Chitosan/Poly(vinyl alcohol) Blending Hydrogel Coating Improves the Surface Characteristics of Segmented Polyurethane Urethral Catheters

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Abstract: Segmented polyurethane (SPU) is commonly used to manufacture urethral catheters. Surface modifications for SPU catheters are needed to reduce friction and protein adsorption, in order to minimize catheter-related complications, including urethral trauma, encrustation, catheter obstruction, bacterial colonization, and infection. In this study, a four-step surface modification method was developed to create a thin lubricious layer of chitosan/poly(vinyl alcohol) (PVA) hydrogel on the SPU catheter. Modification steps included oxidation of the SPU surface, functionalities modification, carbodiimide reaction and coupling, and hydrogel crosslinking. The success of each modification step was confirmed by Fourier transform infrared spectroscopy. Measurement of the water contact angle revealed that hydrogel coating created a highly hydrophilic surface and atomic force microscope analyses demonstrated that the surface was slippery. Protein absorption of the SPU catheter was significantly reduced by coating hydrogel. Chitosan in the hydrogel could provide antimicrobial activity, and the hydrogel coating SPU samples showed significant antibacterial effects in this study. In summary, the four-step modification method developed in this study provided a simple and effective way to coat the surface of SPU catheters with a chitosan/PVA blending hydrogel that could help to minimize the risk of complications related to the use of urethral catheters. © 2007 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 83B: 304–313, 2007

Keywords: polyurethane; urethral catheter; surface modification; chitosan; polyvinyl alcohol

INTRODUCTION

Urethral catheters needed to be flexible and nonirritating to the urethral mucosa, as they are used to drain the urinary bladder.1 Because of excellent mechanical properties, biological inertness, and blood compatibility, polyurethanes have already been established as one of the leading polymers used to make several biomedical devices, including urethral catheters.2–4 The molecular structure of segmented polyurethane (SPU) consists of hard and soft segments.5 The soft segment is usually composed of polyl with a low glass transition temperature, whereas the hard segment is typically composed of diisocyanate with a high glass transition temperature. To produce a thermoplastic SPU, low-molecular-weight chain extender, such as ethylene diamine, is employed to prevent crosslink formation. Because SPU lacks a crosslinked network, it can be melted and extruded into a tubular shape, which allows it to be fabricated into urethral catheters.

Complications related to the use of urethral catheters include urethral injury during insertion and removal, encrustation, blood clotting, catheter obstruction, bacterial colonization, and infection.6–9 Those complications usually occur at the contact surface between urethra and catheter. Bacteria adhesion, infection, encrustation, and thrombosis represent a cascade initiated by extensive protein adsorp-
tion, which has been shown to play an essential role in promoting bacterial colonization and infection.\textsuperscript{10} Thus, decreasing protein adsorption at the surface of catheter can lead to a proportional reduction in protein-mediated adhesion of bacteria that is related to the occurrence of infection, encrustation, and thrombosis on the catheter surface.\textsuperscript{10–14} Furthermore, the friction exerted by a urethral catheter can cause irritation of the mucosa and subsequent inflammation.\textsuperscript{15} By reducing this friction, the risk of urethral damage may diminish, which would improve the level of patient satisfaction.\textsuperscript{16,17}

To avoid the aforementioned complications, many polymeric surface modification methods have been reported.\textsuperscript{8–10,18,19} However, none of these techniques allow to minimize multiple complications in a single modification procedure. The ideal surface modification method for the urethral catheter should create a surface that reduces protein adsorption and friction while exhibiting a disinfectant or antibacterial activity. In this study, a four-step surface modification method was developed, without using any organic solvent, to create a thin lubricious layer of chitosan/PVA blending hydrogel on the surface of SPU catheters. Modification steps included oxidation of SPU surface with Jone’s solution, functionalities modification with acrylic acid to generate additional carboxyl group, and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide (EDC) reaction and coupling to activate carboxyl groups, followed by crosslinking of chitosan/PVA blending hydrogel onto the activated SPU surface. After the latter surface modification, a thin lubricious hydrogel layer would create a hydrophilic polymeric surface on SPU. It would be biocompatible and could minimize friction force as well as protein adsorption. Therefore, several complications related to SPU urethral catheters could be avoided by this surface modification method.

**MATERIALS AND METHODS**

**Preparation and Surface Modification for SPU Samples**

SPU pellets (Biomer\textsuperscript{18}, Ethicon, Somerville, NJ) were heated to 150°C and were then pressed into sheets with a thickness of 1 mm. SPU sheets were sectioned into 1 cm \( \times \) 1 cm squares. Sectioned sheets were washed with detergent, rinsed with distilled water, and stored in a sealed plastic bag at room temperature. SPU catheters (Bioteg, Taipei, Taiwan) used in this study were made of the same SPU material as mentioned earlier. Without any coating process, the SPU catheters were sectioned into desired lengths, for subsequent experiments. The sectioned tubular SPU samples were also cleaned and stored for later experiments.

The modification process included four steps, which are described in detail later. No organic solvents were used in the entire modification procedure.

**Oxidation of SPU Surface.** Jone’s solution is a strong oxidizing reagent which can break the C—H bonds or other low energy functional groups of the surface and form carboxyl, hydroxyl, and other intermediate functionalities.\textsuperscript{20} Jone’s solution was prepared by dissolving 7 g of chromic anhydrite (Shimakyu Chemicals, Osaka, Japan) in 500 mL of double distilled water (ddH\(_2\)O), and then slowly adding 65 g of concentrated sulfuric acid (95–97%; Fluka, St. Gallen, Switzerland) into the solution in an ice-water bath. After adding sulfuric acid, the solution was removed from an ice-water bath and mixed continuously until room temperature was obtained. At room temperature, sectioned SPU tubes or sheets were immersed in an appropriate amount of Jone’s solution with continuous stirring at 350 rpm for 30 min. Samples were then rinsed twice with ddH\(_2\)O.

**Modification of Functionalities.** The second step was to polymerize the oxidized surface with acrylic acid to generate additional carboxyl functionalities\textsuperscript{21} that are thought to increase the degree of crosslinking with chitosan/PVA hydrogel in the last modification step. Poly(acrylic acid) was immobilized on oxidized surface to produce additional carboxyl groups. The poly(acrylic acid) solution (50 wt % in H\(_2\)O; Acros Organics, Fairlawn, NJ) was preheated to 70°C, and then oxidized SPU samples were then immersed in the acid for 60 min. Upon completion of the reaction, samples were rinsed twice with ddH\(_2\)O.

**EDC Reaction and Coupling.** The third step was to activate the carboxyl groups on the SPU surface with water-soluble EDC. EDC was used to crosslink the carboxyl groups of the SPU surface with the amine groups of the chitosan/PVA hydrogel via amide linkages. SPU samples from the previous step were immersed in the EDC solution (0.1 g EDC in 30 mL ddH\(_2\)O), with stirring at room temperature for 60 min. At the end of this modification process, SPU samples were rinsed with ddH\(_2\)O and immediately used in the hydrogel crosslinking step.

**Hydrogel Crosslinking.** The last step was to immobilize chitosan/PVA blending hydrogel onto the activated SPU surface. Chitosan and PVA are both biocompatible within hydrogel. Long-chain chitosan was chosen to provide amine groups bound to SPU surface via amide bond formation. Chitosan forms a flexible network in which PVA molecules are entangled. The amine groups on the chitosan molecules and the EDC-activated SPU were crosslinked through amide linkages.\textsuperscript{20} PVA is not crosslinked with SPU or chitosan, but is free to elute upon swelling. Chitosan has also been reported to exhibit an antimicrobial activity.\textsuperscript{22} In addition, PVA was incorporated in the blending hydrogel to inhibit cell adhesion and reduce protein adsorption.\textsuperscript{23,24}

A hydrogel mixture containing PVA and chitosan was prepared beforehand. One gram of food grade chitosan powder (MW 340 kDa, deacetylated >95%; Kiotek, Taipei, Taiwan) and 8 g of PVA powder (MW 30,000–70,000 Da; Sigma, St. Louis, MO) in an adequate weight ratio were mixed before adding to 50 mL of preheated ddH\(_2\)O containing 0.5 mL of 95% acrylic acid (Tedlab, Fairfield, OH).
at 60°C. Acrylic acid was used to lower the pKₐ value of water in order to dissolve the chitosan powder. The heated mixture was stirred slowly for 20 min until all powder disappeared. Small powder agglomerations were further dispersed with a small spatula. Final chitosan/PVA blending hydrogel was allowed to cool at room temperature and was stored in a sterilized container. SPU samples were immersed in an appropriate amount of chitosan/PVA blending hydrogel for 1 min, immediately after the EDC reaction. Hydrogel-coated SPU samples were then dried in a 60°C oven for 20 min and stored in a sealed plastic bag until later characterization.

The surface characteristics of hydrogel-coated SPU samples were compared with LubriLAST™ coating. LubriLAST (AST Products, Billerica, MA) is a solution that is currently used to create a lubricious, hydrophilic coating for a number of approved devices including urinary catheters. The LubriLAST solution was prepared according to the product instructions; 1.5 g of solution B (crosslinking solution) was slowly added to every 260 g of solution A (top coating solution). The final solution was applied to tubular SPU and allowed to dry at 65°C for 120 min.

**Analyses of Chemical and Physical Parameters**

**Fourier Transform Infrared Spectroscopy.** Fourier transform infrared spectroscopy (FTIR) was utilized to identify the functional groups on the modified SPU surface. FTIR measurements were carried out using Jasco FTIR 410 (Jasco, Tokyo, Japan). The samples were analyzed in the transmittance mode in the range of 400–4000 cm⁻¹. The functionalities corresponding to each of the absorption bands were analyzed.

**Water Contact Angle.** The hydrophilic properties were characterized by the water contact angle of tested surfaces before and after modification. An in-house water contact angle measurement apparatus/technique was developed for this study. The apparatus includes a digital camera (Nikon Coolpix 995; Nikon, Tokyo, Japan) with a microscopic lens (CFI Plan Fluor Series Objective Lenses, ×4; Nikon) and a micropipette (Pipetman, 2–20 μL; Gilson, Villiers-le-Bel, France). The measurements were taken within 24 h, after each step of the experiment. A ddH₂O droplet of 4 μL was dropped on the surface of an SPU sheet, and the cross-section photograph was taken after 10 min. The water contact angle is the angle at the junction between three phases, for example, water droplet, SPU, and air. The angle calculation was taken from the droplet base to the apex. Resulting angle multiplied by two gave the correct water contact angle. The measurement was performed on SPU sheets after oxidation step, functionalities modification step, and hydrogel crosslinking steps. In addition, SPU sheets without modification and with LubriLAST coating were also measured. All samples were measured six times independently.

**Atomic Force Microscopy.** The surface friction characteristics of SPU sheets, with or without surface modification, were analyzed by atomic force microscope (AFM) using a SMENA-B (NT-MDT, Zelenograd, Russia) microscope with cantilever NSC17/A1 BS (MikroMasch, Moscow, Russia). The analysis was performed in an area of 5 nm² using lateral force mode of AFM. The samples were adhered to a working table, to ensure a horizontal analysis surface. Two hundred microliters of ddH₂O covered the sample which mimicked the wet environment condition of urethra. Different resolutions were applied on each of the samples to achieve a reliable characterization of a sample and avoiding areas of extreme height change or lateral force due to a possibly uneven coating. Finally, the collected data were calculated for the weighted averages for each individual sample. Unmodified SPU sheets in both wet and dry conditions were measured. LubriLAST and hydrogel-coated sheets were both measured under wet conditions.

**Coating Amount, Absorbed Water Content, and Elution Percentage.** The water content provides a basic understanding of how the hydrogel coating performed under an aqueous environment. The elution amount determined the retention capabilities of PVA chains in the hydrogel blend. Coated SPU tubes with a length of 2 cm were used in this test. Weights of SPU tubes were measured before (Wₐ) and immediately after (Wₐ) surface modification. Samples were incubated at 37°C for 1–5 days, until further weight measurement was performed. Wet weight (Wₐ) of SPU samples was recorded after excess water was shaken off from SPU samples. Dry weight (Wₐ) was measured after samples were dried at 65°C for 10 min. Measurements were performed in six repeats from each coating group. Weights of materials which were initially coated on SPU tubes equaled to Wₐ – Wₐ. Weight of materials which remained on SPU tubes after immersion in ddH₂O equaled to Wₐ – Wₐ. The water content which was absorbed by residual coating materials equaled to Wₐ – Wₐ. Elution percent of coated materials was determined by dividing Wₐ – Wₐ by Wₐ – Wₐ.

**LDH Cytotoxicity Detection.** Sections of chitosan/PVA hydrogel-coated, LubriLAST-coated, and unmodified SPU tubes were sterilized with 75% alcohol for 3 min and subsequently washed with phosphate-buffered saline (PBS) for 5 min to remove residual alcohol. Nine centimeters of each sterilized tube was immersed in 3 mL of cell culture medium, to extract toxicants according to ISO 10993-12. According to the standard, the extraction ratio of composite tubing wall is 3 cm²/mL for a sample thickness greater than 0.5 mm. The surface area of the SPU tubes tested in this study was 1 cm²/cm. Therefore, 1 mL of culture medium was required for 1 cm of tested SPU tube in this study. Because toxicant concentration in culture medium is possibly related to the length of extraction time, toxic culture medium was retrieved after 1, 3, or 5 days of immersion. About 6500 fibroblasts were seeded into a well of a 96-well microplate 1 day before addition of toxic culture medium. Subsequently, 200 μL of culture medium contain-
ing 100 μL of toxic extract was added after removal of previous culture medium. LDH detection was performed after 1 day of cultivation. Final culture medium (100 μL) was pipetted into a well of the new 96-well microplate. LDH detection solution (100 μL; Takara Bio, Shiga, Japan) was added into each tested well, and then the microplate was covered with an aluminum foil to avoid light disturbance. The mixtures were incubated at room temperature for 15 min. Upon completion of incubation, OD_{500} was measured in a microplate absorbance reader (TECAN Austria, Grödig, Austria). All experiments were repeated six times independently. The extract from unmodified SPU tubes was used as the negative control. Normal culture medium was used as a background reading.

Protein Adsorption Assay. The detection of adsorbed protein was performed by bichinchoninic acid (BCA) protein assay (Sigma). Hydrogel- and LubriLAST-coated SPU tubes were sectioned into a length of 2 cm. Three samples from each group were immersed in eppendorfs containing 2 mL of albumin solution (200 μg/mL). Samples were incubated at 37°C for 24 h, which allowed PVA in hydrogel blend to elute away, in order to evaluate the effectiveness of PVA elution to minimize protein adsorption. At the end of the adsorption period, samples were removed from the albumin solution and rinsed with PBS twice. Rinsed samples were transferred into new eppendorfs, with 2 mL of 1 wt % SDS solution. These eppendorfs were shaken at 1000 rpm for 5 min. Then 25 μL of SDS solution containing albumin were transferred to a 96-well microplate by addition of 20 μL of BCA working reagent. The 96-well microplate was further incubated at 37°C for 30 min, before the measurement of OD_{562}. The amount of absorbed protein in each sample was estimated by comparing a linear standard curve obtained from albumin standards (0–1000 μg/mL).

Antibacterial Test. Chitosan was chosen not only for the amine moieties but also for the antiseptic property. Clinically isolated Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli were used for checking the antibacterial properties of hydrogel coating and LubriLAST coating SPU samples. SPU sheets (1.5 × 1.5 cm²) were first coated with LubriLAST or chitosan/PVA blending hydrogel, and then placed in the center of agar plates. Bacteria solutions were smeared gently across the surface of testing samples and agar plates. The bacteria-cultured agar plates without SPU samples served as the control groups. The agar plates were incubated at 37°C for 12 h. Then photos were taken for both control and experimental groups in order to determine the antiseptic regions of bacteria. Diameters of the antiseptic regions in each experimental group were measured to determine the antibacterial effect of both coating methods.

Statistical Analysis

Two-tailed Student’s t test was employed for determining the statistical significances of water contact angle, OD value detected in LDH assay, the amount of protein absorption, water content and elution, and diameters of antiseptic regions among unmodified, LubriLAST-coated, and hydrogel-coated SPU samples. A p value of less than 0.05 was considered to be statistically significant.
RESULTS

FTIR Analysis

Spectra of FTIR results after each modification step were summarized in Figure 1. After the oxidation step of the SPU samples, additional functionalities were found on the SPU surface, including hydroxyl groups (adsorption bands at 1226, 1292, and 1322 cm\(^{-1}\), aldehyde groups (adsorption bands at 1415 and 1608 cm\(^{-1}\)), ketone groups (adsorption band at 1751 cm\(^{-1}\)), and carboxyl groups (adsorption bands at 2842 and 2908 cm\(^{-1}\)).

After the functionalities modification step, an additional adsorption band at 1153 cm\(^{-1}\) was observed, indicating that acrylic acid was crosslinked onto the SPU. Since EDC contained imide bond, amide bond and urea (adsorption bands at 1482, 1524, and 1692 cm\(^{-1}\)) were apparent after EDC was crosslinked onto the SPU. Additional carboxyl groups (adsorption band at 2933 and 2838 cm\(^{-1}\)) indicated chitosan and PVA molecules crosslinked onto the SPU in the hydrogel coating step.

The FTIR results confirmed the success of each modification step.

Physical Analyses

Water Contact Angles. The average water contact angle (Table I) on the unmodified SPU sheets was 80.7° ± 1.9° (range 79.0°–82.8°). After the oxidation and functionalities modification steps, the average water contact angle dropped to 39.9° ± 1.8° (range 38.2°–42.4°). This decrease was statistically significant (\(p = 3.18 \times 10^{-12}\)). The average water contact angle on the chitosan/PVA blending hydrogel coating SPU sheets was 24.5° ± 1.5° (range 23.0°–26.4°). It was significantly lower than that detected on the SPU sheets before any modification (\(p = 6.58 \times 10^{-14}\)) and after oxidation and functionalities modification (\(p = 1.85 \times 10^{-8}\)). The average water contact angle on the LubriLAST coating SPU sheets was 30.8° ± 3.6° (range 26.8°–35.3°) and was significantly lower than that on the unmodified SPU sheets (\(p = 3.38 \times 10^{-11}\)). However, it was still significantly higher than that on the chitosan/PVA blending hydrogel coating SPU sheets (\(p = 0.0026\)). These results indicated that chitosan/PVA blending hydrogel coating created a highly hydrophilic surface on the SPU surface.

Atomic Force Microscopy. In the lateral force mode of AFM, higher ampere implies higher force exerted on the probing tips, which indicates a greater frictional force. Since data were given as number of counts for each ampere reading, weighed averages of each material were calculated by multiplying the number of ampere and the number of counts divided by the number of total counts (Figure 2). The weighed average ampere was 0.904 mA on the surface of dry unmodified SPU sheet, 0.338 mA on the wet unmodified sample, 0.107 mA on the LubriLAST coating SPU sample, and −0.164 mA on the chitosan/PVA blend-

<table>
<thead>
<tr>
<th>Unmodified SPU sheets</th>
<th>80.7° ± 1.9° (79.0°–82.8°)(^a)</th>
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<tr>
<td>SPU after functionalities modification step</td>
<td>39.9° ± 1.8° (38.2°–42.4°)</td>
</tr>
<tr>
<td>SPU after chitosan/PVA blending hydrogel coating</td>
<td>24.5° ± 1.5° (23.0°–26.4°)</td>
</tr>
<tr>
<td>SPU after LubriLAST(^\text{TM}) coating</td>
<td>30.8° ± 3.6° (26.8°–35.3°)</td>
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\(^a\) Values in parentheses indicate ranges.

Figure 2. The result from the lateral force mode of AFM showed the number of counts for each ampere reading on each of the tested SPU samples. The ampere readings on hydrogel-coated samples were concentrated and low. This finding indicates that the surface of SPU became slippery after being coated with chitosan/PVA blending hydrogel.
ing hydrogel coating SPU sample. In comparison to unmodified and LubriLAST coating SPU samples, the amperereadings on hydrogel coating samples were concentrated and low, which indicated that the surface of SPU became very slippery after being coated with chitosan/PVA blending hydrogel. The negative value of hydrogel coating SPU sample was probably caused by the inertia generated from a higher friction area (outside hydrogel coating SPU sheet) to a very low friction area (hydrogel coating SPU sample). The hydrogel coating produced a highly lubricious surface on SPU.

Coating Amount, Absorbed Water Content, and Elution Percentage. Immediately after coating processes, the amount of LubriLAST coated onto 2-cm SPU tubes (average 9.4 ± 0.4 mg, range 8.8–10.0) was significantly larger than that of chitosan/PVA blending hydrogel (average 5.0 ± 0.6 mg, range 4.0–6.0). The amount of coated LubriLAST was also significantly higher than that of hydrogel through the 5-day experiment (Figure 3). Cumulative elution percentages of both coating materials were summarized in Figure 4. Cumulative elution percentage of coated hydrogel from SPU tubes was 53.3% ± 8.2% in the first day, remained the same in the second day, 66.9% ± 8.7% in the third day, 73.6% ± 15.2% in the fourth day, and 83.1% ± 15.4% in the fifth day. These values were significantly higher than that of coated LubriLAST (which was 39.2% ± 12.2% in the first day, 42.3% ± 10.5% in the second day, 43.0% ± 18.1% in the third day, 48.1% ± 14.0% in the fourth day, and 48.8% ± 13.4% in the fifth day). Water content absorbed by coated chitosan/PVA blending hydrogel was 23.8 ± 4.4 mg in the first day, 23.3 ± 3.3 mg in the second day, 19.3 ± 3.3 mg in the third day, 13.6 ± 1.6 mg in the fourth day, and 12.9 ± 1.0 mg in the fifth day. These values were significantly higher than that of coated LubriLAST for first 3 days (18.1 ± 4.9 mg in the first day, 14.8 ± 4.7 mg in the second day, 12.8 ± 3.9 mg in the third day), and the water content absorbed by both coating materials were similar thereafter (Figure 5). These results indicated that a smaller amount of chitosan/PVA blending hydrogel coating on SPU tubes could manifest significantly better water binding capacity than LubriLAST initially and comparable water absorption ability later on.

Chemical Analyses

LDH Cytotoxicity Detection. The results of LDH cytotoxicity detection were summarized in Table II. After 1 day culture at different toxicant extracting levels, significant higher OD_{500} values were detected in LubriLAST and chitosan/PVA blending hydrogel coating groups than that in the control group (unmodified SPU). In terms of comparison between hydrogel and LubriLAST coating groups, hydrogel performed equally well as compared to LubriLAST in 1-day (0.888 ± 0.011 vs. 0.902 ± 0.009, p = 0.33) and 3-day toxicant extracts (1.005 ± 0.009 vs. 0.988 ± 0.011, p = 0.22). However, fibroblasts released significantly lower amounts of LDH in the hydrogel coating group than in the LubriLAST coating group in 5-day toxicant extracts (1.003 ± 0.006 vs. 1.072 ± 0.009, p = 6.2 × 10^{-6}).

Protein Adsorption Test. The protein absorption by unmodified SPU tubes (118.7 ± 10.1 μg/cm², range 108.9–123.3) was significantly higher than that by LubriLAST
coating samples (108.3 ± 2.5 μg/cm², range 104.4–111.1, p = 0.035) and chitosan/PVA blending hydrogel coating samples (average 103.0 ± 5.1 μg/cm², range 95.6–108.9, p = 0.007). The amounts of protein absorption were also statistically higher in LubriLAST coating samples than in hydrogel coating samples (p = 0.043).

Antibacterial Test. Photos obtained from the antibacterial test were shown in Figure 6. When incubated with S. aureus, the average diameter of antiseptic region was 39.0 ± 6.8 mm around hydrogel coating samples and 17.2 ± 0.8 mm around LubriLAST coating samples. When incubated with P. aeruginosa, the average diameter of antiseptic region was 28.0 ± 2.5 mm around hydrogel coating samples and 17.8 ± 1.3 mm around LubriLAST coating samples. When incubated with E. coli, the diameter of antiseptic region was 23.8 ± 2.2 mm around hydrogel coating samples, but there was no antiseptic zone observed.

Figure 4. The cumulative elution percentages of coating materials on SPU samples: Cumulative elution percentages of coated hydrogel from SPU tubes were significantly higher than those of coated LubriLAST.

Figure 5. The calculated water content absorbed by coating materials on the SPU samples: The water content absorbed by coated chitosan/PVA blending hydrogel was significantly higher than that by coated LubriLAST in first 3 days. The water contents absorbed by both coating materials were similar thereafter.
around LubriLAST coating samples. The diameters of antiseptic regions were significantly larger around hydrogel coating samples in the antibacterial experiments of all three tested bacteria ($p < 0.001$). Therefore, it can be concluded that chitosan/PVA blending hydrogel coating SPU samples possessed significantly better antibacterial effects to $S.$ aureus, $P.$ aeruginosa, and $E.$ coli than LubriLAST coating samples.

**DISCUSSION**

Surface properties of urethral catheter may influence the occurrence of urethral complications as well as patient satisfaction and preference.$^{17}$ The four-step surface modification method developed in this study aimed to coating chitosan/PVA blending hydrogel onto the surface of SPU urethral catheters in order to increase hydrophilicity, reduce protein adsorption, promote surface homogeneity, decrease friction force, and gradual elution of antimicrobial agent chitosan. This modification method is supposed to relieve the occurrence or severity of multiple catheter-related complications.

Hydrogels are crosslinked macromolecular polymers that absorb relatively large volumes of liquid within their cross-linked, polymeric structures.$^{26,27}$ Hydrogel coating results in the formation of a thin water film on the contacting surface, thus improving its smoothness and lubricity. This is of particular importance in urethral catheters, to minimize insertion difficulties and trauma. Even though the hypothesis that hydrophilic-coated catheters exert less urethral friction than uncoated catheters is not generally agreed on,$^{17}$ acute urethral trauma, hematuria, and patient satisfaction have been demonstrated to be reduced in patients using hydrophilic-coated catheters compared with the patients using uncoated catheters.$^{16,17,28}$ Decreased friction on catheter surface could also diminish irritation of the urethral mucosa and subsequent inflammation during catheterization.$^{15}$ In this study, chitosan/PVA blending hydrogel coating samples showed a significant smaller water contact angle on SPU surface and absorbed significant higher amount of water than unmodified and even LubriLAST coating samples. Both findings indicated that the hydrogel produced a very hydrophilic surface on SPU. In addition, AFM study revealed that chitosan/PVA blending hydrogel coating surface was not only lubricious but also homogeneous. All these characteristics created by chitosan/PVA blending hydrogel coating could decrease the possibility of urethral trauma in patients needing urethral catheterization.

In order to produce an ideal anti-infective surface, it is desirable to both reduce the bacterial adhesion and kill the bacteria adhered onto the surface at the same time. It has been demonstrated that decreased protein adsorption could lead to a proportional reduction in protein-mediated adhesion of bacteria.$^{10}$ Several surface modification methods have been developed to decrease protein adsorption on the surface of biomedical devices.$^{29–32}$ The chitosan/PVA blending hydrogel coating SPU catheter developed in this study adsorbed significantly less amount of protein than unmodified and LubriLAST samples. This phenomenon is probably because hydrogel coating created a highly hydrophilic surface and incorporated PVA inhibited cell adhesion and reduced protein adsorption.$^{23,24}$ Several previous studies have also reported the benefits of modifying polymer

![Figure 6. Observation of antiseptic regions around LubriLAST (left column) and hydrogel coating SPU sheets (right column): Staphylococcus aureus (A, B), Pseudomonas aeruginosa (C, D), and Escherichia coli (E, F). Significantly larger antiseptic areas were observed around hydrogel coating samples. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

### Table II. $OD_{500}$ Values in LDH Cytotoxicity Detection

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<th>$OD_{500}$ Value</th>
<th>$p$ Value</th>
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<tr>
<td>Unmodified SPU samples</td>
<td>0.813 ± 0.014</td>
<td>0.33</td>
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<tr>
<td>In 1-day toxicant extracts</td>
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<tr>
<td>Hydrogel coating samples</td>
<td>0.888 ± 0.011</td>
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<tr>
<td>LubriLAST coating samples</td>
<td>0.902 ± 0.009</td>
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</tr>
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<td>LubriLAST coating samples</td>
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<td>In 5-day toxicant extracts</td>
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<td>6.2 × 10$^{-6}$</td>
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<td>LubriLAST coating samples</td>
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DOI 10.1002/jbmb
surfaces by the application of a hydrophilic coating to reduce bacterial adherence to the polymers.33–35 In addition, hydrophilic biomaterials may be more resistant to the development of encrustation in vitro and in vivo.36–38

The other attempts to reduce the incidence of infection in catheterized patients have been made by adding a disinfectant or antibacterial agent and by continuously discharging bactericidal into the urinary system.39–40 Chitosan is a natural biocompatible cationic polysaccharide derived by the deacetylation of chitin and processes antimicrobial and antifungal activity.41–44 The anti-infective effect of chitosan could take place when it stayed on the catheter surface expected in this study. The modification procedure provided a simple and effective way to modify the SPU surface. Not only was the resulting SPU catheter lubricious and biocompatible, but it also adsorbed minimal amounts of protein, and the eluded chitosan could suppress bacteria growth. In various aspects, chitosan/PVA blending hydrogel coating surpasses the performance of the FDA-approved LubriLAST. The chitosan/PVA blending hydrogel can help to minimize the risk of complications related to the use of urethral catheters, including urethral trauma, encrustation, and infection.

Authors thank Dr. Jann-Tay Wang from the Department of Internal Medicine, National Taiwan University Hospital for providing clinical isolated bacteria used in the antibacterial experiments.

CONCLUSION

Chitosan/PVA blending hydrogel coating performed as expected in this study. The modification procedure provided a simple and effective way to modify the SPU surface. Not only was the resulting SPU catheter lubricious and biocompatible, but it also adsorbed minimal amounts of protein, and the eluded chitosan could suppress bacteria growth. In various aspects, chitosan/PVA blending hydrogel coating surpasses the performance of the FDA-approved LubriLAST. The chitosan/PVA blending hydrogel can help to minimize the risk of complications related to the use of urethral catheters, including urethral trauma, encrustation, and infection.

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