address these needs, substantial attention has been given to the modification of polymeric surfaces.[4–7] Surface modification methods can be divided into three different categories: grafting, noncovalent coating, and blending strategies. Surface coating modifications include physical adsorption via intermolecular interactions or dip-coating,[8,9] self-assembled monolayers technology,[10–13] plasma deposition,[14,15] Langmuir-Blodgett techniques,[16,17] layer by layer,[18,19] and more recently mussel-inspired surface modification strategies.[20–22] Grafting technologies are classified into two categories referred to as "grafting to" and "grafting from" and include covalent reactions such as ozone-induced grafting,[23] chain growth grafting via surface initiated atom transfer radical polymerization (ATRP),[24] graft-to-surface via dipping, crosslinking, or reaction of the specific groups of polymers with the substrate,[25] and plasma treatments.[26] Although many of the above coating and grafting strategies have been applied extensively toward the improvement of blood contacting materials, they present a few drawbacks (i.e., low adhesive stability with the substrate for surface coatings and/or often complicated processes for surface grafting).

This article was published online on 07 January 2014. An error was subsequently identified. This notice is included in the online and print versions to indicate that both have been corrected 13 March 2014.

Under the grouping of simple techniques, the "blending" strategy is particularly attractive and several of the polymers that have been used in this manner are listed in Tables (I–III). This approach can be divided into three subgroups which include "entrapment," "interpenetration polymer networks (IPN)," and "migration". The entrapment concept has been primarily applied toward the modification of biodegradable polyesters such as polylactic glycolic acid (PLGA),[27] PLLA,[28] and polycaprolactone (PCL),[29] and for polymers with more long-term degradation profiles such as traditional PU,[30] PP, and PET. This technique was first defined by Ruckenstein and Chung[31] under the term of a "two-liquid deposition process." A few years later, it was redefined by Desai and Hubbell as the "surface physical interpenetration networks."[32,33] This surface modification technique has been applied to the entrapment of hydrophilic polymers and oligomers, for example, polyethylene glycol (PEG)[34,35] and amphiphilic triblock copolymers such as polyethylene oxide–polypropylene oxide–polyethylene oxide (PEO–PPO–PEO) polymers, referred to as pluronics.[36] The entrapment approach has been effectively used to embed natural biopolymers into surfaces to mimic the extracellular matrix and has included polymers such as gelatine,[27] hyaluronic acid,[37] chitosan,[38,39] heparin,[28,37] poly(L-lysine), and alginates derivatives.[40] This latter surface modification is achieved by inducing a reversible gelation of the polymer matrix. After swelling the base polymer base surface with a large excess of a solvent containing solubilized amphiphilic or hydrophilic oligomers, the entrapment of the latter molecules is carried out by exposing the system to a second solvent which causes deswelling of the base polymer surface.[34] Recent work has shown that PEG is not efficiently retained with nonpolar surfaces such as PP, whereas nonionic amphiphilic substances, especially tri-block copolymers (pluronics), are very effective for this type of surface modification. The superior behavior for pluronics is believed to be related to the self-association of the nonpolar solvent as a reversible micelle, thus yielding a higher modification efficiency in terms of wettability when the process is performed around the reverse critical micellar concentration (CMC).[41]

IPNs are typically based on the in situ polymerization of a functional vinyl monomer and a divinyl crosslinking copolymer in a solvent swollen surface of a semicrystalline polymeric substrate. Their reaction forms an IPN which has a durable immobilization of the functional polymer formed at the surface. This surface modification technique is hypothesized to work on all semicrystalline polymers and is defined as a thermoplastic semi-IPN. The surface modification produced by this technique is stable unless the polymer substrate is dissolved or melted. However, this is usually avoided by design. This technique has been applied to generate surfaces with entrapped oligomers. For example, pluronics have been entrapped in a PU film and subsequently crosslinked with dicalcium phosphate, a well-known crosslinking agent for poly ethers.[42] Different polymers have been interpenetrated in PU and PET polymeric surfaces for biomedical applications. Examples of these polymers have included pluronics,[42] poly methacryloyloxyethyl phosphorylcholine (MPC)-based polymers[43] and poly(sulfobetaine methacrylate).[44,45]

Over the last decade, polymer surface modification via blending of a surface modifier into a base polymer, and allowing its subsequent surface "migration" to the air/solution interface, has received considerable attention. This technique has been demonstrated to be a convenient, versatile, and effective strategy for generating blood compatible material surfaces with lasting effects.[46] Three types of surface modifiers, SMMs, SMAs, and surface-modifying end groups (SMEs), have been reported in the literature to increase the hemocompatibility and biostability of polymers such as PU, polyethersulfones (PES), PLGA, PLLA, and cellulose acetate (CA). SMMs are based on the use of an amphiphilic triblock copolymer formed by a hydrophobic or hydrophilic segment, usually identical or compatible with the polymeric matrix, and end-capping block segments (silicones, fluorinated segments, olefins, and others) with low polarity, of which perfluorinated segments have been among the most commonly used. SMAs were first introduced by Ward et al.[47] and are amphiphilic diblock or triblock copolymers where one of the blocks has higher affinity for the bulk material and the other block has little attraction for the base polymer which is usually caused by lower polarity or higher hydrophilicity. In the case of the SMEs, they are not considered additives since they are part of the base polymer backbone itself.

This review highlights the current advancements in the functionalization of surfaces using SMA and SMM methods between polymeric biomaterials and oligomeric chains ($M_n \sim$ 12,000 g/mol or M_w on the order of 10^4 or less).

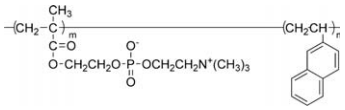
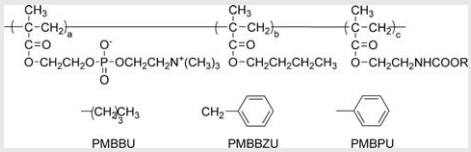
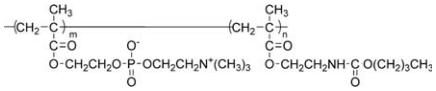
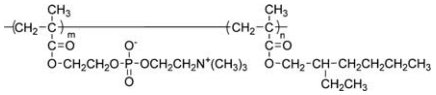
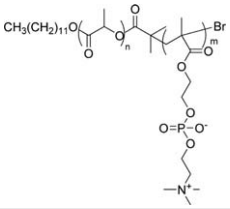
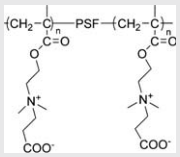
SURFACE MODIFYING ADDITIVES WITH NONFLUORINATED OLIGOMERIC CHAINS

Zwiterionic Structure Oligomers

The structures of several zwiterionic molecules are provided in Table I. There has been much interest in the utilization of materials containing zwitterion groups for non-biofouling and antithrombogenic polymeric surfaces. Zwitterionic structure monomers, such as phosphorylcholine (PC),[48–51] sulfobetaine,[52,53] and carboxybetaine,[54,55] have been demonstrated to reduce protein absorption and platelet adhesion. In particular, the biomimetic PC groups, a hydrophilic moiety naturally present among phospholipids head groups in the cell membrane, have received considerable attention. It has been shown that PC polymeric materials can produce an ionic solvation and induce hydration of the surface due to the electrostatic interactions with water molecules, also known as "free water," therefore reducing protein adsorption and cell adhesion[56–58] and contributing to their good hemocompatible properties.[59–65]

The above findings motivated the development of low molecular weight 2-MPC-based copolymers consisting of poly (MPC-*co*-PMB30) (30 mol % MPC and 70% *n*-butyl methacrylate label for (PMB)). These oligomers were blended at 1 wt % with CA via phase inversion to yield materials with improved blood compatibility for hemofiltration. X-Ray photoelectron microscopy (XPS) confirmed the presence of MPC units on the surface

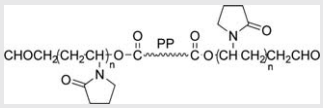
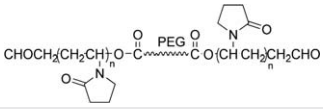
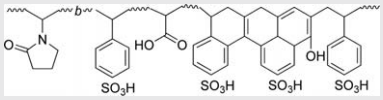
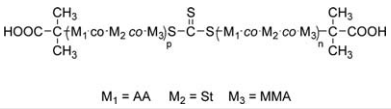
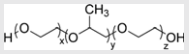
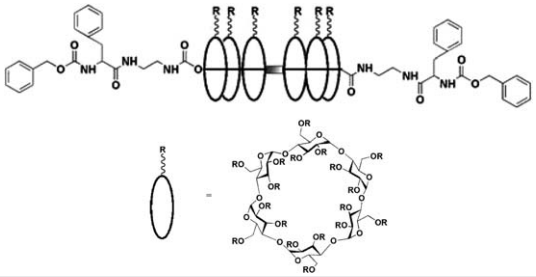
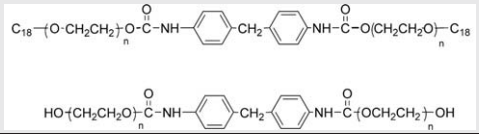
Table I. Typical Nonfluorinated Surface Modifying Additives Containing PC Headgroups That Have Been Used in a Blended Form and Showing Demonstrated Ability to Modify the Surface Chemistry of a Base Polymer

Oligomer	Structure	Technique	Reference
PMB 30 (MPC)-*co*-(BMA))		Blended with CA membrane	66,67
PMvN ((MPC)-*co*-2-vinylnaphthale (vN))		PET coated with PMvN by a solvent evaporation method	68
PMBBU PMBBZU PMBPU Copolymers of (MPC), (BMA), and MA with a urethane bond (MU)		Blended with segmented PUs (SPUs)	69
PMBU (MPC-MBU)		Blended with biodegradable PEUU scaffolds (electrospun)	70
		Blended with PSf	71
PMEH (MPC–EHMA)		Blending with PLGA by solvent evaporation technique	72
		Hybridization with Tecoflex PU	73
PLA-*b*-PMPC		PLGA and PLA-*b*-PMPC blending and subsequently dip-coating over PET surface	8
PDMAEMA-*b*-PES-*b*-PDMAEMA		Blended with PSf	74

of the CA/PMB30 membrane. Water contact angle (WCA) analysis showed that the hysteresis between the advancing contact angle and the receding contact angle of the membrane was increased from 16.8° to 21.1° by the addition of PMB30 to CA, indicating a higher surface hydrophilicity than that of the original CA membrane. This supported that the MPC units were present on the surface of the CA/PMB30 membrane. Due to the zwitterionic nature of MPC and its capacity to promote hydration on the surface, the CA/PMB30 membranes showed excellent blood compatibility,[66] which contributed to a decrease in the protein adsorption for albumin, immunoglobulin-G (IgG), and fibrinogen (Fg) when compared to CA membranes, thereby leading to reduced fouling. Also, the number of adhered platelets on the CA/PMB30 membrane was very low in comparison with that of the original CA membrane. However, the application of PMB to single-use medical devices is challenged by the fact that it requires a preconditioning period to fully wet the membrane. This results from the significant presence of hydration hysteresis during immersion. Other work has addressed the latter challenge with new low molecular phospholipid copolymers consisting of poly(MPC-*co*-2-vinylnaphthalene (vN)) (PMvN).[68]

Low molecular MPC–PMB-based copolymers synthesized with urethane chemistry, as poly(2-methacryloyloxyethyl phosphorylcholine-*co*-methacryloyloxyethyl butyl-urethane) (PMBU), have been used to prepare biodegradable fibrous scaffolds using electrospinning by blending with poly(ester urethane)urea (PEUU), at PMBU weight fractions of 0–15%.[70] XPS analysis showed that the surface N/C and P/C ratios increased from 2.6 to 5.8% and from 0 to 1.23%, respectively, with an increase of PMBU content and the corresponding MPC units in the modified scaffolds. In vitro studies showed that platelet deposition and rat smooth muscle cell proliferation on the scaffold surfaces decreased with increasing PMBU content. Moreover, the PEUU/PMBU scaffolds reduced the in vivo thrombogenicity when

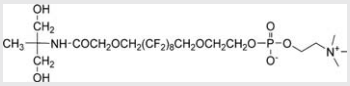
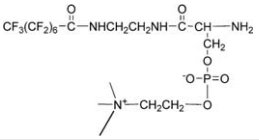
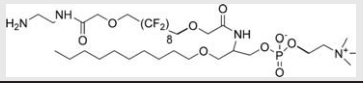
Table II. Typical Nonfluorinated Surface Modifying Additives That Have Been Used in a Blended Form and Reported to Demonstrate an Ability to Modify the Surface Chemistry of a Base Polymer

Oligomer	Structure	Technique	Reference
PP-*b*-PVP		Blended in PP	86
PVP–PEG–PVP) copolymer		Blended with PU (PEG)	90
HSLM P (SSt-*co*-AA)-*b*-PVP-*b*-P(SSt-*co*-AA)		Blended with PES to prepare flat-sheet membrane by liquid–liquid phase separation technique	91,92
P(SS-*co*-MMA) P(AA-*co*-MMA) (P(SS-*co*-AA-*co*-MMA)		Blended with PES	93
PEO-PPO-PEO-RGD (Pluronic-RGD)		Blended with PLA	94
(PRx-SO3's)		Blending with PU	95
MSPEO MPEO		Blended with PEU	96,97

compared to the unmodified PEUU scaffolds and allowed for complete endothelialization.

PSf has also been blended with PMBU (7 and 15 wt %) to prepare porous membranes with improved hemocompatibility and hydrophilic properties for hemodialysis, without any change in the mechanical strength when compared with the PSf membrane. The permeability of solute through the membrane, below a molecular weight (M_w) of 2.0×10^4, increased due to the presence of the PMBU copolymer, which conferred a higher hydrophilic character

Table III. Fluorinated PC Oligomers for Blending with PUs (FCPUs)

Fluorinated PC chains		Polymer component/molar fraction in feed	Reference
Name	Structure		
HFDAPC		MDI/PHPCD/BDO MDI/PTMG/BDO 2 : 1 : 1	165
FASPC		MDI/BDO/PHPC/EC HDI/BDO/PHPC/EC MDI/BDO/PTMG/EC HDI/BDO/PTMG/EC 3 : 0.2 : 2 : 1.6	164,166
ACFPC		MDI/BDO/PTMG/EC MDI/BDO/PEG:PTMEG/EC MDI/BDO/PPG/EC MDI/BDO/PHPCD/EC 3 : 0.5 : 2 : 1	163,167

and rendered the interaction between the modified membrane surface and proteins very weak. Like the other PC oligomeric derivatives described above, a reduction in adsorbed protein and platelet adhesion on the PMBU/PSf membrane was observed.[71]

Oligomers of poly(2-methacryloyloxyethyl phosphorylcholine-2-ethylhexyl methacrylate) (PMEH) have been synthesized by radical copolymerization and were used to demonstrate the application of MPC oligomeric additives not only as non-biofouling strategies but also for providing anti-inflammatory character to the base polymer. PLGA/PMEH biodegradable blended membranes with a PMEH concentration of 0–1 wt % were prepared by a solvent evaporation technique.[72] XPS analysis revealed that the MPC unit was exposed on the PLGA/PMEH membrane and that the surface concentration of the MPC unit on the membrane was increased with a higher concentration of the PMEH in the blended membrane. Differential scanning calorimetry (DSC) measurements of the modified membranes yielded only one T_g, suggesting that PLGA and PMEH were homogeneously mixed.

3T3 mouse fibroblasts were cultured on the PLGA/PMEH membrane for 2 days and were evaluated for the number of adherent cells, which decreased when the concentration of the PMEH was increased. In addition, the expression of Interleukin-1b (IL-1b) mRNA (inflammatory cytokine expressed from adherent human premyelotic leukemia cells)[75] on PLGA/PMEH membranes containing 0.2 wt % of PMEH was significantly lower than that on PLGA membrane.[72] MPC–EHMA-based copolymers have also been prepared in the form of diblock polymers, poly(MPC-*block*-2-ethylhexyl methacrylate (EHMA)) (B-PMEH), by reversible addition-fragmentation chain transfer (RAFT)-controlled radical polymerization.[73]

MPC-based oligomers have also been used to enhance the biodegradability of polymers.[76,77] This has been achieved with blends of the oligomers and biodegradable polyesters such as PLGA and PCL. An example of such molecules includes the amphiphilic diblock copolymer poly(DL-lactide)-*block*-poly (2-methacryloyloxyethyl phosphorylcholine) (PLA-*b*-PMPC) generated via ATRP[78] and blended with PLGA using 0, 5, 10, and 15 wt % of PLA-*b*-PMPC content.[8]

Attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy showed how the signal of the phosphoric ester and trimethyl ammonium groups became intense with the increase of PLA-*b*-PMPC content to 10 and 15 wt % in the membranes. The contact angle hysteresis was increased from 31° to 53° by the addition of PLA-*b*-PMPC (indicating a higher surface hydrophilicity), and being similar for 10 and 15 wt %. This indicated that the MPC was able to saturate the membrane surface when 10 wt % of the additive was used. Studies looking at the clotting time delay using blood plasma recalcification times showed that the polymer coating prolonged coagulation, and the amount of adherent platelets found on coated surfaces was decreased by increasing the PLA-*b*-PMPC content in the membrane. The synthesis of end-capped PCL with PC groups has also been reported.[79] However, it should be noted that there has been limited commercial use of the zwitterionic copolymers as membrane additives because of their low solubility in aprotonic solvents such as *N,N*-dimethyl formamide and *N*-methylpyrrolidone.[80,81] Hence, new approaches to solve this problem have been conceived. One example, is the preparation of PSf-modified membranes using surface zwitterionicalization from a PSf-based block copolymer additive containing poly(*N,N*-dimethylamino-2-ethylmethacrylate) (PDMAEMA) blocks.[74] The low molecular weight additive, PDMAEMA-*b*-PSf-*b*-PDMAEMA, was synthesized via the combination of condensation polymerization and ATRP and blended with PSf to form membranes with additive content between 0 and 20 wt % (M0-M20) by a nonsolvent-induced phase separation process. The enriched PDMAEMA chains on the membrane surface were further transformed into zwitterionic poly(carboxybetaine methacrylate) (PCBMA) by quaternizing the M20 membrane with 3-bromopropionic acid for a period of 12, 24, and 48 hours. The surface elemental mole percentages of the prepared membranes and the surface-zwitterionicalized M20 membranes were determined by XPS. As a result, the N/S mole ratio increased from 0.56 for M0 to 3.40 for M20, indicating the higher concentration of PDMAEMA on the surface. These values increased with the M20 quaternization reaction time due to a further segregation of PDMAEMA chains at the surface following their transformation into PCBMA chains. Moreover, with an increase of the block copolymer concentration in the membrane and quaternization reaction time, the initial contact angle of the blended membranes decreased, leading to an enhanced hydrophilicity. As a result of this surface character, fouling-resistance and inhibition of platelet adhesion were significantly enhanced.

Low molecular weight PUs and pluronics containing PC and sulfobetaine have been synthesized as block oligomers showing high potential for their use in polymer blends to improve the hemocompotability of base polymers.[82–85]

Polyvinylpyrrolidone (PVP), PEG, Heparin-Like Structures and Negatively Charged Acrylic Oligomers

Several other nonfluorinated oligomers, with and without charged structures, have simulated biomacromolecule function such as that found in proteins, heparin, and glycocalyx structures (Table II). PP-*block*-poly(vinylpyrrolidone) (PVP) triblock (A-B-A) oligomers were synthesized through the esterification of dicarboxyl-terminated PP with monohydroxyl-terminated PVP[86] and blended with PP to prepare PP-*b*-PVP/PP films. For example, the WCA of the film was reduced from 99.51° for PP to 55.49° for the modified PP at a loading of 5 wt % PP-*b*-PVP triblock copolymer. With these changes, it was found that PP-*b*-PVP/PP films showed lower platelet adhesion and less hemolysis when the additive was increased, as well as longer prothrombin reaction times in comparison with unmodified PP films.[87] The host-philic segment (PP) within the PP-*b*-PVP yielded good affinity with the PP base, thus providing more resistance to erosion and extraction by solvents.[88,89] In a similar manner, the modification of PU was achieved by blending the base polymer with low molecular weight PU-*b*-PVP copolymer (1–5%) and forming films by solution-casting.[90]

Another promising strategy involves the synthesis of antithrombogenic ionic macromolecules with heparin-like

structures.[91,93,98–100] Sulfonated poly(St-*co*-AA)-*block*-poly(VP)-*block*-poly(St-*co*-acrylic-acid (AA)) low molecular copolymer, with a concentration between 0 and 7 wt %, was blended with PES to prepare membranes by liquid–liquid phase separation technique. It was observed with scanning electron microscopy and atomic force microscopy (AFM) that with the increased content of the additive, more pores appeared in the membranes and the surface was roughened with many tiny grooves and fine pores. The latter resulted from the tendency of the copolymer (due to its partial hydrophilicity) to move toward the water/polymer interface when phase separation occurred. The abundance of the additive on the surface was further confirmed by FTIR and XPS analysis. It was found that the blood clotting was prolonged in the modified membranes when compared with PES membrane. As well, with the increase of the amount of copolymer, the blood clotting time was also increased significantly. It was also found that platelet adhesion decreased when the additive was increased in the modified membranes. The mechanism was explained to be dependent on the presence of anionic or polar groups (SO_3H, COOH, and OH) which were abundant on the surface of the membrane and mimic the anticoagulant character of the heparin, as well as providing wetting properties provided to the membrane.

However, retention in the membrane was reported to be a concern. Hence, similar low molecular poly(St-*co*-AA)-*block*-poly(VP)-*block*-poly(St-*co*-AA) copolymers were generated without sulfonation, and these were blended with PES at 0–5 wt %.[92] In this latter work, the adhesion of bovine serum albumin (BSA) and Fg was reduced and low platelet adhesion and prolonged activated partial thromboplastin time were reported when compared to bare PES membranes.

Another approach toward generating ionic membranes with oligomers is based on the biomimetic engineering of glycocalyx-like surfaces. Glycosylated molecules are located in the external region of a cell membrane and they are involved in specific interactions such as cell–cell recognition. They also contribute to the steric repulsion that prevents undesirable nonspecific adhesion of other molecules and cells.[101] Low molecular weight pluronics were activated by methyl sulfonyl chloride and amino acid and peptides were tethered to prepare an additive with both nonadhesive (PEO) and cell attachment properties.[94] Modification of poly(DL-lactic acid) (PDL-LA) was carried out by blending the PLA with the PEO–PPO–PEO or its amino acid and an RGD derivatized form, at 0.5%, 2%, 5%, and 10% of the additive in the whole polymer. ATR-FTIR, XPS, and contact angle confirmed the possible self-segregation behavior of PEO–PPO–PEO amphiphilic copolymer on the surface of PDL-LA matrix where the PPO segments are entangled with PDL-LA and PEO chains elongate and form an outer layer which may serve to reduce the nonspecific adhesion of cells and proteins. The PEO chains can also covalently bind amino acid sequences such as RGD at the terminal ends to induce specific cell interactions. It was observed that the PEO–PPO–PEO amino acid and RGD derivatized/PDL-LA films promoted chondrocyte attachment and growth which could have potential for tissue engineering applications.

Polyrotaxanes are polymers in which cyclic molecules are threaded onto linear polymeric chains and capped with bulky end groups to mimic supramolecular systems from nature. In this sense, low molecular sulfonated polyrotaxanes (PRx-SO_3's) composed of PEO-*b*-PPO-*b*-PEO and capped with (*Z*)-1-phenylalanine tri-block copolymers and cyclodextrins were prepared and blended with PU forming films.[95] Reduced protein adsorption for albumin and fibrinogen was observed for material with oligomer concentrations from 0.5 to 4 wt %. As well, the relative content of the additives and the enhanced surface hydrophilicity was reported to be correlated with the inhibition of platelet activation and bacterial adhesion. Another low molecular weight polymer based on poly(ethylene oxide) (MPEO) and steryl poly(ethylene oxide) (MSPEO) blended with polyether urea (PEtU) providing improved endothelial cell adhesion and better resistance to the clotting process.[96,97]

SMMS BASED ON FLUORINATED OLIGOMERS

PUs are one of the most important classes of thermoplastic elastomers used in healthcare today and have been widely applied as biomedical materials because of their tailored stability, excellent mechanical and physical properties, thermoplasticity, and relatively good biocompatibility.[102–108] However, their function as long-term blood-contacting implants for in vivo applications is limited by their susceptibility to hydrolysis under the environmental conditions of the body. Similarly, persistent long-term issues with hemocompatibility related to protein adsorption on the material surface and platelet activation to amplify coagulation has limited their long-term effectiveness.

The versatility of the PU block segment structure led to the use of this chemistry in the synthesis of oligomeric fluorinated PUs (FPUs), also referred as SMMs and SMAs in the literature, as a means of masking hydrolytically sensitive groups.[109,110] The presence of terminal fluorinated chains in the PU confers to the final polymer a set of desirable properties such as enhanced thermal and environmental stability, water and oil repellency, low coefficient of friction, good chemical resistance, and generally good blood compatibility with low denaturing of coagulation proteins.[111–114] Most commonly reported in the literature, fluorinated segments are incorporated into PUs via fluorinated polyester or polyether diols as soft segments,[115–117] using fluorinated diisocyanates or fluorinated chain extenders as hard segment components,[118–121]or via end-capping active functionalized fluorinated segments.[110,119,122] Although showing promising blood compatible behavior, some reported disadvantages of classical linear FPU structures have included limited control over the surface's hydrophobicity associated with the restricted surface migration of the fluorinated hard segments, the loss of some mechanical properties associated with a decrease in the molecular weight, particularly reported for long-term biomedical applications.[123–126]

Examples of these additives have also included block copolymers having one fluorine-containing block[127,128] and end-capped acrylic or polyester oligomers.[129] Polymeric blends based on SMMs show advantages over small molecular weight nonoligomeric additives because they are anchored to the modified

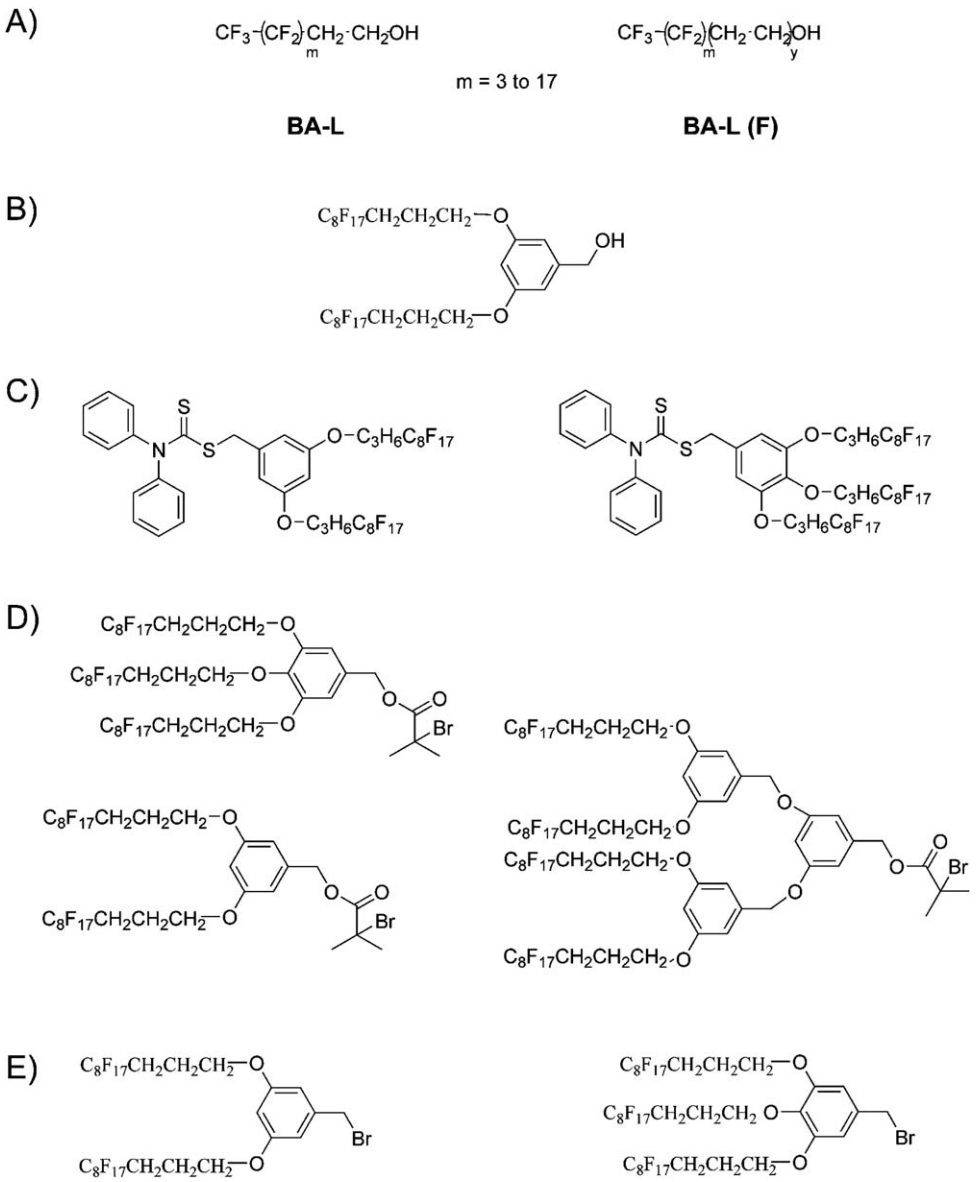


Figure 1. Fluorinated structures for SMMs and multi-end functionalized SMAs synthesized: (A) SMMs end-capping, (B) fluorocarbon functionalized benzyl alcohol initiator (ROP), (C) fluoroalkyl functionalized CTAs, (D) ATRP initiator, and (E) living anionic polymerization initiators.

polymeric matrix via physical entanglement and noncovalent interactions, achieving a more stable modified surface. The noncovalent interaction could be H-bonding interactions between the base polymer and the SMMs; however, the specific nature of the interaction is usually established by the chemistry of the SMM.[130] The driving force that promotes the migration of the fluorinated SMMs to the surface is mainly thermodynamic, where the fluorine chains, with the lowest critical surface tension, rise to the air–polymer interface thereby lowering the interfacial free energy which is a condition well known to produce less protein adsorption.[131,132] However, other parameters such as the molecular weight of both the SMMs and the base polymer and the nature of the interactions between the components of the blended system are also important in the migration mechanism.[133]

The following section focuses on the different forms of fluorinated SMMs, which have been blended with all types of polymeric matrices, with PUs being the most frequently modified matrices.

Oligomeric End-Capped Fluorinated Segments Based on SMMs and Fluorinated SMAs

End-functionalized fluorinated oligomers appear to have yielded the greatest success in terms of surface and blood contact properties achieved. This appears to be mainly due to their inherent compatibility with the corresponding base polymers and free mobility of the terminal fluorinate groups. The end-functionalized oligomeric additives can be divided into two different groups based on their synthetic strategies: mono-end functionalized fluorinated oligomers (SMMs) based on PU chemistry[109,134] and multi-end

functionalized fluorinated SMAs based on ATRP, RAFT, and ring opening polymerization (ROP) reactions.[129] The fluorinated end-capping groups and the fluorinated initiator for those strategies are provided in Figure 1.

The SMM synthesis is based on the two-step solution polymerization method. In a first step, a prepolymer with terminal isocyanate functional groups is obtained from the reaction between a polyol and a diisocyanate. In the second step, the end-capping of this prepolymer is carried out by reaction with a monofunctional fluorinated alcohol (BA-L).[109,110,135,136] Following this protocol, Tang et al.[109] synthesized a series of SMMs using 1,6-hexanediisocyanate (HDI), two polyols of similar molecular weight (1000), PPO and polytetramethylene oxide (PTMO), and monofunctional fluorinated alcohol BA-L of three different lengths (see structure in Figure 1). These SMMs were synthesized with the desire to assess if the fluoroalcohol chain would have the ability to enhance the surface biostability of the base polymer and influence protein interactions. These SMMs showed lower fluorine content in the final oligomers than the anticipated theoretical values. The authors have suggested several explanations such as the low reactivity of the hydroxyl end-functional group of BA-L associated to the electronegativity of the adjacent fluorine atoms, chemical incompatibility of the prepolymer and BA-L in the second step reaction, and the possible changes in reaction temperature control which could cause side reactions.

The surface characterization of a series of SMM-modified materials at 5 wt % in PEUU-based polymers, where the base was synthesized with 2,4-toluene diisocyanate/PCL/ethylene diamine, was reported. The good migration of the SMMs to the surface was confirmed by an elevated advancing and receding WCA, similar in nature to fluoropolymers such as Teflon, and an increase in the fluorine content within the upper 10 nm of the surface, determined by XPS.[110,122] The materials showed very little change in thermal transition temperatures, determined by DSC and suggested that the bulk PU matrix microstructure was minimally altered by the SMMs, a reflection that most of the SMM migrated toward the surface versus remaining in the bulk.[122] The SMM surface migration was shown to be an effective strategy for inhibiting the hydrolytic degradation of the PEUU by cholesterol esterase, a lysosomal enzyme that could be released by inflammatory cells.[137] However, they found that not all SMMs enhanced the hydrolytic stability of the PEUU in the same manner, even though XPS data suggested that the surface was dominated by the SMMs.[110,122] These observations would indicate that the surface stability of the SMMs is conditioned by their compatibility with the substrates. As well, a study of Fg adsorption showed a reduction in the adhesion of this coagulation protein onto the PEUU material blended with 5% of SMM in comparison to the native PEUU, which suggested their potential application for improving blood compatibility.[122]

SMMs based on HDI/PTMO/BA-L and HDI/PPO/BA-L chemistry with different molar ratios 2 : 1 : 2 and 3 : 1 : 2, using different oligomeric fluoroalcohol end capping molecules such as BA-L (F) (Figure 1), have been studied as potential additives to promote the blood compatibility of traditional PUs, such as polyether urea urethane (PEtUU).[130,138] Interestingly, the WCA analysis showed a poor direct correlation between the fluorine content and the increased hydrophobicity of the surface, suggesting that other physicochemical properties of the SMM were contributing to the wettability characteristics. SMM-PEtUU based on BA-L (F) produced the lowest increase in surface hydrophobicity while SMMs based on PPO soft segment showed the highest hysteresis. This implied that the flexibility of the terminal fluorine chain, the SMM chemistry and mobility, the length of the fluorine tail, and the nature of the central chains can influence the surface wettability. In vitro studies, looking at Fg, fibronectin, and vitronectin surface adsorption and platelet adhesion, showed lower protein adhesion and platelet adhesion for all SMM-modified PEtUU surfaces relative to unmodified PEtUU. The platelet adhesion was significantly lower for the surfaces containing SMMs based on the soft segment PPO (PPO 212L) and the SMMs synthesized with BA-L (F) (PTMO212F). Therefore, platelet adsorption and activation onto the polymer surfaces appear to be influenced by multiple factors including chain mobility, fluorine content, diisocyanate : soft segment ratio, and the morphological surface features induced by the SMMs.[138]

The above studies based on SMM-modified PEtUUs suggest that the surface distribution of Fg rather than the amount of Fg is a more predictive character of platelet morphology/activation. This deduction was based on the results obtained from in vitro experiments in which SMM-modified PEtUU surfaces (control and SMM modified) were compared after their immersion in whole human blood and platelet free human plasma. The elevated statistical correlation of the area and length morphology parameters, between the Fg distribution and the platelet adhesion morphology in the blended surface, suggested that the aggregation of Fg leads to a platelet activation state.[111] Additional experiments based on lactate dehydrogenase and ^{51}Cr showed that the reduction in platelet adhesion for SMM-modified PEtUU surfaces is not associated with platelet lysis but rather reduced activation and adhesion. Therefore, factors such as Fg binding affinity, spatial distribution, and conformational states were hypothesized to be responsible for the reduced platelet adhesion on the SMM-treated materials.[139] ENDEXO is an example of fluorinated SMMs that have been introduced in the Canadian, European, and United States markets as nonthrombogenetic materials. ENDEXO technology has been developed by Interface Biologics to improve the blood contacting properties of medical devices with minimal change in manufacturing procedures for the traditional devices and has shown excellent results in terms of platelet adhesion and thrombus formation (see Figure 2).

PES membranes have been widely applied for blood purification[140,141] applications due to their thermal and chemical stability and mechanical properties. However, these membrane systems suffer from poor blood compatibility properties. Hence, the blending of SMMs additives with the materials may be one possible approach in improving performance.[135] A variety of SMMs based on methylene diphenyl diisocyanate (MDI), one of the following two diols, PCL or PPO, and the end-capping fluoro-oligomers BA-L or BAL (F) have been blended in a

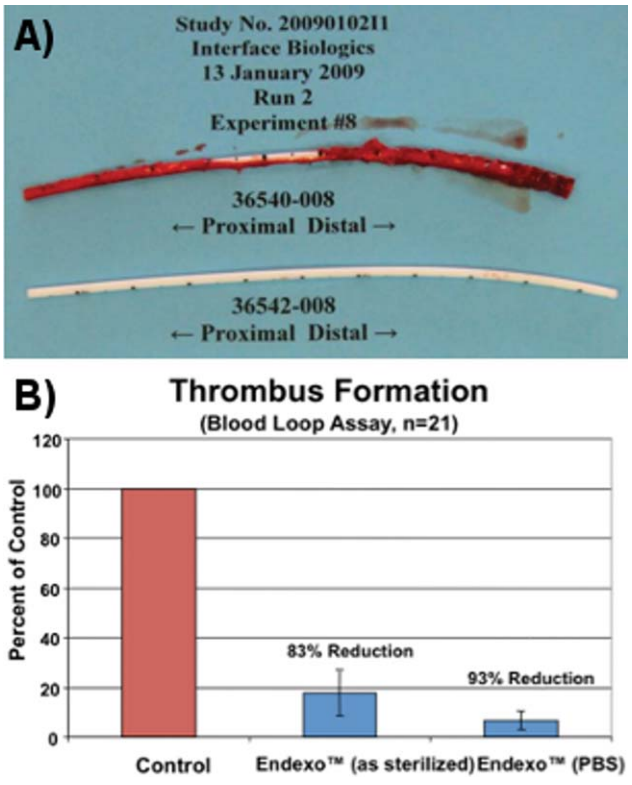


Figure 2. Previously unpublished data. (A) Vascular device modified with ENDEXO additive (bottom tube) and no additive control (top tube), after their "In vitro blood loop" test. (B) Thrombus formation percentage versus control device (Reproduced with permission from Interface Biologics). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

concentration of 4 wt % in a PES matrix to determine their surface character with respect to energetic and protein adhesion. These modified membrane surfaces have shown an increase in their advancing WCA as well as an increase in fluorine group content at their surface and varied depending on the chemical composition of the SMMs. SMMs promoted an increase in surface heterogeneity due to their surface enrichment and formed microdomains at the surface.[135]

Functionalized fluorinated SMAs with multiple perfluoro chains provide an alternative approach to the preparation of polymeric additives, with the main chain carrying multiple CF_n groups (2–4 CF_n) at one end, which can help to reduce the amount of macromolecular additives required to reach PTFE-like surface properties.[129] Moreover, the chemistry involved using this approach offers the dual benefits of being applied for a variety of polymerization mechanisms. This offers a wider range of polymers or oligomeric additives as well as provides good control over the final molecular weight achieved. Multi-end functionalized fluorinated SMAs are generated based on a dendron-type structure constituting low generation (G0, G1, or G2) head groups, functionalized with different numbers of fluoroalkyl (CF_n) groups, and a linear oligomeric chain that is usually compatible with the polymeric matrix.[142] The dendritic multifunctional group has been used as an initiator in a large variety of polymerization processes to impart end functionality to the growing homopolymer chain. Up to now, they have been used as initiators for ATRP reactions of styrene (Sty) and methylmethacrylate (MMA),[114,142,143] and in the living anionic polymerization of butadiene, polyethylene, and Sty.[144–146] Also, fluorine containing benzyl alcohol has been used during the ROP of lactide.[147] More recently, SMAs have been generated based on PVP by RAFT via the use of CF_n functionalized chain transfer agents (CTAs) (Figure 1).[148] The blended material generated with a PVP matrix as the base polymer and the fluorinated additive showed a reduced surface energy, rendering their surface more hydrophobic and lipophobic. Generally, variables such as the additive's molecular weight, matrix molecular weight, number and size of the CF_n groups in the dendron end-groups, additive concentration, and postannealing process determine the effectiveness of these additives as surface modifiers.[129] In general, higher additive concentration and number of CF_n groups produce an increase in the static water and dodecane contact angle, while the increase in the additive molecular weight produces the opposite effect.[148,149] For example, PLA blended with 5 wt % of dendron functionalized-PLA bearing, two C_8F_{17} groups at the end, produced a 30° increase in the static WCA relative to the unmodified PLA. Similar behavior was noted for the PS, PVP, and PMMA analogs in their respective matrices.[147] An important finding, using Rutherford backscattering for annealing studies of these blended systems showed that a plateau for static WCA was observed at higher additive concentration. This was explained based on the surfactant behavior of these additives rather than invoking surface saturation.[145,148,149] At higher concentrations, above the critical aggregation concentration, the polymeric chains can form aggregates in the bulk matrix just as micelles do in solution. The latter systems have not yet been studied for their hemocompatibility but they have demonstrated high potential for use in this field.

SMMs with Pendant Fluorinated Chains

An alternative to the fluorinated SMMs-end-capped molecules is the synthesis of SMMs where the fluorine-containing pendant groups are part of the soft segment. A recent example of this included the FPU with a low molecular weight (M_n = 7000 g/mol) oligomer prepared using a fluorinated polyether glycol.[150] A more promising system could be the new SMMs defined as "polymeric surface modifiers" (PSMs), reported by Wynne et al.[151] and synthesized as PU having a co-polyoxetane soft blocks (P[AB]). This soft block is made up from a 1,3-propylene oxide main chain with different side chains (A and B) where A is a trifluoroethoxymethyl side chain $-CH_2OCH_2CF_3$ and B is a PEG chain,[127] among others. [151,152] This strategy is based on two established concepts, first the tendency of soft segments with low T_g to concentrate at the surface[153,154] and second, the "chaperone" function of the fluoro-carbon group A, which can help in the surface migration of additional functional groups. This phenomenon has already been reported for fluorinated SMMs consisting of additional functional groups such as biocides[155] and bioactive molecules.[156,157] The idea of introducing both fluorinated side chains and hydrophilic chains comes from the recent anti-biofouling strategies based on SMAs that combine hydrophilic and hydrophobic surface active blocks which can self-assemble to generate amphiphilic surfaces. These SMAs are copolymers that present both, low surface energy side chains as PDMS[158] or fluoro-carbon (C_nF)[128] and hydrophilic side chains based on PEG. It is thought that the phase segregation that these amphiphilic block copolymers may experience

could be useful for applications in preparing blood compatible materials.[127,159]

Hybrid Phosphorylcholine Fluorinated Surface Modifier

Despite the promising results demonstrated from blending strategies based on PC or SMMs on their own (see Tables I and II), there are still limitations that have not been overcome in blood contacting applications. For instance, the poor compatibility between MPC homopolymers and the base substrates promotes the detachment of the PC chains from the surface, causing loss of integrity and erosion of the polymer blends.[160,161] Moreover, there is difficulty to achieve the migration of phosphatidylcholine moieties to the surface when they are incorporated through the hard[60,61] or the soft segments.[59] An increase in the ratio of phospholipid monomer is required but this leads to a reduction in mechanical properties within the base polymers.[61] On the other hand, the use of small molecules that combine fluoroalkyl and PC moieties simultaneously could address this challenge as it has been shown with low density polyethylene.[162] In this sense, the concept of such SMMs provided a promising strategy since fluorinated alkyl chains can direct the biomimetic phosphatidylcholine moieties toward the surface and simultaneously limit water uptake given the fluorine chemistry's inherent hydrophobicity.[163,164] Examples of these systems are described in Table III.

Tan and Liu (2006) have reported on the synthesis of a fluorinated alkyl phosphatidylcholine diol (2-[2-2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluoro-10-ethoxy-decyloxy-*N*-(2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-acetamide] phosphotidylcholine (HFDAPC).[165] This monomer has been used in the synthesis of both poly(carbonate urethane)s (FPCPCU)[165] and poly(ether urethane)s (FPCPEtU)[168] by a conventional polyurethane synthesis method with different ratios of both chain extenders, butanediol (BDO) and HFDAPC. Despite yielding adequate mechanical properties of cast films based on these oligomers, the ultimate tensile strength of FPCPCU is two times lower than that of the base polycarbonate urethane (PCNUs). This has been attributed to a reduction of hydrogen-bonding for the carbonyl groups in the hard segments and polycarbonate segments, and consequently an increase in the phase mixing. However for the FPCPEtU, an increase in the phase separation is observed.[113] BSA, IgG, and Fg adsorption for the FPCPCU synthesized with 5% of HFDAPC showed a reduction in the amount of adsorbed protein when comparing the material with its respective analog PCNU and high molecular weight fluorinated FPCU. These FPCPCU polymers have been blended as additives into PEtU matrices and were characterized by WCA, XPS, and AFM. The data not only demonstrated that fluorinated PC units were enriched on the surface but also demonstrated alternating changes in hydrophobic character between the hydrophobic fluorinated group and hydrophilic PC group depending on the environmental condition presented (i.e., dry vs. wet conditions).[169]

New end-capping monomers, 2-amino-3-oxo-3-(2-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctan amido) ethyl amino) propyl phosphorylcholine (FASPC)[166] and amino-functionalized hybrid hydrocarbon/fluorocarbon double-chain phospholipid (ACFPC),[167] have been recently synthesized. FASPC is a new amine monomer that possesses both fluoro and PC functionalities in its structure. This end-capping molecule has been applied in the synthesis of a series of PUs based on HDI and MDI, two different soft segments, PTMG) and PHMC (poly(1,6-hexyl-1,5-pentyl carbonate)), and BDO as a chain extender. The preliminary hemocompatibility studies of films based on these polymers have shown between 87% and 98% reduction in Fg adsorption with respect to the conventional PEtU as well as a minor number of platelets attached to the surface films. Moreover, these platelets were not deformed and activated when compared to the conventional PEtU.[166] One polymer in this latter series has been blended with PEtU to improve the hemocompatibility of this PU. P-(HFPC) (3/2/0.2/1.6 molar ratio of HDI/PHMC/BDO/FASPC) at 5% additive content was shown to retain the original base polymer's mechanical properties but yet yielded an 87% reduction in fibrinogen adsorption with respect to the native PEtU. As well, it showed almost no appreciable platelet adhesion. The addition of further oligomer did not show any improvement in blood contact character. This was consistent with the XPS results where no changes in phosphorous or fluorine concentration were observed on the surface for concentrations higher than 5%.[164]

The ACFPC materials also have the potential to self-assemble at the surface, yielding very stable structures when compared with non-amino functionalized hydrocarbon chains of phospholipids. This is a result of its lower CMC and its higher zeta potential at physiological pH.[167] Different FPCPUs based on MDI and BDO as the hard segment, and using four soft segments, polytetramethylene glycol (PTMEG), polypropylene glycol (PPG), poly(1,6-hexyl-1,5-pentylcarbonate) diol (PHPCD) and PEG, have also yielded structures which rearrange to mimic the surface of biomembranes under aqueous conditions as was showed by AFM. These structures are believed to contribute to their favorable hemocompatibility, with a 95% reduction in Fg adsorption relative to a conventional PEtU. Although, they have not been blended on PUs yet, it is believed they can show a high potential as blending SMAs.[163]

BIOACTIVE FLUORINATED SURFACE MODIFIER

Despite the favorable protective character provided by fluorinated-SMM to hydrolytic degradation, the coverage and shielding effect to hydrolysis and oxidation is not 100%.[170] Therefore, it was conceived to present additional chemical function at the surface that may control the interaction of macrophages with the biomaterial substrate and simultaneously provide more protection against oxidation. Labow and Santerre[171] introduced a new concept based on the utilization of the fluorinated terminal end group surface migration to provide the simultaneous delivery of biologically active moieties to the surface along with the passifying nature of the fluoro-oligomer. These new additives have been termed bioactive fluorinated surface modifiers (BFSM). One example of these additives involved the coupling of vitamin E, a natural antioxidant molecule with established benefits in preventing oxidation in polymer blends.[172] The SMM was synthesized using lysine diisocyanate (LDI), polycarbonate diol (PCN), and a fluoroalcohol in which the pendant LDI ester was derivatized with vitamin E

immediately adjacent to the terminal fluro-oligomer of the SMM. Blended films of polycarbonate PU with 5 wt % of bioactive/non-bioactive SMMs were prepared by solvent casting and showed antioxidant activity relative to base polymer and non-Vitamin E-SMM/polymer blends, demonstrating greater resistance to degradation than non-bioactive SMMs.

A similar approach was used to couple a cell adhesive peptide sequence to the SMM, which was blended into PCNU to limit nonspecific cell adhesion, and to promote desirable cellular interactions.[156] In this latter work, the fluorinated additive structure was modified to include a labile ester and was subsequently reacted with an NH_2-GK*GRGD-$CONH_2$ peptide sequence (referred to as RGD), coupled via carbodiimide conjugation chemistry. When the additive (RGD BFSM) was blended with PCNU at a concentration of 5 wt % by solvent casting, the migrating RGD BFSM in the PCNU blended film was confirmed by XPS analysis. The number of U937 macrophage-like cells and human monocytes that were adhered to the surface of the films were significantly increased on the RGD BSFM-modified materials when compared to PCNU alone and the non-bioactive fluorinated surface modifying macromolecule substrates.

Another example of such molecules includes strategies for the incorporation of elastin peptides onto the surface. Elastin is an important extracellular matrix protein[157] since materials adsorbed with elastin-derived peptides and recombinant elastin-like polypeptides (ELPs) have previously been demonstrated to yield a low incidence of platelet deposition.[173,174] In this latter work, elastin crosslinking peptides (ECPs, M_w: 1.8 kDa) were conjugated to the SMM, LDI ester, and blended with PCNU in an ECP-BFSM concentration of 0.05 or 0.5 wt % to form films by solvent casting. It was demonstrated that the ECP-BFSM migration to the polymer–air interface was able to generate a saturated surface using 0.05 wt % under specific casting conditions. In addition, it was demonstrated using a bicinchonicic acid assay, contact angle measurements, and XPS analysis that these surface-ECP-BSFM/PCNU films could be used as a site of attachment for ELPs (M_w:31 kDa), through a crosslinking method that simulated in vivo conditions,[175] resulting in a stable and elastin-like rich surface. Preliminary in vitro studies with vascular smooth muscle cells (VSMCs) demonstrated enhanced cell adhesion, spreading and retention on the elastin-modified films compared to the PCNU base polymer controls. Using the same procedure, elastin-modified films reduced platelet adhesion and bulk platelet activation, when in contact with reconstituted human blood, when compared to uncoated base PU controls. The elastin-modified films also promoted endothelial cell adhesion, showing actin cytoskeleton and enhanced endothelial nitric oxide synthase expression relative to the control surfaces.[176] Based on these results, the elastin containing fluoro-oligomer represented a practical alternative to the use of native elastic fibre for vascular applications. Using the latter materials, electrospun scaffolds and films were prepared by blending PCNU with or without 0.05 wt % ECP-BSFM to assess the importance of the electrospun architecture with respect to VSMC adhesion and function.[177] The crosslinking of the elastin peptide to both electrospun and smooth films were conducted as previously described on flat films. Elastin surface-modified PCNUs were shown to enhance VSMC adhesion and maintenance of cell numbers over a 1-week period relative to controls. VSMCs seeded on the elastin surface-modified materials were also shown to exhibit the cell morphology and biological markers of a contractile phenotype including a spindle-like morphology, actin filament organization, and smooth muscle myosin heavy chain expression, with good organization in the fibre structures. Competitive inhibition experiments demonstrated that the elastin–laminin cell surface receptor and its affinity for the VGVAPG peptide sequence on the elastin peptide molecules are likely involved in the initial SMC contact with the elastin-modified materials.

CONCLUSIONS

Despite the recent contributions in materials science related to the innovation of promising blood contacting novel biomaterials,[178,179] the strategy toward improving the surface properties of the existing materials is still widely being explored with the goal of implementing practical surface modification strategies. Among the many surface modification techniques available, the blending strategy is still considered one of the most important approaches for improving surface hemocompatibility while minimizing the compromised physical state and mechanical properties of the base polymer.

Over the past decade, surface modifying oligomers have been synthesized based on two migration chemistries, namely hydrophilic and zwiterionic chains such as PEG, PVP, and PC, and second, low polarity chains such as fluorinated alkyl chains (C_nF). Nonfluorinated SMAs have shown some limitations due to their hydrophilicity which renders them more susceptible to leaching from the surface, thus producing an unstable surface modification. However, recent advances in living radical polymerization such as RAFT and ATRP have allowed researchers to generate SMAs with desirable chemistry and controlled molecular weight, thereby providing better compatibility with the polymeric matrix and reducing the amount needed to be blended in order to affect a surface change.

The chemistry of fluorinated SMMs based on PUs has allowed researchers to produce PUs with desirable surface properties. More recently, advances in controlling polymerization has allowed the field to extrapolate the fluorinated SMMs concept to other types of polymers such as PMMA, PS, PVP, and so on.

In addition to the above passive approaches, another concept that has been introduced is related to the introduction of bioactive functional groups such as RGD, elastin, and vitamin E into the fluorinated SMMs to generate biomimetic surfaces. Thus, the fluorinated end-chains can promote the migration of these additional functional groups to the surface so they can promote a desirable cell response.

SMMs constituted from both hydrophobic and oleophobic pendant side chains and hydrophilic side chains are receiving considerable attention because they can aggregate at the surface to yield desirable phase separation which may produce an optimal nanoscale topography to avoid undesired protein adsorption.

In general, the success of the blended systems, in terms of the degree of protein adsorption and platelet adhesion, depends on the contribution of different factors such as the final surface chemistry, hydrophilicity, surface microphase separation, and roughness.

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