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ARTICLE *in* ANALYTICAL CHEMISTRY · SEPTEMBER 2002

Impact Factor: 5.64 · DOI: 10.1021/ac025604v · Source: PubMed

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Improving the Blood Compatibility of Ion-Selective Electrodes by Employing Poly(MPC-*co*-BMA), a Copolymer Containing Phosphorylcholine, as a Membrane Coating

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The hydrogel poly(2-methacryloyloxyethylphosphorylcholine-*co*-butyl methacrylate), or poly(MPC-*co*-BMA), was used as a coating for polyurethane- and poly(vinyl chloride)-based membranes to develop ion-selective electrodes (ISEs) with enhanced blood compatibility. Adverse interactions of poly(MPC-*co*-BMA) with blood were diminished due to the phosphorylcholine functionalities of the hydrogel, which mimic the phospholipid polar groups present on the surface of many cell membranes. As demonstrated by immunostaining, hydrogel-coated PVC membranes soaked in platelet-rich plasma showed less adhesion and activation of platelets than uncoated PVC membranes, indicating an improvement in biocompatibility owing to the hydrogel. Furthermore, little differences in the potentiometric response characteristics, e.g., slope, detection limit, and selectivity, of ISEs employing uncoated and coated membranes were observed.

Sensors have found many important applications in the bioanalytical and biomedical fields.[1,2] For instance, short turnaround time (stat) instruments with integrated sensors are routinely employed at bedside to closely monitor concentrations of physiologically relevant ions (K^+, Na^+, Ca^{2+}, Mg^{2+}, etc.) as well as other important analytes in ill patients. In vivo determination of such analytes would potentially reduce the analysis turnaround time by allowing real-time monitoring and eliminating the need for blood collection. For this reason, there is a high interest in developing sensors capable of performing accurate and reliable in vivo measurements.[3] As with any foreign object introduced into the body, biocompatibility is one of the most important requirements of these sensors. Additionally, in the case of blood-contacting devices, the hemocompatibility of in vivo sensors is an important consideration, as well.[4]

The adsorption of proteins on surfaces of implanted sensors and devices constitutes the first step of several biological responses, including the activation of the coagulation cascade. Following protein adsorption, cell adhesion occurs. This is generally an undesirable event, since it could lead not only to the alteration of the sensor output but also to harmful side effects on the subject, e.g., thrombi formation after adsorption and activation of platelets.[4] Therefore, one of the goals in the design of biocompatible polymers is the development of materials that resist protein adsorption.[5] In particular, poly(vinyl chloride) (PVC), the conventional material used for the preparation of ion-selective electrode (ISE) polymeric membranes, is not fully biocompatible.[6] Several strategies have been employed to improve the biocompatibility of materials used in polymeric membrane sensors, including the preparation of ISE membranes with surface-immobilized anticoagulants such as heparin,[7] the continuous release of biologically active molecules such as nitric oxide,[8] grafting biocompatible polymers such as poly(ethylene oxide) and silicone on the outer surface of the membrane,[9] and using more inherently biocompatible polymers such as polyurethanes.[10,11]

In this paper, we describe the use of a biocompatible hydrogel containing phosphorylcholine groups (see Figure 1), poly(2-methacryloyloxyethylphosphorylcholine-*co*-butyl methacrylate) (poly(MPC-*co*-BMA)),[5] as a coating on the surface of conventional ISE membranes to improve their biocompatibility. The phosphorylcholine groups mimic the functionalities of phospholipid molecules found in membranes of many blood substituents and have been shown to reduce protein adsorption onto surfaces modified with the hydrogel.[12,13] Therefore, using the hydrogel as a coating for

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10.1021/ac025604v CCC: $22.00
Published on Web 06/25/2002

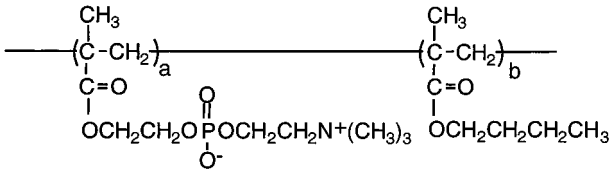

Figure 1. Biocompatible hydrogel containing phosphorylcholine groups poly(2-methacryloyloxyethylphosphorylcholine-*co*-butyl methacrylate) (poly(MPC-*co*-BMA)). The mole fraction of MPC is 0.30.

sensor materials should provide the sensor with improved blood compatibility. Poly(MPC-*co*-BMA) is primarily employed as a coating rather than a sensing membrane matrix due to its unfavorable mechanical properties. This polymer has been employed previously in the fabrication of glucose sensors[14,15] and has been used successfully to coat the tip of two fiber-optic sensors for oxygen and pH.[16,17] Additionally, the copolymer was recently reported as coating for one PVC-based ISE in a rapid communication.[18]

Herein, we confirm the possibility of obtaining hydrogel-coated ISEs with the same potentiometric properties as uncoated PVC and expand the applicability of the hydrogel coating to ISEs based on other common membrane materials, i.e., Tecoflex. Moreover, an immunostaining protocol was employed to compare platelet interactions with coated versus uncoated PVC-based membranes after being soaked in human platelet-rich plasma. Results from the immunostaining study indicate an improved blood compatibility of poly(MPC-*co*-BMA)-coated electrode membranes versus uncoated analogues.

EXPERIMENTAL SECTION

Reagents. Poly(MPC-*co*-BMA), the polymer investigated in this report, was a gift from Dr. K. Ishihara, from the Institute for Medical and Dental Engineering of the Tokyo University. Bis(2-ethylhexyl) sebacate (DOS), PVC, tetrahydrofuran (THF), and potassium tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (KTFPB) were purchased from Fluka-Aldrich (Milwaukee, WI). Tecoflex SG-80A polyurethane was donated by Thermedics (Woburn, MA). Tris(hydroxymethyl)aminomethane (Tris) was obtained from Research Organics (Cleveland, OH). Hexamethyldisilazane (HDMS) was purchased from Aldrich (Milwaukee, WI). Platelet concentrates (PCs) were provided by the Central Kentucky Blood Center (Lexington, KY) and were obtained from healthy volunteers 1 day prior to use. FITC-labeled CD62P antibody was purchased from Pharmingen Transduction Laboratories (San Diego, CA). Tyroded buffer (TB) was prepared with the following composition: 137 mM NaCl, 2.8 mM KCl, 1 mM $MgCl_2$, 12 mM $NaHCO_3$, 10 mM HEPES, 0.4 mM Na_2HPO_4, 5.5 mM glucose, and 0.35% (w/v) bovine serum albumin, pH 7.4. Absolute ethanol was obtained from AAPER Alcohol and Chemical (Shelbyville, KY). All other reagents were of the highest purity available. All aqueous solutions were prepared with 14-MΩ deionized distilled water obtained with a Milli-Q water purification system from Millipore (Bedford, MA).

Preparation of the Membranes. In general, 2 mg of the ionophore valinomycin (corresponding to 1 wt %), 60 mol % (with respect to the ionophore) of the lipophilic salt KTFPB, and DOS-plasticized PVC with a mass ratio PVC/DOS of 1:2 (or DOS-plasticized Tecoflex with a mass ratio of 1:1 Tecoflex/DOS) were dissolved in 2 mL of THF. This cocktail was poured in a 22-mm-diameter glass ring on a glass plate, and the membranes were formed after controlled evaporation of the solvent at room temperature. Smaller disks were cut from the cast membranes and placed at the tip of Philips IS-561 electrode bodies (Glasblaserei Möller, Zurich, Switzerland).

To study the effect of coating different polymeric membranes with poly(MPC-*co*-BMA), PVC and Tecoflex membranes, prepared as described above, were coated with poly(MPC-*co*-BMA) by dipping the membranes three times for 5 s each time in a 2% (w/v) solution of this material in ethanol (the membranes where allowed to air-dry for 1 h between coatings). The coated membranes were left overnight in a desiccator at room temperature to completely evaporate the solvent. Prior to use, membranes were soaked in water for 24 h, cut in smaller disks, and then placed at the tip of the electrode bodies. The electrodes were conditioned for 12 h in 10 mM NaCl prepared in 10 mM Tris-HCl buffer, pH 7.2, prior to selectivity studies. The response to potassium was then evaluated after conditioning overnight in a 10 mM KCl solution in 10 mM Tris-HCl buffer, pH 7.2.

Potentiometric Studies. Membrane potentials were recorded with an in-house custom-built, four-channel, high-impedance amplifier with unity gain, coupled to an analog-to-digital converter (G.W. Instruments, Somerville, MA) connected to a Macintosh computer running Superscope v. 1.2 software (G. W. Instruments).

Potentiometric measurements were obtained by using the following cell assembly:

Ag/AgCl|KCl (saturated)||buffer||sample|membrane|
10 mM KCl|Ag/AgCl

The change in the potential of the cell, ΔE, was recorded for every addition of an aliquot of standard solutions to 50.0 mL of 10 mM Tris-HCl, pH 7.2, buffer. Selectivity coefficients were determined by following an "unbiased" selectivity protocol and the separate solution method as recommended by Bakker.[19]

Immunostaining Protocol. PCs with a cell count of ~ 6−15 × 10^{12}/L were diluted with autologous serum to 3.0 × 10^{12} platelets/L in 15-mL Falcon tubes. Membranes to be tested were completely submerged in TB for 30 min at 37 °C. The membranes were transferred into the diluted platelet suspension and incubated for 2 h at 37 °C. The platelet-coated membranes were then washed twice with TB. Membranes were transferred into 15-mL Falcon tubes containing 0.4 mL of TB and 0.8 μg/mL FITC-CD62P fluorescently labeled antibody. The membranes in solution were incubated for 20 min at 4 °C and then washed twice with TB.

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Images of stained membranes were obtained via confocal fluorescence microscopy (Leica TCS NT SP laser scanning confocal microscope, Leica Microsystems, Wetzlar, Germany).

RESULTS AND DISCUSSION

Many of the proposed strategies that have been followed in order to improve the biocompatibility of polymer matrixes for biomedical applications deal with the modification of the polymer surface in order to reduce protein adsorption.[12,20−22] In particular, several authors have proposed the modification of material surfaces with phosphorylcholine.[13,23−26] Since this functionality is present in the polar head of one of the primary lipids that compose many natural cell membranes (including erythrocytes), a surface exhibiting the phosphorylcholine moiety should display good hemocompatibility. Ishihara and co-workers described the synthesis of a family of methacrylate-based polymers containing such phosphorylcholine groups, namely, copolymers of 2-methacryloyloxyethylphosphorylcholine with alkyl methacrylates.[24] In particular, one polymer, poly(MPC-*co*-BMA), containing 30 mol % MPC, decreased protein adsorption significantly on surfaces where it was coated.[21]

Poly(MPC-*co*-BMA) is soluble in ethanol and swells in water, becoming a hydrogel. Although some hydrogels have been explored in the development of sensors, in particular for coated wired ISEs,[27] there are some problems associated with their use. Hydrogels, in general, lack mechanical strength, and in fact, ISE hydrogel membranes cast in our laboratory from ethanolic solutions of poly(MPC-*co*-BMA) displayed poor physical properties once they were soaked in water (the membranes exhibited mechanical failure after 2−3 days of use). Additionally, electrodes prepared from membranes composed of hydrogel as a matrix and the potassium-selective ionophore valinomycin (the membranes were, again, cast out of 10% (w/v) solutions of poly(MPC-*co*-BMA) in ethanol) demonstrated selectivity behavior virtually identical to membranes constructed from only poly(MPC-*co*-BMA). In other words, no selective interactions were observed in either case regardless of incorporation of ionophore into the matrix. This observation was likely due to a loss of ionophore from the polymer prior to experiments (during the conditioning phase). Most importantly, the plot of the potential versus the logarithm of the concentration of potassium exhibited a sigmoidal shape for both membrane compositions with a short linear range for potassium (between 10^{-4} and 10^{-2} M) and a sub-Nernstian slope of ~20 mV/decade for this ion. The shape of the curve and the poor slope of this response indicate a lack of permselectivity, which is a requisite for optimal ISE response, of the hydrogel and some resultant Donnan exclusion failure. Davies and Tighe reported a similar type of response profile from an ISE that had been prepared by coating a platinum wire electrode with a copolymer of 2-hydroxyethyl methacrylate and methyl methacrylate.[27]

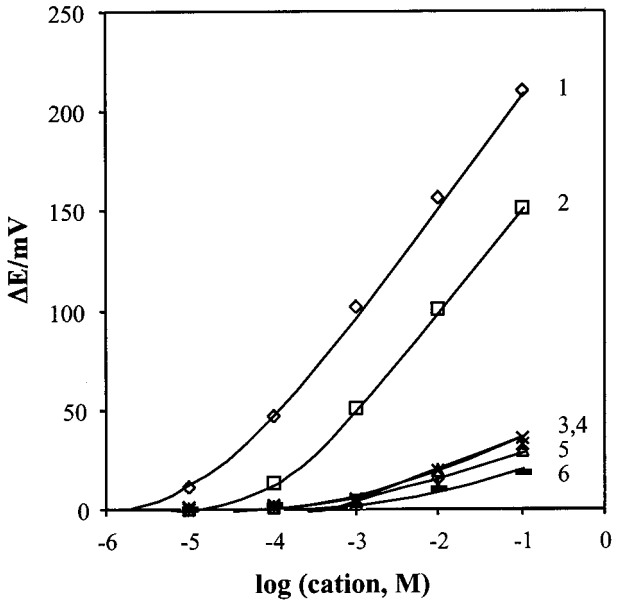

Figure 2. Response of ISEs prepared with PVC membranes coated with poly(MPC-*co*-BMA): (1) potassium, (2) ammonium, (3) lithium, (4) calcium, (5) magnesium, and (6) sodium.

The drawback of mechanical strength, however, can be overcome by using the hydrogel as a coating over a substrate with a higher stability.[28] It should be noted that it has been reported previously that coating different polymeric substrates with a 2% (w/v) solution of poly(MPC-*co*-BMA) in ethanol resulted in less thrombogenic surfaces, as compared to 1 and 5% (w/v) solutions.[16] We, therefore, chose a concentration of 2% (w/v) solution of poly(MPC-*co*-BMA) in ethanol to coat all polymer membranes throughout our experimentation.

When coated and uncoated PVC membranes were compared, no significant difference could be observed in the performance of the corresponding electrodes. The response of ISEs with poly(MPC-*co*-BMA)-coated PVC membranes to a broad array of ions is presented in Figure 2. Calculated slopes and detection limits for potassium, as well as selectivity data for the respective ISEs (based on both PVC and Tecoflex) studied herein, have been included in Table 1. There is no significant difference in the slope of the potassium response of coated versus uncoated PVC (54.4 mV/decade for uncoated vs 54.7 mV/decade for coated) demonstrating that the coating exerts little influence/disruption of the response mechanism of the ISE. The detection limit for potassium remains practically unchanged after coating (1.4×10^{-5} vs 1.3×10^{-5} M), as well. A similarly small change in the detection limit is observed when Tecoflex membranes are coated with poly(MPC-*co*-BMA) (1.4×10^{-5} vs 1.3×10^{-5} M). While these differences in detection limit may be statistically insignificant, it may be the case that the coating influences ion diffusion by reducing ion fluxes in the aqueous layer. The responses of the coated and uncoated PVC- and Tecoflex-based ISEs toward potassium are practically equivalent (as demonstrated in Figure 3), indicating that response in this case is dependent upon the binding characteristics of the

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Table 1. Summary of the Response Characteristics and Selectivity Coefficients ($n = 3$) of Electrodes Based on PVC or Tecoflex Plasticized with DOS and Either Uncoated or Coated with Poly(MPC-*co*-BMA)

	PVC	coated PVC	Tecoflex	coated Tecoflex
K^+ detn limit (μM)	14(±1)	13(±1)	14(±1)	13(±1)
K^+ slope (mV/dec)	54.4(±0.4)	54.7(±0.3)	55.8(±0.3)	54.5(±0.5)

	log $K^{pot}_{K^+,j}$				
	PVC	coated PVC	Tecoflex	coated Tecoflex	required[a]
K^+	0	0	0	0	0
NH_4^+	−1.4	−1.2	−1.4	−1.5	< 0.1
Na^+	−4.3	−4.4	−4.0	−4.5	<−3.6
Li^+	−4.3	−3.9	−4.0	−4.0	<−1.3
Ca^{2+}	−4.1	−3.9	−4.4	−4.0	<−2.9
Mg^{2+}	−4.1	−4.2	−4.1	−4.1	<−2.8

[a] Required selectivity coefficient for blood analysis (1% error).[29]

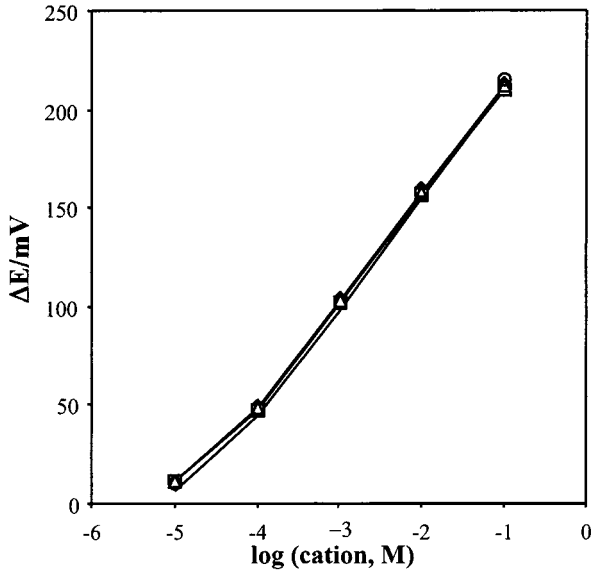

Figure 3. Superimposed responses of ISEs prepared with PVC and Tecoflex membranes with or without being coated with poly(MPC-*co*-BMA): PVC (diamonds), coated PVC (squares), Tecoflex (triangles), coated Tecoflex (circles). Some of the symbols are obstructed, especially at lower concentrations of ion, due to the high degree of overlap of the four plots.

ionophore with little influence exerted by the coating. These results fit what would be expected from a mechanistic perspective since, as the coating is a hydrogel, ion mobility in the coating layer should be significantly much more similar to mobilities in the aqueous phase than either the PVC or Tecoflex membranes. From this point of view, then, the hydrogel can be considered an extension of (or a part of) the aqueous phase.

With regard to the selectivity of the corresponding ISEs, there is a slight increase (a larger log $K^{pot}_{K^+,j}$ value) in the interference of calcium relative to potassium for both PVC and Tecoflex matrixes when the membranes are coated with the phosphorylcholine-containing hydrogel. Most likely, this difference in selectivity can be attributed to the interaction of the hydrogel phosphoryl groups with calcium. As a matter of fact, it is has been shown in previous reports that ionophores containing phosphoryl groups display selectivity toward divalent cations such as calcium.[1]

Immunostaining followed by fluorescence microscopy was employed to visualize whether platelets attach to the membrane surface and become activated upon contact with the polymer. This process involves incubating membranes with a platelet suspension containing 3.0×10^{12} platelets/L in TB buffer with fluorescently labeled antibody; herein the labeled monoclonal antibody FITC-CD62P, which is specific for the platelet activation marker CD62P (i.e., P-Selectin), was employed.[30,31] When the surface is imaged with fluorescence microscopy, the presence of adhered and activated platelets can be visualized. This technique not only confirms the presence of platelets on a surface but also provides more useful information about the nature of the platelets than scanning electron microscopy (SEM), which is traditionally used for imaging platelets on surfaces.

Both hydrogel-coated and uncoated PVC surfaces were studied by immunostaining with the results presented in Figure 4. Platelet/antibody complexes have a green fluorescence (characteristic of FITC, the fluorescent tag) that can be readily observed over the black polymer background. In micrograph A, where the PVC polymer is coated with poly(MPC-*co*-BMA), very few fluorescing regions are observed. On the other hand, in micrograph B where bare PVC was studied, there is a significant increase in the fluorescence density, i.e., in the concentration of activated platelets present on the PVC surface. Additionally, several of the observed features range from 5 to 15 μm, which is much larger than the size of individual platelets (~2−4 μm). Furthermore, these features are distorted from spherical, indicating that platelets are activated and have begun to aggregate. The summary of these microscopy results leads to the conclusion that the hydrogel employed in this work acts as an effective barrier against platelet adhesion, which is a critical step toward thrombogenic response in the body. Traditional SEM images taken of both coated and uncoated PVC surfaces yielded similar results, i.e., significantly reduced platelet adhesion for hydrogel-coated PVC membranes versus uncoated (data not shown).

CONCLUSIONS

It has been demonstrated that a new blood-compatible polymeric material, poly(MPC-*co*-BMA), can be used to coat ISE membranes thereby increasing the biocompatibility of such sensors. Electrodes prepared from PVC and Tecoflex membranes coated with this polymer show equivalent potentiometric response characteristics (slope and detection limit) to electrodes based on equivalent uncoated membranes. It is demonstrated that the hydrogel coating is compatible with multiple membrane materials. Selectivity coefficients of the hydrogel-coated potassium-selective electrodes studied in this work vary only slightly (in the case of selectivity toward potassium relative to calcium) from selectivities reported for uncoated, analogous electrodes. The small reduction in selectivity of coated sensors over calcium can be attributed to the presence of phosphoryl groups in the hydrogel coating that possibly interact with the metal. Immunostaining studies indicate

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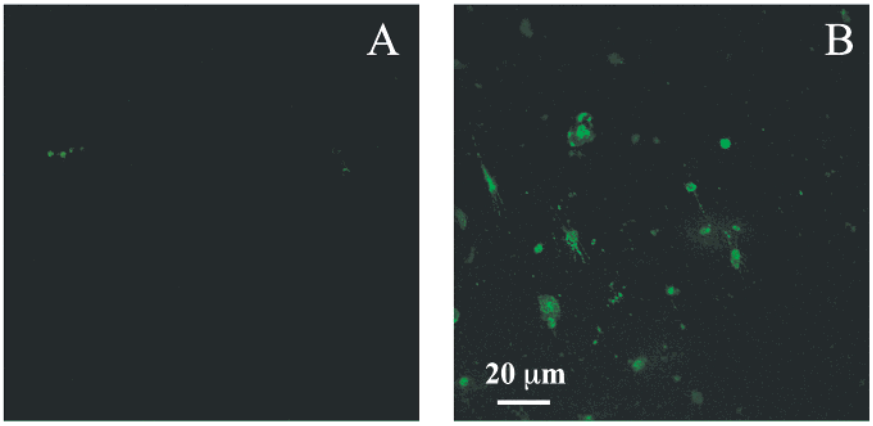

Figure 4. Fluorescence micrographs of platelet-exposed, immunostained PVC with and without a poly(MPC-*co*-BMA) coating: (A) coated PVC and (B) uncoated PVC.

that there is little to no platelet adhesion to coated PVC membranes in stark contrast to bare PVC, thereby demonstrating that the biomimetic polymer can be employed to reduce the thrombogenicity of sensors intended for in vivo applications.

ACKNOWLEDGMENT

The authors thank Dr. Ishihara for providing us with poly(MPC-*co*-BMA). We also thank Dr. Douglas A. Harrison for assisting with fluorescence microscopy. Additionally, we thank the National Aeronautics and Space Administration, the National Science Foundation (IGERT), and the Kentucky Research Challenge Trust Fund for supporting this work financially.

Received for review February 27, 2002. Accepted April 29, 2002.

AC025604V