New Bactericidal Surgical Suture Coating

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Ⓢ *Supporting Information*

ABSTRACT: This paper demonstrates the effectiveness of a new antimicrobial suture coating. An amphiphilic polymer, poly[(aminoethyl methacrylate)-*co*-(butyl methacrylate)] (PAMBM), inspired by antimicrobial peptides, was bactericidal against *S. aureus* in time-kill experiments. PAMBM was then evaluated in a variety of polymer blends using the Japanese Industrial Standard (JIS) method and showed excellent antimicrobial activity at a low concentration (0.5 wt %). Using a similar antimicrobial coating formula to commercial Vicryl Plus sutures, disk samples of the coating material containing PAMBM effectively killed bacteria (98% reduction at 0.75 wt %). Triclosan, the active ingredient in Vicryl Plus coatings, did not kill the bacteria. Further Kirby-Bauer assays of these disk samples showed an increasing zone of inhibition with increasing concentration of PAMBM. Finally, the PAMBM-containing coating was applied to sutures, and the morphology of the coating surface was characterized by SEM, along with Vicryl and uncoated sutures. The PAMBM-containing sutures killed bacteria more effectively (3 $\log_{10}$ reduction at 2.4 wt %) than Vicryl Plus sutures (0.5 $\log_{10}$ reduction).
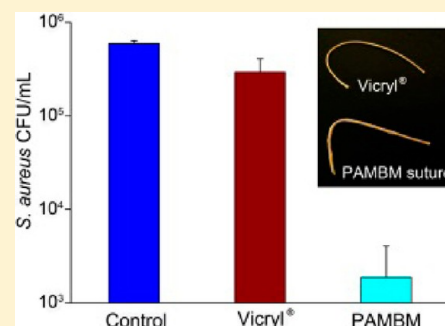
INTRODUCTION

Surgical site infections (SSIs) are some of the most common nosocomial infections, and most are localized at the incision.[1,2] SSIs result in patient mortality and high medical costs for society.[3] *Staphylococcus aureus* (*S. aureus*), a type of Gram-positive bacteria, is able to colonize on the surfaces of surgical implants and sutures and is responsible for 23% of SSIs.[1,4] Eliminating this source of infection would greatly reduce the incidence of SSIs.[5] One approach is to coat the surface of medical devices such as sutures with antimicrobials, which can prevent the formation of bacterial colonies without compromising the mechanical properties of the sutures. To date, the most commonly used antimicrobial surgical suture is the Vicryl Plus Antimicrobial Suture (VPAS), in which the active ingredient is triclosan (2,4,4′-trichloro-2′-hydroxydiphenylether), a neutral small molecule. The presence of triclosan in VPAS inhibits the colonization of a broad spectrum of bacteria on its surface.[6]

However, over decades, triclosan has been extensively used in many consumer products including soaps, toothpastes, shower gels, deodorants, fabrics, paints, etc., because of its low toxicity to humans. In many cases, for example, soap, triclosan is not a necessary ingredient.[7] As a result of the abuse of triclosan, bacteria have started to develop resistance to it by multiple mechanisms, including target mutation (bacterial fatty acid biosynthetic enzyme, enoyl-ACP reductase, or *FabI*) and overexpression of active efflux pumps and degradative enzymes.[7,8] Recently, safety issues regarding triclosan have also emerged. Triclosan bioaccumulates in human milk, umbilical cord blood, human fat tissue, and urine, which may negatively alter immune, endocrine, and reproductive functions.[9] Therefore, suitable substitutes are urgently needed.

Natural antimicrobial peptides (AMPs) are a group of amphiphilic short peptides found in all classes of living organisms, containing both cationic and hydrophobic residues. Their highly amphiphilic conformation allows AMPs to easily partition into and then disrupt the cytoplasmic membrane of bacteria, leading to cell death.[10−12] Because of their simple physical mechanism of action, AMPs display broad-spectrum activity against both Gram-positive and Gram-negative bacteria, and it appears difficult for bacteria to develop resistance against them.[10,13] These unique features of AMPs make them ideal candidates for developing new antibiotics. However, significant pharmaceutical issues, including limited in vivo stability, poor tissue distribution, and the high cost of manufacturing have severely hampered their development as antimicrobial agents.[14−16] As an alternative, many new synthetic systems have been prepared that mimic the basic features of AMPs.[17−21]

Degrado and co-workers[22] reported a copolymer, poly-[(aminoethyl methacrylate)-*co*-(butyl methacrylate)] (PAMBM, Figure 1), that showed good antimicrobial activity against both Gram-positive [*S. aureus*: MIC (minimum inhibitory concentration) = 12.5 μg/mL] and Gram-negative bacteria (*E. coli*: MIC = 25 μg/mL). Similar to natural AMPs,
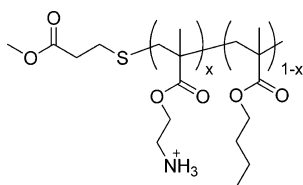
Figure 1. Chemical structure of poly[(aminoethyl methacrylate)-*co*-(butyl methacrylate)] (PAMBM); *x* = 0.65, MW ≈ 3000 Da.

PAMBM is a bactericidal agent, because its membrane-disrupting ability causes leakage of cytoplasmic contents and ultimately cell death. Triclosan, on the other side, is known as a bacteriostatic agent at low concentrations, only preventing growth and reproduction of bacteria.[23] This essential difference makes PAMBM advantageous over triclosan as an active ingredient in antimicrobial suture coatings.

In this paper, we studied the killing kinetics of triclosan and PAMBM against *S. aureus*. PAMBM was blended with common biomedical polymers and the activities of the resulting polymer blends were determined to evaluate the versatility of this new antimicrobial agent. We also explored the effect of calcium stearate (CaSt) on the antimicrobial activity of PAMBM, since this anionic surfactant is used in VAPS as a lubricant. Finally, coated sutures containing PAMBM were prepared and the antimicrobial activity was compared side by side with that of triclosan-containing sutures. It was shown that the PAMBM-containing coating was able to kill bacteria more effectively than triclosan.

■ MATERIALS AND METHODS

Materials and Instruments. Poly(lactic-*co*-glycolic acid) [PLGA, (65/35 and 50/50, M_w = 40 000−75 000)], polysulphone (M_w = 67 000 Da), poly(styrene-co-butadiene) styrene (45 wt %), and polystyrene (avg M_w ≈ 280 000 Da) were purchased from Sigma-Aldrich. Vicryl Plus Antimicrobial sutures (VCP259) were purchased from Ethicon Inc. Calcium stearate was purchased from Alfa Aesar. Tetrahydrofuran (THF), methanol, and dimethylsulfoxide (DMSO) were purchased from Fisher Scientific. PAMBM was prepared according to literature procedure.[22] Scanning electron microscope (SEM) images were taken using a FEI Magellan 400 Field Emission SEM and a JEOL 6320FXV Field Emission SEM. Methicillin-Resistant *S. aureus* (MRSA, ATCC33591) was used for the time-kill experiments. *S. aureus* (ATCC 25923) was used for the JIS, Kirby-Bauer, disk, and suture microbiological experiments. All microbiological assays were performed using sterile techniques under a laminar flow hood.

Time-Kill Experiments. Antimicrobial stock solutions of 10 mg/mL in DMSO were prepared, and the stock solutions were diluted to 2×, 5×, and 10× the MIC value for *S. aureus*, and the *S. aureus* inoculum was added to adjust the resulting bacterial solutions to OD600 of 0.001 for 3 mL. The tubes with the resulting solutions and the DMSO control were incubated for 0 to 48 h at 37 °C while shaking. Aliquots were taken at the time points of 0, 0.5, 1, 2, 4, 6, 8, 24, and 48 h. At each time point, 5 μL of the inoculum was added to 45 μL of sterile water and serially diluted to obtain a concentration of $1:10^6$ in a 96 well plate. Five μL of the inoculum was spotted from the serially diluted tubes onto a Mueller Hinton agar plate in duplicates. The agar plates were incubated for 18 h at 37 °C, and then all of the colony forming units (CFU) on all plates were counted and recorded.

Preparation of Thin-Film Polymer Blends. The preparation of 0.13 wt % of PAMBM in PLGA (50/50) given as an example: PAMBM (2.5 mg) and PLGA (1.0 g) were dissolved in 1 and 2.5 mL of DMSO, respectively, to form PAMBM and PLGA stock solutions. Then 200 μL of the PAMBM stock solution was added dropwise to 1 mL of the PLGA stock solution. The resulting solution was sonicated

for 30 s, and then a film was cast in a Teflon mold, followed by evaporation of solvent under vacuum.

Preparation of Disk Samples. PLGA (65/35) (80 mg) was dissolved in THF (1.5 mL), and the resulting solution was combined with a solution of PAMBM in methanol (20 mg/mL) to form a cloudy mixture. The mixture was sonicated for 30 s, and then CaSt (80 mg) was added, followed by 5 min of sonication. The final slurry was transferred to a circular Teflon mold (30 mm in diameter, 2 mm in depth) and air-dried overnight to form a circular disk. The disk was removed from the mold and dried under vacuum for another 2 h. Disc samples with different weight concentrations of PAMBM or triclosan were prepared by varying the amount of active agents.

Removal of Coatings from Vicryl Plus Sutures. VPAS samples (∼15 cm) were immersed in THF (15 mL) and sonicated for 5 min. The sutures were then transferred to fresh boiling THF (30 mL) and the solvent was kept in reflux for 2 h. After washing with fresh THF, the suture samples were dried under high vacuum. The removal of the coating was confirmed by SEM [Figure 6c,d].

Preparation of Sutures Coated with PAMBM. A coating slurry that contained 10 wt % PAMBM was prepared first: PLGA (65/35) (105 mg) and PAMBM (23 mg) were dissolved in 5.5 mL THF and 1 mL methanol, respectively. The PAMBM solution was slowly added into the PLGA solution dropwise with magnetic stirring. The resulting cloudy solution was sonicated for 1 min and then CaSt (105 mg) was added. The slurry mixture was sonicated for 5 min and then ready for suture coating. A piece of uncoated suture (∼20 cm) was weighed (W_1) and then immersed in the coating slurry for 30 s. The suture was taken out of the slurry, pulled tight by tweezers at each end, and tilted to move any droplets of coating solution between the two ends of the suture back and forth until the droplets were visibly gone. The dipping step was repeated for several times and the suture was dried under vacuum for 30 min. The dried coated suture was weighed (W_2), and the weight concentration of PAMBM in the suture was determined according to eq 1

$$\text{wt\%} = \frac{(W_2 - W_1)10\%}{W_2}100\%$$

(1)

Antimicrobial Activity Assays. Japanese Industrial Standard Assay (JIS Z 2801). A suspension of *S. aureus* (10^5 cells/mL) in sterile phosphate buffered saline (PBS) was prepared and put into a chromatography sprayer. Disc samples with varying amounts of PAMBM were sprayed equally and evenly with the bacteria solution. After 3 min, 50 μL of sterile PBS (1:10 dilution) was added onto each sample surface. After 5 min, 20 μL of PBS solution was removed from the surface, diluted ($1:10^3$ dilution), and spread onto Mueller Hinton agar plates. The plates were incubated at 37 °C for 24 h and viable colonies were counted. All colony counts were calculated into colony forming units per mL (CFU/mL), and bactericidal activity was determined in comparison to colony growth on control samples containing no PAMBM.

Disc Diffusion Susceptibility Testing (Kirby-Bauer Assay).[24] A *S. aureus* bacterial suspension at the 0.5 McFarland standard was spread onto Mueller Hinton agar plates. The PAMBM or triclosan-containing disk samples were placed onto an agar surface, and plates were incubated at 37 °C for 24 h. The resulting zones of inhibition were compared.

Testing of Disc Samples. Disc samples were placed in individual Petri plates. A 100 μL droplet of *S. aureus* bacterial suspension (∼10^6 cells/mL) was placed onto the disk surface and allowed to sit for 30 min. The disk with the droplet was then sonicated for 2 min. Then 20 μL of this droplet was collected, diluted by 150 folds in sterile PBS, and spread onto Mueller Hinton agar plates. The plates were incubated for 24 h at 37 °C, and resultant viable colonies were counted and recorded. All of the colony counts were calculated into CFU/mL, and bactericidal activity was determined relative to colony growth on control samples.

Testing of Suture Samples. A 1 cm piece of suture was immersed into a 1 mL *S. aureus* bacterial suspension (∼10^6 cells/mL) for 30 min. The immersion was timed for 2 min, and the solution was diluted by

1250 folds in sterile PBS with a 96 well plate, spread onto Mueller-Hinton agar plates, and incubated at 37 °C for 24 h. The resultant viable colonies were counted. All colony counts were calculated into CFU/mL, and bactericidal activity was determined relative to colony growth on control samples.

■ RESULTS AND DISCUSSION

Killing Kinetics of PAMBM and Triclosan. Killing kinetics were performed with PAMBM to evaluate its bactericidal activity and compare it with that of triclosan. The killing kinetics for *S. aureus* were obtained by measuring the time required to reduce the initial inoculum by 3 $\log_{10}$ units.[25] These studies showed that the bacteria were reduced by >3 $\log_{10}$ units in 30 min at 10 × MIC of PAMBM, and in less than 3 h for the 2 × MIC treated culture (Figure 2b). In contrast,
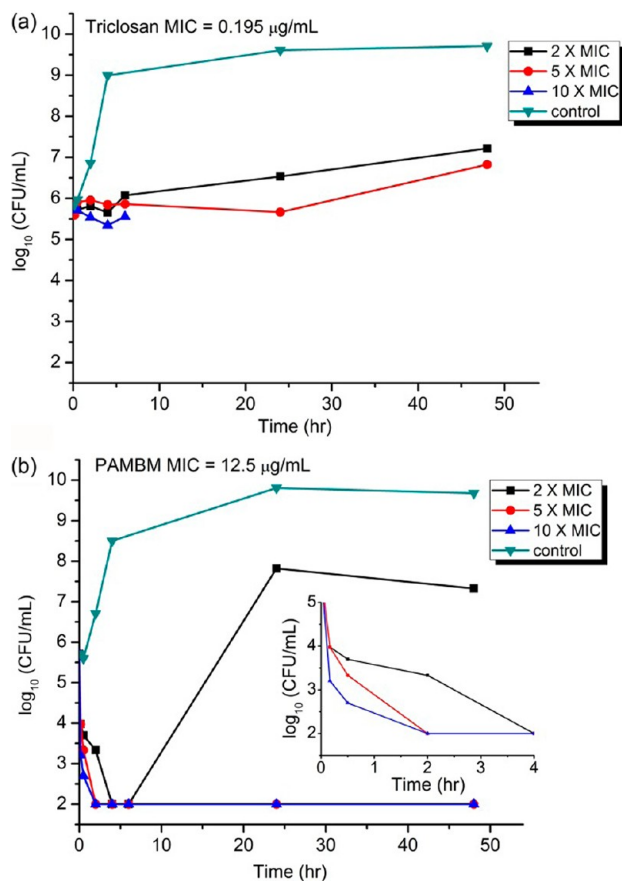

Figure 2. Bacterial growth as a function of time when treated with (a) triclosan and (b) PMBAM at 2×, 5×, 10 × MIC, and control.

triclosan demonstrated only bacteriostatic activity, even at 10 × MIC (Figure 2a), as indicated by the minimal change in the $\log_{10}$ units. Although regrowth was evident in the 2 × MIC treated culture with PAMBM, it was probably caused by sequestration of the compound in the bacterial biomass as opposed to "resistant" strains since in all the cases examined, the MIC of the culture following regrowth was identical to the original MIC (data not shown). The killing kinetics clearly demonstrated the bactericidal nature of PAMBM, and differentiated it from triclosan, which is only bacteriostatic.

Antimicrobial Activity of Polymer Blends Containing PAMBM. Blending active agents into polymers is one common approach to creating antimicrobial materials.[26] In order to evaluate the activity of PAMBM, it was blended into five widely

used biomedical polymers: poly(lactic-*co*-glycolic acid 50/50) (PLGA 50/50), polystyrene (PS), polyvinylchloride (PVC), polysulphone (PSu), and poly(styrene-butadiene-styrene) (SBS). The antimicrobial activities of these blends were evaluated using the JIS assay,[24] which was developed to measure the antibacterial activity of hydrophobic materials. Thin films were created by casting solutions of the various polymers with PAMBM and drying them under vacuum overnight. Bacterial suspensions were sprayed onto the polymer surfaces and bacteria viability was measured after 5 min.

The results of the JIS assay are shown in Figure 3. In each case, the base polymer was treated identically to the test
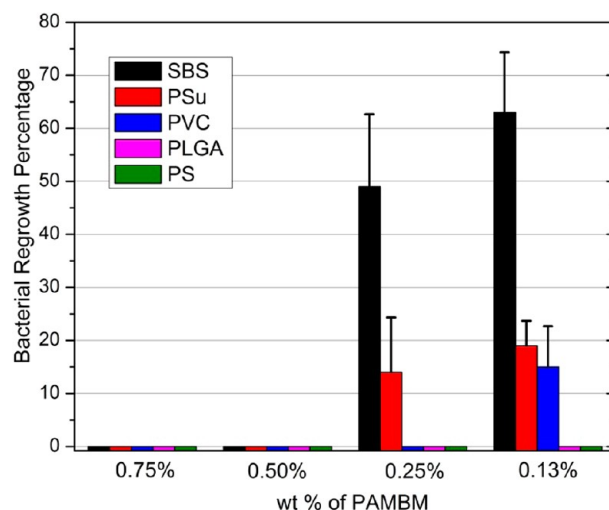

Figure 3. Percent regrowth of *S. aureus* as a function of the weight concentration of PAMBM in different polymer blends. Data represent averages of three independent experiments and the error bars are standard errors.

samples, so that there is a direct comparison among polymer surfaces with and without PAMBM, and the data is plotted as percent inhibition, taking PAMBM-free surfaces as the controls. Figure 3 shows that at 0.50 wt % PAMBM and above, no bacterial regrowth was observed for all polymer surfaces. Reducing the concentration of PAMBM showed that at 0.25 wt % only PVC, PS, and PLGA gave 100% inhibition. At only 0.13 wt % of PAMBM, PS and PLGA still showed 0% regrowth while PVC and PSu had 20% regowth and SBS ~62%. It was difficult to quantitatively control the spray volume, therefore maintaining a constant number of bacteria exposed to each surface was hard to achieve. As a result, a new method was employed to test the activity of the suture coating materials. Nevertheless, the high activity of PLGA, even at low concentrations, was encouraging since both the VPAS base suture and suture coating are made from this polyester.

Evaluation of Suture Coating Materials. Commercial VPAS has an inner core of braided PLGA (10/90) fibers and a coating material consisting of CaSt, PLGA (65/35), and triclosan. CaSt is used as a lubricant to help sutures pass through tissues smoothly. PLGA (65/35) is a film-forming, biodegradable material, used as a binder for the other two materials. In order to directly compare the antimicrobial activities of triclosan and PAMBM in coating materials, a similar formulation of the VPAS coating was prepared by essentially replacing triclosan with PAMBM. Equal weights of PLGA (65/35) and CaSt were mixed with a different amount of

PAMBM in organic solvents and cast to form disk-like film samples (Figure S1). Similar disk samples containing triclosan were also prepared for direct comparison. This test evaluated the performance of PAMBM in conditions similar to a commercial coating, including any possible effects of CaSt.

Instead of using the JIS method, a new assay was employed to quantify the antimicrobial activity of these disk samples. A droplet of a *S. aureus* bacterial suspension, containing a known count of bacteria, was placed onto the disk surface and exposed for 30 min, at which time an aliquot was removed and bacterial viability was determined by plating and counting the overnight colonies. As shown in Figure 4, there was ~2 $\log_{10}$ reduction
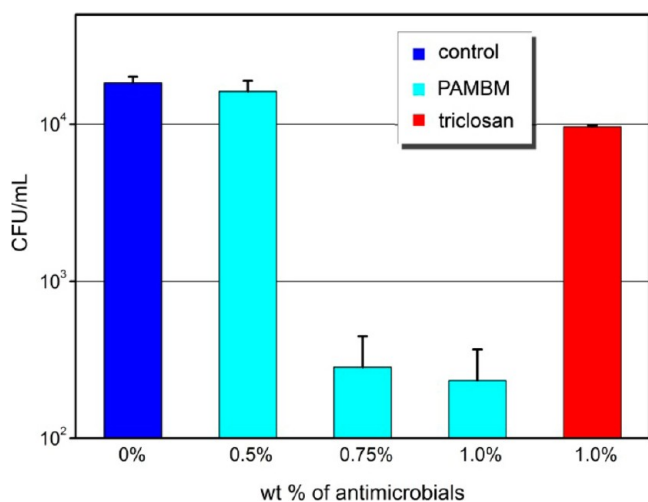

Figure 4. Comparison of bacterial growth from solutions exposed to suture coating materials (PLGA 65/35 and CaSt) containing PAMBM (cyan bars), triclosan (red bar), and no antimicrobial agent (blue bar). Significant difference ($p < 0.01$) is between PAMBM disk samples (0.75 and 1.0 wt %) and triclosan disk sample (1.0 wt %). Data represent averages of three independent experiments and the error bars are standard errors.

measured in samples containing 0.75 and 1.0 wt % PAMBM. On the other hand, the samples with 1 wt % of triclosan were not able to kill bacteria effectively. These results indicated a clear advantage of PAMBM over triclosan in preventing bacterial growth and the presence of CaSt did not eliminate the antimicrobial activity of the PAMBM. This huge difference is perfectly consistent with the fact that PAMBM is bactericidal while triclosan is bacteriostatic.

Kirby-Bauer susceptibility tests,[27,28] also known as zone of inhibition (ZOI) assays, are well-known for VPAS since triclosan readily leaches from the coating. Therefore, it seemed reasonable to compare the ZOI activity of coatings containing PAMBM. Figure 5 shows the results for a series of PLGA/CaSt materials containing increasing PAMBM concentrations against *S. aureus*. The results are generally consistent with our previous evaluation; where the concentration of PAMBM was 1.0 wt % and above, a ZOI was clearly visible, and the area increased as the concentration of PAMBM increased. When compared to triclosan-containing samples at the same concentrations (Figure S2), the ZOIs of PAMBM-containing samples were much smaller, indicating the leaching ability of PAMBM from the coating material was lower than triclosan. This is not surprising, given that the MW of triclosan is 290 Da, compared to the MW of PAMBM, which is 3000 Da, making the triclosan more mobile. In addition, the amphiphilic nature of PAMBM makes
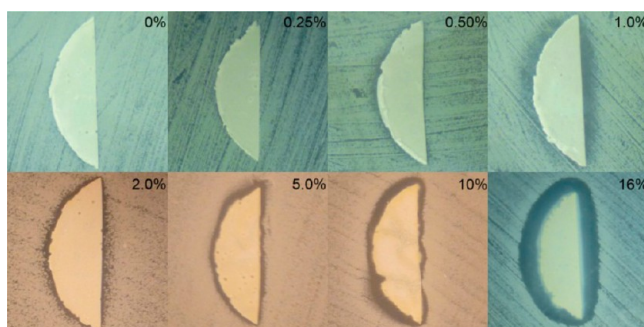

Figure 5. Kirby-Bauer tests of PLGA/CaSt materials containing various concentrations of PAMBM (0−16 wt %). Disc samples show an increasing zone of inhibition with increasing weight percent of PAMBM.

it interfacially active and likely less mobile. The benefits of leaching are debatable, since the purpose of the antimicrobial coating is to prevent bacteria from colonizing on the medical devices,[29] instead of sterilizing the wound area. In this respect, PAMBM has an advantage over triclosan because the antimicrobial stays embedded in the suture coating longer with less leaching and is bactericidal.

Characterization of Suture Coatings. The technical details of the VPAS coating, including coating thickness and weight concentration of triclosan in the coating material, are not fully published. Due to the difference in solubility between the coating [PLGA (65/35)] and the core of the suture fibers [PLGA (10/90)], the VPAS coating was easily removed by soaking in hot THF. Upon removal of the coating, the weaves of the suture appeared to loosen (Figure S3, Figure 6c).
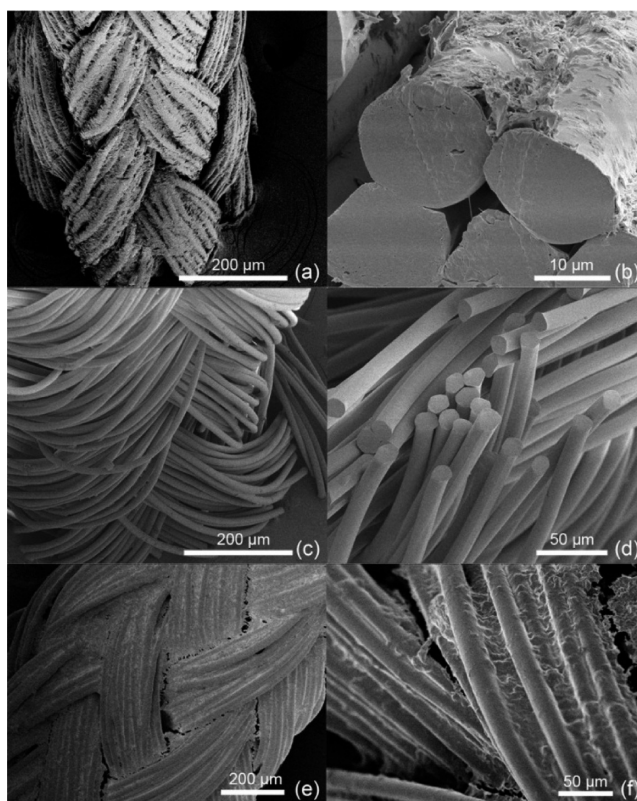

Figure 6. SEM images of Vicryl sutures (a and b), uncoated sutures (c and d) and sutures with coating containing PAMBM (e and f).

Scanning electron microscopy (SEM) was employed to image the surface of both the VPAS and uncoated sutures. The diameter of PLGA (10/90) fiber, as observed through SEM (Figure 6b), was ~20 μm. The cross section showed that some of the fibers were woven into a hollow tubing-like structure, and the rest of the fibers were stuffed in the tubing coaxially (Figure S4a). The suture coating is a thin layer with a coarse surface on the fiber's exterior. A highly magnified SEM image (Figure S4b) showed that the inner fibers had a smoother surface compared to the outer ones, suggesting that the coating material only covers the outer surface of the suture, instead of individual fibers. After treatment with hot THF, the surface of every fiber in the suture became smooth (Figure 6c,d), confirming that the coating was completely removed. The diameter of the suture fibers did not change indicating that PLGA (10/90) was not dissolved or swollen by THF.

By measuring the weight loss after removing the coating, the mass of the coating was determined to be ≤ 3.0 wt % of the suture. According to the product description of Vicryl sutures, every meter of suture (120 mg) contains ~472 μg of triclosan, meaning that the triclosan concentration is ~0.4 wt % of the entire suture. Thus the weight concentration of triclosan in the coating layer was calculated to be >13 wt %.

Antimicrobial Evaluation of Coated Sutures. VPAS with their coating removed were then recoated with PLGA/CaSt/PAMBM by the dipping-method[30] and their antimicrobial activities were evaluated. In order to compare with VPAS, a coating mixture was prepared containing 10 wt % of PAMBM or triclosan along with PLGA and CaSt in THF, and the resulting slurry was used for dip-coating. The weight gain of the suture after dipping and drying was measured to determine the weight concentration of PAMBM in the whole suture and the coating process was repeated until the suture samples achieved a desired weight concentration of PAMBM or triclosan.

Unlike the disk samples, the suture samples have a very small and nonflat surface; therefore, the previous method used to evaluate the disk samples was modified for the suture samples. Instead of placing a droplet of known volume on the coating, the known volume was placed in an Eppendorf tube and a piece of suture was immersed in this volume. After 30 min, the bacteria viability was measured by dilution, plating and overnight incubation. Like the previous droplet method, and unlike the ZOI assays, this approach also quantifies bacteria killing. Using this method, the coated sutures containing 0.8−2.4 wt % PAMBM or triclosan were evaluated, along with commercial VPAS.

As shown in Figure 7, the suture test results are consistent with the results obtained from the disk tests. Even after contact with sutures containing high concentrations of triclosan, the bacterial solution still contained a large number of viable bacteria. After overnight incubation; the number of viable bacteria was statistically similar to the untreated control. The commercial VPAS showed a slight decrease in bacterial count compared to our self-coated triclosan sutures in which we know the exact concentration of triclosan. The difference between the results of our self-coated triclosan sutures and VPAS likely resulted from a higher concentration of triclosan in the VPAS coating.[31] Additionally, the dipping coating method, as mentioned before, coated all of the fibers [Figure S4(c)], whereas VPAS appear to be coated only on the exterior. Therefore, the surface of VPAS contains an even higher concentration of triclosan than our self-coated sutures, even if the overall triclosan concentrations were the same.
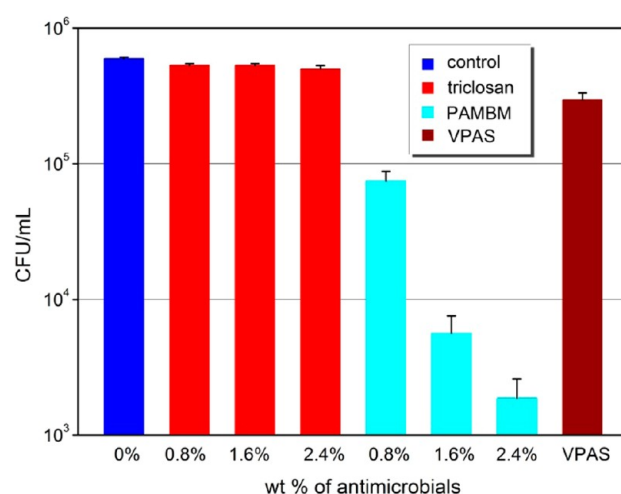

Figure 7. Comparison of bacteria survival from solutions exposed to sutures containing different concentrations of triclosan (red bars) and PAMBM (cyan bars) along with VPAS (brown bar) and the uncoated sutures (no antimicrobial reagent) (blue bar). Significant difference ($p < 0.05$) is between PAMBM coated sutures (1.6 and 2.4 wt %) and VPAS. Data represent three independent experiments and the error bars are standard errors.

In contrast, sutures coated with PAMBM significantly reduced bacterial growth. The sample with 0.8 wt % PAMBM killed ~1 $\log_{10}$ of bacteria, whereas 2.4 wt % PAMBM killed ~3 $\log_{10}$ of bacteria. PAMBM was thus shown to be a far more effective antibacterial compound for sutures than triclosan.

■ CONCLUSIONS

The amphiphilic polymer PAMBM was demonstrated to be a bactericidal agent able to rapidly kill *S. aureus*, whereas the widely used antimicrobial agent triclosan was only bacteriostatic. We also confirmed that CaSt, the anionic lubricant in commercial VPAS did not eliminate the activity of PAMBM. Due to its bactericidal mechanism, PAMBM outperformed triclosan as an active antimicrobial agent in suture coatings. When PAMBM was formulated into the coating of VPAS, it remained bactericidal. Both films of the coating material and sutures coated with PAMBM outperformed coatings containing similar concentrations of triclosan. As bacterial resistance to current agents continues to increase, with resistance to triclosan now documented, the discovery of new antimicrobial agents that remain active in biomedical device coatings is essential.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Images of disk samples of coating materials. Kirby-Bauer assay results of triclosan disk samples. More SEM images of VPAS and PAMBM coated sutures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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